Uncomplicated Malaria Infection and Severe Malaria Disease Case Management in Sussundenga District, Mozambique

A DISSERTATION
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Abstract

Malaria case management through prompt diagnosis and artesunate treatment within 24 hours of symptom onset reduces malaria mortality [1]. The Mozambican National Malaria Control Program (NMCP) supports universal access to care; however, malaria health disparities persist [2]. Sussundenga District is a rural community in Western Mozambique, with moderate-high *Plasmodium falciparum* transmission [3,4]. Research focused on health access and case management are traditionally research priorities in settings close to elimination. Few community-based studies on malaria prevention and treatment have occurred in Western Mozambique, although malaria prevalence for children under five was 48% higher in Manica compared to Maputo province in 2019 [5]. This dissertation aimed to (1) measure the community *Plasmodium falciparum* prevalence and symptomatic malaria health-seeking behaviors in a cross-sectional study, (2) determine the impact of ecological health access domains on severe malaria case management based on a case-control study, and (3) identify the facilitators and barriers to severe malaria case management through provider and traditional medicine practitioner interviews at the Sussundenga-Sede rural health center (RHC).

In Manuscript 1, I designed surveys for a pilot cross-sectional study in Sussundenga village. The cross-sectional study occurred from December 2019 to February 2020. The community prevalence and health-seeking behaviors analysis was published in 2022. I analyzed individual and household data on malaria infection risk and factors impacting health-seeking. I identified the community *Plasmodium falciparum* prevalence and individual, household, and provider-level determinants of malaria treatment. I found significant gaps in individual health-seeking behaviors, while the primary site of care to receive the standard diagnosis and treatment was the Sussundenga-Sede RHC.

In Manuscript 2, I designed a convergent parallel mixed-method study based at Sussundenga-Sede RHC from April 2023 to August 2024. I designed surveys, piloted with local providers, and led the completion of a case-control study for quantitative data collection. I compared severe malaria hospitalized cases and non-malarial hospitalized controls to understand ecological health access determinants. The exploratory factor analysis and generated composite variables indicated the built, social, and physical environment components impact health access. I found less built or social environment health access increased the average predicted probability for severe malaria hospitalization.

In Manuscript 3, At the same time as the hospital based case-control study, I designed semi-structured interviews, piloted them with local providers, and led the qualitative data collection. I used thematic analysis, joint display tables, and data integration at multiple levels to understand severe malaria case management facilitators and barriers from diverse key decision makers. I found traditional medicine and traditional medicine practitioners could improve delayed health seeking, a common barrier from all key decision makers.

In partnership with Sussundenga-Sede RHC, the Ministry of Health, and Consultores Associados de Manica, I identified multi-level determinants of malaria infection and severe disease. Future research on key determinants could improve outcomes in Sussundenga district, Mozambique.

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List of abbreviations

ACT: Artemisinin Combination Therapy
AL: Artemether lumefantrine
CARMAL: Community Access to Rectal Artesunate for Malaria study
CM: Cerebral malaria
CHW: Community health workers
DHS: Demographic and Health Surveys
EFA: Exploratory Factor Analysis
iCCM: integrated community case management
ITNs: Insecticide-treated nets
IRB: Institutional Review Board
IRS: Indoor residual spraying
IPTp: Intermittent preventive treatment in pregnancy
KMO: Kaiser Myere Oklin
MIS: Malaria indicator survey
NMCP: National Malaria Control Program
SMA: Severe malaria anemia
SMC: Seasonal malaria chemoprevention
SPAQ: Sulfadoxine-pyrimethamine plus amodiaquine
TA: Thematic analysis
TMP: Traditional Medicine practicioners
RD: respiratory distress syndrome
RDT: rapid diagnostic test
REDCap: Research Electronic Data Capture
RHC: Rural health center
P. falciparum: Plasmodium falciparum
PCR: Polymerase Chain Reaction
WHO: World Health Organization

Chapter 1. Introduction

Malaria transmission occurs due to complex interactions between human hosts, mosquito vectors, and protozoan parasites. In sub-Saharan Africa, there are five species of protozoans including *Plasmodium vivax*, *P. ovale*, *P. malariae*, *P. knowlesi*, and *P. falciparum* . Over 95% of sub-Saharan African malaria cases are attributed to *P. falciparum* transmitted by female *Anopheles* mosquitos [4,6]. Warm temperatures, humidity, abundant sources of standing water, and vegetation promote *Anopheles* mosquito development [7,8]. For the last decade, the predominant vectors with the highest proportion of sporozoites are *An. Gambiae* and *An. Funestus* in Mozambique [9]. Unlike *An. Funestus, An. Gambiae* are resistant to increasing temperatures due to climate change based on longitudinal studies in Southern Mozambique [10].

Malaria life cycle:

The malaria life cycle begins after an infected female *Anopheles* mosquito takes a human blood meal and injects sporozoites, an asexual stage, from the salivary gland into the capillaries of the host's skin [11]. The sporozoites migrate to the liver and replicate asexually for seven to ten days, causing no symptoms. Merozoites are released from the liver into the bloodstream, multiplying within erythrocytes, causing cell lysis. Most merozoites continue this cycle, leading to the hallmark malaria symptom of fever, while some mature into gametocytes, a sexual stage. The gametocytes travel in the bloodstream and are taken up into the mosquito midgut during another human blood meal. The gametocyte matures into gametes, becomes fertilized, and forms sporozoites to complete the life cycle.

Malaria infection and disease

After inoculation, the parasite can remain in the human host for seven to 20 days, before developing symptoms [12]. Infection caused by *Plasmodium falciparum* can last more than a decade, depending on existing immunity, and present with a range of symptom severity[12,13]. Malaria is difficult to detect among asymptomatic infections, caused by exposure to previous malaria infections and age-related acquired immunity [12], while symptomatic infections present with non-specific symptoms such as fever, chills, nausea, fatigue, diarrhea, headache, and vomiting [14]. The pathophysiology of the progression from symptomatic infection to severe disease is unknown and can occur rapidly [1,15]. Severe malaria disease can manifest as convulsions, coma, jaundice, shock, pulmonary edema, and organ failure.

Severe malaria disease commonly falls within three main subtypes cerebral malaria (CM), severe malarial anemia (SMA), and respiratory distress syndrome (RD) related to age and transmission intensity [15]. CM is most common among children in low, seasonal transmission settings due to parasite sequelae in the brain microvasculature [16]. Children within any level of seasonal transmission are at risk for SMA, caused by an accumulation of parasitized red cell destruction, impaired splenic function, and insufficient reticulocyte production [17]. RD is the predominant form affecting children in environments with low and moderate seasonal transmission intensities, as a result of metabolic acidosis and pulmonary edema [17,18].

Host protection and vulnerability

Malaria infection and severe disease are also influenced by immunological and hematological susceptibility. Immunocompetent adults with developed immunity due to age and repeated

malaria exposure in endemic settings often experience asymptomatic infection [19]. Adolescents and children in endemic settings lack these immunological advantages, making them susceptible to symptomatic infection and malaria disease. Individuals living with chronic diseases, such as HIV/AIDS, and pregnant people are at increased risk for symptomatic infection and severe disease [20–22]. Some hematological factors protect against malaria infection and disease, such as the morphology of red blood cells in individuals with sickle cell trait and the predominance of fetal hemoglobin among infants less than three months [23,24]. The role of host hemoglobinopathies, red blood cell enzymatic function, and immune cells in guarding against malaria infection and disease are primary research priorities [24,25].

Global malaria epidemiology

In 2023, there were an estimated 263 million malaria cases and 597,000 deaths [4]. Although malaria prevention and vector control have decreased global malaria cases and deaths between 2000 and 2014, since 2015, the progress has slowed due to the COVID-19 pandemic and other humanitarian crises. There were an additional 11 million annual malaria cases in 2023 compared to 2022. Global malaria incidence from 2020 to 2023 has been stable at 60.4 cases per 1,000 population at risk, which is similar to the incidence in 2015 (59.8 per 1,000 population at risk). The COVID-19 pandemic complicated ongoing access to health care, the disruptions led to an increase of 32,000 malaria deaths between 2019 and 2022 [4,26]. The malaria deaths decreased between 2022 and 2023, however, malaria mortality disparities have remained unchanged [4].

The WHO African region has been impacted most by stalled progress. There were an additional 23 million malaria cases and 24,000 malaria deaths in the WHO African region between 2019 and 2023 [4]. Extreme malaria disparities exist in the WHO African region, as globally it accounts

for 94% of cases and 95% of malaria deaths. In 2023, children under five years old in the WHO African region disproportionately reported 76% of global malaria deaths [4]. Only Egypt and Cabo Verde, which are located in the Northern African region and not in high-burden Sub-Saharan Africa, have achieved malaria elimination since 2000.

The WHO high burden to high impact approach encompasses country-led, setting-dependent interventions to reduce malaria morbidity and mortality among 11 of the highest malaria-burden countries [27]. Burkina Faso, Cameroon, the Democratic Republic of the Congo, Ghana, South Sudan, Mali, Niger, Nigeria, Uganda, the United Republic of Tanzania, and Mozambique account for 66% and 68 % of global cases and deaths [4]. Beyond disruptions due to COVID-19, several global threats are contributing to delays in progress.

The stagnant progress in the global malaria burden is related to parasite, vector, and environmental determinants. *Plasmodium falciparum* malaria targets have evolved to evade diagnosis and treatment. Deletions in *P. falciparum* histidine-rich protein 2 and protein 3 antigens, which are the main proteins detected in malaria rapid diagnostic tests, continue to be researched in endemic settings to understand their impact on malaria surveillance [28]. Therapeutic efficacy studies have tracked potential antimalarial drug resistance and treatment failure in the WHO African region. Mutations in *P. falciparum Kelch13* gene are associated with delayed parasite clearance after artemisinin combination treatment (ACT), which is the first-line treatment for most countries in the WHO African region [29]. Studies in Burkina Faso, Kenya, and Uganda have reported treatment failure rates greater than 10% after ACT between 2015 and 2022 [30]. Research continues to assess *P. falciparum Kelch13* polymorphisms associated with ACT partial resistance [29,31,32].

Vector resistance to insecticide, used in vector control interventions, has also contributed to delayed malaria progress. Most countries in the WHO African Region have identified *Anopheles* species resistant to the four classes of vector insecticides, including pyrethroids, organophosphates, carbamates, and organochlorines [30]. Humanitarian crises due to geopolitical violence and natural disasters have also impacted global malaria progress [33]. The WHO has suggested climate change and the associated direct and indirect pathways will exacerbate the global malaria burden. The warmer temperatures and changes in precipitation associated with climate change have directly led to more frequent and intense cyclones and floods in the WHO African region [34,35]. Indirectly, climate change has caused disruptions in access to care after natural disasters and seasonal changes have reduced food and resource production in settings where the economy is largely based on farming [30,36,37].

Malaria epidemiology in Mozambique

Mozambique is a large coastal country in Southeastern Africa with low, moderate, and high transmission malaria settings. Mozambique is one of eleven high-burden to high-impact countries that accounted for 66% of global malaria cases in 2023 [4]. Overall, Mozambique contributes to 4% of the global malaria cases and deaths. Bordering the Indian Ocean to the east and five countries, including Zambia, South Africa, Zimbabwe, Malawi, and Swaziland, Mozambique has the highest malaria burden compared to all other border countries [4]. This suggests malaria prevention and vector control in Mozambique could make a dramatic change in malaria burden metrics in the Southeastern African region.

Malaria transmission is drastically different across the country, with Southern provinces near malaria elimination and Western and Northern provinces with moderate to high malaria

transmission. Data from the most recent Malaria Indicator Survey (MIS) in 2018 suggested the population-weighted malaria prevalence to be 38.9%, with prevalence estimates ranging from 1% in Southern provinces to 57.3% in Northern provinces [5]. In Western and Northern Mozambique, malaria transmission is seasonal with peak transmission during the rainy season from September to April. There were an estimated 11.7 million *P. falciparum* cases in Mozambique in 2023 [4]. Malaria is the leading cause of death for Mozambican children under 5 [2,38]. Provincial mortality studies suggest malaria deaths peak in January and can account for up to half of all deaths in a community [39,40.] Mozambique had an estimated incidence of 156.3 severe malaria cases per 100,000 in 2015, which was five times the incidence compared to Zimbabwe and the fourth highest in WHO Southeastern Africa region [38].

The Mozambican NMCP supports universal access to diagnostics and treatment; however, coverage remains poor, which perpetuates malaria infection and severe malaria disease disparities. Few studies have studied severe malaria cases and case management capacity in high-burden countries like Mozambique. Individual health behaviors, such as health-seeking behaviors and malaria prevention behaviors, and care coordination are potential modifiable factors to improve severe malaria outcomes. My dissertation in partnership with Sussundenga Health Center, Ministry of Health, and Consultores Associados de Manica identified modifiable behaviors and barriers to effective case management to address at the largest health center in Sussundenga District. I reported interdisciplinary, clinical and social determinants, including Mozambican epistemic knowledge of traditional medicine, for malaria infection and severe malaria disease case management at Sussundenga-Sede Health Center. In the following three manuscripts, I aimed to:

Manuscript 1

P. falciparum community prevalence and health-seeking behaviors in rural Sussundenga District, Mozambique

Aim 1A: Measure the community-level *P. falciparum* prevalence in Sussundenga village

Rationale: Manica province has increased malaria transmission compared to neighboring Southern Provinces, and few previous studies have evaluated the malaria burden in this bordering region near Zimbabwe.

Aim 2A: Describe health-seeking behaviors for malaria infection in rural Sussundenga village

Rationale: Prompt symptom recognition, deciding where to seek care, and access to standard diagnosis and treatment are primary components of health-seeking. I aimed to measure delayed and timely care seeking, and understand possible interruptions in this process in a rural setting.

Aim 1 Approach: I conducted the household sampling, designed individual and household surveys, and analyzed data from a cross-sectional pilot study from December 2019 to February 2020 in Sussundenga village. With descriptive statistics, I generated findings on the *P. falciparum* community prevalence, health seeking process, use of malaria prevention, and delayed care gaps.

Manuscript 2

Ecological health access determinants of health access for severe malaria hospitalizations at Sussundenga-Sede rural health center

Aim 2A: Identify the primary determinants to describe ecological health access among hospitalized cases and controls

Rationale: Previous research in Sussundenga District, a rural high-burden area, determined a high degree of health-seeking, diagnosis, and treatment of uncomplicated malaria infections, but provided limited information about malaria hospitalizations and case management from the provider perspective. Referral care, the process of transporting a patient to a higher level of care, and distance to care are prominent barriers to accessing treatment for rural, high malaria transmission communities[13–17]. However, few studies have evaluated health access and associated determinants among severe malaria hospitalizations in the Sussundenga district, Mozambique, at the largest rural health center.

Aim 2B: Develop ecological health access indicators from the determinants identified

Rationale: The healthcare environment, social environment, and built environment could be leveraged to reduce severe malaria risk, but access varies among endemic settings. I can develop a specific composite measure to examine the health access of rare, severe malaria hospitalizations.

Aim 2B: Examine the association between ecological health access composite variables and severe malaria hospitalizations

Rationale: Although the composite variables have not been validated, the indicators of ecological health access can explore health accessibility disparities. I can assess the associations between health access indicators and severe malaria hospitalizations, and measure how the association differs by malaria risk factors (age, delayed care, season).

Approach: I first conducted exploratory factor analysis for data reduction and identified the primary ecological health access determinants. I generated a factor score-weighted indicators

from the factor structure to understand the built, healthcare, and social environment describing ecological health access. I computed the unadjusted and adjusted predicted probability of each ecological health access indicator by age category, season, and employment. The log odds for the built, healthcare, and social indicators were used to calculate predicted probabilities and average weighted predicted probabilities, adjusted for age category, season, and employment**.**

Manuscript 3

Training, Health Navigation, and Integrating Traditional Medicine into Rural Health Center Severe Malaria Referral Care – A Mixed Method Approach

Aim 3A: Assess education and training for severe malaria training from diverse key decision makers involved in treatment and prevention in Sussundenga district

> **Rationale:** There is evidence of the lack of compliance and use of standardized interventions for severe malaria case management in Mozambique. By evaluating key providers involved in patient care or health decision making, I aimed to understand the severe malaria training duration, National Malaria Control Program policies knowledge, and instructors who influence preparation for key decision makers in severe malaria case management.

Aim 3B: Compare facilitators and barriers to effective severe case management from key decision makers to health navigation data from severe malaria hospitalizations.

> **Rationale:** Delayed care is a well-studied barrier to effective severe malaria treatment, however these studied primarily consider patients only. The providers and community leaders are rarely considered, I combined key decision makers themes and health

navigation statistics to understand factors contributing to the complex care coordination issue.

Aim 3C: Identify perspective from key decision makers on the use of traditional medicine and referral program with traditional medicine practitioners and compare to traditional medicine use among severe malaria hospitalizations

Rationale: Few studies have considered the positive, culturally aligned aspects when evaluating traditional medicine practices and severe malaria disease. Semi-structured interviews were developed to capture the impact of local culture and post-colonial, to potentially inform the importance of these constructs when attempting to understand access and use of severe malarial prevention in Western Mozambique.

Chapter 2. Background and Rationale

Malaria prevention, case management, and novel interventions

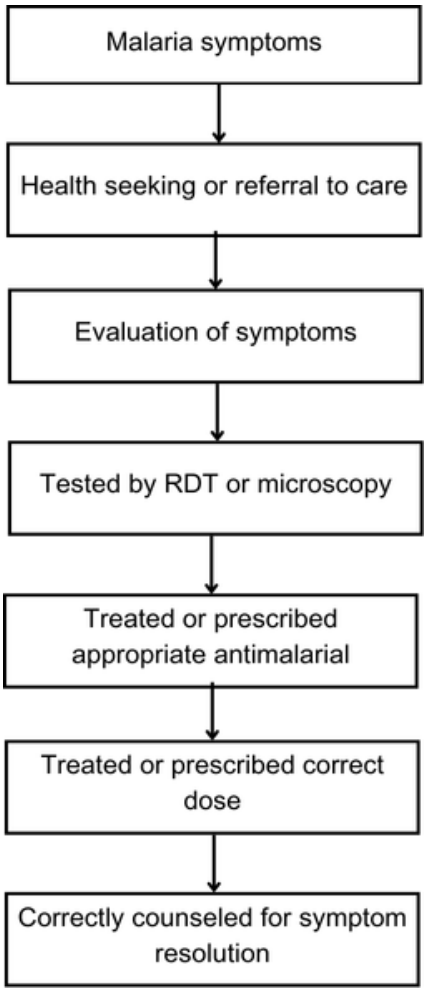
Malaria prevention can occur at the level of the individual, household, and community. Insecticide-treated nets (ITNs) are the most widely available malaria prevention for individuals in Mozambique [44,455,30]. ITNs are distributed in national campaigns, most recently in a partial launch in 2020, and antenatal clinics continuously [2,41]. The NMCP seeks to distributes one ITN for every 1.8 people in each household every three years . Although 82% of households own an ITN for every two people, only 51% reported sleeping under an ITN the previous night [5]. The large disparity in ITN use and ownership from 2018 MIS and 2022 Demographic and Health surveys (DHS) data likely widened due to COVID-19 disruptions similar to other endemic settings [30,41].

Secondary malaria prevention methods are primarily vector control interventions that are not widely available in Mozambique [5]. Indoor residual spraying (IRS) is a preventative household-level intervention that sprays insecticide indoors to prevent mosquito reproduction and repel mosquito biting [42]. Physical barriers such as eaves for roofing and window screens can limit mosquito indoor biting [43]. Additionally, drainage of standing water around homes and cutting back shrubbery minimize mosquito habitats [44,45]. Anthelmintic treatments have an indirect larvicidal mechanism and are distributed to neighborhoods through mass campaigns [2,46].

Malaria case management consists of referral care, malaria diagnosis, malaria treatment, and symptom resolution (Figure 1.1). There are differences in referral care and treatment between symptomatic malaria infection and severe malaria disease. Individuals with severe malaria

symptoms must receive care within 24 hours of symptoms onset [15]. In Mozambique, malaria infection and disease are diagnosed with either microscopy or *P. falciparum* rapid diagnostic test *(*RDT). Leishman/Giemsa stained thick blood smears via manual microscopy are the gold standard for malaria diagnosis and parasitemia measurement [47]. RDT is an immuno-chromatographic antigen-detection test for finger prick blood samples that detects histidine-rich protein-2 produced from red blood cells infected by asexual or gametocyte stage *P. falciparum.* Polymerase chain reaction (PCR) is a diagnostic method rarely available in Mozambique compared to microscopy or RDT.

Figure 1.1 Malaria Case Management



Pre-referral treatment is recommended for children under six years old with severe malaria symptoms who do not have access to the first-line treatment, parenteral artesunate [2]. It is common for individuals with severe malaria in rural settings to have limited to access to health centers, which leaves health posts as a first contact for treatment with rectal artesunate before referral to higher levels of care [48]. Community health workers, drug shops, and traditional medicine practitioners may also be the first point of care for individuals. Community health workers are trained to diagnose and treat malaria infection and can aid in referral to care for individuals with severe

malaria disease. Drug shops only offer treatment without a confirmed diagnosis. Traditional medicine practitioners are trusted members of the community based on shared cultural and spiritual backgrounds. Reactive case detection is another treatment-based intervention, which provides treatment without diagnosis to households suspected of asymptomatic malaria infection. Artemisinin combination therapy (ACT), specifically artemether lumefantrine (AL), is the main treatment for malaria infection in Mozambique [2]. AL acts on blood stage *P. falciparum* rapidly and reduces gametocyte carriage to lower transmission [49]. The half-life for AL is 3-4 days and maintains therapeutic efficacy for up to seven days. ACTs were implemented to limit the emergence of resistance.

Clinical trials have validated the use of intravenous artesunate as the first-line treatment for severe malaria for adults and children [50,51], but there is inconclusive and often conflicting evidence for adjunctive therapy to treat complications of severe malaria such as severe anemia, acute kidney injury, and convulsions [52]. In Mozambique, treatment for severe malaria disease first uses parenteral artesunate and supportive care, followed by ACT at discharge [2]. The NMCP policies support universal access to diagnostics and treatment; however, in Mozambique only 48% of febrile illnesses received a malaria diagnostic test and 33% received treatment in 2018 [2].

Several novel interventions for preventing malaria infection and disease are being studied or prepared for implementation in Mozambique. Seasonal malaria chemoprevention (SMC) was recently tested in a pragmatic trial in Northern Mozambique in 2020-2021 [53]. SMC is a community-based intervention to distribute monthly doses of sulfadoxine-pyrimethamine (SP) plus amodiaquine (AQ), or SPAQ to children between three months and five years old during the peak malaria transmission seasons. This treatment regime consists of one dose of SP and three

doses of AQ over three days. SP distributes parasite DNA synthesis during the liver and blood stage, while AQ reduces fever and inflammation of the blood-stage parasites. The study was able to achieve high coverage, acceptability, and feasibility among the intervention communities [54]. The hazard of clinical malaria during peak malaria seasons was 85% lower for children who received SMC compared to those without SMC [55].

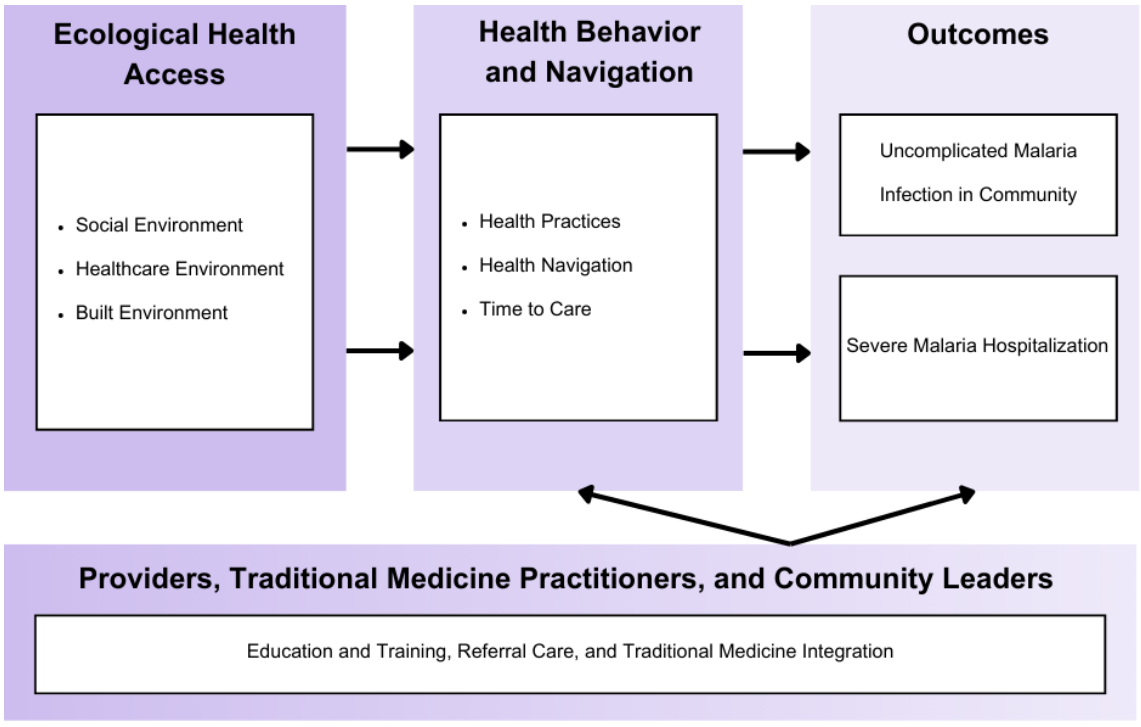
Mozambique was approved for support to roll out the RTS,S/AS01 malaria vaccine, the first WHO-approved vaccine in 2021, although implementation has not occurred [30]. The RTS,S/AS01 malaria vaccine acts on the circumsporozoite protein to prevent liver stage infection over four doses among children at least five months old [56]. Phase III clinical trials determined a 39% efficacy against symptomatic malaria, 29 % efficacy against severe malaria, and 37 % efficacy against malaria hospitalizations, which all increase when used in combination with other malaria prevention methods [57,58].

Conceptual Framework

Mozambique has the highest incidence of malaria infection and disease compared to six other border counties in Southeast Africa [30]. Malaria is the leading cause of death for children in Mozambique and 7.6% of all Mozambican children under five who experienced malaria infection had severe malaria disease in 2018[1,23]. Despite the progress in reducing the malaria burden in Mozambique, through malaria prevention and vector control strategies, malaria infection and disease continue to threaten the quality of life for communities. Unlike severe malaria disease, uncomplicated malaria infection presents with mild symptoms that are not life-threatening and do not require immediate care.

In Mozambique, uncomplicated malaria infection is common, especially among school-aged children, as a result of repeated exposure to malaria-infected mosquitos and immunity[19,40]. The direct costs of uncomplicated malaria are low, although indirect costs can be high due to lost wages for health seeking and missing days of school [59,60]. Community-level *P. falciparum* transmission is preventable through the availability of household health resources, understanding individual health behaviors, and receiving high-quality malaria care. Southern Mozambique and most countries bordering Mozambique have markedly reduced malaria transmission or initiated malaria elimination programs as a result of addressing these multi-level factors [30,61]. Identifying their contributions to uncomplicated malaria infection prevention and treatment in rural, Western Mozambique is essential for improving community health.

Figure 1.2 Adapted Behavioral Ecological Model



Although the pathogenesis of severe malaria disease is unknown, some evidence suggests accessible, prompt treatment of uncomplicated malaria prevents severe malaria morbidity and mortality. Prospective cohort studies that followed children with uncomplicated malaria infection between three to four years in various low, moderate, and high transmission settings have reported minimal cases of severe malaria. This could suggest that low barrier, efficient access to treatment prevents severe malaria disparities among the highest-risk group [62–64]. Additionally, a meta-analysis of 13 observational studies in malaria-endemic settings determined that averted treatment delays among individuals with uncomplicated malaria would prevent 29% of severe malaria anemia [1]. Severe malaria disparities are preventable under optimal conditions and previous studies rarely consider the multi-level determinants of these outcomes.

Figure 1.2 describes an adapted behavioral-ecological conceptual framework developed by Ryvicker et al to guide this study [65]. The research to date has tended to focus only on individuals' health behaviors influencing malaria infection and severe malaria disease without considering the neighborhood or provider factors that influence these behaviors. My dissertation applied this framework to contextualize the structural factors across the interpersonal, organizational, and community levels and their influence on health behaviors.

Risk Factors for Uncomplicated Malaria Infection and Severe Malaria Disease

Personal Environment: Household Health Access and Resources

Household-level health access and availability of health resources can prevent uncomplicated malaria infection and reduce community-level malaria transmission. There is a strong association between measures of income or wealth and uncomplicated malaria infection in various malaria-

endemic settings [66]. A meta-analysis of 30 studies in Sub-Saharan estimated that every one-unit increase in the categorical wealth index is associated with 20% lower odds of uncomplicated malaria infection [66]. Household occupations such as farming and porous housing construction like the use of wooden slate flooring are also associated with uncomplicated malaria risk, as a result of increased exposure to malaria-infected mosquitos [7,67,68]. Other household demographic factors, largely associated with poverty and driven by colonialism and global wealth inequality, determine whether households can afford indirect costs for health seeking [60,69–71].

Personal Environment: Ecological Domains

Ecological access to care influences health behaviors. Previously published studies on severe malaria case management focus on household-level determinants of severe malaria disease rather than understanding the community-level social determinants of severe malaria disease. My dissertation utilizes the behavioral-ecological model which captures the dynamic relationship between the built, healthcare, and social environments at the individual, household, and community levels. Data from the 2015 World Malaria Report and 2014 Mozambican MIS data suggested 40% of incident malaria mortality could be averted through increasing access to in-patient care[27]. Despite well-defined evidence-based practices from the Mozambican NMCP, improvement of outcomes remains stagnant. Neighborhood access to community health workers and ambulatory care influences whether patients use malaria prevention or seek care and this dissertation evaluated their impact on severe malaria disease.

The social environment of individuals with severe malaria disease also influences health access and navigation. Several studies suggest mothers are more likely to make healthcare decisions within households [72]. Although the evidence is mixed, most often caregivers with lower

education and socioeconomic status are associated with seeking care at drug shops compared to formal public health facilities [73,74]. Caregiver severe malaria symptom recognition is often low within households, although the presence of dangerous symptoms increases the odds of prompt health seeking [73].

Vector control and malaria prevention interventions distributed at the community level influence severe malaria risk. ITNs are the most effective malaria prevention intervention, and when used at night by no more than two individuals can lower malaria incidence by 51% compared to no intervention[1,7,8,28]. The Mozambican NMCP distributes nets through national campaigns (most recently in 2020) and continuously in antenatal clinics, however only 68.5 % of Mozambique had ITNs at their residence in 2018[3]. Although ecological access to healthcare is rarely considered concerning health behaviors, my dissertation sought to identify whether health access is an upstream driver for malaria outcomes.

Health behavior: Health-seeking and treatment-seeking

Despite free malaria diagnostics and treatment offered through health facilities, health seeking and treatment seeking remain a public health challenge for rural households in Mozambique. Fever is the most common indication of an uncomplicated malaria infection, which makes distinguishing malaria from other common childhood illnesses difficult. The non-specific symptoms associated with uncomplicated malaria could influence whether symptomatic individuals decide to seek care and where they seek treatment. Several studies have described the use of self-medication with antipyretics and receiving treatment at informal drug shops without a malaria diagnosis in rural communities [75–77]. These health and treatment-seeking behaviors are

often shaped by longer distances to care, indirect costs, and quality of care at public health facilities [66,75–77].

Health behavior: Health behavior domains

Health navigation or where individuals seek care are important determinants of severe malaria outcomes. Appropriate health navigation ensures individuals receive a diagnosis, obtain treatment, and achieve symptom resolution. There is evidence to support navigating to appropriate care and receiving artesunate within 24 hours decreases the risk of severe malaria mortality. Delayed health seeking is the primary risk factor for severe malaria disease [1,78,79]. Studies evaluating risk factors for delayed care seeking in Mozambique have found home delays, use of home treatment, and transportation delays contribute most to delayed health seeking[17,20,30–33]. My dissertation evaluates factors contributing to delays at the Sussundenga-Sede rural health center (RHC), focusing on the most cited barriers to effective severe malaria care management conducted in other countries. Personal health behaviors also influence severe malaria disease risk, such as the decision to properly use an ITN with no more than two people each night. The COVID-19 pandemic has further disrupted access to care and exacerbated poor health seeking[34–37], which was also a component of this dissertation.

Provider factors: Uncomplicated malaria case management

Treatment for uncomplicated malaria infection is influenced by household demographic factors and health seeking, but the quality of care ultimately determines whether an individual will achieve symptom resolution. The Mozambican NMCP provides clinical guidelines for malaria diagnosis and treatment for providers to deliver free malaria care at public health facilities [2]. The NMCP details that uncomplicated malaria infection should be diagnosed with a rapid diagnostic

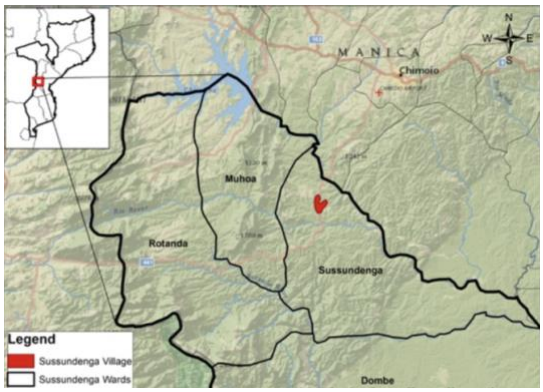
test or microscopy and treated with artemisinin combination therapy. Several studies in Mozambique have documented malaria care gaps such as lack of malaria diagnosis, lack of malaria treatment, or delivery of treatment without malaria diagnosis [80–82].

Provider factors: Severe malaria case management

Care coordination, especially the role of provider delays in diagnosis and treatment, is understudied within malaria case management research [83–85]. Severe malaria disease manifests with non-specific symptoms, which often leads to misdiagnosis and mistreatment [13,86,86]. The controversial findings based on the Community Access to Rectal Artesunate for Malaria (CARAMAL) study that undermined the effectiveness of rectal artesunate as pre-referral treatment due to lack of care coordination at clinical sites suggests care coordination should be a research priority[87–92]. An observational study on the use of referral care in Uganda, Nigeria, and the Democratic Republic of Congo determined use of pre-referral treatment compared to no treatment decreased the odds of seeking care at a public health facility [93]. Traditional medicine practitioners are trusted members of the community that caregivers often first seek care from [94,95]. In this dissertation, traditional medicine practitioners are included to evaluate a unique referral program between traditional medicine practitioners and the Sussundenga-Sede RHC for patients with severe symptoms.

Study Area

Figure 1.3 Study Setting



The dissertation was conducted in Sussundenga district, which is located 44 km from the largest provincial city, Chimoio, Mozambique. Chimoio also contains the nearest provincial-level hospital with in-patient and specialty care for complex health conditions. The primary languages spoken are Chiute, ChiManyika, Ndau, and Portuguese. Sussundenga district is one of nine districts and 34 administrative regions in Manica Province. The district has area of 7,017 km^2 and the district population was 171,056 residents in 2017 [96]. Sussundenga district is a rural community and shares a border with Zimbabwe (Figure 1.3).

Agriculture accounts for most of Sussundenga district's income and employment through the production of corn, cassava, fruits, and nuts. There are six main rivers and forests to support the mosquito life cycle and survival in the district. From September to March, Manica Province has high temperatures and increased rainfall which contributes to the reported seasonally high malaria incidence. Nearly 90% of malaria prevention and vector control is funded through international funding including the US Agency for International Development, the Global Fund, and other non-profit organizations.

The main RHC in the village is the Sussundenga-Sede RHC, with 14 smaller RHCs and health posts located in the district. The Sussundenga-Sede RHC is considered tertiary level care and the smaller RHCs and health posts are quaternary care. The Sussundenga-Sede health center has 35

in-patient beds and 109 providers. The Sussundenga-Sede RHC provides the highest level of care in the district through the delivery of in-patient care and primary care, unlike other smaller RHCs and health posts in the district. Rural communities in the Sussundenga district also primarily use the Sussundenga-Sede RHC for referral to the provincial-level hospital in Chimoio.

Chapter 3 (Manuscript 1) *P. falciparum* community prevalence and health seeking behaviors in rural Sussundenga District, Mozambique

Abstract

Background: Impacts of nationally directed malaria control interventions hinge on understanding malaria transmission and prevention at the community level. The decision to seek care or health-seeking behaviors provide valuable insight on knowledge of malaria, access to care, and efficacy of malaria case management. Thus far, few studies have focused on central Mozambique. The aim was to describe community level *Plasmodium falciparum* prevalence and health-seeking behaviors among residents of Sussundenga, Mozambique, a rural village in Manica Province with high malaria incidence reported at the Sussundenga-Sede RHC.

Methods: A cross-sectional community-based survey was conducted from December 2019 to February 2020. A random household sampling method was used, based on enumerated households from satellite imagery. All consenting participants completed a survey about malaria risk, prevention, and health-seeking behaviors, and received a *P. falciparum* malaria RDT.

Results: The study enrolled 358 individuals from 96 households. The *P. falciparum* prevalence was 31.6% (95% CI [26.6–36.5%]). Ninety-three percent of participants reported using the Sussundenga-Sede RHC for healthcare. Sixty-six percent of participants (N = 233) experienced at least one malaria symptom in the past month, with self-reported fever most frequently reported (19.3%). Of these, 176 (76.5%) sought care in a health facility and 174 (79%) received an RDT with 130 (63%) having a positive test. Of those with a positive RDT, 127 (97%) received artemether-lumefantrine. Following treatment, 123 (97%) participants' symptoms resolved

within a median of 3 days (IQR: 3–5) ranging from 2 to 14 days. In this high transmission setting, a high proportion of participants recognized malaria related symptoms then received a proper diagnostic test and treatment in a health facility.

Conclusions: Future interventions that leverage this health-seeking behavior and strengthen health systems for community interventions will improve malaria control and inform the efficacy of potential interventions at this particular international border.

Background

The globally estimated 241 million cases of malaria disproportionately impact sub-Saharan Africa [6]. Mozambique was one of 29 countries that claimed 96% of global malaria cases. This high burden country reported 8,921,081 malaria cases and 1114 deaths in 2018, which represented approximately 4% of cases and deaths globally [97]. Mozambique has eleven provinces and based on data from the most recent MIS determined that Cabo Delgado, Nampula, and Manica Provinces have the highest malaria prevalence for children under five [5]. Manica Province, unlike the other high transmission provinces, is located within the central region.

Manica Province shares a border with Tete, Sofala, Inhambane, and Gaza Provinces as well as Zimbabwe. Manica Province in comparison to the surrounding border regions had a higher malaria burden. Based on 2018 MIS data, the malaria prevalence for children under five for Manica Province was 19% higher than Tete and Sofala Provinces [5]. During 2018, the World Health Organization (WHO) reported malaria deaths were five times higher in Mozambique compared to Zimbabwe [6]. However, previous epidemiological studies that evaluated malaria control measures have not focused on the central region of Mozambique, particularly Manica

Province located outside of Chimoio City [98,99]. Manica Province had 821,775 malaria cases in 2019 [100]. Intermittent preventive treatment in pregnancy (IPTp) was available in Manica Province with 49% of pregnant women receiving at least three sulfadoxine-pyrimethamine doses [5]. In Manica Province, 87% of households had at least one insecticide-treated nets (ITNs) [5].

Sussundenga District was one of nine districts in Manica Province. This district contains 14 different RHCs and had a documented high annual incidence of malaria cases [5]. ITNs were the main preventive measure accessible to most households [5]. In Sussundenga, prompt diagnosis and treatment with artemether-lumefantrine at an RHC was the standard of care for uncomplicated malaria illness. There were recent plans to expand the use of community health workers (CHWs) for integrated community case management (iCCM) throughout Mozambique in the coming years [101].

The primary objective of this analysis was to describe community-level *P. falciparum* prevalence and health-seeking behaviors in rural Sussundenga village in Manica Province, Mozambique. This analysis was part of a pilot study, which sought to measure the community malaria prevalence, perceptions of malaria risk, utilization of malaria prevention, and health-seeking behavior patterns to inform future malaria control efforts. The pilot study was performed in partnership with Sussundenga RHC, Sussundenga District Ministry of Health, and community leaders.

Methods

Study Area

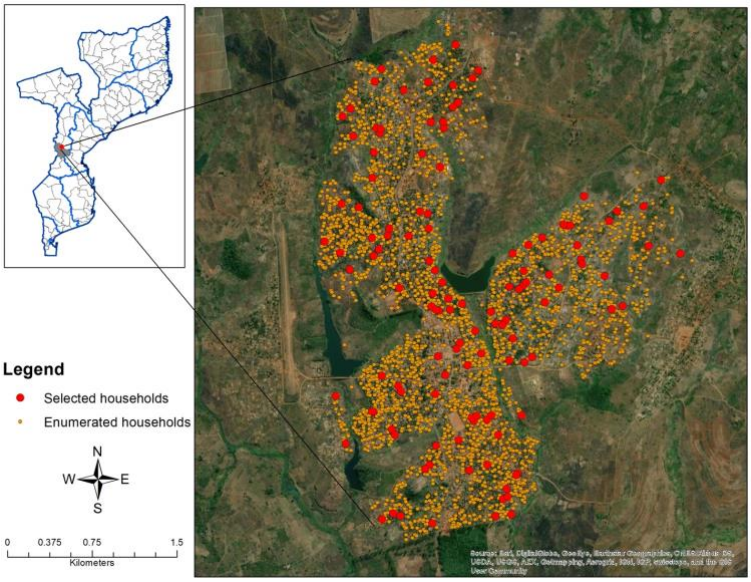
The survey was conducted in Sussundenga-Sede catchment area, a region within Sussundenga district. This is approximately 42 km from the Provincial capital of Chimoio city in central Mozambique (Figure 3). Sussundenga District is a rural agrarian community that shares a border with Zimbabwe. The district had area of 7017 km^2 and the district population was 171,056 residents [5]. From September to March, Manica Province has high temperatures and increased rainfall which contributes to the reported seasonally high malaria incidence. The main rural health centre (RHC) in the village was the Sussundenga-Sede health centre, with 14 smaller RHCs located in the district. The study sampled households from Sussundenga District because of the high incidence, proximity to the Zimbabwe border, and accessibility to several RHCs. The Mozambican NMCP initiated a national ITN campaign from 2019 to 2020 to improve coverage [100]. ITNs and IPTp were accessible to Sussundenga District residents through the antenatal care centers, while IRS became available to central districts in 2018.

Study design and data collection

A cross-sectional community-based survey was administered from December 2019 to February 2020 in Sussundenga village. This analysis focused on health-seeking behaviors data from a larger survey for the pilot study which evaluated malaria risk based on sociodemographic, environmental, migration, housing construction, and other risk factors. Satellite imagery was used to enumerate 2889 households in Sussundenga catchment area (Figure 1.4). To account for potential misclassification of household structures and refusals, a random sample of 125 households were selected for screening from satellite imagery. Data collectors used GPS coordinates to approach selected households for participation and enrolled 100 households. The

household size assumption was an estimated 5–6 total residents per household at the time of survey administration. Data collectors determined eligibility through a notification visit with the head of the household and assigned each household member a unique identifier. As a pilot study the sample size was determined to estimate the community prevalence and detect differences in specific risk factors between those with and without *P. falciparum* infection measured by RDT.

Figure 1.4 Map of enumerated and selected households



Data collectors also obtained informed consent for all adult residents and parent/guardian permission for children between 3 months and 12 years old and assent for minors between 13 and 17 years old. Enrollment eligibility criteria was any full-time resident older than 3 months. After the notification visit, data collectors administered the electronic survey and recorded household GPS coordinates on a tablet computer using a REDCap® (Research Electronic Data Capture) mobile application. All participants present at the time of survey administration who were older than 12 years old completed the survey and parents provided responses for children 3 months old to 12 years old.

A study nurse collected a finger prick blood sample and administered a malaria RDT [Right Sign Malaria Pf (Biotest, Hangzhou Biotest Biotech Co, China]. All participants with positive results were referred to Sussundenga-Sede RHC for confirmation of diagnosis and treatment. All

symptoms reported to data collectors were self-reported based on malaria cases that occurred in the previous month. All data were collected and stored using the REDCap® server hosted at University of Minnesota School of Public Health and was treated confidentially [82,102]. Ethical review and approval for the study was completed by the Institutional Review Board (IRB) at the University of Minnesota [STUDY00007184] and from A Comissão Nacional de Bioética em Saúde at the Ministry of Health of Mozambique [IRB00002657].

Data analyses

All data analyses were performed using R (version 4.1.1). In this analysis, individuals older than 12 years old were adults and individuals 12 years old and younger were children. This cut-off was determined by the age at which individuals transition from pediatric to adult care. Children less than 13 years old were not included in the education level and malaria prevalence analysis to understand the association among adults. Community *P. falciparum* prevalence was determined by RDT results at the time of the survey. Pearson Chi square tests were used to compare the socio-demographic characteristics between malaria positive and negative individuals. Age, sex, employment, education, bed net usage, and regular health center usage were compared between those with positive and negative RDT results without adjusting for covariates.

Health-seeking behaviors were described as proportions with 95% confidence intervals. The variables to describe the care continuum included care seeking with malaria symptoms, diagnosis, and treatment. All health-seeking behavior variables were nominal categorical variables in the survey. The primary health-seeking and RDT malaria diagnosis variables were among all participants who in the past month reported at least one of the following malaria

symptoms: fever, headache, chills, vomiting, nausea, diarrhea, cough, joint pain, or body aches. In the survey, participants reported where they first went to retrieve medication to treat their malaria symptoms which could include a RHC, informal shop, relative or friend, and others.

The primary health-seeking variable was defined as the proportion of individuals that sought care at an RHC among participants who in the past month reported malaria symptoms. In the survey, participants reported malaria diagnosis by RDT, smear, or none performed. The RDT malaria diagnosis variable was defined as the proportion of individuals who received a RDT among participants who in the past month reported malaria symptoms. In the survey, participants reported use of various malaria medications including traditional medicine, paracetamol, and other anti-malarial drugs. The received treatment variable was defined as the proportion of participants who reported artemether-lumefantrine treatment among participants who reported a positive malaria diagnosis by RDT within the past month.

Symptom resolution was defined as malaria positive individuals who received treatment that reported symptom resolution. The proportion of participants that reported a resolution of their symptoms after completing prescribed treatment was calculated. The time to symptom resolution after treatment described treatment compliance and prompt symptom resolution, which suggested participants completed the treatment dosage and experienced parasite clearance. The days until symptoms resolved variable was a continuous variable that was reported based on an individual's most recent malaria infection. A violin plot was created to compare the number of days until symptoms resolved by all participants, adults, and children.

Results

Socio-demographic characteristics

The study enrolled 96 households with 358 individual household members who were present at the time of the study visit (Table 1.1). The age range was 1–80 years and children aged 1–12 years old represented 36% of participants. The malaria prevalence in the study population was 31.6% (95% CI [26.6–36.5%]). There were no gender differences in malaria prevalence ($p = 0.84$). There were statistically significant differences in malaria prevalence by age ($p < 0.001$). The highest malaria prevalence was among children aged 5–10 years old (26.4% [95% CI 18.0–34.8]).

Table 1.1 Sociodemographic characteristics among malaria positive and negative

	Malaria negative	Malaria positive	95% CI
	N(%)	N(%)	
Age			P < .001
< 5 years	23(9.8)	19(17.9)	(10.6–25.23)
5–10 years	33(14.1)	28(26.4)	(18.0–34.8)
10–15 years	28(12.0)	20(18.9)	(11.4–26.3)
16–20 years	43(18.4)	16(15.1)	(8.28–21.9)
20–30 years	48(20.5)	10(9.4)	(3.87–15)
> 30 years	59(25.2)	13(12.3)	(6.02–18.5)
Sex			P = .84
Male	99(43.2)	47(44.3)	
Female	130(56.8)	59(55.7)	
Employment			P = .39

Farmer	38(56.7)	17 (81)	
Miner	1(1.5)	0(0)	
Health worker	1(1.5)	0(0)	
Teacher	15(22.4)	1(4.8)	
Coroner	1(1.5)	0(0)	
Business owner	11(16.4)	3(14.2)	
Education			P < .01
Grades 1–5	8(7.5)	14(6)	(3.00–9.18)
Grades 6–7	8(7.5)	30(12.8)	(8.69–17.4)
Grades 8–10	17(16)	61(26.1)	(20.8–32.2)
Grades 11–12	9(8.5)	40(17.1)	(12.5–22.3)
University	0(0)	2(2.6)	(0–2.07)
N/A	64(60.5)	83(35.4)	(29.9–42.3)
Bed net usage			P < .01
No	72(30.9)	50(46.3)	(36.9–55.7)
Yes	161(69.1)	58(53.7)	(44.3–63.1)
Regular Health Center			P = .33
Sussundenga-Sede	215(91.9)	105(97.3)	
Munhinga	3(1.3)	1(0.9)	
Dombe	0(0)	1(0.9)	
Muôha	1(0.4)	0(0)	
Rotanda	1(0.4)	0(0)	
Other	14(6)	1(0.9)	

There were statistically significant differences in malaria prevalence by level of education ($p < 0.01$). The highest malaria prevalence was among adults who received education up to

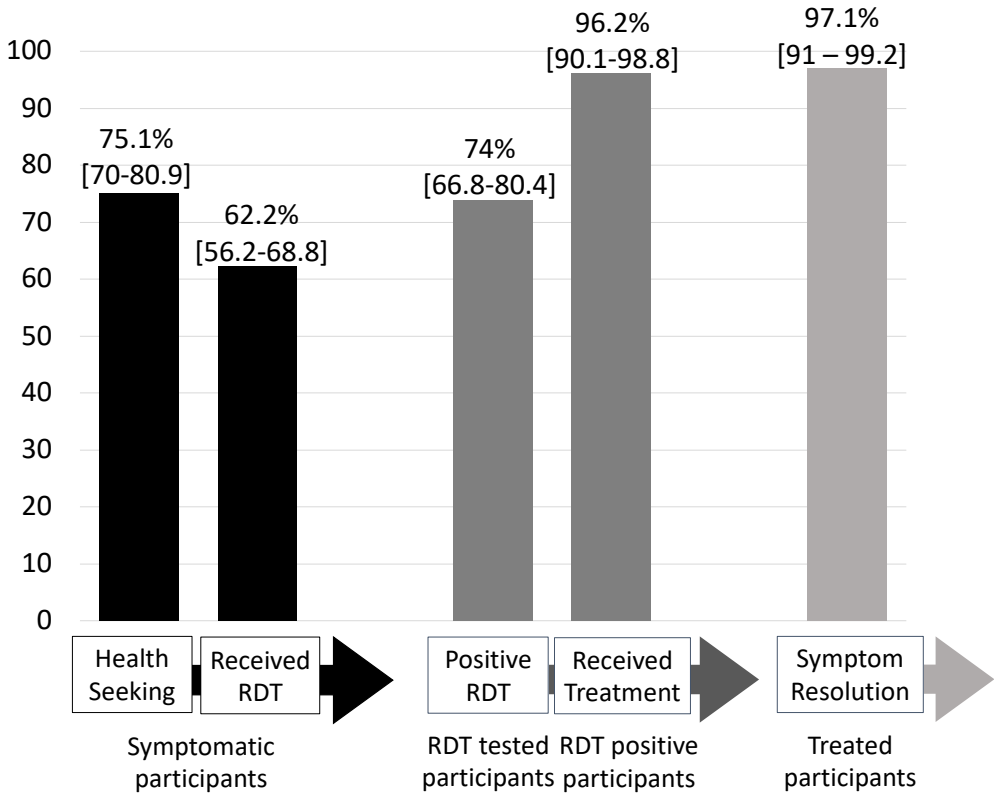
grades 8–10 (26.1% [95% CI 20.8–32.2%]). Reported ITN use was moderate with 65% of participants reporting sleeping under an ITN the previous night. There were not statistically significant differences in ITN use by age. ITNs were protective among those who reported use the previous night, with 26.5% (95% CI [20.1–32.9%]) prevalence among those who did report usage compared to 41.0% (95% CI [32.3–50.3%]) prevalence among those who did not report ITN use the previous night ($p < 0.01$). There were not statistically significant differences in malaria prevalence by occupation, although farmers had the highest malaria prevalence compared to other occupations. Ninety-three percent (93%) of participants reported using the Sussundenga-Sede RHC for their last episode of malaria symptoms.

Health-seeking characteristics and timeline

Sixty-six percent (66%) of participants (N = 233) reported at least one malaria related symptom in the past month, with fever most frequently reported (19.3%). Of the participants that reported symptoms, 75.1% (95% CI [70.0–80.9%]) sought care at a health and 62.2% (95% CI [56.2–68.8%]) received an RDT. Among all participants tested with an RDT, 74.0% (95% CI [66.8–80.4%]) were malaria positive. Of the RDT positive participants, 96.2% (95% CI [90.1–98.8%]) reported receiving artemether lumefantrine, the standard of care for uncomplicated malaria in Mozambique, and 97.1% (95% CI [91.0–99.2%]) of participants treated with artemether-lumefantrine reported symptom resolution after completing the treatment. Of the four participants that reported not receiving artemether-lumefantrine, one participant reported having severe malaria and received quinine, and the remaining participants had not reported receiving the standard of care (Figure 1.5).

Three participants (2.9%), which were school-aged children, reported unresolved symptoms after receiving the standard of care at the Sussundenga-Sede RHC (diagnosis with an RDT and treatment with artemether-lumefantrine). Of those three participants, one continued to be malaria positive at the time of the survey. Four (3.3%) participants had a malaria related hospitalization after reported symptoms within the last month. Two of the individuals with reported severe disease requiring hospitalization were adults older than 40 years and the other two individuals were children. All of the malaria related hospitalizations reported seeking care, received treatment other than standard of care, and required additional treatment. Three of the four hospitalized individuals reported symptom resolution.

Figure 1.5 Health Seeking among symptomatic, RDT positive, and Coartem® treated participants



Efficacy and access to care

Median time until reported symptoms resolved was 3 days (IQR: 3–5) and ranged from 2 to 14 days. Figure 1.6 shows the distribution of reported days until reported symptoms resolved among all participants, children, and adults. There were no significant differences in median days until symptoms resolved between children and adults. Adults had a greater probability of having reported symptoms resolve in 3 days compared to children. The distribution of reported days until symptoms resolved was bimodal for children compared to a multimodal distribution among adults. Nearly all (97.7%) participants reported preference for care at the Sussundenga-Sede RHC, the majority reported this preference because it was close to their home (94.8%).

Figure 1.6 Reported days until symptoms resolved amongst participants that sought care

Discussion

In this study, the Sussundenga community *P. falciparum* prevalence was highest among children aged 5–10 years old compared to other ages. Findings from this study indicate a high degree of treatment seeking behaviors among children and adults which led to prompt reported symptom resolution, specifically at the Sussundenga-Sede rural health center. The high level of health-seeking behaviors could be explained by the close proximity of the largest rural health center in the village, as several studies have demonstrated the association of shorter travelling distance and utilization of malaria healthcare [82,103,104].

The 2018 Mozambique MIS similarly reported a high malaria prevalence in Manica Province among children under five (39%), the third highest in Mozambique [5]. In the study, 65% of participants reported use of an ITN the previous night, which is similar to Manica Province data from MIS (68.8%). Although a high proportion of participants who reported a malaria positive diagnosis received proper treatment and reported symptom resolution, fewer participants who reported malaria symptoms sought care at an RHC and received an RDT. Data from the 2018 MIS reported from households in Manica Province, determined 60% of individuals with fever sought treatment at a RHC and 39.2% of individuals with fever received a RDT. In the study, reported health-seeking at a RHC and reported RDT testing among participants who reported malaria symptoms was higher than 2018 MIS Manica Province data.

NMCP interventions that promote malaria social and behavioral change could improve initiation of treatment seeking behaviors in Sussundenga District, leading to a greater proportion of symptomatic individuals to be tested [100]. Expansion of the thousands of community health

workers (CHWs) within the national integrated community case management (iCCM) strategy could increase access to treatment, diagnostics, and ITNs [5,104]. The study demonstrated persistent health-seeking behaviors among households, suggesting a high degree of malaria symptom recognition. Possible interventions like utilizing CHWs could be effective to close existing gaps in testing and access to treatment [105]. Additional resources for CHWs to deliver ITNs and treat asymptomatic malaria cases could reduce transmission in high burden settings like Sussundenga district [106–108].

There were several limitations to this study, the first being the cross-sectional design which hindered observing the potential for changing health-seeking behaviors over time. The study relied on self-reported metrics and lacked information directly from RHCs. Additional understanding of RHC diagnostic and treatment policy compliance as well as patient treatment compliance could further explain our findings [107]. Yet, with self-reported responses there is the potential that recall bias could have impacted the accuracy of responses about information surrounding previous malaria symptoms and care.

Prior studies in Manica province determined rural regions have higher prevalence in comparison to urban areas [5], but have not yet quantified the community prevalence in the majority of these rural regions. Few studies have determined the community prevalence of regions in Sussundenga district, especially Sussundenga village. The study found households promptly sought care to treat their malaria symptoms, which suggests that the RHCs and individual households are strengths to incorporate into future studies and interventions. Efforts to understand the drivers of community prevalence in well-resourced, high burden areas could inform innovative community driven malaria prevention and vector control measures.

In this study, a majority of participants who reported malaria diagnosis by RDT received treatment at a health facility and had symptom resolution. The high community prevalence in Sussundenga District could be driven by reduced treatment seeking upon malaria symptom development, malaria diagnosis by RDT, and ITN utilization. This suggests additional prevention methods like increasing ITN coverage and CHWs to improve malaria treatment seeking and diagnosis are necessary to address the malaria burden in the district.

Chapter 4 (Manuscript 2) Determinants of health access for severe malaria hospitalizations at Sussundenga-Sede rural health center

Abstract

Background: Prompt diagnosis and artesunate treatment of malaria within 24 hours of symptom onset are crucial for reducing mortality [1]. The Mozambican NMCP advocates for universal access to care, yet disparities in care-seeking and malaria prevention remain [2]. One in three children with febrile illness did not seek medical care in 2018, increasing the risk of severe malaria disease [109]. ITNs coverage, one ITN for every two people, was 82% among households yet only half of the households reported sleeping under an ITN the previous night, indicating gaps in malaria prevention [5].

Sussundenga District is a rural community in Western Mozambique, with moderate-high *Plasmodium falciparum* transmission [3,30]. Individual health behaviors and the determinants that shape ecological health access are potential modifiable factors to improve malaria outcomes in this community setting. Modifying individual health behaviors and addressing factors influencing access to health could improve malaria outcomes. This study evaluated social, behavioral, and clinical characteristics to identify the main determinants of severe malaria in the Sussundenga District.

Methods: I conducted a case-control study among 121 patients experiencing a hospitalization with severe malaria and 122 patients experiencing a hospitalization without malaria enrolled at a rural health center in Sussundenga District, Mozambique. Cases were test-confirmed malaria positive (by RDT or microscopy) and had at least one severe malaria symptom, while controls

were non-urgent hospitalizations without malaria test-confirmed (by RDT or ruled out by differential diagnosis).

Data were collected on demographic factors, health-seeking behaviors, malaria prevention methods, and indicators of ecological health access with a survey. An adapted behavioral-ecological model and exploratory factor analysis (EFA) were employed to select relevant variables representing ecological health access domains. Composite variables, weighted according to factor loadings, were developed to characterize these domains, guided by the behavioral-ecological framework and an anti-colonialism paradigm. The association between these composite variables and severe malaria hospitalizations was assessed using conditional logistic regression, and results were presented as average predicted probabilities with confidence intervals. Additionally, interactions between composite variables and delayed care were evaluated through relative excess risk due to interaction measures with corresponding p-values.

Results: One-hundred and twenty-one persons had severe malaria hospitalizations, and 122 were non-malarial controls. Sex, age category, employment, and household size were distributed similarly between cases and controls. Over 80% of the sample sought care after 24 hours of symptom onset. EFA was conducted for data reduction and identified ecological health access indicators —encompassing aspects of the built, social, and health environments—influencing healthcare utilization in Sussundenga. The indicators explained a limited portion of the variance in healthcare use (22%), indicating that other factors may contribute to health-seeking behavior. Less built or social environment health access increased the average predicted probability for severe malaria hospitalization.

However, these estimates were imprecise and would require an improved sample for confirmatory factor analysis. Timely care, compared to delayed care, did not reduce the likelihood of severe malaria hospitalization. This association, both significant and of small magnitude, indicated timely and delayed care populations were similar. Larger samples that could include neighboring districts and higher levels of care within the health system could provide sufficient power to confirm and validate these ecological indicators.

Conclusion: This study re-evaluated modifiable, structural barriers to effective severe malaria care and health access determinants in the Sussundenga district. The magnitude of delayed care and minimal ecological health access in the district indicated the few healthcare resources available were not accessible. At the district's largest health center, future implementation science research is needed to tailor community-based interventions for specific barriers, such as transportation challenges and difficulties navigating the healthcare system.

Background

In 2023, there were an estimated 246 million malaria cases and 569,000 deaths in Sub-Saharan Africa, with 76% of deaths among children under five [4]. Severe *P. falciparum* malaria disease can be prevented when malaria-related symptoms are treated within the first 24 hours [110]. Over the past 30 years, numerous endemic countries in Southeastern Africa significantly reduced their malaria burden. However, despite this progress, rural communities in Mozambique remained disproportionately affected. Household-level estimates derived from the 2018 MIS reported that 5-10% of children with malaria infections developed severe malaria disease [111]. Furthermore, Mozambican children continue to experience higher rates of severe malaria compared to their

counterparts in the five neighboring countries (Tanzania, Malawi, Zambia, Zimbabwe, South Africa, and Eswatini) [4,38,111,112].

Healthcare coverage varies across Mozambique, and distance to care is a significant determinant of healthcare utilization [3,109,112–114]. Malaria care can be accessed from the public health sector including hospitals, health centers, health posts, and community health workers. Drug shops offer first-line treatment, AL, and alternative medications; including anti-pyrectics, quinine, and sulfamethoxazole piperaquine [78,115–117]. Traditional medicine practitioners are trusted members of the community and frequently are the first point of contact for individuals with severe malaria at the direction of their caregivers [118–121].

Previous research understanding the barriers to health access and the availability of care for severe malaria in Mozambique has predominantly focused on large urban hospitals [80,107,122]. This limits potential insights into health utilization patterns within rural communities, where individuals initially seek care at rural health centers and may require extensive referrals to reach urban medical facilities. Epistemic injustice, primarily stemming from the funding and power dynamics of high-income institutions, could have influenced the value placed on community knowledge within hospital-based malaria research [69,123,124].

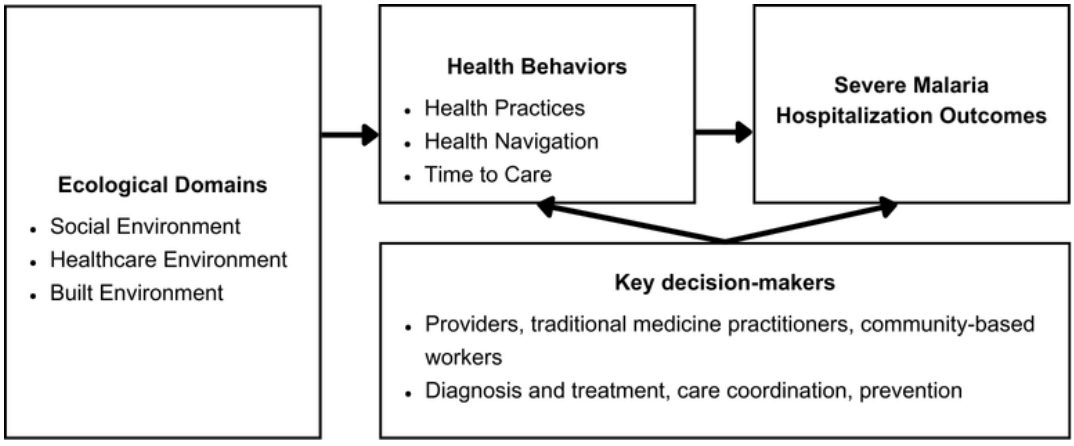
Existing research at the household level has typically emphasized individual health behaviors or caregiver perceptions. However, this focus could have obscured the broader influences of neighborhood-level health determinants and care coordination on these individual health behaviors [118,119,121,125]. By employing a post-colonial framework and a multi-level health access

conceptual model, this research re-evaluated the relationships between interdisciplinary determinants and health access in Sussundenga, Mozambique [65,126,127].

Conceptual framework

The behavioral ecological conceptual framework and post-colonial paradigm established the interdisciplinary determinants to evaluate [65,126,128]. Figure 2.1 described how the core dynamics in the behavioral ecological framework were maintained indicating adaptive health navigation strategies are necessary to reach effective treatment. In align with the framework, overcoming the role of structural barriers in the environment and social interactions with key decision-makers influencing care seeking and prevention were considered. This study specifically examined the role of traditional medicine practitioners and non-Western health approaches as key determinants, aligning with Mozambican epistemological perspectives and the post-colonial paradigm. A previous community-based cross-sectional study and publicly available MISs, guided which clinical and malaria prevention determinants were measured [5,117]. The questionnaire underwent pilot testing with the trained data collectors in August 2022.

Figure 2.1 Adapted behavioral ecological framework



Adapted from Ryvicker et al, our framework describes key multi-level factors that influence severe malaria hospitalization outcomes.

Reflexivity

I identify as a Black American, light-skinned cis-het woman. I have lived experiences within majority black and multi-racial communities in the US, which did not represent all research participant identities. My worldview is shaped by anti-racism, anti-colonialism, and social justice-based frameworks. I considered reflexivity from research question development to analysis and assessed how my middle-class background, advanced education from high-income institutions, and lack of lived experiences of colonialism could have introduced bias. I relied on Indigenous post-colonial frameworks rooted in health equity to evaluate epistemological bias and unequal power dynamics throughout the study [124,126,128]. In particular, financial and time constraints introduced unequal power dynamics between American and Mozambican collaborators during data collection and analysis.

Methods

Study setting, design, and participants

Collaborators, trained study members, and I implemented a case-control study at the Sussundenga-Sede RHC, which compared the associations between ecological health indicators and severe malaria hospitalizations from April 2023 to July 2024. The study was conducted in Sussundenga district, which is located 44 km from the largest provincial capital city, Chimoio, in Manica Province, Mozambique. Sussundenga District is a rural agrarian community that shares a border with Zimbabwe. Environmental health studies indicated that Manica Province experiences high temperatures and increased rainfall from September to April, suggesting a lagged association between seasonal rainfall and higher malaria incidence [7,40].

In Mozambique, the healthcare sector has a tiered structure, operated at the national, provincial, and district levels [129,130]. This system included four levels of healthcare delivery: provincial hospitals (primary), district hospitals (secondary), health centers (tertiary), and clinics or health posts (quaternary). All urban and rural health centers have provided primary care at no cost offering malaria diagnostics with a RDT. In addition, AL, treatment for malaria infection, and preantral artesunate treatment for severe malaria disease, were available. The main RHC in the village is the Sussundenga-Sede RHC, with 14 smaller RHCs located in the district. The Sussundenga-Sede RHC has 35 in-patient beds and 109 providers, most of which are nurses and technicians, similar to the national healthcare workforce [131,132].

This RHC is the largest and only health center with in-patient care for severe malaria hospitalizations in the Sussundenga district. The RHC is also the primary referral RHC for rural communities in moderate-high-transmission regions in central Mozambique. Study staff fluent in Mozambican Portuguese and other local languages screened potential participants based on the following eligibility criteria: hospitalization length for four or fewer days, age older than three months, and ability to provide consent or obtain guardian permission. Individuals fluent in Portuguese or other local Mozambican languages, illiterate, and members of disenfranchised groups will be included in the study. Pregnant women, prisoners, adults lacking the capacity to consent, children less than three months old, members of the military, and employees of the researchers were excluded.

Prior research has consistently reported distance to the RHC as the significant predictor of health access and behavior. The effect size 2.01-2.25 was robust, while smaller compared to the effect of delayed health seeking (OR: 5.50)[78]. Assuming the proportion among the exposed=0.355,

power =0.85, and alpha=0.05, and adjusting for 20% non-response bias, the analysis indicated that a minimum sample size of 240 participants (120 cases and 120 controls) could detect the effects of interest.

Cases were malaria positive based on malaria RDT or microscopy and one or more severe malaria symptoms (impaired consciousness, acidosis, hypoglycemia, hyperparasitemia, severe malarial anemia, acute kidney injury, jaundice, pulmonary edema, bleeding, or shock). In this time-matched case-control study, controls were matched within one week of case admission and were malaria-negative based on RDT or excluded following a comprehensive differential diagnosis. Burns, workplace or violence-related injuries, vehicle accidents, and other diagnoses are associated with urgent care seeking.

Diagnoses associated with exposures of interest were excluded to limit potential inappropriate control selection bias. Data collectors confirmed eligibility to obtain consent for all adult patients, parental/guardian permission, and assent for minors 13 years and older. Data collectors administered a questionnaire and abstracted medical charts to assess clinical, malaria prevention, health navigation, health behavioral, and social determinants.

Table 2.1 Exposures, outcomes, and confounding variable measures

Variables	Items	Interpretation (Coding)
Exposures	Does the neighborhood have one of the following available: ambulatory care, community health workers, traditional medicine doctors, and drug stores? [a]	Yes, it is available (1) No, it is not available (0)
	What was the distance to the nearest: health post, drug store, traditional medicine doctor? [a]	Continuous per 5 km

	Was transportation a barrier to accessing the RHC?	Yes, it is barrier (1) No, it is not a barrier (0)
	Were transportation costs a barrier to accessing the RHC ?	Yes, it is barrier (1) No, it is not a barrier (0)
	What type of transportation did you take to the RHC?	Ordinal (1-8, from low cost to high cost transportation)
	Sex	Females (0) Males (1)
	Does the neighborhood have one of the following available: indoor residual spraying, reactive case detection, or deworming?	Yes, it is available (1) No, it is not available (0)
	What distance was traveled to Sussundenga-Sede RHC?	Continuous per 5 km
	Was a ITN used the previous night?	Yes, an ITN was used (1) No an ITN wasn't used (0)
	Did you have malaria infection or disease in the previous month?	Yes, positive malaria history (1) No, negative malaria history (0)
	What were the number of ITNs in your household?	Continuous
	Which severe malaria symptoms were recognized?	Nominal (1-13)
	Did COVID-19 have an impact on health seeking to the RHC?	Yes, COVID-19 had no impact (1) No, COVID-19 had an impact (0)
	Do you attend school locally?	Yes, I attend school locally (1) No, I do not attend school locally (0)
	Did you seek additional care?	Yes, I did seek additional care (1) No, I didn't seek additional care (0)
	Were you referred to care?	Yes, I was referred to care (1) No, I was not referred to care (0)
	How time did it take to reach care at Sussundenga-Sede RHC?	Continuous per hour

	How much time did it take for the following to occur: diagnosis, treatment, or discharge? [a]	Continuous per hour
	How timely was health seeking to the RHC?	Delayed care (1) Timely care (0)
	How many days of symptoms or delayed care days before reaching RHC?	Continuous per day
	Did you seek care to a Traditional Medicine Practitioner or for traditional medicine?	Yes, I sought care (1) No, I did not seek care (0)
	Did you seek care at the following: drug shops or community health workers? [a]	Yes, I sought care (1) No, I did not seek care (0)
Outcomes	Case: malarial hospitalization, Control: non-malarial hospitalization	Case (1) Controls (0)
Confounding Variables	Rainy season	Rainy season (1) Dry season (0)
	Age at enrollment	Continuous
	Employment	Nominal (1-7)

The quantitative exposures included in the EFA are listed. The exposures were based on the measures from the larger pilot study described in manuscript 1. [a] Neighborhood availability, distance, and care-seeking choices with two or more responses were individual items in EFA.

Data handling, study variables, and data analysis

Trained data collectors administered questionnaires and abstracted medical charts using tablets. Data was entered directly into the REDCap Mobile app and transferred to storage [133]. All data was stored on an encrypted database and RStudio (version 2021.09.0+351) was used for data analysis[134]. Data was evaluated for patterns of missingness, with 21% missingness in the sample. The correlation between variables without missingness and missing data suggested missingness at random. To minimize possible selection bias, multiple imputation for variables with less than 10% missingness were performed under the missing at random assumption. Conditional multiple imputation by chained equations, adjusted for case status and age, produced five duplicate datasets with imputed values for missing data [134]. This approach preserved the variability and uncertainty associated with the imputed values, ensuring robust estimates with limited bias[135].

Table 2.1 describes the self-reported exposures, outcomes, and confounding variables considered in the analysis, including the type of data. The exposure variables were determinants of health access, navigation, and behaviors that were re-examined and compared in the analysis. These exposures were generated based on the pilot Delayed care seeking was defined as care seeking with fever or the onset of symptoms before 24 hours (coded as 0) or after 24 hours (coded as 1). COVID-19 health seeking was defined as COVID-19 being a barrier to care at RHC (coded 0) and COVID-19 was not a barrier to care (coded 1). The rainy season represented months January to April (coded as 1) and months May to December the dry season (coded as 0). All binary variables were positive (coded as 1) or negative (coded as 0). Nominal variables, often with fewer than ten responses, were coded beginning at 0 with a 1 unit increase for every additional response. Ordinal variables were coded starting at the reference or lowest value by response proportion (coded as 0) with a 1 unit increase for every additional level.

Bivariate analysis summarized demographic characteristics and case status with medians and interquartile ranges. Multivariate logistic regression assessed the associations between severe malaria disease and health access indicators. Predicted probabilities with 95% confidence intervals were reported for unadjusted and adjusted models. The average predicted probabilities for adjusted models held covariates (age category, employment, and season) at the weighted proportions in the sample[136]. Plots assessed interactions between health access indicators and delayed care, which were adjusted for age category, season, and employment status on average.

EFA was suitable for data reduction of health access and navigation determinants to the RHC. All binary, continuous, and ordinal exposures or determinants with sufficient variability were included in the EFA. Of all the variables (N=54) evaluated for EFA, 23 were removed for

insufficient variability. The EFA included 31 variables and N=7,533 observations from 243 participants. Primary items were loaded onto retained factors to identify associations among determinants, leading to composite variables for ecological health access indicators. Sample adequacy was assessed with the Kaiser-Meyer-Olkin (KMO) measure [137].

Factor retention was based on diagnostic plots (scree plot and parallel analysis) and eigenvalues greater than one [138,139]. Bartlet's test of Sphericity was used to determine factor rotation [140]. Factor loading criteria were based on the .40 item loading cutoff, 0.20 communalities cutoff, low correlation (<.20) between retained factors, and alignment with an adapted behavioral ecological conceptual model[138,139]. The factor scores, communalities, and proportion of total variance explained were reported to describe the retained items and factors. The final factor structure was compared to other EFA models with additional factors to measure factor structure consistency. Items with negative factor scores were reverse-scored and re-evaluated in the EFA model to confirm that the strength of their associations remained.

Determinants or loaded items were generated into indicators or composite variables, describing ecological health access domains. All determinants were transformed with maximum-minimum normalization, and determinants with negative factor scores were reverse-scored [141]. Transformed determinants were weighted based on the absolute value of factor scores [142]. The determinants were standardized and weighted by factor loading score, a proxy for the strength of association of the item and factor. Data were transformed into binary or quintile variables based on the distribution of composite scores using histograms and statistical tests. Indicator variables were classified as ecological health access based on correlations with associated determinants.

No factors were linked to health behaviors or health-seeking practices, so the focus of this manuscript was on ecological health access indicators.

Table 2.2 Ecological health access indicators

Ecological Health Access Indicator	Scale	Interpretation
Built environment (BE) or travel-related challenges that are affected by variations in the physical environment[65]. BE, a prominent indicator for health access, is defined as: • **Travel time to RHC per hr** • **Distance to RHC per 5 km** • **Distance to traditional medicine practitioner per 5km**	**Shorter distance and time to care**  **Longer distance and time to care**	**More** built environment access **Some** built environment access **Less** built environment access
Social environment (SE) or social capital can provide access to transportation to the RHC, in a community with limited transportation options[65,143]. SE, an important social indicator for accessing health, is defined as: • **Accessible transportation** • **Affordable transportation**	**Transportation is not a barrier**  **Transportation is a barrier**	**More** social environment access **Less** social environment access
Healthcare environment (HE) or healthcare systems and their availability [65]. HE, an indicator for access to the health system, is defined as: • **Access to ambulatory care** • **Access to community health workers (CHW)** • **Access to referral care** • **COVID-19 impact on RHC**	**Health system available**  **Health system not available**	**More** healthcare environment access **Less** healthcare environment access

The determinants retained for EFA are grouped by health access environment, either built, social, or healthcare. The definitions for the three health access environments based on the adapted behavioral ecological framework are provided [65]. The scale and interpretation for the generated indicators are listed.

The ecological health access indicators, along with their determinants, scale, and interpretation, are detailed in Table 2.2. The built environment (BE) indicator measured travel time to the RHC and distance to care (RHC or traditional medicine practitioner). Quintiles were established for the BE indicator: less health access (longer distance/time coded as 2, referent), some health access (moderate distance/time/coded as 1), and more health access (shorter distance/time coded as 0). The social environment indicator assessed the influence of social capital on transportation access, categorizing individuals with transportation barriers as having less social access (coded as 0) and those with access as having more social access (coded as 1).

The healthcare environment indicator assessed access levels, where less access (coded as 0) indicated reduced availability of community health workers (CHWs), referral care, ambulatory services, and a negative impact from COVID-19 on rural healthcare (RHC) access. In contrast, more access (coded as 1) indicated increased availability of CHWs, referral care, ambulatory services, and that COVID-19 had no impact on RHC access. Crude logistic regression models evaluated the association between these indicators and severe malaria hospitalizations, reporting predicted probabilities and 95% confidence intervals.

Adjusted models presented average predicted probabilities while holding covariates at their weighted proportions. Models incorporating ecological health access indicators were adjusted for age category, season, and employment-seeking status. Marginal predicted probability plots compared ecological health access indicators by age category and instances of delayed care.

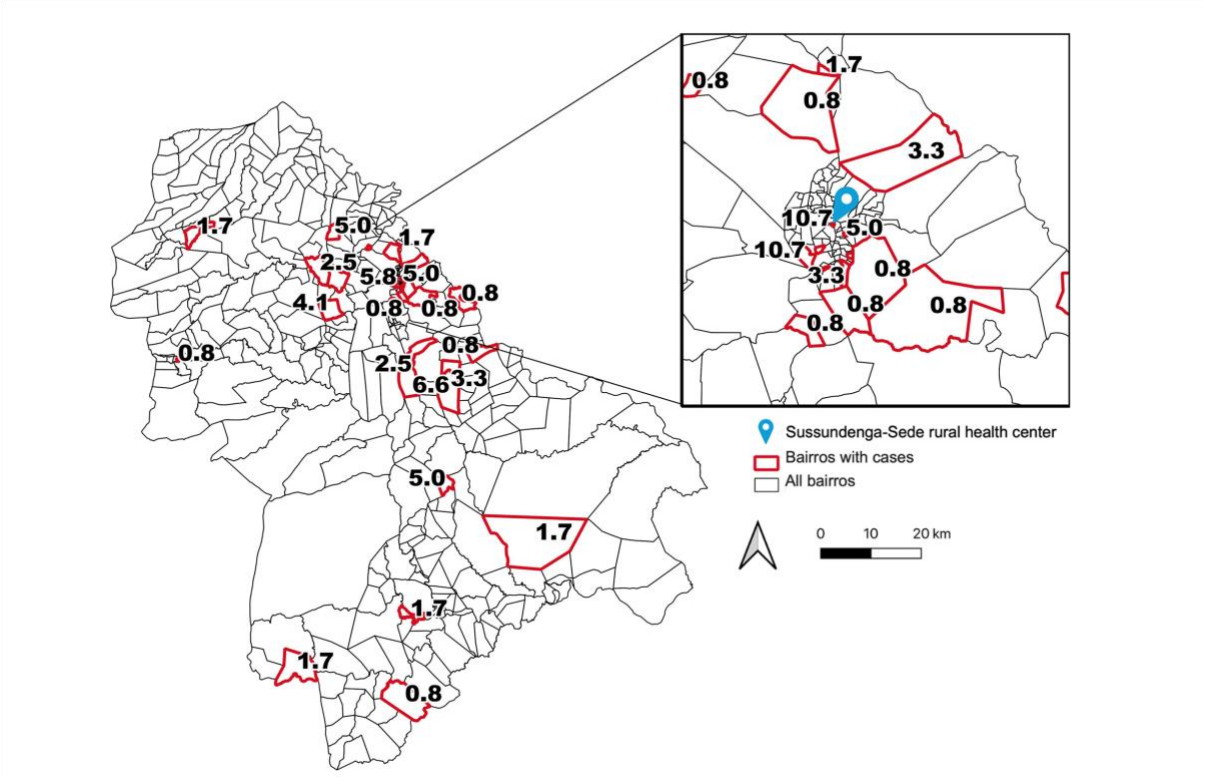
Interactions on the additive scale between composite variables and delayed care were measured using the relative excess risk due to interaction (RERI) and corresponding p-values.

Ethical review

The study has received Institutional Review Board approval from the University of Minnesota (STUDY00016387) and Comissão Nacional de Bioética em Saúde in Mozambique (IRB00002657).

Results

Figure 2.2 Proportion of severe malaria hospitalizations by bairro in Sussundenga district



The proportion of severe malaria hospitalizations enrolled by bairro, an indicator of neighborhood, in Sussundenga district is depicted. The red outlined bairros indicate severe malaria hospitalizations were enrolled from that location and the black outline shows a bairro boundary.

Recruitment and demographic characteristics

Of the 243 participants, 121 individuals experienced severe malaria that resulted in hospitalization, while 122 served as non-malarial controls. The enrollment of both cases and controls increased during the second year of recruitment, peaking toward the end of the rainy season. Notably, cases were enrolled during the dry season, contrary to the trends observed in pediatric malaria hospitalizations in Chimoio, the nearest district city [40]. Figure 2.2 illustrates the proportion of total severe malaria cases by bairros, or neighborhood, in Sussundenga District to assess potential sampling bias. The severe malaria hospitalization cases originated from 39 different bairros, indicating that case selection was independent of bairro origin. Nhamarenza and Nhamizara had the highest proportion of severe malaria cases (10.7%), bairros located closest to the Sussundenga-Sede RHC.

The most common case definitions were severe malaria anemia (81.6%), followed by severe malaria complicated by chronic comorbidities (9.2%), and severe malaria due to previous treatment failure (3.4%). The patterns of severe malaria disease were similar to those observed in moderate to high transmission settings [1]. Severe malaria treatment failure was likely not attributed to full artemisinin anti-malarial resistance, as no studies have documented this in Mozambique. Surveillance for artemisinin-based anti-malarial resistance in the WHO African region recently detected *P. falciparum* Kelch13 polymorphisms in Mozambique that were associated with partial resistance to artemisinin-based therapy and treatment failures [144].

More than half of the non-malarial hospitalized controls were diagnosed with gastrointestinal infections or severe malnutrition. Table 2.3 summarizes the demographic characteristics of all participants and by case status. The median age of the sample was 3 years old [IQR: 1.5 – 11

years]. Over 60% of the sample were males and worked as farmers, which aligned with previous community-based studies in the region[117]. The median household size for both cases and controls was 6 people. Households had a median duration of having insecticide-treated nets (ITNs) in the house, and about 85% of participants used an ITN the night before. One in ten participants reported a malaria infection or disease in the previous month.

Table 2.3 Demographic characteristics of participants

	Cases Severe Malaria Hospitalizations	Controls Hospitalizations without Malaria	Total
Study Participants N (%)	121 (49.8%)	122 (50.2%)	243(100%)
Sex N (%)			
Female	53 (43.8%)	56 (45.9%)	109 (44.9%)
Male	68 (56.2%)	66 (54.1%)	134 (55.1%)
Age Category N (%)			
Children under five	84 (69.4%)	71 (58.2%)	155 (63.8%)
School aged children	8 (6.6%)	13 (10.7%)	21 (8.6%)
Adolescents	8 (6.6%)	8 (6.6%)	16 (6.6 %)
Adults	21 (17.4%)	30 (24.6%)	51 (21.0%)
Occupation N(%)			
Farmer	80 (77.7%)	72 (76.6%)	152(77.2%)
Miner	3 (2.9%)	2 (2.1%)	5 (2.5%)
Health worker	3 (2.9%)	0 (0%)	3 (1.5%)
Teacher	2 (1.9%)	3 (3.2%)	5 (2.5%)
Self-employed	6 (5.8%)	10 (10.6%)	16 (8.1%)
Religious Leader	3 (2.9%)	3 (3.2%)	6 (3%)
Unemployed	6 (5.8%)	4 (4.3%)	10 (5.1%)
Household size			
Median[Q1-Q3]	6 [4-8]	6 [4-7]	6 [4-7]

The demographic characteristics for cases, controls, and the sample are described. All measures were self-reported.

Delayed care seeking and distance to care

Delayed care seeking was common among all cases and controls, as 80% experienced a delay in seeking care or sought care more than 24 hours after the onset of symptoms. Average predicted probabilities from unadjusted and adjusted conditional logistic regression models, which

compared delayed care seeking and distance to care, are shown in Table 2.4. On average, across seasons, age categories, and employment statuses, the predicted probability for severe malaria hospitalization among delayed care seeking was 52% [0 -100%], while for timely care was 79% [0 -100%].

This finding was unexpected, as comparable case-control studies consistently reported a higher likelihood of delayed care-seeking among severe malaria cases. After adjusting for averaged factors such as season, age category, and employment, the predicted probabilities for cases traveling 10 km to reach the RHC were 0.56 [0-1.00], TMP were 0.65 [0-1.00], and for the nearest health post were 0.51 [0-1.00]. The cases exhibited similar probabilities of traveling 10 km to access the TMP and health post, although these estimates were imprecise.

Table 2.4 Conditional logistic regression models for delayed care and access to care

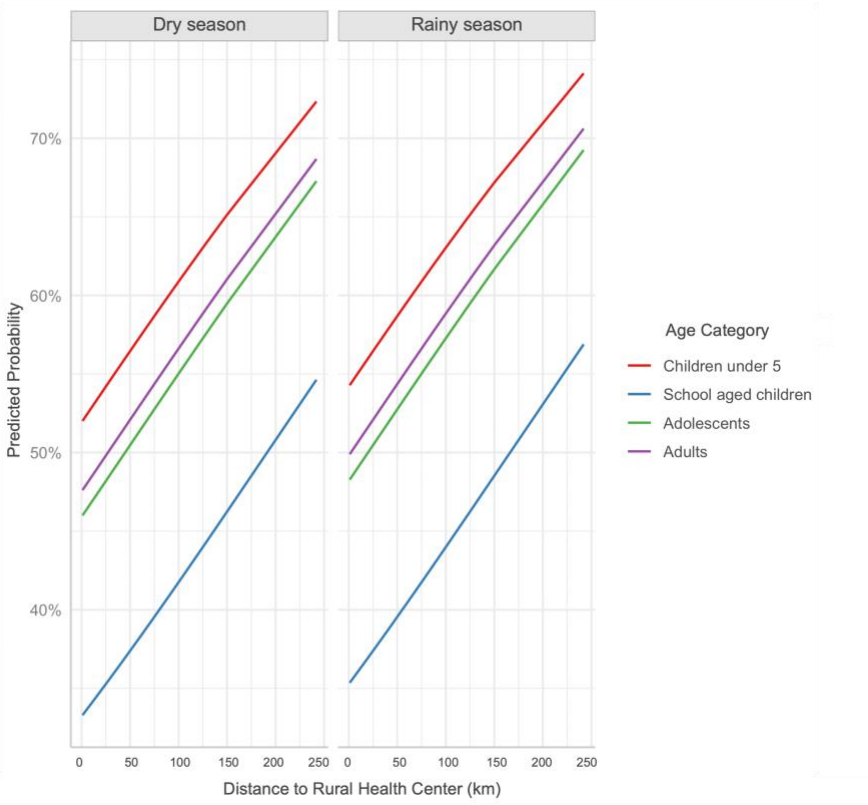
	Crude Predicted Probabilities [95% CI]	Adjusted Average Predicted [a] [95% CI]
Delayed care (Reference: timely care)	0.33 [0.20-0.48] 0.63 [0.50-0.77]	0.52 [0-1.00] 0.79 [0-1.00]
Distance to rural health center (RHC) (ref = 10 km)	0.48 [0.41-0.55]	0.56 [0-1.00]
Distance to Traditional Medicine Practitioners (ref = 10 km)	0.57 [0.46-0.67]	0.65 [0-1.00]
Distance to health post (ref = 10 km)	0.49 [0.43-0.56]	0.51 [0-1.00]

[a] *All models reported average predicted probabilities based on a weighted average of the following covariates age category, employment, and season.*

Marginal predicted probabilities for distance to care by season and age category is reported in Figure 2.3. Longer travel distances to the RHC increased the likelihood of severe malaria hospitalizations compared to the control group, considering factors like season, age category, and

employment status on average. Specifically, the predicted probability of hospitalizations rose during the rainy season across all age groups when compared to the dry season. The highest likelihood of severe malaria hospitalizations was among children under five years old, while school-aged children had the lowest probability.

Figure 2.3 Marginal predicted probabilities for distance to the Sussundenga-Sede RHC (km)



Marginal predicted probabilities were generated from a conditional logistic regression model that adjusted for average age category, season, and employment. The rainy season were month January to April and the dry season were months May to December.

This was anticipated given the moderate to high transmission of malaria and the heightened risk faced by this vulnerable group. The overlapping confidence intervals across the predicted probabilities indicated that there were no significant differences between the age categories in either the rainy or dry season. However, in this rural setting, longer distances to the RHC were

associated with an increased probability of severe malaria hospitalization. Thus, distance to the RHC emerged as a key determinant of the likelihood of severe malaria hospitalization.

Exploratory Factor Analysis

The factors, loaded items, measures of association, and proportion of variance explained from the EFA are in Table 2.5. Based on eigenvalues greater than 1, a scree plot, and a parallel analysis plot, three to seven factors were suggested. Among all the potential factors, three factors, comprising nine items, were selected using oblique rotation based on Bartlett's Spearman test and the correlations between the factors. These three factors, which fell within the ecological health access domain, described the built, social, and healthcare environments. The structure of the items loaded onto the factors indicated that structural factors significantly influenced health access in this rural, malaria-endemic setting.

The three factors together explained 22% of the total variance in the data and the correlation between factors was minimal (<.20). The low cumulative variance among the factors indicated that additional factors could better explain the data. The three identified factors, along with their corresponding loaded items or determinants, were combined into composite variables or indicators for multivariate logistic regression. There was a low correlation between the indicators themselves, but a high correlation between the indicators and their determinants. Although this analysis was not appropriate for factorization, the EFA successfully achieved data reduction. The number of determinants decreased from 31 to nine and conceptually aligned with the behavioral ecological model[65].

Table 2.5 Exploratory factor analysis

Domain	Factors or indicators	Items or determinants	Factor Loading	Communalities	SS Loading	Average Variance Extracted
Ecological Health Access	(1) Built Environment	Travel time to RHC (hr)	0.92	0.995	2.06	7%
		Distance to traditional medicine practitioner (per 5 km)	0.68	0.486		
		Distance to RHC (km)	0.48	0.235		
	(2) Social environment	Transportation affordability	0.91	0.969	2.17	7%
		Transportation as a barrier	0.80	0.764		
	(3) Healthcare Environment	Access to ambulance	0.91	0.830	2.60	8%
		Access to CHW	0.64	0.468		
		Access to referral care	-0.60	0.454		
		COVID-19 health seeking to RHC	-0.61	0.382		

The EFA findings for the retained indicators are listed for the ecological health access domain. The determinants and corresponding EFA measures of association and variance are listed.

Built environment access indicator

The built environment was a proxy for the physical environment. It described the distance and time traveled to care. Average predicted probabilities for case outcomes were adjusted for season, age category, and employment status on average (Table 2.6). The probability of severe malaria hospitalizations increased as built environment access decreased (*longer distances and time to care*). The predicted probability for severe malaria hospitalizations was 46% [0-100%] with more built environment access and 64% [0-100%] with less built environment access.

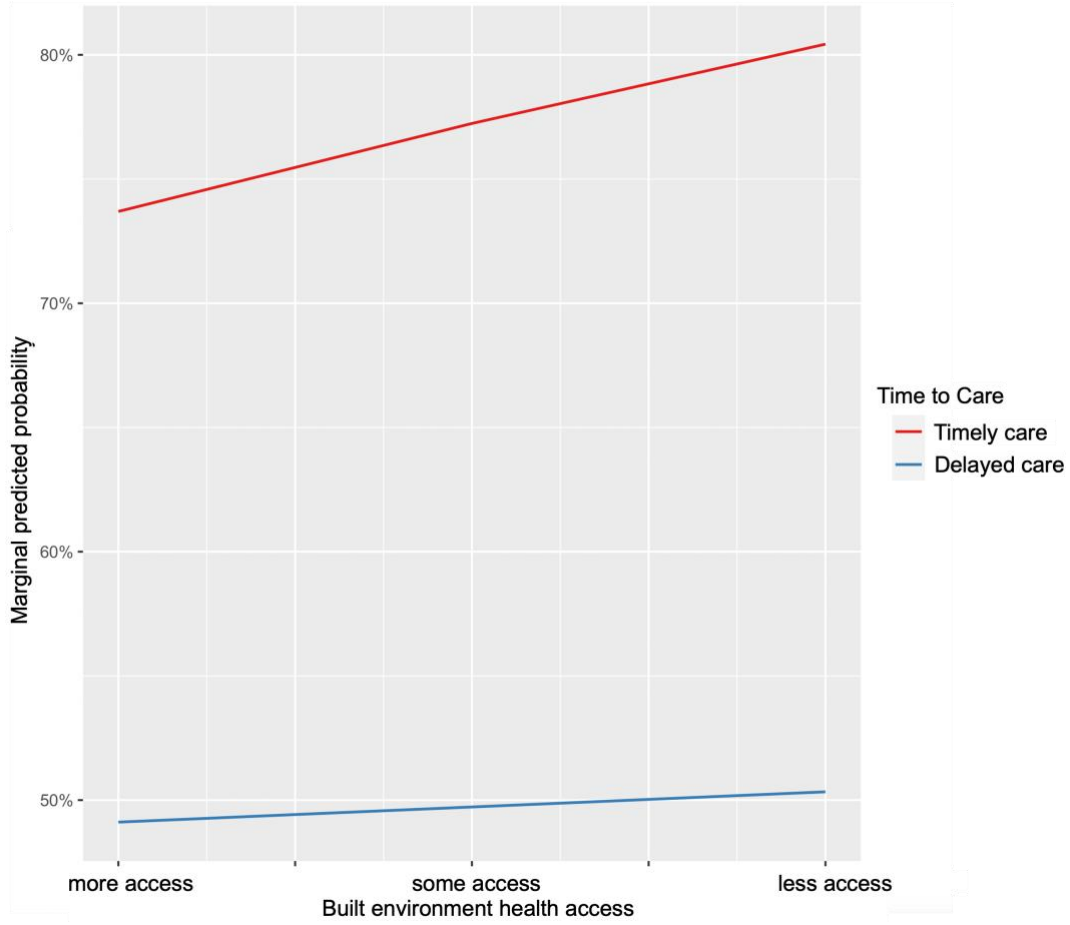
Table 2.6 Conditional logistic regression models for ecological health access indicators

Ecological Health Access Indicators	Variables	Crude Predicted Probabilities [95% CI]	Adjusted Average Predicted Probabilities [a] [95% CI]
Built environment access	*More*[b]	0.60 [0.48-0.71]	0.46 [0-1.00]
	Some	0.29 [0.17-0.43]	0.64 [0-1.00]
	Less	0.44 [0.48-0.71]	0.64 [0-1.00]
Social environment access	*More*[b]	0.43 [0.31-0.55]	0.55 [0-1.00]
	Less	0.54 [0.44-0.63]	0.60 [0-1.00]
Healthcare environment access	*More*[b]	0.52 [0.39-0.64]	0.58 [0-1.00]
	Less	0.48 [0.39-0.58]	0.56 [0-1.00]

Models reported as average predicted probabilities held adjusted covariates at the weighted average for the season, age category, and employment. [b] More built, social, and healthcare environment access indicators were the referent groups in the models.

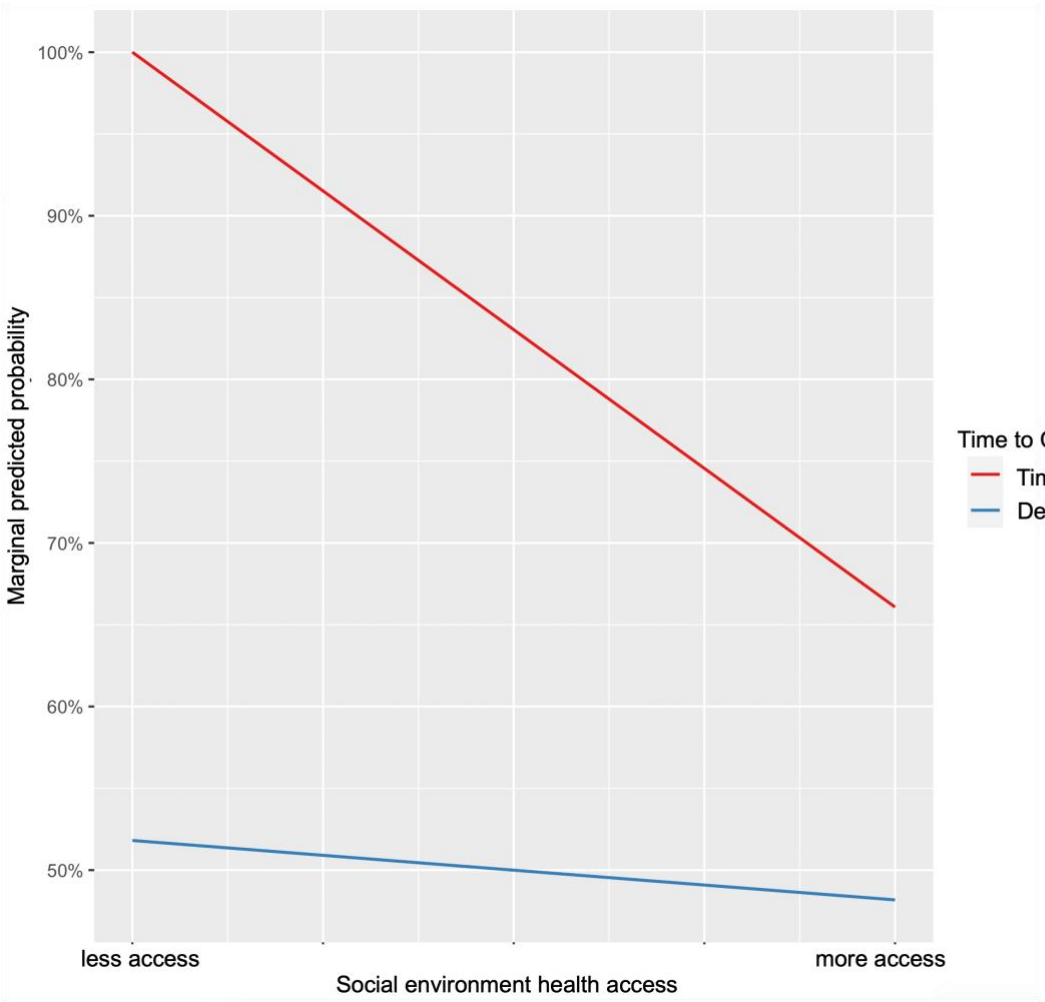
Existing barriers in the physical environment adversely affected healthcare navigation for severe malaria hospitalizations, which also depended on whether care-seeking was delayed. Adjusting for season, employment, and age category on average, with less access to the built environment the marginal predicted probability of severe malaria hospitalization for delayed care was lower than for timely care (Figure 2.4).A sub-additive interaction suggested delayed care compared to timely care had minimal differences in likelihood for severe malaria [RERI: -0.04, $p < 0.001$]. Furthermore, with reduced access to the built environment, seeking healthcare within 24 hours following the Mozambican NMCP did not decrease the likelihood of severe malaria hospitalization.

Figure 2.4 Marginal predicted probabilities for built environment access by delay care



Marginal predicted probabilities were generated from a conditional logistic regression model that adjusted for average age category, season, and employment. Delayed care was seeking care after 24hrs of symptom onset and timely care was within 24hrs. Built environment was a proxy for navigation through the physical environment or distance and time traveled to care. A small sub-additive interaction for delayed care compared to timely care is displayed in the plot [RERI: -0.04, p<0.001]

Figure 2.5 Marginal predicted probabilities for social environment access by delayed care



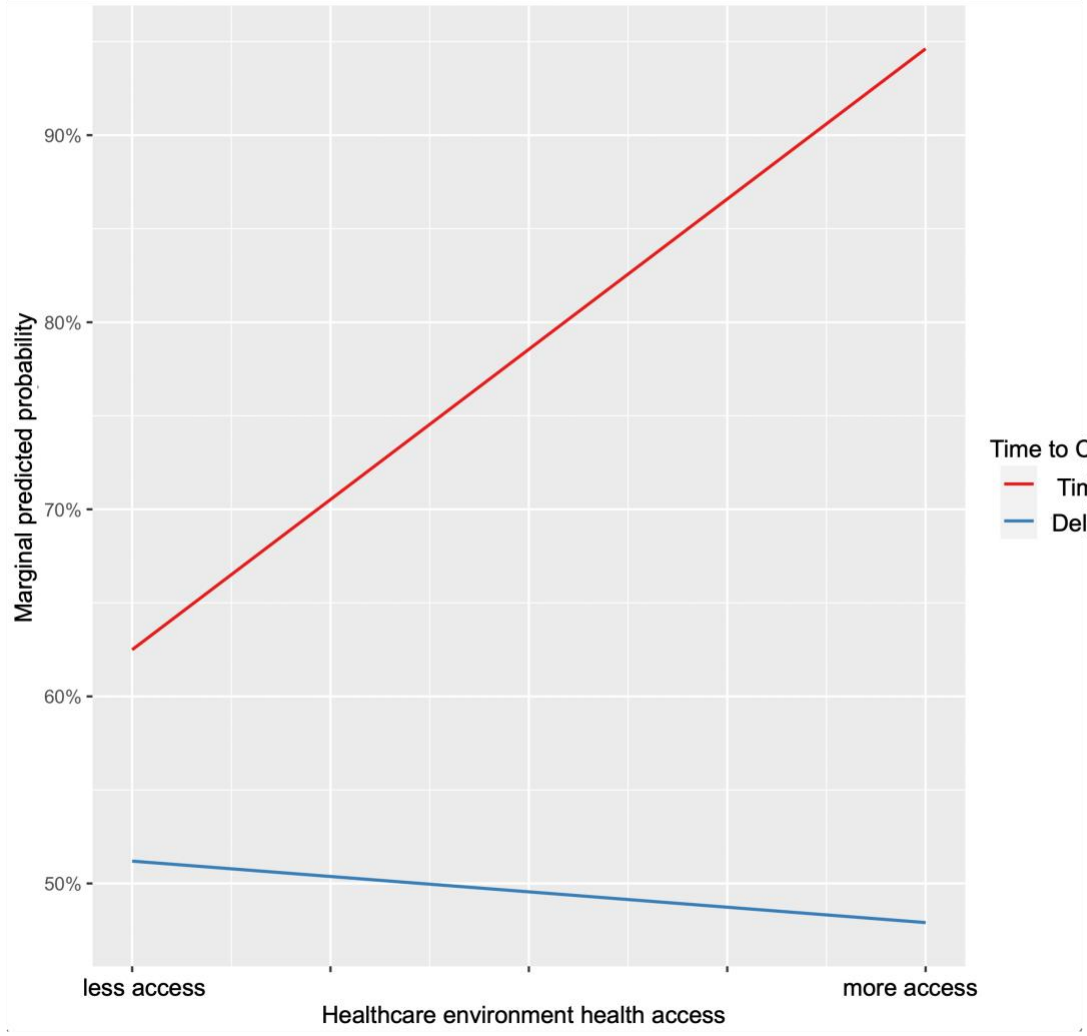
Marginal predicted probabilities were generated from a conditional logistic regression model that adjusted for average age category, season, and employment. Delayed care was seeking care after 24hrs of symptom onset and timely care was within 24hrs. The social environment was a proxy for social capital for transportation to care. This plot suggested a possible sub-additive interaction for delayed care compared to timely care [RERI: -0.04, p=0.005].

Social environment access indicator

The social environment access indicator described the social capital necessary to overcome transportation barriers to care. The average predicted probability of severe malaria

hospitalization was 55% [0-100%] for individuals with more social environment access and 60% [0-100%] for those with less access, after adjusting for season, age category, and employment status on average (Table 2.6). Although these differences were not statistically significant, the association varied based on the timing of care. The marginal predicted probability interaction plot for social environment access and delayed care is presented in Figure 2.5.

Figure 2.6 Marginal predicted probabilities for healthcare environment access by delayed care



Marginal predicted probabilities were generated from a conditional logistic regression model that adjusted for average age category, season, and employment. Delayed care was seeking care after 24hrs of symptom onset and timely care was within 24hrs. The healthcare environment was a proxy for the availability of healthcare resources, including ambulatory services community health workers, referral care, and COVID-19 barriers to care. This plot indicated a small sub-additive interaction for delayed care compared to timely care [RERI: -0.01, p=0.005].

As social environment access increased, the marginal predicted probability of severe malaria hospitalization was higher for timely care compared to delayed care, while adjusting for average age category, season, and employment status. A potential sub-additive interaction between timely and delayed care suggested that timely care was not protective for individuals with lower social environmental health access [RERI: -0.04, p = 0.005].

Healthcare environment access indicator

The healthcare environment explained the available healthcare resources in the community. Average predicted probabilities for severe malaria hospitalization were similar for individuals with varying levels of healthcare environment access, after adjusting for average season, age category, and employment status (Table 2.6). However, the estimates were imprecise. The marginal predicted probabilities illustrating the association between healthcare environment access and severe malaria hospitalizations by delayed care are presented in Figure 2.6. Among individuals who experienced delayed care compared to those who received timely care, the marginal predicted probability for severe malaria hospitalization decreased as healthcare environment access increased, after adjusting for average season, age category, and employment [RERI: -0.01, p=0.005].

Ecological health access indicators summary

The study highlighted differences in ecological health access determinants related to social, built, and healthcare environments. The decreased access to built environments was associated with a higher likelihood of severe malaria hospitalization. Delays in receiving care, regardless of social, built, or healthcare access, did not reduce the likelihood of severe malaria hospitalizations. With

all ecological health access indicators, interactions that compared delayed care to timely care conferred a decreased likelihood of severe malaria hospitalization or a slight sub-additive interaction.

Discussion

This analysis re-examined determinants for health access at an RHC in Sussundenga, Mozambique, considering social, healthcare, and built environment domains. The study broadened the scope of established determinants, such as delayed care and distance to care, by adding interdisciplinary factors [73,78]. The availability of care during COVID-19 and social factors affecting transportation access were significant determinants in this analysis, aligning with findings from health access studies in endemic regions [145–148]. The relationship between ecological health access indicators and severe malaria hospitalizations emphasized the substantial influence that social determinants of health exerted on severe malaria outcomes within the community.

Consistent with prior malaria health-seeking research conducted in the Sussundenga district, this analysis demonstrated that health-seeking behavior predominantly occurred at the Sussundenga-Sede RHC [117]. In contrast to the 33% delayed care-seeking reported nationally pre-COVID-19 pandemic and 25% reported among households previously reported in manuscript 1, three out of four participants hospitalized for severe malaria delayed seeking care [5,117]. This delay occurred regardless of case status in this rural setting, with most non-malaria control hospitalizations reporting delayed care-seeking. Interruptions in health-seeking behavior had consistently been reported concerning other infectious disease outcomes in Mozambique [149,150] and across Sub-Saharan African malaria-endemic countries [145,146]. Inconsistent malaria resources have been

attributed to increasingly severe weather events and health worker strikes from 2023-2024 [68,151,152]; which could explain the critical gap in health-seeking.

Additionally, the indicators assessed social capital for transportation and the availability of health services, such as community health workers (CHWs), referral care, and ambulatory services. The generated indicators prioritized health access and availability within the community, over health behaviors or provider determinants. Research examining the gap between the onset of malaria symptoms and subsequent treatment has often lacked the guidance of conceptual frameworks and paradigms [21,80,107,153,154]. Consequently, a considerable body of evidence detailing patient health-seeking behaviors and provider non-compliance with the Mozambican NMCP treatment guidelines appear unrelated to health access and navigation [113,143].

Our previous cross-sectional study conducted in Sussundenga village measured significant gaps in care-seeking behaviors and access to diagnostics, in comparison to instances of not receiving treatment or receiving improper treatment following care-seeking [117]. The EFA indicated that a combination of minimal physical travel-related barriers, access to transportation, and multiple healthcare options were determinants for health access in this endemic setting. However, the low total variance explained by the indicators, along with the unsuitable statistical metrics of EFA performance, limited the generalizability and reliability of these indicators [138,139,142]. It is likely that additional determinants also influenced health utilization within this community.

Limited access to ecological health indicators was associated with an increased likelihood of severe malaria hospitalization. The analysis revealed an inverse correlation, particularly notable in the built and social access indicators. However, the likelihood of severe malaria

hospitalization did not significantly differ between individuals with and without access to these ecological health indicators. Although these generated indicators were imperfect measures of ecological health access, they aligned with studies evaluating barriers to severe malaria health access and existing health navigation theory [65,114,155].

Housing construction and socio-economic status are established determinants of malaria risk in Mozambique [35,68,78,113]. The increased average predicted probabilities for severe malaria hospitalizations associated with less ecological health access from the social and built environment support the importance of these social determinants of health in Mozambique. In line with the behavioral ecological model, our analysis revealed barriers to navigation are essential to eliminating malaria disparities [65].

The community-based case-control study was in partnership with health providers at Sussundenga-Sede RHC and trained data collectors efficiently sampled rare cases of severe malaria hospitalizations in a moderate to high transmission setting. Guided by a post-colonial paradigm, the questionnaire evaluated interdisciplinary determinants of health access and health behavior related to community malaria prevention and treatment. Possible recall bias from the self-reported data collection and measurement error from data entry could have introduced bias. Control selection bias could have occurred because malaria negative confirmation by diagnostic test (RDT or microscopy) was not applied to every control included.

The EFA suggested indicators defined by interdisciplinary determinants, however, the indicators did not fully explain the sample. The analysis was not powered to evaluate interactions, which caused wide, imprecise estimates of severe malaria hospitalization probabilities associated with

ecological health access indicators. Future research, with larger sample sizes and the other tiers in the health system, is necessary to understand the potential of the generated indicators as valid measures of health access.

Conclusion

Our findings indicated clear public health messaging about delayed care seeking was needed to decrease the risk for severe malaria disease and local malaria transmission [147,156]. The interdisciplinary determinants within indicators suggested future research should explore disparities in transportation and navigating the physical environment to care. Delayed care seeking and lack of transportation seemed to impact the district, regardless of case status. Disease-agnostic interventions to reduce delayed care-seeking and community-engaged transportation approaches have been studied with success in Mozambique and could be expanded [155,157]. Previous studies have evaluated interventions that consider walking distance for malaria care and place-based malaria posts to improve malaria health navigation disparities [125]. This study suggested that community-based approaches should be considered to improve ecological access to health in the future.

Chapter 6 (Manuscript 3) Training, Health Navigation, and Integrating Traditional Medicine into Rural Health Center Severe Malaria Referral Care – A Mixed Method Approach

Abstract:

Background: The Mozambique NMCP policies support universal access to diagnostics and treatment; however, among febrile patients, only 48% underwent malaria diagnostic testing, with merely 33% receiving antimalarial treatment in 2018[3]. Mortality increases after delaying treatment for more than 24 hours following symptom onset. Several modeling studies have suggested improvements in access and use of in-patient care could reduce severe malaria disparities. Many key decision makers, beyond patients, affect severe malaria outcomes, including clinical providers at multiple levels, traditional medicine practitioners, and community champions [158]. Community champions mobilize rural communities to engage in vector control and malaria prevention education. Severe malaria prevention and treatment, especially the role of provider delays, have been understudied within malaria case management research [83–85]. This study assessed facilitators and barriers to severe malaria training and health navigation from different relevant groups, including a unique referral program between traditional medicine practitioners and the Sussundenga-Sede RHC.

Methods: Collaborators in Mozambique, trained data collectors, and I collected patient and provider data about severe malaria case management, including local knowledge and traditional medicine practices. To handle the complex history of colonialism in the Mozambican public health system and multiple perspectives among key decision makers, dialectical pluralism and

post-colonial indigenous paradigms were applied [128,159]. This study compared key decision makers' perspectives on facilitators and barriers to effective severe malaria care, evaluating education, delayed care, and traditional medicine. The convergent parallel mixed method study simultaneously collected quantitative data from a case-control study and conducted semi-structured interviews (i.e., the qualitative component) at the Sussundenga-Sede RHC, the largest health center in Sussundenga district, Mozambique [160,161].

In the quantitative phase (case-control study), a survey collected health navigation and health-seeking behaviors among 120 hospitalized cases with severe malaria disease and 120 hospital-based controls from April 2023 to August 2024. During the same period, qualitative semi-structured interviews among doctors, nurses, lab technicians, community champions, and traditional medicine practitioners involved in severe malaria case management were conducted (n=15) to gauge care at the same RHC from June to August 2024. The quantitative data were prioritized to capture rare, severe malaria cases in this rural setting. The quantitative and qualitative data were analyzed separately and mixed during data interpretation. This approach developed a more complete understanding of delayed care-seeking from multiple relevant groups involved in severe malaria case management [160,161]. Meta-inference, narrative review, and joint displays examined the parallels and distinctions among the data [162,163].

Results: Findings revealed that on-the-job prepared key decision-makers the most for severe malaria case management, though gaps persisted in training consistency for several roles. Health navigation challenges emerged as critical barriers, with delayed care frequently reported and discrepancies observed between patient and provider perspectives on pre-treatment practices. TMPs played a dual role—acting as both care access points for referral and malaria prevention

education. While TMPs provided culturally meaningful support, concerns about referral timeliness underscored the need for structured collaboration between traditional medicine practitioners and public health systems to optimize care-seeking pathways in high-risk rural areas.

Conclusions: The findings on severe malaria hospitalizations and qualitative data from key decision-makers offered complementary data to understand the facilitators and barriers to training, health navigation, and traditional medicine. The findings about traditional medicine utilization and the unique referral system could be adapted to malaria-endemic settings beyond the Sussundenga district, Mozambique.

Background

Mozambique accounts for 4% of the global *P. falciparum* malaria morbidity and mortality [4]. Unlike uncomplicated malaria infection, severe malaria disease requires prompt diagnosis and treatment within 24 hours to prevent long-term deficits in quality of life and death [110]. It is unclear whether untreated individuals with uncomplicated malaria infection will progress to severe disease, but understanding the multi-level determinants of delayed treatment is essential to prevent excess malaria deaths [1,110]. Delayed malaria treatment is multi-factorial, with patients, caregivers, providers, and the wider community all contributing to prompt treatment [73,80,164]. Often individuals with severe malaria and their caregivers must discern their symptom severity and decide the first point of care. Several qualitative studies on caregiver perceptions of treatment delays are attributed to themes about the use of home treatment or distance to care, but few studies guided their analysis from a post-colonial indigenous paradigm or used community

engagement to reduce epistemic bias [165–167]. Substantial evidence on healthcare provider contributions to severe malaria treatment delays has elucidated poor referral care, misdiagnosis, or mistreatment as primary factors [80,90,153]. Previous studies in Mozambique have suggested delaying diagnosis among symptomatic individuals has contributed to poor malaria case management [80,107]. However, these studies were cross-sectional quantitative studies that did not document severe malaria cases [107,117]. Previous mixed-method studies about malaria case management have collected qualitative data from patients and providers, without consideration for traditional medicine [1,2], whereas this study integrated qualitative data from TMPs.

TMPs have been trusted community members who influence the time to care and the first site of care for severe malaria patient caregivers [170,171]. The role of TMPs in severe malaria case management has been reported as a barrier to treatment [170,172,173], rather than as first responders for individuals with severe malaria. Sussundenga district utilizes a novel referral process between TMPs and the Sussundenga-Sede RHC. This study was designed to assess herbal malaria treatments and traditional medicine practitioners, which are healthcare resources used by the community and are often excluded from western-centered global health research.

Malaria care coordination research has been overlooked, despite the ubiquitous challenge it manifests across post-colonial public health systems. This was most evident in the controversial CARAMAL study, an observational quasi-experimental study in Nigeria, Democratic Republic of Congo, and Uganda to scale up rectal artesunate pre-referral treatment with over 400,000 children under five and 5,000 health workers [87,88]. The study largely ignored neo-colonial power imbalances conceptually and in the study design. External, international organizations without representation from the local communities, including partnerships between NGOs, WHO

leadership, pharmaceutical suppliers, and consultants to maintain a novel patient surveillance system for data collection were prioritized. Anti-colonial, grass-roots community engagement with those most impacted was not a focus of the study. The CARAMAL study disclosed overlooking structural health system barriers, like transportation; however, considerable resources went to behavior change communication.

Ultimately, the CARAMAL study highlighted the overemphasis on health behaviors, and omission of the social and structural determinants of health, a common practice rooted in colonialism. Disease-agnostic evaluation of Mozambican health systems through the Millennium Development Goals indicated resource monitoring, staffing, and systems limitations as potential bottlenecks [132]. This dissertation, unlike most malaria delayed care seeking research, evaluated severe malaria care coordination social and structural determinants guided by a post-colonial indigenous paradigm within this rural Mozambican community.

Objectives

The aim was to compare and contrast perceptions of identified themes on facilitators and barriers to effective severe malaria care coordination and referral care from diverse key decision-makers; and self-reported health seeking and traditional medicine use quantitative data from manuscript 2 of severe malaria hospitalizations. Data integration generated meta-inferences for: 1) formal education and training, 2) health navigation and delayed care, and 3) traditional medicine and practitioners.

Methods, study design, and participants

Study setting

The study was conducted in the Sussundenga district, located 44 km from the largest provincial city, Chimoio, Mozambique. Sussundenga district is a rural agrarian community that shares a border with Zimbabwe. From September to March, Manica Province has high temperatures and increased rainfall, which has contributed to seasonally high *P. falciparum* malaria incidence. This lagged association was observed at the provincial hospital in Chimoio, a secondary-level care setting for the most challenging severe malaria hospitalizations. The main RHC is the Sussundenga-Sede RHC with 14 smaller RHCs also in the district, providing tertiary-level care without intensive care. The Sussundenga-Sede RHC has 35 in-patient beds and 109 providers, with mostly nurses and technicians. The RHC refers patients to the provincial hospital, with specialized surgical care from doctors.

Study design and participants

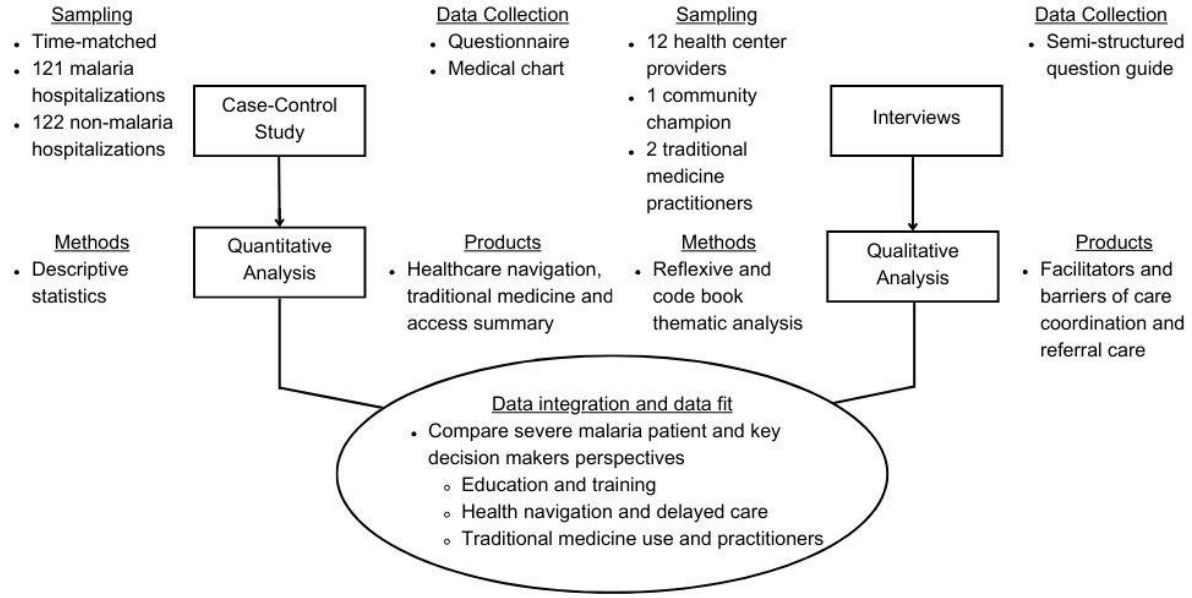
This convergent parallel mixed method study collected quantitative and qualitative components over the same study period (Figure 3.1). A hospital-based case-control study compared severe malaria hospitalizations and non-malaria hospitalizations at the Sussundenga-Sede RHC. The study design, sampling method, data collection, and case definitions used in the quantitative component were described in manuscript 2. For the qualitative component, semi-structured interviews were conducted with a convenience sample of 15 eligible key decision-makers who influence care-seeking and effective management of severe malaria disease. The key decision-makers included: administrators (3), nurses (4), lab expert (1), technicians (2), community

champion (1), and local traditional medicine practitioners (2). The key decision-makers were sampled from the Sussundenga-Sede RHC and in Sussundenga village.

Ethical Review

The study has received Institutional Review Board approval from the University of Minnesota (STUDY00016387) and Comissão Nacional de Bioética em Saúde in Mozambique (IRB00002657)

Figure 3.1 Mixed method data collection, analysis, and integration summary



This figure illustrates the integrated approach used for data collection, analysis, and synthesis in the study, highlighting the sequential and interconnected processes involved in both qualitative and quantitative methodologies.

Data Analysis

Conceptual framework

In this dissertation, a post-colonial indigenous paradigm was applied to address and reduce epistemic injustice by centering the knowledge and experiences of Mozambican participants,

recognizing their lived realities as valid sources of understanding. This paradigm seeks to challenge the dominant, western-centric frameworks that often marginalize or distort indigenous perspectives, thus ensuring that local knowledge systems are valued in their own right. Dialectical pluralism, an approach for contending dynamic complexity of the multiple realities, ways of knowing in the study [159]. In particular, this paradigm enabled this dissertation to find commonalities among the mixed data, all while highlighting the continua of local perspectives of from key decision makers and binaries between them [159].

Reflexivity

Participants were local to Mozambique, while a significant part of the analysis team were high-income institution researchers, including myself, without a Mozambican background. Data collectors were nurses at Sussundenga-Sede RHC and provided feedback in the study design and data collection. I acknowledge that my identity may have introduced biases, potentially limiting the depth of the analysis or distorting local perspectives. My external position may have resulted in a lack of full understanding of the cultural and contextual nuances within the data, and the power imbalance between local participants and the research team could have hindered the richness of the findings. While the post-colonial indigenous paradigm guided my efforts to reduce these biases, I recognize that the absence of local engagement in the analysis—such as member checks with Mozambican healthcare providers—may have further limited the opportunity for the voices of the participants to shape the final interpretation, reinforcing the very epistemic injustices the research sought to address.

Quantitative components

All quantitative measures were self-reported based on survey questions administered by a trained data collector. Pre-treatment at home before seeking care was a nominal variable to define the use of traditional medicine at home. Access to transportation and affordability of transportation to reach the RCH were separate binary variables and were combined to define severe malaria transportation. Use of traditional medicine referral to the RHC was a binary variable. The self-reported days of symptoms before reaching care at the RHC was transformed into a binary variable defining timely or delayed care. Timely care was seeking care within 24 hours of symptom onset and delayed care was reaching care after 24 hours of symptom onset.

Descriptive statistics reported the mean and standard deviation for continuous variables between cases and controls. For categorical variables, proportions and interquartile ranges were reported. Qualitative data from key decision makers on training length, instructor, origin of education, NGO training, and barriers to training were transformed into quantitative data. Descriptive statistics compared the years of education and the length of severe malaria training between key decision-makers. Demographic characteristics and case definitions for severe malaria hospitalizations were reported (control data was reported in manuscript 2).

The following severe malaria hospitalization quantitative data were reported as statistics in joint display tables including delayed care, delayed care days, use of pretreatment, first treatment site, traditional medicine use, transportation barriers to care, and use of traditional medicine practitioner referral. A Sankey diagram detailed the first site of care for severe malaria hospitalizations comparing delayed and timely care seeking.

Qualitative components

A trained interviewer, AB, led the semi-structured interviews for severe malaria prevention and treatment in Portuguese. The interview guide examined traditional medicine integration, education and resources for training, facilitators and barriers to the key decision-maker's role, and post-colonial health system function and dysfunction. The interview guide was initially developed in English and translated into Mozambican Portuguese. The semi-structured interview guide went through two rounds of pilot testing among the study team and providers at Sussundenga-Sede RHC in 2022 and 2023.

The interviews were recorded on an audio recorder in Portuguese. NVivo V.15 Pro transcribed the audio recording into a Portuguese transcript [174]. The Portuguese transcript was translated into English using Google Translate. AB, the interviewer and trained coder fluent in English and Mozambican Portuguese, and I corrected errors in the transcription and translation process with linguistic and cultural translation for Mozambican epistemology and local phrases. Data were prepared to have English and Mozambican Portuguese transcripts for bi-lingual analysis to reduce linguistic bias. The data were cleaned to remove any identifiable information.

Data collectors, DE and AB, were trained in a mix of reflexive and codebook thematic analysis (TA) elements [175,176]. An adapted post-colonial Indigenous paradigm guided the TA, which considered subjectivity, the intersectionality of the multiple identities and post-colonial power dynamics impacting severe malaria disease. The interview questions were developed to account for the impact of colonial health systems, the influence of foreign monetary contributions on Mozambican malaria resources, and other neocolonial inequities[5,69,83,123,132,155,177]. Multiple approaches for reflexivity were used to maintain the cultural and linguistic meaning.

Self-reflection questions were conceptualized based on decolonial methodologies and an adapted post-colonial Indigenous paradigm [126,175,178,179]. The questions were reviewed to acknowledge bias, generate guiding principles, and document bias throughout reflexive TA. During the analysis, DE and AB iteratively reflected upon the following principles: 1) key decision-maker perspectives were equally valued regardless of background, 2) prioritize key decision-maker comfortability, and 3) consideration for unequal geo-political power dynamics in malaria public health. Traditional medicine themes and identifying community innovation were prioritized to adjust for epistemic bias.

Techniques from template codebook TA were used for coding, while reflexive TA guided theme generation and interpretation[175,176]. This process suited the level of experience of the data collectors and enabled a more nuanced approach for more complex themes. Google documents and NVivo V15 Pro were used to complete the TA across countries [174,180]. DE and AB generated a priori codes from semi-structured interview questions and iteratively from line coding. All the codes were agreed upon by DE and AB for an analytical code book, and discrepancies were discussed with qualitative experts [176]. The transcripts underwent two rounds of coding, including descriptive and inductive coding, and coding differences were resolved with group discussion. Due to time constraints, training and education topics were descriptive themes. Inductive themes described codes related to colonialism and system power dynamics.

Power

The power calculation for the case-control study sample size was described in manuscript 2. The sample size for the semi-structured interviews was 15 based on the budgetary and time

constraints, which was sufficient because there were 109 providers at Sussundenga-Sede RHC. Health provider socio-political strikes at the Sussundenga-Sede RHC reduced provider availability for interviews and could have biased the sample. . The depth of the qualitative data collected was sufficient to address this mixed methods study's principal research questions [160,163].

Data Integration

Dialectical pluralism and post-colonial indigenous paradigms guided data integration in multiple dimensions [128,159]. This was preferred to compare the key decision-makers perspectives, identify different ways of knowing, and understand how AB's and my viewpoints impacted the data integration. The key decision-makers represented diverse levels of education, socio-political capital, knowledge of Mozambican rural settings, and experience with severe malaria disease. This facilitated an analysis of severe malaria disease case management from key decision-makers with different roles and levels of care in three analysis phases. Bivariate analysis (quantitative), followed by a separate TA (reflexive and template code-book) were combined for data integration [163,175,176].

The identities of the participants and data collectors shaped the findings. DE and AB had different levels of experience, ethnicities, and genders, facilitating an intersectional lens in line with a post-colonial indigenous paradigm [126]. In addition to data integration during sampling and within the research team, it also occurred at the interpretation and reporting level [181]. Merged themes and statistics were compared to create side-by-side joint display figures for 1) education and training, 2) health navigation and delayed care, and 3) traditional medicine [181,182].

Data on provider education length, the origin of education, and the amount of severe malaria training were quantified to support identified themes on education and resources for severe malaria training. For public health education topics, themes from qualitative analysis about training for malaria prevention and treatment were compared to transformed quantitative data about the length and quality of severe malaria care instruction. Quantitative data from severe malaria hospitalizations about delayed care, use of pre-treatment, and first site of care were reported as descriptive statistics. This was compared to key decision-maker themes on barriers to health navigation and delayed care perspectives. Themes about traditional medicine practitioner referral, traditional medicine treatment knowledge, and the impact on severe malaria outcomes were compared to severe malaria hospitalization data. Traditional medicine access, use, and its influence on health navigation for severe malaria hospitalizations were reported as descriptive statistics.

In line with best practices, these three areas were selected based on comparability (qualitative and quantitative data) and comprehensiveness (multiple levels, key decision-makers, severe malaria hospitalizations) [163,181,183]. Confirmation, expansion, or discordance of data integration were reported as meta-inferences for all topic areas [181,184]. To understand data integration across topic areas, a tabular summary of the meta-inferences and narrative summary on the influence of data collector bias on these interpretations were reported[181,182,184]. Weaving, a data integration method to connect meta-inferences and supporting evidence, was used through narrative review in the discussion on a concept-by-concept basis for all topic areas [181]. Integration through data transformation compared training and education themes with statistics generated from semi-structured interviews on the length and degree of severe malaria disease training [181].

Results

Quantitative results

There were 121 hospitalized malaria cases and 122 non-malaria hospitalized controls. There were no significant differences in sex, median age, employment, minor employment, and median household size between cases and controls. The median days of delayed care were 4 days for controls and 3 days for cases (IQR: 2-30 days; 2-30 days, respectively). A complete analysis with key covariates from the case-control can be found in Manuscript 2. Table 3.1 illustrates the demographic and clinical characteristics for severe malaria hospitalizations. Cases were mostly female, children under five, diagnosed with severe malaria anemia, and did not report malaria infection in the previous month. This was similar to previous studies in Sussundenga and other moderate-high malaria transmission settings [117,185].

Table 3.1 Demographic and clinical characteristics associated with cases at Sussendenga-Sede RHC

Severe Malaria Hospitalizations (N=121)	Count(%)
Sex	
Female	53 (43.8%)
Male	68 (56.2%)
Age Category	
Children under five (4 months – 4 years)	84 (69.4%)
School aged children (5 – 8 years)	8 (6.6%)
Adolescents (9-12 years)	8 (6.6%)
Adults (≥ 13 years)	21 (17.4%)

Case Definition [a]	
Cerebral malaria	4 (4.6%)
Severe malaria anemia	71 (81.6%)
Severe malaria complicated by respiratory distress syndrome	1 (1.2 %)
Severe malaria complicated by co-morbidities	8 (9.2%)
Severe malaria complicated by treatment failure	6 (3.4%)
Malaria history in the past month [b]	
Malaria infection	16 (13.2%)
Severe malaria disease	1 (0.1%)
No malaria history	104 (86.7%)

Quantitative data for severe malaria hospitalized cases were included in the case-control study for the Sussundenga-Sede RHC. The case definition was defined from medical chart abstraction at time of discharge. Severe malaria complicated by treatment failure was defined as severe malaria disease diagnosed after a previous treated malaria infection. [b] *Malaria history in the past month was self-reported.*

Qualitative results

The sample of key decision-makers had diverse roles with varying experience levels across different care settings. Nurses were a significant portion of the sample, including three trained in Mozambique working at Sussundenga-Sede RHC and another highly experienced nurse with 15 years at Instituto Nacional De Ciencias Superior De Saude Central Hospital. Additionally, nurse technicians, community health workers (with up to 24 years of experience), and traditional medicine practitioners were included, though some lacked complete training or experience records. Administrative and technical staff, such as district hospital administrators and a lab professional with 12 years of experience, further contributed to the sample's diversity.

Table 3.2 Roles of Key Decision-Makers at Sussundenga-Sede RHC for semi-structured interviews

Level	Site	Role (n=15)
Primary	Central Hospital	Nurse (1)
Secondary	Provincial Hospital	Technician (1) Nurse (1) Administrators (3)

		Laboratory expert (1)
Tertiary	Sussundenga-Sede RHC	Nurse (2) Community health worker (1)
Community	Sussundenga and Langa village	Community champion (1) Traditional medicine practitioners (2)

This table detailed the site and roles of key decision-makers, by level of care. A tiered system of healthcare is delivered within four levels including provincial hospitals (primary), district hospitals (secondary), health centers (tertiary), and clinics/health posts (quaternary). The community level described roles not within public health facilities yet offered services to the community at large.

The participants represented a range of healthcare environments, from rural clinics to central hospitals, with experience durations spanning two to 24 years. However, data gaps existed, particularly in training locations and exact experience lengths for specific roles. Despite these limitations, the sample reflected a broad spectrum of expertise, highlighting the diverse contributions of clinical, community-based, and administrative personnel in severe malaria care at Sussundenga-Sede RHC. Of the 15 key decision makers in the sample, 13 were directly involved in severe malaria disease diagnosis and treatment. All key decision-makers were engaged in community malaria infection and disease prevention. Table 3.3 describes the formal severe malaria education by role, including the range in education duration. The community health worker and traditional medicine practitioners all received an education, however, the instruction was shorter compared to other roles.

Table 3.3 Severe malaria disease education for key-decision makers

Role (N=15)	Proportion with severe malaria education	Range of severe malaria education duration
Community health worker (1)	100 %	1- 6 months

Traditional medicine practitioner (2)	100 %	1 week - 3 months
Nurse (4)	75%	1 month - 2 years
Administrator (3)	33%	1 month
Community champion (1)	0%	0
Technician (2)	0 %	0
Laboratory expert (1)	0 %	0

This table showed the proportion of severe malaria training and length of severe malaria training by role The data was quantified from semi-structured interviews with key decision makers.. There were the following number of key-decision makers: community health worker (1), Traditional medicine practitioners (2), nurses (5), administrators (3), community champion (1), technicians (2), and an laboratory expert (1).

Integration of qualitative and quantitative results

Formal education and on-the job-training

The meta-inferences from qualitative and quantitative data integration were based on semi-structured interviews in Table 3.4. Of all the key decision makers, 53% indicated only receiving on-the-job training for severe malaria disease, and the remaining received formal severe malaria education in addition to on-the-job training. All key decision-makers with severe malaria disease formal education received education in Mozambique. Meta-inferences from data integration indicated competency in severe malaria case management, including the NMCP guidelines.

Only two key decision-makers (a traditional medicine practitioner and a technician) did not know these guidelines, suggesting on-the-job training has been effective in providing evidence-based care. This training modality consistently emerged as a helpful method for the practical application of clinical guidelines in real-world scenarios from colleagues in similar roles. However, our analysis highlighted the significant variability in training quality and accessibility, when comparing formal education and on-the job training experiences. A notable limitation of

these findings was the variability of education and training locations, which may have introduced bias in comparing the quality of severe malaria training experiences.

Table 3.4 Joint display tables for formal education and on-the-job training

Statistics and Themes	Quotes (English)	Quotes (Portuguese)	Meta-inferences
53 % indicated only on the job training for severe malaria disease care *Severe malaria disease education was limited, but on the job- training was common*	*[But do you know the lines of the National Malaria Control Program for Malaria Treatment Policies or did you know it during your training?]. "Yes, yes. For malaria. Yes, of course it does. When malaria is severe, we will have to give artesunate according doctor's prescription according to the weight., height etc, because malaria is a serious case." Community health worker*	*[Se você conhece as linhas do Programa Nacional de Controle da Malária para as Políticas de Tratamento da Malária grave ou conheceu durante a sua formação?] "Sim, sim. Para a malária. Sim, claro que sim. Quanto a malária grave, nós vamos ter que dar artesunato injetável, a dose vai de acordo com o peso. Se não é malária grave vai depender do que vai estar a complicar com ele." - Agente comunitário de saúde*	Statistics on training length and type of instruction **expanded** the themes on confidence of diagnosis and treatment for severe malaria disease care while also providing more context to gaps in training for key decision-makers (CHW, traditional medicine practitioners), and supporting the predominance of on the job training and limitations of education opportunities
	"We have had artesunate [tablets], we have injectable artesunate, we treat malaria [patient] as soon as it arrives, the dosage is given according to the patient, if is a child or an adult, for children we give medications I collaboration with their parents." Nurse	*"Temos tido artesunato, temos artesunato injetável, tratamos malária logo que a criança chega, faz esse tratamento internamente e as primeiras horas que ela chega, contamos o tempo de 08 horas, contamos com ajuda dos pais. Faz se uma vez por dia, cinco, seis, sete vezes. A criança não sabe." - Enfermeiro*	
	"During this training of referring to the hospital I learned that can stay two hours. When the person stays two or three days without treatment, the person have problems taking him to death. I don't know.[the guidelines of the National Program for the Control of Severe Malaria]" - Traditional medicine practitioner	*"Durante essa formação de encaminhar a pacientes para o hospital, aprendeu que quanto tempo uma pessoa deve demorar antes de receber o tratamento de uma maneira grave e grave. Quando a pessoa faz três, no máximo três ou dois dias sem fazer tratamento, a pessoa pode ter problemas para tomar. Não conheço a Vera, mas posso dar algumas.[diretrizes do Programa Nacional de Controle da Malária Grave]" - Medico tradicional*	
	" [On the job training] This helped a lot so that, as we have done those training that I was referenced a long time ago, there we have exchanged some experiences with some colleagues from other points and it has been an exchange of experience for a positive one. So, generally the training we have had here usually makes it much easier in these aspects.", - Technician	*"Isso ali ajudou bastante, porque, na medida em que nós temos feito aquelas capacitações, que era uma referência, há tempo atrás. Ali temos trocado algumas experiências com alguns colegas de outros pontos/lugares."- Técnico de enfermagem*	

60 % involved in NGO training *Peer instructors mainly instruct providers on severe malaria disease care, while NGOs and peer instructor training could improve*	*"The training on how to refer the serious patients to the nearest health center for medical exams. And during the training and referral of a patient with severe malaria to the Health Centre. We learned how to recognize the symptoms a patient with severe malaria. It was given by the technicians of public health from the Ministry. It's a challenge for you to realize, Many patients presenting joint pain. Sometimes vomiting, headaches etc those can be symptoms of severe malaria." – Traditional medicine practitioner*	*"treino para fazer esse encaminhamento para os doentes, para os exames de saúde. Aqui foi feito pelos técnicos de saúde nacionais, aqueles que fizeram a saúde pública. Durante a sua formação e encaminhamento de paciente com a malária grave para o Centro de saúde. Aprendeu como reconhecer os sintomas da malaria grave? Já é um desafio você perceber, mas depois de um tempo nós teremos capacidade de identificar, na verdade. Muitos pacientes apresentavam como dores de articulações, às vezes vômitos temperatura alta, pálpebra amarelado,são sintomas de malária, dor de cabeça forte, frio, sentir muito calafrio, entre outros olhar ou entre outros sintomas." - Medico tradicional*	Statistics of severe malaria disease care training from NGOs were **complementary** to themes describing the quality of instruction from NGOs and peer instructors. The themes on peer instructors compared to NGO training quality informed possible gaps in training for different key decision-makers
	"The negative experience I had in a case of severe malaria and we didn't have anyone to talk to us because it was one of the complications of severe malaria, differently from the one I explained before, I had someone to help [us]. It was a very negative experience on my part, because I expected more that one of our superiors would come to see us, to teach us how to manage cases." - Community health worker	*"Sim, é uma das experiências negativas. Foi quando nós tivemos um caso de malária grave e não tivemos alguém para nos falar porque tinha muitas complicações, diferente dos casos que nós temos tido dia após dia. Então devíamos ter alguém para nos falar como manejar aquele tipo de caso, aquele paciente . Eu achei isso uma experiência muito negativa da minha parte, porque eu esperava mais que um dos nossos superiores viesse nos ver, nos ensinar como se maneja esses casos" - agente comunitário de saúde*	
	"The challenges are many, because each NGO has its policies, but it also good because we learn one another. *Or maybe I'll do it again. What a learning experience! To have for having been trained or for having worked with your NGO. I also learned how to discover if the patient has malaria or not even without testing him, through the symptoms the person is presenting ." - Nurse*	*" Os desafios são muitos, porque cada ONG tem suas políticas, mas também é bom porque aprendemos um com o outro, talvez eu faça isso de novo. Que experiência de aprendizado! Por ter sido treinado ou não tendo trabalhado com sua ONG, também aprendi como descobrir se o paciente tem o paciente." - Enfermeiro*	
	"The NGO challenges are enormous, because the NGOs when arrive to work, it shows how things should work and that they have conditions of working with them , but these policies are against the Health Ministry policy [or National Malaria Control Program guidelines]." - Administrator	*"Desafios de ONG são enormes e digo são enormes , porque a ONG quando chega para trabalhar , tem nos mostrado como é que as coisas devam funcionar e que tem nos dado condições naquele momento . Mas no momento em que eles vão embora , já torna nos difícil para mantermos as coisas como elas estavam , então eles só funcionam como se fosse um espelho de vida . É possível fazer os trabalhos enquanto eles (ONG) estiverem presentes, porque ainda temos recursos, mas quando o*	

		projeto terminar já não será sustentável , para o manter o pé também daria trabalho , como estava dando" - Administrador	

Quantitative data was transformed from qualitative data collected in semi-structured interviews with key decision maker. Qualitative data were presented as themes analyzed separated from quantitative data. Qualitative data were presented with supporting English and Mozambican Portuguese quotes. Data integration as meta-inferences were described. Narrative review offers additional information on bias in data integration.

Peer colleagues or NGOs conducted the on-the-job training instruction. Peer-to-peer instruction demonstrated particular efficacy in promoting diagnosis and treatment guideline adoption. The data integration indicated highlighted inconsistencies in instruction across roles, specifically a technician and community health worker had negative experiences because specific treatment guidelines were missed during on-the-job training. Technicians and community health workers represent front-line providers in public health facilities, which disproportionately impact severe malaria outcomes in the Mozambican health system. Themes from key decision makers suggested NGOs, like peer instruction could be improved. Among the 60% of key decision-makers with NGO training experience, half expressed concerns about their local and clinical relevance. Discrepancies between NMCP guidelines and awareness of existing public health inventions for malaria prevention were identified as barriers to effective NGO training.

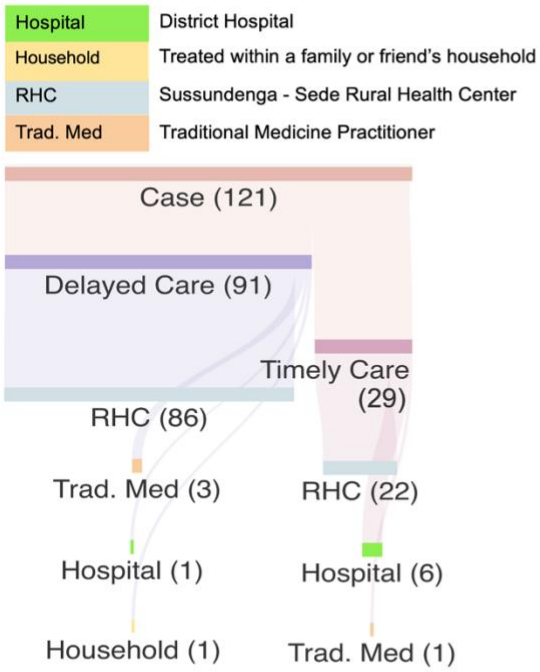
Health Navigation and Delayed Care

Significant delays in treatment initiation were identified in the case-control study, with approximately 75% of severe malaria patients seeking care occurring 24 hours after symptom onset. There was a median of 3 [IQR: 2-4] days before seeking care at the RHC for cases, similar to non-malaria hospitalized controls. Figure 3.2 jointly displays the integration of qualitative and

quantitative data to understand severe malaria hospitalizations delayed care by the first site and contextualizing themes from key decision makers.

Delayed care seeking was care seeking to the RHC after 24 hours of symptom onset or timely care seeking within 24 hours of symptom onset. The RHC was the most frequent first location for treatment, followed by traditional medicine practitioners among delayed health-seeking cases. All key decision-makers indicated delayed care as a primary barrier to their role in severe malaria case management, including traditional medicine practitioners, concordant with Sankey diagram findings.

Figure 3.2 Joint graph for health navigation to first site of care and delayed care qualitative data



Theme

Delayed care is a major barrier for providers. Some patients immediately seek care, still, effective treatment after reaching care remains a complex issue

Quotes

"Negative aspects that I already had is the process of referring patients to go [to] hospitals because [they] refuse to go."
- Traditional medicine practitioner

"Many times we have seen the issue of over-prescribing…….They go to pharmacies, pay for medicines there and start medicating without any indication from a doctor or nurse. And so it has complicated [things] even more. We have seen many people overdose" - Nurse

"When it [severe malaria disease] is not treated early. Some patients are treated at home and sometimes not in good conditions." - Administrator

"Sometimes patients go to the hospitals and there are no medications, they prefer to go to the traditional doctor, leaving their room empty at [the] hospital."
- Traditional Medicine Practitioner

This Sankey diagram provides counts for cases at various first sites of care, including the hospital, within a family or friend's household, Sussundenga-Sede RHC, or a traditional medicine practitioner. Care seeking is defined as care seeking after the onset of symptoms before 24 hours (timely care) or after 24 hours (delayed care). Commonly the first site for care was the RHC, despite the case status or time to care. The qualitative data was based on semi-structured interviews with key decision-makers to give additional context to first site of care data for severe malaria hospitalizations.

Timely and delayed care seekers overwhelmingly first sought care at the RHC, however, the quotes from key decision-makers expanded these findings. Before presenting to public healthcare facilities, key decision makers have observed patient-led self-treatment complicating the effective treatment and even risking overdose. Key decision makers reported patient pre-treatment from pharmacies or drug shops, in contrast to 12% of severe malaria cases reporting pretreatment at home without antimalarials in the case-control study. Cases reported traditional medicine, pain medication, and antipyretics for pre-treatment without medical advice.

Key decision-makers, especially traditional medicine practitioners, suggested care seekers with severe malaria disease use public health facilities, but some do not prefer this care, preventing effective case management. Methodological limitations emerged as some key decision-makers exhibited discomfort during structured interviews regarding patient dissatisfaction as a barrier to timely care. Integration of health navigation data demonstrated two critical findings: first, delayed care represented a fundamental constraint on effective severe malaria management; second, marked discordance existed between patient-reported treatment histories and provider perceptions of pretreatment practices. Additional factors like patient trust, provider communication, and system-based constraints for availability of medical supplies and time to cultivate patient-providers relations probably underlie patient care delays.

Traditional Medicine and Practitioners

The utilization of traditional medicine and practitioners emerged as a complex topic based on data integration of key decision-maker interviews and severe malaria hospitalization self-reported data. Table 3.5 describes the meta-inferences generated for traditional medicine and practitioner themes and statistics. Few severe malaria hospitalizations reported traditional

medicine before receiving treatment at the RHC (<3%). However, some key decision-makers viewed traditional medicine as a barrier to timely severe malaria treatment, aligning with colonial perspectives of non-western medicine. Moreover, nearly all key decision-makers who identified knowledge of traditional medicine or observed patients' traditional medicine use indicated *bafo* was a common treatment for malaria symptoms, an herbal steam treatment using a local herb mixture and hot stones given under a blanket to inhale. *Cacana*, an herbal tea given three times a day, has been used for the cyclical fevers. Traditional medicine was used for mosquito prevention, specifically, *muchana* and *mabaranonbe* were herbs identified that were burned around houses to prevent biting.

Provider perspectives on traditional medicine utility were notably ambivalent, reflecting both recognition of their cultural embeddedness and concerns about treatment efficacy. While most healthcare providers demonstrated familiarity with TMP practices, their assessments of TMP effectiveness varied considerably—some viewed them as valuable community partners, while others expressed reservations about delayed referrals. In contrast to statistics explaining traditional medicine self-administration was limited among severe malaria hospitalizations at the Sussundenga-Sede RHC, the qualitative data from key decision makers implied traditional medicine was commonly used before and during care in public health facilities.

Table 3.5 Joint display traditional medicine and practitioners

Statistics	Themes	Quotes		Meta-inferences
		(English)	(Portuguese)	
Of all 121 severe malaria cases • **3 used traditional medicine at home before the RHC**	*Providers have mixed emotions on the utility, but familiar with TMP*	*"I learned the traditional medicines, but today we have grown, we do not use much like in the past to treat malaria, are used plant leaves, of moringa ,and we also make bafo. The traditional treatment is normally done in the mornings and night. " - Laboratory expert*	*"Aprendeu como é o tratamento da malaria através da medicina tradicional, mas hoje crescemos sim. Tanto soubemos que algumas fórmulas que antigamente usavam para tratar a malária, tais como o uso de folha de planta, de abacate, aloé vera." - especialista de laboratório*	data integration produced **discordant** understanding of traditional medicine, statistics show it is utilized less frequently while key decision makers commonly observed use among patients
		"There are people resorting to traditional treatment, when the treatment at hospitals is not efficient, they boil cacana and give a cup of it in the morning and another at night, or they make bafo." - Administrator	*"Podendo descrever o tratamento da tradicional onde a pessoa tem tratado a doença de malária e há pessoas a recorrer ao tratamento tradicional na base de que pode ser eficaz. Mandam ferver ervas e dá se uma chávena de manhã, e outra à noite. Às vezes fazem esse bafo. O que sã? uma pedra depois de bem queimada ao fogo, poe num balde com agua quente misturada com as ervas e começam a cobrir a pessoa doente com uma manta... para dar efeitos feitos do tratamento tradicional." - Administrador*	
		"I don't think that traditionally we can treat Malaria with the roots, the leaves, and through we can make bafo for a while and can alleviate, but the big problem is the dosage. These treatments are for "normal malaria" not for severe malaria, like intestinal, that's why we advise the patients to go early to hospital." - Nurse	*"E não acho que tradicionalmente a malária pode ser tratada, podemos fazer bafos com as raízes, com as folhas de árvores que temos E esse é o tratamento que você pode tentar tratar malária. Me lembro que a malaria intestinal, por exemplo, se aconselha quando você a tem, sim você pode tomar essas raízes, mas devemos encontrar um ambiente [tratamento] hospitalar." - Enfermeiro*	

55% of severe malaria cases indicated transportation or associated costs were a barrier to care seeking	*TMPs are advocates for those most at risk*	*"It's a challenge. Because parents think that the traditional doctor can treat everything at that moment. They end up being afraid for a long time, so later they accept to go to hospitals to get better medications while the time had gone, sometimes is too late." - Traditional medicine practitioner*	*"É um desafio. Porque os pais acham que o médico tradicional pode tratar tudo naquele momento. Acabam a ficar muito tempo com medo e sai desse médico para o outro à procura de melhoria. Mas chega das vezes em que o paciente pode perder a vida no próprio dia, em casa do próprio medico. . E às vezes acabamos o tempo à procura do melhor remédio e chega já a ideia de ir para o hospital tardiamente." - Medico tradicional*	the themes and statistics offered **complementary** information on the need for support in overcoming health seeking challenges, while showing how severe malaria patients and services provided by TMP improve access to care
		"Often has no means of transportation or even communication to communicate with the hospital when faced with the problems of patients with severe malaria, [we] will eventually be able to communicate later. Another thing is not having money to take chapas (public transport) to take to the health center, sometimes happens at night, at dawn or even we could not have another means of transportation. Taxi driver costs are high, this is the big challenge we are facing. " - Traditional Medicine Practitioner	*"Geralmente não tem meios de transporte ou mesmo comunicação para se comunicar com o hospital quando confrontado com os problemas de pacientes com malária grave, acabará sendo capaz de se comunicar mais tarde. Outra coisa é que não tem dinheiro para que não tenham um grande transporte." - Medico tradicional*	
		"Communication is very important because sometimes we don't have any way to inform the hospital that we have case of someone who is sick because no network coverage , or the roads are not good , we do not access to any transport." - Traditional medicine practitioner	*"Primeira dica é, A comunicação é muito importante porque às vezes não temos comunicação para entrarmos em contacto com centro de saúde , por exemplo, pode ter um transporte público, pode ter disponibilidade de transporte, mas às vezes nós não conseguimos por problemas de comunicação [que já se referiram acim]."*	

			- Medico tradicional	
Of all 121 severe malaria cases • **16 were referred to the RHC from TMP** **Of those referred to the RHC from TMP, 25 % had timely care**	*TMP referral integrates local beliefs and pre-colonial Mozambican epistemology*	*"Yes. In my point of view, it is possible allowing the patients to use them , but without causing interference others and the nurses, there should have an explanation to the patients the advantages and the disadvantages of doing that. "* *- Traditional Medicine Practitioner*	*"Sim. Na minha opinião, é dizer que o centro de saúde deveria trabalhar mais com esses medicamentos, os pacientes devem ser explicados como prevenir se da malária, devem também chamar a medicina tradicional para poder explicar à população para não ter esses problemas fazer bichas nos curandeiros em vez de ir ao hospital em primeiro lugar."* *- Medico tradicional*	the themes and statistics indicate this referral program and traditional medicine is useful for severe malaria disease patients, which was **expanded** by the statistics on use from severe malaria hospitalizations.
		"However, at that time, for example, in the times we live in a long colonial time, it is difficult for blacks, for example, to sometimes be seen and be well cared for in hospitals because they always prioritized whites. Now… we are independent, we know the truth. In colonial era it was difficult for black people to have access to hospitals, the more for the whites, that's why many people opted for traditional treatment." *- Community leader*	*"No entanto , naquele tempo , por exemplo , no tempo colonial era difícil um negro , por exemplo , às vezes ser visto e ser bem atendido nos hospitais porque priorizavam sempre os brancos . Agora , agora que já estamos um pouco independente. Hoje sabemos a verdade ."* *- Activista da comunidade*	
		" I say that it helped because many things have improved now and because, on the basis of that training, we are also managing to raise awareness in the community that has malaria so that they can go to the health center." *- Traditional Medicine Practitioner*	*"E a dizer que não ajudou ou não ajudou nisso? Digo que ajudou porque muitas coisas só melhoraram agora e porque, na base daquela capacitação nós também estamos a conseguir sensibilizar a comunidade que tem malária para poder ir ao posto de saúde."* *- Medico tradicional*	

Quantitative data were self-reported metrics among severe malaria hospitalizations. Qualitative data was collected in semi-structured interviews with key decision makers. Qualitative data were presented as themes analyzed separately from quantitative data. Qualitative data were presented with supporting English and Mozambican Portuguese quotes. Data integration was described in meta-inferences, and a narrative review offers additional information on bias in the analysis.

The remaining data integration prioritized qualitative data from traditional medicine practitioners to evaluate the unique traditional medicine referral program between local traditional medicine practitioners and public health facilities. Two traditional medicine practitioners were included who offered services to Sussundenga village with referral to Sussundenga-Sede RHC. The referral program education and training differed between practitioners, with differences in duration and inclusion of NMCP guidelines. Both traditional medicine practitioners reported positive experiences in training to recognize severe malaria symptoms and encourage time-sensitive care seeking. Traditional medicine practitioner themes signaled that the referral program has helped to advocate for high-risk populations who might otherwise delay or avoid public health facilities.

Cost and lack of access to transportation were community needs that traditional medicine practitioners fulfilled. Offering resources necessary for transport to public health facilities and spiritual support to families in crisis were identified as components of successful referral. Complementary to qualitative findings, 55% of severe malaria hospitalizations reported transportation or associated costs were a barrier to care seeking, indicating that traditional medicine practitioners address a key concern from patients and caregivers.

Of the 121 severe malaria hospitalizations, 16 were referred to the Sussundenga-Sede RHC after consultation with traditional medicine practitioners. However, only 25% of those care-seeking after a traditional medicine practitioner referral had timely health seeking or reached care within 24 hours of symptom onset. Quotes from interviews with traditional medicine practitioners expressed that patients' lack of trust and previous negative care experiences in public health facilities contribute to referral hesitation. Data integration between themes and severe malaria

hospitalization statistics generated expanded meta-inferences to understand the context for traditional medicine practitioners' influence as trusted health navigators.

Discussion

Qualitative themes from interviews with key decision-makers, integrated with quantitative data on severe malaria hospitalizations, offered more contextual data on facilitators and barriers to effective severe malaria management. The study found that on-the-job training was the most common method for preparing healthcare decision-makers to manage severe malaria. Education and training data integration revealed knowledge of severe malaria treatment protocols, however, NMCP guidelines were not consistently known. Health navigation data identified delayed care as a significant barrier to effective prevention and treatment. The dual engagement with public health facilities and traditional medicine highlighted their persistent role as access points, though concerns remained about delays in initiating appropriate treatment. These findings underscored the complexity of care-seeking pathways in malaria-endemic settings.

Gaps in severe malaria training were evident, particularly for laboratory technicians and CHWs, with inconsistencies in content and duration. Post-colonial constraints in domestic higher education and economic barriers to accessing education likely influence the limited access to formal education. The education and training limitations have been emphasized as key barriers to effective severe malaria treatment in Mozambique and malaria-endemic settings in East Africa [80,153], without considering the post-colonial dynamics. On-the-job training could be prioritized in Mozambique to standardize severe malaria interventions delivered by providers who may have knowledge gaps due to inaccessible education opportunities. However, training in public health

facilities by peer colleagues, in addition to NGOs-led instruction in private health facilities, could contribute to training variability.

Conflicting priorities between the NMCP guidelines and NGOs have been well documented across Mozambique since the introduction of chloroquine [186,187]. Pfeiffer, Chapman et al. contended that Mozambique's NGO expansion has contributed to both provider deficits and diminished public health system investment [188]. In line with the post-colonial Indigenous paradigm, themes from key decision-makers indicated NGOs consider institutional interests rather than community needs [126,128,188]. Future research should evaluate NGO-led training for provider competency and severe malaria disease protocol compliance.

Health navigation challenges were pervasive, with delayed care frequently evidenced by decision-maker themes and severe malaria hospitalization statistics, similar to other Mozambican studies [1,82,189]. Discrepancies emerged between patient and provider accounts of pretreatment practices, potentially influenced by recall or social desirability bias. Knowledge of traditional medicine was common among key decision-makers, observing patient use before and during treatment at public health facilities. Key decision-makers believed traditional medicine was neither harmful nor therapeutic for severe malaria. Our findings diverged from colonial perspectives of traditional medicine or TMPs [170,172,173], despite the cultural and spiritual support for patients and caregivers.

Caregivers and patients have sought care from TMPs based on the consistent, culturally grounded care they have provided to communities before, during, and after Portuguese colonization [190,191]. Colonial-era public health facilities discriminated against and traumatized

Black families, barring their use and forcing reliance on traditional medicine practitioners [190,191]. Data integration implied that the legacies of colonialism underlie TMPs' preferences. Key decision-makers suggested that integrating traditional medicine into existing approaches could improve health-seeking at the RHC. Leveraging the shared epistemology and spirituality with community members, TMPs have transparent communication with high-risk groups on malaria prevention and vector control.

Integrated data analysis identified concerns among some decision-makers about traditional medicine practitioner-related treatment delays, but also recognized their potential as referral allies. Our findings and qualitative data from a previous study in Southern Mozambique indicated that traditional medicine practitioner referral could be an effective way to overcome patient treatment hesitation for treatment at public health facilities [192]. Traditional medicine practitioner training could be improved to learn NMCP guidelines and standardize instruction duration, to maximize public education for prevention and referral to care. However, balancing the appraisal of traditional medicine epistemiology and western malaria policies should be a priority in training optimization. Traditonal medicine and NMCP guidelines should not be considered as a binary. Qualitative studies have reported that traditional medicine practitioner referral has improved community severe malaria treatment access and reduced care delays in Ghana and Nigeria [120,193].

This study captured diverse perspectives from key decision-makers involved in severe malaria hospitalization care at Sussundenga-Sede RHC. Data integration occurred at multiple levels, including in the analysis as joint displays and meta-inferences. Quantitative data was measured in an efficient case-control study, with interviews conducted in Mozambican Portuguese by a

native speaker to enhance contextual and cultural accuracy. Lastly, combining dialectical pluralism and post-colonial indigenous paradigms provided a layered analysis and understanding of mixed data, all while valuing Mozambican epistemiology.

Convenience sampling for key decision-maker interviews and quantitative data sourced from one public health facility could have biased data integration.The limited inclusion of TMP voices in this study (only two interviewees) represented a significant evidence gap, potentially biasing our understanding of referral dynamics and the collaborative potential between traditional and public health systems. However, less rigorous translation procedures due to budgetary and time constraints likely biased thematic analysis. Sociopolitical constraints may have underreported critical perspectives on training quality, NGO partnerships, and self-administered pre-treatment.

Conclusion

This study used a post-colonial indigenous paradigm and community-engaged approaches to capture severe malaria case management facilitators and barriers based on Mozambican epistemology. Inclusive studies directly encompassing traditional medicine practitioners are needed to address delays while maintaining culturally appropriate support. Such strategies could advance severe malaria treatment and prevention in endemic regions.

Chapter 7: Summary and Conclusion

This dissertation analyzed malaria infection and severe malaria disease case management in a rural, understudied malaria endemic setting. In the first manuscript, I used descriptive methods to understand *P. falciparum* prevalence and health-seeking among households in Sussundenga village, Mozambique. For the second manuscript, I collected ecological health access data from hospitalized severe malaria cases and non-malaria hospitalized controls to generate health access and navigation indicators. The third manuscript integrated quantitative data from the case-control study and semi-structured interviews with key decision makers to discern concordant and diverging barriers and facilitators to severe malaria case management.

7.1 Summary

In manuscript one, I sampled households from satellite imagery and enrolled 358 individuals living in Sussundenga village, Mozambique. I designed and collected survey data on malaria infection status via *P. falciparum* malaria RDT, malaria risk factors, and health-seeking behaviors. The community *P. falciparum* prevalence indicated moderate-to-high malaria transmission, similar to provincial data. The individuals in Sussundenga village in the sample primarily used the Sussundenga-Sede rural RHC for malaria infection diagnosis and treatment, leading to symptom resolution. However, delayed care seeking was common among all age categories, including children under five.

In manuscript two, I planned the study design and data collection for a hospital-based case-control study to compare severe malaria hospitalizations and non-malarial controls at Sussundenga-Sede rural health center. I designed the survey to assess ecological health access

determinants, which are commonly ancillary measures on DHS and MIS. I reduced the number of key determinants identified from exploratory factor analysis; the retained items to loaded factors indicated the built, healthcare, and social environment as primary determinants. I generated indicators of the built, healthcare, and social environment that provide a proxy for local ecological health access.

I evaluated the association between the ecological health access indicators and severe malaria hospitalizations. Findings suggested that less access to the built environment was associated with a higher likelihood of severe malaria hospitalizations, controlling for age category, employment, and season. After evaluating an interaction between delayed care seeking and ecological health access indicators, the likelihood of severe malaria hospitalization did not reduce. This indicated that the large proportion of delayed care seeking likely influenced this association. Delayed care seeking, regardless of case status, is an important public health issue in the Sussundenga district.

In manuscript three, I designed and conducted the qualitative component for the parallel convergent mixed-method study. Fifteen key decision-makers involved in severe malaria disease treatment and prevention were interviewed to understand facilitators and barriers to effective severe malaria case management at Sussundenga-Sede rural health center. I analyzed the qualitative and quantitative data from the case control for mixed-method data integration at multiple levels. I compared and contrasted severe malaria hospitalization data and key decision maker perspectives on training and education, health navigation and delayed care, and traditional medicine and practitioners. A post-colonial indigenous framework guided the assessment of a community-based approach for traditional medicine integration to reduce delayed care and prevent severe malaria hospitalizations. The findings indicated key decision makers mostly rely

on job training, compared to formal education, to feel confident in severe malaria care and prevention. Concordant with the severe malaria hospitalization data, key decision makers identified delayed care as a primary barrier for patients navigating to care. The traditional medicine practitioners' perspectives were concordant with severe malaria hospitalization data that suggest transportation access and cost significantly contribute to delayed care seeking. These findings highlighted the helpful role that traditional medicine and traditional medicine practitioners fulfill in motivating the community to reach care and provide comfort one does not have access to standard anti-malarial treatment.

7.2 Public health impacts

A strength of this dissertation is the inclusion of community members from Sussundenga District, from providers at the largest rural health center to traditional medicine practitioners. Most studies have not encompassed perspectives from providers and community leaders, in addition to health access and health-seeking indicators from rare severe malaria hospitalizations. The unique referral program at Sussundenga-Sede rural health center trains traditional medicine practitioners to recognize and refer suspected severe malaria disease in the community. The findings from this dissertation provide evidence for the potential role of traditional medicine integration in delayed care seeking for severe malaria disease. The dissertation identified several strengths-based community-based solutions from key decision makers. The inclusion of traditional medicine treatment for individuals receiving care at the rural health center was identified. Additional malaria prevention education training based on the National Malaria Control Program guidelines could improve the existing traditional medicine practitioner referral program.

The exploratory findings from this dissertation were exploratory, and future research based on the evidence could generate effective malaria prevention and treatment interventions. Potential research on mitigating transportation costs or access could have a drastic effect on delayed care seeking. Community-based approaches to identifying care delays, through grass-roots development or community leadership, should be prioritized in future research on malaria navigation. Applying the post-colonial Indigenous framework, among malaria research conducted in endemic settings, is needed to interrogate the complex colonial legacies in public health systems, research institutions, and research methodologies. Patient and providers perspectives on trust in public health systems should be explored to continue to unravel drivers of incomplete care coordination. Transportation to care, resourced providers, and national malaria control program informed community champions, and traditional medicine practitioners are all essential components to address malaria care-seeking gaps in the Sussundenga district.

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