SOCIOECONOMIC DETERMINANTS OF EARLY HEALTH CARE UTILISATION AND ASSOCIATION WITH MALARIA HOSPITALISATION AMONG UNDER FIVE YEARS CHILDREN IN MANHIÇA, MOZAMBIQUE

Alberto Aniceto Chauque

(1644123)

SUPERVISORS:

Innocent Maposa – Senior Lecture, University of Witwatersrand

Arsenio Nhancolo – Senior Biostatistician, Manhiça Health Research Centre

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Declaration

I, Alberto Aniceto Chauque, declare that this Research Report is my own unaided work. It is being submitted for the Degree of Master of Science in Epidemiology and Biostatistics at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

Alberto Aniceto chauque

(Signature of candidate)

05 days of March 2023 in Johannesburg

I dedicate this monograph to them with much gratitude for the love, affection, dedication and care that my parents gave me throughout my existence and for the sacrifices they made so that my brothers and I could study.

Abstract

Introduction

Malaria is one of the significant health problems in the world, and the greatest burden of the disease is concentrated in Africa, which accounts for about 95% of cases. The WHO (World Health Organization) indicates that early seeking for treatment is crucial to avoid worsening the disease and, consequently, death. This work, was evaluated the factors that influence early health care seeking in children under five years old and the effect of early health care seeking on hospitalisations.

Methods

It was conducted a health facility-based observational longitudinal study where malaria cases were identified in an ongoing surveillance database. Using the first visit for all children that visited a Health Facility with fever and malaria and defined early health care seeking as a visit to a health centre within 48h after the onset of fever. Multilevel logistic regression was used to identify the factors related to early health care seeking and the association between early health care seeking and hospitalisation.

Results

A total of 66 620 children aged 0 to 15 years were screened. Excluding all children who did not meet the study criteria, ending up with 2 299 children with malaria and fever, but only 1 603 children had demographic information. A kilometre increase in the distance to a health facility reduces the odds of early health care seeking (aOR = 0.89**;** CI: [0.83-0.95]; p=0.001). Early health care seeking reduces the odds of hospitalization (aOR = 0.56; 95% CI: [0.34 -0.93]; 0.024) and year increase in the year of the visit also increases the odds of hospitalization (aOR = 1.66; 95% CI: [1.41-1.93]; p<0.001).

Conclusions

Increasing the distance to health facilities reduces the likelihood of early health seeking, whereas early health care reduces the risk of hospitalisation. Maluane and calanga lead the hospitalisation cases in the study area in children with malaria and cases of delay in health-seeking.

Acknowledgements

I have the happy opportunity to formally thank all those who helped me in some way to complete one more step in my life, and I feel gratified for this chance.

I thank my family for understanding and supporting me in this important decision of leaving them a little bit far away physically, but not in my heart. I know there were difficult moments, but they will be compensated in the future, to Niria for her patience, understanding, affection and love. I also thank all my friends, old and new, and thank you very much for your support.

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To thank all the children and families of the district of Manhiça that have allowed the collection of information that helps in the creation of knowledge and consequently in the fight against malaria as well as several other diseases in their community and the world.

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Abbreviation and Acronyms

WHO: World Health Organization

EHCS: Early Health Care Seeking

NMCP: Mozambican National Malaria Control Programme

RBC: Red Blood cell

PCR: Polymerase Chain Reaction

OR: Odds Ratio

RDT: Rapid diagnostic tests

SES: Social Economic Status

CISM: Manhiça Health Research Centre

PI: Poverty Index

NCDI: Noncommunicable Diseases and Injuries

1. INTRODUCTION

1.1. Background

In a list of the world's major health problems, malaria is the primary cause of mortality in many nations. Almost half of the people on Earth reside in countries where malaria is endemic. The world Health Organization (WHO) predicted that there would be 241 million cases worldwide in 2021 (1).

Globally, from 2000 to 2019, malaria cases have shown a steady decrease, and the incidence of the disease reduced from 80 cases per 1000 in 2000 to 57 cases per 1000 in 2019. The deaths of children under five years old with malaria also decreased in the same period from 84% to 67% (2).

The most significant burden of malaria morbidity in the world is concentrated in sub-Saharan Africa. As according to estimates about 95% of cases and 96% of deaths from malaria worldwide in 2020 occurred in sub-Saharan Africa, where, although the incidence of the disease is falling, the absolute number of cases continues to increase due to the rapidly growing population in this region (3). Nevertheless, the incidence of the disease in sub-Saharan African countries reduced from 363 in 2000 to 225 cases per 1000 in 2019. For the same period, the mortality rate reduced from 121 to 40 per 100 000 people at risk (2).

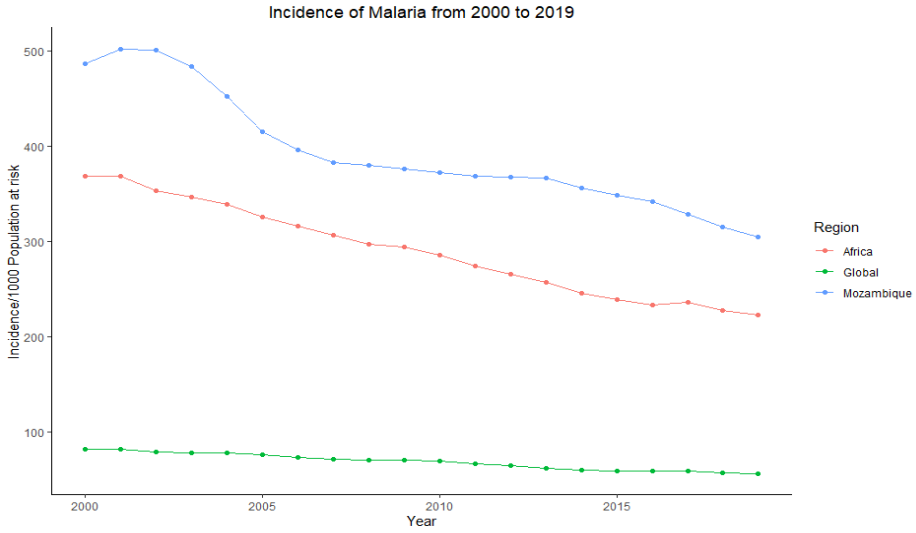

Figure 1: Estimated incidence of malaria in the world, in WHO African Region and Mozambique (data source WHO)

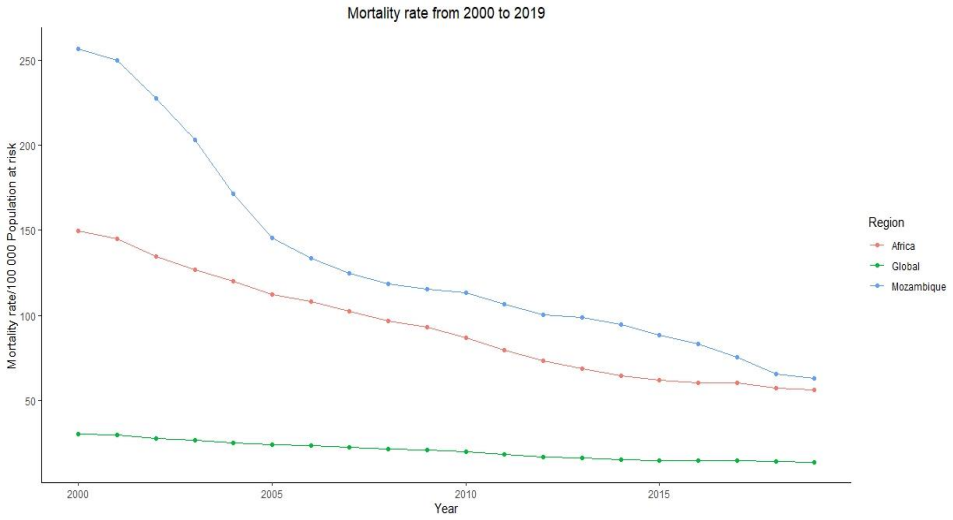

Figure 2: Estimated malaria mortality rate in the world, in WHO African Region and Mozambique (data source WHO)

Since the study will take place in Mozambique, further information will therefore focus more on this country, which in 2019, accounted for about 4% of cases and deaths of malaria in the world (2). However, malaria incidence in Mozambique decreased from 486.4 per 1000 in 2000 to 315.3 per 1000 in 2018 (4).

Maputo province also shows a reduction in the prevalence of malaria in children. From >60% in 2000 to <3% in 2015, probably as a result of the combination of the Mozambican National Malaria Control Programme (NMCP) effort to control malaria with various government and non-government initiatives and socioeconomic changes that took place during the last decades in the country (5). However, even though Maputo City presents the most significant reduction in malaria prevalence in the country, the same cannot be said about cases of severe malaria and consequent mortality. As a result, Maputo has one of the country's highest malaria case mortality rates (6).

1.1.1. Malaria Disease Burden in the Study Area

CISM was established in 1996 in the district hospital of Manhiça, having as its study area the administrative post of Manhiça. However, the study area of CISM expanded and, in 2014, covered the entire district of Manhiça. The district has an area of about 2 373 km² and a population of 178 000 inhabitants.

Manhica is a sub-tropical region with a rainy season which lasts from November to April. The area is endemic to malaria (7).

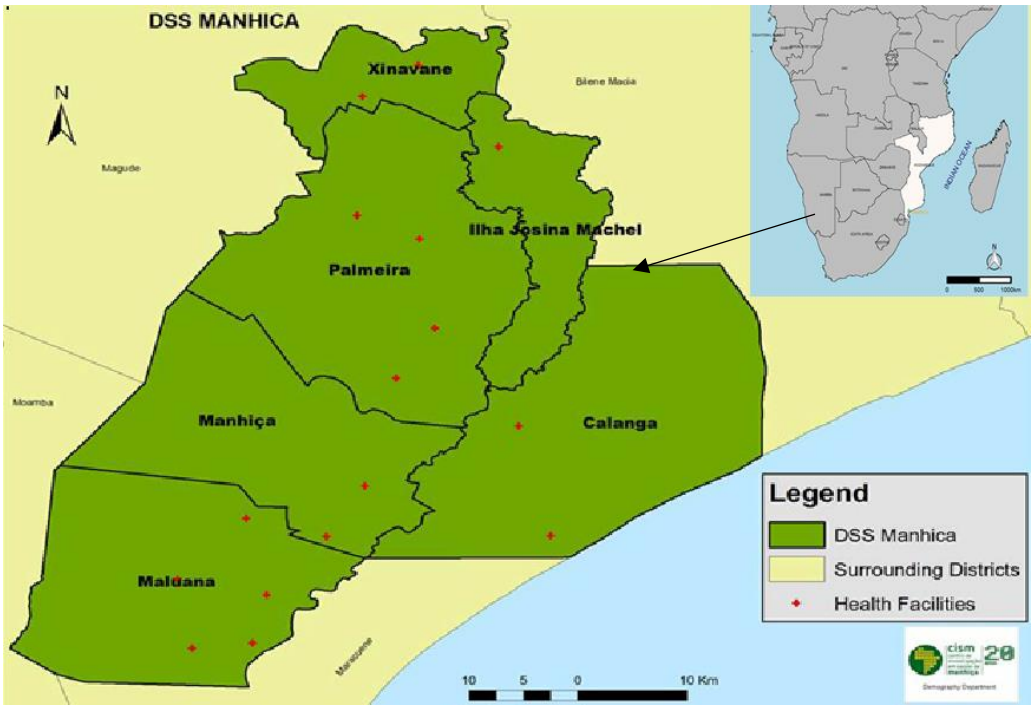

Figure 3: Manhiça district, CISM study area

From 1997 to 2017, children under five years old dominated the prevalence of malaria in hospital admissions in the study area. From 1997 to 2003, the prevalence increased, peaking at approximately 250 per 1000 children. Whereas from 2003 to 2017, the prevalence was characterised by consistent decreases despite some fluctuations.

The prevalence of malaria in children aged 5-15 years was low when compared with that of children under five years old, with a peak of approximately 25 per 1000 children in 2003. However, it also showed the same trend for children under five years of age (8).

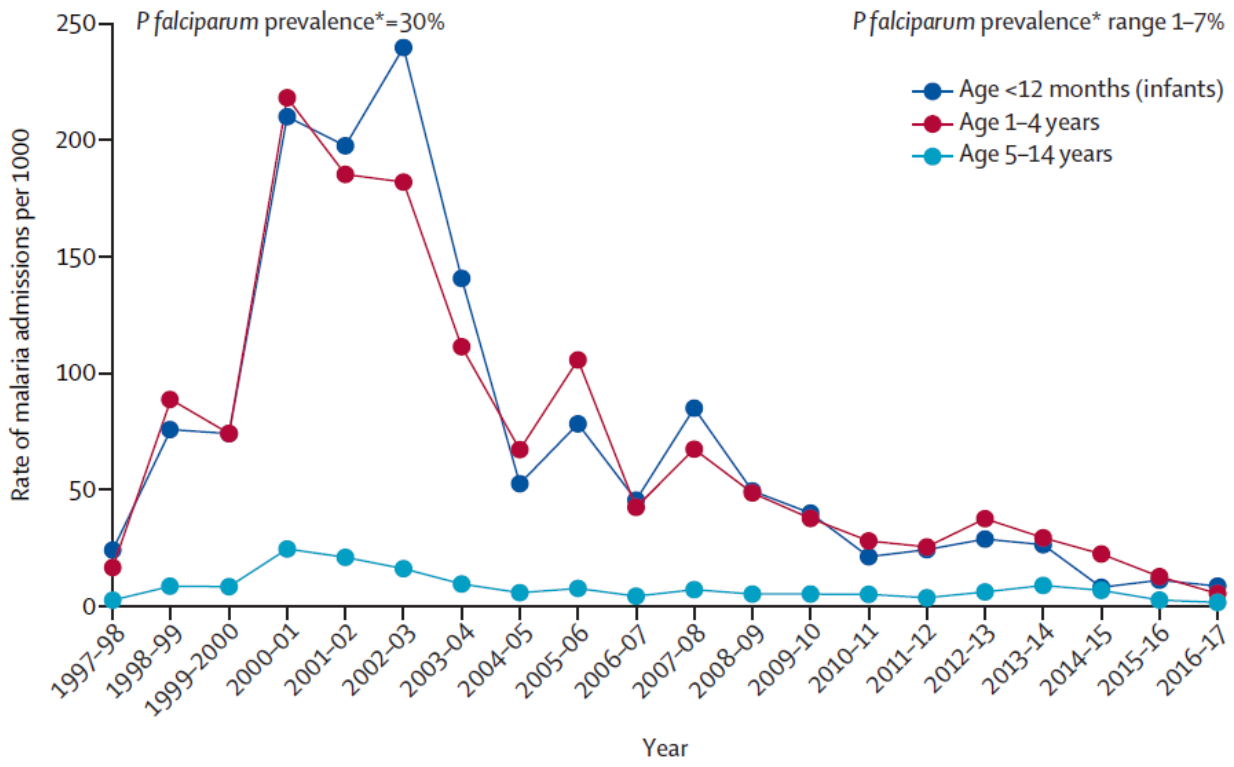

Figure 4: Minimum community-based incidence rates of malaria admissions in children from the original Manhiça Health and Demographic Surveillance System study area by age group (Source: (8))

1.2. Literature Review

1.2.1. Malaria

Malaria is an acute febrile illness characterised by fever, headache and chills. It is an ancient human disease. In Africa, records of the disease were found in Egyptian papyri of the XV century before Christ. From the beginning, early Greek scientists associated the disease with swamps. However, they erroneously indicated miasmas as the cause of the disease (9). This theory persisted for almost 2 500 years up to 1898 when AMICO BIGNAMI in Rome discovered that the mosquito was the vector transmission of human malaria one year after Ronald Ross had discovered that the mosquito was the vector transmission of avian malaria (10).

Malaria is caused by genus *Plasmodium* parasites transmitted by female mosquitoes of the genus Anopheles (11). The parasite's life cycle involves the (mosquito) vector and humans.

Plasmodium parasite's life cycle

In Humans

The cycle starts when an infected mosquito feeds on a human and injects *sporozoite* (a form of *plasmodium* parasite) that goes directly to the liver. In the liver, the *merozoite*, which is a later stage of *sporozoites*, multiplies asexually for more than a week without symptoms.
The *merozoites* are discharged into the bloodstream and start the red blood cell invasion (*erythrocytes*). After the invasion and inside of the cells, the *merozoites* keep multiplying asexually until the cells burst, and then they move to other cells and repeat the same process, and it is in this stage that start the onset of the symptoms. Some *merozoites* leave the asexual multiplication process and develop a sexual form called *gametocytes* that go to the bloodstream.

In Mosquitos

During a blood meal, the non-infected mosquito ingests the infected *gametocytes*, which in the mature stage develop into sex cells called *gametes*. The fertilised *gametes* develop and turn into *ookinetes* that form *oocysts* using the mosquito's midgut wall. The *oocysts* grow and burst, releasing *sporozoites*. The *sporozoites* travel to mosquito salivary glands.

The cycle restart when an infected mosquito bites an uninfected human (12,13)

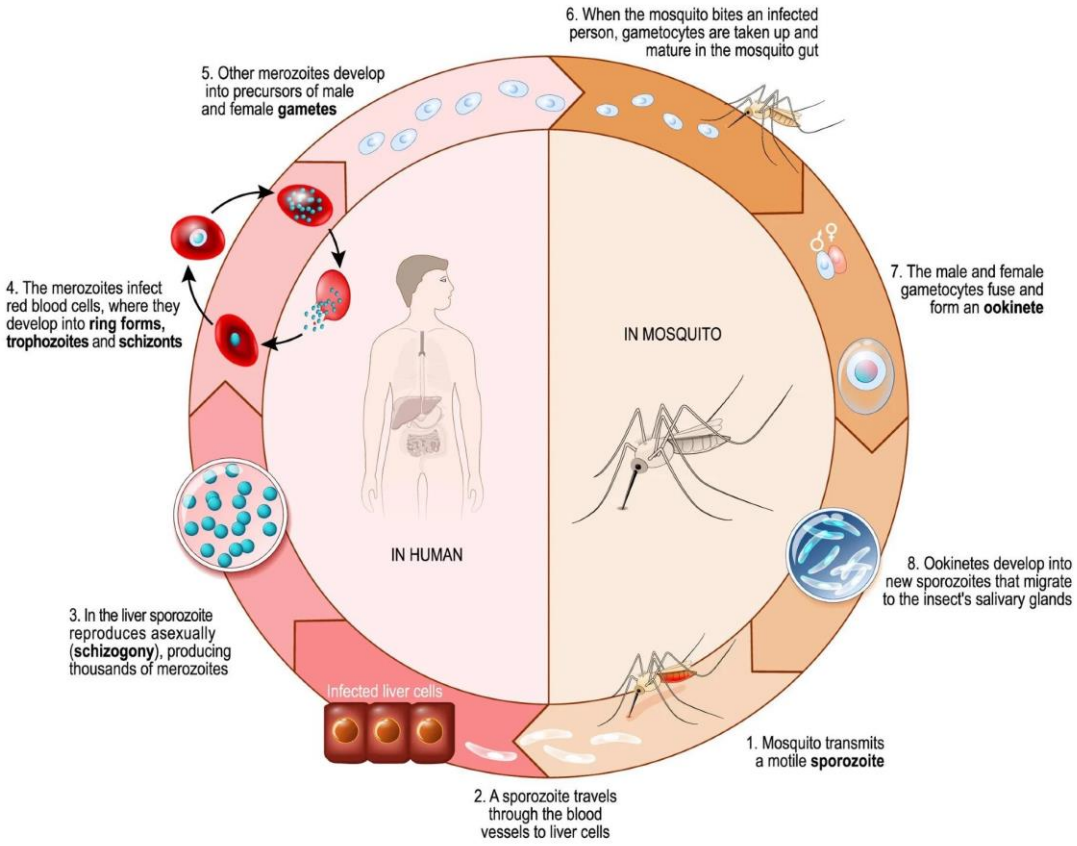

Figure 5: Malaria transmission and life cycle (source: https://www.shutterstock.com/image-vector/life-cycle-malaria-parasite-vector-diagram-1435662671)

Parasite species and characteristics

There are five parasite species that cause disease in humans, namely: ***Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malariae and Plasmodium knowlesi*** (14).

Plasmodium falciparum

Characterised by the production of high quantities of parasites in the blood and modification of the infected *Red Blood Cell* (RBC) surface, which results in an *adhesive phenotype* that sequesters *RBC* inside tiny and medium-sized vessels (14).

It is the deadliest worldwide malaria parasite and most prevalent in Africa. This parasite is responsible almost for 98% of malaria cases worldwide (3).

Plasmodium vivax

Characterised by the ability to survive in mosquitoes in low temperatures and the long dormant period of the parasite in the human liver, which can take years (15).

It has long been distinguished from other parasites by the way it enters the red bloodstream through Duffy-positive people (Ménard, 2010). Although it is more frequent in Duffy-positive regions, recent studies have shown cases of infection of this parasite in Duffy-negative people in Africa and America. It is considered more widespread when compared with P. falciparum and is associated with a high level of morbidity. (16).

Plasmodium ovale

According to the latency period, this parasite can be subdivided into *P. ovale curtisi and P. ovale wallikeri*. Nevertheless, they have the same syndrome and the same response to the therapy (14).

It has a "dormant phase" in the liver that can take weeks or months. It usually infects only young RBC called *reticulocytes* leading to fewer *erythrocytes* infected; consequently, severe morbidities or deaths are rare. It is found in western Africa (17).

Plasmodium malariae

Characterised by low parasitemia, a fact attributed to the restricted age range of targeted RBC. This characteristic leads to an underestimation of the prevalence of this specie (18).

In contrast to *P.vivax* and *P. ovale* where relapse can be caused by the parasite lying dormant in the liver, *P. malariae* remains in the host's blood long after the disease's symptoms have passed. Infection with this parasite is generally found in the same area where *P. falciparum* is found, sub-Saharan Africa and southeast Asia (19).

Plasmodium knowlesi

It is characterised by the shortest asexual blood-stage development (24h). It uses Duff antigen to invade human *erythrocytes* but does not have a latent liver stage as the other four parasites (20).

There is still no evidence of human-to-human transmission of this parasite. However, it was possible to verify a strong association between the circulation of the parasite and the presence of the *Macaca fascicularis*, *Macaca nemestrina* and *Presbytis melalophos* considered the natural host of the parasite. Consequently, this parasite can only be found in Southeast Asia, where those monkeys are present (21).

1.2.2. Malaria Parasites in Mozambique

Three parasites have been identified in Mozambique: *P. falciparum*, *P. malariae* and *P. ovale* (22), although the last national survey on malaria did not identify any case of *P. ovale*. There is consistent information indicating that the majority of infections in the country are due to the *P. facilparum* parasite. Indeed previous studies show that Plasmodium falciparum represents about 90% of malaria cases, followed by *P. malariae* with approximately 9% and 1% of *P. ovale* (22,23).

1.2.3. Diagnostic

Microscopic Diagnosis

The gold standard test for malaria is microscopic examination (24). The technique consists of spreading a thick or thin smear of the collected blood on a glass slide where it is possible to visualise the parasite (25). This technique is simple, fast and can provide the malaria specie and the parasite. However, the main disadvantage is reliability of theirs result, which depends on the reliability of the laboratory performing the test (24).

Rapid Diagnostic Tests (RDTs)

The rapid diagnostic test is an alternative test to assist diagnosing malaria. Several types of RDTs are available varying in format and targets.

RDTs tests detect a specific antigen (protein) produced by malaria parasites. The main advantage of this test is the ability to be used in places with few logistical conditions since they do not require the use of electricity and trained laboratory technician. The disadvantage is the difficulty of detecting an infection with a low density of parasites. It is also impossible to determine the malaria species and the type of parasite (24).

Several other tests diagnose or help diagnose malaria, such as Serological tests and or Polymerase Chain Reaction (PCR) technique. However, these tests are not practical for routine diagnosis because of the time it takes to obtain the result and the costs of using these tests.

Risk Groups

Although the disease can occur in any age or region where there is low and/or unstable transmission, some factors increase the risk of the disease. Low or absent immunity is considered one of the major contributing factors to severe malaria (26). So children under five years old are at high risk since they have not yet acquired immunity, which is mainly due to previous infections, which reduces the risk of severe malaria in adults (27).

In addition, pregnancy increases the risk of severe malaria, mainly during the second trimester. However, the risk may vary according to the woman's age and the number of pregnancies the woman has had, with the first pregnancy increasing the risk.

Symptoms

The first symptom usually appears 10 to 15 days after the bite by the infected mosquito (28). The symptoms are associated with the rupture of erythrocytes following the invasion of red blood cells. Generally, the first rupture is silent and causes no symptoms, but as asexual reproduction is repeated, the number of parasites increases and the immune system response increases (27). It is believed that cellular substances released during the immune response are responsible for the onset of symptoms (29).

Fever is the main symptom of malaria, however in many cases it is accompanied by other symptoms such as muscle pain, nausea and vomiting, general malaise, chills and sweats (30).

1.2.4. Fever

The association of cyclic fever with malaria and its classification goes back a long time, even before the discovery of plasmodia. The Chinese, Greeks, and Indians documented the relationship between the symptom and the disease and the relationship with homes located in swamps. Currently, fever is considered one of the most common symptoms of uncomplicated malaria (30).

The fever in malaria cases can be classified according to parasite type. For Plasmodium *ovale* and plasmodium *vivax* where the brood of schizonts reaches maturity every 48 hours, the fever is called terterian. Plasmodium falciparum also has the brood schizonts maturity of 48 hours, but the fever usually is irregular, as it does not have fixed periodicity. For *P. malariae,* where the periodicity is 72 hours, the fever is called quartian (29).

Not all cases of fever mean malaria, and not all cases of malaria have a fever. Several studies across the world have explored the relationship between fever and malaria. In countries with high transmission of the disease in Sub-Saharan Africa and Oceania, the proportion of malaria-positive cases within cases with self-reported fever was estimated to range from 45 to 76% (31,32), while the proportion of malaria-positive cases of 3% was found in febrile patients (temperature >=38^{o}C) in Colombia (33).

Many cases of malaria are asymptomatic, and other diseases cause the fever. However, when testing people with a fever, these cases test positive for malaria, overestimating the cases of fever caused by malaria. This phenomenon creates a need to estimate the proportion of fever that is attributable to malaria. Several studies using different techniques have been used to estimate the proportion of fever cases caused by malaria. Some of the techniques include the following two: the first using arithmetic methods and the second using logistic regression (34).

The fraction of fever attributed to malaria was estimated by a cross-sectional study in Ghana to be 48% in the dry season and 77% in the rainy season (35). However, this approach is imprecise, especially in high transmission areas where the parasite prevalence can be high in afebrile cases compared with the febrile group. In these cases, it is advisable to use logistic regression (36).

Using logistic regression, studies in Africa ranged the proportion of fever attributable to malaria from 50.20 to 69% in the rainy season and 11 to 47.90% in the dry season (37,38).

The proportion of fever attributed to malaria in Mozambique in 2009 was estimated to be 37.8% (95% CI 32.9% - 42.7%) (39). In 2014 the estimated proportion increased to close to 60% (40).

A case-control study using multiple surveys estimated the proportion of fever attributable to malaria in the CISM study area as 36% and adjusting per age and survey increase up to 41% (95% CI 38 – 44%) (41).

1.2.5. Health Care Utilisation

According to WHO, to reduce complications in cases of malaria, the patient should be diagnosed and treated within 48 hours after the onset of symptoms (26) and considering that fever is the main symptom of malaria, it was defined:

Early health care utilisation as the patient's attendance at the health facilities no more than 48 hours after the onset of symptoms (fever).

Hospitalisation in the peripheral health centres (without conditions for inpatient) is the transfer of the patient to the referral hospital, while for those treated directly in the referral hospital is the referral of the patient to the short-stay inpatient.

Early Health Care Utilisation and Hospitalisation

A survey conducted in sub-Saharan region households from 2015-2019 found a country median proportion of 64% of children under five who reported fever in the last two weeks sought treatment (2). In Mozambique, the proportion of children reporting fever and, thereafter, seeking treatment was estimated in 2018 to be 69% (42).

Several studies have been done to study the relationship between early or delayed health care and severe malaria. Case control studies have been the most prominent in these studies. For example, considering a delay in effective treatment as a result of drug resistance, a case-control study in the Gambia found a positive association between severe malaria and chloroquine resistance-associated of 1.27 to 1.65 Odds Ratio (OR) for *pfmdr1 86Y* and *pfcrt 76T + pfmdr1 184F* alleles respectively. However, it was not statistically significant at the 5% level (43).

Studies using the days after the onset of fever that the patient takes before seeking health care have found a positive association between delay in seeking health care and severe malaria. However, this association varies depending on the region where the study was conducted, the number of days considered, the definition of delay in seeking medical care and the study type (44–47).

A systematic review exploring the delay in malaria diagnosis in non-endemic regions in North Africa, Europe and the USA investigating people with malaria acquired during travel to endemic

areas concluded that a delay of more than 4 days in diagnosis was associated with the development of severe malaria (48).

Another systematic review using pooled data of 13 studies from different regions of the world, including Mozambique and considering a delay in health care seeking as >24 hours after onset of symptoms found a statistically significant association between delay to health care seeking and severe malaria with OR 1.33,95% CI:1.07–1.64 (49).

1.2.6. Socioeconomic Factors Associated with Early Health Care Utilisation

Several studies around the world have attempted to explore the factors that lead people with malaria and fever symptoms to seek health care services. In general, they identify five groups of determinants that influence the early or late seeking of health services:

Health facility-related factors, such as distance to the health facility and quality of service; **mother-related factors**, such as age, education and marital status; **child-related factors**, such as age, immunisation, insecticide-treated nets, number of children in the household; **social environment-related factors**, such as habits, infrastructure; and **disease-related factors**, such as symptoms presented and the severity of symptoms (50).

Despite convergence on some factors, such as living with both parents and distance to the nearest health centre, factors vary across studies (50–53), which makes sense in a way because ethnicity and beliefs also influence the attitudes of a community, and these characteristics are unique to each community.

Another determinant that has been identified is social-economic status (SES), as being highly associated with delayed health seeking (54–56).

1.3. Problem Statement

In Mozambique, despite an improvement in seeking medical care for children with fever from 56% in 2011 to 63% in 2015 and 69% in 2018 (in the last two weeks prior to the survey). In 2018 among those who sought treatment, only 64% sought it in a health facility, and this reveals that the challenge still exists in sensitising communities to seek health services (26).

Malaria must be diagnosed and treated as soon as possible because even uncomplicated malaria, if left untreated, can progress rapidly and become severe, especially in people with low

immunity. Severe malaria cases result in death and hospitalisation, causing enormous expenditures for local government (42). However, there is little evidence of this relationship in Mozambique, particularly in the study area. Bringing evidence of this relationship in the study area will not only support the WHO's warning regarding the importance of early health care seeking but also provide the national health authorities with local data to guide evidence-based health policies.

In the last 20 years, malaria cases and mortality have decreased in the country. However, this reduction was not uniform. Understanding the factors that influence the early seeking of health services may help to accelerate the reduction of malaria cases and mortality through campaigns to reduce the risk factors for the late seeking of health services.

1.4. Justification

This work produces information that can help reduce malaria morbidity and mortality in the community through evidence that early health care seeking reduce the risk of severe malaria, guiding to improvement of public health policies in the community and the country.

1.5. Research Question

1. What is the relationship between early healthcare utilisation and malaria hospitalisation among under-five-year children in Manhiça, Mozambique?

2. What factors are associated with early healthcare utilisation among under-five-year children with malaria in Manhiça, Mozambique?

1.6. Aim

The aim of this study is to determine the socioeconomic factors associated with early healthcare utilisation and its effect on hospitalisation among under-five year children with malaria in Manhiça, Mozambique.

1.6.1. Specific Objectives

- To describe the distribution of socioeconomic factors, early healthcare utilisation, and malaria hospitalisation among under five years old in Manhiça, Mozambique.
- To determine the association between early health care utilisation and hospitalisation among under-five-year children in Manhiça, Mozambique.

- To determine the association between demographic and socioeconomic factors and early healthcare utilisation among under-five-year children in Manhiça, Mozambique.

2. METHODS

2.1. Study Design

It was conducted a health facility-based observational longitudinal study where malaria cases were identified in an ongoing surveillance database and their exposure information to evaluate the association.

In this study, were considered only the first visit on the first contact with health centre of all children that visited any of Manhiça health facilities during the study period.

2.2. Primary Study

The study used data from demographic and morbidity surveillance established in the health centres of Manhiça district in Mozambique by the Manhiça Health Research Centre (CISM, initials in Portuguese).

Morbidity surveillance is carried out in five peripheral health centres and two district hospitals. In the peripheral health centres, there is only a screening or outpatient, and the children with severe symptoms are transferred to the district hospital. The district hospitals have services that include screening, short-stay outpatient and inpatient.

Morbidity surveillance consists of two forms, the outpatient and inpatient forms.

The outpatient form collects information at the health facility, from screening up to short-stay inpatient (less than one day). This form collects demographic information, anthropometrics information, malaria sample identification, clinical symptoms information, and information on the physical examination, screening and short-stay inpatient diagnostics and outcome.

The inpatient form collects information on middle and long-term inpatients. This form is only filled in the district hospital. It collects demographic information, clinical symptoms information at the hospitalisation time, information on the physical examination at the hospitalisation time, neurological information, laboratory exams and the respective results, the treatment and the outcome.

Demographic surveillance has several forms. The core or main forms are: A birth form that registers all births in the study area, the form of the deaths that registers all deaths in the study area, the household form that collects socioeconomic information of the household and the

individual form that collects information of all individuals. The individual form also collects information about immigration and outmigration.

2.3. Study Site

The study was conducted by CISM. The CISM research area is the entire district of Manhiça, a semi-rural area located in southern Mozambique.

2.4. Study Population

In 2015 there were 81 147 children under 15 years of age in the study area, of which 28 138 (34.68%) were children under five.

The current study population was all children under five years of age and permanent residents of Manhiça (residing for more than 3 months) with fever, who attended the outpatient screening in the CISM surveillance health facility from 2016 to 2019 and tested positive for malaria.

2.5. Sampling

The current study used secondary data. The cases were a first visit to the outpatient departments of the CISM study area and with malaria confirmed by RDT or blood smear.

2.6. Data Collection

The data were collected as a routine procedure in the study area. All outpatient visits filled out a form with the patient's morbidity information. In addition, demographic information, socioeconomic status and mobility information are collected during the household visits that occur at least once a year in the study area.

The morbidity data were collected using a paper form and digitalised using a double data entry system OpenClinica for outpatients. The Demographic data were collected using electronic platforms combining OpenHDS and ODK systems. Continuous data cleaning is carried out for all the platforms.

2.7. Data Management

The first outcome was the early health care seeking, a binary variable indicating whether the attendance was no more than two days with fever or not. The explanatory variables were the categorical variables poverty index, head of household, mother education, mother occupation,

living with parents and age of parents. The continuous variable was the distance to the health centre.

The second outcome was a binary variable hospitalisation (hospitalisation or transfer to a referral hospital was considered as a consequence of complicated malaria). The explanatory variables were the binary variable early health care seeking (no more than 2 days with fever), categorical variable malnutrition (an indicator of low immunity), poverty index, head of household, mother education, mother occupation, living with parents, and the continuous variables age of parents and distance to health facilities.

Variable definition

Poverty Index

The **poverty index (PI)** used was a modified multidimensional poverty index. The measure is based on eight indicators that classify households as being in need of assistance or not. The indicators consist of all school-age children in the household attending school, the maximum number of years any household member can have been in school (over five), the presence of electricity, improved access to water and sanitation, the type of flooring, the type of cooking fuel used, and a list of assets. Families who have more than four depraved indicators are considered poor. This index was used by Lancet Noncommunicable Diseases and Injuries (NCDI) Poverty Commission.

The poverty index is a binary variable coded 1 for a poor family and 0 for not poor.

Distance to the health facility

For the distance to the health facility, it was used the distance to the nearest health centre from the residence of the child's household in the year of the visit. The distance was calculated between two geographical points to obtain the distance in kilometres.

Early Health Care Seeking

The variable early health care attendance was coded 0 for children who sought treatment after more than 48 hours and 1 for those who sought treatment within 48 hours of fever.

Time

A time is a calendar year extracted in visit date.

Hospitalisation

According to our definition, the hospitalisation variable was coded 0 for children sent home and 1 for those hospitalised.

Missing Data

All records missing data in the outcome variables (hospitalisation and early health care utilisation) were removed from analyses.

A previous year's forward missing imputations to reduce the loss of participants due to missing demographic information. The imputation was done on the demographic database before merging with the screening visit database. First, the demographic database was expanded so that all individuals have all five years of study. Then the imputation was done (filling the information in a specific year with information from the previous year). Finally, it was merged with the screening visit database afterwards.

2.8. Data Analysis

The data analysis was done using R 4.04 and Stata 14.2 software. A flow diagram that describes all outpatient visits, people with and without fever, and people with and without malaria was the first description of the study result.

2.8.1. Descriptive Analysis

The frequency distribution of the explanatory variables in the two groups of the dependent variable was presented in a table.

The chi-square statistical test or the fisher exact test was used to compare the frequency distributions between the two groups for the categorical variables. The Wilcoxon Rank Sum test was used to compare the medians for continuous variables.

2.8.2. Multivariate Analysis

Model Selection

The model was built from an empty model, and new variables were added in order to improve the model. In the first step, the univariate model was estimated, and the model with the explanatory variable with the lowest p-value was chosen as the first reference model. In the second step, a nested model with a new variable was estimated and compared to the reference model using the likelihood ratio test (LRT) to see if the new variable improves the model. If the new model with the additional variable is found to be better than the previous model, in that case, the new model becomes the reference model, and the process is repeated.

Multilevel Analysis

Longitudinal data is a particular case of multilevel cluster data with two-level or clusters with a nested subject, where the subject can be considered a cluster. A particular feature of longitudinal data is that the individual is ordered over time (57).

Using Longitudinal data allows for a more efficient estimation of the parameter, and with the additional information for the same individual, It also provide more reliable estimates. In addition, longitudinal data has the advantage of controlling for individual heterogeneity (58).

The regression model is:

$$y_{it} = \alpha + \beta x_{it} + u_{it}$$

Where i represent the cluster and t a time: $i = 1,2,3 \ldots \mathrm{N}$ and $\mathrm{t} = 1,2,3..\mathrm{T}$ =

The error component has the specification

$$u_{it} = \mu_i + \gamma_{it}$$

Where the μ_i's are cross-section specific components and γ_{it} are remainder effects. In the literature, μ_i is also called unobserved component, latent variable and unobserved heterogeneity.

The parameter of the model above can be estimated using:

Pooled OLS

The Pooled OLS estimators are considered consistent if the error components are not correlated with the explanatory variable $E(x_{it}u_{it}) = 0$ (59).

Fixed Effects Model

This model assumes that the cross-section-specific components are fixed parameters, so (μ_i) is treated as a parameter to be estimated. And the error component becomes.

$$u_{it} = \sum_{i=1}^{N} \mu_i D_i + \gamma_{it}$$

Where D_i is a dummy variable for $i - th$ cluster, the γ_{it} are independent and identically distributed with mean 0 and variance σ_γ^2. However, this method has two main problems. First, the high number of dummy variables also increases the risk of multicollinearity (58). Second is the loss of degrees of freedom due to the high number of parameters to be estimated. In logistic regression, this leads to inconsistent estimators because the number of cluster-specific intercept increase with the number of clusters (57).

Random Effects Model

It is also known as the mixed effects model. In this model, the cross-section-specific component is assumed random. That is $\mu_i \sim idd(0, \sigma_u^2)$, $\gamma_i \sim idd\left(0, \sigma_\gamma^2\right)$ and γ_i and μ_i are independent $E(\gamma_{it}|x_i, \mu_i) = 0$.

The independence in the assumption above implies that $var(u_{it}) = \sigma_\mu^2 + \sigma_\gamma^2$ for all $i \; and \; t$. The covariance matrix over time of the error component of the same individual will be:

$$cov\left(u_{it}, u_{js}\right) = \sigma_\mu^2 + \sigma_\gamma^2 \text{ for } i = j, t = s$$

$$cov\left(u_{it}, u_{js}\right) = \sigma_\mu^2 \text{ for } i = j, t \neq s$$

And zero otherwise. The interclass correlation coefficient will be:

$$\rho = 1 \text{ for } i = j, t = s$$

$$\rho = \frac{\sigma_\mu^2}{\sigma_\mu^2 + \sigma_\gamma^2} \text{ for } i = j, t \neq s$$

The correlation ρ is a valuable measure of the relativity importance of cross-section-specific or unobserved components (59).

In a generalised linear model, the random effect model becomes:

$$logit\{\Pr(y_{it} = 1|x_{it}, \mu_i)\} = \alpha + \beta x_{it} + \mu_i$$

And the intraclass correlation

$$\rho = \frac{\sigma_\mu^2}{\sigma_\mu^2 + \frac{\pi^2}{3}}$$

The equation parameters are estimated using Maximum likelihood (ML), representing the population mean for the population cluster. The odds ratios are interpreted normally with the null hypotheses $H_0: OR = 1$ (57).

In this study the clustering was done at a health center level.

2.9. Ethical Considerations

The national ethical committee approved the primary study protocol for Mozambique. CISM's internal scientific committee granted permission to use the data through approval of the secondary data analysis application (Appendix two).

Wits Human Research Ethics Committee (Medical) approved the protocol. The clearance certificate number is M220433, and a copy of the ethical approval is attached (Appendix one).

3. RESULTS

3.1. Study Profile

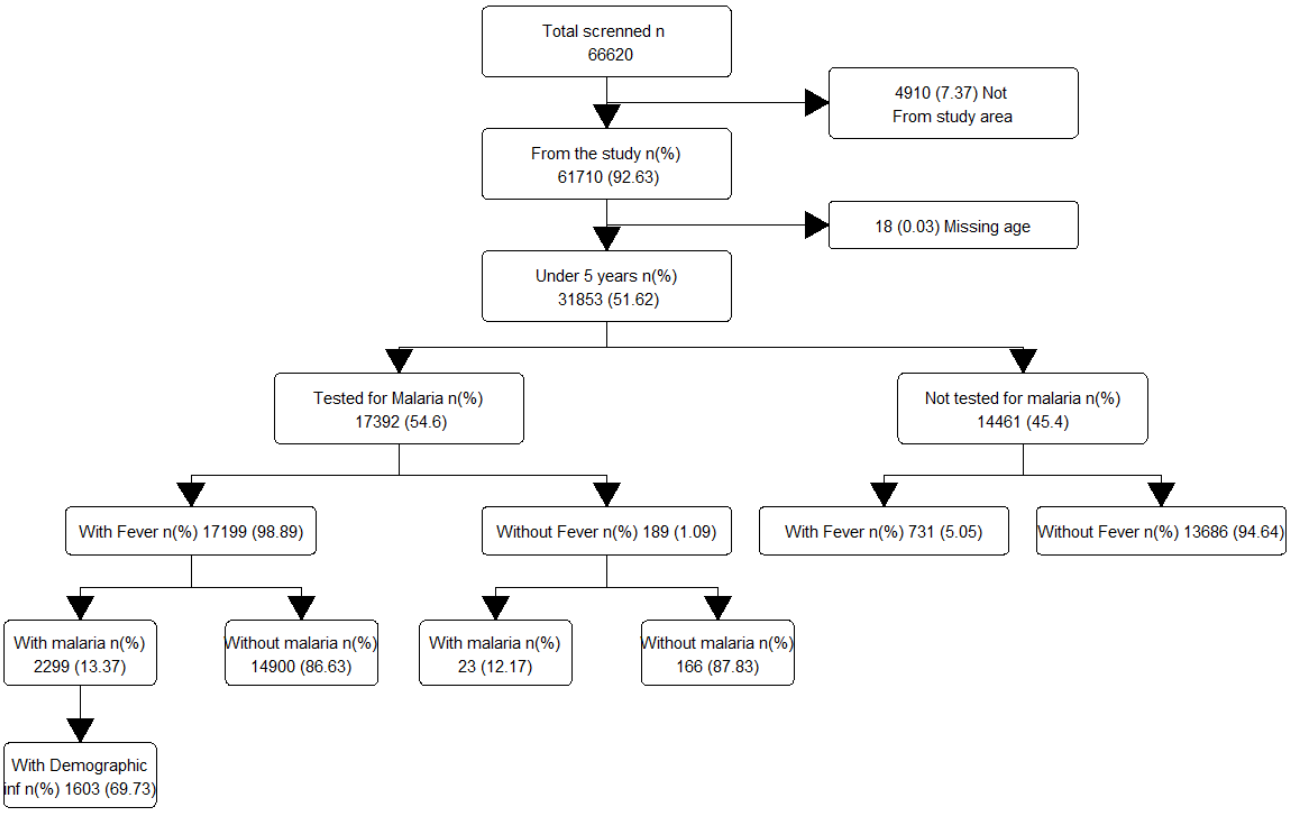

Figure 6. Profile of children under 15 years old on their first visits to health centres from 2016 to 2020

From 1 January 2016 to 31 December 2022, the health centres in the study area received 66 620 children in screening aged 0 to 15 years. Were excluded 4 910 children that do not belong to the study area and 18 children that have missing age information. Excluding children over five years, remaining with 31 853 children for further analysis.

The malaria test was performed on 17 392 children (54,60%), of which 17 199 children (98.89%) reported fever, while only 5.05% of 14 461 children from those who were not tested reported fever.

In total, for children under five years tested for malaria, 7 765 (44.65%) children were tested using a blood smear test, 9 542 (54.86%) children were tested using RDT and only 85 (0.49%) children tested using both blood smears and RDT tests during the study period.

Of the children with fever, 2 299 (13.37%) had malaria confirmed, while 23 (12.17%) of children in the group of children without fever had malaria confirmed.

Subsequent analyses are restricted to children with fever who tested positive for malaria and have demographic information.

3.2. Association Between Hospitalization and Early Health Care Utilization

3.2.1. Prevalence of Early Health Care Seeking by Administrative Area

The prevalence of Early Health Care Seeking varies across the administrative area, from the worse region, Maluane, with 81.06%, to the best region Ilha Josina Machel with 94.57%.

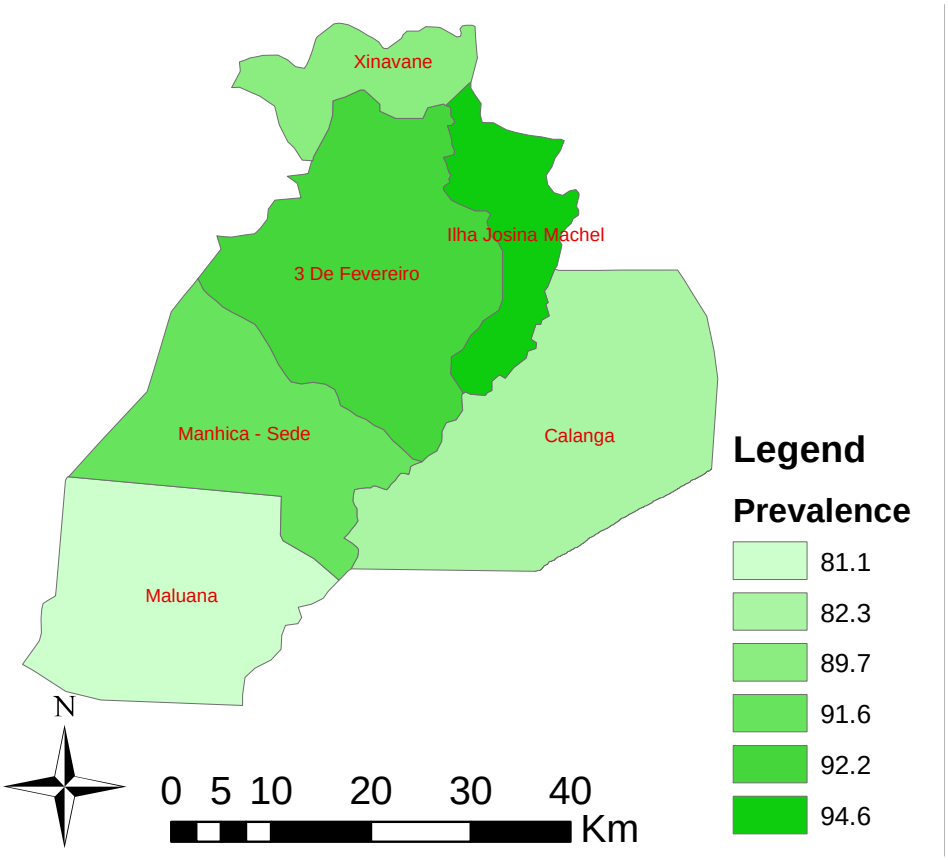

Figure 7: Prevalence of early health care seeking by administrative area

3.2.2. Prevalence of Hospitalisation by Administrative Area

In the study area, hospitalisation varies in the administrative posts, with the best scenario in Ilha Josina, with a prevalence of hospitalisation of 0.45% and the worst scenario in Maluane, with a prevalence of 33.33%.

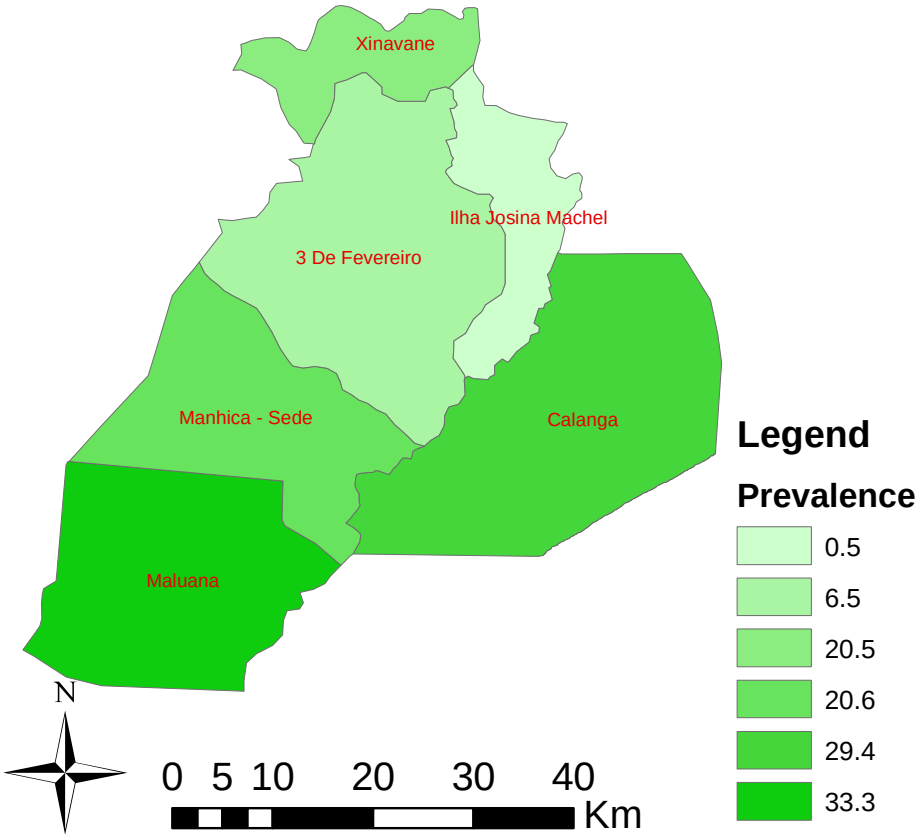

Figure 8: Prevalence of hospitalisation by administrative area

3.2.3. Characteristics of Children Recruited for the Study

The socioeconomics caracteristics of children recruited to the study are presented and compared between the groups in outcome variable. In table 1 it is presented all socioeconomics caracteristcs that was found relevant to explain early health care seeking according to the literature and available in the database.

The education was coded accoding to the national education system where from grade 1 up to grade 7 correspond the primary education. The mother and head of household age was calculated in years, and, the distance from the household to the helth center was calculated in kilometres.

Factors Associated with Early Health Care

Regarding the factors associated with an early search for health care seeking (table 1), it was found that out of 1603 children recruited to the study, only 133 (8.30%) sought health care services late.

It was found statistically significant differences in the distribution of the mother's education in the two groups of children, those who sought health services early and those who sought them late (p-value =.0203). was also found statistically significant differences between the median distances to the nearest health centre between the two groups.

t was shown that, there is a marginally significant difference in the frequency distribution of children according to their mother's age between the two groups (p-value = 0. 0800), as well as in frequency distribution between children according to the head of household education between the two groups.

Table 1. Characteristics of children by time to health centre visits in the first outpatient visits to the health facility from 2016 to 2019

Variable		Early Health Care Seeking		p-value
		No	Yes	
Severe Malnutrition	No	133 (95.68)	1,404 (95.90)	0.9015 [1]
	Yes	6 (4.32)	60 (4.10)	
Living with parents	Not with father or mother	10 (7.19)	71 (4.85)	0.5853 [1]
	live only with father	3 (2.16)	26 (1.78)	
	live only with mother	54 (38.85)	624 (42.62)	
	live with both	72 (51.80)	743 (50.75)	
Mother education	Without formal education	27 (19.42)	312 (21.31)	0.0203 [1]
	Primary education	99 (71.22)	1,091 (74.52)	
	Secondary and higher	13 (9.35)	61 (4.17)	
Head education	Without formal education	35 (25.18)	405 (27.66)	0.3444 [1]
	Primary education	98 (70.50)	1,024 (69.95)	
	Secondary and higher	6 (4.32)	35 (2.39)	
Mother Occupation	Unemployed	18 (12.95)	171 (11.68)	0.6766 [1]
	Employed	121 (87.05)	1,284 (87.70)	
Head Occupation	Unemployed	11 (7.91)	106 (7.24)	0.7365 [1]
	Employed	118 (84.89)	1,271 (86.82)	
Mother age	12-<18	2 (1.44)	53 (3.62)	0.0800 [1]
	18-<24	62 (44.60)	506 (34.56)	
	24-<30	33 (23.74)	380 (25.96)	
	>-30	42 (30.22)	525 (35.86)	
Head age	10-<18	0 (0.00)	11 (0.75)	0.7330 [2]
	18-<24	10 (7.19)	80 (5.46)	
	24-<30	20 (14.39)	218 (14.89)	
	>-30	109 (78.42)	1,155 (78.89)	
Poor billion Index	No	51 (36.69)	467 (31.90)	0.2483 [1]
	Yes	88 (63.31)	997 (68.10)	
Distance to the nearest health centre (Km) median (IQR) n		2.62 (2.79) [139]	2.12 (2.06) [1464]	0.0008 [3]
Health Center	Manhica	66 (47.48)	371 (25.34)	< 0.01 [1]
	Maragra	6 (4.32)	159 (10.86)	
	Ilha Josina	12 (8.63)	213 (14.55)	
	Taninga	7 (5.04)	67 (4.58)	
	Nwamitibjana	12 (8.63)	437 (29.85)	
	Malavela	36 (25.90)	217 (14.82)	

1: Chi-squared test; 2: Fisher's exact test; 3: Wilcoxon Rank Sum test

Table 2. Characteristics of children in the first outpatient visits to the health facility from 2016 to 2019

Variable		Hospitalisation		p-value
		Home n(%)	Hospitalized n(%)	
Early health care attendance	No	105 (7.40)	34 (18.38)	< 0.0001 [1]
	Yes	1,313 (92.60)	151 (81.62)	
Severe Malnutrition	No	1,362 (96.05)	175 (94.59)	0.3485 [1]
	Yes	56 (3.95)	10 (5.41)	
Living with parents	Not with father or mother	71 (5.01)	10 (5.41)	0.9360 [2]
	live only with father	27 (1.90)	2 (1.08)	
	live only with mother	599 (42.24)	79 (42.70)	
	live with both	721 (50.85)	94 (50.81)	
Mother education	Without formal education	316 (22.28)	23 (12.43)	0.0001 [1]
	Primary education	1,046 (73.77)	144 (77.84)	
	Secondary and higher	56 (3.95)	18 (9.73)	
Head education	Without formal education	409 (28.84)	31 (16.76)	0.0001 [2]
	Primary education	978 (68.97)	144 (77.84)	
	Secondary and higher	31 (2.19)	10 (5.41)	
Mother Occupation	Unemployed	154 (10.86)	35 (18.92)	0.0016 [1]
	Employed	1,255 (88.50)	150 (81.08)	
Head Occupation	Unemployed	102 (7.19)	15 (8.11)	0.6202 [1]
	Employed	1,232 (86.88)	157 (84.86)	
Mother age	12-<18	49 (3.46)	6 (3.24)	0.2607 [1]
	18-<24	501 (35.33)	67 (36.22)	
	24-<30	356 (25.11)	57 (30.81)	
	>-30	512 (36.11)	55 (29.73)	
Head age	10-<18	10 (0.71)	1 (0.54)	0.2122 [2]
	18-<24	83 (5.85)	7 (3.78)	
	24-<30	202 (14.25)	36 (19.46)	
	>-30	1,123 (79.20)	141 (76.22)	
Poor billion Index	No	445 (31.38)	73 (39.46)	0.0271 [1]
	Yes	973 (68.62)	112 (60.54)	
Distance to the nearest health centre (Km) median (IQR) n		2.10 (1.98) [1418]	2.81 (3.19) [185]	< 0.0001 [3]
Health Center	Manhica	277 (19.53)	160 (86.49)	< 0.0001 [1]
	Maragra	158 (11.14)	7 (3.78)	
	Ilha Josina	225 (15.87)	0 (0.00)	
	Taninga	74 (5.22)	0 (0.00)	
	Nwamitibjana	436 (30.75)	13 (7.03)	
	Malavela	248 (17.49)	5 (2.70)	

1: Chi-squared test; 2: Fisher's exact test; 3: Wilcoxon Rank Sum test

Factors Associated with Hospitalisation

As shown in table 1, the first visit to a health facility during the study period, was found that between children who were hospitalized 18.38% sought health service later. While for those who were sent home only 7.4% of the children sought for health service later. The difference between the two proportions was statistically significant ($p < 0.001$) table 2.

It was also found a statistical difference in the distribution of mother and head education, mother occupation and health facilities between the group of children hospitalised and those who were not hospitalised. There was also a statistical difference between the median distance from the child's household to the nearest health facility in hospitalised and non-hospitalised groups.

The difference between the proportions of children with severe malnutrition in those who were hospitalized (5.41%) and those who were not hospitalised (3.95 %) after screening was not statistically significant.

Model one - Hospitalisation

Table 3. Result of multivariate analysis of factors associated with hospitalisation adjusted for a clustering at health center level.

Variables		**Adjusted analyses**	
		OR	**95% CI**
Early health care attendance	No	Ref	
	Yes	**0.56**	**0.34-0.93**
Severe Malnutrition	No	Ref	
	Yes	1.83	0.80-4.21
Time (year)		**1.66**	**1.41-1.93**
Intraclass correlation		**0.06**	**0.02-0.09**

There is a statistically significant difference between the variability of observation in different health centres. The variability attributable to the health facility in the model is 6.1% (p-value <0.001) of the total variance.

The hospitalisation model includes early health care seeking, malnutrition and year of visit

On average, children that sought early health facilities had 0. 56 times less odds of hospitalisation when compared to those who sought health facilities later (aOR = 0. 56 ; 95% CI: [0.34 -0.93]; p-value =0.001). This reduction is statistically significant.

For each unit increase in time (year), the odds of hospitalisation have a significant statistical increase on average by 66.2% (aOR = 1.66; 95% CI: [1.41-1.93]; p-value <0.001).

Model two – Early Health Care Seeking

There is a statistically significant difference between the variability of observation in different health centres. The variability attributable to the health facility in the model is 13,19% (p-value <0.001) of the total variance.

Looking at the factors associated with EHCS, the model included the explanatory variables, distance to the nearest health centre (km) and mother's age.

It was found that for each unit increase in the distance to the health centre, the odds of early health care seeking have, on average, a statistically significant reduction of 11.10% (p-value <0.001).

Although not statistically significant, was found that the odds of early health care seeking were reduced among older mothers (-66.85%) for 18-<24 age, (-53.00%) for 24-<29 age and (-52.40%) for >30 age group when compared to mother of 12-<18 years age group.

Table 4. Result of multivariate analysis of factors associated with early health care seeking adjusted for a clustering at health center level.

Variables		**Adjusted analyses**	
		OR	**95% CI**
Mother age	12-<18	Ref	
	18-<24	0.70	0.07-1.27
	24-<30	0.47	0.12-2.05
	>-30	0.48	0.13-2.05
Distance to the nearest health centre		**0.89**	**0.83-0.95**
Intraclass correlation		**0.13**	**0.04-0.36**

4. DISCUSSION

The study determined the socioeconomic factors associated with early health care seeking and the effect of early health care seeking in hospitalisation among under-five years children with malaria in Manhiça.

In this study was found that early health care seeking can be explained by health facility-related factors and mother-related factors. The distance to the nearest health facility was the statistically significant factor associated with early health care seeking. In turn, looking at factors associated with hospitalisation, the early health care seeking and time (in years) were found to be statistically associated with hospitalisation.

The prevalence of early health care seeking and hospitalisation in the different administrative areas in the study area suggest a relationship between the two phenomena. The regions with a higher prevalence of early health care seeking have a lower proportion of hospitalisations compared to areas with a higher prevalence of early health care seeking.

It was found that in the study area, fever is an essential criterion for malaria testing, where 95.92% of children who had fever were tested for malaria as recommended by WHO in the endemic malaria area (26). The study found only 13.37% of children with fever that have malaria, while 99.01% of children with malaria have a fever. This result should be interpreted carefully, as this region has high malaria transmission. The proportion of fever cases in which fever can be seen as a result of malaria may be overestimated, as asymptomatic malaria children who have fever from other causes when tested for malaria will be confirmed as malaria-positive cases even if the fever was not caused by malaria as reported in previous studies (34,39). This can be supported by the fact that the proportion of malaria in children with fever 13.37% is approximately equal to that of malaria in children without fever 12.17%, making it even more difficult to discuss any causal relationship between fever and malaria.

The study found that the increased distance between the nearest health centre and the child's residence reduces the risk of early seeking health services. This finding confirms already reported association by the malaria indicator survey that the distance to the health centre was the main reason for not seeking health services(42). It is also in line with the results of several studies done in African and Asian countries that suggested an association between early health care seeking

and distance to health facilities (45,46,52–55). A long distance to the health centre also implies a long time outside of the home, and for a mother with more than one child, it means leaving other children at home, which can influence the mother's decision to seek health services. Studies show that families with more than one child are more likely to seek health services late when compared with those with only one child(52). On the other hand, the distance implies costs considering the economic difficulties of many families in the study area and the country in general. Therefore, it is very likely that a mother will have to consider the cost of transport when deciding to seek health services.

To achieve the country's goal of reducing or eliminating malaria, the government should consider the construction of health centres and reduce the distance to the health centre and, consequently, the number of hospitalisations.

Although not statistically significant, the study also suggests a low odds of early health care seeking for mothers aged 18 years and over compared to mothers aged 12 to 18 years. In previous studies, were reported evidence suggesting that mothers with more than one child are more likely to delay seeking health services when compared with mothers with only one child(52). It can hypothesise that older mothers are more likely to have more than one child, and the result can be seen firstly as a consequence of the experience of older mothers with their other children as well as the difficulty mentioned above that mothers should leave their underage children alone when they go to the health centre. This finding is consistent in both self-report in community studies as well as hospital-based studies (60–62).

This study did not find evidence that was living with parents or not, mother occupation, mother education, head age, head education and poor billion indexes have any association with early health care seeking.

Further, it was found that early health care seeking has a strong association with the reduction of hospitalisation OR = 0.56 (0.34-0.93). Untreated malaria can progress to severe malaria, where the infected person has a risk of developing cerebral malaria, severe anaemia, haemoglobinuria, acute respiratory distress syndrome, abnormalities, low blood pressure, acute kidney injury, hyperparasitemia, metabolic acidosis, coma and death. This result is in agreement with all the studies that evaluated the relationship between early health care seeking and the development of

severe malaria regardless of the mechanism used to measure early health care seeking or severe malaria (42,43,45–49)

Although not statistically significant, it was found that children with severe malnutrition have higher odds of hospitalisation when compared with children without malnutrition. This result also confirms what the literature says about malnutrition as a significant risk factor for developing severe malaria in people with moderate malaria (26,63).

The study started in 2016 and ended in 2020. It suggests that an increment in a year of visits to the health centre also increased the odds of hospitalisation in children with malaria. However, southern Mozambique has seen a decrease in the number of malaria cases in recent years(5). This association may be the result of the constant reduction of malaria cases in the south of the country where the CISM is located and, consequently, a greater rigidity in the management of cases with malaria where cases that at first would not be considered serious and consequently hospitalised, as the number of children with the pathology reduces in the region, less serious cases tend to be seen as serious and hospitalised.

4.1. Limitations and Strengths

According to WHO, the early seeking of health services has more impact on people with low immunity. However, in this study was used malnutrition as an indicator of low immunity, and the unavailability of traditional biomarkers affected our study.

Some people in the population, especially in urban areas, use the drug directly from the pharmacy. Self-medication can alter the normal cycle life of a disease by changing the period of onset of symptoms. In this study the information regarding self-medication before a health centre visit was not available.

The use of a retrospective study design relies on data previously collected with other objectives. Using the data for this study means losing control of data collection techniques and data cleaning.

Another limitation is associated with the sample's representativeness as the cases were recruited from the health centre, which makes it representative only of the population who use health services, excluding all other individuals who, for various reasons, do not use the health services.

Despite the shortcomings mentioned above, this study is among very few studies that analyse the factors associated with early health care in Mozambique and the effect of early health care on hospitalisation. The study also has the advantage of recruiting from the hospital, which helps us to base on facts regarding whether or not mothers seek health care services.

The study also has a large sample size, giving us more robust results.

5. CONCLUSION AND RECOMMENDATIONS

The findings of this study highlight the importance of early health care seeking in reducing hospitalisation. Furthermore, early health care seeking reduces the odds of hospitalisation. We, therefore, recommend advocacy work with the community to encourage parents to take their children with fever to the health centre within 48 hours.

The southern region of the study area has more significant problems in early health care seeking and consequently a higher rate of hospitalisations, leading us to recommend more attention in the regions of Maluane and Calanga in raising awareness for early health care seeking for children with fever.

Reducing distance to the health facility significantly contributes to increasing early health care seeking, thus reducing hospital admissions. Therefore, the government must make an effort to increase the number of health centres in the community in order to reduce the distance that families have to the health centres.

Another alternative canbe having a focal point in the community with basic health training to do a first triage and advice members of community regarding health issue. Canalso be solution to allocate ambulance for distant community to transport patient to the health center it would not only reduce time but also costs for caregivers.

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7. APPENDIX

Appendix one – Plagiarism declaration report

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Alberto Aniceto Chauque (Student number: 1644123) am a student registered for the degree of Master of Science in Epidemiology and Biostatistics in the academic year 2022.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: Alberto Aniceto Chauque Date: 10-11-2022

1

Appendix two – Ethics clearance certificate

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R49 Mr AA Chauque

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M220433

NAME: (Principal Investigator)	Mr AA Chauque
DEPARTMENT:	School of Public Health Division of Epidemiology and Biostatistics Medical School University
PROJECT TITLE:	*Socio-economic determinants of early health care utilization and association with malaria hospitalization amongst under-five year old children in Manhiça, Mozambique*
DATE CONSIDERED:	2022/04/29
DECISION:	Approved unconditionally
CONDITIONS:	
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Dr I Maposa
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2022/06/29

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **April** and therefore reports and re-certification will be due in the month of **April** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Alberto Amieeto Chaúque — 05-07-2022

Signature of Principal Investigator — Date

Appendix three – CISM's internal scientific committee approval

cism
centro de investigação em saúde de manhiça

INTERNAL SCIENTIFIC COMMITTEE OF CISM
(CCI)

Attention:
To Whom it may concern

Ref: CCI/017/JUN/2022 Manhiça, 07th June 2022

Subject: Institutional authorization to the utilization of the CISM Data Base by the study entitled *"Socio-economic determinants of early health care utilization and association with malaria hospitalization among under-five year children in Manhiça, Mozambique;*

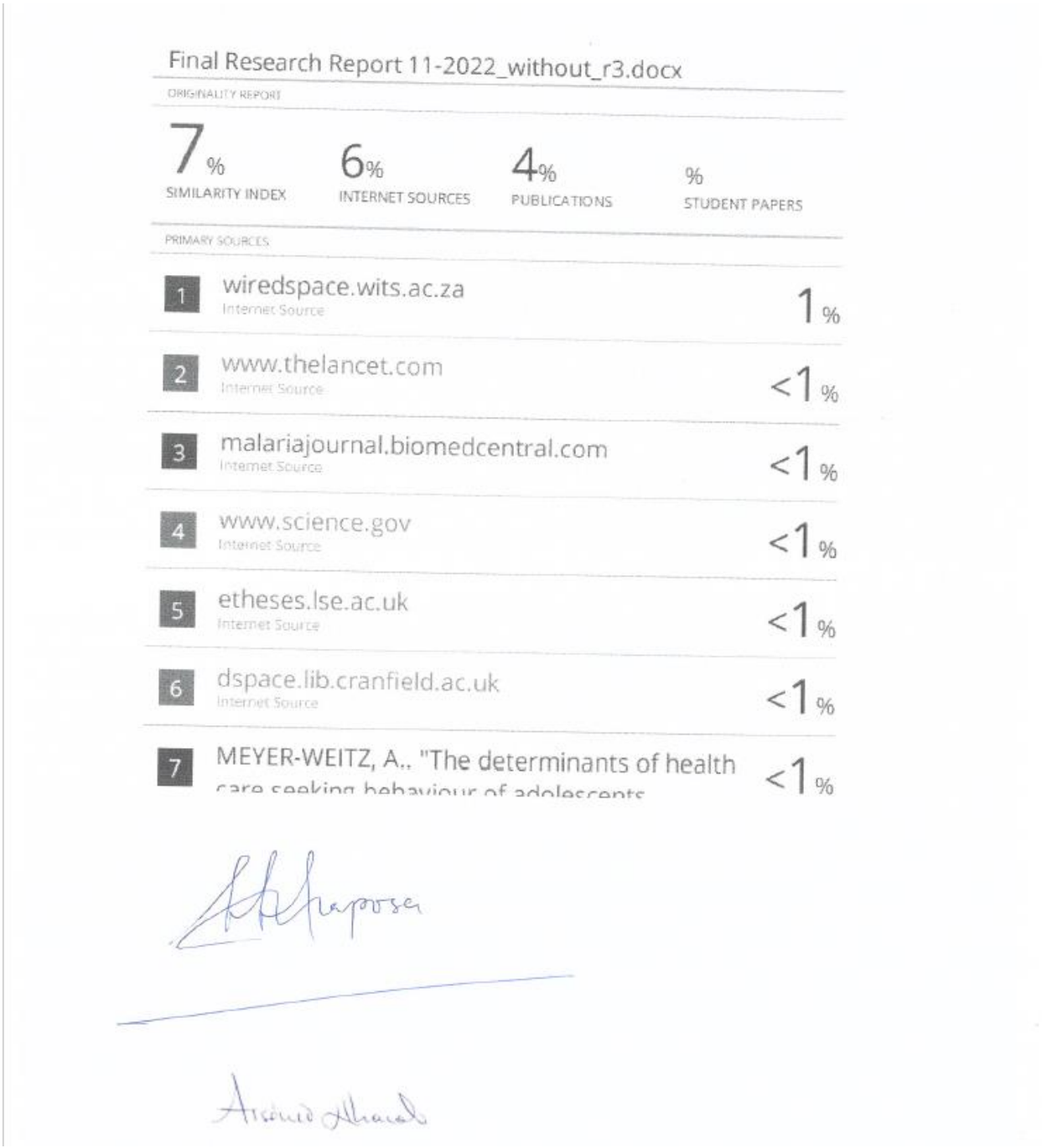
The Internal Scientific Committee, strongly support the implementation of the aforementioned scientific protocol using the CISM scientific database. However, it is emphasized that the provided data should only be used as described in the protocol and should not be shared to third parties without prior authorization from this Committee according to the CISM internal procedures. Furthermore, the results from this study should be shared with this committee prior to publication.

Yours sincerely,

Pedro Aide

Chairperson of CCI

Appendix four – Turnitin report signed by supervisor



Final Research Report 11-2022_without_r3.docx

ORIGINALITY REPORT

7%	6%	4%	%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

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2	www.thelancet.com Internet Source	<1%
3	malariajournal.biomedcentral.com Internet Source	<1%
4	www.science.gov Internet Source	<1%
5	etheses.lse.ac.uk Internet Source	<1%
6	dspace.lib.cranfield.ac.uk Internet Source	<1%
7	MEYER-WEITZ, A.. "The determinants of health care seeking behaviour of adolescents	<1%

Appendix five – CISM Outpatient questionnaire (Original in Portuguese)

	Centro de Saúde de Manhiça Centro de Investigação em Saúde de Manhiça INQUERITO DE TRIAGEM OPD 5 SOP_HO_004_A01_v03_PT	Número de serie

DADOS DE INQUERITO

1. Lugar de consulta |__|
2. Data do inquérito (dd/mm/aa) |__|__|/|__|__|/|__|__|
3. Referido de outra triagem CISM (1=Sim, 2=Não) |__|
   Se Sim, número de inquerito de Triagem de referencia |__|__|__|__|__|__|__|

DADOS DA CRIANÇA

4. Número de Estudo |__|__|__|__|-|__|__|__|__|
5. Número de Identificação da criança (perm_id) |__|__|__|__|-|__|__|__|-|__|__|
6. Nome da Criança |__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|
7. Data de nascimento (dd/mm/aa) |__|__|/|__|__|/|__|__|
8. Sexo (1=homem, 2=mulher) |__|
9. Nome da Mãe |__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|
10. Nome do pai |__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|
11. Chefe agregado |__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|
12. Bairro/Povoação/Acampamento |__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|

MEDIDAS

13. Frequência respiratória (1 minuto) |__|__|__|
14. Peso (Kg) |__|__|.|__|
15. Temperatura axilar (° C) |__|__|.|__|
16. Refere febre nas últimas 24 horas? (1=Sim, 2 =Não) |__|

AMOSTRAS DE SANGUE

17. Tomou amostra de sangue (capilar e as duas laminas) (1=Sim 2=Não) |__|
18. Se Sim, colar NIDA e preencher a folha de amostras
19. Se Não colhida: (1=Sem criterios, 2=Resultados prévios < 24h, 3=Recusou, 4=Outro) |__|
20. Se já tem resultados prévios, copiar o NIDA |__|__|__|__|__|__|__|.|__|

DADOS CLINICOS DA DOENÇA ACTUAL

21. Febre (1=Sim, 2=Não. Nº de dias) |__| ? |__|__|
22. Tosse (1=Sim, 2=Não. Nº de dias) |__| ? |__|__|
23. Dificuldade ao respirar (1=Sim, 2=Não. Nº de dias) |__| ? |__|__|
24. Diarréia (1=Sim, 2=Não. Nº de dias) |__| ? |__|__|
25. Se Diarreia, Nº Fezes nas ultimas 24 horas |__|__|
26. Se Diarreía, Caracteristicas Fezes (1=Aquosas, 2= com sangue) |__|
27. Vómitos (1=Sim, 2=Não. Nº de dias) |__| ? |__|__|
28. Convulsões (1=Sim, 2=Não) |__|

29. Se Tem convulsões, Nº de ataques (convulsões) nas ultimas 24 horas |__|__|
30. Queimaduras (1=Sim, 2=Não) |__|
31. Acidentes (1=Sim, 2=Não) |__|
32. Outro |__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|

EXAME FÍSICO

33. Fontanela (1=Normal, 2=Deprimida, 3=Tensa, 4=N/A) |__|
34. Prega cutanea (1=Sim, 2=Não) |__|
35. Desidratação (1=Não, 2=Leve, 3=Moderada, 4=Grave) |__|
36. Palidez * (1=Sim, 2=Não) |__|
37. Ictericia (1=Sim, 2=Não) |__|
38. Edema (1=Sim, 2=Não) |__|
39. Ouvido supurativo (1=Sim, 2=Não) |__|
40. Tiragem (1=Sim, 2=Não) |__|
41. Adejo nasal (1=Sim, 2=Não) |__|
42. Crepitaçoes/ Sopro tubárico (1=Sim, 2=Não) |__|
43. Sibilos/Roncos (1=Sim, 2=Não) |__|
44. Figado palpável (1=Sim, 2=Não) |__|
45. Baço palpável (1=Sim, 2=Não) |__|
46. Rigidez da nuca (1=Sim, 2=Não) |__|
47. Letargia (1=Sim, 2=Não) |__|

* **Se tem palidez e não tirou amostra de sangue (HTC e HTZ); tirar amostra de sangue**

DIAGNÓSTICO E TRATAMIENTO NA TRIAGEM

48. Resultado de gota espessa (Cruzes) (0=NSE 1=+, 2=++ 3=+++, 4=++++, 5=+++++, 6=Não feito) |__|
49. Resultado de hematocrito (%) (99 = Não feito) |__|__|
50. Diagnostico 1 _____ |__|__|__|__|__|__|
51. Diagnostico 2 _____ |__|__|__|__|__|__|
52. Diagnostico 3 _____ |__|__|__|__|__|__|
53. Diagnostico 4 _____ |__|__|__|__|__|__|
54. Destino após triagem (1=Casa, 2=ICD, 3=Transferência, 4=Abandono) |__|
55. Se for para casa, tratamento (1)|__|__|__|__|__|__| (2)|__|__|__|__|__|__| (3)|__|__|__|__|__|__| (4)|__|__|__|__|__|__|
56. Código , Assinatura, Data |__|__|__| _____ |__|__| / |__|__|/|__|__|

Se tem critérios de inclusão a outros estudos, favor preencher respectivos inqueritos

DIAGNÓSTICO E TRATAMIENTO NO ICD

57. Diagnostico ICD 1 _____ |__|__|__|__|__|__|
58. Diagnostico ICD 2 _____ |__|__|__|__|__|__|
59. Diagnostico ICD 3 _____ |__|__|__|__|__|__|
60. Destino apos ICD (1=Casa, 2=Internamento, 3=Transferencia, 4=Obito, 5=Abandono) |__|
61. Se for para casa, tratamento (1)|__|__|__|__|__|__| (2)|__|__|__|__|__|__| (3)|__|__|__|__|__|__| (4)|__|__|__|__|__|__|
62. Código , Assinatura, Data |__|__|__| _____ |__|__| / |__|__|/|__|__|

REVISÃO FINAL DO INQUÉRITO

63. Código , Assinatura, Data |__|__|__| _____ |__|__| / |__|__|/|__|__|

Appendix six – CISM Outpatient questionnaire (English translation)

OPD5

Database propierties

Form	Paediatrics outpatient questionnaire 5
Group	PCD
VFP format	.T.
Unique expr	SERIALNO
Comment	SOP_HO_004_A01_v03_PT

Indexes

TAG	Expression
__1D70WOVW	SERIALNO

Fields

		Field	Description	Categories	Type	Len	Dec	Min	Max	Format	Error if empty	Active
0	1	QESNUM	Questionnaire number		N	6	0				.T.	.T.
0	2	SERIALNO	Serial number		N	7	0	1			.T.	.T.
1	0	PLACE	Place of visit	PLACE	N	1	0				.T.	.T.
2	0	DATE	Date of visit		D	8	0	01/09/2000			.T.	.T.
3	1	REFERRED	Refered from othre CISM's OPD	YNOU	N	1	0				.T.	.T.
3	2	REF_SERIAL	If refered, refered OPD serial number		N	7	0	0	999999			.T.
4	0	STUDYNO	Study number		C	9	0					.T.
5	0	PERM_ID	Identification number		C	11	0			9999-999-99	.T.	.T.
6	0	NAME	Child's name		C	25	0				.T.	.T.
7	1	DAY_BIRTH	Day of birth		N	2	0	01	31			.T.
7	2	MON_BIRTH	Month of birth		N	2	0	01	12		.T.	.T.
7	3	YEA_BIRTH	Year of birth		N	4	0	1985			.T.	.T.
8	0	SEX	Sex	SEXO	N	1	0				.T.	.T.
9	0	MOTHER_NAM	Mother name		C	25	0				.T.	.T.
10	0	FATHER_NAM	Father name		C	25	0				.T.	.T.
11	0	HEAD_NAM	Household head's name		C	22	0				.T.	.T.
12	0	REGION_NAM	Neighbourhood/Village/Camp		C	15	0				.T.	.T.
13	0	RESPRATE	Respiratory rate per minute		N	3	0				.T.	.T.
14	0	WEIGTH	Weight (kg)		N	4	1				.T.	.T.
15	0	TEMP	Temperature (C)	MISSING	N	5	2	35	44		.T.	.T.
16	0	FEVER2YNO	Referred fever in the past 24 hours	YNOU	N	1	0				.T.	.T.
17	0	SLIDESYNO	Two slides and capilar taken	YNOU	N	1	0					.T.
18	0	BRADY	Sample id		N	9	1			9999999.9		.T.
18	1	BRADYTIME	Sample Time		C	5	0			99:99		.T.
19	0	SLIDESWHY	If not taken, why	SLIDESWHY	N	1	0					.T.
20	1	BRADY2	if previous sample, brady		N	9	1			9999999.9		.T.
21	1	FEVERYNO	Fever	YNOU	N	1	0				.T.	.T.
21	2	FEVERDAYS	Days with fever	MISSING	N	2	0	1				.T.
22	1	COUGHYNO	Cough	YNOU	N	1	0				.T.	.T.

22	2	COUGHDAYS	Days with cough	MISSING	N	2	0	1			.T.
23	0	BREATHYNO	Problems to breath	YNOU	N	1	0			.T.	.T.
23	2	BREATHDAYS	Days with problems to breath	MISSING	N	2	0	1			.T.
24	1	DIARRYNO	Diarrhoea	YNOU	N	1	0			.T.	.T.
24	2	DIARRDAYS	Days with diarrhoea	MISSING	N	2	0	1			.T.
25	0	DIARRNUM	Number of stools in the last 24 hours	MISSING	N	2	0	1			.T.
26	0	DIARCHAR	Stools characteristics	DIARCHAR	N	1	0				.T.
27	1	VOMITYNO	Vomiting	YNOU	N	1	0			.T.	.T.
27	2	VOMITDAYS	Days vomiting	MISSING	N	2	0	1			.T.
28	0	FITTEDYNO	Fits	YNOU	N	1	0			.T.	.T.
29	0	FITTEDNUM	Number of fits	MISSING	N	2	0	1			.T.
30	0	BURNYNO	Burn	YNOU	N	1	0			.T.	.T.
31	0	ACCIDENYNO	Accidents	YNOU	N	1	0			.T.	.T.
32	0	OTHERSYMP	Other symptoms		C	19	0				.T.
33	0	FONTANELLE	Fontanelle	FONTANELLE	N	1	0			.T.	.T.
34	0	FOLDSKIN	Skin fold	YNOU	N	1	0			.T.	.T.
35	0	DESHIDRAT	Deshidratation	DESHIDRAT	N	1	0			.T.	.T.
36	0	PALLOR	Pallor	YNOU	N	1	0			.T.	.T.
37	0	JAUNDICE	Jaundice	YNOU	N	1	0			.T.	.T.
38	0	OEDEMA	Oedema	YNOU	N	1	0			.T.	.T.
39	0	EARDISCHAR	Ear discharged	YNOU	N	1	0			.T.	.T.
40	0	INDRAWIN	Indrawin	YNOU	N	1	0			.T.	.T.
41	0	NASA_FLAR	Nasal flaring	YNOU	N	1	0			.T.	.T.
42	0	CRA_CRE_BT	Crackels/Creps/Bronquial breath	YNOU	N	1	0			.T.	.T.
43	0	WHEEZE_RON	Wheeze/Roncus	YNOU	N	1	0			.T.	.T.
44	0	HEPATOMEGA	Hepatomegaly	YNOU	N	1	0			.T.	.T.
45	0	SPLENOMEGA	Splenomegaly	YNOU	N	1	0			.T.	.T.
46	0	NECK_STIFF	Neck stiffness	YNOU	N	1	0			.T.	.T.
47	0	LETHARGIC	Lethargy	YNOU	N	1	0			.T.	.T.
47	1	RDT	Resultado TDR	RDT	N	1	0				.T.
48	0	THICKSMEAR	Thick smear result	THICK	C	1	0			.T.	.T.
49	0	HTO	Haematocrite Result	MISHTO	N	2	0	5	55	.T.	.T.
50	0	DIAG1	Diagnostic OPD 1		C	5	0	0		.T.	.T.
51	0	DIAG2	Diagnostic OPD2		C	5	0	0			.T.
52	0	DIAG3	Diagnostic OPD 3		C	5	0	0			.T.
53	4	DIAG4	Diagnostic OPD 4		C	5	0				.T.
54	0	AFTERPCD	After OPD	AFTERPCD	N	1	0			.T.	.T.
55	1	TTOPCD1	Treatment OPD 1		C	5	0				.T.
55	2	TTOPCD2	Treatment OPD 2		C	5	0				.T.
55	3	TTOPCD3	Treatment OPD 3		C	5	0				.T.
55	4	TTOPCD4	Treatment OPD 4		C	5	0				.T.
56	0	FIELDWRK1	Initials Code OPD		C	3	0			.T.	.T.
57	0	ICD_DIAG1	Diagnose ICD 1		C	5	0				.T.
58	0	ICD_DIAG2	Diagnose ICD 2		C	5	0				.T.
59	0	ICD_DIAG3	Diagnose ICD 3		C	5	0				.T.
60	0	AFTERICD	After ICD	AFTERICD	N	1	0				.T.
61	1	TTOICD1	Treatment ICD 1		C	5	0				.T.
61	2	TTOICD2	Treatment ICD 2		C	5	0				.T.