Challenges for Malaria Prevention and Control in Mozambique: A Literature Review

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Signature:……

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Abstract

Background information

Mozambique is a tropical country, considered one of the poorest in the world in 2011, located in Sub-Saharan Africa, with a population of about 21.254.817 inhabitants and a population density of 28.4 inhabitants/km^2. The country is endemic for malaria, actually in the control phase. A literature review was conducted to identify the main challenges on malaria program control in the country and propose solutions in order to support the local government on a rational use of funds.

Results

The weak monitoring of drug and insecticide resistance and the poor monitoring of existence of counterfeit or poor quality drug and were the main challenges in the country, with lack of updated data as well as representative data from whole country. Besides the abnormal rainfall registered in the country in 2013, the low number of children and pregnant women sleeping under LLIN, low coverage of intermittent preventive treatment for pregnant women and low number of houses covered by the indoor residual spraying contributed to increase on malaria cases in the same year.

Conclusions

Considering that different factors, some of them not directly related to the health sector are contributing for actual scenario of malaria in the country, a strong coordination between the ministry of health and other ministries is crucial to improve the malaria control program in Mozambique. A strong drug resistance monitoring and farther surveys to identify the reasons of low percentage of children using LLIN and low coverage of intermittent preventing treatment for pregnant women are also required.

Word count: 250

Key words: malaria control Mozambique challenges

List of Acronyms

AACD	Aggressive Active Case Detection
ACT	Artemisinin-based combination treatment
ANC	Antenatal care
AS	Arstesunate
CDC	Center for Disease Control and Prevention
DTP	Diphtheria, Tetanus, and Pertussis *Vaccine*
EPI	Expanded Program on Immunization
FAO	Food and Agriculture Organization
GDP	Gross Domestic Product
HIV	Human Immunodeficiency Virus
IPTi	Intermittent Preventive Treatment for pregnant form infants
IPTp	Intermittent Preventive Treatment for pregnant women
IRS	Indoor Residual Spraying
ITN	Insecticide treated nets
Km	Kilometer
Km2	kilometer square
LLIN	Long lasting Insecticide treated Nets
LSM	Larval Source Management
m	meters
MDA	Mass Drug Administration
oC	Degrees Celsius
PMI	President Malaria Initiative
RCT	Randomized-controlled trial
RDT	Rapid Diagnostic Test
SMC	Seasonal Malaria Chemoprophylaxis
SP	Sulfadoxine and Pyrimethamine
UNICEF	**United Nations Children's Fund**
USAID	United States Agency for International Development
USD	United States Dollar
WHO	World Health Organization

Glossary

Adult Literacy rate: "Percentage of the population ages 15 and older who can, with understanding, both read and write a short simple statement on their everyday life" [MALIK, Khalid. "Human Development Report 2013. The rise of the South: Human progress in a diverse world." (2013)].

Antimalarial drug resistance: is considered when a parasite strain keeps multiplying and surviving in the presence of the antimalarial drug in the blood stream, in at least the minimum doses recommended for treatment and not higher than the tolerable doses for the patient. In this case, the drug must be able to reach the parasite or the infected red blood cells for enough time required for its action [WHO, 1986].

Behavioral resistance: happens when the vector changes its behavior in order to avoid the contact with the insecticides. These changes may include changes on time and place for feeding and rest. For instance, the vector may prefer to bite outside instead of inside of the houses or bite during the day instead of during the night, and so on[WHO, 2012].

Biological control: introduction of larvae predators or other natural enemies into the breeding sites to fight the aquatic stages of the vector. The larvae predators may be some kind of fishes or invertebrates. Some parasites or other organism causing disease to the larvae may also be used for the biological control of the larvae[WHO, 2013].

Cuticular resistance: is the change on the cuticle of the vector, making it resistance to the absorption of the insecticide. Although the behavioral and cuticular resistance are less common, the same vector may have a combination of two or more of the mechanism described above [WHO, 2012]

Gross domestic product (GDP): "Sum of gross value added by all resident producers in the economy plus any product taxes and minus any subsidies not included in the value of the products, expressed in 2005 international dollars using purchasing power parity rates".

GDP per capita: GDP divided by total population during the same period" [MALIK, Khalid. "Human Development Report 2013. The rise of the South: Human progress in a diverse world." (2013)].

Habitat manipulation: Temporary changes to the environment in order to destroy the breeding sites. It includes the manipulation of the water level and exposition of the breeding sites to sunlight or shade depending on the species of the mosquito[WHO, 2013].

Habitat modification: Permanent changes made to the environment in order to reduce or eliminate the breeding sites, and it includes the landscaping, water drainage and land reclamation[WHO, 2013].

International poverty line: income of less than 1.25 USD per day [Word Bank 2013]

Larviciding: Application of the chemical or biological products into the breeding sites. The chemical products may be surface oils and films and synthetic organic chemicals, while the biological products may be some bacteria like Bacillus thurigiensis and Bacillus sphaericus, metabolites extracted from some bacteria and insect growth regulators that inhibit the transformation of aquatic stages into adult mosquitoes [WHO, 2013].

Metabolic resistance: when the vector produces or increases the production of the enzymes that destroy the insecticides before they reach the target sites[WHO, 2012].

The target site resistance: conformational change of the target sites for the insecticides in the nervous system of the vector. This alteration makes difficult for the insecticides to bind to the target sites and thereby exert their actions. The pyrethroids and DDT usually act in the same target site, thereby the resistance to one leads to a cross-resistance to the other[WHO, 2012].

1. Background information

Mozambique is located at the east coast of the sub-Saharan Africa, in between 10° 27' and 26° 57' of latitude south and 30° 12' and 40° 51' of longitude east [1]. This location makes Mozambique a tropical country, crossed by the tropic of Capricorn and bordering South Africa, Swaziland, Zimbabwe, Zambia, Malawi and Tanzania [2]. With a surface of about 749.380 km^2 [1], Mozambique is also bathed by the Indian Ocean, which makes a very large coast at the east of the country (Figure 1) [2], with about 2.700 Km of extension [3].

Figure 1 – The location of Mozambique in Africa (on the left) and the map of Mozambique (on the right) showing some important geographic details about the country [2].

The most important rivers crossing the country are the Zambeze River, Rovuma River and Lúrio River with 820 Km, 650 Km and 605 Km of length respectively inside of Mozambique, besides so many other rivers and lakes [1]. The inland waters, including rivers, lakes and reservoirs comprise about 2% of the surface of the country.

With a tropical climate, the weather in the country has two main seasons, namely the hot and rainy season, from October to April, and the cold and dry season from May to September. The precipitation is higher at the littoral zone. The annual average temperature in 95% of the country is above 20°C. Nevertheless, the temperature may reach 49°C in some locations, especially

during the rainy season, or below 16^{o}C in some locations with higher altitude in the north and center of the country during the dry season. More than 50% of the country has more than 200 meters of altitude above the sea level, including 5% with more than 1000 meters [4].

According to the census 2007, Mozambique has a population of about 21.254.817 inhabitants [5], with a population density of 28.4 inhabitants/km^2, one of the lowest in the world [6]. The under-5 years old children comprise about 17% of the total population, and the total fertility rate is about six births per woman. The population in the rural areas represents approximately 71% of the total population.

The census 2007 also showed that about 50% of the total population in the country is illiterate [5].

In 2011, Mozambique was one of the 3 poorest countries in the world with 861USD of GDP per capita and 59.6% of the population living with less than $1.25 a day, being thereby below the international poverty line [7]. The agriculture, forestry and fishery were the main source of income for 93.3% of the population in rural areas and 46.3% of the population in urban areas in 2009 [8]. According to the report from National Institute of Statistics, the three activities contributed to 22% of the GDP in the country in 2013[9]. In 2010, the country spent 3.7% of the GDP in public spending on health [7]. In 2012, about 69% of the budget allocated to the health sector came from external funds, including the funds allocated directly to the provincial level [10].

According to the health demographic survey conducted in 2011, the infant mortality rate in Mozambique was 64 deaths/1000 live births and the under-five mortality rate was 97/1000 live births [11]. About 74% of all deaths occur in the houses [12]. These two mortality rates in are above the average in the world [7]. Only 40% of the population in the country has access to the health facilities, majority of them concentrated in urban areas [13]. Considering that one physician for 1000 inhabitants is the ideal recommended by the WHO, Mozambique has few physicians with only 0.03 physicians for 1000 inhabitants, located especially in urban areas [14].

2. Problem Statement, Objectives and Methods

Malaria is a parasitic disease caused by the parasites of the genus *Plasmodium* and transmitted from one person to another by the bite of the mosquito of the genus *Anopheles*. Nowadays, the transmission of malaria occurs only in tropical and sub-tropical countries, 99 of them being considered actually endemic countries. About 81% of the cases and 91% of the deaths occur in Africa. The majority of the deaths occur in under-5 years old children, representing 86% of the deaths globally. The pregnant women and newborn babies are also vulnerable groups for malaria, with 100 000 and 200 000 deaths respectively, every year in all over the world. Nevertheless, the malaria transmission occur in few isolated places in some tropical and sub-tropical countries, including some African countries like South Africa, Lesotho, Botswana, Namibia and Swaziland. In Lesotho, the malaria transmission does not occur at all in all over the country [15].

Mozambique is an endemic country, with high transmission at the littoral zone, low transmission in highlands and moderate transmission in remain of the country. The country is actually in the control phase of malaria [16].

There are five species of *Plasmodium* able to cause disease in Humans, namely the *Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale*, *Plasmodium malariae* and *Plasmodium knowlesi*. The *P. falciparum* is the most dangerous one, causing about one million deaths every year, majority of them in sub-Saharan Africa. The *P. knowlesi* was recently described and causes zoonotic malaria, transmitted from macaques to humans, especially in south East Asia [17]. In Mozambique, 97% of the malaria infections are caused by *P. falciparum*. In 9.9% the cases, occurs a co-infection of *P. falciparum* and *P. malariae*, 3.3% of *P. falciparum* and *P. ovale* and 0.3% of *P. falciparum* and *P. vivax* [18].

Although the number of cases, including unconfirmed cases, and deaths related to malaria tended to decrease in Mozambique until 2012 [13], malaria still the major cause of deaths among adults and among under-5 years old children in the country. According to National Survey on causes of mortality 2007/8, malaria represents 28.8% of all deaths in general and 35.2% of deaths in under-5 years old children [12]. The malaria survey 2007 showed the presence of the malaria parasite in the blood of 38.5% of children under-5 years old and 16.3% of asymptomatic pregnant women [18]. Despite the support received from different donors like Global Found, World Bank,

USAID/PMI, WHO, UNICEF and other donors, the number of confirmed cases has increased gradually since 2009 (figure 2)[19].

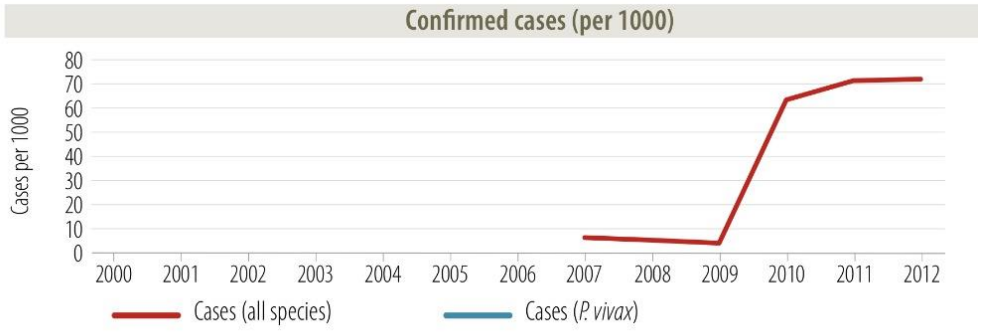


Figure 2 – Graph showing the trends of confirmed cases of malaria in Mozambique, from 2007 to 2012 [19].

According to the weekly epidemiological reports from Ministry of Health, from 2012 to 2013, the number of cases and deaths related to malaria in the country has increased from 135 cases per 1000 inhabitants and 2 789 intra-hospital deaths in 2012 to 161 cases per 1000 inhabitants and 2941 intra-hospital deaths in 2013 (figure 3) [20].

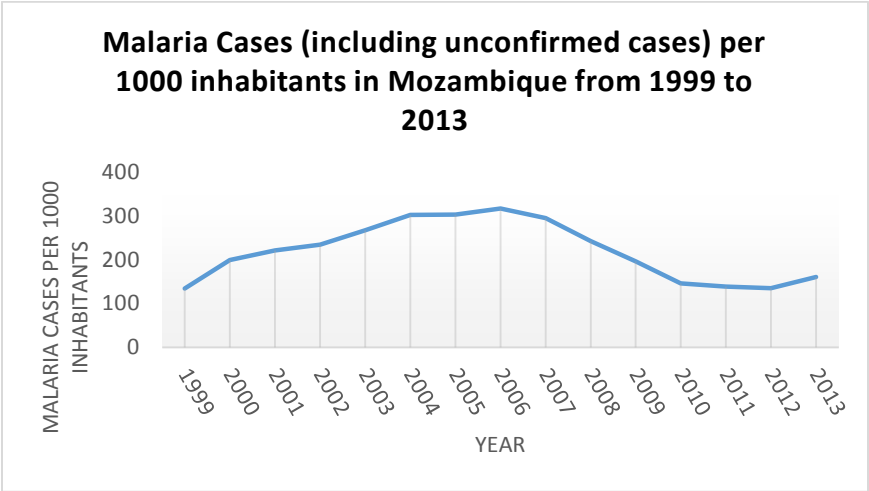


Figure 3 – Graph showing the trends of malaria cases per 1000 inhabitants, including the unconfirmed cases in Mozambique, from 2007 to 2012, basing on routine data [20].

In order to achieve the millennium development goals 4 (reduce the child mortality) and 6 (combat HIV/AIDS, malaria and other diseases) [21], it is crucial to ensure a good quality of the malaria control program in the country. Nevertheless, the data show that there still some challenges in Mozambique.

2.1 Objectives

2.1.1 General Objective

- To identify the main challenges on malaria program control in Mozambique and propose solutions in order to support the local government on a rational use of funds.

2.1.2 Specific Objectives

- To get understanding the determinants of the malaria prevention and control in Mozambique.
- To describe how the Mozambican government is addressing the determinants of malaria prevention and control in the country.
- To identify the good practices on the malaria program from elsewhere.
- To analyze the strengths and challenges of the malaria program in Mozambique
- To use the findings to give recommendations to the government for improvements of the malaria program in the country and rational use the funds.

2.2 Methods

A literature review was conducted to access the different factors contributing to the actual scenario of malaria in Mozambique.

The source of the scientific publications were the PubMed and Google Scholar. The information not available via PubMed and Google Scholar as well as the information available only as a citation were sought either directly in the websites of the specific journals like Malaria Journal or via google search engine.

For the grey literature, the information were sought either in the websites of the National Institute of Health, National Institute of statistics, ministry of health, central government of Mozambique, WHO, CDC, UNICEF and Roll Back Malaria

The combinations of words to find the scientific publications were the combination of the words included in the conceptual model with “Mozambique” and “Malaria”, “Africa” and “Malaria” or only “Malaria” as a first approach. Many other combinations were also used according to specific questions that came out during the literature review. For example, combinations like “deforestation” and “Mozambique”, “tropical forests” and “Mozambique” and “agriculture” and

"Mozambique" were used to find out the levels of deforestation, the extension of tropical forests and practice of agriculture respectively in the country.

Although the most recent articles have been selected first, all the articles published from 1984 to 2014 were considered. Nevertheless, an article from 1930 and another one from 1948, both cited in some recent articles were also included in this review, since these articles were consulted in order to clarify some relevant information. Only publications in Portuguese and in English were selected.

The information from the media websites, personal websites or blogs, social networks and advertisements without any official character were excluded from this paper.

2.3 Conceptual Framework

The data analysis were based on the conceptual model proposed by Protopopoff, Natacha, et al.[22], since this model includes the majority of the factors influencing the malaria transmission in Africa, including the preventive measures and treatment. (Figure 4)

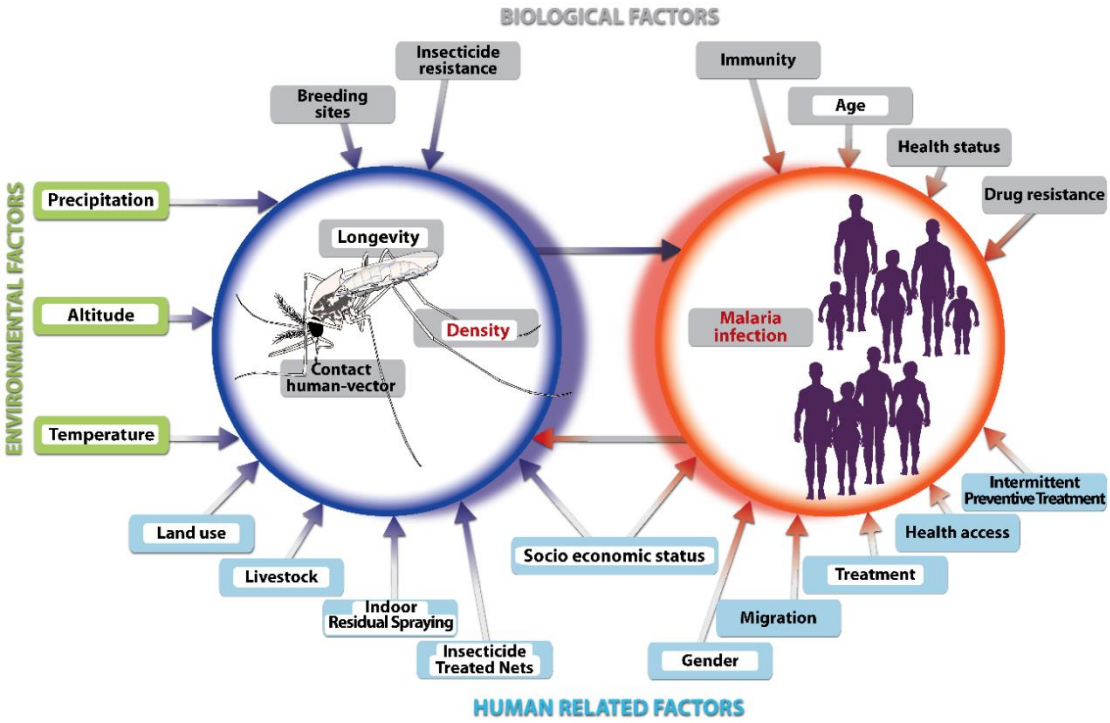


Figure 4: The conceptual Model to access the risk factors for malaria [22].

The immunity, age and health status were discussed together, since these three factors are strictly related to immunity of the person.

2.4 Study limitations and ethical considerations

The limitations of this paper were to find updated data, since the quality of the routine data in Mozambique is very poor [23]. The data are usually incomplete or not available at all via internet. Considering Mozambique as a country with very few resources, especially complementary exams to confirm or exclude malaria, some information biases about the number of cases and deaths attributed to malaria in the reports based on routine data are probably present. There are very few articles about malaria in Mozambique available via internet, especially qualitative studies, being thereby another limitation.

An ethical approval was not required for this paper, since it was a literature review. Additional data, not published or not available for public consultation were not included in this paper, except updated epidemiological data provided via email by the ministry of health of Mozambique.

3. Determinants of Malaria Transmission in Mozambique

3.1 Environmental Factors

3.1.1 Temperature

Some studies suggest that the temperature influences the development and the survival of the vector in both the larvae stage and adult stage of the *Anopheles* mosquitoes [24, 25].

Although about 30-40 species of Anopheles are able to transmit malaria [26], the most important vectors in Mozambique are the *An. gambiae*, especially *An. gambiae arabiensis* and *An. funestus* [16, 26].

According to Bayoh et al, the ideal temperature for the larvae of the *Anopheles gambiae sensu stricto* become adults is from 20 to 28^{o}C [24]. Although it may vary according to the species, the larvae of the *Anopheles* loses gradually the capacity of becoming adult in temperatures below 16^{o}C and above 34^{o}C. The mortality of the adult mosquitoes also increases sharply above 38^{o}C [25].

A study conducted in a rural area of moderate transmission in Mozambique showed that malaria is seasonal in that region, with higher incidence in December, the peak of the hot and rainy season [27]. Nevertheless, unlike the precipitation, the average temperature in the country does not suffer a considerable variation from the cold to the hot season, varying from 20^{o} C to 26^{o} C respectively (figure 5) [28].

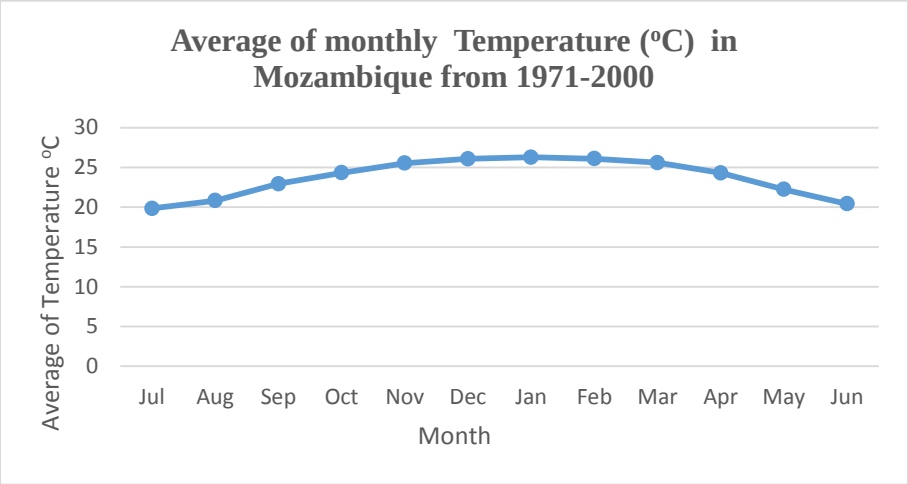


Figure 5: Average of monthly temperature (^{o}C) in Mozambique from 1971 to 2000

3.1.2 Precipitation

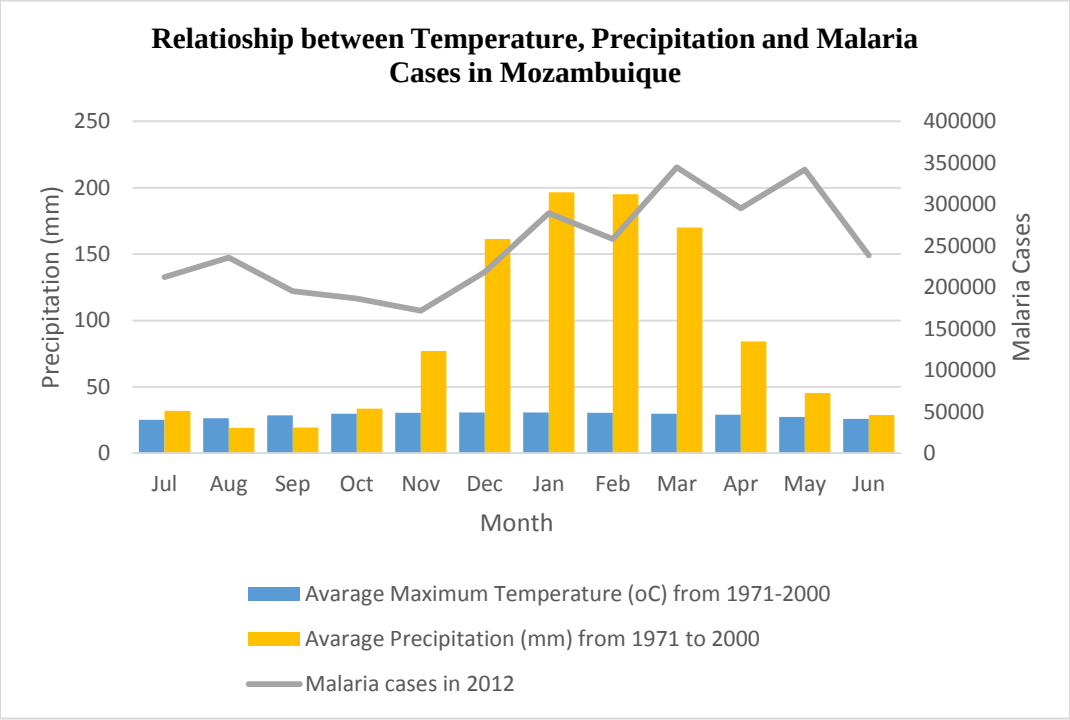
Besides the temperature, the precipitation is also a critical factor influencing the malaria transmission. Overall, the rain provides a good environment for development of the aquatic stages of the mosquito [22], although the heavy rains may have an opposite effect, killing the young larvae. The impact of the drops of a heavy rain may damage directly the young larvae, because they are usually present near the water surface. Considering that the larvae usually need to be at air-water interface to get oxygen, the heavy rains also force the young larvae to dive and stay long time without oxygen, crucial for their metabolism [29].

The rain also increases the relative humidity [22]. A study conducted in India suggests that the longevity of the mosquitoes increases dramatically when the relative humidity gets higher than 42%, and the reproduction is also very high above 80% of relative humidity [30].

In Mozambique, the rainy season and the hot season occur at the same time, increasing the breeding sites for the malaria vector and contributing to the seasonality of the transmission as well [31]. The routine malaria data from Mozambique, when compared to the rainfall show an

increase on malaria cases after the peak of the rain fall during, confirming the seasonality of the malaria transmission in the country (figure 6) [20,28].

Figure 6: Graph showing the relationship between the number of malaria cases and precipitation in Mozambique in 2012.



A study conducted in Maputo showed a stable number of *An. funestus* during the year, while the *An. gambiae complex* had a considerable variation, with a highest number of *An. gambie arabiensis* during the rainy season [32].

3.1.3 Altitude

The lower temperatures in regions of higher altitudes reduce the probability of malaria transmission. The temperature gets 0.5^{o} C lower in each 100 meters of altitude above the sea level. The malaria transmission hardly occurs in altitudes above 1800-2000 meters, although it is possible especially during epidemics [22].

In Mozambique, only 5% of the surface has altitude above 1000 meters [4]. However, those places are surrounded by areas with high and moderate transmission [16].

3.2 Biological Factors

3.2.1 Breeding sites

The majority of the mosquitoes of the genus *Anopheles* prefer the clean water for the aquatic stage of their development, although it may vary according to the species. In general, any stagnant water may act as a breeding site for *Anopheles* mosquitoes. Depending also on the species, the *Anopheles* may reproduce in stagnant water like the temporary rain pools, edges of rivers and streams, tree holes and rice fields, with or without sunlight and with or without vegetation [26].

Although about 30-40 species of *Anopheles* are able to transmit malaria worldwide [26], the most important vectors for the malaria transmission in Mozambique are the mosquitoes *An. funestus* and *An. gambiae* complex [32-33]. In general, while the *An. gambiae* prefer the sunlit temporary pools and rice fields as breeding sites, the *An. funestus* besides the temporary pools, prefer also the permanent and semi-permanent waters with vegetation like in swamps, slow streams and ditches edges [34].

A study conducted in Maputo has showed higher incidence of malaria among people living near the breeding sites for mosquitoes [31]. However, the locations of the potential breeding sites in Mozambique are not mapped yet [16].

3.2.2 Insecticide resistance

Nowadays, the use of the long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS) are the main approaches for the vector control in endemic countries for malaria [35].

In Mozambique, the two strategies are being implemented simultaneously [16].

Considered the best insecticides ever in terms of effectiveness and safety, the pyrethroids are the insecticides of choice to treat all the LLINs. For the IRS, besides the pyrethroids, the organochlorines (dichlorodiphenyltrichloroethane, DDT), organophosphates and carbamates are also used as insecticides in all over the world. Nevertheless, the resistance to pyrethroids and other insecticides groups among the malaria vectors is getting common in many endemic countries due the long-term exposure of the insecticides to those vectors. The resistance to pyrethroids is the most common. The resistance to at least one insecticide has been reported in 64 endemic countries for malaria, particularly in Sub-Saharan Africa and India.

There are four main mechanism of insecticide resistance, namely the target-site resistance, metabolic resistance, behavioral resistance and cuticular resistance (definitions in glossary) [35]. Several studies confirm the presence of resistance to pyrethroids and carbamate among *An. gambiae s.l, An. arabiensis* and *An. funestus* in some locations in Mozambique. The studies also report very low levels of resistance to DDT among the same species of vector in the same locations [36-39]. Nevertheless, the resistance to pyrethroids may lead to a cross-resistance to the DDT as well, since the both have the same mechanism of resistance.

3.2.3 Drug Resistance

When the effective antimalarial drugs are available and provided in time for every uncomplicated malaria cases by *P.falciparum*, the case fatality rate by malaria is only 0.1%. The mortality gets higher when the early effective treatment is not provided and the patient develop a severe malaria manifested by severe anemia, jaundice, renal failure, hypoglycemia, pulmonary edema or seizures. In these cases, the case fatality rate may reach 15-20% even with appropriate treatment [40]. Thereby, the antimalarial drug resistance leads to higher burden of the disease, with higher hospital admissions and higher malaria transmission [40].

Besides the higher burden of the disease, the antimalarial drug resistance leads also to higher global cost for development of new drugs, as well as other issues related to malaria control [40].

Several factors may lead to antimalarial drug resistance. First, a gene mutation in one of the parasites leads to some structural and enzymatic changes that inhibit the binding of the drug to the target sites on parasite, the entrance of the drug to inside of the parasite or increasing the

degradation of the drug inside of the parasite and thereby reducing its concentration. Usually, the gene mutation occurs when the parasites are exposed to lower drug concentration than required to be effective. Second, the resistant parasites multiply themselves and are transmitted from person to person [40].

The development of drug resistance may be influenced by the pattern of the malaria transmission in the region, quality of the antimalarial drugs, pattern of antimalarial drug use and absorption either individually or in the community. The regions with lower transmission are the most susceptible to develop drug resistance because the people in those regions have lower immunity for *Plasmodium*. The host immunity is able to destroy both resistant and non-resistant parasites. Therefore, in the regions with higher transmission, when a parasite develop the antimalarial drug resistance has more chance to be killed by the host immunity before spreading, comparing to the places with lower transmission, and thereby lower immunity of the people [40].

The drug resistance for every antimalarial drugs has already been reported in several countries. Recently, artemisinin resistance, the most effective drug to treat severe malaria, was reported in Cambodia [40].

In Mozambique, some studies confirm the existence of resistance to chloroquine and SP in the country [41-43].

3.2.4 Immunity, Age and Health Status

In places with higher transmission, the children develop immunity against severe malaria before age five, after several exposures to the parasites. After the age five, they continue developing malaria although not getting the severe malaria. During the adult phase, many people living in higher transmission areas does not develop malaria at all, although exposed to the parasites and mosquito bites several times. Thereby, the majority of the deaths related to malaria happen while the children are developing the immunity, therefore before the age five. Nevertheless, unlike other infectious diseases, like viral diseases for instance, the immunity for malaria requires long time and several mosquito bites to be complete or at least strong [44].

A study conducted in a rural area of moderate transmission in Mozambique confirmed that the under-5 years old children were the most affected age group in that area [27].

Besides the adaptive immunity, several other factors may explain the immunity against malaria in some people, especially factors related to the structure or function of erythrocytes. The parasites need to bind to specific receptors on the surface of the red blood cells before invade them. The absence of those receptors makes the red blood cells protected against the invasion of the parasites. For example, the *P.vivax* needs to bind to a receptor called Duffy antigen. The absence of Duffy antigen in some people makes them immune against the infection by *P.vivax* [44].

Despite being extremely rare the infection by P. vivax in Mozambique, there are lack of studies about the prevalence of Duffy antigen in the country.

The plasmodium also needs healthy red blood cells to multiply inside of them. Thereby, people with abnormal erythrocytes may be protected against severe malaria because the parasites either will not multiply inside those cells or will easily be destroyed by the host immune system together with the abnormal cells. This mechanism explains why people with heterozygous state of the Hemoglobin S responsible for sickle cell anemia, Hemoglobin E, α-thalassemia [44], deficiency of the enzyme glucose-6-phosphate dehydrogenase (**G6PD**) in the erythrocytes [45], are protected against severe malaria by *P.falciparum* [44,45].
The prevalence of sickle cell trait (HbAS) in the north of Mozambique is about 4%, while the prevalence of G6PD deficiency among men in the same area is about 18% [46]. The prevalence of sickle cell trait among pregnant women is about 5.6% in all over the country [47].

Several trials are being conducted in different countries to access the efficacy of a new malaria vaccine candidate. Mozambique is one the countries involved in those trials. Nevertheless, the recent trials show low efficacy of the vaccine, of about 50% when administered to children from 5-17 months of age. The duration of protection, so far is less than 5 years [48]. Once the first exposure to the parasite does not confer a protection against a new infection, regardless to the age of the patient at the time of the exposure [49], several doses of the vaccine is required to confer some protection [48].
A survey conducted in Mozambique in 2008 showed that about 52% of the children in the country are not able to complete the immunization schedule [50] due the difficulties to access the

health facilities, lack of information about the immunization schedule, poor quality of health services delivery and other reasons. [51].

Regarding to the health status of the patient, the most important factors identified are Human Immunodeficiency virus (HIV) infections and severe malnutrition [52].
A study conducted in Mozambique showed higher severity of malaria and higher mortality among HIV positive patients, regardless to their antiretroviral treatment status. The case fatality rate was 13% in patients co-infected with malaria and HIV, while in those without HIV the case fatality was 1.7%. The prevalence of HIV in Mozambique is about 11.5% [53].
Severely malnourished people, besides the low immunity [22], usually have difficulties to absorb the antimalarial drugs due the diarrhea, vomiting, rapid intestinal transit and atrophy of the intestinal mucosa. The reduced muscle among those patients makes difficult the administration of intramuscular drugs [52].
In Mozambique, the prevalence of chronic and acute malnutrition among under-5 years old children are 44% and 4% respectively [51].

3.3 Human Related factors

3.3.1 Land Use

The need to practice subsistence agriculture, expand urban areas [54] and exploring the natural resources [55] is leading to change on the natural landscape to be used by man in tropical countries [54]. Those changes include the deforestation [54-56]. Some studies suggest that land use and the deforestation increase the number of malaria cases in the region, since they create some potential breeding sites exposed to sunlight and increase the average temperature and humidity [55]. In Cameroon, the *An. gambiae* was responsible for 13% of the malaria transmission in a place that suffered a deforestation for construction of a new airport, comparing to 0% of the transmission in places located in more than three kilometers away of that area [57].
Another study conducted in Kenya showed that the deforestation was associated with an increase of the mosquito density, biting frequency, and longevity of the *An. gambiae*, thereby increasing its vector capacity in 77.7% [58].
The land use, even without involving deforestation, may lead to higher ground and water temperature as well [59]. The presence of breeding sites exposed to sunlight, higher temperature

and higher humidity make those places favorable for development of *An. gambiae complex* [26], one of the two most important malaria vector in Mozambique [32].

The agriculture in Mozambique is the most important source of income for 80-85% of the people living in rural areas [60-62], and represented 29.3% of the total GDP in the country in 1995 [62] and 22% in 2009 [63]. The percentage of people practicing agriculture or livestock in all over the country reduced slightly from 64% in 2002 to 58% in 2007 [64]. However, the central government has a plan to expand agriculture in the next 10 years in order to duplicate the production and increase the food security.

Some districts in Mozambique are also facing a rapid urbanization over the years [65]. The urban population in the country has a growing of 4% a year. Actually, about 35% of the population in Mozambique is urban and in 2019 the urban population will be estimated in about 45%. [63].

The exploitation of natural resources is another cause of deforestation in Mozambique. A study conducted in Maputo confirmed a severe deforestation around the capital of Mozambique for charcoal extraction [66].

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3.3.2 Livestock

The livestock plays an important role on malaria prevention when is taken into account that some of the *Anopheles* species feed with animal blood besides the human blood. The female of *An. gambieae* and *An. funestus* mosquitoes, the most important malaria vector in Mozambique, strongly prefer the human blood to feed themselves, thereby, increasing their potentiality to transmit malaria [26]. Nevertheless, some studies conducted in Kenya and Ethiopia suggest that the two species mentioned also feed with animal blood, especially when they feed outdoor [67,68]. 20.2% of the blood found in *An. gambiea* during the study conducted in Kenya was cattle blood and 12.8% was mix of cattle and human blood. The same study showed that 90% of the mosquitoes *An. gambiae arabiensis* that fed outdoor and only 9% that fed indoor, fed with cattle blood [67].

In 2002, cattle composed about 80% of the livestock units in Mozambique. The total number of the head of cattle was estimated in about 1.3 million, and the livestock in general contributed to

about 4.3% of the GDP of the country [60]. Usually people in rural areas in Mozambique keep the livestock in pens near the houses during the night and free-ranging during the day [69].

3.3.3 Indoor Residual Spraying

Indoor Residual Spraying (IRS) is the application of a residual and long-lasting insecticide to the surfaces where usually the malaria vectors rest inside of the houses and domestic animal shelters. This intervention play important role in malaria control, reducing the density and longevity of the vectors, especially those feeding and/or resting inside of the houses or domestic animal shelter. The IRS may also prevent the contact human-vector since the mosquitoes may avoid to go inside of a room with insecticides. The IRS is one of the two most important interventions for malaria control, besides the LLINs. The results are better when two interventions are implemented simultaneously [70].

The two most important malaria vectors in Mozambique, *An. gambiae* and *An. funestus* may rest indoor or outdoor, although majority of the time, they prefer to feed and rest indoor [71]. Thereby, the IRS is suitable for malaria control in Mozambique.

The details about the IRS in Mozambique are described below in this paper.

3.3.4 Insecticide Treated Nets

Long-lasting insecticidal nets (LLINs) is one of the most effective preventive measures for malaria control. The mosquito nets not treated with insecticides provide a physic barrier against the mosquito bites. Nevertheless, this barrier is not 100% effective, since the contact human-vector may happen through the skin that eventually may get in touch with the net or through some eventual holes in the nets allowing the mosquitoes going inside while the person is sleeping. Thereby, the insecticide treated nets provide extra protection by repelling or killing the mosquitoes exposed to the insecticides. The pyrethroids are the only insecticides approved to treat the mosquito nets. Therefore, the protection by LLINs are not 100% effective in places with higher levels of resistance to pyrethroids. Unlike the IRS, the LLINs is also suitable for people sleeping outdoors during the summer or for some cultural reasons.

Therefore, the LLINs are suitable for everyone in every countries with malaria transmission, including Mozambique [70].

In many African countries, the under-5 years old children compose less than 20% of the whole population, and the adults are more attractive to mosquitoes. Thereby, a mathematical model suggests that if 50% of the whole population sleep under LLIN, 100% of the children under-5 years old will have also protection even not sleeping under mosquito nets, since 50% of LLIN coverage is enough to confer a communal protection. The repellent and insecticidal effects of the LLIN also help to achieve this communal protection [72].

The malaria survey conducted in Mozambique in 2007 showed that only 9.5% of the families had at least one LLIN. However, only 51% of the people with nets used them the night before the survey [18]. In 2010, 57% of the visited households during a survey had at least one mosquito net, including the non-treated with insecticides nets, and 28% had at least one LLIN [11].

A study conducted in Luangua District in Zambia [73], bordering Zumbu District in Mozambique [2] showed that only 3% of the families that received LLINs, misused the nets for instance for fishing, wedding or other things. Nevertheless, it was not clear if the 3% of the nets misused were not already in poor conditions to still be used, since the lifetime of the mosquito nets usually is about 2-3 years. In Luangua District, the coverage of LLINs is about 80% and the one of the first source of income is fishing [73]. The district is separated to the Zumbu District in Mozambique by the Zambezi River and is crossed by the Luangua River as well [2].

The details about the LLINs in Mozambique are described in the next sections of this paper.

3.3.5 Socioeconomic Status

Although the direct link between the socioeconomic status of a person and malaria infection is controversial, usually the poor people have less access to the malaria preventive measures due the prices and accessibility of those measures [74]. Some studies show higher prevalence of malaria among poor households [75]. People living in poor construction houses are the most exposed to the mosquito bites [34]. The incidence of severe malaria is also higher among the poor people due to the difficulties for those people to access the proper and early malaria treatment. Thereby, the probability of getting complicated malaria among the poor people is higher [74].

3.3.6 Gender

In Africa, the women usually are responsible for taking care of the children and the sick family members, while the fathers are responsible to provide the payment for the health care and other family expenses [76]. Nevertheless, the African women have less power of decision-making. [77], making sometimes the husbands and in-laws refusing to allow a mother to take a sick child to a health facility due some beliefs and cultural reasons, for instance believing that seizures in severe malaria is due witchcraft and the best treatment is the traditional one. [76].

In 2007 in Mozambique, the traditional medication to treat malaria was the choice of treatment for 2.4% of the mothers, while 11.6% of the mothers self-medicated the children according to a survey [18].

The literacy of the mothers plays also an important role. The same survey showed that among illiterate mothers, 30.8% of the sick children for malaria did not receive any treatment comparing to only 5.7% among literate mothers [18].

3.3.7 Migration

The migration of people from one place to another may affect the malaria transmission and control in different ways. On one hand, some people with lower immunity against malaria may move from places with low transmission to places with high transmission, making them susceptible to get severe malaria. On the other hand, some people moving from places with high malaria transmission to places with low transmission may lose their immunity after sometime, making them susceptible to get severe malaria when they return to the hyper-endemic areas [78].

Like in other developing countries, in Mozambique migration may occur within the country, for instance from rural to urban areas or people living Mozambique to go abroad. People from the south of the country, usually migrate to South Africa, looking better conditions of life, since the agriculture in the south of Mozambique is very poor due the poor soils in that region [79]. In 2000, South Africa had about 72.000 immigrant workers from Mozambique, including 57.034 miners. [80].

However, there are not any published study about the burden of malaria among the miners when they return to Mozambique.

Usually, people migrating from rural to urban areas looking for better conditions of life live in poor houses, poor drainage of the surface water and sometimes, lack of piped water. The lack of piped water makes people reserve water in containers, sometimes unprotected, and thereby, making them potential breeding sites. However, the movement of people from rural areas with higher transmission to urban areas with low transmission may not affect the malaria transmission if good housing and proper sanitation are available [78].

According to a survey conducted in 2007, only 47% of the urban population in Mozambique have access to improved sanitation facilities, and only 43% of people in all over the country have access to safe water, including piped water [50].

3.3.8 Treatment

Besides the protection against the mosquito bites and vector control, the early and proper treatment is crucial for malaria control. The treatment of malaria in developing countries depends on the drug resistance pattern in the country, availability and accessibility to the recommended drugs. The costs of the drug is also a problem, but nowadays minimized by founds that developing countries receive from the donors.

The main goal of the treatment of uncomplicated malaria, besides the rapid cure to avoid the patient to get the severe malaria that may lead to death, is also to reduce the transmission killing the gametocytes, the transmissible stage of life-cycle of the *Plasmodium*. The proper combination of drugs also avoids the emergence or spread of drug resistance.

Nowadays, the Artemisinin-based combination (ACT) therapy is the best combination of drugs to treat malaria due the low levels of resistance to artemisinin, rapid effect and capacity to kill gametocytes [40,81].

The ACT is suitable for Mozambique once the country never reported resistance to Artemisinin. However, the combination should not include chloroquine and SP due the resistance to those drugs in the country [41-43]. Therefore, In Mozambique, artemisinin-based monotherapy was removed in 2010 and the country is actually implementing the ACT as recommended. The chloroquine was removed from the guideline of malaria treatment in Mozambique in 2002 [16] due the resistance, while the primaquine has never been included in the national guidelines [82], due the insignificant percentage of infections by *P. vivax* in the country.

More details about the actual scenario of malaria treatment in Mozambique are described in the next sections of this paper.

3.3.9 Health Access

The health access is crucial to provide an early and proper treatment for malaria as well as preventive measures for the population [34]. One of the main barriers for the health care access in general is the lack of availability of health facilities providing basic services, basic needs for poor people and with enough human resources. Another barrier is the geographic access for the health facilities when they are available. The people may need to walk long distances to reach a health facility when transportation or roads in good conditions are not available [83].

The dispersed population, some physical barriers like rivers, lakes or mountains, make it challenging the reach of the patients for preventive activities like IRS [70].

In Mozambique, only 40% of the total population had geographic access to the health care in 2010 [13].

In 2007, in rural areas only 48.8% of the pregnant women had access to health facilities for ANC within one hour of distance and 21.2% of the women took more than 2 hours, majority of them walking [18].

The country is also vulnerable to natural disasters due tropical cyclones formed in or affecting the Mozambique Channel. These cyclones usually lead to higher precipitations and higher risks of flooding [3]. The most recent flooding registered in the country was in 2013 [84], interestingly the same year when the malaria cases increased in the country.

3.3.10 Intermittent Preventive Treatment

The three main types of intermittent preventive treatment for malaria recommended by WHO are the Intermittent preventive treatment in pregnancy (IPTp) [85], Intermittent preventive treatment during infancy (IPTi) [86] and Seasonal Malaria Chemoprevention (SMC) [87].

IPTp consists in administration of two or more doses of sulphadoxine-pyrimethamine (SP) to the pregnant women during the second and third trimesters of pregnancy, especially when they visit the anti-natal care (ANC). The first doses should be given as soon as the women gets in the second trimester of pregnancy [85].

Despite the resistance to SP in P.falciparum reported in some African countries, including Mozambique [41-43], the SP still effective to prevent severe malaria among pregnant women. Thereby, the inclusion of IPT in ANC is a useful measure to reduce transmission of malaria and reduce the maternal deaths due severe malaria by P.falciparum regardless to the level of SP resistance. Three or more doses of SP comparing to less than three doses, reduces the number of parasites in placental vases, therefore, reducing also the incidence of low birth weight. Thereby, three or more doses should be administered during the antenatal visits [85].

A study conducted in Manhiça in Mozambique, confirmed that IPT with SP reduces the incidence of malaria among pregnant women, especially in the first pregnancy [88]. Probably, the women in first pregnancy are the most vulnerable due the lack of placental immunity. In the next gestations, the placental antibodies acquired during the first gestation protect the women [89]. A combination of IPT and LLINs is safe, according to a different study conducted in Mozambique [90]. The reduction of prevalence of malaria after IPTp was 28.8% in a study conducted in Ghana [91].

The details about coverage of the IPTp in Mozambique are described in the next sections of this paper.

The IPT with SP is also suitable for infants (IPTi) living in places with moderate or high transmission [41].

In a double blinded RCT conducted in Mozambique in Manhiça District from 2002 to 2004, the incidence of malaria among infants reduced by 22% after the administration IPTi at 3, 4 and 9 months of age, without a rebound after discontinuation [92], despite the high levels of resistance to SP in that district [41].

To minimize the transmission of the seasonal malaria by P. falciparum, especially among under-5 year's children, the WHO recommends nowadays the Seasonal Malaria Chemoprevention (SMC) with Sulfadoxine/Pyrimethamine (SP) plus Amodiaquine (AS), once a month during 4 months of higher malaria incidence each year, in addition to other interventions. The main goal of this chemoprevention is to reduce in 75% the malaria cases and 75% the severe malaria among under-5 year's old children. Although effective, safe and cost-effective, this intervention is suitable for places where the efficacy of SP is 90% or higher [87]. Basing on studies conducted

only in rural areas in Maputo Province, the level of resistance to SP was getting higher until 2008. Although five studies conducted from 2001 to 2006 included in a literature review showed lower levels of resistance, two studies conducted in 2008 included in the same literature review [41] and another study conducted in 2007 [42] showed less than 50% of the efficacy of the SP in Maputo Province.

There are neither data published about SP resistance outside of Maputo Province, including Maputo city nor data published after 2008 (figure 7).

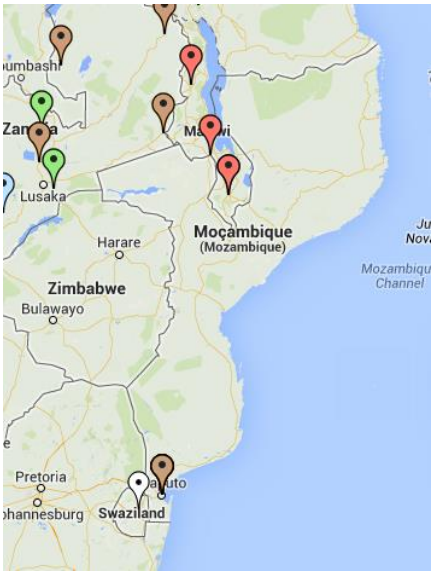

Figure 7: Mapa of Mozambique showing the location of the only place with data about drug resistance in the country [41].

Nevertheless, a study conducted in a rural area in Maputo Province from 2002 to 2005, and another study conducted in Tanzania from 2004 to 2008, suggest that, despite the pattern of resistance described before, the chemoprevention with SP when integrated in the normal immunization schedule may reduce the incidence of malaria in those areas with moderate transmission [93, 94].

4. Recommended interventions, current responses in Mozambique and Good practices from elsewhere

In this section, we describe the current responses to reduce the malaria transmission in Mozambique regarding to the determinants described in the previous sections of this paper. Some of the determinants like IRS, LLINs, Treatment and IPT, are at the same time interventions influencing the other determinants. Thereby, the basic information about these interventions are

described in previous sections of this paper, while in this section we describe the details about the current responses in Mozambique comparing to the WHO recommendations and good practices from other countries.

Mozambique has a national strategic plan to fight malaria to be implemented from 2012 to 2016. This plan contains the most important information about the actual scenario of malaria program in Mozambique, including the coverages of the main interventions, challenges, actions to be taken by the ministry of health until 2016 and the expected impacts [16]. Thus, the main interventions described in this paper are based in this plan.

4.1 Environmental Factors

The three main environmental factors, namely the temperature, precipitation and altitude cannot be modified. However, the impact of these factors can be minimized by other interventions included in the conceptual framework and described separately in this paper.

4.2 Biological Factors

4.2.1 Breeding sites

The larval source management (LSM) is the most important intervention for change or eliminate the breeding sites.

There are four main ways of LSM, namely the habitat modification, habitat manipulation, biological control and larviciding (definitions in glossary) [95].

According to the WHO, the larval control by larval source management (LSM) together with other vector control approaches should be considered in urban and semi-urban areas, because in those areas the breeding sites are somehow permanents, few and easy to know and reach their locations. The opposite happens in rural areas, where the breeding sites besides being so many, are also dispersed and difficult to reach. Thereby, the LSM is difficult to implement in rural areas [95].

Although the LSM is not being implemented regularly in Mozambique, the integrated vector source management is one of the priorities in the national strategic plan of malaria 2012-2016 from Mozambique. The two main actions are the mapping of the breeding sites and larviciding in semi-urban areas [16].

Recent studies show good results when LSM is integrated in the other malaria control strategies in Sub-Saharan Africa as well. A study conducted in Dar Es Salaam in Tanzania in 2006 showed a dramatic reduction on the malaria cases when LSM using the *Bacillus thuringiensis* and *Bacillus sphaericus* for larviciding was combined with other interventions like the use of the mosquito nets and early treatment of the cases [96]. A controlled trial conducted in Kenya from 2004 to 2005 also showed excellent results in the reduction of the malaria cases when the biological control using the *Bacillus thuringiensis* and *Bacillus sphaericus* was combined with Insecticide-treated bed nets (ITNs) in comparison to the use of the ITNs alone [97].

The LSM is also cost-effective in east Africa. In Tanzania and Kenya, the biological control with Bacillus thuringiensis costs about $0.79 to US$2.50 per person protected. The costs of other interventions are estimated in approximately US$0.88-4.94 per person protected by Indoor residual spraying, US$1.21-6.05 for each conventional Insecticide-treated bed net and US$1.38-1.90 for each long-lasting insecticide-treated net (LLIN) [96, 98]. A literature review showed that the environmental management in Zambia, including the vegetation clearance along the rivers, modification of river boundaries and removal of obstructions and draining flooded areas and swamps, besides reducing dramatically the malaria cases was also cost-effective and sustainable in comparison to the other interventions [99].

4.2.2 Insecticide resistance

In order to delay the spread of the resistance, the WHO recommends the rotation of the insecticides, combined interventions, mosaic spraying and mixtures of insecticides (to be considered in the future). In places like Mozambique, where LLINs and IRS are implemented simultaneously, regardless to the level of resistance to the pyrethroids, the recommendation is to continue using the LLINs normally, but stop using pyrethroids for IRS and replace them by non-pyrethroids insecticides, preferably used in annual rotations[35].

In Mozambique, the main insecticide used for IRS is the DDT, although the other insecticide may also be used in case of need [100].

Since the insecticides used for LLINs are only exclusively the pyrethroids, is also recommended the regular entomological monitoring for resistance every year or every six months in each sentinel site that the countries have to select beforehand. The ideal is one sentinel site per 1

million people. The rationality for continue using the LLINs is that, despite the resistance, is preferable still using the mosquito nets rather than leave the persons without any protection at all [35].

The monitoring of the resistance in Mozambique is not implemented regularly as recommended, although it is a part of malaria national plan from 2012 to 2016 [16]. Therefore, the insecticide resistance are detected in some eventual surveys in some isolated places in the country.

4.2.3 Drug Resistance

In order to reduce the development and spread of the antimalarial drug resistance, the WHO recommends the use of combined therapy and avoid the use of monotherapy, considering that the drug resistance may develop by different mechanisms. Therefore, to combine drugs with different mechanisms of action, particularly artemisinin-based combination is recommended nowadays. Artemisinin is good for combination since the levels of resistance to this drug still low worldwide [40, 81]. The countries should remove the monotherapy from the national essential medicines list [101].

Although the artemisinin based-monotherapy is not part of malaria treatment in Mozambique, the Ministry of Health plans to ban completely the monotherapy involving other antimalarial drugs as well in between 2012 and 2016 [16].

A good surveillance system to monitor drug resistance is also recommended in order to allow early interventions in case of emergence of drug resistance. Sentinel sites, ideally 4-8 sites distributed in different locations in the country are required. This distribution should be representative for all country and the tests for drug resistance should be performed once every 2 years [102].

Although it is not being implemented regularly in the country, the malaria national strategic plan from Mozambique includes the intention of conducting drug efficacy tests every 24 months. However, the details about the implementation of the monitoring, like the number and locations of the sentinel sites are not provided in the plan [16].

The monitoring for drug resistance in sentinel sites in Burkina Faso from 2008 to 2010 confirmed that the pattern of the insecticide resistance might differ between the places in the

same geographical area and between the anopheles species. Moreover, this pattern may change dramatically in very few years [103].

To avoid the spread of artemisinin resistance, the WHO recommends to target the interventions to the mobile population and migrant population coming from the countries with confirmed resistance to artemisinin. The interventions include rapid diagnostic test or microscopy and early treatment combined with other methods of prevention. Only the confirmed cases should receive the antimalarial drugs. Other target groups to be considered are the forest workers and militaries [101].

Thereby, the WHO recommends the countries to identify the presence of fake and substandard drugs in the country, provide incentives and tools for authorized sellers to identify and remove low-quality drugs from their facilities. The quality control screening and field operations are also recommended to remove poor-quality drugs [101].

The identification of unregulated drug vendors and screening and field operations to remove the poor-quality drugs is not part of malaria program in Mozambique [16], being probably task of other departments of the Ministry of Health.

Cambodia is an example of monitoring counterfeit drugs in sentinel sites. The sentinel sites are located in different points of country to monitor the quality of the drugs in public and private sector. Thanks to this system, in 2003 was possible to discovery that 79% of the drugs selected for the survey in that year were not registered at the Cambodia Department of Drugs and Food and 27% of those drugs had poor quality. The appropriate actions were taken, including television campaigns discouraging people to buy those drugs [104].

4.2.4 Immunity, Age and Health Satus

Considering that these three factors are related to immunity, the vaccine against malaria is the only specific intervention to address for example the age related factors and pregnant women. Nevertheless, other general interventions like IPTi, IPTp, SMC and prioritizing them on treatment and other control measures described in this paper may reduce the burden of malaria among these vulnerable groups.

The WHO recommends a special attention for the HIV patients with malaria. Those patients should receive early and appropriate antimalarial drugs as recommended in specific guidelines. To avoid drug interactions between antiretroviral and antimalarial drugs, patients receiving zidovudine or efavirenz to treat HIV and amodiaquine to treat malaria should not be given together. The WHO also recommends prioritizing also HIV-positive people for LLINs if the nets are not available for whole population [101]

The malnourished children should be tested for malaria and the positive cases should be treated according to the national guidelines [105].

In Mozambique, the treatment of malaria, according to the national guidelines are provided to the acute malnourished children with RDT or blood smear positive for malaria. The health education about sanitation and manipulation of breeding sites are also provided to the mothers of those children [106].

4.3 Human Related factors

4.3.1 Indoor Residual Spraying (IRS)

Mozambique is one the countries implementing the IRS for malaria prevention [82].

The malaria survey conducted in Mozambique in 2007 showed that 52% of the households were sprayed within the last 12 months before the survey. Nevertheless, 2.7% of the households refused to receive the IRS. Although the capital of the country Maputo is entirely covered [18], the IRS is implemented in only 50% of the districts of the country [16]. A new survey conducted in 2010 showed that only 19% of households were sprayed, 30% of them in urban areas and only 13% in rural areas [11].

Besides the DDT, Mozambique also uses pyrethroids and carbamates as the insecticides of choice [16].

4.3.2 Insecticide Treated Nets

The WHO recommends the universal distribution of the LLINs when enough resources are available. Otherwise, the vulnerable groups like under-5 years old children, pregnant women, people living with HIV, people living in areas with high malaria transmission, all the beds in the hospitals and therapeutic feeding centers should be priority [34].

In Mozambique, the LLIN are distributed to all age groups as recommended [16,82], but prioritizing the pregnant women and under-5 years old children [16].

According to a malaria survey conducted in Mozambique in 2007, 15.7% of the children slept under a mosquito net in the day before the survey [18]. In 2011, the number of children sleeping under a mosquito net increased to 39%, although only 18% have used LLIN [11].

The distribution of mosquito nets in the country is free of charge for the pregnant women during the ANC as well. According to the malaria survey conducted in 2007, 19.3% of pregnant women slept under mosquito net in the night before the survey [18]. In 2011, the percentage increased to 37% of the pregnant sleeping under a mosquito net, although only 20% sleeping under LLIN [11].

A randomized controlled trial conducted in Togo showed that the levels of mosquito nets usage after a distribution campaign are 5-10% higher when volunteers perform one door-to-door visit to provide information, clarify doubts about the importance of the use of the nets, and support the families on correctly hang up the nets. The levels of use are even higher after a second and a third visit. 8 months after the campaign, after three door-to-door visits by the volunteer, use of the nets was 11.3% higher among the under-5 years old children and 14.5% higher among the pregnant women who received the visits in comparison to those who did not receive [107].

4.3.3 Socioeconomic Status

Thus, the Mozambique government distributes mosquito nets free of charge in public sector [82]. Nevertheless, the malaria survey conducted in 2007 showed that 47.3% of the mosquito nets in the possession of the population were obtained in the commercial sector and only 40.0% were obtained in the public sector. Moreover, 66.9% of the nets obtained in the commercial sector were bought in the markets [18].

The RDT and treatment with ACT for all age groups are also free of charge in the public sector of the country [82].

4.3.4 Gender

In Mozambique, especially in rural areas and remote places, the women does not have power of decision-making to take the children to the health facilities when they are sick. Thereby the

Mozambican government trains some community health workers to provide health education about signs and symptoms of malaria, the preventive measures and treatment, not only for women, but also for men, including the community leaders.

The malaria national plan includes the information, education and communication using the local media. Some campaigns and social mobilization are also included in the plan [16].

4.3.5 Migration

The WHO recommends a special attention for migrants, refugees, militaries and forest workers. The countries should prioritize these groups of people on preventive measures like IRS and LLINs as well as early treatment with ACT [34].

Mozambique, Swaziland and South Africa are coordinating the malaria control activities around the border of the three countries. The program is called Libombo spatial development initiative and was launched in 1999. The activities include information, education and communication, as well as coordination on the use of appropriate insecticide and ACT around the Libombo mountains. The Mozambican side of the region verified a dramatic reduction of the malaria cases (92%) from 2000 to 2008 [13]. In the same period, Swaziland and South Africa verified similar results [108]. The challenges for the sustainability of the initiative for the Mozambican side are the lack of money and human resources as well as the lack of coordination of the ministry of health and other ministries [13].

The prevalence of malaria cases by P.falciparum among the mountain workers in the island of Hainan in China reduced from 4.03% to 1.44% after a successful implementation of behavior change communication strategy (BCC). Some basic information like the signs and symptoms of malaria, treatment and the prevention measures like the importance of using mosquito nets were provided to the workers using local media, slogans, hats, t-shirts and bags [109].

4.3.6 Treatment

The WHO strongly recommends a confirmation of the malaria diagnosis either by RDT or microscopy depending on availability the tests and workload of the health workers. The clinical diagnosis should be considered only when none of the tests is available. Usually, the RDT are more expensive than microscopy, but is preferable in situations of high workload of the health workers receiving many patients with fever in endemic areas and places without electricity [101].

In Mozambique, the combination of artemeter and lumefantrin (AL) is the first line of treatment for confirmed and unconfirmed malaria [16,82] and quinine for severe malaria since 2011. The combination of Amodiaquine (AQ) and Artesunate (AS) is the second line of treatment, and AS or quinine parenteral are used to treat the severe malaria. In remote health facilities and communities, the rectal AS is also administered to children with severe malaria before the referral [16].

Nonetheless, according to the malaria survey conducted in 2007, only 36.3% of the children with fever received any kind of treatment within the first 24 hours of the onset of the fever. 59.9% of those children received treatment in public health facilities, while 0.4% received in private health facilities [18]. In 2011, a new survey showed that only 38% of the under-5 years old children with fever received antimalarial drugs 2 weeks before the survey. The AL was the treatment provided to only 11.2% of the children, while 4.9% received SP, 0.9% received quinine and 0.2% received amodiaquine. Surprisingly, the cloroquine was administered to 0.7% of the children [11].

The confirmation of the diagnoses with microscopy or RDT is strongly recommended by the government of the country since 2005. Nevertheless, only 23.3% of the health facilities have microscopy. The lack of qualified human resources to work in the labs and the lack of quality control system are barriers for implementation of this recommendation [16].

The mass drug administration and mass screening and treatment is also an option to be considered by the countries [101].

The Ministry of Health from Brazil is implementing a strategy called aggressive active case detection (AACD) since 1996. In this strategy, every member of a community is test for malaria using either RDT or microscopy and treated in case of positive results. The intervention is similar to the traditional passive case detention (PCD) in terms of cost-effectiveness and efficacy of the treatment [110].

4.3.7 Health Access

For the places with difficult access to the health facilities, the WHO recommends the training of people from the community and supply them with basic drugs including antimalarial drugs and RDT to diagnose and treat non-complicated malaria cases close to their houses [52].

In Mozambique, some people selected in remote communities receive a basic training on detection and treatment of uncomplicated malaria. The government provide to those community health workers some basic medicines, including antimalarial drugs and RDT. The improvement of the logistic capacity and infrastructures are also priorities for the government. The community health workers are also responsible to provide health education to the population [16].

4.3.8 Intermittent Preventive Treatment

IPTp using SP is recommended by the WHO for every countries, regardless to the levels of SP resistance in the country [85].

This intervention is part of malaria control in Mozambique since 2006 [16]. However, in 2007 only 20.3% of the women who had one birth the year before the survey received at least two doses of SP as recommended. The majority of the women (31.4%) received only one doses and 14.6% received three doses. [18] In 2011, only 19% of the women received the recommended two doses during the past two years before the survey [11].

The lack motivation of the health staff and the lack of information by the pregnant women may constitute a barrier for the implementation of IPT as suggested by a qualitative study conducted in Malawi [111].

The WHO recommends also the IPTi to be administered during the normal expanded program on immunization (EPI) at 10 weeks together with the vaccine DTP- Hepatitis B 1, 14 weeks with DTP-Hepatitis B 2 and at 9 months with measles vaccine. However, the level of resistance to SP should be less than 50%. The countries with high levels of resistance to SP, should consider the implementation of IPTi in provinces or districts with lower level or resistance, since the pattern of resistance may vary within a country [41].

Nevertheless, the IPTi is not part of malaria program in Mozambique, probably due the resistance levels to SP [16].

5. Discussion

5.1 Environmental Factors

The precipitation is the most important environmental factor influencing the malaria transmission in Mozambique. The increase on malaria cases in 2013, in the same year that the country registered rainfall above the normal and flooding, especially in the south, suggests some relationship between the flooding and the malaria cases that year. Thereby, the impact of the flooding on malaria cases would be smaller if preventive measures were taken beforehand.

Although it is not possible to change the environmental factors, it is possible to predict the months and the years of higher precipitation and natural disasters like flooding, in order to intensify the preventive measures before the cases start increasing. The early warning on abnormal rain, natural disasters and therefore the increase on malaria cases would allow the government to provide some extra commodities for instance for 3 months, including RDTs, drugs for early treatment and mosquito nets to the places with risk of became inaccessible during the rainy season. However, this approach would require a strict collaboration between the Ministry of Health and the National Meteorological Services, besides an accurate warning system to avoid spending resources and time due a false alert. The presence of skilled people, constantly updated on drug stock management and malaria prevention and control and infrastructures to store the commodities in the high-risk places would be limitations for this approach. Nevertheless, it is an option to be considered by the government, once the emergency responses after the flooding happen are usually very expensive [84], and probably more expensive than the preventive measures.

5.2 Biological Factors

The finding on this paper suggest that for a better malaria control program in Mozambique, all the biological factors should be addressed simultaneously.

For instance, despite the efforts made by the government to distribute mosquito nets for children, the number of children sleeping under LLIN still very low, in only 18% in 2011, suggesting that, so far, the distribution of LLIN without other interventions is not enough to reduce the burden of malaria among children. The reason for this very low percentage of children using mosquito nets in Mozambique is not clear in this review due lack of qualitative studies accessing this factor in the country. The study conducted in Zambia, the only study available that somehow can be

extrapolated to Zumbu District in Mozambique due the geographical location of both districts suggest that the people do not use the nets simply because they do not have. The percentage of misusage of the nets in that study was insignificant. More studies are required in other locations in Mozambique once the scenario may be different in places with different characteristics, beliefs and cultural habits.

Anyway, the door-to-door visit performed by volunteers to provide information, clarify doubts about the importance of the use of the nets, and support the families on correctly hang up the nets, using the example of Togo would be a good option, at least to increase the number of people using the nets. The data from Togo should be taken into account for implementation of the approach in Mozambique as well because, besides sub-Saharan Africa like Mozambique, the data were based on a randomized controlled trial.

The percentage of houses with at least one LLIN in Mozambique is also extremely low, with only 28%, very far from the required 50% of the population using the LLINs for a communal protection, despite the distribution free of charge in public health facilities. Thereby, a collaboration between the Ministry of Health and the Ministry of Finance would allow more people without access to the nets via public sector, to get them via commercial sector. For instance, the Ministry of Finance can reduce the taxes related to mosquito nets or negotiate with the sellers the other ways of reduce the prices of the nets.

The Ministry of Health is planning to start a universal distribution of the mosquito nets, but the numbers presented in this paper suggest that this approach should not be a priority before to have evidences that the populations will have access to the nets and use them properly.

The monitoring of drug resistance is also a challenge in Mozambique. The few studies about the drug resistance in the country are not enough to access the real scenario in the country. The decisions about implementation or not of some interventions that depend on drug resistance levels in country are based on data about only one province, being thereby not generalizable for whole country, considering that the resistance may vary from place to place in the same country. Even considering the data about only one province, the last study was conducted in 2008, being therefore outdated actually, once the monitoring of drug resistance should be implemented every 2 years or less.

The country is not implementing some important interventions like SMC and IPTi basing on those few data. The fact that some studies conducted in Mozambique in the few places with high levels of SP show important reductions on malaria cases after implementation of SMC and IPTi, suggest that implementing the interventions in places with or without data, may be better than not implementing at all. However, more studies are required in other locations before consider the implementation of this approach.

Although to conducting drug efficacy tests every 24 months is a priority in malaria plan from Mozambique, it is not clear whether the sentinel sites will be located in the places recommended by the WHO or not. Probably, this issue still under discussion.

Besides the monitoring of drug resistance, the monitoring of the monitoring of drug quality and presence of counterfeit drugs is also required in the country. Is not clear in reports from Ministry of Health if this activity is being implemented in the country or not.

The available information suggest that, if this monitoring is being implemented, it is not in a strict collaboration with malaria program. Considering that the malaria is one of the most important diseases in the country and the antimalarial drugs are some of the most used drugs every day, this collaboration would bring out important information to improve the malaria program.

In 2010, some people received chloroquine to treat malaria, suggesting that they got the drugs either in private places out of control of the government or in illegal markets with high risk of presence of poor quality and fake drugs. Thus, the monitoring of drug quality and counterfeit drugs, using for instance the example of Cambodia in order to reduce the risks of drug resistance is also required in Mozambique.

The sentinel sites would be important also to monitor the insecticide resistance. To invest the funds for monitoring for insecticide resistance may cost about US$ 0.01 per person protected per year, less than 1% of the cost of one LLIN [35], being thereby rational for the poor countries.

The researches about the vaccine are also important, but still with very low efficacy so far and requires many doses to confer some protection. The data from the expanded program on immunization show that is a challenge for children in Mozambique to complete the

immunization schedule. Thus, in our point of view, the vaccine is not more important than other interventions like improvement of sanitation, improvement of the houses, vector control and proper treatment.

5.3 Human Related factors

Although all the human related factors suggested in the conceptual model are determinants of malaria transmission in Mozambique, the most important ones are the IRS, LLIN, IPT and early and proper treatment in terms of cost-effectiveness.

The coverage of houses as well as geographic areas receiving IRS still very low in the country with 19% of the houses and 50% of the districts respectively. The fact that the *Anopheles funestus* became zoophagic when exposed to an extreme insecticide pressure inside of the houses [71] suggests that to prioritize houses with livestock for IRS may be a good approach to explore in the future, once the livestock is part of the culture in some rural places in Mozambique. Nevertheless, a research is required before the implementation of this approach.

The number of patients receiving antimalarial drugs is also a challenge in Mozambique. The fact that only 36% of people are receiving the drugs in the first 24 hours after the onset of the fever, 40% of them receiving from private health facilities, suggests that the accessibility to the public health facilities by the population is very poor in the country. The training of the community health workers to treat patients in remote places is a good example from Mozambique, but still not enough to provide drugs for everyone needing. The training of teachers and shop owners in RDT and first line antimalarial treatment in remote places with high malaria transmission, following the example of Suriname is an alternative to minimize the problem. However, some researches are required before start this intervention once Suriname and Mozambique are countries with different characteristics geographically and culturally.

The government is doing effort to provide treatment and preventive measures free of charge for everyone in order to minimize the effects of the socioeconomic status. However, the coverage of the IPTp is very low in Mozambique, for unknown reasons, but probably due lack of accessibility. Some qualitative studies are required to access the reasons of this low coverage.

The cooperation between Mozambique, Swaziland and South Africa to minimize the malaria transmission in the border of these three country is a successful example of importance of the coordinated activities between the countries. This collaboration allow the countries to synchronize the activities and support each other in case of difficulties in one of the sides. The dramatic reduction on malaria cases in the three countries simultaneously show that is essential to keep this collaboration. However, is also crucial to improve the collaboration between the Ministry of Health and other ministries in the country.

6. Conclusions and Recommendations

6.1 Conclusions

The transmission of malaria in Mozambique is multifactorial, and the control does not depend exclusively on the Ministry of Health. Therefore, a collaboration between the ministry of health and other ministries, as well as keeping the cross-bordering collaboration with neighboring countries to synchronize the activities about malaria control is crucial for improvement of malaria control program in the country.

To minimize the impact of abnormal rainfall and flooding on malaria cases, an accurate early warning system is required, to allow planning of preventive measures beforehand. Considering that it will be implemented for the first time in the country, some studies are required before the implementation of this approach.

Once the percentage of pregnant women and under-5 years old children with LLINs still very low in the country, the universal distribution should not be a priority for now. The priority should be the use of different approaches to ensure the availability of nets for more children and more pregnant women. The population get about 50% of the nets on the commercial sector. Therefore, to work in collaboration with the Ministry of Finance to make the prices of the nets reasonable for everyone is an option.

The door-to-door visit performed by volunteers to provide information about the correct use of mosquito nets, besides other preventive measures about malaria is an important intervention to increase the number of children sleeping under LLINs after distribution.

The training of teachers and shop owners on RDT and first line antimalarial treatment in remote places with high malaria transmission is an option to increase the antimalarial treatment in those places.

The country requires an aggressive drug resistance, insecticide resistance and counterfeit or poor quality drug monitoring in different location in the country, using sentinel sites, in order to provide updated data about whole country.

Some qualitative studies are required to access the reasons of the low coverage of IPTp.

6.2 Recommendations

6.2.1 Coordination

- Improve the coordination between the Ministry of Health and other ministries, including the ministry of finance and meteorological services and keep the cross-border coordination between Mozambique, Swaziland and South Africa.

6.2.2 Researches and Surveillance

- To establish sentinel sites distributed in the country to monitor drug resistance, insecticide resistance and counterfeit or poor quality drugs.
- To conduct a qualitative study to access the very low percentage of children using mosquito nets and low coverage of IPTp in the country.
- Conduct a study to access the impact of IRS in houses with livestock in comparison to other houses receiving IRS.

To conduct research to access the use of rainfall data temperature to monitor malaria early warning.

6.2.3 Training

- To train volunteers to perform door-to-door visits to support the families on correct use of mosquito nets and provide health education.
- To consider the training of teachers and shop owners on RDT and first line antimalarial treatment in remote places with high malaria transmission, depending on results of the research about the use of rainfall data temperature to monitor malaria early warning.

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