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Characterising, modelling and mapping malaria occurrence and its mortality trend for Precision Public Health

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PhD

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Abstract

This work considers characterizing, modelling and mapping malaria occurrence and its mortality trend for Precision Public Health in Chimoio. Mozambique. Malaria is an ancient disease and a major public concern especially in the African continent. The majority of deaths occur among children living in Africa (91 %), where a child dies every minute and half from malaria. The data for malaria cases and mortality were obtained from the weekly BES from 2006 to 2014 and Civil Registration books from 2007 to 2014respectively. To model malaria cases ARIMA was used while for mortality trends, Intervention time series analysis (ITSA) was used. Package *tscount* and R version 3.3.2, Biestat 5.0 and SPSS were employed to fit, assess and predict model and statistical analysis. In Chimoio, malaria occurrence and mortality is increasing annually and presents a spatial and temporal pattern peaking during weeks 1 to 12 (January to March). The rural areas of the municipality have more malaria and mortality cases, followed by suburbs, and urban areas have fewer cases. Children under 5 years of age are three times more prone to get malaria than the rest of the population. The Chimoio climate seems ideal for malaria occurrence. Children between 1 – 4 years old are 13% of Chimoio population, but represent 25% of malaria mortalities. The entire municipality presents a malaria risk, 96% with moderate risk and 4% with high-risk areas. The use of Intervention time series analysis approach for modelling malaria mortality is suggested, and on owing to its flexibility and interpretation. The practicality of the statistical modelling method was validated to detect the lagged relationship between malaria cases and mortality. Based on the results, malaria cases and mortality can be predicted two months in advance. This modelling approach is robust, and can predict the expected number of malaria and mortality cases in advance. Thus, timely prevention and control measures can be effectively planned in Chimoio, such as the elimination of vector breeding places, correct time and place to spray insecticides, and awareness campaigns weeks before the

malaria peak season. This can lead to a reduction in malaria cases, by knowing the best moment for spraying, saving time and cost of insecticide application and preventive programmes, and guiding smart environmental care (Precision Public Health).

Resumo

Considera-se neste trabalho a caracterização, modelagem e mapeamento da ocorrência da malaria e suas tendências de mortalidade, para a Saúde Publica de Precisão em Chimoio, Moçambique. A malária é uma doença milenar sendo um grande problema de Saúde Pública, especialmente em África onde ocorre o maior número de mortalidade em crianças (91%) estimando-se que em cada minuto e meio uma criança morre de malária. Os dados de malária e mortalidade foram recolhidos dos Boletins Epidemiológicos Semanais de 2006 a 2014 e dos livros de registos dos Serviços de Registo e Notariado no período entre 2007 a 2014 respetivamente. Para a modelação da malaria foi usado o ARIMA enquanto para as tendências de mortalidade o a análise de série temporal de intervenção (ITSA). Os pacotes estatísticos *tscount*, R versão 3.3.2, Bioestat 5.0 e o SPSS versão 20 foram usados para modelar, aceder e realizar predição do modelo e testes estatísticos apropriados. Em Chimoio a ocorrência da malaria e mortalidade tendem a crescer anualmente, exibindo padrões temporais e espaciais sendo o seu pico entre as semanas 1 a 12 (janeiro a março) e as áreas rurais apresentam mais malária e mortalidade, seguida dos subúrbios sendo a zona urbana a que menos casos apresenta. +As crianças com menos de 5 anos de idade tem três vezes mais suscetibilidade de contrair malária. O Clima de Chimoio parece ser ideal para a ocorrência da malária. As crianças entre 1 – 4 anos de idade constituem13% da população, entretanto representam 25 % dos casos de mortalidade por malária. Toda a superfície municipal apresenta risco para contrair malaria sendo, 96% áreas de risco moderado e 4% de risco alto. Sugere-se o uso da abordagem de series temporais generalizadas para a modelação devido a sua flexibilidade e facilidade de interpretação. A praticabilidade da modelação estatística foi validada para detetar a distância entre a ocorrência da malária e mortalidade. Com base nos dados a ocorrência de malária e mortalidade podem ser previstos com antecedência.

Esta forma de abordar a modelação é robusta, pode fazer a previsão atempada da malária e mortalidade, permitindo medidas de prevenção e controlo atempadas e uma planificação efetiva em Chimoio consistindo em eliminação de áreas para a reprodução do vetor, tempo e local correto para a pulverização com inseticidas, fazer as campanhas de prevenção antes do pico da malária. Estas medidas podem resultar em poupança de custos e tempo nas medidas preventivas para além de reduzir os efeitos nefastos para o ambiente (Saúde Publica de Precisão).

Palavras-chave: Malária, mortalidade, modelação, previsão, ARIMA, ITSA.

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1. Introduction

One of the United Nation's sustainable development goals for 2030 is to end the epidemics of AIDS, tuberculosis, malaria and other neglected tropical diseases (United Nations, 2015). Malaria is a very old disease and is a major public health problem in Africa. Sub-Saharan Africa carries a disproportionately high portion of the global malaria burden. In 2015, the region was home to 88% of malaria cases and 90% of malaria deaths. The number of malaria deaths globally was 438,000 in 2015 (WHO, 2013a). Most deaths occur amongst children living in Africa, where a child dies every minute and half from malaria (CDC, 2014b; WHO, 2013a).

According to the Mozambican Ministry of Health, the country recorded over six million cases of malaria in 2015 (Norheim, Admau, Godal, Hum, & Kruk, 2015) and deaths due to malaria (per 100,000 persons) was 42.75 in 2013 (Ranking, 2016). Malaria killed 3,245 people and is the second cause of death in the country, at 19.2% (GDB profile, 2016).

Mozambique was recently ranked fifth in Africa for the number of malaria cases (Global Fund, 2015) and reported over six million cases of malaria in 2015 (MISAU, 2016). Malaria represents 45% of all cases in outpatient visits, 56% of inpatient visits at paediatric clinics, and around 26% of all hospital deaths (UCSF Global Health Group, 2013).

According to the Ministry of Health the country registered in the first quarter of 2017 over two million cases of malaria. The provinces of Manica, Tete, Gaza and Inhambane presented the highest numbers. Malaria is broadly recognised as endemic in Mozambique, with seasonal peaks during the wet season, between November and March, but predominantly in February. (Zacarias & Andersson, 2010).

Malaria undermines not only the people's health but also their working capacity, hampering the social and economic development of the countries involved. The disease constitutes an enormous cost both to individuals and

governments. Costs to individuals and their families include purchase of drugs for treating malaria at home; expenses for travel to, and treatment at, dispensaries and clinics; lost days of work; absence from school; expenses for preventive measures; expenses for burial in case of deaths.

Several institutions and the Mozambican Government have initiatives to combat malaria and despite the efforts, the number of cases continues to increase annually. Most research projects focus on the clinical aspects of the disease such as chemoprophylaxis, and vaccine development. However, disease eradication should not only involve the medical disciplines, but also health economics, geography and ecology, and the social sciences to design and implement control strategies in real life settings (Alilio, Bygbjerg, & Breman, 2004).

The Mozambican strategy for malaria combat includes: i) integrated vector management through indoor residual spraying to eliminate the mosquitoes, and bed net usage; ii) diagnosis and cases management through effective diagnosis and treatment (WHO. 2015a).

The malaria life cycle has three components: (i) the growth of the *Anopheles* female mosquito from egg to adult to parasite transmission; (ii) the development of the *Plasmodium* parasites (gametocyte to sporozoites) that are able to infect humans; and (iii) the incubation period in the human host from infection to malaria symptoms CDC (2014b); Crutcher and Hoffman (1996).

Chimoio is the capital of Manica Province in the Centre of Mozambique. It is the fifth-largest city in Mozambique, with an estimated population of 324,816 (IDS, 2013), all of whom are at risk of contracting malaria. The major cause of death in the municipality in 2013 was malaria at 15%. The incidence of malaria is 20.1%, and the attributable factor 16% with differences in weekly and yearly malaria occurrence. (João & Ferrão, 2013)

Urban malaria in Africa is a problem of substantial and growing proportions since these areas are growing quickly, especially in suburbs with poor houses and drainage, farming activities, large amount of vegetation, fruit

trees, and persistent poverty. Children and pregnant women are severely and disproportionately affected by malaria in high malaria burden countries (UNICEF, 2015).

An association between malaria prevalence and socioeconomic status of households was established in Mozambique. (IDS, 2013).

There are conflicting reports regarding the impact of urbanization on malaria endemic trends. Some authors (Hay, Guerra, Tatem, Atkinson, and Snow (2005); Hay, Smith, and Snow (2008)) claim that the urbanization process results in profound socio-economic and landscape changes that reduce malaria in urban areas, while some report an increase in malaria in urban regions due to population increase, over-crowding, and poor sanitation (Qi et al. (2012); Saraiva, Amorim, Moura, Martinez-Espinosa, and Barbosa (2009)).

Few spatial studies of malaria have been reported for Mozambique and most studies on malaria variation are based on monthly data (Thompson et al. (1997); Zacarias & Andersson, 2010).

The maps that exist on malaria were produced at the National or Continental level, such as MARA (2004), and have limited operational use to support local programme activities.

The patterns of malaria transmission at the local level, especially in Chimoio, have not been studied or precisely defined. This type of research is needed in order to develop cluster risk maps and identify locations and populations at risk for appropriate planning and implementation of targeted and epidemiologically sound preventive and control measures against the disease.

Precision Health is defined as improving the ability to prevent disease, promote health, and reduce health disparities in populations by: 1) applying emerging methods and technologies for measuring disease, pathogens, exposures, behaviours, and susceptibility in populations; and 2) developing policies and targeted public health programmes to improve health (CDC, 2014b).

Many time-series studies and studies of epidemics have been carried out to determine explanatory variables for changes in malaria transmission, but most fail to take climatic factors into account (Srimath-Tirumula-Peddinti, Neelapu, & Sidagam, 2015). It is well known that the practice of precision health was enabled by the advent of Global Positioning Systems (GPS) and Global Navigation Satellite Systems (GNSS). The Geographical Information System (GIS) is a powerful tool for the health practitioner and researchers due to its ability to incorporate data from different sources to produce new information that permits the creation of maps of spatial variability (Milla, Lorenzo, & Brown, 2005).

Malaria transmission is highly influenced by environmental and climatic conditions, but the effects are often not linear and varies over areas covered by different agro-ecological zones Gosoniu, Vounatsou, Sogoba, Maire, and Smith (2009), thus resources for control have to be spread in time and space. Climatic factors such as temperature, relative humidity, precipitation and evaporation influences the lifecycle and development of both the mosquito vector and the parasite (An, 2011). As mentioned by The Global Fund, 90% of malaria cases are related to environmental factors.

Understanding the trends and variation of deaths is of paramount importance for precision public health. Precision public health is a relatively new concept and its ultimate goal is to develop and implement health interventions that can benefit the right population at the right time (M..J. Khoury, 2015). Civil registration constitutes the most timely and accurate source of information on mortality and causes of death. In Mozambique registration of deaths falls under the Ministry of Justice (UTREL, 2005).

Geographic information systems can help to describe variations in malaria mortality and this is important to identify areas at high risk, to assist in designing appropriate interventions, or lead to further investigations to identify important risk factors (Kazembe, Kleinschmidt, & Sharp, 2006).

As stated elsewhere, the best ways to help the living is by counting the dead. Few data on malaria mortality, trends and characteristics of malaria

death exist in Mozambique, particularly in Chimoio. The few existent data are from hospitals and do not represent the entire community.

Malaria can be cured in cases where the *Plasmodium* parasite is susceptible to the anti-malaria drug, and it can be prevented using indoor and outdoor spraying, mosquito repellents, and bed nets. For significant reduction and elimination, strong and long-term actions are needed. Daily or weekly variations in the values of weather elements and disease data are often of greater importance in determining the efficiency of a climate-disease model. However, most studies only use monthly data WHO (2013a) and Omonijo, Matzarakis, Oguntoke, and Adeofun (2011).

Mathematical models can describe, explain, or predict disease trends/occurrence, they can test multiple scenarios, combine strategies for intervention, and provide a verifiable prediction on what can be expected from implemented schemes (Nakul, Schapira, Smith, Hay, & Richard, 2010).

This thesis consider the case of Chimoio municipality in the central region of Mozambique (Map 1).
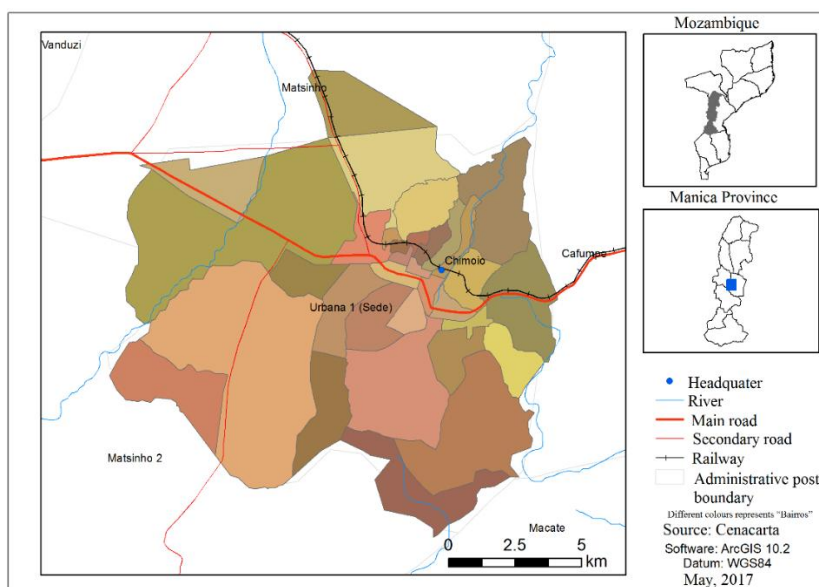
Map 1: Chimoio Map

Source: Ferrão, Mendes, Painho, & João, 2016

1.1. Malaria

1.1.1. Malaria facts

Malaria is an ancient disease and poses a substantial public health problem in Africa. Almost half of the population lives in areas susceptible of malaria. In 2008, 139 countries reported malaria cases (CDC, 2014) as presented in Map 2.
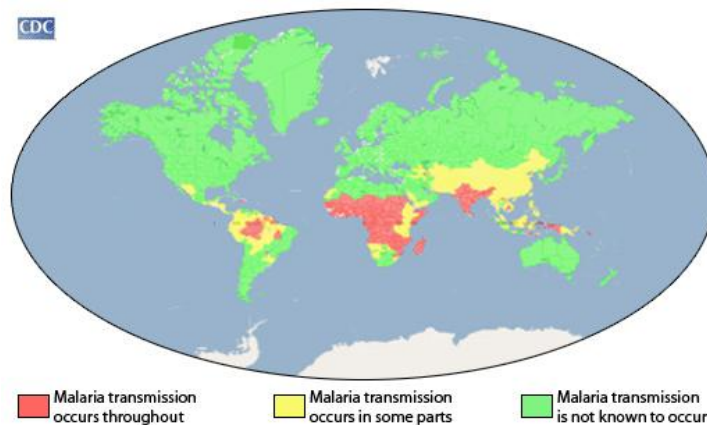
Map 2: Approximation of the parts of the world where malaria transmission occurs

Source: (CDC, 2014b)

In 2015, 212 million malaria cases were reported that resulted in 429,000 deaths worldwide. Most of the deaths (91%) occurred in Africa (WHO, 2015b). Children and pregnant women are the most at risk.

A very efficient mosquito (*Anopheles gambie complex*) is responsible for the high transmission. The parasite species infecting humans are:

- ***Plasmodium falciparum,*** a parasite found in the tropics and subtropics, especially in Africa, being the predominate specie, and it can cause anaemia. The parasite can also clog small blood vessels and if it occurs in the brain, may result in cerebral malaria that can be fatal.

- ***Plasmodium vivax,*** a parasite that is mainly found in Asia, Latin America and some parts of Africa. This parasite can activate and

inactivate in the blood (relapse) several months or years after the biting of an infected mosquito.

- **_Plasmodium ovale,_** a parasite found manly in West Africa and Western Pacific islands. This parasite can infect persons that are negative for the Duffy blood group, being the case for several sub-Saharan Africa habitants.

- **_Plasmodium malariae_**, a parasite found globally. If not treated _P. malariae_ causes a long lasting chronic infection that can last a lifetime. The disease can cause serious complications such as nephrotic syndrome.

- **_Plasmodium knowlesi,_** a parasite found in South East Asia, it has in recent years proved to be a significant cause of zoonotic malaria in the region, especially in Malaysia. It is a natural pathogen of long and pig tailed macaques (CDC, 2014b).

Malaria affects five times more people than AIDS/HIV, leprosy, measles and tuberculosis combined (WHO, 2013a). Malaria symptoms include high fever, headache, vomiting and joint aches, and generally symptoms appear 10 to 15 days after the infected mosquito bite. If not rapidly treated, the disease can quickly become life-threatening by disrupting the blood supply to vital organs. (WHO, 2013a).

Clinical illness is caused by erithocityc stage of the parasite. No diseases is associated with sporozoites, the developing liver stage of the parasite, the merozoites released from the liver, or gametocytes. The initial symptom's and signs are associated with the rupture of the red blood cells when erythrocytic-stage schizonts mature. The symptoms includes fever, chills, sweating, headache, weakness, and other symptoms. Later, severe disease may develop, with an abnormal level of consciousness, severe anaemia, renal failure, and multisystem failure (Crutcher & Hoffman, 1996).

Malaria undermines people's health and their working capacity, hampering the social and economic development of a country. Malaria imposes enormous cost both to individuals and governments and for

individuals costs include purchase of medicines to treat the disease; expense to travel to clinics; loss of working days since in average a person with malaria will stay absent for three days; school absenteeism, preventive measures expenses such as indoor spraying and repellent usage; expenses for burials in cases of fatalities. Government costs includes maintenance, supply and staffing health facilities, purchase of medicines and supplies; public health interventions against malaria, such as spraying with insecticides, distribution of bed-nets, loss of working days resulting in income loss; lost days of work with resulting loss of income; and lost opportunities for joint ventures and tourism (Gallup, Sachs, & Mellinger, 1999); (CDC, 2014b).

1.1.2. Malaria life cycle

The malaria life cycle has three components: (i) the development of the *Anopheles* from egg to adult stage for parasite transmission; (ii) the development of the *Plasmodium* parasites (gametocyte to sporozoites) to infect humans; and (iii) the incubation in the human host from invasion to malaria symptoms (Crutcher & Hoffman, 1996).

(i)   The growth of the Anopleles female mosquito from egg to adult to parasite transmission.

The *anophenine* mosquitoes undergo four stages in their life cycle that is: egg, larva, pupa, and adult (Figure 1). The first three development stages are aquatic and they last 8 to 14 days, depending on the species and the ambient temperature. The *Anopheles* mosquito acts as malaria vector in the adult stage. In this stage the adult female can live up to a month (or more in captivity) but most probably do not live more than 1-2 weeks in nature.

Once ingested by a mosquito, and before they are infectious to humans, malaria parasites must undergo development within the mosquito (Figure 2). The expected time for the development in the mosquito (the extrinsic incubation period) ranges from 10 to 32 days, and it depends on the parasite species and temperature. If a mosquito does not survive longer than the extrinsic incubation period transmit any malaria parasites (CDC, 2014b)
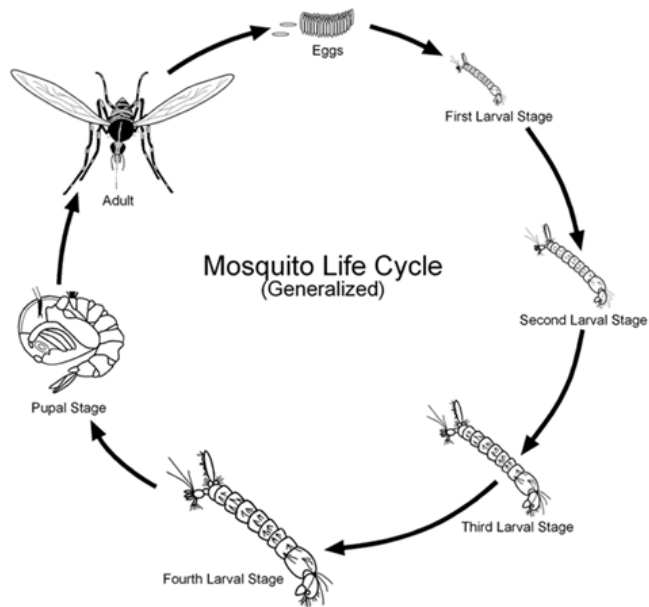
Figure 1: The mosquito life-cycle
Source: (malaria.com)

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(ii)   The development of the *Plasmodium* parasites (gametocyte to sporozoites) that are capable to infect humans.

In nature, mononucleate sporozoites in the salivary glands of female infected mosquitoes are injected into a human host through a bite, when the mosquito feeds. The sporozoites quickly invade liver parenchymal cells, where they mature into liver-stage schizonts, which burst to release 2,000 to 40,000 mononucleate merozoites. In the case of *Plasmodium vivax* and *Plasmodium ovale* infections, maturation of the schizonts may be delay for 1 to 2 years.

(iii)   The incubation period in the human host from infection to malaria symptoms.

Each merozoites can infect an erythrocyte. Within erythrocyte, the merozoites a mononucleate gametocyte – the sexual stage, infectious for *Anopheles* mosquitoes or, over 48 to 72 hours, into an eritocytic stage containing 10 to 36 merozoites. Rupture of the schizont releases these

merozoites, which infect other red cells. If a vector mosquito ingests gametocytes, the gametocytes develop in the mosquito gut gametes, which undergo fertilization and mature in 2 to 3 weeks to sporozoites (Crutcher & Hoffman, 1996).
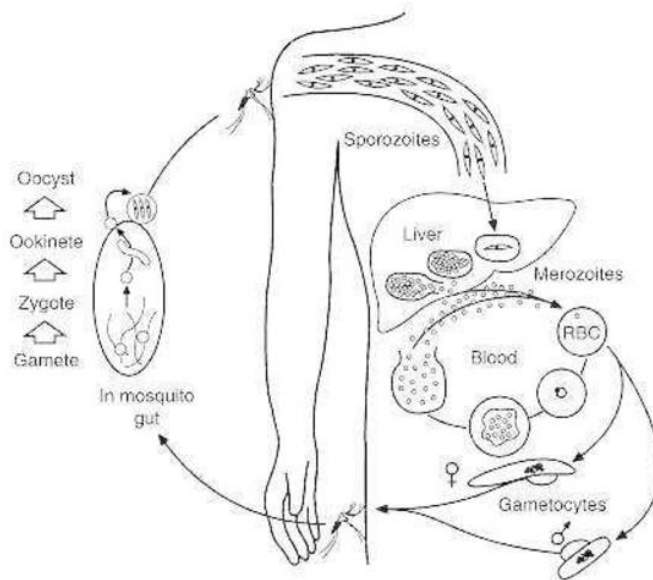
Figure 2: The Malaria life cycle

Source: (Crutcher & Hoffman, 1996)

1.1.3. Major factors for malaria occurrence

Malaria transmission is highly influenced by environmental, climatic conditions and non-climatic conditions.

1.1.3.1. Environmental and climate conditions

The weather affects the malaria occurrence by affecting the mosquito vector (species, population dynamic, gonotrophic cycle and survival). An estimated 90 % of malaria cases are related to environmental factors (WHO, 1997). The environmental and climate factors that influence malaria occurrence are:

a)   **Temperature:** the ranges of maximum and minimum temperature greatly affects the development of the malaria parasite and its

mosquito vector, determining the malaria transmission. Temperature affects the life cycle of the malaria parasite. The time required for the parasite to complete its development is 10 days, but this time can be shorter or longer depending on temperature. Temperature lower than 18°C and higher than 40°C are not conducive to the mosquito and parasite gonotrophic cycle and survivorship. Malaria transmission in environments colder than 18°C may occur because the mosquito often lives in houses which tend to be warmer than the outside temperatures Blanford et al. (2013), Beck-Johnson et al. (2013), Yé, Kyobutungi, Louis, and Sauerborn (2007). Temperature between 25 to 35°C is the optimum for mosquito and malaria development (Parham & Michael, 2010). In Chimoio weeks 16 to 18 and weeks 20 to 40 presents an average temperature bellow 18 °C.

b)   **Altitude**: altitude influences the malaria distribution and transmission indirectly, through its effect on temperature. Beyond 1500 meters mosquitoes will hardly survive and over 2,400 meters, malaria will not occur (LabSpace, 2014). Areas over 1100 meters are classified as having a low malaria risk (Chikodzi, 2013). In Chimoio the altitude is below 771 meters (Map 3) and 100 % of the area presents a high and moderate risk for malaria occurrence.

c)   **Precipitation:** malaria occurrence increases during the rainy season. When the rains fall, pools are created for mosquito breeding since malaria vectors mainly breed in stagnant water and rarely in moving water (Chikodzi, 2013). A weekly precipitation of more than 10 mm will propitiate the development of the mosquitoes. The average annual precipitation for Chimoio is 917 mm and the weekly average precipitation is 17 mm. The all of Chimoio presents a precipitation risk for malaria.
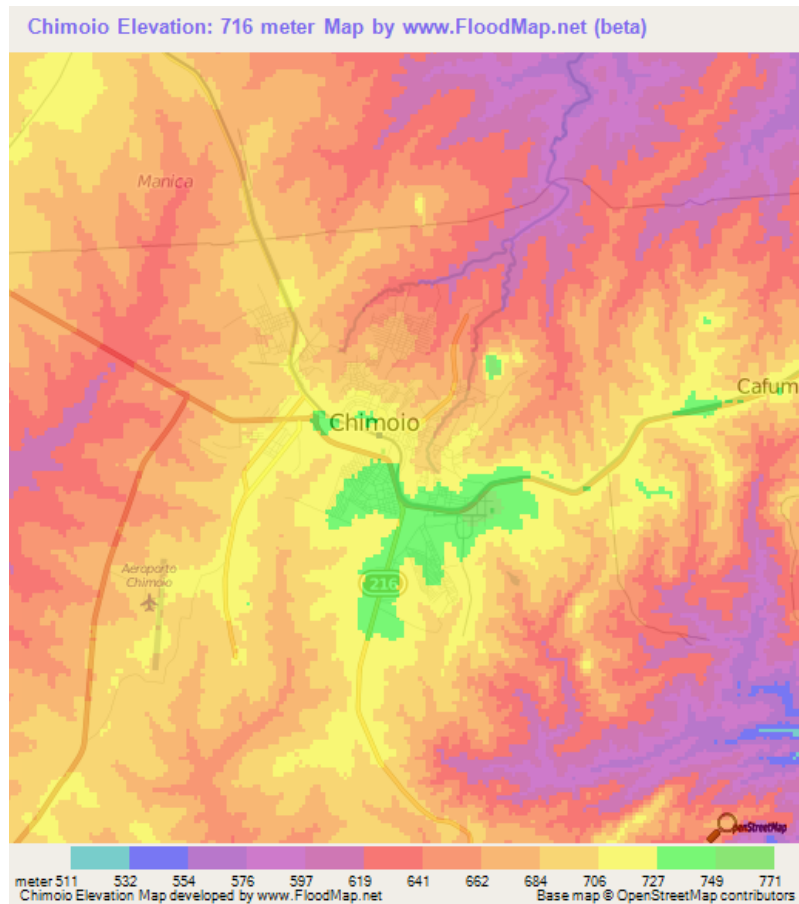
Map 3: Chimoio elevation Map

Source. (Google maps, 2016)

d) **Relative humidity (RH):** RH below 60 % shortens the life span of the mosquitoes. That is the reason why the mosquitoes are more active and prefer feeding during the night, where the relative humidity is higher than the day time. If the average monthly relative humidity is below 60%, it is believed that the life of the mosquito is so short that very little or no malaria transmission is possible. LabSpace (2014), Yamana and Eltahir (2013), (Gao et al., 2012). In Chimoio, only seven weeks of the year that is week 30 to 31 and week 35 to 38 presents a relative humidity below 60 %.

e) **Normal differencing index (NDVI): t**he trees can be a good resting area for the mosquitoes since they keep a fresh and humid environment during the day, ideal for the mosquitoes. In Brazil de Oliveira,

dos Santos, Zeilhofer, Souza-Santos, and Atanaka-Santos (2011) noted that high numbers of notified malaria cases were located near areas with high NDVI values. Based on NDVI, Chimoio presents 88 % of high-risk of malaria.

f) **Land Use and Land Cover (LULC)**: The areas with crops, grass and water bodies as the high-risk areas of malaria. Areas such as shrubs and mosaic cover vegetation are classified has having a moderate risk of malaria, while the areas with forest, bare, and urban settlements are classified as having the lowest risk of malaria (Chikodzi, 2013). Chimoio presents 4 % high risk of malaria occurrence).

g) **Slope:** Areas on flat ground are more prone to accumulate water from rain increasing the malaria risk Krefis et al. (2011); Framcis Mulefu (2016). In Chimoio 66 % of the area is a high risk are for malaria.

1.1.3.2.   Non-climatic factors

Several non-climatic factors influence malaria occurrence and include:

a) **Malaria vectors:** not all mosquitoes transmit malaria, only female *Anopheles* can carry the malaria parasite. Distinct species of Anopheles differ in their transmission capacity, depending on the biology and behavior of the mosquito. Mosquitos in the *Anopheles gambiae group* feed on humans or animals*. A. gambiae* are very good malaria vectors since they prefer to feed on humans rather than animals (LabSpace, 2014), (CDC, 2014b). The main vectors of malaria in Mozambique belong to the groups *A. funestus* and *A. gambiae* (Arroz, 2016).

b) **Malaria parasites:** As stated previously there are five malaria parasites. In Mozambique *Plasmodium falciparum* is the most frequent parasite, responsible for 90.0% of all malarial infections, while *Plasmodium malarie* and *Plasmodium ovale* represent 9 and 1 % of the cases respectively Instituto Nacional de Estatistica (2011), WHO (2015a). Malaria cases diagnosed by health personnel in Chimoio indicated that over 21% prevalence were classified as being the highest malaria risk areas, between 14 and 21% were classified as being of moderate malaria risk and, less than 14% were classified as having the lowest risk of malaria occurrence.

c) **Water development projects and distance from water bodies:** big and small development projects, e.g. dams and ponds, can increase the malaria incidence, in villages that are located near them. They create more breeding habitats and more vectors implies more malaria transmission. Thompson et al. (1997) reported that in Maputo, Mozambique, the risk of malaria was 6.2 times greater for individuals living less than 200 meters from the breeding sites than that of individuals living 500 meters or more away from the breeding sites. In Tanzania, improved socioeconomic status due to rice growing has been found to lead to reduced malaria prevalence, in spite of increased mosquito populations among villages adjacent to flooded rice fields (Mutero, MCcartney, & Boelee, 2006). In Chimoio 43 % of the total area is at high risk of malaria.

d)   Distance from Roads (DTR)

The Euclidian distance for the nearest road measure the accessibility of rapid treatment for a malaria patient. Places over 5 kilometres from the roads are classified as having a high risk to malaria, those between 2.6 km and 5 km from roads are classified to be of moderate risk and those less than 2.5 km from the roads are classified as having the lowest risk of malaria infection. In Chimoio 40 % of the area is at high risk for malaria.

e) **Population movements and migration:** population movements have significant implications for malaria transmission. War, migrations and tourism may expose non-immune individuals to an environment with high malaria transmission (CDC, 2014b).

f) **Urbanization:** the incidence of malaria is generally lower in urban areas than in rural areas. There are several reasons for this:

- Although there is plenty of space for vector breeding in rural villages, mosquito breeding sites in urban areas are limited because more space is covered by houses.

- People in urban areas may have more access to health care and malaria prevention strategies than people in rural villages.

However, rapid urbanization of areas within or on the outskirts of urban centres is commonly done in an uncontrolled fashion without thought or planning. Conditions are crowded, and settlers tend to dig pits to extract stone and soil for house construction, creating numerous breeding grounds for mosquitoes. According to Tatem, Gething, Smith, and Hay (2013) the urbanization process results in profound socio-economic and landscape changes that reduce malaria transmission. Socio-economic and demographics: Aspects such as poverty, population density, distance from roads. Malaria prevalence can also influence in malaria occurrence.

g)   Population density (Pop dens)

Data on population density were calculated from the National census population projections for 2014. In the study places over 9000 people/ km^2 were classified to be at highest risks to malaria, those between 6001 to 9000 people/ km^2, were classified to be of moderate risk, and those less than 6000 person/ km^2 were classified to be as low-risk of malaria infections. In Chimoio only 8 % of the total area is at high-risk for malaria occurrence.

h)   **Human host factors:** human factors include:

- Genetic factors: biologic characteristics present from birth can protect against certain types of malaria. Two genetic factors, both associated with human red blood cells, have been shown to be epidemiologically important. Persons who have the sickle cell trait (heterozygotes for the abnormal haemoglobin gene HbS) are relatively protected against *P. falciparum* malaria and thus enjoy a biologic advantage).

- Acquired immunity: acquired immunity greatly influences how malaria affects an individual and a community. After repeated attacks of malaria a person may develop a partially protective immunity. Such "semi-immune" persons often can still be infected by malaria parasites but may not develop severe disease, and, in fact, frequently lack any typical malaria symptoms.

- Pregnancy: pregnancy decreases immunity against many infectious diseases. Women who have developed protective immunity against *P. falciparum* tend to lose this protection when they become pregnant).

- Behaviours: Agricultural work such as harvesting (also influenced by climate) may force increased night-time exposure to mosquito bites. Raising domestic animals near the household may provide alternate sources of blood meals for *Anopheles* mosquitoes and thus decrease human exposure.

- Age: Children under five years of age have weak immunity to malaria infection. Immunity to malaria develops slowly after several infections and children need at least five years to develop their immunity.

i) **Vector resistance to insecticides:** Some insecticides are used to kill mosquitoes and protect communities from mosquito bites. However, after repeated application of these chemicals, the mosquitoes develop insecticide resistance. This means a large number of mosquitoes will survive in the community, and the risk of malaria infections rises and many people can be affected (CDC, 2014b), (WHO, 2015a).

j) **Drug resistance in malaria parasites:** drugs kill the malaria parasite inside the human body. However, after repeated use of an anti-malaria medicine, the parasite can develop resistance to that particular drug or to similar medicines. As a result, the parasites inside the human body can no longer be killed and patients cannot be cured unless new drugs are developed for treatments. In Mozambique drug resistance to cloroquine and lumefantrine drugs has been reported by Raman et al. (2011).

Malaria is a curable disease if the parasites remain susceptible to available treatments, and it can be prevented by using several methods. However, long-term and sustained implementation of prevention and control measures is necessary to significantly reduce or eliminate the problem from a country or a specific geographic area. As a result of long-term successful interventions, a local population can lose their immunity to malaria in an area where it has been reduced to a low level for some time.

1.1.4. Mathematical Modelling

Models using climate variables can predict malaria risk and transmission, and following up such models with research on climate change may help lay the groundwork for effective malaria prevention and control in Chimoio municipality.

Although the history of modelling mortality is very long, malaria mortality forecasting is much more recent. Mortality forecasting is generally a low-cost implementation solution, and its use may help in Precision Public Health and help in malaria eradication.

Mathematical modelling uses computer-based models to describe, explain, or predict behaviour or phenomena in the real world. It is particularly useful in investigating questions or testing ideas within complex systems. For this reason, modelling can be especially helpful in informing decision-making in global malaria control and eradication efforts because they involve extensive changes to a complex web of interconnected biological systems (Heesterbeek et al., 2015).

Establishing optimal policies and programs to support these efforts is complicated by the potential for parasites and vectors to evolve, the waxing and waning of human immunity, behavioural changes in human and vector populations, and interactions among large numbers of heterogeneous sub-populations of the organisms involved. Mathematical modelling can build on available data, test multiple scenarios and combinations of intervention strategies, and make verifiable predictions on what can be expected from these strategies (RBMP, 2015).

1.1.4.1. Malaria modelling

Mortality modelling has a very long history. Numerous models have been proposed since Gompertz published his law of mortality in 1825. Mathematical modelling of malaria transmission also has a long history. It has helped us to understand the transmission mechanism, design and improve

control measures, forecast disease outbreaks, etc. The so-called Ross–Macdonald model is the earliest malaria model (Bacaër, 2011). The Macdonald studies resulted in very beneficial impacts in the collection, analysis, and interpretation malaria epidemiology (Molineaux, Gramiccia, & World Health Organization, 1980).

Spatial heterogeneities have also been incorporated into epidemiological models by using reaction-diffusion equations by some researchers (Murray & Kirschner, 1989), (Smith & Ruktanonchai, 2010), (Mandal, Sarkar, & Sinha, 2011), and (Reiner, Niermann, Jekauc, & Woll, 2013).

Maude et al. (2014), produced a free, internet-based, user-friendly and interactive mathematical model of malaria elimination as a tool for policy makers that enable optimisation of local malaria elimination strategies before commitment of valuable resources.

Zacarias and Andersson (2010) studied the spatial and temporal patterns of malaria incidence so as to determine the means by which climatic factors such as temperature, rainfall and humidity affect its distribution in Maputo province, Mozambique. They presented a model of malaria that evolves in space and time in Maputo province Mozambique.

Gomez-Elipe, Otero, van Herp, and Aguirre-Jaime (2007) forecasted malaria incidence based on monthly case reports and environmental factors using ARIMA in Burundi. The Box-Jenkins modelling procedure was used to determine an ARIMA model for malaria in Zambia (Jere & Moyo, 2016). In Ghana, time Series Analysis of Malaria Cases was used Alhassan, Isaac, and Emmanuel (2017), in Sudan. Hussien, Eissa, and Awadalla (2017), developed a simple applicable and accurate model to predict malaria incidence using ARIMA model.

1.1.4.2. Malaria mortality modelling

Mortality forecasting is a more recent endeavour. Only three decades ago, the methods in use were relatively simple and involved a fair degree of subjective judgment (Pollard et al., 1987). It is only in the last 15 years or so

that more sophisticated methods have been developed and applied (Booth & Tickle, 2008).

There are some studies in malaria mortality forecasting using ARIMA. Aregawi et al. (2014) conducted a study in Ethiopia using ARIMA for forecasting malaria mortality. In Nigeria modelling and Forecasting Malaria Mortality Rate using SARIMA Models was performed by (Ekezie, Opara, & Okenwe, 2014).

The common time series procedure to analyses interventions is based on autoregressive integrated moving average (ARIMA) models (Box & Tiao, 1975). In the ARIMA framework, there is a need to for transform the non-stationary series to a stationary prior to the analysis. The Intervention Time Series method (ITS) provide an alternative method to the modelling interventions (Harvey, 1989).

Intervention time series analysis is an important method for analysing the effect of sudden events (unplanned) on time series data. ITSA methods are quasi-experimental in nature and the validity of modelling with these methods depends upon assumptions about the timing of the intervention and the response of the process to it. ITSA was used in Australia in a heroin shortage case and enabled valuable insights about consequences of unplanned and poorly identified interventions while minimizing the risk of spurious results (Gilmour, Degenhardt, Hall, & Day, 2006).

ITSA was also used in crime rates in Virginia, USA (Sridhar, Seymour, & Shepherd, 2003).

The principal advantages of the ITSA over the ARIMA method are:

a) Whereas trend and seasonal are explicitly modelled, in the ARIMA models they are removed from the series before any analysis is performed;

b) In the ARIMA models the observed time series is differenced prior to the analysis, in order to obtain an approximation to stationary time series, while in the ITSA approach the time series is modelled directly in levels, whether stationary or not;

c) Missing data, stochastic explanatory variables, and multivariate data are easily incorporated into the ITSA methodology, whereas within the ARIMA framework this is not so straightforward (Sridhar et al., 2003).

1.1.5. Malaria Mapping

Mapping refers to the creation of graphic representation of information and it uses spatial relationship within the graphic to represent some relationship within the data (Kraak, 2005). Several projects exist to map malaria. The Malaria Atlas Project aims to disseminate free, accurate and up-to-date information on malaria and associated topics, organized on a geographical basis (MAP, 2014).

Malaria Program and the Medicines for Malaria Venture (MMV) launched a newly-designed mapping tool that allows users to build customized maps using data from WHO's World Malaria Report. There is a free platform called Global Malaria Mapper that is accessible to interested individuals and organizations over the world (MMV, 2014).

Building spatial models of disease prevalence and risks, including maps is one of the central objective of epidemiology. The risk maps can be used for the identification of appropriate strategies to respond to disease outbreaks and vector, reservoir and agent control. Various technique can be employed to build a risk map usage of clinical data, distribution of the disease agents, reservoir's and vectors, based on surveys or expert opinion (Chikodzi, 2013).

1.1.6. Precision Public Health

The concept of Precision Public Health is relatively new and was probably derived from the Agricultural term Precision Agriculture (PA), an innovative concept of agricultural production based on information technologies in crop production (Sarauskis et al., 2015).

Precision Health is defined as improving the ability to prevent disease, promote health, and reduce health disparities in populations by: 1) applying emerging methods and technologies for measuring disease, pathogens,

exposures, behaviours, and susceptibility in populations; and 2) developing policies and targeted public health programmes to improve health (Muin, Takes, Hosli, & Lapaire, 2015). This technique is based on specific site observation, and measuring and responding to variability in disease trends. If related to socio-demographic characteristics, using weekly data, it can lead to decision support systems that help to eradicate disease, optimise resources, and minimise the impact on the environment.

Public precision health strategies can support decisions to reduce malaria by optimising resource use (M. J. Khoury, Iademarco, & Riley, 2016). For example, decisions can focus spraying efforts to reduce vector numbers, where to build a water body, and when to drain it.

1.2. Thesis structure and motivation
1.2.1. Thesis structure

This thesis in structured in six sections inter-correlated starting from accessing the malaria profile in Chimoio over 9 years, modelling the climate data and their relationship with malaria in the same period, access the death caused by malaria in the municipality. Based on the information a malaria map of risk for Chimoio was produced and conclusions were derived.

The spatio-temporal variation and socio-demographic characters of malaria are presented in section 2. Weekly malaria data for nine years (2006 to 2014) were collected from the district Epidemiological Bulletin and incidence by season, age, gender, and residence was calculated. SPSS version 20 was used for statistical analysis and ArcGis 10.1 was used to produce maps.

The evidences indicated that Malaria is increasing in the suburbs, and rural areas present more cases of malaria compared to urban areas, suggesting that malaria varies in time and space, and that a precision public health strategy should be used to control malaria occurrence.

In section 3, modelling the influence of climate on malaria occurrence in Chimoio was carried out. Time series analysis was conducted using data on weekly climatic variables and weekly malaria cases in Chimoio, from 2006-2014. Cross-correlation analysis, linear processes, namely ARIMA models and regression modelling, were used to develop the final model. The evidence found was that the Chimoio climate seems ideal for malaria occurrence. Malaria occurrence peaks during January to March in Chimoio. As the lag effect between climatic events and malaria occurrence is important for the prediction of malaria cases, this can be used for designing public precision health measures. The model can be used for planning specific measures for Chimoio.

In section 4 the malaria mortality characterization and the relationship between malaria mortality and climate in Chimoio was established. The malaria mortality data and climate data were extracted from the Chimoio Civil

Registration records, and from the Regional Weather station, from 2010 to 2014. ANOVA, Tukey's, Chi-square, and time series analyses were carried out and an intervention analysis model (ITSA) developed. The evidences were that malaria mortality is increasing in Chimoio; children between 1 – 4 years old represent 13% of Chimoio population, but account for 25% of malaria mortality. Malaria mortality shows seasonal and spatial characteristics.

In section 5, using the climate, socio-demographic and clinic variables the malaria risk areas of Chimoio were mapped and modelled. A 30m*30m Land sat image, ArcGis 10.2 and, BioclimData, and Weather station climatic data were used. A conceptual model for spatial problems was used to create the final risk Map. The evidence found was that Chimoio presents 96% of the area with moderate risk and 4% with high-risk. The central and south-west "Bairros" namely Centro Hipico, Trangapsso, Bairro 5 and 1o de Maio have a high-risk, while the rest of the "Bairros" having a moderate risk of malaria. September is the month with the lowest risk to contract malaria.

In section 6, based on the results it is concluded that Precision Public Health strategies that target malaria occurrence and mortality weekly, and temporal and spatial distribution can be formulated to combat and eradicate malaria in Chimoio Municipality. The model are robust and, can predict the expected number of malaria cases at least two months in advance, and timely prevention and control measures can be effectively planned in Chimoio, such as the elimination of vector breeding places, correct time and place to spray insecticides, and awareness campaigns weeks before the malaria peak season. This can lead to a reduction in malaria cases and mortality.

1.2.2. Thesis objectives

1.2.2.1. Main Objective

The main objective of this theirs is to assess the malaria variation in Chimoio Municipality to derive appropriate measurements for malaria reduction or eradication

1.2.2.2. Specific objectives

The specific objectives of this thesis are:

a) To Model malaria and cases mortality in Chimoio
b) To Map malaria in Chimoio.
c) From the model and the map derive strategies for Precision Public Health for malaria eradication in Chimoio municipality.

1.2.3. Thesis contribution

The major contributions of the work are:

a) We expect to demonstrate how ARIMA modelling can be used to forecast malaria occurrence
b) How ITSA can be used to forecast malaria mortality
c) How spatio-temporal variation can be used for Precision Public Health and help local communities in malaria combat and eradication in Chimoio and perhaps throughout Mozambique.

1.2.4. Thesis motivation

The motivation to carry out this work includes the following reasons:

- The need to contribute to malaria eradication in Mozambique, in general, and Chimoio, in particular.

- Swaziland is a relative small neighbouring African country with a landscape and weather similar to Chimoio Municipality and using an integrated strategy for malaria eradication, managed to eradicate malaria in 2016.

- With commitment from everybody willing to eradicate the disease, it is anticipated that Chimoio municipality can achieve the same results.

- Despite all individual measures to control malaria, personally I suffer on average 3 malaria per year with a peak of six malaria in 7 months.

2. Spatio-temporal variation and socio-demographic characters of malaria in Chimoio municipality, Mozambique (*)

Abstract

Background

In Africa, urban malaria is a major concern, since the towns and especially their suburbs are growing quickly. In Mozambique, malaria represents 45% of all cases of outpatient visits and 56% of inpatient visits at paediatric clinics. Malaria is a major public health burden in Chimoio Mozambique and few studies on malaria exist.

Methods

The study was carried out to establish the spatiality and temporality of malaria and describe socio-demographic characteristics of malaria patients in Chimoio. Weekly malaria data for nine years (2006 to 2014) were collected from the district Epidemiological Bulletin and incidence by season, age, gender, and residence was calculated. SPSS version 20 was used for statistical analysis and ArcGis 10.1 was used to produce maps.

Results

The annual overall average of malaria incidence was 20.1 % and the attributable fraction (AF) of malaria was 16%. There were differences in weekly and yearly malaria occurrences throughout the period. There was no difference in malaria cases between male and female patients. Children under five years of age are three times more prone to malaria than adults ($p < 0.05$). Three temporal clusters of malaria were identified: Cluster 1, weeks

25 to 47 with average weekly cases of 618 (sd= 251.9), Cluster 2, weeks 18 to 24 and 48 to 51 with average weekly cases of 1,066 (sd= 317.4). Cluster 3, weeks 1 to 17 and 52 with average weekly cases of 1,587 (sd= 722.4). Similarly, three different clusters were identified according to residential areas: cluster 1 (10%) mostly urban, Cluster 2 (22%) mostly suburbs, Cluster 3 (28%) mostly rural areas.

Conclusion

Malaria is increasing in the suburbs, and rural areas present more cases of malaria compared to urban areas. This article is an initial step to understand the dynamics of malaria in Chimoio. Results suggest that malaria varies in time and space, and that precision public health strategy should be used to control malaria occurrence. Studies on weather factors affecting malaria cases, bed net usage, and others should be undertaken.

2.1. Research objective

The goal of this study was to determine the spatial and temporal patterns or clusters of malaria distribution and socio-demographic characteristics of malaria patients in Chimoio Municipality to help decision-making in Precision Public Health strategies in malaria prevention and eradication, using weekly data.

2.2. Methods

2.2.1. Study area and population

Chimoio is a municipality in Manica Province in the central region of Mozambique, -19° 6' 59 S, 33° 28' 59 E (Map 6).
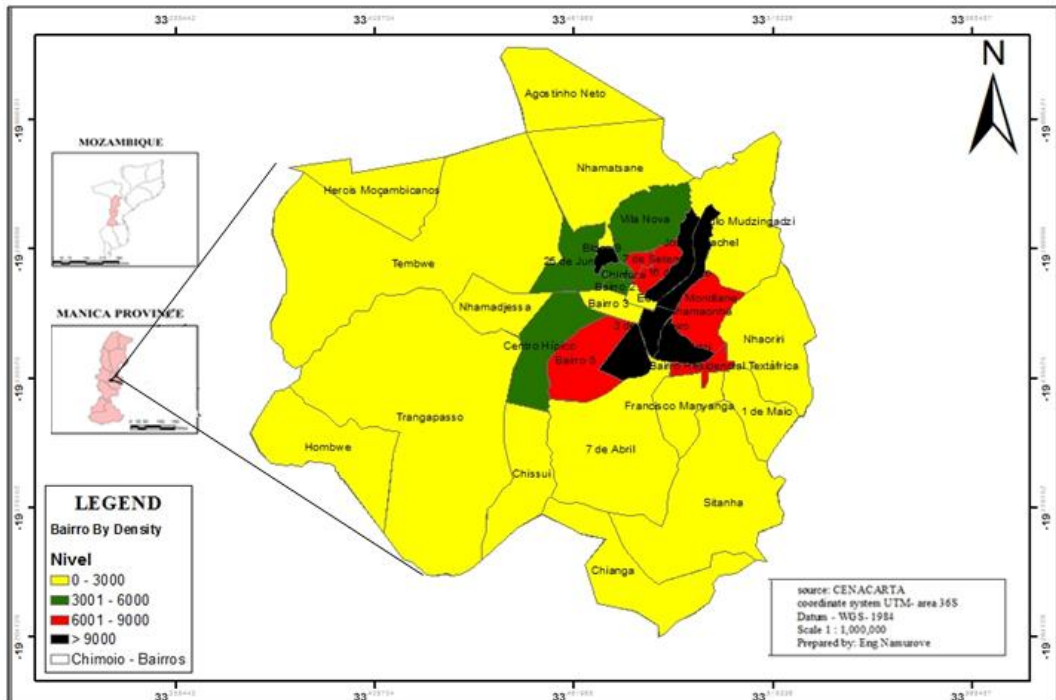
Map 4: Administrative Map of Chimoio, with Population Density (person/km2)
Adapted from CENACARTA

The population of Chimoio was 237,497 inhabitants in 2007, with a 3.5% annual growth rate. Men and women represent 52% and 48% of the population respectively. Population from 0 to 5 years comprises 17% of the inhabitants (INE, 2012). The city is administratively divided into three urban districts with 33 residential areas called ´Bairros´, (Map 7) comprised of urban, suburban, and rural areas.

Source: (Google maps, 2016)
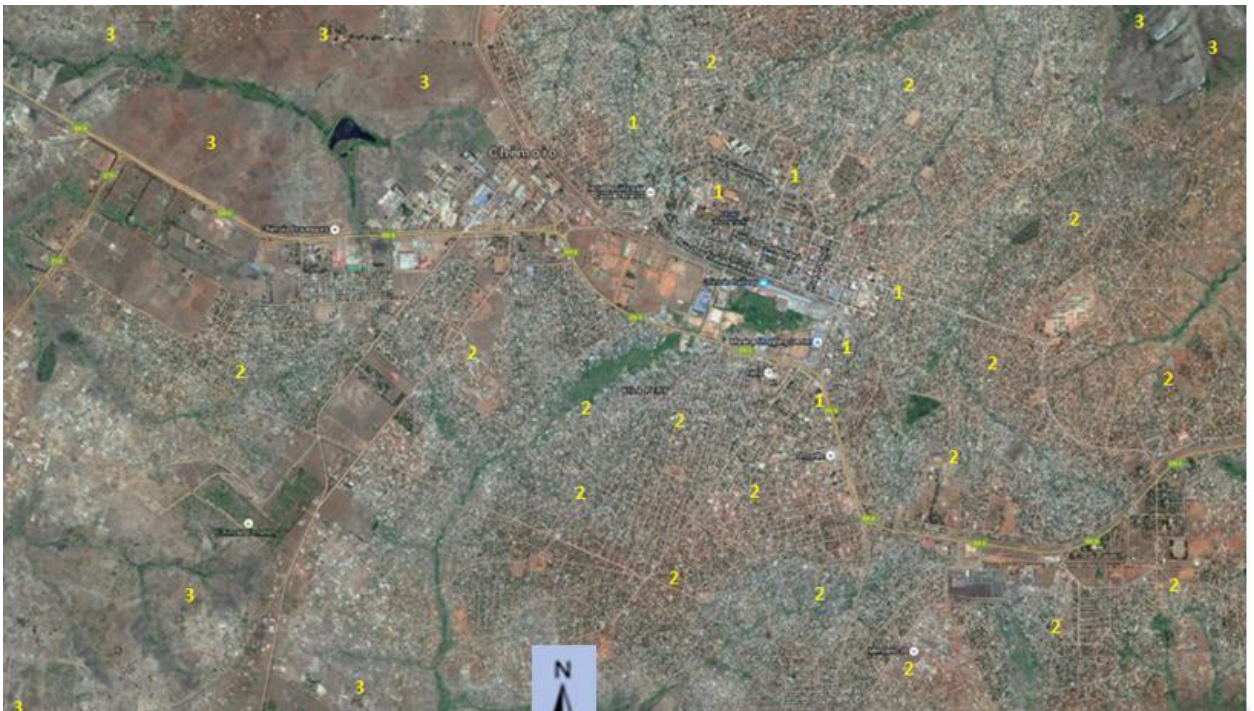
Map 5: Partial view of Chimoio. 1=Urban, 2=Suburb, 3=Rural

The urban area consists of colonial buildings; one to four storey brick houses with large streets and large areas of private open space. There are sewage and sanitation facilities in place. The residents of these areas have medium to high-income levels. On the contrary, most of the suburbs are crowded; some housing units are made of bamboo and wooden poles, and few are of bricks and concrete. In those areas there is poor sanitation, narrow or non-existent streets, and the income levels are low to medium. Rural areas

consist of scattered houses, covered with grass, and that are inhabited by low-income residents. There is no electricity and running water and they are continuously expanding.

The area is 174 km² at an altitude of 750 meters. 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. The average temperature in Chimoio is 21.5 °C. With an annual rainfall average of 1143 mm, Chimoio has 201 dry, 41 intermediate, and 123 wet days, and the wet period is from 26 November to 29 March (Westerink, 1995).

Chimoio has six public health centres', one Provincial hospital, and two private clinics. The oldest health centres (more than ten years) are Centro de Saúde Eduardo Mondlane (CSEM), Centro de Saúde 1º de Maio (CS1Maio), Centro de Saúde Namahonha (CSNh) and Centro de Saúde Chissui (CSCh). The other two centres, Centro de Saúde 7 de Abril (CS7Abril) and Centro de Saúde Vila Nova (CSVN) are more recent (less than five years).

2.3. Study subjects

In the public health centres and in the provincial hospital malaria cases and other occurrences are compiled daily to produce the Weekly Epidemiological Bulletin (BES) and then sent to the Chimoio Directorate of Health, where data are summarized into a Weekly District Epidemiological Bulletin and channelled to the Provincial Directorate of Health (DPS). Weekly malaria data from the nine years period (2006 to 2014) were collected from the district BES: missing bulletins were completed at DPS. The data collected provides information on cases of malaria, gender, and age of the patients. Total malaria cases for each week for the nine year period (2006 to 2014) were added and averaged. The aggregated values starting with Week 1 to Week 52 for the nine-year period represent the variables of the study.

Data from the area of residence of the patients were collected from Centro de Saúde Eduardo Mondlane (CSEM), Centro de Saúde 1º De Maio (CS1Maio), and Centro de Saúde Nhamaonha (CSNh), (see Map 6), which are the largest and oldest clinics in Chimoio Municipality. Proportional randomized sample data from daily record books of the clinics (n = 35,864) were used of which 18,292 were from CSEM, 9,185 from CS1Maio, and 8,387 from CSNh. Data collected were from 2009 to 2014 due to data availability and aggregated on a weekly basis.

Malaria cases from 2006 to 2009 included cases confirmed either by microscopy or rapid diagnostic test (RDT), and also clinical malaria (fever) diagnosed by health personnel. From 2010 to 2014 malaria cases that were recorded were only from microscopy and RDT. An adjustment for clinical malaria was made for the years 2006 to 2009 since from 2010 to 2014 of the total fever cases, 78% were malaria cases.

To compute the attributable fraction (AF) of malaria, monthly data from CSEM were used from 2006 to 2014 and aggregated on a monthly basis. This clinic is the oldest health centre in Chimoio accounts for 57% of all malaria cases in the period (227,814).

The AF of malaria was calculated using the following formula:

$$AF(\%) = \frac{Malaria\ Cases}{Total\ Visits} \times 100$$

Population estimates for Chimoio by locality, gender, and age for the years 2006 to 2014 were calculated based on the 2007 national census using the mean annual population growth rate for Chimoio of 3.5%. Average population for the study period was calculated (Table 1).

2.4. Data analysis

Total malaria cases per week were derived from the collected data adjusted to the population increase per year (3.5%). The malaria incidence per 100 person-year was calculated from the total number of cases occurring

in each week in each Bairro divided by the total person-week and then multiplied by 100.

$$Incidence\ rate\ (\%) = \frac{No.\ of\ cases}{Population\ Size} \times 100$$

Linear trend analysis, and multi-way ANOVA to test difference between years and weeks using Tukeys' test for mean separation were performed. Chi-square for proportion of gender and age and Phi, Cramer's V test was used for statistical significance. Regression analysis to test association between malaria cases and population density of residential areas was performed. Temporal and spatial hierarchical cluster analysis using square Euclidean distance was performed to identify cluster between the weeks and between residential areas in malaria incidence and dendrograms were produced. All tests were performed using Microsoft Excel (Analysis ToolPak) and SPSS IBM version 20; spatial maps were produced to analyse spatial variation along the years using ArcGis version 10.1.

2.5. Results

2.5.1. Malaria cases and incidence in Chimoio

Table 2 reports that malaria cases in Chimoio between 2006 and 2014 amounted to 490,555. In 2010 the fewest cases were recorded, 41,925, and then in 2014 they almost doubled to 84,707. The incidence of malaria decreased from 2006 to 2010 and increased from 2012 to 2014. The annual average incidence of malaria was 20.5% with a maximum of 25.3% in 2007 and a minimum of 15.5% in 2010.

Table 1: Weekly cases of Malaria in Chimoio 2006 to 2014

Year	2006	2007	2008	2009	2010	2011	2012	2013	2014	Overall
Nr. Cases	45,458	60,306	58,333	39,874	41,925	47,107	52,463	60,381	84,707	490,555
Week Average	874	1,160	1,122	767	806	906	1,009	1,161	1,629	1,048
SD	316.6	477.4	584.4	397.5	349.4	477.4	498.2	715.4	1126.6	642.1
Max	1,75	3,06	3,09	1,7	1,78	2,17	2,26	3,22	4,44	2,61
Min	438	222	397	276	317	332	425	281	489	353
Population	231,462	238,768	250,088	259,764	269,818	280,263	291,116	302,392	314,108	270,864*
Incidence **(%)**	19.6	25.3	23.3	15.4	15.5	16.8	18.0	20.0	27.0	20.1**

* Average Population, **average cases/divided by average population x 100

Figure 3 presents the temporal linear trend of malaria in Chimoio. Figure 3 A shows the temporal distribution of Malaria for each year and Figure 3 B shows the average variation over the 9 years. In terms of weeks, the lowest week recorded was 222 cases per week in week 27 in 2007 and the highest record was 4438 in week 8 in 2014. There is a high weekly variation in malaria cases ranging from 222 to 4438 cases per week, CV, 61% (3A).
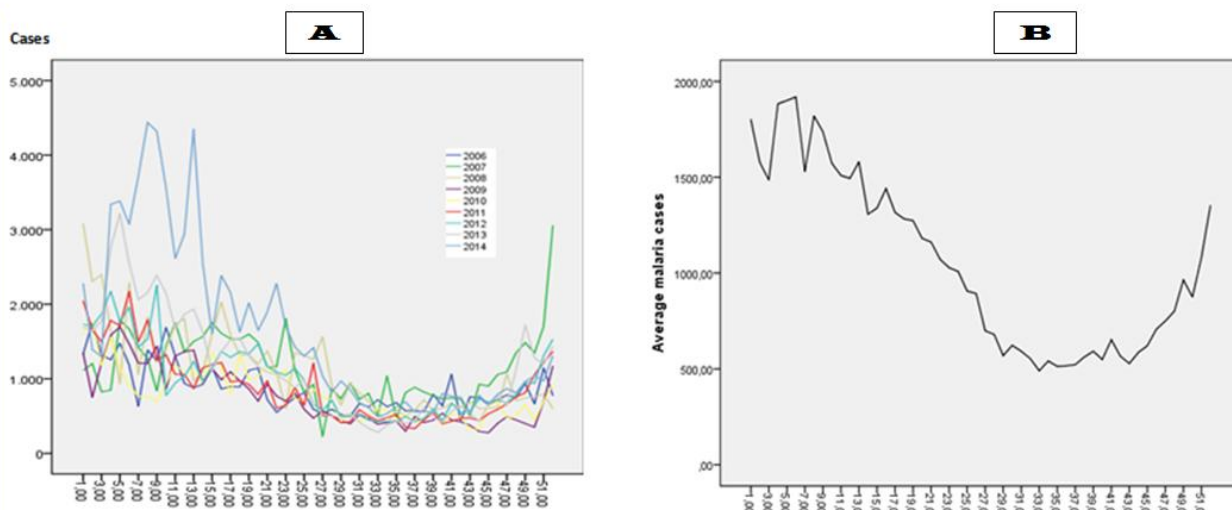
Figure 3: Weekly malaria Cases in Chimoio 2006 to 2014. Annual (A), Average (B)

On average week six presents the highest cases of malaria with 1,919 cases and week 33 the lowest 419 (3B). Malaria weekly average was 1,048 (sd 642.1) cases ranging from 806 cases in 2010 to 1,629 cases in 2014. Malaria cases (1,048) presented a difference between years ($p < 0.05$), the calculated F value was 22.1while the critical table value was 1.96. Malaria cases (1,048) also shows a difference between weeks ($p < 0.05$), the calculated F value was 11.55 while the critical table value was 1.38.

Table 3 presents the summary and the mean separation of malaria cases between the years. Years 2009 and 2010 differs from years 2006, 2007, 2008, 2011, 2012, and 2013; and year 2014 differs from the other years in malaria cases.

Table 2: Summary and malaria cases mean separation between years

(year)	2009	2010	2006	2011	2012	2008	2007	2013	2014
N	52	52	52	52	52	52	52	52	52
Mean*	767[a]	806[a]	874[b]	906[b]	1009[b]	1122[b]	1160[b]	1161[b]	1629[c]
SD	397.5	349.43	316.56	477.44	498.16	584.45	477.45	715.42	1126.62

*Different letter indicates difference between years. Tukeys' test (p<0.05)

2.5.2. Temporal clusters of malaria in Chimoio

A temporal cluster analysis of malaria occurrence was performed, and the results are summarized in the dendrogram in Figure 4. Three temporal clusters of malaria were identified: Cluster 1 comprises weeks 25 to 47 with an average of weekly cases of 618 (sd = 251.9), 44% of the total weeks, representing the dry season; Cluster 2 comprises weeks 18 to 24 and 48 to 51 with an average for weekly cases of 1066 (sd = 317.4), 21% of the total weeks, the intermediate season; Cluster 3 comprises weeks 1 to 17 and 52 with an average for weekly cases of 1587 (sd = 722.4), 35% of the total weeks, the wet season.
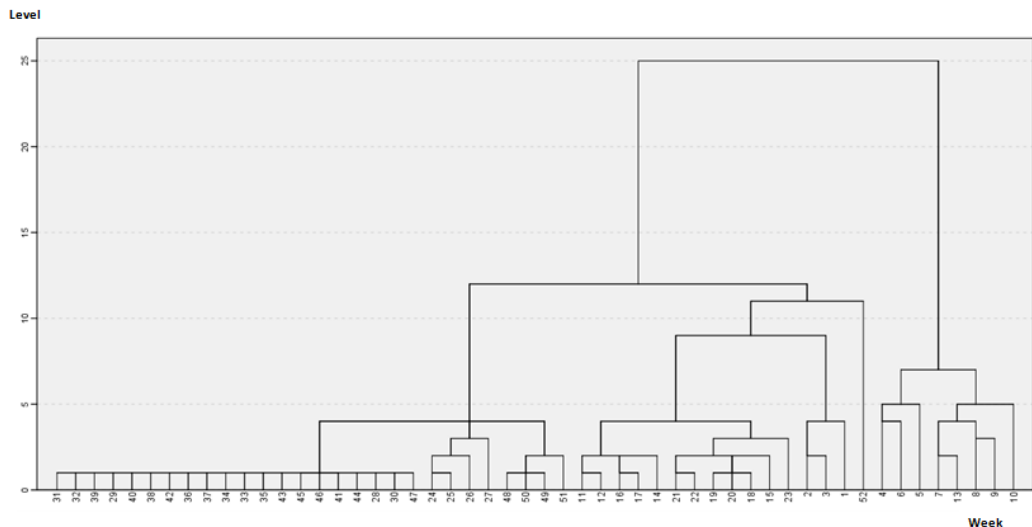
Figure 4: Temporal Cluster of Malaria in Chimoio 2006 to 2014

There is a difference (p<0.05) between cluster 1 (618), cluster 2 (1,066) and cluster 3 (1,587). The calculated F value was 185.35 while the critical table value was 3.02. Table 4 presents the malaria cases mean separation between the three clusters.

Table 3: Summary week cluster malaria mean separation

Groups	Cluster 1	Cluster 2	Cluster 3
N	207	99	162
Mean*	618[a]	1066[b]	1587[c]
SD	215.89	371.37	722.42

*Different letter indicates difference between years. Tukeys' test (p<0.05)

2.5.3. Malaria cases by gender and age

In terms of gender, there is no overall difference (p > 0.05) between women (51%), and men (49%), between adult women (52%) and adult men (48%), or female children (50.3%) and male children (40.7%), Chi square 2, df = 1. In terms of age, out of 490,555 cases of malaria in Chimoio, 235,830 (48%) were in children under five years and 254,725 (52%) in patients over five years old. A difference (p < 0.001) is clear between these two groups, the calculated Pearson Chi-Square was 48; df = 1.

2.5.4. Attributable fraction of malaria in Chimoio

Figure 5 presents the trend of malaria cases and patient visits to CSEM from 2006 to 2014 and the monthly AF. From 2006 to 2014 CSEM was visited by 1,885,195 patients and 259,252 were tested positive for malaria (5A). The monthly peak of malaria was in February for years 2006, 2007, 2010, 2011, 2012, 2013, March for years 2009 and 2014, and December for year 2008 (5B). The annual average AF of malaria was 16%.
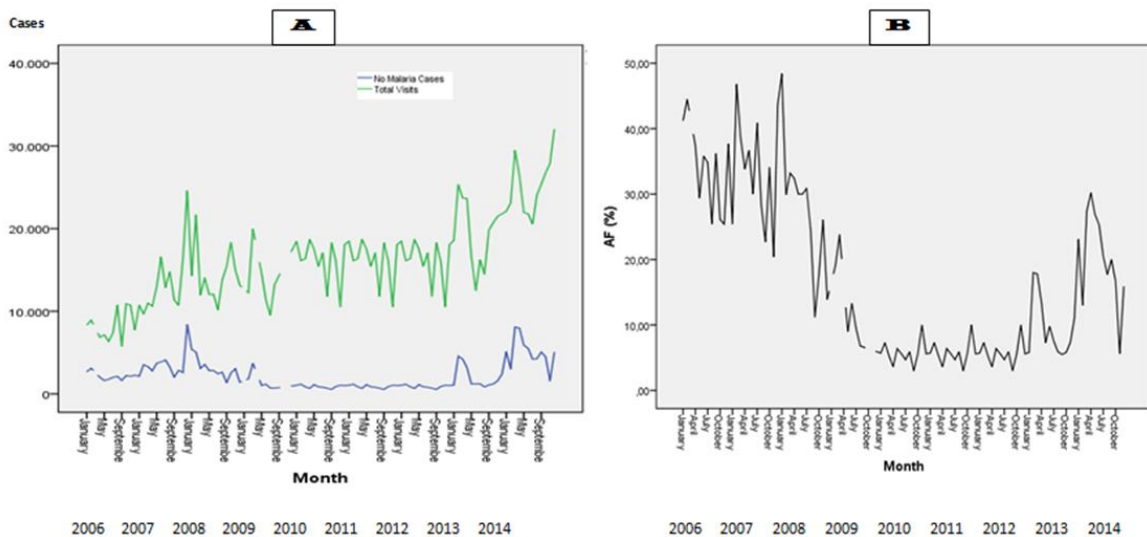
Figure 5: (A) Malaria cases and patient visits (B) Attributable Fraction of Malaria

Years 2010, 2011, and 2012 recorded the lowest AF of malaria in Chimoio, 5.7% and the year 2009 the highest, 27%. There is no difference (p >0.05) in AF malaria among years, the calculated Pearson Chi-Square was 54.00, df = 48. There is a difference (p<0.001) in AF malaria among months, the calculated Pearson Chi-Square was 913.349, df = 693.

2.5.5. Relationship between malaria cases and population density

Map 6 presents the Chimoio population density per bairro, and the population density varies from 28 to 17,049 (person/km^2). A regression analysis was performed to determine the association between population density by residential area and malaria cases. From Table 5 there is a medium positive correlation, r = 0.407 between malaria cases and population density and the r^2 value indicates 0.165, which implies that 16.5% of malaria cases are attributed to population density. At 0.05 significance level the calculated F value is 5.741 while the critical table value is 1.344. Thus, malaria cases significantly depend on population density.

Furthermore, from the coefficients in Table 6, the beta value is positive (0.407), That is, as population density increases malaria cases increase as well.

Table 4: Model Summary Regression Malaria cases and Population Density

Model	R	R^2	Adjust R^2	Std. Error Estimate	R^2 Change	F Change	df1	df2	Sig F Change	Durbin - Watson
1	.407a	0.17	0.14	1529.74	0.17	5.74	1	29	0.02	1.62

a. Predictors: (Constant), Population density (Km^2)
b. Dependent Variable: Malaria Cases, R^2= R square

Table 5: Regression Coefficients. Malaria Cases and Population Density

Model	Unstan (b) Coeffic.		Stand (c) Coeffic	Beta	T	Sig.	95% confidence interval	confidence for B	Collineraty Tolerance	VIF
	B	Std. Error								
1	(Cosntant)	1071.4	400.498		2.68	0.01	252.3	1890.508		
	Population density (Km2)	0.145	0.061	0.41	2.4	0.02	0.021	0.269	1	1

a. Dependent Variable: Malaria Cases
b) Unstandardized
c) Standardized

2.5.6. Malaria Clusters per Residential Area.

Figure 6 presents the dendrogram clusters by residential areas. Three clusters were identified. Cluster 1 comprises the following bairros: Bairro 1, 2, 4, Herois Mocambicanos, 7 de Abril, 7 de Setembro, Bloco 9, Nhamatsane, Tembwe, Agostinho Neto and Eduardo Mondlane. The average incidence is 10.6% and represents 35% of the Bairros of the municipality, most of them urban areas. Cluster 2, comprises the following Bairros: Hombwa, Josina Machel, 3 de Fevereiro, Vila Nova, Mudzingazi, Bairro 3, 5, Nhamadjessa,

Nhamaonha, Francisco Manyanga, 25 de Junho, Centro Hipico, Textafrica, 16 de Junho, and Chinfura. The average incidence is 21.9% and represents 8% of the Bairros of the Municipality, most of them are suburbs. Finally, cluster 3 comprises the following Bairros: Nhauriri, Chissui, Sitanha, 1 de Maio and Trangapasso. The average incidence is 28.4% and represents 16% of the bairros of the municipality, which are mostly rural areas. There is a difference (p <0.05) between malaria clusters, and the calculated Pearson Chi-Square was 7.99, df = 2.
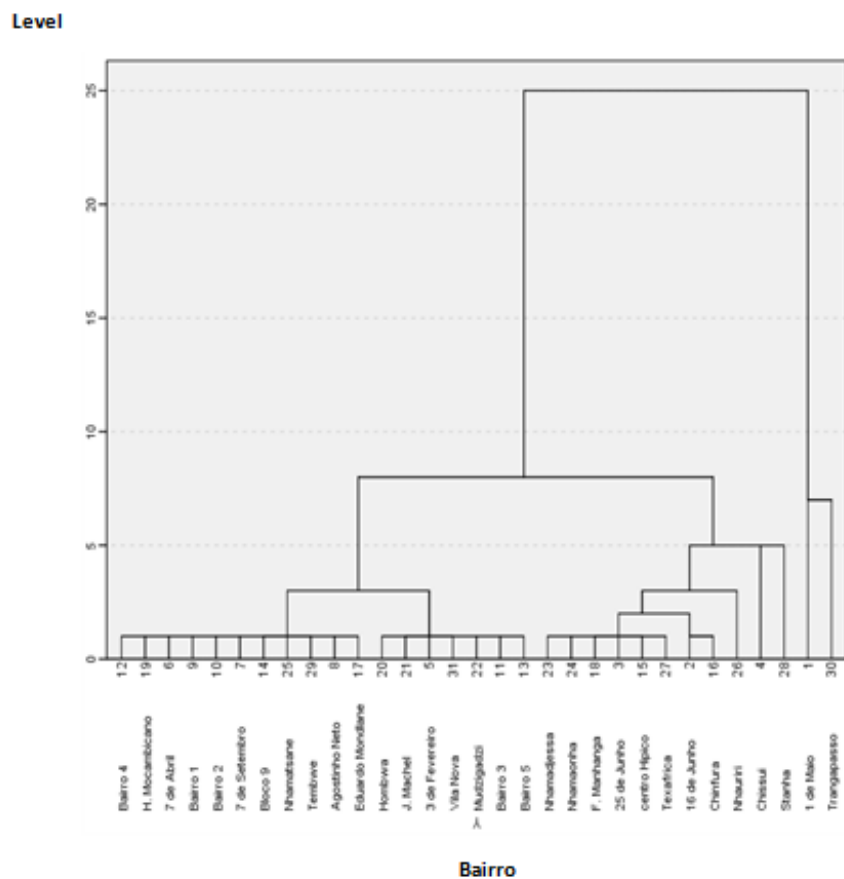
Figure 6: Malaria Clusters by Residence in Chimoio 2006/2014

2.5.7. Malaria incidence from 2010 and 2014

Map 8 depicts the incidence of malaria for the 5 years under analysis (2010–2014). Map 8a–e shows the spatial distribution of malaria for each year and Fig. 7f shows the spatial variation over the 5 years. It is possible to see that the incidence of malaria varies spatially in the Chimoio the municipality (Agostinho Neto, Heróis Moçambicanos, Tembwe, and Hombwa) show values consistently below average of up to 1.5 standard deviations whereas areas located in the southeast (Trangapasso) and southwest (Nhaurire and Textafrica) of the district show values consistently above the average of up to 2.5 standard deviations.

In terms of malaria variation, from 2009 to 2014 Sitanha, the most rural bairro, presented a reduction of malaria incidence of 5 to 15%; Nhamatsane, Herois Mocambicanos, Tembwe, and Hombwa, rural bairros, and Bairro 1, 2, 3, 4, and Bloco 9 urban bairros, presented a reduction of 4 to 6%. Bairros 1º de Maio, Francisco Manhanga and Nhamaonha, new suburbs, presented the highest increase of 7 to 26% and the rest of the bairros, which are old suburbs had an increase from 7 to 16%. Overall, and for the five years, malaria incidence has increased between 7 and 26% in the bairros situated in the central eastern part of the municipality (suburbs) and decreased between 4 and 15% in the other areas (rural and urban).
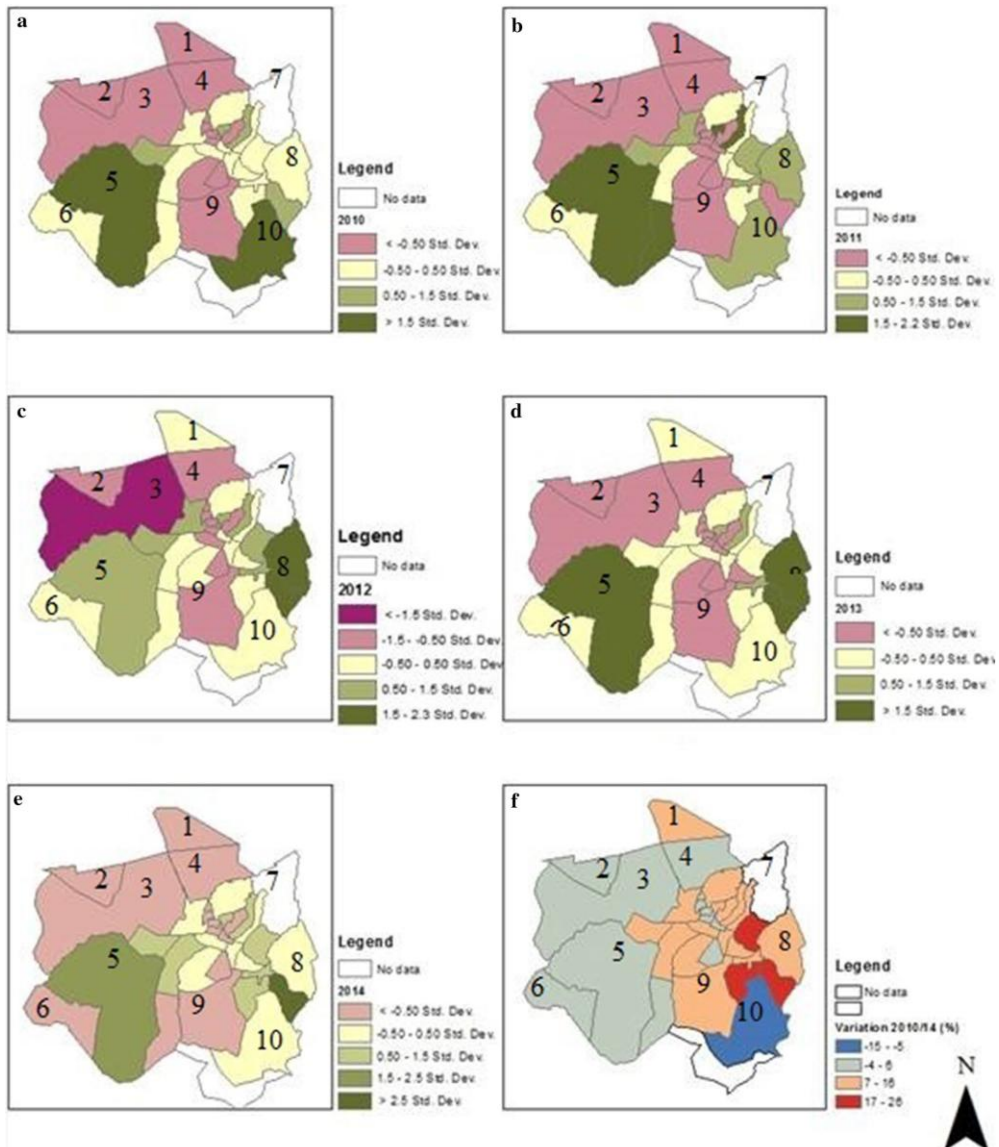
Map 6: incidence of Malaria. a–e **Spatial distribution.** f **Spatial variation.**

Major Chimoio Bairros: 1= Agostinho Neto, 2= Herois Moçambicanos, 3= Tembwe, 4= Trangapasso, 5=Hombwa 6=Nhamadjessa, 7=Nhamatsane, 8= 25 de Junho, 9= Vila Nova, 10= Circulo Mudzingadzi, 11= Nhauriri, 12= 1 de Maio, 13=Sitanha, 14=Chianga, 15= 7 de Abril, 16=Bairro 5, 17= Chissui, 18= Centro Hipico, 19= Francisco Manyanga, 20= Nhamaonha, 21= Bairro 4, 22= Mudzingadzi, 23= Eduardo Mondlane, 24= Bairro 1, 25= Bairro 2

2.6. Discussion

Malaria epidemiology has never been investigated in the study area before. The overall annual incidence of malaria in Chimoio was 20.5%. Maputo city reported 15.7% Macedo de Oliveira et al. (2011) and Manica Province 43% (IDS, 2013). Incidence of malaria in Chimoio is lower than in Manica Province due to the fact that Chimoio is an urban area and residents have more resources for malaria prevention, and the weather is cooler than in many parts of the country. Overall malaria cases and incidence have been increasing in Chimoio in recent years, especially in suburbs. After a decrease in 2010 with 41,925 cases reported and 15.5% incidence, 84,704 cases were reported in 2014, showing an incidence of 27%.

These results are in concordance with a study of patterns and trends of malaria conducted in Kenya that found an increase of 111.13% and 109.52% per annum in 1988-2002 and 1998-2005 respectively for morbidity and hospitalization (Ernst et al., 2009). This increase in the Chimoio results is probably due to the 3.5% annual increase in population, reduced efforts to combat malaria and persistent poverty. However this is contrary to reports of a substantial reduction of malaria incidence in sub-Saharan Africa (WHO, 2013a) and (WHO, 2015b).

The greatest number of cases occurs mostly in February (peak of the rainy season) and the fewest number of cases in September (dry season). This is in concordance with Zacarias and Andersson (2010) who finds that the peak of malaria in Mozambique occurs during the rainy season. It should the noted that the 20.5% incidence may be overestimated as it does not consider the same people being diagnosed more than once in a year, or underestimated since generally there are cases that are not reported, especially those which are far from health centres, self-medication, and use of traditional healers.

It was reported that in Chimoio the land cover is changing towards less vegetation M.A.M. and J.A.A. (2015); Hay et al. (2005) and Hay et al.

(2008) claim that the urbanization process results in profound socio-economic and landscape changes that reduce malaria in urban areas, this is in line with findings of this study that the incidence of malaria is decreasing in rural areas. The results of this study differ from those in Amazonia, where the population increase resulted in occupation of more space and increases in disease incidence (Saraiva et al., 2009). There is a difference in malaria occurrence between years and this is in line with CDC (2014b) and Zacarias and Andersson (2010).

Contrary to most research UNICEF (2015) and WHO (2015b), this study did not find any difference between women and men in malaria cases, between adult women and adult men, or between female children and male children. The chances of getting malaria are the same (gender equality) in Chimoio. This can be explained by the high malaria incidence in the area, which puts the entire population at risk (Zacarias & Andersson, 2010).

There was a difference between children under 5, (48%) and population over five (52%). Children under five comprise 17% of the population of Chimoio but accounted for 48% of the malaria cases, almost three times more. This disproportion is also reported by other authors UNICEF (2015) and IDS (2013). This is probably due to the fact that children under five years of age have little immunity to the malaria parasite.

Very few studies have been carried out using weekly data Kim, Park, and Cheong (2012) and Krefis et al. (2011). Most use monthly data and differentiate malaria cases between dry and rainy season or cooler and hot seasons Omonijo et al. (2011), Tonui, Samuel, Kabiru, Ephantus, and Kiplagat (2013) and Yeshiwondim, Gopal, Hailemariam, Dengela, and Patel (2009). The results of this study almost coincide with the results of Westerink (1995) who reported that Chimoio has 201 dry (29 weeks), 41 intermediate (6 weeks), and 123 wet days (17 weeks), suggesting that malaria cases vary in these three periods. In terms of Precision Public Health, the three distinct periods should have different approaches regarding prevention and combat.

The attributable fraction of malaria was 16%. In Mozambique 45% of all cases in outpatient visits are due to malaria UNICEF (2015) in Manica Province 43% IDS (2013), meaning that the AF of malaria in Chimoio is almost a third of the province and the country value. This may be due to the cooler weather and the fact that country averages include rural areas, where there is more malaria than in cities, and in the cities there are more malaria control interventions.

In terms of malaria cases related to population density, there was a medium positive correlation r = 0.407 between the population density and malaria incidence and the R^2 value indicates 0.165, which implies that 16.5% of malaria cases are attributed to population density. The extremes of both low and high population density modify malaria transmission and have profound consequences for estimates of Chimoio´s Mozambique public health burden.

In terms of residential areas, annual malaria incidence varies from 9% to 45%, meaning that Chimoio is an area with hypo endemic and mesoendemic malaria (Worrall, Basu, & Hanson, 2005). In terms of malaria spatiality, in rural areas malaria incidence is decreasing, probably due to the reduction in vegetation cover and deforestation, and in urban areas probably due to availability of better measures and living conditions. In suburban areas malaria incidence is increasing, probably due to increasing poverty, poor sanitation and poor living conditions. Other studies report the same pattern of findings IDS (2013) and WHO (2015b).

2.7. Conclusions

This study concludes that in Chimoio the incidence of malaria presents a spatial and temporal pattern. Malaria cases have been increasing over the years, especially in suburbs, and there is a difference in malaria cases by year and weeks. There is no gender difference in malaria cases.

Children under 5 years of age are three times more prone to get malaria than the rest of the population. There are three different periods of malaria in Chimoio: hot and rainy season, dry and cool season, and hot and dry season (dry, wet, and intermediate). Sixteen percent of visits to the health centres are from malaria patients.

The rural areas of the municipality have more malaria cases, followed by suburbs, and urban areas have fewer malaria cases. Overall, and for the 5 years studied malaria incidence has increased between 7 and 26% in the bairros situated in the east central part of the municipality (suburbs) and decreased between 4 and 15% in the other areas (rural and urban). Precision Public Health strategies that target malaria weekly according to the positive cases, and temporal and spatial distribution can be formulated to combat and eradicate malaria in Chimoio Municipality. Studies on weather and climate factors affecting malaria, bed net usage, and others should be undertaken.

3. Modelling the influence of climate on malaria occurrence in Chimoio Municipality, Mozambique (*)

(*) To a large extend, this chapter corresponds to "Modelling the influence of climate on malaria occurrence in Chimoio Municipality, Mozambique" published in "Parasites & Vectors, volume;10:260" in 2017.

Abstract

Background

Mozambique was recently ranked fifth in the African continent for the number of cases of malaria. In Chimoio municipality cases of malaria are increasing annually, contrary to the decreasing trend in Africa. As malaria transmission is influenced to a large extent by climatic conditions, modelling this relationship can provide useful insights for designing precision health measures for malaria control. There is a scarcity of information on the association between climatic variability and malaria transmission risk in Mozambique in general, and in Chimoio in particular. Therefore, the aim of this study is to model the association between climatic variables and malaria cases on a weekly basis, to help policy makers find adequate measures for malaria control and eradication.

Methods

Time series analysis was conducted using data on weekly climatic variables and weekly malaria cases (counts) in Chimoio municipality, from 2006 to 2014. All data were analysed using SPSS-20, R 3.3.2 and BioEstat 5.0. Cross-correlation analysis, linear processes, namely ARIMA models and regression modelling, were used to develop the final model.

Results

Between 2006 and 2014, 490,561 cases of malaria were recorded in Chimoio. Both malaria and climatic data exhibit weekly and yearly systematic fluctuations. Cross-correlation analysis showed that mean temperature and

precipitation present significantly lagged correlations with malaria cases. An ARIMA model (2,1,0) (2,1,1)52, and a regression model for a Box-Cox transformed number of malaria cases with lags 1, 2 and 3 of weekly malaria cases and lags 6 and 7 of weekly mean temperature and lags 12 of precipitation were fitted. Although, both produced similar widths for prediction intervals, the last was able to anticipate malaria outbreak more accurately.

Conclusion

The Chimoio climate seems ideal for malaria occurrence. Malaria occurrence peaks during January to March in Chimoio. As the lag effect between climatic events and malaria occurrence is important for the prediction of malaria cases, this can be used for designing public precision health measures. The model can be used for planning specific measures for Chimoio municipality. Prospective and multidisciplinary research involving researchers from different fields is welcomed to improve the effect of climatic factors and other factors in malaria cases.

3.1. Research objective

The objective of this study was to model the effects of several climatic variables (i.e. maximum, minimum, and mean temperature, relative humidity, precipitation, wind speed, visibility and precipitation) on malaria occurrence in Chimoio municipality, using weekly data to define the role of each variable in malaria occurrence.

3.2. Methods

3.2.1. Study area and population

Chimoio is a municipality in the central region of Mozambique (19°6'59"S, 33°28'59"E). The population of Chimoio is currently estimated to be 324,816 within an area of 174 km^2 at a mean altitude of 750 meters (INE,

2012). The climate is warm and temperate with dry winters from April to July, hot, dry summers from August to October and hot, humid summers from November to March. The average mean temperature is 18°C, the minimum average temperature is 13.9°C, and the maximum average temperature is 24°C. The annual precipitation average is 1,143 mm and the wet period is from November to March. The average annual relative humidity (RH) is 67.4% (Westerink, 1995).

3.2.2. Study subjects

Weekly malaria data from the nine-year period (2006 to 2014) were collected from the district Weekly Epidemiological Bulletin (BES) as described elsewhere (Alilio et al., 2004). Daily climate variables such as daily mean temperature (T), minimum temperature (Tm), and maximum temperature (TM) (°C), relative humidity (RH) (%), wind speed (W) (km/h), visibility (V) (km) and precipitation (P) (mm) were collected from Chimoio Weather Station and, Tutitiempo weather records from the years 2006 to 2014 (Tutitiempo, 2015).

3.2.3. Data analysis

Weekly cases of malaria and weekly average values for TM, Tm, T, RH, W, V, and P (week 1 to week 52) were calculated and used to estimate the effect of climatic factors on malaria occurrence. All data from climate and clinical records were checked for missing values. Missing values were replaced by the average of nearest values. ANOVA to test differences between years was performed. The model used was:

$$Y_{ij} = \mu + \tau_i + \varepsilon_{ij} \qquad (1)$$

where: μ is the grand mean, τ_i are deviations from the grand mean due to the treatment levels and, and ε_{ij} are the error terms (ANOVA, 2016).

The modelling strategy followed included: (i) exploring malaria cases and climatic variables data through descriptive statistics; (ii) using a Box-Jenkins approach to time series analysis (including transformation and differentiation for stationarity); (iii) using cross-correlation analysis between climatic variables and malaria cases for identification of climatic variables predictor lags; (iv) regression analysis of malaria cases on a malaria moving average forecast (simple exponential smoothing) and on its lags 1, 2 and 3 and lags 6 and 7 of mean temperature and lag 12 of precipitation; and (v) forecasting at regular intervals of 4 weeks for last 52 weeks (2014) left out of model estimation processes.

All statistical analyses were performed with SPSS-20, R 3.3.2 and BioEstat 5.

3.3. Results

Figures 7 and 8 present box plots of malaria and climate variables for Chimoio by malaria season (October to September 2006 to 2014) along with values for maximum, minimum and the median. Between 2006 and 2014, 490,561 cases of malaria were recorded in Chimoio.
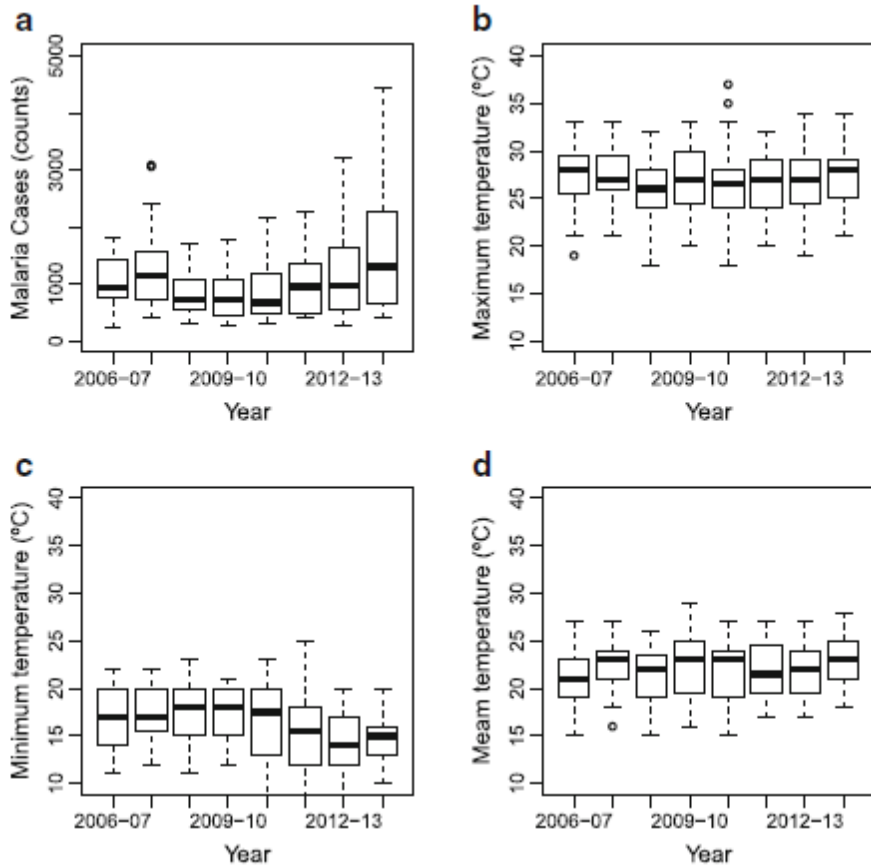
Figure 7: box plots of malaria and climate variables for Chimoio by malaria season (October to September 2006 to 2014)
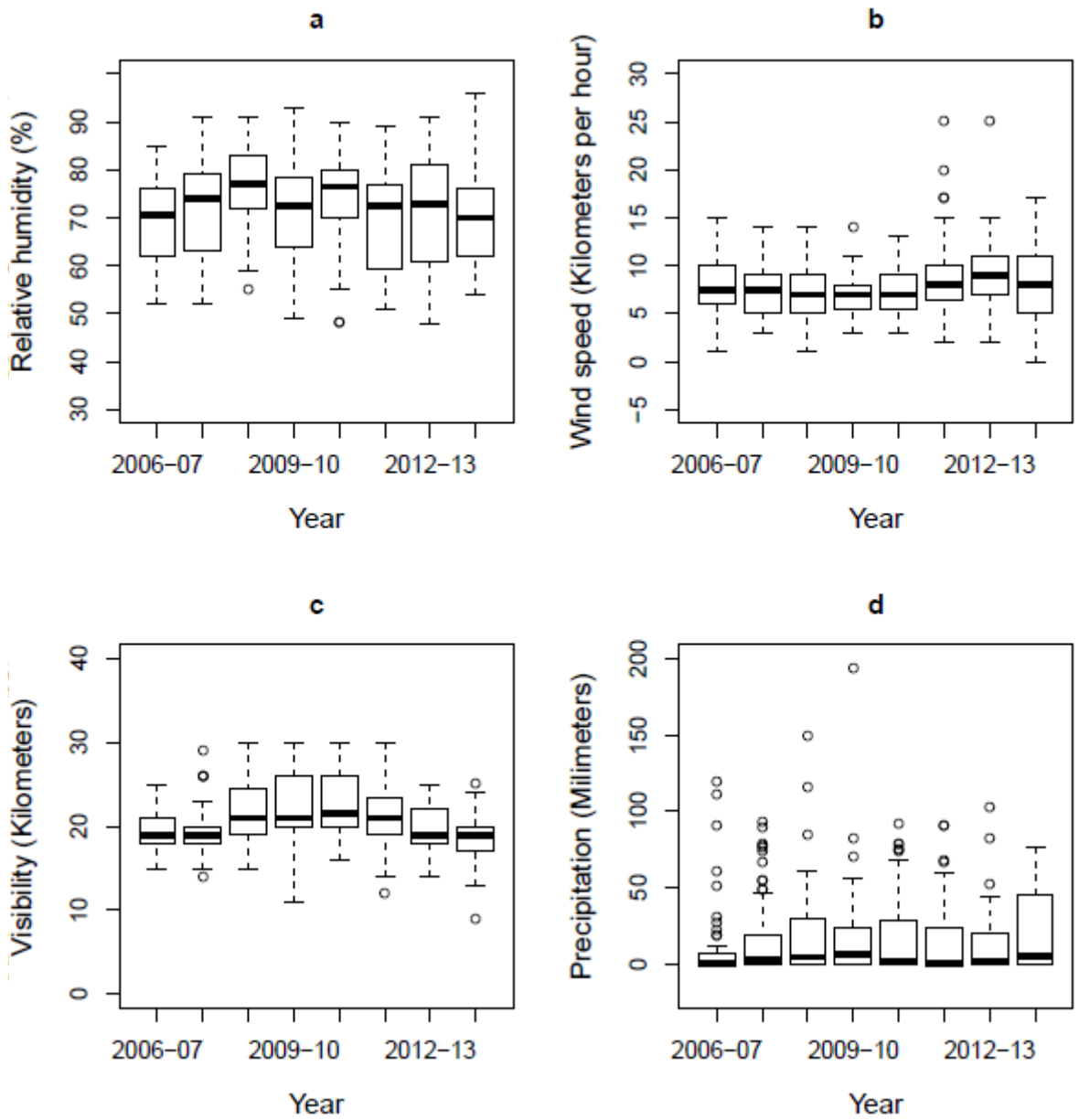
Figure 8: box plots of malaria and climate variables for Chimoio by malaria season (October to September 2006 to 2014)

The weekly average number of malaria cases was 1,048 (SD = 642.12). There were differences in the mean number of cases between malaria season years ($F_{(8, 51)}$ = 22.1, P = 0.0001). Week 40 (in 2006/2007)

presented the lowest number of cases, 222, and, week 21 (in 2013/2014) presented the highest number of cases, 4,438. The maximum temperature weekly average was 26.9 °C (SD = 3.28), and there were no differences in TM between malaria season years ($F_{(8,51)}$ = 2.46, P = 0.0132). The minimum temperature weekly average was 16.2°C (SD = 3.49), and there were significant differences between malaria season years ($F_{(8, 51)}$ = 20.8, P = 0.0001). Mean temperature weekly average was 21.9°C (SD = 2.92), and there were significant differences between malaria season years ($F_{(8, 51)}$ = 39.9, P = 0.0001). Relative humidity weekly average was 71.7% (SD = 9.86), and there were significant differences between malaria season years in RH ($F_{(8, 51)}$ = 2.65, P = 0.0079). The wind speed weekly average was 7.9 km/h (SD = 3.21), and there were significant differences between malaria season years ($F_{(8, 51)}$ = 4.88, P = 0.0001). Visibility weekly average was 20.7 km (SD = 43.75), and there were significant differences between malaria season years ($F_{(8, 51)}$ = 4.88, P = 0.0001). Precipitation weekly average was 17.5 mm (SD = 31.95), and there were no differences between malaria season years ($F_{(8, 51)}$ = 1.5, P = 0.144). Annual average precipitation was 913.4 mm (SD = 166.20).

Figures 9 and 10 present time series plots of malaria cases (solid black line) and climatic variables (dashed red lines). Both malaria cases series and climatic time series from 2006 to 2014 exhibited seasonal patterns.
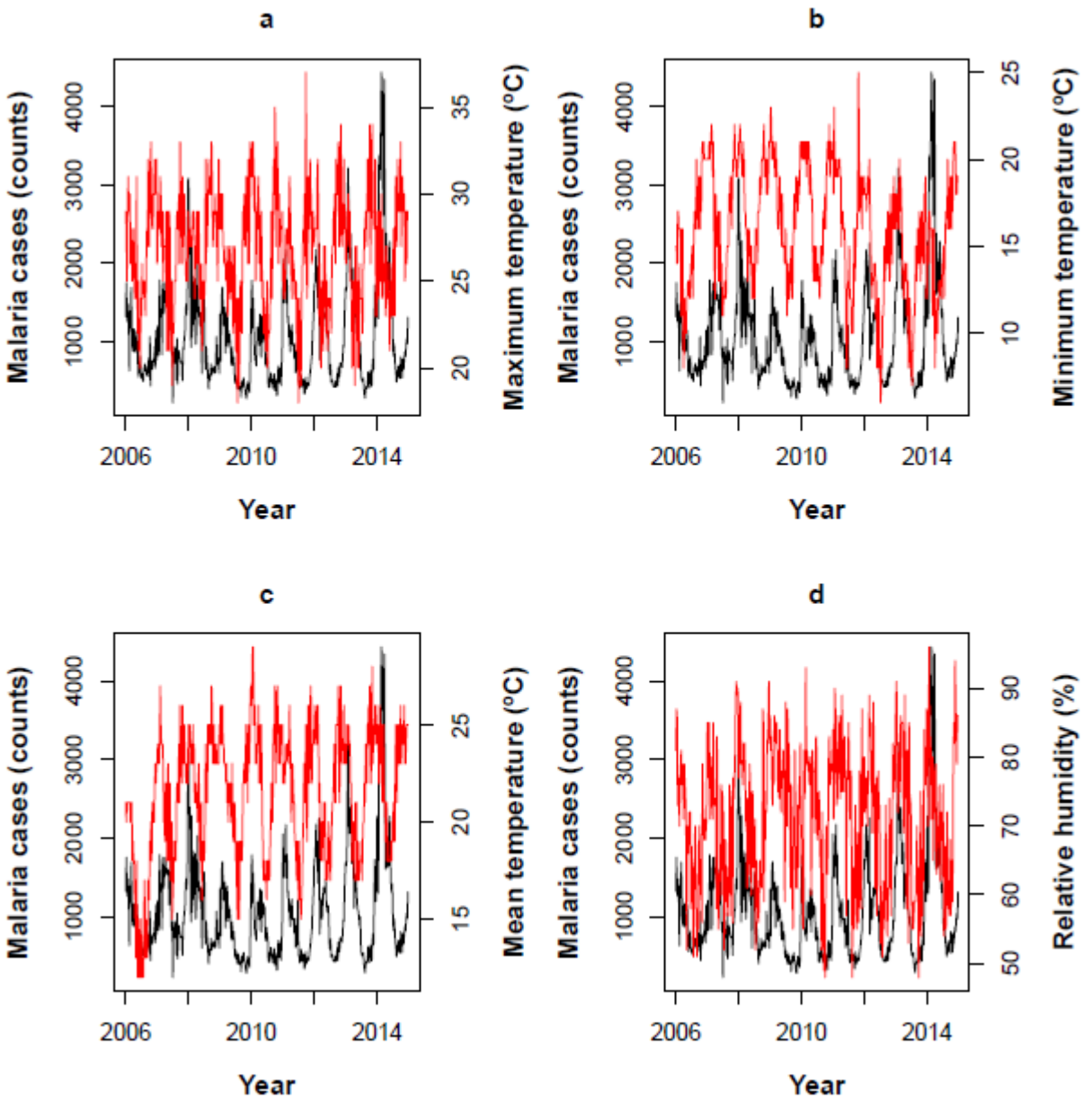
Figure 9: box plots of malaria and climate variables for Chimoio by malaria season (October to September 2006 to 2014). 9a-malaria and maximum temperature, 9b-malaria and minimum temperature, 9c- malaria and mean temperature, 9d- malaria and relative humidity

All series presented several peaks and fluctuations. The weekly peaks in the series seem to be separated by more than few weeks indicating a cyclical

pattern.
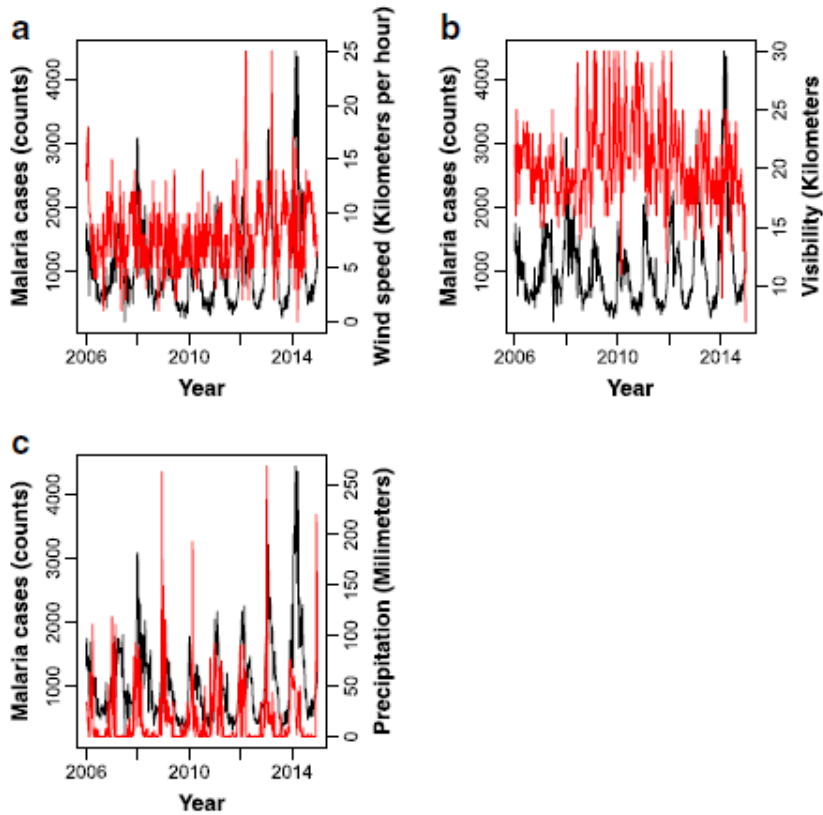
Figure 10: box plots of malaria and climate variables for Chimoio by malaria season (October to September 2006 to 2014). 9a-malaria and wind speed, 9b- malaria and visibility, 9c- malaria and precipitation

Figure 11 presents the time series of malaria cases before and after Box-Cox transformation (λ = -0.5). Figure 11a suggests increasing variability in the malaria cases series along with a slightly increasing trend suggesting both first non-seasonal and seasonal differences might be necessary to turn the series weakly stationary. After applying a Box-Cox transformation (Fig. 11b)
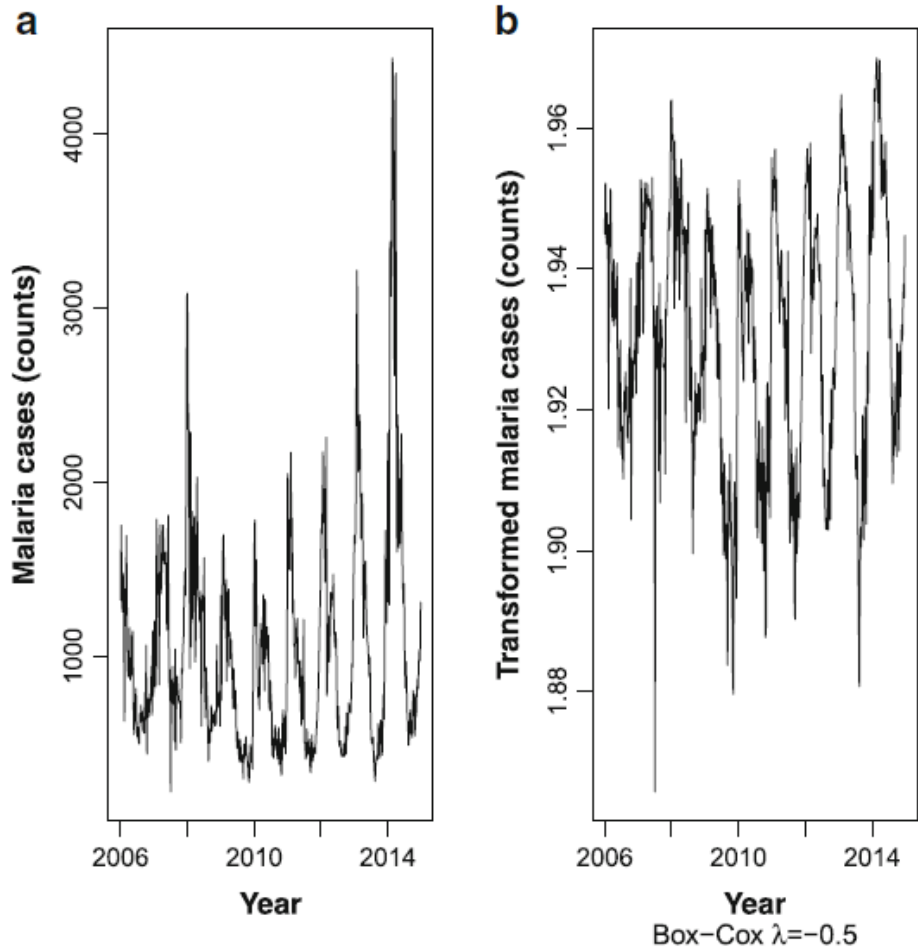
Figure 11: Malaria cases between 2006 and 2014, before (a) and after (b) Box-Cox transformation (λ = -0.5)

Figure 11a suggests increasing variability in the malaria cases series along with a slightly increasing trend suggesting both first non-seasonal and seasonal differences might be necessary to turn the series weakly stationary. After applying a Box- Cox transformation (Fig. 11b), the variance was clearly stabilized, and no trend can be overtly observed.

Figure 12 presents the time series of malaria cases, between 2006 to 2014, after Box- Cox transformation (λ = -0.5) and non-seasonal first (lag 1) and seasonal differences (lag 52).

Box Cox λ=−0.5 and differences
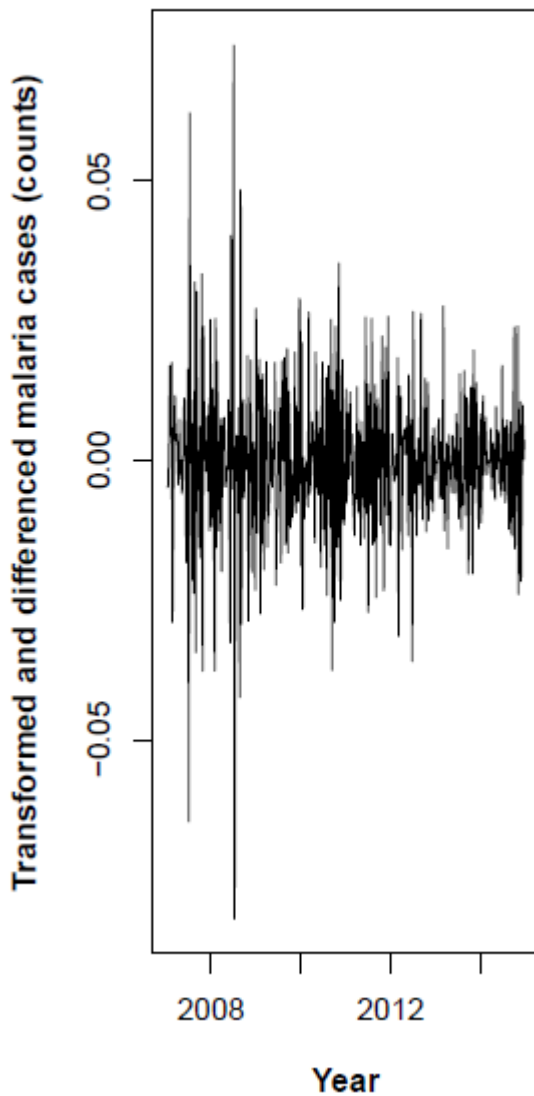
Figure 12: time series of malaria cases, between 2006 to 2014, after Box- Cox transformation (λ = -0.5) and non-seasonal first (lag 1) and seasonal differences (lag 52)

Figure 13 presents the autocorrelation (ACF) and partial autocorrelation (PACF) functions of the transformed and differenced malaria cases time series in Chimoio. Autocorrelation is plotted up to lag 150. For

modelling purposes, the last 52 weeks, starting at week 1, 2014 (January 2014 through December 2014), were left out for forecasting assessment.

a

b
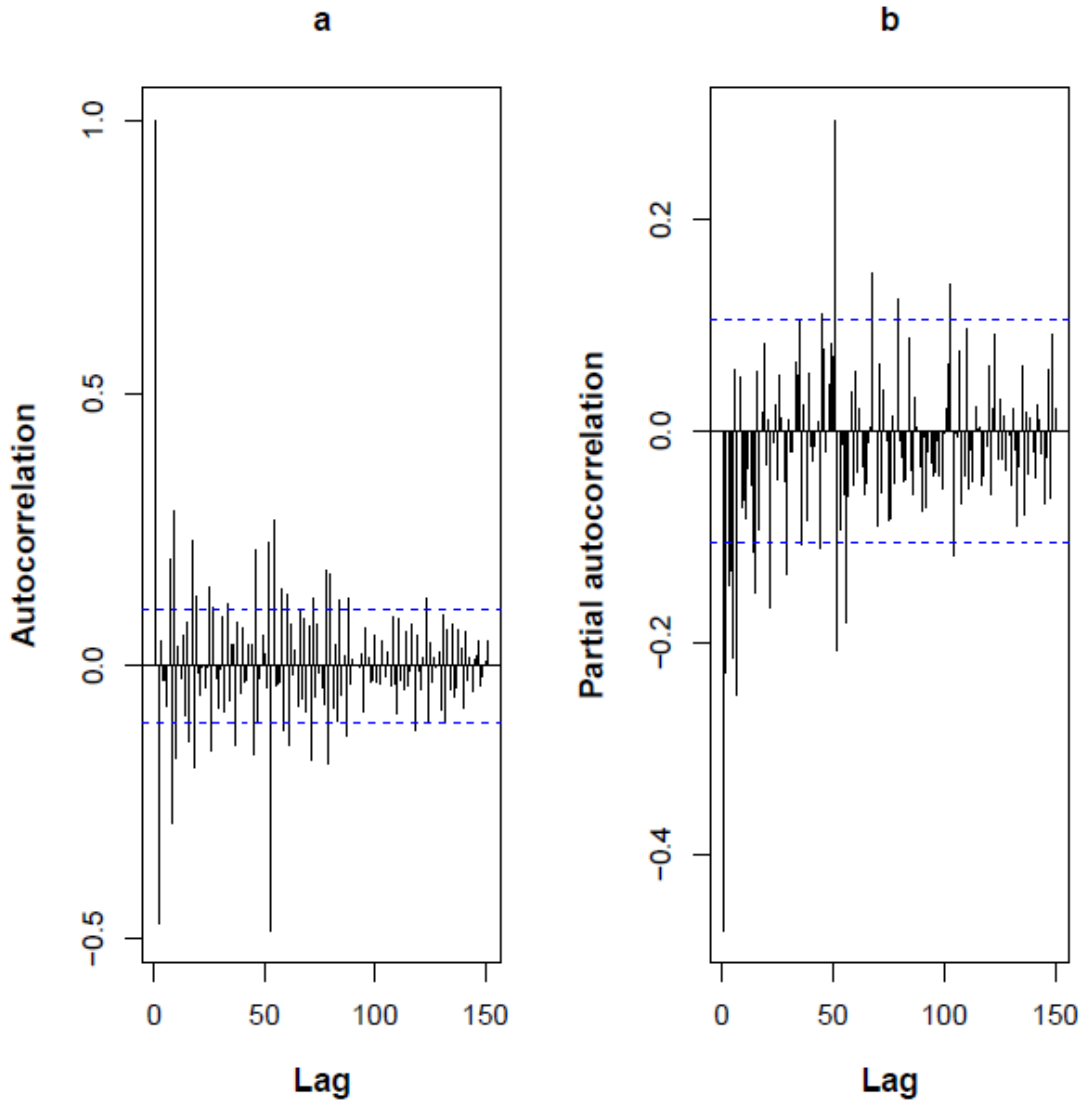
Figure 13: Autocorrelation (a) and partial autocorrelation (b) functions of the transformed and differenced malaria cases time series in Chimoio, 2006 to 2014. Last 52 weeks, starting at week 1, 2014 (January 2014 through December 2014) were left out for model forecasting assessment. Autocorrelation is plotted up to lag 150

Both the ACF and PACF suggest ARMA(2,0) and ARMA(2,1) patterns for non-seasonal and seasonal components leading to a Seasonal ARIMA(2,1,0)(2,1,1)$_{52}$. Indeed, among the all experimented models (up to the second order in autoregressive and moving average components) ARIMA (2,1,0) (2,1,1)^{52} was the one leading to the smallest AIC to the Box-Cox transformed series:

$$(1-\phi_1 B-\phi_2 B^2)(1-\Phi_1 B^{52}-\Phi_2 B^{104})(1-B^{52})(1-B)y_t = (1+\Theta_1 B^{52})e_t \quad (2)$$

Where y''_t is the Box-Cox transformed malaria cases series, e_t is considered white noise and ϕ_1 = -0.3395 (standard error, SE = 0.0518), ϕ_2 = -0.2323 (SE = 0.0511), Φ_1 = -0.4299 (SE = 0.0551), Φ_2 = -0.2672 (SE = 0.0426), and θ_1 = -0.3267 (SE = 0.0843). All the coefficients were statistically significant at 0.05. Diagnostic checks for residuals of the estimated model are presented in Fig. 14.
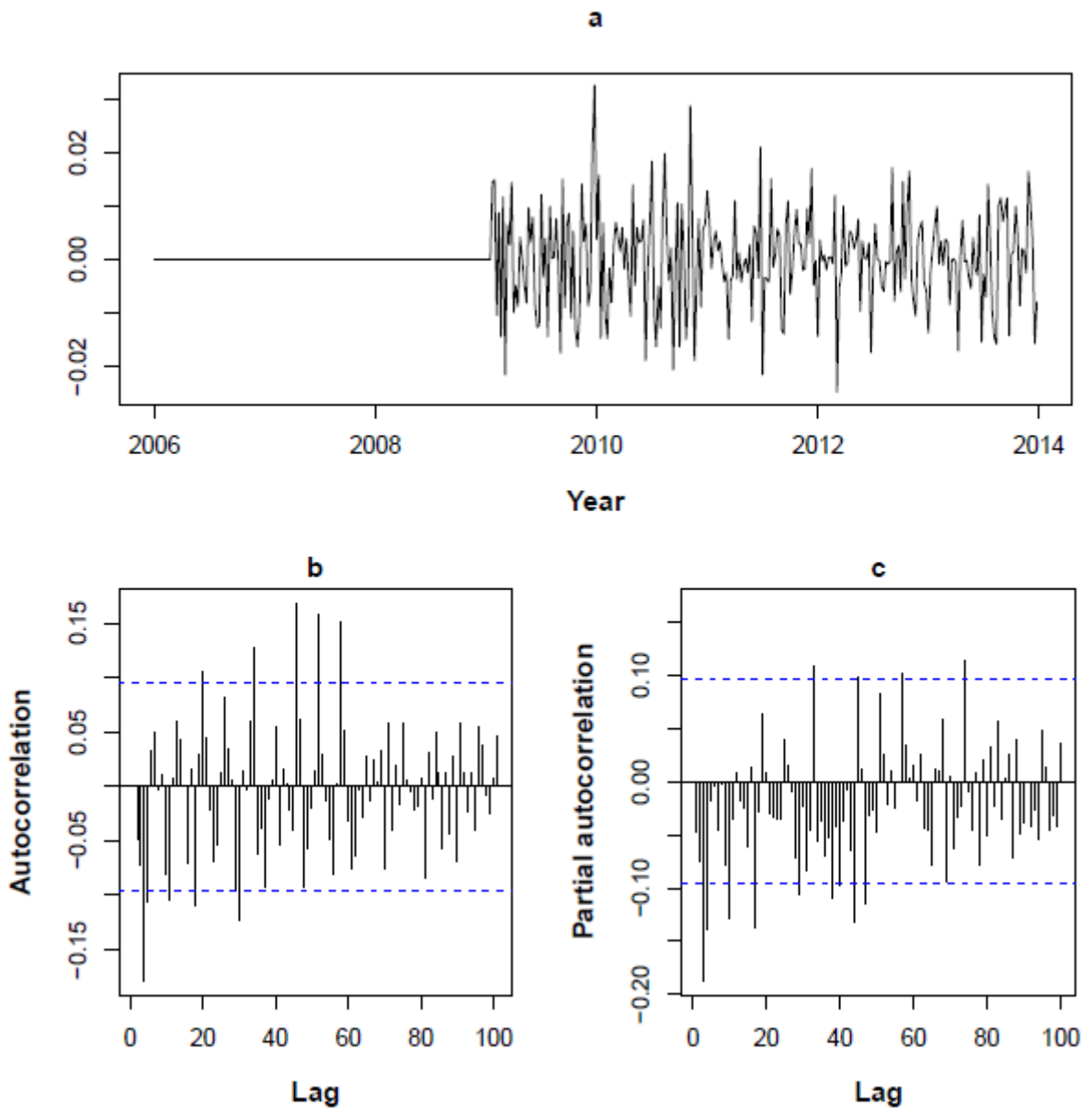
Figure 14: Diagnostic checks of ARIMA (2,1,0) (2,1,1)[52] residuals. a Time series of residuals. b Autocorrelation function of residuals. c Partial autocorrelation function of residuals

Residual autocorrelation was still significant for some lags. Prediction for the last 52 observations (the entire year of 2014, which contains the last

malaria outbreak peak) that were left out of the modelling procedure is presented in Fig. 15.

Forecasting was done on a 4-week long period basis (*t+1*, *t+2*, *t+3*, *t+4*), based on an estimated seasonal ARIMA model for data up to *t*. On the one hand, a 4-week long forecasting period is not large enough to produce inaccurate forecasts by a seasonal ARIMA model. On the other hand, it is sufficiently large to anticipate perfectly manageable Precision Public Health malaria outbreak evolution. Figure 9b, besides the data, mean forecasts and respective 80% confidence prediction limits, also contains the historical means of weeks 1 to 52 (dashed yellow vertical lines), which given the rising pattern of malaria cases in the last years tends to underestimate the outbreak peak. Although the last weeks' forecasts followed the actual values, it seems to be underestimating the outbreak peak.
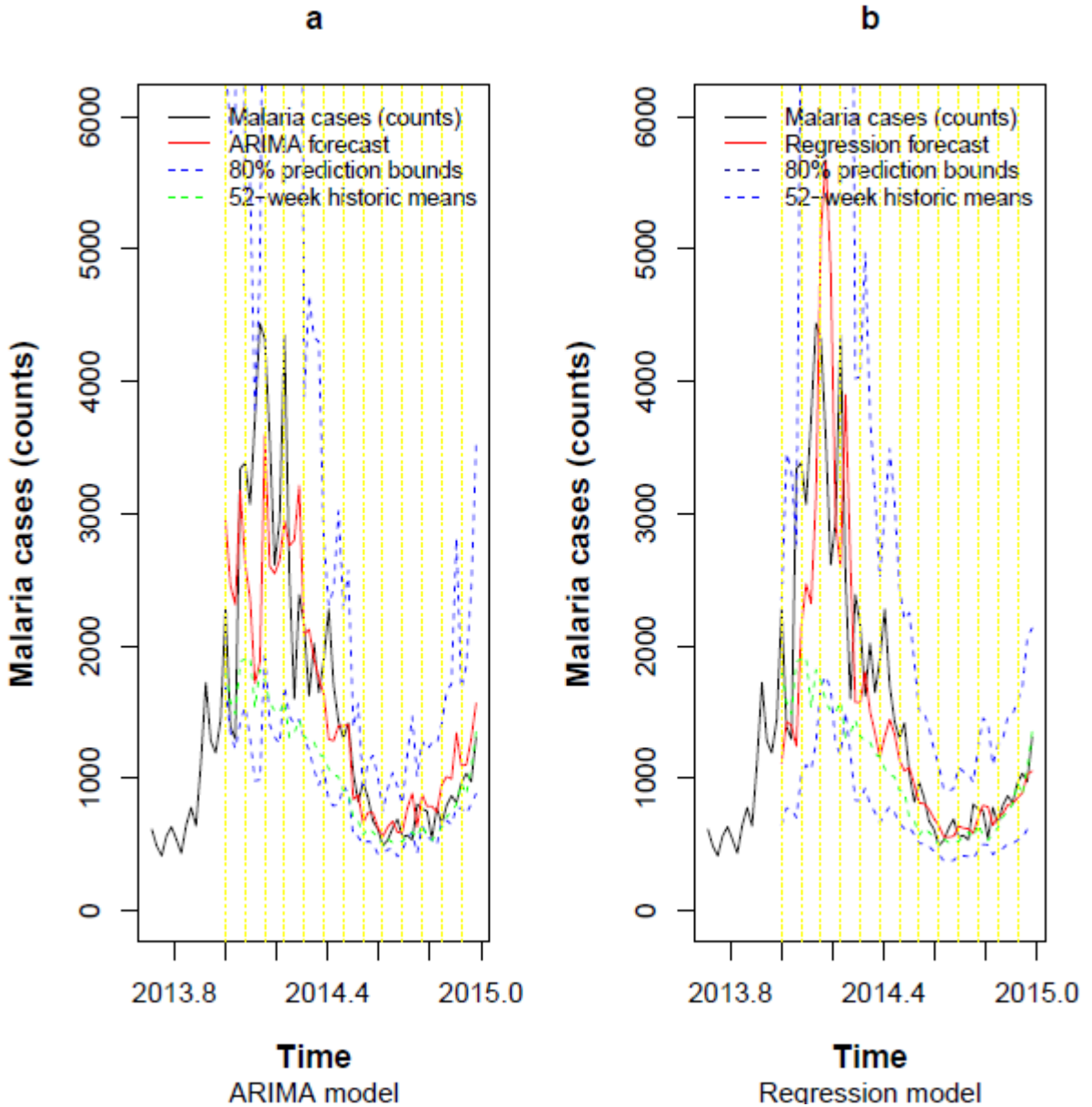
Figure 15: ARIMA (2,1,0) (2,1,1)[52] (a) and regression (b) forecasts of the last 52 observations that were left out of the modelling procedure. Black, red dashed blue and green lines represent, malaria cases (counts) and their forecasts, 80% confidence limits and 52-week historic means, respectively. Dashed yellow vertical lines denote the thirteen 4-week long prediction periods

Although the purpose of this first modelling step was to approximate a possible model for malaria cases time series, the goal of this study was to find a prediction model for malaria cases that can take advantage of the relationship between malaria and climatic variables.

A cross-correlation analysis was performed to find the best predictor lags of the climatic variables. To keep interpretability, first and seasonal differences (lag 52) were applied to climatic variables prior to cross-correlation calculation. No stabilising variance transformation was applied as the predictors will be used in a regression setting where the predictors are assumed non-stochastic variables. Several climatic variables exhibited significant cross-correlations with malaria past (negative) lag 52. Therefore, attention was drawn to (negative) lags that are known to be closely related to parasite life cycle, namely lags -1, -2, , 12 weeks. Only minimum temperature (lags -6 and -7) and precipitation (lag -12) exhibited significant cross-correlation. Figure 10 presents the cross-correlation functions between minimum temperature and precipitation (after first and seasonal differences) and Box-Cox transformed and differenced malaria cases. Lags -1, -2, and -3 of the Box-Cox transformed malaria cases series and lags -6, and -7 of minimum temperature and lag -12 of precipitation were used in the regression model (figure 16).
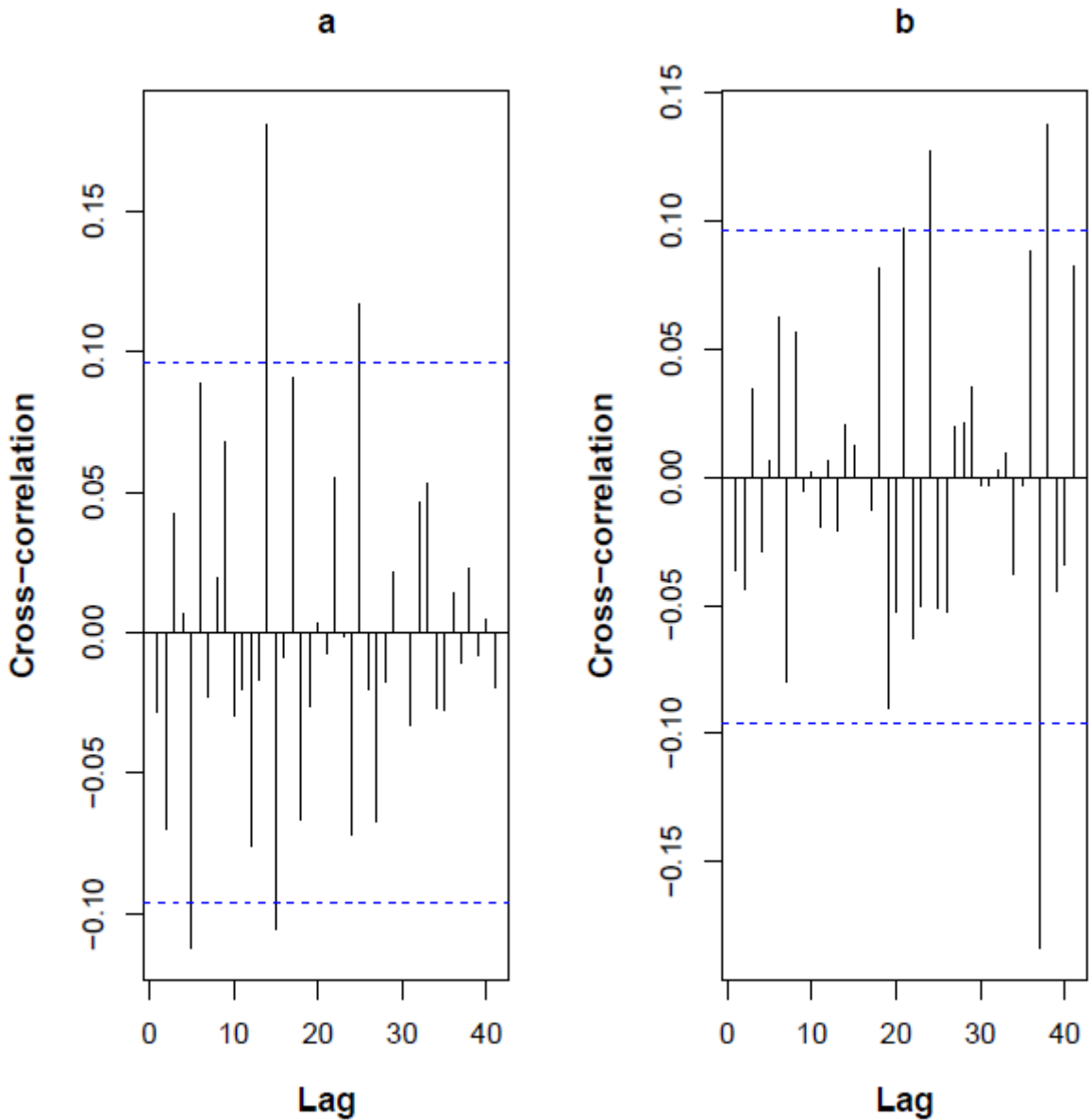
Figure 16: cross-correlation functions between minimum temperature and precipitation (after first and seasonal differences) and Box-Cox transformed and differenced malaria cases

Historical means of malaria cases (already discussed) could provide insightful information for the regression model. To introduce in the regression model the memory of the time series process, it was decided to

include in the regression model, as an independent variable, one-step-ahead forecasts of a simple exponential smoothing model (α=0.6). The estimated model is:

$$y_t^* = \beta_0 + \beta_1 y_{t-1|t}^{ses} + \beta_2 y_{t-1}^* + \beta_3 y_{t-2}^* + \beta_4 y_{t-3}^* + \beta_5 Tm_{t-6} + \beta_6 Tm_{t-7} + \beta_7 P_{t-12} + \eta_t,$$ (3)

where y_t^* denotes for Box-Cox transformed malaria cases series (with no differences), y^{ses} is the simple exponential smoothing forecast at t, using data up to t-1 (α=0.6) and Tm and P correspond to minimum temperature and precipitation time series. The regression coefficients β_0 = 0.0701 (SE = 0.0152), β_2 = 0.0370 (SE = 0.0065), β_3 = 0.0194 (SE = 0.0056) and β_6 = 0.0008 (SE = 0.0003) were marginally statistically significant at P = 0.05 and R^2 = 0.726. Residual analysis shows the model can capture almost all temporal dependence, as despite some autocorrelations being statistically significant, they are smaller than 0.2 (Fig. 16).

To compare with previous ARIMA model, in the estimation process, the last 52 observations were left out for forecast assessment purposes. Figure 9b presents last 52-point forecasts of the regression model (3) along with the 95% confidence limits in the original scale, i.e. after applying inverse Box-Cox transformation (λ = -0.5). Forecasts were done on 4-week forecast bases as before. Point's forecasts seem to follow closely malaria series values, though the outbreak peak is being overestimated. The width of prediction intervals was like the ones produced by seasonal ARIMA model (close to 600 cases, an accuracy perfectly manageable by Public Precision health), though anticipation of outbreak's peak seems to be more accurate (last observations of 2014). (Figure 17).
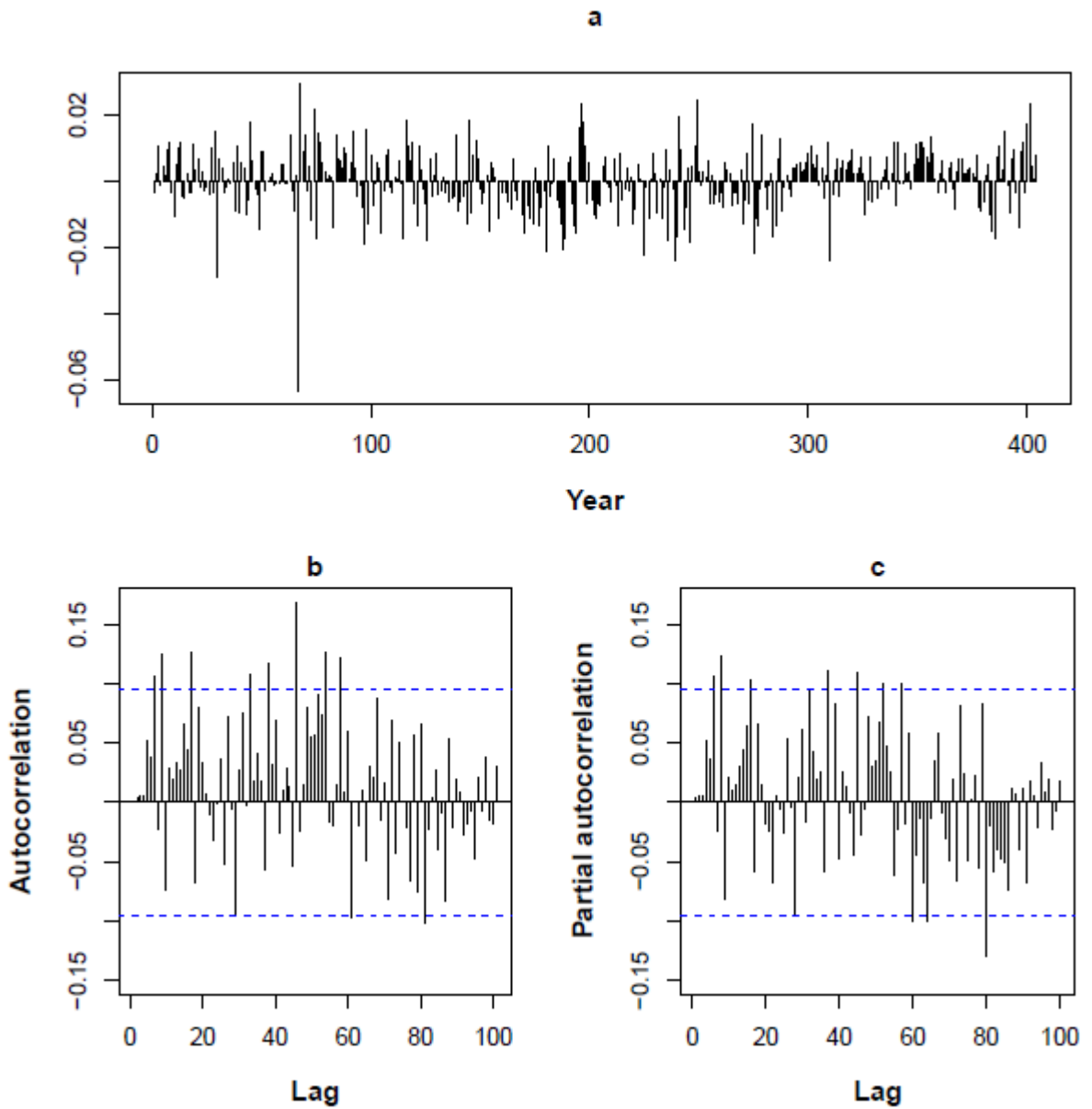
Figure 17: Diagnostic checks of regression model (3) residuals (coefficient of determination R^2 = 72.5. a Time series of residuals. b Autocorrelation function of residuals. c Partial autocorrelation function of residuals

65

3.4. Discussion and conclusions

Although malaria shows seasonality according to the climate, very few studies have been conducted on the association between the malaria occurrences with climate variables using weekly resolution and with high malaria occurrence volume in the Southern region of Africa, giving more accurate results.

In this study, malaria cases are increasing, contrary to the decreasing tendency reported in neighbouring Malawi Kazembe, Kleinschmidt, and Sharp (2006), and, South Africa (Ngomane & de Jager, 2012). The increasing tendency, could be probably due to improved accessibility to health centres and decreased vector control due to the scarcity of resources for malaria control.

On average, week 6 presented the peak of malaria cases and week 33 the lowest number of cases of malaria; these results are consistent with previously published studies in Mozambique, Maputo Zacarias and Andersson (2010), and Chimoio (Ferrão et al., 2016). The ARIMA model developed in this study, ARIMA $(2,1,0)$ $(2,1,1)_{52}$, attempted to provide an easy technique to predict the expected number of malaria cases per week based on past observed cases, although it does not account for climate factors.

Cross-correlation analysis showed that mean temperature, and precipitation presented significantly lagged correlations with malaria cases. A regression model of a differenced (lag1 and lag 12) Box-Cox transformation (λ = -0.5) of malaria cases on lag 1, 2 and 3 of weekly malaria cases and lag 6 and 7 of weekly mean temperature and lag 12 of precipitation was found as the best prediction model for weekly malaria cases.

As shown in Fig. 15, historical means failed completely, especially at the peak of the malaria occurrence. Although the two models developed in this study produced prediction intervals having widths of some hundred cases, the regression model was the one able to anticipate accurately the peak of the occurrence. ARIMA model was also used for malaria forecasting

in South Africa Ngomane and de Jager (2012), Zambia Jere and Moyo (2016), Burundi Gomez-Elipe et al. (2007) and India Kumar et al. (2014) with comparable results.

Malaria transmission occurs throughout the year with peaks between weeks 1 to 12. The onset of rain occurs in mid-November. This indicates that malaria occurrence has a strong association with rainfall six to eight weeks before, coinciding, with the malaria cycle three components: (i) the growth of the *Anopheles* female mosquito from egg to adult to parasite transmission; (ii) the development of the *Plasmodium* parasites (gametocyte to sporozoites) that are able to infect humans; and (iii) the incubation period in the human host from infection to malaria symptoms CDC (2014b) and (Krefis et al., 2011). Thus malaria occurrence peak can be expected 45 to 60 days after the onset of rain. Similar results were also found in Mozambique Ferrão et al. (2016) and South Africa (Ngomane & de Jager, 2012). Increased precipitation can provide more breeding sites for mosquitoes, but excess rain can also destroy breeding sites (Bai, Morton, & Liu, 2013).

Temperature affects the development of malaria; the parasite does not develop below 18 °C and over 40 °C Pascual, Ahumada, Chaves, Rodo, and Bouma (2006) and (EFE & Ojoh, 2013). A rise in temperature can reduce the time for production of new generations and also shortens the incubation period of the parasite in mosquitoes. Sporogonic cycles take about 9 to 10 days at temperatures of 28 °C, but temperatures above 30 °C and below 16 °C have a negative impact on parasite development (Alemu, Abebe, Tsegaye, & Golassa, 2011). The highest proportion of vectors surviving the incubation period is observed at temperatures between 28–32 °C (Sena, Deressa, & Ali, 2015). In this study, the average maximum temperature recorded was 26.8 °C ranging between 22.3–31°C suggesting that Chimoio is the ideal location for malaria breeding. Minimum temperature in the present study was below 18 °C from week 10 to 40, coinciding with an accentuated reduction in malaria occurrence. In this study, the mean temperature was found to be a significant

predictor for malaria occurrence, similar to studies carried out in South Africa Ngomane and de Jager (2012) and Burundi, Gomez-Elipe et al. (2007).

Relative humidity (RH) also plays a role in malaria episodes, and mosquitoes become more active when humidity rises. If the average monthly relative humidity is below 60%, it is believed that the life of the mosquito is so short that very little or no malaria transmission is possible Arab, Jackson, and Kongoli (2014) and Yamana and Eltahir (2013). Relative humidity in this study was 72.1% and only four weeks of the year presented RH less than 60% implying that humidity does not restrict malaria occurrence in Chimoio. Similar results were also reported in a study in Ghana (Krefis et al., 2011).

Wind speed was found to be a significant influence in malaria occurrence in Nigeria Omonijo et al. (2011) and EFE and Ojoh (2013). In this study, the wind speed was not found to be a significant predictor for malaria occurrence in Chimoio. Visibility was not found to be a significant predictor for malaria occurrence consistent in studies in Nigeria Omonijo et al. (2011) and South Africa (Ngomane & de Jager, 2012). Most *Anopheles* mosquitoes are crepuscular (active at dusk or dawn) or nocturnal (active at night) (Suárez-Mutis, Fé, Alecrim, & Coura, 2009).

It has been found that fog day frequency had a positive effect on malaria incidence in the following year (Tian et al., 2008).

The *R*-square in this study was 0.725 implying that 72.5% of the variance in malaria occurrence can be explained by variance in the predictive variables. In Burundi, 82% was reported (Gomez-Elipe et al., 2007). The results are higher than a study in Nigeria that found 66% ANOVA (2016) and lower than the Global Fund Report Global Fund (2015) that indicated that 90% of malaria cases are related to environmental factors. Other factors such as poor prevention strategies, lack of funds, poor sanitation, inadequate drainage systems, and planning problems, amongst others, also contribute to the occurrence of malaria. Geographical and environmental factors such as altitude and land cover are also variables that influence malaria occurrence (CDC, 2014a).

The assumption the factors other than climate remained constant over the period, is a limitation of the present model that makes it difficult to generalize the results to other regions. From the results of the present study, it can be stated that malaria occurrence in Chimoio depends on to a large extent on precipitation, and mean temperature. The results also indicate that if strong actions are not taken at the right time and place, malaria cases will continue to occur in the municipality.

This model is robust and, can predict the expected number of malaria cases 3.5 months in advance and, timely prevention and control measures can be effectively planned in Chimoio, such as the elimination of vector breeding places, correct time and place to spray insecticides, and awareness campaigns weeks before the malaria peak season. This can lead to a reduction in malaria cases, by knowing the best moment for spraying, saving time and cost of insecticide application and, preventive programmes, and guiding smart environmental care.

The Chimoio climate seems ideal for malaria occurrence. A seasonal pattern was observed in malaria occurrence in Chimoio with peaks during weeks 1 to 12 (January to March). Since the lag effect between climatic events and malaria occurrence is important for malaria cases prediction this can be used for designing Precision Public Health measures. The model can be used for planning specific measures for Chimoio municipality.

The results from this study cannot confirm or rule out a prediction for areas with similar altitude and precipitation as Chimoio. Prospective and multidisciplinary research involving researchers from different fields is welcomed to improve the effect of climatic factors and other factors in malaria cases. The model can also be applied to analyse the spread of other infectious diseases and in optimising management efforts.

4. Malaria mortality characterization and the relationship between malaria mortality and climate in Chimoio, Mozambique (*)

Abstract

Background

The United Nation's sustainable development goal for 2030 is to eradicate the global malaria epidemic, primarily as the disease continues to be one of the major concerns for public health in sub-Saharan Africa. In 2015, the region accounted for 90% of malaria deaths. Mozambique recorded a malaria mortality rate of 42.75 (per 100,000). In Chimoio, Mozambique's fifth largest city, malaria is the fourth leading cause of death (9.4%). Few data on malaria mortality exists in Mozambique, particularly in relation to Chimoio. The objective of this study was to characterize malaria mortality trends and its spatial distribution in Chimoio.

Methods

Malaria mortality data and climate data were extracted from the Chimoio Civil Registration records, and the Regional Weather station, from 2010 to 2014. The malaria crude mortality rate was calculated. ANOVA, Tukey's, Chi-square, and time series were carried out and an intervention analysis ARIMA model developed.

A total of 944 malaria death cases were registered in Chimoio, 729 of these among Chimoio residents (77%). The average malaria mortality by gender was 44.9% for females and 55.1% for males. The age of death varied from 0 to 96 years, with an average age of 25.9 (SE = 0.79) years old. January presented the highest average of malaria deaths, and urban areas presented a lower crude malaria mortality rate. Rural neighbourhoods with good

accessibility present the highest malaria crude mortality rate, over 85 per 100,000. Seasonal ARMA (2,0) (1,0)$_{12}$fitted the data although it was not able to capture malaria mortality peaks occurring during malaria outbreaks. Intervention effect properly fit the mortality peaks and reduced ARMA's root mean square error by almost 25%.Malaria mortality is increasing in Chimoio; children between 1 – 4 years old represent 13% of Chimoio population, but account for 25% of malaria mortality. Malaria mortality shows seasonal and spatial characteristics. More studies should be carried out for malaria eradication in the municipality.

4.1. Research objective

The objective of this study is to determine malaria mortality trends, characterize malaria mortality, describe its spatial distribution and variation in Chimoio, and verify its relationship with climate parameters to help local authorities in programmatic malaria activities for the prevention and eradication of the disease.

4.2. Methods

4.2.1. Study area and population

Chimoio is a municipality in Manica Province in the centre of Mozambique, located at -19° 6' 59 S, 33° 28' 59 E. The current population projection by the "Instituto Nacional de Estatística" (National Statistics Institute) is 324,816, being 50.4% males and 49.6% females. The population percentage by category is: age 0 (3%), 1 – 4 (13%), 5 – 14 (28%), 15 – 44 (48%), 45 – 59 (6%) and over sixty (2%) (INE, 2016). Chimoio is divided into 33 residential areas known as "Bairros" or neighbourhoods with an area of 174 Km^2 (Map. 9).
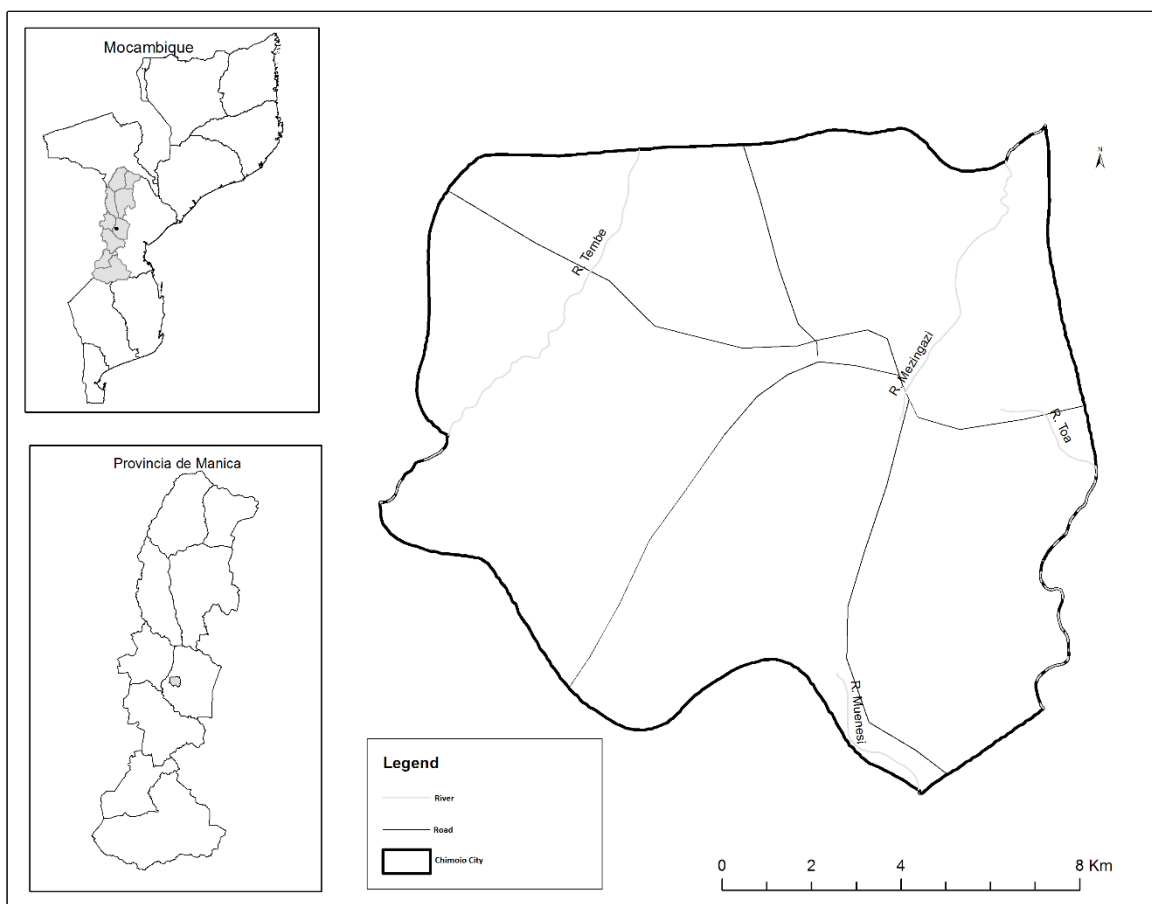
Map 7: Chimoio map

4.2.2. Study subjects

Death cases and monthly malaria mortality data were extracted from the Chimoio civil registration books from 2010 to 2014. Data entered in the books come from death certificates produced by qualified health personnel. The variables extracted were sex, month of death, cause of death, age, place of death, time of death, and the origin of the deceased. Population data were extracted from the population projection data by the "Instituto Nacional de Estatística" of Mozambique (Buescher, 2008).

For malaria cases, data reported elsewhere were used (WHO, 2013b). Monthly climate data from 2010 to 2014 were obtained from the Chimoio Regional Weather Station and comprised of the following parameters: mean, maximum and minimum temperature (°C), relative humidity (%), precipitation (millimetres) and evaporation (millimetres). The evaporation data had three missing data which were imputed using nearest data as donors.

4.2.3. Data analysis

The malaria crude mortality rate was calculated per malaria year by age-specific, gender and residential area (Bairro). Malaria crude mortality rate (MCMR) was calculated dividing the number of deaths-per year of residents by the total population for the same geographic area and multiplied by 100,000:

MCMR=$\frac{\text{Number of deaths−per year}}{\text{Total population for the same geographic}} \times 100{,}000$

Age-specific malaria mortality rate was calculated dividing the number of deaths-per age per year of residents by the total age population and multiplied by 100,000 (Kumar et al., 2014). The ages (categories) used were: 0 (infants), 1 – 4 (Children), 5 -14 (adolescents, 15 – 44 (young adults), 45 – 59 adults and over sixty (elderly).

Chi-square for a proportion of gender and age-specific category was performed and Phi, Cramer's V test was used for statistical significance. Analysis of Variance (ANOVA) was used to test difference between years and months using the following model:

$$Y_{ij} = \mu + \tau_i + \varepsilon_{ij} \qquad (1)$$

Intervention analysis with the specification $z_t = \frac{\delta_0}{1-wB} P_t$, where $|w| < 1$, B stands for the traditional time series backshift operator, $Bz_t = z_{t-1}$, and P_t denotes a pulse function such that $P_t = 0, t < t_0$ or $, t > t_0$ and $P_t = 1, t = t_0,$

where t_0 is the moment of intervention (Jere & Moyo, 2016) was used. All tests were performed using R 3.3.2, SPSS, IBM version 20 and Biosat 5.0. Spatial maps for year variation were produced using ArcGIS version 10.1.

4.3. Results

4.3.1. Deaths, malaria cases and malaria mortality trends in Chimoio

During the period, 18,508 cases of all death causes occurred, yearly average of 3,702 (SD=137). Malaria cases were 286,583. A total of 944 malaria death cases were registered, 729 of them among Chimoio residents (77.2 % %). A time series plot indicates that malaria is increasing annually (Fig. 18).
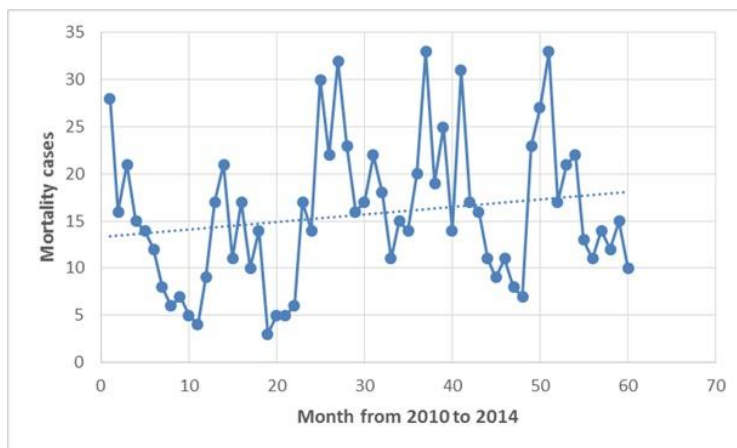
Figure 18: Monthly mortality trend in Chimoio between 2010 and 2014

Year 2014 recorded the highest number of deaths 159, and the average death cases per year was 146 (SD=38). From 2010 to 2014, the average malaria crude mortality rate (MCMR) was 51 per 100,000 (Table 7).

Table 6: Malaria Crude mortality rate from 2010 to 2014 in Chimoio

Year	2010	2011	2012	2013	2014	Average	SD**
Population	267,456	276,468	285,716	295,189	304,873	285,940	14,794
Malaria cases	41,925	47,107	52,463	60,381	84,707	57,317	16,765
All cause death	3,676	3,893	3,509	3,706	3,724	3,702	137
Malaria death	111	111	201	147	159	146	38
Mortality rate (per100,000)	1,374	1,408	1,228	1,255	1,221	1,298	78.1
Incidence (%)	15.7	17	18.4	20.5	27.8	20	5
MCMR*	41.5	40.1	70.3	49.7	52.1	51.0	12.1

*MCMR = Malaria crude mortality rate **SD = Standard deviation

4.3.2. Malaria mortality by gender and place of death

The average mortality in malaria by sex was 44.9% for females and 55.1% for males. There is no difference, (x^2 = 0.415, df = 1, P = 0.615), between malaria mortality in females and males in Chimoio. The deaths from malaria registered in Chimoio indicated that 77% of deaths occurred at public hospital, 22% at residence and 1% at private clinics.

4.3.3. Malaria death by age and age-specific

Fig. 19 presents the malaria death by age. Fig. 19a presents age of death and Fig. 19b, malaria age-specific death.
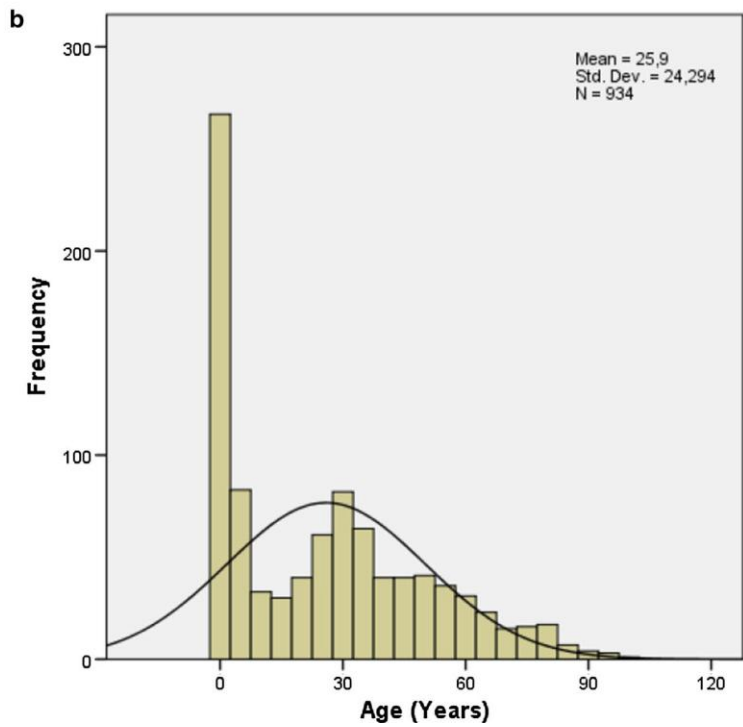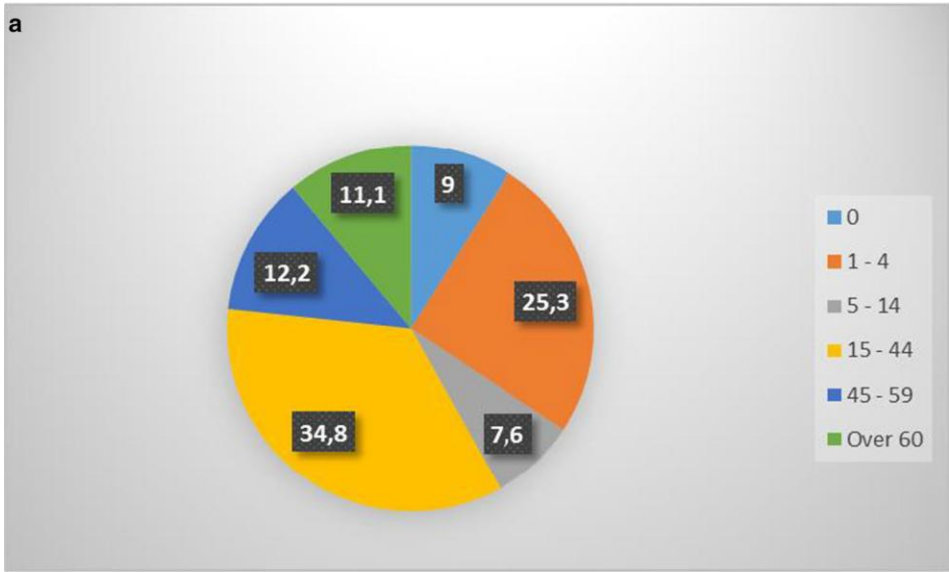
Figure 19: Malaria death by age. a Present age of death and b age-specific death

The range of age of death was from 0 to 96 years, the average age of death was 25.9 years old (SE=0.79). The first quartile (25%) of malaria deaths occurs at age of 2 and the third quartile of malaria deaths at age of 43. Out of all Chimoio residents' registered cases, 9 % were of age, 0, 25.3 % were of 1 to 4 years old, 7.6 % were of 5 – 14 years old, 34.8 % were of 15 – 44 old, 12.2 % were of 45 – 59 years old and 11.1 % for the elderly. There is a difference (χ^2 = 15.65, df = 1, P < 0.001) between age categories in malaria mortality in Chimoio.

4.3.4. Malaria death per year and month

Fig. 20 presents mortality trend in Chimoio per month and year. Year 2012 presented the highest number of malaria deaths, 210 (SD=6.3) and year 2011 the lowest number of cases, 140 (SD=11). There is a difference ($F_{(4, 59)}$ = 7.91, P = 0.0001) in malaria mortality in Chimoio, between years. January presented the highest malaria average death, 26 (SD=6.3), while August presented the lowest average cases of death 9 (SD=3.5). There is a difference ($F_{(11, 59)}$ = 8.12, P = 0.0001) in malaria mortality between months.
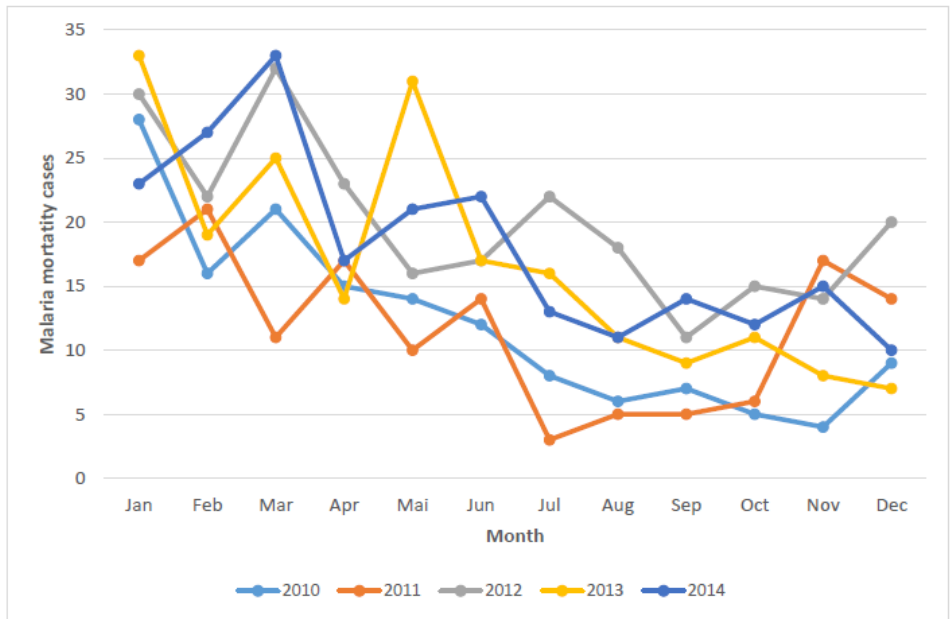
Figure 20: Malaria mortality trend in Chimoio per month and year

4.3.5. Malaria mortality per time of death

Fig. 21 presents the malaria mortality by time of day. The highest proportion of malaria mortality was recorded in the evening, at 8:00 PM with 6.3% of the cases, and the lowest time of death was recorded during the day at 12:00 and 2:00 PM with 3% respectively. There is no difference (p > 0.05) between hours of death by malaria in Chimoio (G = 3.6754, df = 23, P = 0.001).
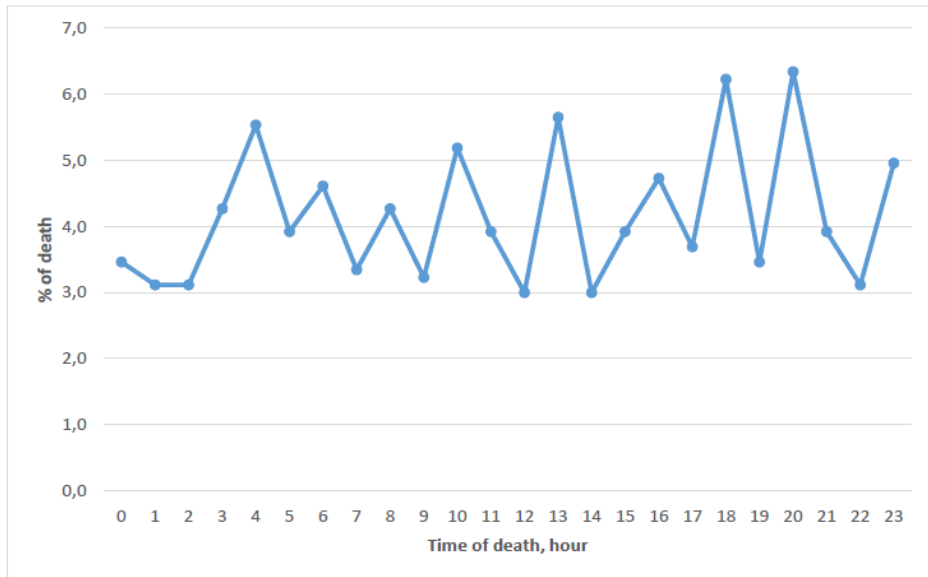
Figure 21: Malaria mortality by time of day

4.3.6. Geographic malaria mortality variation in Chimoio

Map.10 presents the crude malaria mortality rate per residential area. Out of 33 neighbourhoods, six bairros (18%) presented low CMMR, eleven (33%) presented moderate CMMR, ten (30%) high and six (18%) very high CMMR per 100,000. The urban neighbourhoods (low population density, Bairros 1, 2, 3) and rural neighbourhoods, with lack of accessibility (Hombwa, Chissui, Circulo Mudzigandzi, and Chianga) presented a lower malaria crude mortality rate (0 to 27) per 100,000. Most the neighbourhoods present a moderate malaria crude mortality rate, 27 to 55 per 100,000 and, rural neighbourhoods with good accessibility present the highest malaria crude mortality rate, over 85 per 100,000.
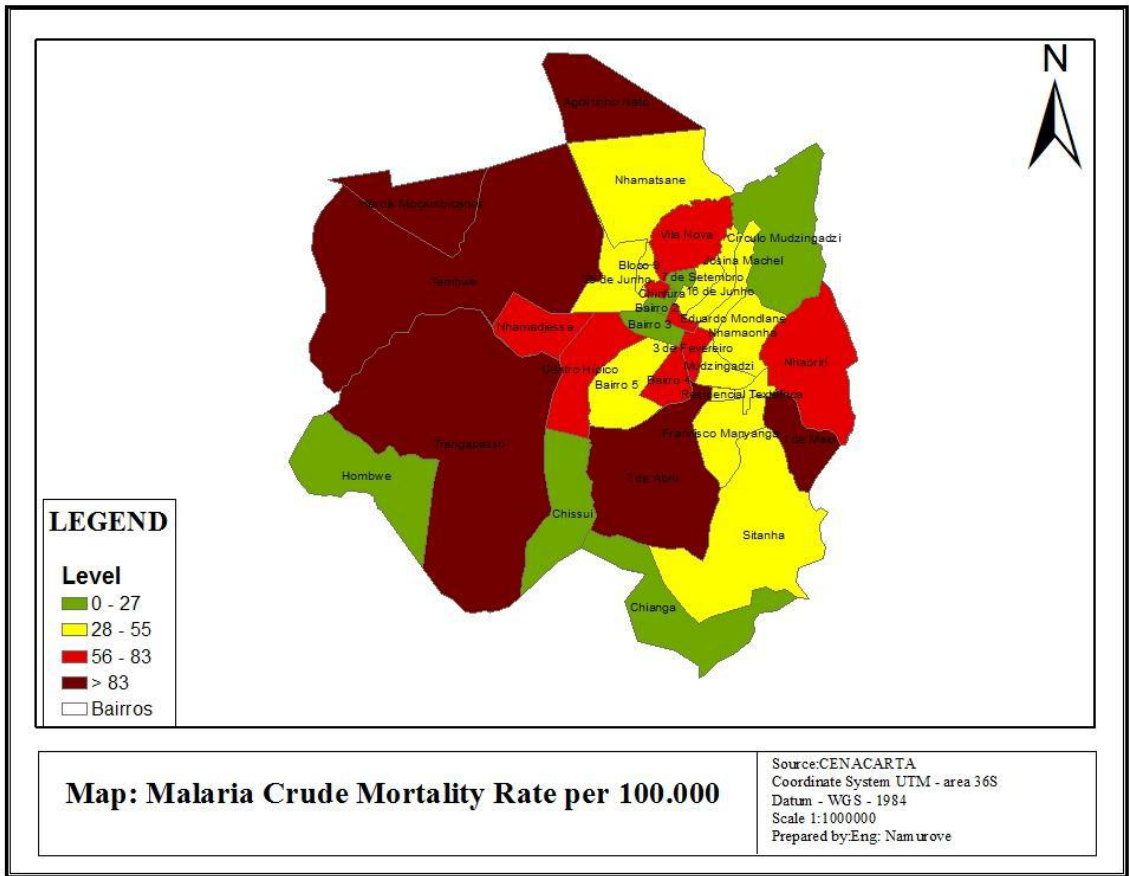
Map 8: Crude malaria mortality rate per residential area in Chimoio

4.3.7. The relationship between death by malaria mortality and climate

Fig. 22 shows monthly malaria deaths (left y axis) and malaria cases counts (right y axis) between 2010 and 2014. As expected, deaths peak between January and March, the period of malaria outbreaks. Previous work has that shown climate factors, such as temperature, precipitation and relative humidity, are determinant to malaria outbreaks, and consequently to the number of deaths caused by malaria. Indeed, malaria transmission occurs throughout the year with peaks between January and March.
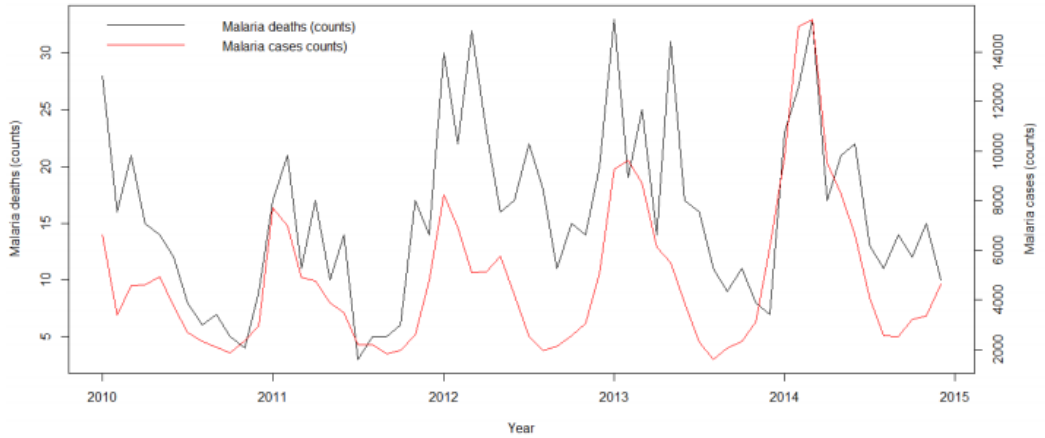
Figure 22: Times series of malaria deaths (solid black line, left y axis) and malaria cases (solid red line, right y axis) between 2010 and 2014.

Fig. 23 exhibits the temporal relationship between malaria death counts and those climatic factors. Temporal behaviour of deaths and its close relationship with climatic factors suggests the changes in the location might be properly modelled by intervention analysis as described by Jere and Moyo (2016) Indeed, Fig. 24 shows the level of malaria deaths reaches a peak every January. The level of deaths decays then to previous levels at a decreasing rate. Following Box and Tiao (1975), the specification $z_t = \frac{\delta_0}{1-wB} P_t$ where $|w| < 1$, B stands for the traditional time series backshift operator, $Bz_t = z_{t-1}$, and P_t denotes a pulse function such that $P_t = 0, t < t_0$ or $, t > t_0$ and $P_t = 1, t = t_0$, where t_0 is the moment of intervention (in this case the abrupt increase of malaria cases during malaria outbreaks every January illustrates an intervention with an abrupt temporary effect δ_0 that gradually decays at rate w with a return back to original or pre-intervention level.
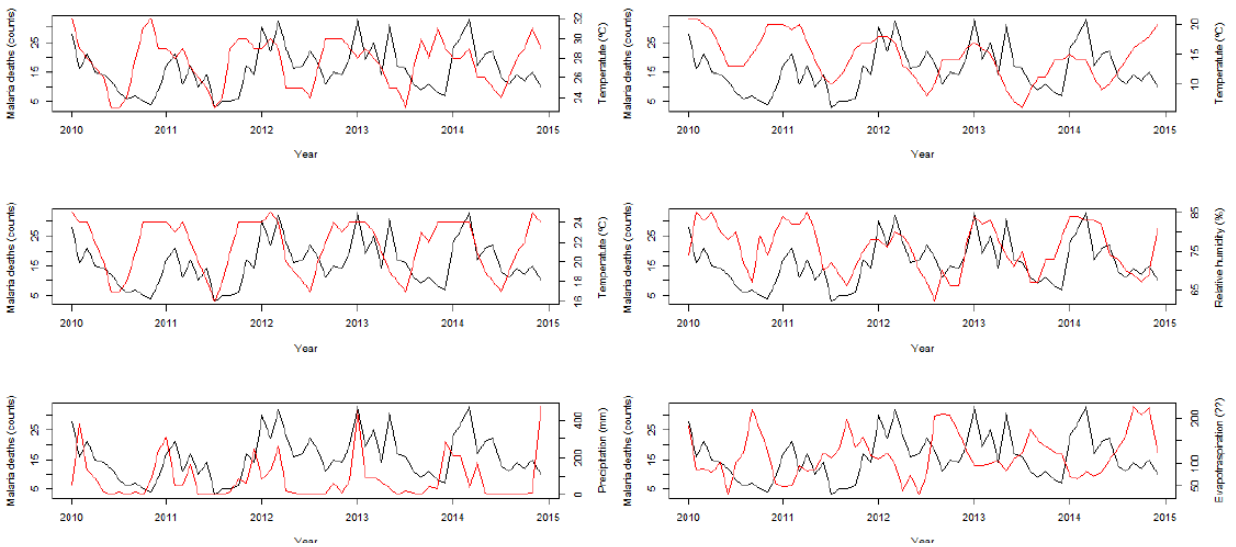
Figure 23: Times series of malaria deaths (solid black line, left y axis) and maximum, minimum and mean temperatures, relative humidity, precipitation and evapotranspiration (solid red line, right y axis) between 2010 and 2014.

A seasonal ARMA model, ARMA (2,0) (1,0)$_{12}$ fits these data, but it is not able to capture the sudden change occurring during malaria outbreaks, despite the three statistically significant parameters. Introducing the intervention effect described above where $P_t = 1, t = January, P_t = 1, otherwise$ allows for an improvement in the fit of death peaks. In particular, the seasonal ARMA model with intervention reduces root mean square error by almost 25%. (Figure 24).

4.4. Discussion and conclusions

Figure 25. The civil registration covers all registered malaria mortality cases from hospitals and from private residences. In this study, 78% of malaria deaths occurred in hospitals and the 22% at private residences. A previous study in Chimoio reported that in all-cause deaths, 86.1% of the deaths took place in hospitals and 11.7% at private residences (Ferrão et al.,

2016). Malaria deaths at private residences is two times greater than in all-cause of death in Chimoio. These disparities can probably be because malaria patients delay the treatment of the disease resulting in fatalities.
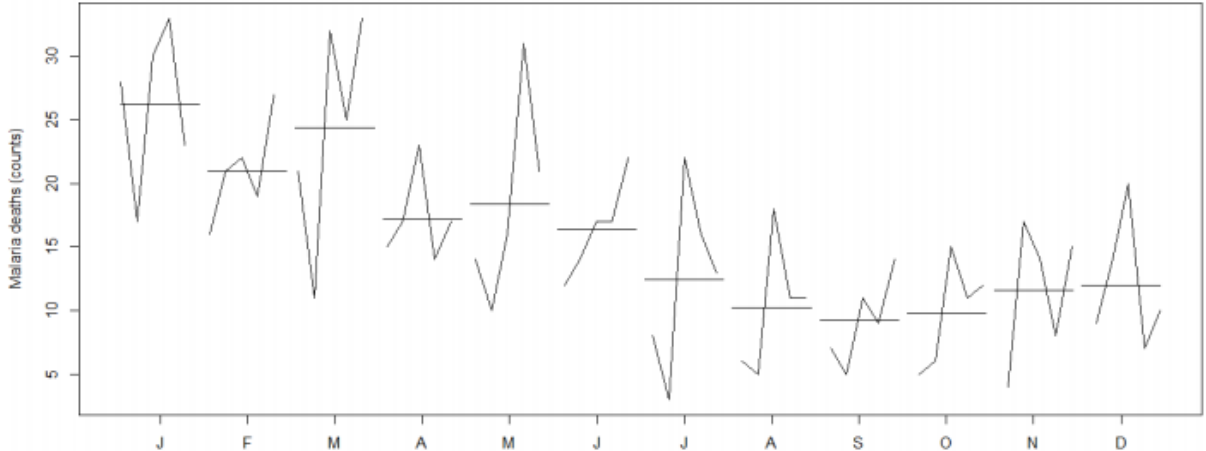
Figure 24: Month plot of malaria deaths. Solid broken line represents malaria deaths level and solid horizontal lines represent monthly means

Trend analysis indicates that in Chimoio, cases of deaths, and malaria deaths are increasing over the years, contrary to reports in Kwazulu Natal Ngomane and de Jager (2012), Malawi Kazembe, Kleinschmidt, and Sharp (2006), and Tanzania Selemani et al. (2016) that reported decreasing cases in malaria mortality. The malaria crude mortality rate per 100,000 was 51 per 100,000, higher than the national Mozambique figure of 42.75 for 2014 (Norheim et al., 2015). In terms of malaria mortality by gender, there was no difference between malaria deaths in females and males. Similar results were reported previously by (Kocurkova, 2000).

The results disagree with the findings in Kwazulu Natal and Sudan that reported higher mortality from malaria in males than in females Ngomane and de Jager (2012) and (WHO, 2007). There is evidence that suggests that given equal exposure, adult men and women are equally vulnerable to malaria except for pregnant women (WHO, 2007). In this study, 25% of malaria deaths occur at the age of 2, and 75% of malaria deaths at the age

43. The results are in concordance with a report on all causes of death carried out in Chimoio (Ferrão et al., 2016).

Age category 0 comprises 3% of the Chimoio population and recorded 9% of malaria deaths while, age category 1 - 4 comprises 13% of the Chimoio population, and recorded 25% of malaria deaths. This can be due to the lack of immunity in the first years of life. Similar results were reported in another seven African countries and Bangladesh Kazembe, Kleinschmidt, and Sharp (2006); Abdalla (2005), Streatfield et al. (2014); Kesteman et al. (2014); Otte im Kampe, Müller, Sie, and Becher (2015) and Deressa, Fantahun, and Ali (2007). From the age of 45 onwards the proportion of deaths by malaria and, all-cause mortality is almost the same.

Malaria mortally was significantly different between month and years. Similar results of seasonality were reported in Ethiopia and Burkina Faso Kazembe, Kleinschmidt, and Sharp (2006) and Deressa et al. (2007) and were related to climatic conditions. January, February and March presented the highest percentage of mortality from malaria decreasing thereafter. This peak period occurs two months after the rainy season onset.

There was no difference in times of death from malaria in Chimoio, and this result clearly contradicts a previous report on all-cause mortality in Chimoio, that indicates that peak mortality occurs between 3:00 to 4:00 AM (Ferrão et al., 2016). This result suggests that malaria deaths can occur at any time contrary, to other deaths that were found to peak from 3:00 to 4:00 AM in Chimoio.

The centre of town (low density) presents a low malaria crude mortality rate, 0 to 27 per 100,000 and the rural "Bairros" a very high crude mortality rate, over 80 per 100,000. This can be due to the fact that the centre has better health facilities and infrastructures which means the residents are better-off than in rural areas. Some rural neighbourhoods present low malaria mortality rates. This can be attributed to the fact those areas have poor accessibility and the residents carry out their burials without Civil Registration.

The onset of rain occurs in mid-November. This indicates that malaria occurrence has a strong association with rainfall six to eight weeks before, coinciding, with the malaria cycle's three components: (i) the growth of the *Anopheles* female mosquito from egg to adult to parasite transmission; (ii) the development of the *Plasmodium* parasites (gametocyte to sporozoites) that are able to infect humans; and (iii) the incubation period in the human host from infection to malaria symptoms (Streatfield et al., 2014). Thus, malaria occurrence peaks can be expected 45 to 60 days after the onset of rain. Similar results were also found in Mozambique (World Health Ranking, 2016) and South Africa (Ngomane & de Jager, 2012). Increased precipitation can provide more breeding sites for mosquitoes, however excess rain can also destroy breeding sites (Sewe et al., 2015).

ARMA $(2,0)(1,0)_{12}$ fitted the data well although it was not able to capture the sudden change occurring during malaria outbreaks. Introducing the intervention effect allowed for a better fit of death peaks and the seasonal ARMA model with intervention reduced root mean square error by almost 25%. Other studies reported ARIMA (2,1,1) in Zambia, ARIMA (1,0,0) in Burundi (Gomez-Elipe et al., 2007), and India (Kumar et al., 2014) with comparable results.

Besides the possibility that the malaria mortality was under-reported, especially in the rural areas, another limitation of this study is that it did not take into consideration malaria intervention factors such as bed net distribution and improvement of health coverage. Despite the limitations, one great strength of the study is that this is the first specific study in malaria mortality using civil registration data in Chimoio. More data from other additional data from other parts of the country are needed to generalize the results to the national level.

Malaria mortality is increasing in Chimoio and strong and appropriate actions are needed to counteract the malaria deaths scenario in Chimoio. There is no difference in the malaria mortality rate between males and females. Children between 1 – 4 years old are 13% of Chimoio population,

but represent 25% of malaria mortalities. The last 3 months of the rainy season (January, February and March) present more malaria mortality cases than the dry season. Urban "Bairros" in the centre of town have lower malaria crude mortality rate than the rural "Bairros". More studies should be carried out for malaria eradication in the municipality.
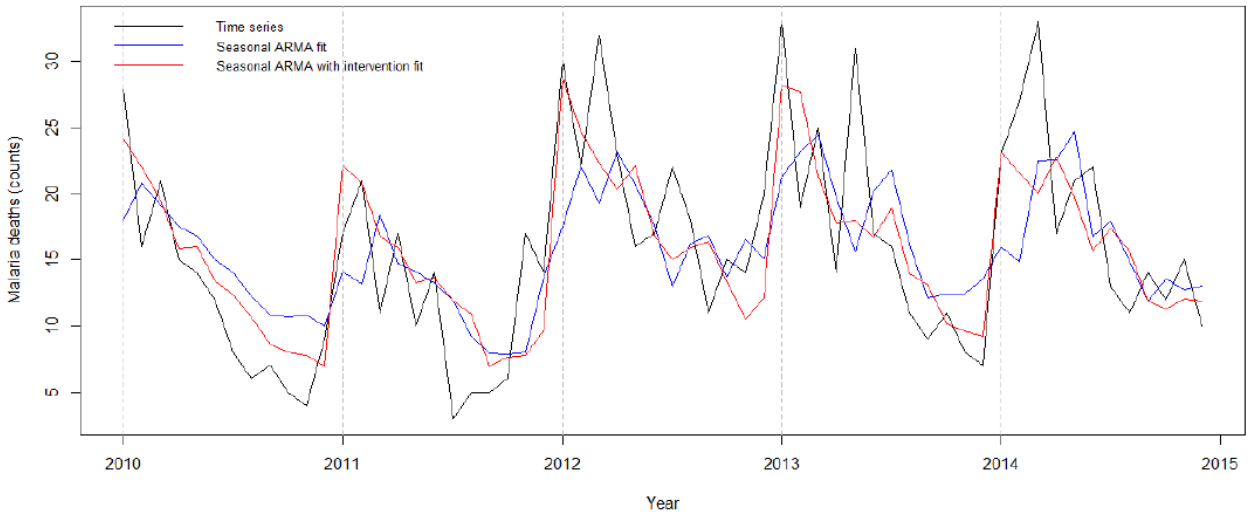
Figure 25: Times series of malaria deaths (solid black line) and fitted values of seasonal ARMA(2,0)(1,0)$_{12}$ without (solid blue line) and with (solid red line) intervention effect.

5. Mapping and modelling malaria risk areas using climate, socio-demographic and clinic variables in Chimoio, Mozambique (*)

Abstract

Background

Malaria disease continues to be one a major public health concern in Africa. Around 3.2 billion persons are still at risk to contract malaria in the World and, in 2015. Approximately 80% of deaths caused by malaria are concentrated in only 15 countries, mostly in Africa. These high-burden countries have achieved lower than average reduction in malaria incidence and mortality and Mozambique is among them. Malaria eradication is therefore, one of Mozambique's main priorities. Few studies on malaria were carried in Chimoio and there is no malaria map risk of the area. This map is important in order to identify areas at risk for Public Precision Health approach. By using GIS-based spatial modelling techniques, the research goal of this article is to map and model malaria risk areas, using climate, socio-demographic and clinic variables in Chimoio, Mozambique.

Methods

A 30m*30m Land sat image, ArcGis 10.2 and, BioclimData were used. A conceptual model for spatial problems was employed to create the final risk Map. The risks factors used were: mean temperature, precipitation, altitude, slope, distance to water bodies, distance to roads, NDVI, land use and land cover, malaria prevalence and, population density. Layers were created in a raster dataset. For the class values comparison between layers, numeric values to classes within numeric each map layers were assigned. Ranks were performed to the input dataset with different weights according to their suitability. The combination of the reclassified outputs of the data was carried out. Chimoio presents 96% with moderate risk and 4% with high-risk areas.

The map depicts that the central and south-west "Bairros" namely Centro Hipico, Trangapsso, Bairro 5 and 1º de Maio have a high-risk, while the rest of the "Bairros" having a moderate risk of malaria. All the Chimoio population is at risk to contract malaria Precise estimation of malaria risk has important implications in Precision Public Health, and the planning of effective control measures such as right time and place to spray for vector combat, distribution of bed nets and other control measures.

5.1. Research objective

By using spatial modelling techniques with GIS, the research goal is to map and model malaria risk areas, using socio-demographic, climate, and clinical variables in Chimoio, Mozambique.

5.2. Materials and Methods

5.2.1. Study area

Chimoio is a municipality located in Manica Province in the central region of Mozambique (-19º6´59S, 33º28´59E). The population of Chimoio is presently estimated to be 324816 (INE, 2016). The area is 174 km² at an altitude that varies between 513 and 786 meters.

The Chimoio climate has a warm temperature with dry winters from April to July, hot and dry summer from August to October and, hot and humid summer from November to April.

In terms of Mozambique agro-ecological zones Chimoio lies in the region 4, midland areas of the central region (IIAM, 2012).The major economic activities are: agriculture production, livestock, general trading, metallurgical industry, food industry, tourism, telecommunication, banking and insurances and energy supply (Governo de Manica, 2012).

5.2.2. Material

30m*30m Landsat image.

ArcGis 10.2.

Bioclimatic (1950 to 2000) (WorldClim).

5.2.3. Methods

Figure 26 presents the schematic representation of data flow and analysis for malaria risk map for Chimoio.
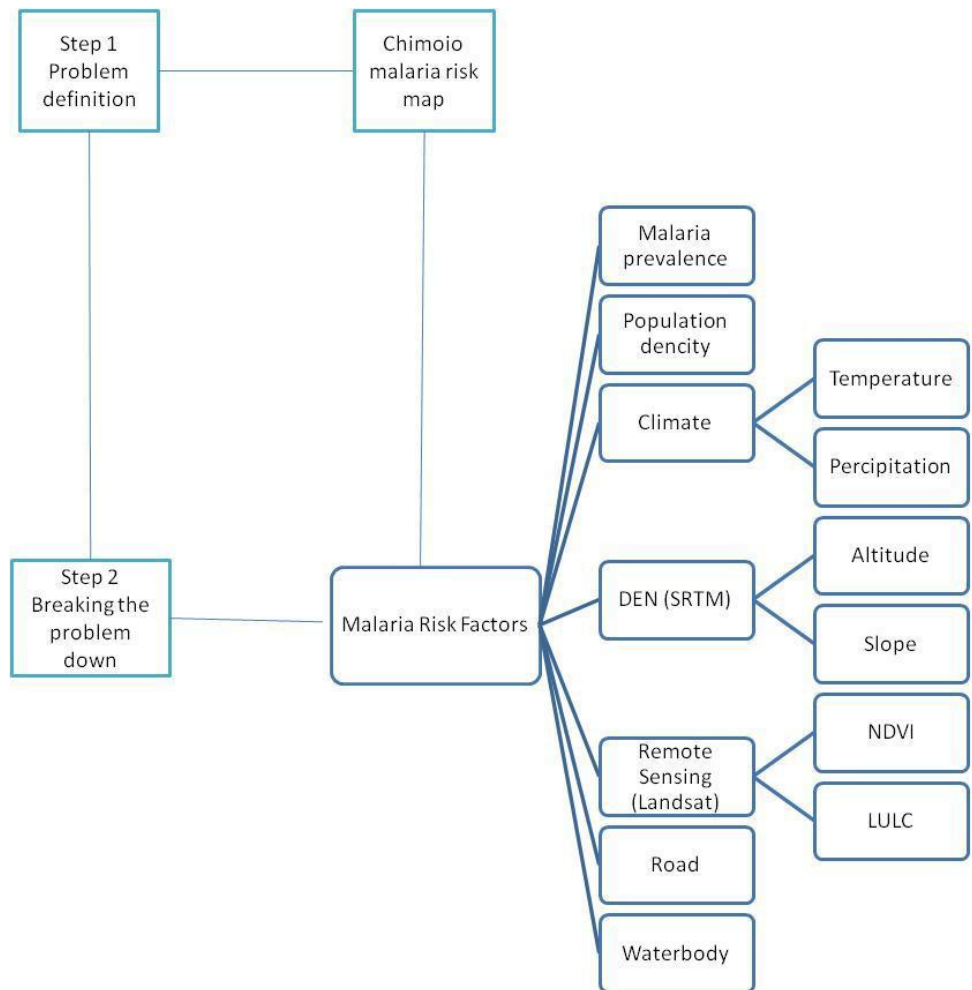
Figure 26: schematic representation of data flow and analysis for malaria risk map for Chimoio

The conceptual model to solve spatial problems was used to create the Chimoio Map risk (ArcMap, 2016b).

The process involved the following steps:

Step 1	Step 2	Step 3	Step 4	Step 5
State the Problem	Problem breaking down	Analytical hierarchical process	Analysis performing	Result verification.
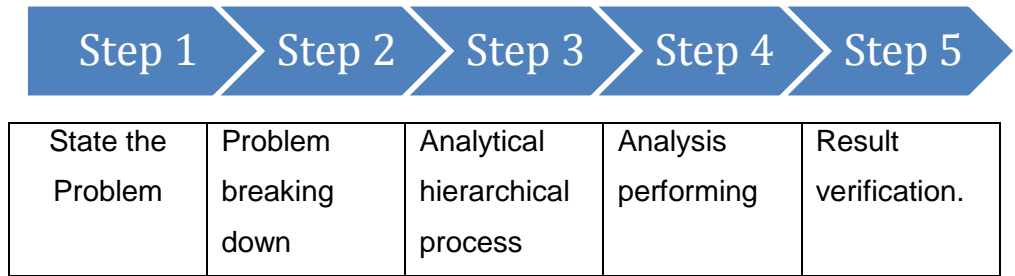
Step 1. In this stage the problem was stated and was:

Mapping malaria risk for Chimoio

Step 2. Problem breaking down

Table 7 presents the malaria factors, their weight, classification and the rationale for the classification adapted from literature from Zimbabwe, Tanzania and Latin America (Chikodzi (2013); Fuller, Troy, and Beier (2014); Mulefutu (2016); Alimi, Fuller, Herrera, Herrera, and Qinone (2016).

For this stage the input data set or malaria risk factors were the following: average temperature (Tmean), precipitation (PP), altitude (Alt), slope (SLP), distance to water body (DTWB), distance to road (DTR), Normalised Difference Index (NDVI), land use and land cover (LULC), malaria prevalence (Mal prev) and population density (pop dens).

Average temperature (Tmean)

Long-term minimum and maximum temperature was extracted from the Bioclim (WorldClim) and the average temperature calculated. In this study average temperature below 22°C were classified as low risk for malaria transmission, while those from 22°C-28°C were classified as high-risk for malaria transmission and temperatures above 32°C were classified as of moderate risk.

Precipitation (Prec)

Precipitation data were extracted from the Bioclim Data. In the study, areas that received the precipitation less than 450 millimetres were classified as low risk, those that received a precipitation between 450 to 700 millimetres

were classified as a moderate risk, and the ones over 700 millimetres were classified as having high-risk.

Table 7: Classification, weighing and rationale of malaria risk factors

Factor	Weight	Class	influence	Rationale
Tmean	0.224	< 22°C	Low	Bellow 22°C sporogony is not completed
		> 28 °C	Moderate	Over 28°C sporogony is affected
		22 - 28oC	High	22 - 28°C ideal for incubation
Precipit	0.208	<450 mm	Low	< 450 mm is arid and mosquitoes will have
		450 – 700 mm	Moderate	difficulties to survive > 700 mm is wet and .
		> 1000 mm	Low	inappropriate for mosquitoes breeding
Altitude	0.123	< 200 m	High	< 200 m low land and high risk of vector
		200 – 500 m	Moderate	proliferation, 200 to 500 m upland
		>500 m	Low	>1000 m highlands and low risk of mosquitoes survival
Slope	0.082	0 – 5°	High	Appropriate conditions for water stagnation
		5 – 15°	Moderate	
		>15°	Low	>15° inappropriate for water stagnation
LULC	0.082	crop, grass and water bodies	High	Suitable for mosquitoes proliferation
		shrubs and mosaic vegetation	Moderate	
		forest, bare, urban	Low	Not suitable for mosquitoes breeding
DTWB	0.123	< 500 m	High	The mosquito fly range is 1500 m.
		500 – 1500 m	Moderate	Less than 500 m from WTBD
		>1500m	Low	the risk of malaria is high
DTR	0.038	< 2.5 Km	Lowe	< 2.5 km walking distance to clinic
		2.5 – 5 Km	Moderate	2.5 to 5 km clinic can be reached by bicycle
		> 5 Km	High	< 5 Km interventions are difficult
Pop dens	0.051	< 6000 pers/Km2	Low	High populated area have higher risk
		6000 – 9000pers/m2	Moderate	since mosquitoes have abundant
		>9000 pers/km2	High	blood meal close by.
Malar prev	0.051	< 14%	Low	High prevalence areas have higher
		14 – 21%	Moderate	risk since mosquitoes do not have
		> 21%	High	to travel long for blood meal
NDVI	0.047	-0.2777 – 0	Low	
		0 – 0.255	Moderate	
		0.255 – 1	High	High NDVI is related to high malaria risk

Altitude (Alt)

A digital elevation model at 30*30 m resolution was used to estimate the altitude. Areas below 200 m (lowlands) were classified as being the highest risks for malaria occurrence, areas between 201 to 500 metres

(uplands) were classified as having moderate risk and over 500 m (midlands) were classified as having the least risk of malaria exposure.

Slope (SLP)

The slope was derived from the 30m*30m digital elevation model, obtained from the spatial analysis tool from ArcGis. In the study, areas of from 0 to 5 degrees were classified as being high-risk, those from 5 to 15 degrees were classified as of moderate risk, while those over 15 degrees were classified as having the lowest risk.

Land cover and Land-use (LCLU)

Land-use and land cover data were retrieved from the most recent (April 2016) the 30m*30m Landsat satellite image (GIS Geography, 2016). The image was reclassified into different LULC classes. Areas with crops, grass and water bodies were classified as having the high-risk of malaria. Areas such as shrubs and mosaic cover vegetation were classified has having a moderate risk of malaria, while the areas with forest, bare, and urban settlements were classified as having the lowest risk of malaria.

Distance from Roads (DTR)

Euclidean distance to nearest road was calculated using ArcGIS, classifying a 2016, 30m*30m Landsat image. Distances of places from the road were then calculated using the measuring distance function in ArcGIS software. In the study, places over 5 km from the roads were classified to be at highest risks to malaria, those between 2.6 km and 5 km from roads were classified to be of moderate risk and those less than 2.5 km from the roads were classified as having the lowest risk of malaria infection.

Distance to Water Bodies (DTWB)

Distance to the nearest water body were calculated with ArcGIS, classifying a 2016, 30m*30m Landsat image for water and undefined. Distance from water bodies were then calculated using the measurement distance function in ArcGIS software. In this study, areas with less than 500 metres from a water source were classified as being an high-risk area, those between 501 to 1500 metres were classified as moderate risk areas while

those above 1500 metres from water bodies were classified as being of low risk to malaria.

Population density (pop dens)

Data on population density were calculated from the National census population projections for 2014. In the study places over 9000 people/ km^2 were classified to be at highest risks to malaria, those between 6001 to 9000 people/ km^2, were classified to be of moderate risk, and those less than 6000 person/ km^2 were classified to be as low risk of malaria infections.

Malaria Prevalence (Mal prev)

Malaria cases diagnosed by health personnel as described elsewhere Ferrão et al. (2016) were used. In the study over 21% prevalence were classified as being the highest malaria risk areas, between 14 and 21% were classified as being of moderate malaria risk and, less than 14% were classified as having the lowest risk of malaria occurrence.

Normalized Difference Vegetation Index (NDVI)

The NDVI was extracted from a Landsat image. The NDVI map has been grouped into three principal categories: -0.288 to 0, and classified as moderate risk, 0 to 0.255 classified as moderate risk and 0.255 to 0.986 classified as high risk was classified as being of high malaria risk (Ray, 2012).

Step 3: Analytical hierarchical process (AHP)

The analytical hierarchical process is a method that uses hierarchical structures to represent a problem and makes judgments based on expert panels to derive priority scales (Saaty, 2008). In this step, the input datasets were explored to understand their content and attributes within and between data sets are more important for solving the stated problem and searching for trends in the dataset (Ray, 2012).

To obtain the weights for each individual factor for the map the following step was as follows:

a) Formulation of a pair-wise comparison matrix for each of the input variables.

b) Establishment of the relative weights of each input variable.

c) Checking for consistency in the pairing process (Chikodzi, 2013).

a) The fundamental scale to help in, the weighting process was used to develop the pair-wise comparison matrix (Table 8).

Table 8: Fundamental scale for pair-wise comparison matrix

Extremely less important	1/9
	1/8
Very strong less important	1/7
	1/6
Strongly less important	1/5
	1/4
Moderately less important	1/3
	1/2
Equal importance	**1**
	2
Moderately more important	3
	4
Strongly more important	5
	6
Very strong more important	7
	8
Extremely more important	9

b) Establishment of the relative weights of each input variable

Indeed the malaria risk factors don't have the weight and role in the modelling of the final malaria risk map. Therefore, in order to designate the importance of each variable, they were weighted using a pair-wise comparison method from the AHP template worksheet (Bernard, 2012).

c) Checking for consistency

After computing the pair-wise matrix and, to measure if the derived matrix was derived at an acceptable level, a consistency test was calculated. For this study, a consistency index less than 10% was considered good enough. (Chikodzi, 2013). A result above 10%, the matrix was revised until the indication of an acceptable level of acceptance. (Saaty, 2008).

Step 4: Performing analysis

The spatial analysis depicted in Figure 27 was performed.

-
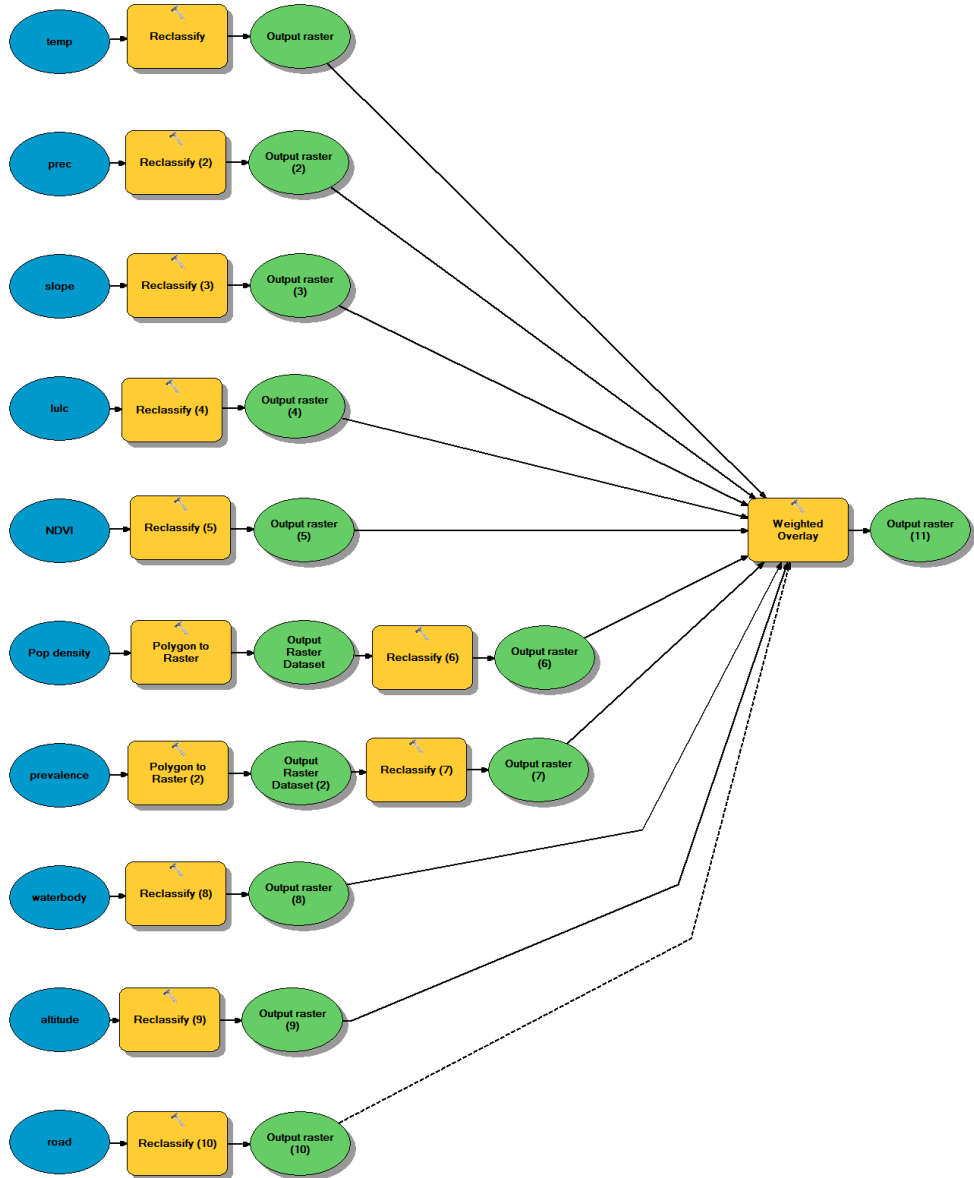
Figure 27: spatial analysis fluxogram

Layers for Tmean, PP, Alt, SLP, DTWB, DTR, NDVI, LULC, malaria prevalence (%) and population density (person/km2) were created in a

raster dataset. To compare the values of the classes between layers, numeric values to classes within each map layer was assigned from 1 to 3 being low, moderate and high-risk respectively. The reclassification was carried out and all measures had the same numeric scale giving them the same level of importance.

For the suitability model, reclassified outputs of Tmean, PP, Alt, SLP, DTWB, DTR, NDVI, LULC, Mal prev, Pop dens were combined. The final suitability map was produced by combining all the maps together. Weights were assigned at the same time as combining the suitability maps (ArcMap, 2016a)

Step 5: Verifying the result

After the result of the spatial analysis the correctness of the findings were discussed with experts and places visited.

5.3. Results

Table 9 shows the 10 x 10 comparison matrix of malaria risk factors used in the study and a value of 1 for example, means that factors under comparison have the same weight, and they affect the malaria occurrence equally. A value of five would mean the factor in the column is five times more important in the malaria risk occurrence than the comparison in the row.

Table 9: 10 x 10 Comparison Matrix of Risk Factors used in the study

	Tmean	Prec	Alt	Slope	LULC	DTWB	DTR	Pop den	Prev	NDVI
Tmean	1.00	1.00	3.00	4.00	4.00	2.00	6.00	4.00	4.00	4.00
Prec	1.00	1.00	3.00	4.00	3.00	1.00	7.00	4.00	4.00	4.00
Alt	0.33	0.33	1.00	3.00	3.00	1.00	4.00	2.00	2.00	3.00
Slope	0.25	0.25	0.33	1.00	1.00	2.00	1.00	3.00	1.00	1.00
LULC	0.25	0.33	0.33	1.00	1.00	2.00	2.00	5.00	1.00	1.00
DTWB	0.50	1.00	1.00	0.50	0.50	1.00	3.00	4.00	4.00	2.00
DTR	0.17	0.25	0.25	1.00	0.50	0.33	1.00	1.00	1.00	2.00
Pop den	0.25	0.50	0.50	0.33	0.20	0.25	1.00	1.00	2.00	4.00
Prev	0.25	0.50	0.50	1.00	1.00	0.25	1.00	0.50	1.00	2.00
NDVI	0.25	0.25	0.33	1.00	1.00	0.50	0.50	0.25	0.50	1.00

The weights of each factor used for the spatial model to produce the malaria risk map are presented in table 8. Tmean (22.4%) and precipitation (20.8%) presented the highest weights followed by DTWB (12.3%) and altitude (10.4%), LULC (8.2%), slope (7.3%), pop dens and malar prev (5.1%), NDVI (4.7%) and DTR (3.8%). The consistency index for the pair-wise matrix was 9%.

The special model to produce the malaria risk map formula was:
[(Tmin*0.224) + (precipitation*0.208) + (altitude*0.104) + (slope*0.073) + LULC*0.082) + (DTWB*0.123) + (DTR*0.038) + (Pop dens*0.051) + (Mal prev*0.051) + (NDVI*0.047)]

Map 9 presents the malaria prevalence, slope, temperature, NDVI and LU/LC. In terms of malaria prevalence, Chimoio presents 42% of the area with low risk, 17 % with moderate risk and, 41% with high-risk areas. It is possible to see that the prevalence risk of malaria varies spatially in the Chimoio Municipality. For slope, Chimoio presents 2% of the area with low risk, 52 % with moderate risk and 46% with high-risk areas. For average temperature, Chimoio presents 100% of moderate risk areas.

For NDVI Chimoio presents 5% of the area with low risk, 12% with moderate risk and 88% with high-risk areas. For LU/LC Chimoio presents 39% of the area with low risk, 4% with moderate risk and 43% with high-risk areas.
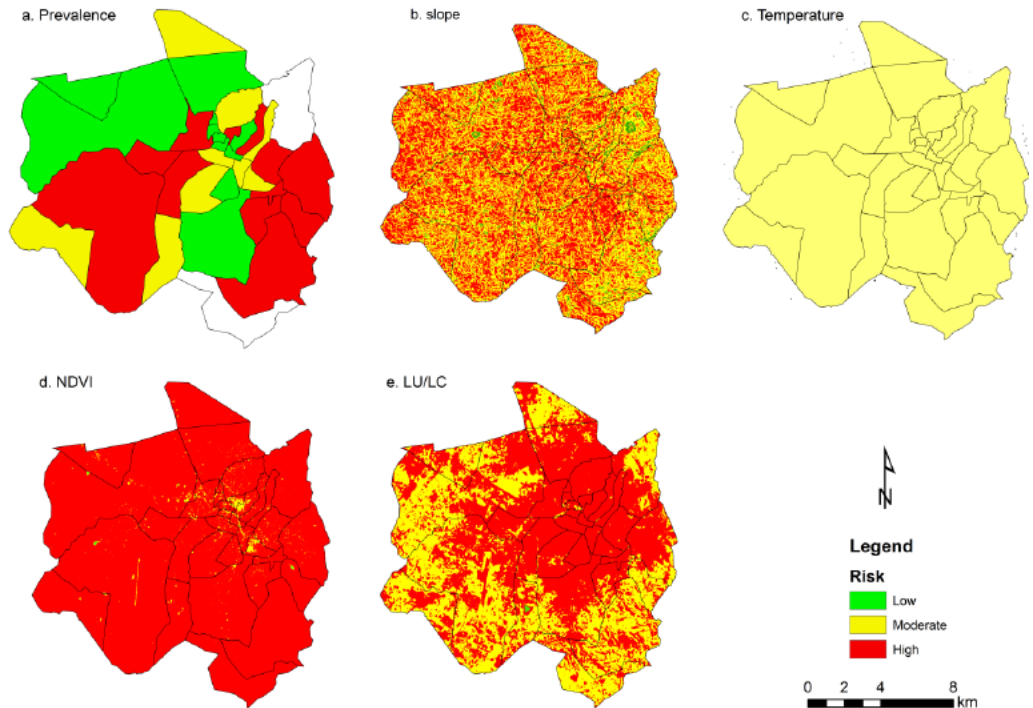
Map 9: Malaria risk for malaria occurrence. a) Prevalence b) Slope c) Temperature d) NDVI e) LULC

Source: (Ferrão et al., 2016)

Map 10 presents the precipitation, altitude, distance to a water body (DTWB), distance to road (DTR), and population density (person/km^2). For precipitation, Chimoio presents 100% moderate risk areas. For altitude, Chimoio presents 34% with moderate risk and, 66% with high-

risk areas. For DTWD, Chimoio presents 44% of the area with low risk, 40 % with moderate risk and, 16% with high-risk areas.

For DTR, Chimoio presents 40% of the area with low risk, 43% with moderate risk and 17% with high-risk areas. For population density, Chimoio presents 92% of the area with low risk, 5% with moderate risk and 3% with high-risk areas.
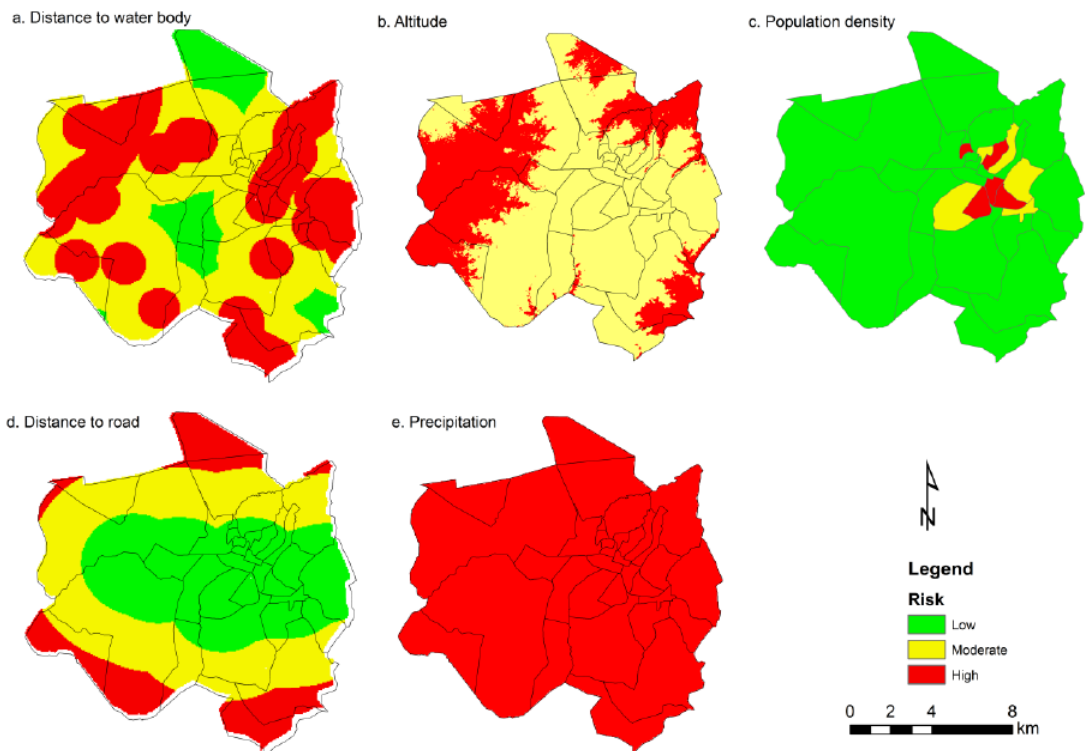
Map 10: Malaria risk for malaria occurrence. a) DTWB, b) Altitude, c) Population density, d) Distance to road, e) Precipitation

Source: (Ferrão et al., 2016)

Map 11 presents the Chimoio map risk for malaria after the consolidation of the weighted malaria risk factors used in the present study. Chimoio presents 0% of the area with low risk, 96% with moderate risk and 4% with high-risk areas. The Map depicts that the central and

south-west "Bairros" namely Centro Hipico, Trangapsso, Bairro 5 and 1o de Maio while the rest of the "Bairros" have a moderate risk of malaria.
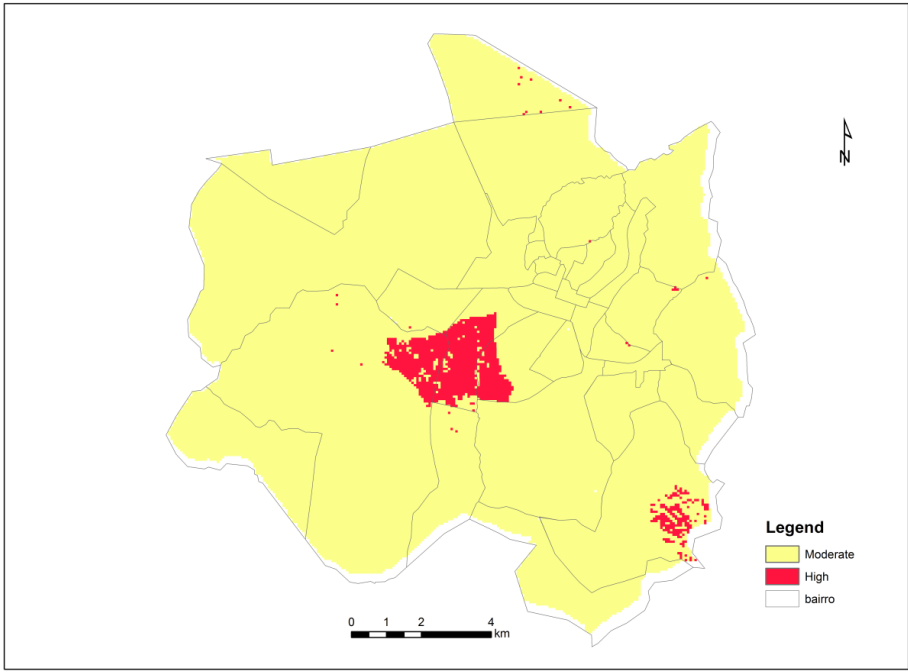
Map 11: Chimoio malaria risk map

5.4. Discussion

In this study it was determined that climatic factors mean temperature and precipitation presented the highest weights followed by DTWB, 12.3% and altitude 10.4% and the other climatic factors presented the least weights. The results are similar to other studies in Mozambique and the World Fuller et al. (2014) (Chikodzi (2013); Fuller et al. (2014) (Hagenlocher & Castro, 2015) Mulefutu (2016) except in Kenya Alimi et al. (2016).

The Mozambique risk Map produced by other authors are similar with the findings of this study Fitfortravel (2016); Traveller start (2016); MARA (2015); Abellana et al. (2008).

The malaria risk map produced by the study differs in many ways with other available models. The area is small (174 km^2) and it used ten risk factor variables. It also uses high, sharp and fine spatial and temporal resolutions of risk factors and includes climate variable data that impacts in the factors that affect the mosquito proliferation. It also includes human-induced variables such as distance from roads and LCLU changes and, clinical data. The model is reasonably scaled to present variance in malaria risk at micro-scale level.

A relatively small number of studies have included ten risk factor variables in geostatistical models for malaria risk mapping. Similarly, this approach can also be applied for modelling and prediction of other environment driven diseases.

5.5. Conclusion

The weights used in this map are consistent with several studies and the map is reliable. The entire population of Chimoio his at a risk to contract malaria and, 96 % have a moderate risk and 4 % high-risk. Trees in the Chimoio streets and households are probably resting areas for mosquitoes.

Precise estimation of malaria risk has important implications in Precision Public Health, and the planning of effective control measures such as the right time and place to spray for vector combat the right time to prune the trees

from the trees and homesteads, distribution of bed nets, correct site to build a water body, the correct time and place for drainage and other relevant activities for malaria control and eradication.

The study demonstrated the importance of the possible use of GIS and remote sensing in predicting, mapping and modelling the malaria risk in Chimoio municipality. More studies should be carried out such as bed net usage, the relationship between household presence of trees and malaria and others.

6. Discussion of Results and Conclusions

The focus of this study was the socio demographic characterization of malaria patients and modelling malaria and mortality trends for Precision Public Health and the major evidences are:

Malaria is increasing in Mozambique particularly in Manica Province and Chimoio Municipality and annual average incidence of malaria was 20.5 %. The evidence agrees with data from the Ministry of Health that claims that the first quarter of 2017 Mozambique registered over two million cases of malaria against 1,873,303 cases in the same period of 2016. This tendency contradicts with the decreasing tendency in the neighbouring countries such as Malawi Kazembe, Kleinschmidt, and Sharp (2006) and South Africa (Ngomane & de Jager, 2012). Swaziland almost eradicated malaria in 2016 (Moonasar et al., 2016). Mozambique faces challenges to combat malaria such as inadequate health infrastructures affecting the distribution and availability of treatment, limited funds for indoor residual spraying due to financial crises, limited use and logistical capacity in the distribution of bed-nets and their misuse, scarcity of human resources for health impairing the quality of health care provided at health facilities (WHO, 2015b).

Malaria occurrence and malaria mortality varies over time. Malaria transmission occurs throughout the year with peaks between weeks 1 to 12. The onset of rain occurs in mid-November. This indicates that malaria occurrence has a strong association with rainfall six to eight weeks before, coinciding, with the malaria cycle three components: (i) the growth of the *Anopheles* female mosquito from egg to adult to parasite transmission; (ii) the development of the *Plasmodium* parasites (gametocyte to sporozoites) that are able to infect humans; and (iii) the incubation period in the human host from infection to malaria symptoms (CDC, 2014b), (Crutcher & Hoffman, 1996). Thus, malaria occurrence peak can be expected 45 to 60 days after the onset of rain. Similar results were also found in Mozambique (Zacarias & Andersson, 2010) and South Africa (Ngomane & de Jager, 2012). Increased

precipitation can provide more breeding sites for mosquitoes, but excess rain can also destroy breeding sites (Bai et al., 2013).

Malaria occurrence and mortality varies in space, rural areas and suburbs presents more malaria and malaria mortality cases than the urban areas. The results are in concordance with (IDS, 2013); (Arroz, 2016) that reported that the prevalence of malaria in Maputo City is 2 % while in Zambezia Province it is 55 %. The non-climatic malaria determinates such as poverty increase, poor sanitation, crowdedness, lack of access to health care, low education, type of house construction, and living conditions also plays a role although minute. Other studies report the same pattern of findings (WHO, 2015a).

In terms of gender, there is no overall difference (p > 0.05) between women (51%), and men (49%), between adult women (52%) and adult men (48%), or female children (50.3%) and male children (49.7%). This evidence contradict most research Norheim et al. (2015) and Abdalla (2005), the chances of getting malaria are the same (gender equality) in Chimoio. This can be explained by the high malaria incidence in the area, which puts the entire population at risk.

There was a difference between children under 5, (48%) and population over five (52%). Children under five comprise 17% of the population of Chimoio but accounted for 48% of the malaria cases, almost three times more. This disproportion is also reported by other authors (Ferrão et al., 2016). This is probably due to the fact that children under five years of age have little immunity to the malaria parasite.

In terms of malaria cases related to population density, there was a medium positive correlation r = 0.407 between the population density and malaria incidence and the R^2 value indicates 0.165, which implies that 16.5% of malaria cases are attributed to population density. The extremes of both low and high population density modify malaria transmission and have

profound consequences for estimates of Chimoio´s Mozambique public health burden.

The ARIMA model developed in this study, ARIMA (2,1,0) (2,1,1)$_{52}$, attempted to provide an easy technique to predict the expected number of malaria cases per week based on past observed cases.

Cross-correlation analysis showed that mean temperature, and precipitation presented significantly lagged correlations with malaria cases. A regression model of a differenced (lag1 and lag 12) Box-Cox transformation (λ = -0.5) of malaria cases on lag 1, 2 and 3 of weekly malaria cases and lag 6 and 7 of weekly mean temperature and lag 12 of precipitation was found as the best prediction model for weekly malaria cases.

The ARIMA model was also used for malaria forecasting in South Africa (Ngomane & de Jager, 2012), Zambia (Jere & Moyo, 2016), Burundi (Gomez-Elipe et al., 2007) and India (Kumar et al., 2014) with comparable results.

Temperature affects the development of malaria; the parasite does not develop below 18 C and over 40 °C (Otte im Kampe et al., 2015) and (Deressa et al., 2007). The highest proportion of vectors surviving the incubation period is observed at temperatures between 28–32 °C (Gomez-Elipe et al., 2007). In this study, the average maximum temperature recorded was 26.8 °C ranging between 22.3–31°C suggesting that Chimoio is an ideal location for malaria breeding. In this study, the mean temperature was found to be a significant predictor for malaria occurrence, similar to studies carried out in South Africa (Ngomane & de Jager, 2012) and Burundi (Gomez-Elipe et al., 2007).

Relative humidity (RH) also plays a role in malaria episodes, and mosquitoes become more active when humidity rises. If the average monthly relative humidity is below 60%, it is believed that the life of the mosquito is so short that very little or no malaria transmission is possible (Yamana & Eltahir, 2013). Relative humidity in this study was 72.1% and only four weeks of the year presented RH less than 60% implying that humidity does not restrict

malaria occurrence in Chimoio. Similar results were also reported in a study in Ghana (Krefis et al., 2011).

Wind speed was found to be a significant influence in malaria occurrence in Nigeria (Omonijo et al., 2011). In this study, the wind speed was not found to be a significant predictor for malaria occurrence in Chimoio. Visibility was not found to be a significant predictor for malaria occurrence consistent in studies in Nigeria (Omonijo et al., 2011) and South Africa (Ngomane & de Jager, 2012). Most *Anopheles* mosquitoes are crepuscular (active at dusk or dawn) or nocturnal (active at night) (CDC, 2014b).

The *R*-square in this study was 0.725 implying that 72.5% of the variance in malaria occurrence can be explained by variance in the predictive variables. In Burundi, 82% was reported (Gomez-Elipe et al., 2007). The results are higher than a study in Nigeria that found 66% and lower than the (Global Fund, 2015) that indicated that 90% of malaria cases are related to environmental factors.

The malaria crude mortality rate per 100,000 is 51 per 100,000 in Chimoio, higher than the national Mozambique figure of 42.75 for 2014 (Norheim et al., 2015). In terms of malaria mortality by gender, there was no difference between malaria deaths in females and males. Similar results were reported previously by (WHO, 2007). The results disagree with the findings in Kwazulu Natal and Sudan that reported higher mortality from malaria in males than in females (Ngomane & de Jager, 2012).

Malaria mortality increase contrary to claims of the Ministry of health of decreasing tendencies. This could result from the fact that the Ministry of Health bases their results only on data from clinics while this study gathered data from the Civil Registration which includes data from clinics and deaths occurring at private houses. There is evidence that suggests that given equal exposure, adult men and women are equally vulnerable to malaria except for pregnant women (Ngomane & de Jager, 2012).

Twenty five percent of malaria deaths occur at the age of 2, and 75% of malaria deaths at the age 43. Age category 0 comprises 3% of the Chimoio population and recorded 9% of malaria deaths while, age category 1 - 4 comprises 13% of the Chimoio population, and recorded 25% of malaria deaths. This can be due to the lack of immunity in the first years of life. Similar results were reported in another seven African countries and Bangladesh (Kazembe, Kleinschmidt, & Sharp, 2006), (Abdalla, 2005); (Streatfield et al., 2014); (Kesteman et al., 2014) and (Deressa et al., 2007). From the age of 45 onwards the proportion of deaths by malaria and all-cause mortality is almost the same.

Malaria mortally was significantly different between month and years. Similar results of seasonality were reported in Burkina Faso and Ethiopia (Kazembe, Kleinschmidt, & Sharp, 2006) and were related to climatic conditions. January, February and March presented the highest percentage of mortality from malaria, decreasing thereafter. This peak period occurs two months after the rainy season onset.

There was no difference in times of death from malaria in Chimoio, and this result clearly contradicts a previous report on all-cause mortality in Chimoio, that indicates that peak mortality occurs between 3:00 to 4:00 AM. This result suggests that malaria deaths can occur at any time, contrary to other deaths that were found to peak from 3:00 to 4:00 AM in Chimoio.

The centre of town (low density) presents a low malaria crude mortality rate, 0 to 27 per 100,000 and the rural "Bairros" a very high crude mortality rate, over 80 per 100,000. This can be due to the fact that the centre has better health facilities and infrastructures which means the residents are better-off than in rural areas. Some rural neighbourhoods present low malaria mortality rates. This can be attributed to the fact those areas have poor accessibility and the residents carry out their burials without Civil Registration.

ARIMA $(2,0)(1,0)_{12}$ fitted the data well although it was not able to capture the sudden changes occurring during malaria outbreaks. Introducing

the intervention effect allowed for a better fit of death peaks and the seasonal ARIMA model with intervention reduced root mean square error by almost 25%. Other studies reported ARIMA (2,1,1) in Zambia, ARIMA (1,0,0) in Burundi [Gomes-Filipe], and India [Kumar] with comparable results.

Studies in Africa reported modelling malaria mortality using Sarima in (Dan Dan & Udoka, 2013), in Malawi (Kazembe, Kleinschmidt, Holtz, & Sharp, 2006) using the multiple spatial logistic regression model, in Tanzania (Rumisha, Smith, Abdulla, Masanja, & Vounatsou, 2014) using Bayesian and geostatistical models to assess the relationship between malaria transmission and mortality. No studies exist from Mozambique, and in particular for Chimoio. Time series intervention analysis was used in Criminal cases in Virginia, USA (Vujić, Commandeur, & Koopman, 2016) and in Australia in a heroin distribution case (Gilmour et al., 2006) with results similar to this study.

Conclusions from the study are:

- Chimoio malaria occurrence and mortality presents a spatial (Map 11) and temporal pattern (Table 1). Malaria cases and malaria mortality have been increasing over the years, especially in suburbs. There is no gender difference in malaria cases. Children under 5 years of age are three times more prone to get malaria than the rest of the population. Sixteen percent of visits to the health centres are from malaria patients. The rural areas of the municipality have more malaria cases, followed by suburbs, and urban areas have fewer malaria cases. (Map. 11).
- The Chimoio climate seems ideal for malaria occurrence. A seasonal pattern was observed in malaria occurrence in Chimoio with peaks during weeks 1 to 12 (January to March). Since the lag effect between climatic events and malaria occurrence is important for malaria cases prediction, this can be used for designing Precision Public Health measures.

- There is no difference in the malaria mortality rate between males and females. Children between 1 – 4 years old are 13% of Chimoio population, but represent 25% of malaria mortalities. The last 3 months of the rainy season (January, February and March) present more malaria mortality cases than the dry season. Urban "Bairros" in the centre of town have lower malaria crude mortality rate than the rural "Bairros". More studies should be carried out for malaria eradication in the municipality.

- The use of an Intervention time series approach for modelling malaria mortality is suggested, owing to its flexibility and interpretation.

- The practicality of the statistical modelling method was validated to detect the lagged relationship between malaria cases and mortality. Based on the results, mortality can be predicted two months in advance. This information can lead to Precision Public Health strategies to prevent malaria fatalities in Chimoio.

- Based on the factors that affect malaria, from week 30 to week 40 Chimoio appears to have a low malaria risk. Map 11 indicates the spatial risk of malaria in Chimoio and no area of the Municipality presents a low risk, 96 % of the area presents a moderate risk and 4 % a high risk of malaria occurrence thus, the entire Chimoio populations is at risk to contract malaria.

- The assumption that factors other than climate remained constant over the period, is a limitation of the present model that makes it difficult to generalize the results to other regions. Another limitation of this study is that it did not take into consideration malaria intervention factors such as bed net distribution and improvement of health coverage. Despite the limitations, one great strength of the study is that this is the first specific study in this field in Chimoio.

- Malaria mortality is increasing in Chimoio and strong and appropriate actions are needed to counteract the malaria deaths scenario in

Chimoio. More data from other parts of the country are needed to generalize the results to the national level.

- Precision Public Health strategies that target malaria weekly according to the positive cases, and temporal and spatial distribution can be formulated to combat and eradicate malaria in Chimoio Municipality. Studies on weather and climate factors affecting malaria, bed net usage, and others should be undertaken.

- This model are robust and, can predict the expected number of malaria cases and mortality at least two month in advance, and timely prevention and control measures can be effectively planned in Chimoio, such as the elimination of vector breeding places, correct time and place to spray insecticides, and awareness campaigns weeks before the malaria peak season. This can lead to a reduction in malaria cases, by knowing the best moment for spraying, saving time and cost of insecticide application and preventive programmes, and guiding smart environmental care.

- Prospective and multidisciplinary research involving researchers from different fields is welcomed to improve the knowledge of the effect of climatic factors and other factors in malaria cases. The model can also be applied to analyse the spread of other infectious diseases and in optimising management efforts.

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