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Understanding non-malaria illness in outpatients in Mozambique: An exploration of associated symptoms, diagnoses, and treatments

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Abstract

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By Haley R. Biddle

Background and Objective: A wide variety of illnesses prompt care-seeking at outpatient health care facilities in sub-Saharan Africa. While malaria remains a prominent threat in many of these countries, declines in prevalence over the past several decades, in addition to more readily available rapid diagnostic tests (RDTs) for malaria, have illuminated the substantial portion of non-malaria illness that exists in these settings. As such, there is a need to understand the presentation and case management of non-malaria illnesses in adults and children presenting at health facilities in low-resource areas. This study describes the symptom presentations, diagnoses, and treatments received by outpatients seeking care at health facilities in three provinces of Mozambique and examines associations between these variables.

Methods: A secondary analysis was performed using health facility survey data gathered in Maputo, Zambezia, and Cabo Delgado provinces in Mozambique in 2018. Survey responses regarding symptoms, diagnoses, and treatments were analyzed for frequency by age group. Cross tabulations of risk ratios (RR) were conducted to determine associations between variables, and multivariate logistic regression was used to examine factors associated with antibiotic prescription.

Results: In total, 1,840 outpatients were interviewed and re-examined across 117 health facilities, including 629 children under five years of age (CU5) and 1,211 adults and children older than five. Fever was the most common symptom for both CU5 (74.6%) and older outpatients (60.4%). 53.1% of CU5 remained undiagnosed, as did 65.6% of patients five-and-over. Malaria was the most frequent diagnosis in each group, at 33.1% for CU5 and 16.1% for the older age group. The most commonly received medication was an antipyretic (52.6% of CU5, 51.5% of five-and-over). Nearly 40% of CU5 received a prescription for an antimalarial, while 21.6% of older children and adults received one. Antibiotic treatment was significantly more frequent among the older age group (50.3%) than in CU5 (43.7%, $p<0.01$). Crosstabulations showed that heart and chest symptoms (RR: 0.18), dermatologic symptoms (RR: 0.30), and ear, eye, neck and throat symptoms (RR: 0.31) were associated with a lower chance of malaria diagnosis. Remaining undiagnosed (RR: 2.42) or having a symptom listed as a diagnosis (RR: 1.57) increased the likelihood of receiving an antibiotic. For both febrile and non-febrile patients, antibiotic prescription was more common when patients were RDT-negative or reported not having a RDT performed. In the logistic regression, a positive RDT was the only factor significantly associated with decreased odds of receiving an antibiotic (aOR: 0.03, $p<0.01$). On average, patients received 1.37 unique treatment types.

Conclusion: Surveyed outpatients at health facilities in Mozambique reported a variety of symptom presentations. While fever was the most common symptom for both CU5 and patients 5-and-older, there was a wide spectrum of symptoms and these frequently differed significantly by age group. Reporting no diagnosis from a consult was common, and malaria was a frequent diagnosis when one could be reported. Most patients left their consult with a prescription for at least one medication, with antipyretics being the most widely prescribed. These results help to meet the need of understanding the presentation and case management of non-malaria illness in outpatients, and serve to enhance surveillance, improve algorithms, and guide surveys in similar settings.

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Chapter 1: Introduction

In sub-Saharan Africa, fever and febrile illnesses are common motivators for visits to healthcare facilities (Feikin et al., 2011; Maze et al., 2018; Prasad, Murdoch, Reyburn, & Crump, 2015). Historically, a large portion of such febrile episodes were attributable to malaria. Prior to 2010, the official directive of the World Health Organization was for clinicians in malaria-endemic countries to presumptively treat febrile patients under-five years old with antimalarial medications (WHO, 2006). This strategy was designed to ensure that malaria-positive patients would receive prompt and effective treatment. However, there is evidence that the policy of presumptive treatment allowed for over-diagnosis of malaria and over-treatment with antimalarials, leaving the underlying causes of non-malaria illnesses dangerously untreated (D'Acremont et al., 2011). The development and wider distribution of rapid diagnostic tests (RDTs) for malaria enabled a policy change in 2010, and clinicians are now advised to confirm a diagnosis of malaria in febrile patients through microscopy or RDT prior to prescription of antimalarial treatment (D'Acremont et al., 2011; WHO, 2010). The effects of this policy on clinical practice have been investigated by studies of diagnosis frequency and prescribing practices post-RDT introduction. For example, one study noted marked reductions in the number of patients diagnosed with malaria after RDT's were introduced (D'Acremont et al., 2011).

Malaria remains a formidable force, with 228 million cases occurring in 2018, resulting in an estimated 405,000 deaths worldwide (WHO, 2020). Still, the scale-up in use of evidence-based interventions over the past several decades has resulted in notable reductions in malaria prevalence in many countries and complete elimination in others (Feachem et al., 2010). Strategies including wide distribution of long-lasting insecticidal nets (LLINs), indoor residual spraying (IRS) of insecticides at the household level, and improved case management and

chemoprevention with artemisinin-based combination therapy (ACT), have been widely employed throughout the malaria-endemic world (WHO, 2019). The implementation of these strategies has contributed to the success of the 27 countries reporting less than 100 indigenous cases in 2018, with many more countries poised for elimination in the coming decade (WHO, 2020).

The highest burden of remaining morbidity and mortality from malaria is concentrated in Africa, but this region has also seen significant reductions in prevalence in recent years (WHO, 2019). An implication of this reduction in malaria prevalence is that the number of fever cases that can be attributed to malaria has likewise declined (D'Acremont, Lengeler, & Genton, 2010). Strict adherence to the test-before-treating policy reveals a large group of patients whose febrile illness of unknown origin clinicians must diagnose and treat (Kiemde et al., 2018). Proper case management of this group of patients is critical; evidence from both Asia and sub-Saharan Africa points to higher mortality in non-malaria fever patients than for those testing positive for the parasite (Bottger et al., 2017; Reyburn et al., 2004).

Compounding this challenge is the fact that this type of case management often occurs in a context where additional diagnostic tools and resources are scarce. Furthermore, the health workforce may have minimal knowledge about the management of non-malaria febrile illness (Bottger et al., 2017). For example, the same study that saw a reduction in malaria diagnoses after RDT introduction noted that diagnoses of specified ailments like pneumonia and diarrheal disease did not grow in return (D'Acremont et al., 2011). Rather, an increase in diagnoses listed as “other” or “ill-defined syndrome” was apparent (D'Acremont et al., 2011). In the absence of a clear algorithm and appropriate diagnostic tools, some clinicians may prescribe antimalarials even when confronted with a negative test, a practice which can contribute to drug resistance and

leave patients without a proper treatment for the true etiology behind their illness (WHO, 2013). In these scenarios of uncertainty, the risk of over-use of antibiotics should also not be ignored. Indeed, several studies suggest that rates of antibiotic prescription have risen in areas where the use of antimalarials has declined (D'Acremont et al., 2011; WHO, 2013) .

While it can be difficult to determine the exact etiology of illness, proper case management is essential to reduce morbidity and mortality from non-malaria febrile and non-febrile illness. The causes of non-malarial illness are many, and vary in their type and prevalence by such factors as geography, season, age, immune status, and vaccine coverage (Bottger et al., 2017; D'Acremont et al., 2014; Maze et al., 2018). Information about the presentation and epidemiology of diseases at a local scale can help to guide clinical decisions, as well as inform public health interventions and the distribution of resources (Iroh Tam, Obaro, & Storch, 2016; Maze et al., 2018; WHO, 2013).

Several studies have contributed to building the evidence base around non-malaria illness. Multiple projects in East Africa have utilized advanced diagnostic tests, including blood cultures and radiography, in order to describe the causes of fever in patients testing negative for malaria (Crump et al., 2013; Hildenwall et al., 2016; Nadjm et al., 2012). However, since many health care facilities in sub-Saharan Africa lack the additional diagnostic tools that etiology studies temporarily introduce, it is also important to consider the clinician-perspective- what he or she sees, hears, and decides- during typical consults. Thus, there is a need to better understand the clinical presentations, diagnoses, and selected treatments for non-malarial illnesses in adults and children presenting at health facilities in low-resource settings. Additionally, concerns have been raised regarding the increase in antibiotic use after RDT introduction (Batwala, Magnussen, & Nuwaha, 2011; Ndhlovu, Nkhama, Miller, & Hamer, 2015; Prah, Kizzie-Hayford, Walker, &

Ampofo-Asiama, 2017), and factors associated with their use in outpatient settings should be examined. This is especially important in areas where fewer etiology studies and investigations into clinical presentation of non-malaria illness have been conducted. One such area is Mozambique, located on the south-eastern coast of Africa. Here, additional descriptive and exploratory studies have the potential to inform treatment algorithms and provide guidance to clinicians as they perform consults in outpatient settings with limited access to additional diagnostic tools. The purpose of this study is to describe the frequencies of, and relationships between, the symptoms, diagnoses, and treatments reported and received by outpatients at health facilities in Mozambique. Data previously gathered during health facility malaria surveys in the country provide an opportunity to perform these analyses and inform improved surveillance and treatment efforts in this area.

Chapter 2: Review of the Literature

Introduction

Proper case management during visits to outpatient health facilities is a key component of any effective health care system. In much of sub-Saharan Africa, patients presenting with fever represent a large proportion of these consultations (Bottger et al., 2017; Crump, 2014). As such, correct case management of febrile patients is necessary to reduce morbidity and mortality in ambulatory care settings. Determining the cause of a patient's fever, and the treatment needed, becomes even more multi-dimensional in countries endemic for the malaria parasite. In 2010, the World Health Organization officially put forth the recommendation that antimalaria medications should only be prescribed after confirming the diagnosis via rapid diagnostic test (RDT) or microscopy (WHO, 2010, 2013). While this policy aimed to improve case management and reduce the use of antimalarial medications for treating non-malarial illnesses, a new challenge was introduced. Now, clinicians must frequently decide how to treat non-malarial patients, often with few other diagnostic tools available to help them make these decisions (Kiemde et al., 2018). In light of this challenge, the WHO and other researchers have stressed the importance of continuing to develop diagnostic tools, treatment guidelines, and algorithms that allow febrile patients to be correctly and successfully treated (Hildenwall et al., 2016; WHO, 2013). The ability to describe the suite of etiologies specific to particular geographic areas may also be helpful (WHO, 2013).

Studies throughout sub-Saharan Africa have been conducted to determine the underlying causes of adult and pediatric outpatient fever cases. Usually, this is accomplished by bringing in additional diagnostic tools other than RDT's- tools which may not typically be available at

outpatient facilities in low-resource settings. While helpful for informing treatment guidelines, these studies focus less on understanding how clinicians diagnose and treat patients when few diagnostic tools are at their disposal; the factors, signs, and symptoms that may affect these decisions are not always considered in a strict etiology study. As such, there is a need to understand the clinical presentations, diagnoses, and prescribed treatments for non-malarial illnesses in adults and children presenting at health facilities in low-resource settings.

Several studies have begun the work of building this evidence base and are summarized in this review. As mentioned, etiology studies abound, and a sampling of these is helpful to understand the pathogens at play in the sub-Saharan African environment and the clinical syndromes that they produce. A second segment of literature explores the treatments given to inpatients and outpatients. Many of these focus on antibiotic prescribing practices, while others have explored the diagnoses and treatments offered to patients based on their RDT result. Qualitative methodology has also been used to better understand the perspective of the clinician and the factors affecting their decision making. Together, these studies demonstrate the complicated nature of outpatient treatment, especially in areas where malaria prevalence is declining. While some geographies have benefited from significant research in these areas, other countries in Africa lack descriptive studies that could help to inform improved surveillance and treatment algorithms. The present study aims to meet this need by utilizing existing health facility survey data from Mozambique to describe, and examine associations between, the symptoms, diagnoses, and treatments experienced by outpatients.

Etiology studies in sub-Saharan Africa

In order to fully comprehend the challenges faced by health providers caring for outpatients in low resource settings, an awareness of the pathogens which are provoking clinic

visits is helpful. Multiple etiology studies, primarily from eastern and western Africa, provide this information.

Crump et al. used a prospective cohort design to determine the causes of severe cases of non-malaria febrile illness in adults and children in northern Tanzania (Crump et al., 2013). This study focused on febrile patients who were ill enough to require admission to the hospital. The research team conducted specialized diagnostic tests to supplement the standard protocol of clinical history and physical exam performed at the hospital. Blood smears checked for malaria while blood cultures, serum antigen tests, and urine antigen tests checked for other sources of infection. Microscopic agglutination tests (MATs) were performed to specifically check for Leptospirosis and Brucellosis, enzyme-linked immune-sorbent assays (ELISAs) and immunofluorescence antibody (IFA) assays tested for Q-fever, spotted-fever group, and typhus group rickettsioses, and PCR and RNA reverse transcription were used to identify a variety of arboviruses. HIV-testing was also provided using both rapid antibody tests, ELISAs, and Western Blots. Follow-up serum samples were collected from patients 4-6 weeks later. To make their results more informative, Crump et al. performed statistical analyses by age group (infants and children 2 months to 13 years; adolescents and adults 13 years +). Among infants and children for whom an etiologic agent was identified, bacterial zoonoses were found in 20.2%, and 10.2% tested positive for chikungunya. Adults and adolescents were similarly affected by bacterial zoonoses (33.3%) and acute arboviruses (5.7%), the most common being Leptospirosis and chikungunya, respectively, in both age groups (Crump et al., 2013). In each group, blood stream infections caused by other bacteria, mycobacteria, and fungi were present. A large proportion of children admitted had initially been clinically diagnosed with malaria, but the diagnostic tests revealed that only 1.3% of these patients had a fever caused by the malaria

parasite. Similar results were found in the adolescent/adult demographic, demonstrating significant over-diagnosis of malaria in this setting. Based on the results of their prospective cohort, the authors concluded that significant discrepancies exist between the clinical diagnoses given and the actual cause of fever in severely ill patients in Northern Tanzania, and this divergence may have consequences for the physical care and medications selected for patients (Crump et al., 2013).

Hildenwall et al. (2016) built on this evidence base by focusing their study on febrile outpatients who tested negative for malaria. This team selected 1,028 adults and children outpatients from a hospital in Tanzania, located in an area of declining malaria prevalence (Hildenwall et al., 2016). The enrolled patients, all of whom had a negative RDT test for *Plasmodium falciparum* and a history of fever, were provided with additional diagnostic tests to determine the cause of their illness. The study also noted presenting symptoms and found "cough" to be the most common symptom for both children under five (CU5) and children and adults over five years of age. Diarrhea and vomiting were common symptoms in children 3 months to 12 years, while rapid respiration was a primary complaint of patients 13 years and older (Hildenwall et al., 2016). Chest X-rays as well as blood, urine, and nasopharyngeal cultures were used to determine fever cause. Only 1.3% of the blood cultures showed a bacterial infection. Among these, *Salmonella typhi* accounted for over half of the infections, followed by *Escherichia coli* and *Streptococcus pneumonia* (*S. pnemoniae* only in young children). Isolation of bacteria was more common from urine and nasopharyngeal cultures. *S. pneumoniae* and *Haemophilus influenza* represented the majority of respiratory bacteria, while *E. coli* and *Klebsiella* were the most common pathogens in urine cultures (Hildenwall et al., 2016). Many of

the chest X-rays revealed pathologies suggesting infection with a virus, and the authors noted the relatively low levels of bacteremia in the study population.

Many etiology studies have focused on identifying the causative agent of fever in children only. D'Acremont et al. (2014) took this approach for febrile children under 10 years presenting to rural and urban outpatient clinics, also in Tanzania, both of which were located in areas with currently low-to-moderate malaria prevalence (*Plasmodium* parasitemia ranging from 1-12% in patients with fever) (D'Acremont et al., 2014). Extensive diagnostic capabilities, including RDTs, serologic tests, bacterial cultures, and molecular testing, allowed the research team to identify the bacterial, viral, and parasitic agents provoking illness in 96.8% of the 1,005 children enrolled in the study. Diagnoses based on the results of these tests included acute respiratory infection (ARI) (62.2%), systemic infection (13.3%), nasopharyngeal viral infection (11.9%), malaria (10.5%), gastroenteritis (10.3%), urinary tract infection (5.9%), typhoid fever (3.7%), skin/mucosal infection (1.5%), and meningitis (0.2%) (D'Acremont et al., 2014). The diagnostic testing revealed that 70.5% of study subjects had a viral infection, 22.0% had a bacterial infection, and 10.9% had a parasitic disease. The researchers note that nearly a quarter of subjects received multiple diagnoses, with 51.4% of children diagnosed with malaria having additional diagnoses- most commonly an ARI. Most of the ARIs, and many of the nasopharyngeal viral infections, were determined to be caused by influenza virus, adenovirus, and rhinovirus, while causative agents of systemic infections were identified predominantly as human herpesvirus 6 and parvovirus B19 (D'Acremont et al., 2014). The pathogen behind a gastroenteritis diagnosis was unknown in 55% of these diagnoses, but rotavirus, adenovirus, *Salmonella*, and *Shigella* were implicated in many cases, with amoebic infection causing only 2% of these diagnoses. Together, the results of this etiology study led the researchers to conclude

that, in febrile children presenting to outpatient clinics in Tanzania, a virus is most often the cause (D'Acremont et al., 2014). As such, antimalarials and antibiotics would be ineffective in the majority of these cases. This demonstrates the challenges faced by clinicians diagnosing and prescribing treatments for patients in this population, especially when advanced diagnostic testing is unavailable.

In neighboring Uganda, Kibuuka et al. (2015) took a different approach by conducting diagnostic tests to search for bacterial infections in children with fever who had tested negative for malaria but *still* received antimalarial medication (Kibuuka et al., 2015). Blood smears, complete blood counts, and blood cultures were used for each child. Of the 235 children whom they were able to evaluate in the study, 19.1% had a bacterial infection. Forty-two percent of those with infections were shown to have *Staphylococcus aureus*, while *Salmonella* was the second most common agent, accounting for 24% of infection (Kibuuka et al., 2015). Logistic regression showed that the odds of bacteremia in children who experienced weight loss during the time they were sick were 2.75 times the odds of bacteremia in children who did not experience weight loss. “Pulmonary crackles” and high white blood cell count were also predictors of bacteremia (O.R = 3.63 and 2.21 respectively) (Kibuuka et al., 2015). The results of this study demonstrate the importance of additional diagnostic tools, as well as the need for more careful use of antibiotics in febrile children who do not have malaria.

Moving to the western side of the continent of Africa, we can examine how etiologies compare in this region. Kiemde et al. (2018) conducted a prospective study of febrile children presenting to a hospital and health centers in an area of Burkina Faso hyperendemic for malaria (Kiemde et al., 2018). Blood smears for malaria, complete blood counts, blood cultures, and urine and stool exams were conducted for 684 children. The results of the diagnostic tests

showed that about half of the children had *Plasmodium falciparum* infection. A non-malaria pathogen that could be implicated in fever was found in 10.7% of the study participants (Kiemde et al., 2018). These pathogens were numerous, and included non-typhoidal *Salmonella* isolated from blood cultures, *Escherichia coli* in urine cultures, and Rotavirus from stool samples. 27.3% of the 523 children for whom stool samples could be collected were positive for parasites, including *Giardia intestinalis*, although these parasites may not cause fever (Kiemde et al., 2018). The study also revealed that nearly 50% of the children with malaria had additional infection(s), even if those additional pathogens were unlikely to be the cause of fever. Nevertheless, the authors stress the need for diagnostic tests to be made available to clinicians so that pathogens beyond malaria can be identified, as these separate or additional infections need to be considered for proper case management of all febrile patients (Kiemde et al., 2018).

A brief look at an etiology study from a very different geography is helpful to illustrate the importance of the local environment in determining the most common causes of fever in outpatients. On the island of Madagascar off the eastern coast of Africa, Guillebaud et al. (2018) conducted a cross-sectional prospective study at sites throughout the island in an effort to determine the cause of fever in 682 conveniently-sampled febrile outpatients (age 6 months +) (Guillebaud et al., 2018). In addition to the standard physical exam and clinical examination that assessed each patient based on an established list of signs and symptoms, an RDT and molecular testing of dried blood spots were conducted to check for malaria presence and species. The clinical assessment found common symptoms to include headache (52.8%), ‘asthenia” (52.6%), ‘catarrh’ (51.0%), cough (49.3%), and anorexia (45.7%) (Guillebaud et al., 2018). The patients also received nasopharyngeal/throat swabs and molecular typing to check for viral respiratory pathogens. Sputum samples were taken for tuberculosis testing when appropriate, and blood

samples were tested using PCR microarray assays to detect many different pathogens. The results of these advanced diagnostic tests revealed a distribution of etiologies unique to this island nation and quite different from that seen in other East African countries. 40.5% of all patients tested positive for at least one of the 36 pathogens under consideration (Guillebaud et al., 2018). Over a quarter of all patients tested positive for one or more viruses, including rhinoviruses (8.7%), influenza A and B viruses (8.4%), Epstein-Barr virus (6.5%), and 'respiratory syncytial viruses' (3.7%) (Guillebaud et al., 2018). Isolated cases of cytomegalovirus, varicella zoster virus, *Leptospira spp*, and Rift Valley Fever virus were also identified. Malaria prevalence varied from site-to-site across the country, with 17% of all subjects testing positive for the parasite (Guillebaud et al., 2018). Of importance, the authors note, is the fact that few-to-no bacterial zoonoses and arboviruses were identified in this Madagascar study, a result which differs from the heavy burden that these classes represent in other East African studies (Crump et al., 2013) (Prabhu et al., 2011).

A search of the literature revealed that not all countries in sub-Saharan Africa have been the focus of fever etiology studies, with some countries having few-to-no specific studies that attempt to describe the pathogens responsible for fever in inpatient or outpatient populations. Mozambique is one such example, although a 2009 study by Sigauque et al. did investigate etiologies of bacterial infections in *inpatient* children in southern Mozambique (Sigauque et al., 2009). In this study, alongside a clinical evaluation and blood smears for malaria detection, culturing of blood samples allowed the research team to identify common causes of blood-stream infection. Of the 19,896 blood cultures performed, 8% tested positive for a bacterial pathogen. Results included non-typhoidal *Salmonella* (26% of 1,550 bacterial isolates), *Streptococcus pneumoniae* (25%), and *Staphylococcus aureus* (12%) (Sigauque et al., 2009). Notably, in this

malaria-endemic region, 44% of the patients with positive bacterial cultures were co-infected with malaria parasites. Thus, the authors point to the importance of maintaining an awareness of both causes in order to achieve effective case management of febrile children in this region (Sigauque et al., 2009). While this study is helpful in understanding the types of bacterial pathogens affecting severely ill febrile children in this area of Mozambique, additional etiology studies focused on outpatient febrile patients of all ages would help to develop a more holistic picture of causes of fever in south-eastern Africa.

The above brief overview of etiology studies demonstrates that the causative agent of fever in adult and pediatric outpatients is not likely to be uniform across all geographic regions in sub-Saharan Africa. Researchers have noted that these etiologies may differ according to the pathogens endemic to each region, the vaccination strategies used and coverages achieved, as well as from season-to-season (D'Acremont et al., 2014). For some areas of sub-Saharan Africa, this knowledge base has been well-developed through multiple studies, while in other areas evidence regarding the pathogens provoking fever in outpatients is limited.

Conducting etiology studies, and the diagnostic testing required for this sort of research, can be resource intensive and unfeasible in some settings. Fortunately, other methodologies and data sources can contribute to the evidence base needed to improve case management of febrile outpatients. This sort of alternative approach can be seen in studies that focus on the case management practices of clinicians in low resource settings. Ideally, we would be able to understand both the etiology of febrile illness in an area *and* the clinical diagnoses and treatments being prescribed, in order to examine how these elements of case management may or may not align.

Prescribing practices of clinicians in outpatient clinics in sub-Saharan Africa

One set of key studies has focused on malaria case management practices of clinicians by using cross-sectional surveys at health facilities. These surveys frequently question both clinicians and patients about outpatient or inpatient consult practices and experiences. Information is gathered about presenting symptoms, diagnoses, and the clinical methods, tests, and algorithms used by the clinicians to reach decisions about treatment. While the focus of these studies is malaria case management, they also demonstrate the importance of case management for non-malaria cases. One such survey in Angola determined that, in each province where studies were conducted, 2% of the patients with a negative RDT were still prescribed antimalarials (Plucinski et al., 2017). In another example from Guinea, exit interviews conducted with patients at health facilities were compared to the patient's consult record to judge the quality of malaria case management (Davlantes et al., 2019). This research found that from 3-44% of fever patients who tested negative for malaria were none-the-less treated inappropriately with antimalarials, depending on the health facility (Davlantes et al., 2019). A similar pattern was discovered in an analysis of survey data from several provinces in Mozambique, where treatment of non-malaria cases with antimalarials ranged from 8 to 22% (Candrinho et al., 2019). Together, these studies highlight the need to examine case management of non-malaria fever cases, since a serious consequence of anti-malarial overuse is that febrile patients may not instead receive the treatment that they need (Ndhlovu et al., 2015).

Nwolisa et al. (2005) conducted a treatment-focused study in an outpatient clinic in Nigeria, focusing on the treatments prescribed by doctors to CU5 (Nwolisa, Erinaugha, & Ofoleta, 2006). Over the course of several months, the team retrieved demographic and drug-prescription details from health facility consultation records for 790 CU5 patients, in a region

"holo-endemic" for malaria (Nwolisa et al., 2006, p. 199). An analysis of the data revealed that 3 was the most common number of prescriptions received by the patients, although some received up to 7 unique medications (and/or vitamins and supplements). Antimalarials were the most commonly prescribed medications, with 65% of patients receiving a medication in this group. This was followed by medications that the study grouped as "analgesics/antipyretics" (60.1%), antibiotics (53.7%), vitamin C (32.3%), anti-histamines (23.3%), multivitamins (21.3%), and 'hematenics' (16.3%) (Nwolisa et al., 2006). The authors also provide a breakdown of the particular types of antimalarials and antibiotics prescribed; chloroquine and Sulphadoxine/Pyramethamine were the most common antimalarials, being prescribed to 43.9% and 29.2% of patients, while Cephalexin and Amoxycillin accounted for the greatest percentages of antibiotics prescribed (to 31.1 % and 29.6% of patients, respectively). By examining age of patients, the authors also concluded that a higher percentage of younger children (13-24 months old) received antimalarials than did older children (those 49-59 months). This age-specific pattern held true for antibiotic and analgesic/antipyretic prescription as well, with a higher proportion of younger children receiving medications from each of these groups than did older children. The authors note the frequent instances of "poly pharmacy" seen in the data, and surmise that the limited availability of diagnostic tools may contribute to this phenomenon (Nwolisa et al., 2006, p. 199).

It is important to note that this particular study did not address the symptoms reported by the subjects, nor the clinical diagnoses given, and subjects were not separated by fever status. Examining this information together with the prescriptions data would provide further insight into how clinicians conduct case management and the risk factors for receiving certain kinds of

treatment. Nevertheless, the study contributes to our understanding of prescribing practices for CU5 in an outpatient setting in this particular west African country.

Studies Focused on Antibiotic Prescribing Practices

The above study by Nwolisa was relatively wide in scope in terms of the treatment types examined. A different approach has been taken by other research teams throughout sub-Saharan Africa, whereby one group of medications is made the focus. Most commonly, these studies focus on antibiotic-prescribing practices, and may or may not account for fever status and malaria test result.

In Zambia, Ndhlovu et al. used this focused method to understand the factors associated with antibiotic prescription for patients with fever presenting to primary health care facilities (Ndhlovu et al., 2015). Survey methodology was again used, alongside chart extraction and observation, to characterize antibiotic use in both RDT-positive and RDT-negative febrile patients. The same study took note of presenting symptoms and diagnoses. Cough and vomiting were the most common symptoms reported across both age groups, and both were more common in CU5 than in older children and adults (Ndhlovu et al., 2015). “Ear, nose, and throat problems” and diarrhea were present in over a quarter of CU5. For diagnoses, respiratory tract infections and malaria were diagnosed in the highest frequencies. Older children and adult patients accounted for more ENT issue diagnoses, while CU5 were more often diagnosed with “dermatologic problems” (Ndhlovu et al., 2015, p. 1700). From the survey data and chart extraction, it was determined that antimalarials were prescribed to 18.5% of the patients with a negative RDT and to 25.8% of the patients who were not tested with an RDT. While only 1.3% of RDT-positive patients were prescribed antibiotics, 56.9% of RDT-negative patients received one or more, and 51.1% of non-tested patients were prescribed antibiotics (Ndhlovu et al., 2015).

Logistic regression was used to identify significant predictors of antibiotic prescription in the febrile patients. In terms of diagnoses and symptoms, patients were more likely to be prescribed an antibiotic if they presented with a cough (cOR: 3.68) or an ENT symptom (cOR: 2.43), or if the clinician diagnosed them with a respiratory tract infection (cOR: 3.39), ENT issue (cOR: 5.86) or a "dermatological disease" (cOR: 3.52) (Ndhlovu et al., 2015). A negative malaria test increased the odds of a receiving an antibiotic (cOR: 4.08), as did non-testing (cOR: 2.31) (Ndhlovu et al., 2015).

Several studies in countries in east and west Africa have likewise investigated antibiotic use in febrile outpatient case management. In Uganda, Batwala et al. (2011) specifically aimed to characterize antibiotic use for febrile outpatients across several case management strategies: presumptive malaria diagnosis vs. microscopy or RDT for parasitemia confirmation (Batwala et al., 2011). In total, the treatments of over 52,000 febrile patients were examined in order to determine antibiotic prescription proportions in those who were not tested, in those who tested positive for malaria, and in those who tested negative (Batwala et al., 2011). For those patients who were treated based only on their presenting symptoms, antibiotics were prescribed to 41.5% of the patients (Batwala et al., 2011). Of the patients who were found to be negative for malaria by microscopy (37%) or RDT (8%), 23.9% and 56.2% of those negative patients were prescribed antibiotics, respectively (Batwala et al., 2011). Testing positive for malaria by microscopy or RDT did not always negate use of antibiotics. 25.8% of the malaria-positive patients in the RDT arm received a prescription for antibiotics, while in the microscopy arm 17.6% of malaria-positive patients received antibiotics. In contrasting the two diagnostic arms, the study team found that more patients with negative RDT results received an antibiotic (61.4%) than did patients with a negative microscopy result (39.3%) (Batwala et al., 2011). The study also broke

down antibiotic prescription by age category, and found that a larger proportion of total CU5 patients (63%) received antibiotics than did patients five years of age or older (38.6%) (Batwala et al., 2011). Overall, the researchers noted high rates of antibiotic use that declined when a diagnostic test for malaria was positive, indicating that "diagnostic uncertainty" may be a determinant of antibiotic prescription (Batwala et al., 2011, p. 6).

A separate study of outpatient prescriptions in Ghana, while not focused only on febrile patients, found similarly high rates of antibiotic use (Prah et al., 2017). After examining the prescription of 388 patients, it was found that an antibiotic was included in 55.2% of all prescriptions, and these prescriptions included an average of 3.5 drugs (Prah et al., 2017). The authors in this study note the importance of standardized guidelines for treatment of patients for managing over-use of antibiotics and polypharmacy (Prah et al., 2017). While both this study and the Ugandan study by Batwala et al. demonstrated heavy use of antibiotics as a treatment in outpatient consults, the exact rates and reasons for such use likely differ by region and resource-availability. For this reason, it is important for additional studies to examine prescribing practices in outpatient clinics throughout sub-Saharan Africa, for febrile patients and otherwise.

Qualitative studies

A qualitative approach has also been used to better understand the perspective of the clinician as they decide how to proceed treating a febrile or non-malaria patient. In Tanzania, one team utilized focus groups with community members, as well as in-depth interviews with health care workers, to gauge knowledge, attitudes, and practices relating to non-malaria febrile illness (Chipwaza et al., 2014). By analyzing interviews conducted with 14 healthcare workers of varying levels of experience, the team identified several themes surrounding the treatment of non-malaria illness. While most clinicians reported only prescribing anti-malarial drugs to

patients with a positive RDT, a portion (4 of 14) described the use of antimalarial drugs in patients with a negative test result (Chipwaza et al., 2014). The interviews also revealed inconsistent availability of RDTs, and thus many clinicians were left to diagnose malaria presumptively or based on symptoms. Other cited barriers to correct case management of non-malaria fever were lack of diagnostic tools, medication stock-outs, and a lack of trained staff (Chipwaza et al., 2014).

A similar qualitative study in Zanzibar used semi-structured key informant interviews with health workers to better understand clinician perspectives on treating non-malaria febrile illness in children-under-five (Baltzell et al., 2013). As in the Chipwaza study, participants noted that additional point-of-care diagnostic tests would enable better case management, as would additional trainings and courses on how to manage non-malaria fever cases (Baltzell et al., 2013). Some interviewees reported the usefulness of their training in the WHO Integrated Management of Childhood Illness (Baltzell et al., 2013). Availability of drugs and RDTs were described as challenges, and many clinicians also stressed the importance of increasing awareness among caregivers about early care-seeking for fever (Baltzell et al., 2013).

Together, these qualitative studies add a valuable clinician-based perspective to the issue of case management of non-malaria illness in outpatient facilities. While the etiology studies discussed earlier are informative in the diagnoses that they reveal, many health facilities lack the specialized diagnostic tools used. Thus, data that reveal the patient and clinician perspective on symptoms, diagnoses, and treatments can illuminate challenges and areas for improvement to reduce morbidity and mortality from non-malaria illness.

Conclusion

As control measures improve and the prevalence of malaria decreases across sub-Saharan Africa, attention is shifting to the importance of proper case management of non-malaria illness in outpatient health facilities. Etiology studies from across the continent have used specialized diagnostic tools to reveal the pathogens behind non-malaria illness in children and adult patients (Crump et al., 2013; D'Acremont et al., 2014; Guillebaud et al., 2018; Hildenwall et al., 2016; Kibuuka et al., 2015; Kiemde et al., 2016; Kiemde et al., 2018; Sigauque et al., 2009). However, the above review of literature reveals that not all countries in the sub-Saharan Africa region have received the same attention, with southern and south-eastern Africa representing opportunities for increased etiology research. Furthermore, advanced diagnostic tools are infrequently available at health care facilities in sub-Saharan Africa (Archibald & Reller, 2001), and it is therefore critical to understand how clinicians diagnose and treat patients based on what they hear and see in a verbal and physical examination. For this reason, there is a need to better understand the clinical presentations, diagnoses, and prescribed treatments for non-malarial illnesses in adults and children presenting at health facilities in low-resource settings.

The current study aims to contribute to this body of knowledge by analyzing previously gathered data in the form of malaria health facility surveys from Mozambique. These data provide an opportunity to describe patient presentations and clinician behaviors in a region where such descriptive studies are scarce. This secondary analysis will provide answers to several key questions: What symptoms are patients reporting? What diagnosis are they receiving, having reported these symptoms? What treatments are being prescribed? What associations exists between these variables? By answering these questions, a deeper understanding of case management of non-malaria illness in outpatients in Mozambique can be achieved.

Chapter 3: Methods and Results

Materials and Methods

Introduction

This study is a secondary analysis of an existing data set of factors associated with the presentation and case management of non-malaria illness in outpatient health facilities in Mozambique. Health facility survey data of patient visits were used to determine the frequencies of symptoms, diagnoses, and treatments, and to examine symptom-diagnosis associations, diagnosis-treatment associations, and associations between treatments. Frequency of treatment type was further characterized by the fever status of patients and the results of their rapid diagnostic test (RDT) for malaria. The treatment records were analyzed to determine the average number of treatment types prescribed to individuals, stratified by fever status and RDT result. Finally, a multivariate logistic regression model was applied to establish correlates of antibiotic prescription.

Study Population

The data for this analysis came from a 2018 cross-sectional malaria-focused health facility survey conducted in three provinces in Mozambique (Candrinho et al., 2019; Plucinski et al., 2019). The selected provinces varied in malaria transmission, from low-level (Maputo) to high-level (Zambézia and Cabo Delgado). Forty health facilities per province were randomly sampled from a sampling frame that systematically included all secondary and tertiary health facilities, and a random sample of primary health facilities, in which outpatient care is offered.

The survey process consisted of several elements, including interviews with health care workers and directors of the health facilities, inventories of malaria-related diagnostic tools and medications, and exit interviews with the outpatients. The outpatient exit-interview survey

included questions about the symptoms that the patient spontaneously reported to the health care worker, the diagnosis(es) that they received from the health care worker, and the medications that they were prescribed. A pre-determined list of possible symptoms, diagnoses, and treatment types were provided in the survey tool for the interviewer to easily mark as the patient responded (see Appendix 1 for original survey options). For each of these questions, a write-in option for an "other: specify" response was also available. Finally, a survey team clinician performed a re-examination of exit-interview patients that included a temperature reading and RDT for malaria. Temperature readings ≥ 37.5 °C were considered to indicate fever, and this definition is sustained in the present analysis (Candrinho et al., 2019). The RDTs used were HRP2-based and specific for *P. falciparum* (Candrinho et al., 2019). For exit interviews and re-examinations, outpatients were randomly selected with the goal of selecting up to 10 adults and 10 children from each facility. All information was collected using a tablet-based electronic survey form. For the analysis presented in this paper, only the data from the outpatient survey and the results of the reexamination were utilized.

Procedures for Secondary Analysis

Categorization

To provide a comprehensive description of outpatient presentation and case management, it was necessary to develop more general categories into which the "other: specify" responses could be divided. To do this, the "other" responses in the Excel-formatted data set were individually examined for the variables in question. A preliminary categorization scheme was created for symptoms, diagnoses, and treatment, and then further refined and condensed in consultation with Centers for Disease Control (CDC) subject matter experts. This categorization process was also informed by the results from two additional data sets that resulted from similar

surveys, one from Angola and one from Guinea. This will eventually facilitate analysis and comparisons between the three data sets, and for this reason some of the created categories have a frequency of 0 in the Mozambique data. A detailed record of the symptoms, diagnoses, and treatments in each created category is provided in Appendix 2. New variables were created in the Excel data set to reflect presence/absence of symptoms, diagnoses, and treatments in each new category for every patient.

Statistical Analysis

Analyses of data were performed using R version 3.6.3 (R Core Team, 2019) in RStudio (RStudio Team, 2019). Frequency tables were calculated to describe the most common symptoms, diagnoses, and treatments, stratifying between children less-than-five years of age (CU5) and patients five years of age and older. Fisher's exact test was used to determine if these proportions differed significantly according to age category. Crosstabulations were used to calculate the relative risk (RR) of receiving a diagnosis based on reported symptoms, the RR of receiving a treatment based on a diagnosis, and the RR of receiving one treatment based on another treatment. Chi-Square tests of the RR for each combination determined significant relationships.

Treatment type for all patients was also analyzed by fever status and RDT result. To reflect the consult perspective, patients who self-reported having a fever at the time of their consult, or within the 24-hour period prior, were categorized as febrile. RDT results from the consult, rather than the exit interview, were used. A Chi-square test was used to examine the association between treatments and RDT result within fever-status categories. Simple averages for the number of distinct treatment types received per patient were calculated and stratified by fever and RDT status. Unlike other studies which have tabulated numbers of individual

medications (Nwolisa et al., 2006), the averages provided in the present analysis reflect the number of unique categories of medications rather than the medications themselves. For example, a patient who received two separate antibiotics is counted as having received one treatment type. Finally, logistic regression was used to determine correlates of antibiotic treatment and antimalarial treatment. Age (CU5 or 5 years +), sex, fever status, and RDT result, were the covariates considered. For all analyses, confidence intervals were calculated at the 95% level, and p-values were considered significant at an alpha <0.05.

Ethical considerations

According to the non-human subject research determination form available through the Emory University IRB website, this secondary analysis of de-identified survey data did not require IRB approval through Emory University. A project determination request for the analysis was reviewed by the Center for Global Health (CGH) Office of the Associate Director for Science/Laboratory Science at the Centers for Disease Control (CDC) and approved as non-research. Domestic and international investigators involved in original data collection provided written concurrence.

Methods Limitations

The categorization of the "other" written-in survey responses was subjective and required making judgement calls about how best to classify an extensive suite of responses. To reduce error and promote a more informative analysis, decisions regarding how best to synthesize the data into categories were made in collaboration with an epidemiologist from the original survey team and a physician. The analysis was also limited by the quality of the original survey data, including the spelling and completeness of written-in responses. Several written-in responses for symptoms, diagnosis, and treatment, were incomprehensible and therefore relegated to "miscellaneous" categories. The size of these "miscellaneous" categories limits the level of detail

provided by the analysis. Furthermore, the categorization process considered data sets from health facility surveys conducted in Guinea and Angola as well. The categories were developed to facilitate country-comparisons in future analyses, but this resulted in some categories in the Mozambique scheme containing few or no responses. This study focused only on the data from the Mozambique survey in order to limit the scope and increase feasibility of the analysis.

Results

In total, 1,840 outpatients were interviewed and re-examined across 117 health facilities throughout the three provinces of interest (Candrinho et al., 2019). Participants came from 102 primary facilities and 15 secondary/tertiary facilities. The outpatients consisted of 629 CU5 (347 female, 282 male), and 1,211 patients >5 years of age (725 female, 486 male).

Among CU5, fever was the most common symptom with nearly 75% of the 629 respondents (or their caretaker speaking for them) reporting fever (Table 1). This was followed by cough (270, 42.9%), vomiting (174, 27.7%), and weakness (166, 26.4%). For children over 5 years of age and adults, fever was likewise the most common symptom reported- 60.4% of older children and adult respondents reported fever. In contrast to CU5, the second and third most common symptoms for the 1,211 older children and adult respondents were headache (647, 53.43%) and joint pain (411, 33.94%), respectively. Rates of many symptoms (13 out 23) were statistically different between the two age groups ($p<0.05$).

When there was a diagnosis made, the two most frequent diagnoses were the same for both age groups- malaria and having a symptom listed as a diagnosis (Table 2) . However, most commonly, there was no diagnosis at all- 334 of 629 (53.1%) CU5 were “undiagnosed,” as were 794 of 1,211 (65.6%) patients 5-and-over. Malaria was the second most frequent diagnosis in each group, with 33.1% of CU5 and 16.1% of older patients receiving this diagnosis. A

significantly larger proportion of CU5 were diagnosed with malaria when compared to the older age group ($p<0.01$). Having a symptom listed as a diagnosis was the next most common diagnosis in both groups, although the frequencies were much lower than for the leading diagnoses (4.0% for CU5, 3.1% for children and adults aged 5-and-over). For CU5, pneumonia (2.7%) and viral infections (2.2%) rounded out the top five diagnoses. For adults and children-over-five, this order was reversed with 2.5% receiving a diagnosis of a viral infection and 2.4% receiving a pneumonia diagnosis.

For outpatient treatments, antipyretics, antimalarials, and antibiotics predominated regardless of age group (Table 3.). For CU5, 52.6% were prescribed an antipyretic, as were 51.5% of older children and adults. Nearly 40% of CU5 received a prescription for an anti-malarial. In children 5-and-over and adults, this proportion fell to less than a quarter of patients (21.6%). In contrast, antibiotic treatment was significantly more frequent among the older age group (50.3%) than in CU5 (43.7%, $p<0.01$). Following these three medications, the next most frequent treatments were prescribed to a much smaller proportion of patients. Prescriptions for antihistamines, antiparasitic, vitamins/supplements, and rehydration treatments were each received by 1-2% of CU5. Nearly all patients left with a prescription- less than 1% of CU5 patients received no treatment, while for older children and adults this frequency was only 0.5%.

Multiple symptoms were associated with a higher likelihood of diagnosed malaria, including fever (Risk ratio [RR]: 2.88, 95% CI: 2.24, 3.70), vomiting (RR: 2.06, 95% CI: 1.72, 2.46), breathlessness (RR: 1.93, 95% CI: 1.52, 2.46), chills (RR:1.88, 95% CI: 1.56, 2.27), weakness (RR:1.75, 95% CI: 1.48, 2.08), and lack of appetite (RR: 1.44, 95% CI: 1.18, 1.76) (Table 4). Heart and chest symptoms (RR: 0.18, 95% CI: 0.03, 1.23), dermatologic symptoms (RR: 0.30, 95% CI: 0.12, 0.78), and ear, eye, neck and throat symptoms (RR: 0.31, 95% CI:

0.16, 0.61) were associated with a lower risk of malaria diagnosis. Fever, chills, weakness, and vomiting decrease the likelihood of a person remaining undiagnosed (RR: 0.77, 95% CI: 0.72, 0.83; RR: 0.84, 95% CI: 0.74, 0.94; RR: 0.86, 95% CI: 0.79, 0.94; and RR: 0.85, 95% CI: 0.76, 0.95 respectively). Headache and ear, eye, neck, and throat symptoms showed an association with being diagnosed with a viral infection, while vomiting and diarrhea reduced the likelihood of the same diagnosis (Table 4). Gastrointestinal symptoms showed a positive association with a bacterial infection diagnosis (RR: 76.33, 95% CI: 8.86, 657.93), as did genitourinary symptoms (RR=51.57, 95% CI: 7.48, 355.7).

Malaria was the only diagnosis that resulted in a significantly elevated likelihood of receiving an antimalarial- patients with this diagnosis were 11.6 times more likely to receive an antimalarial medication than those patients who did not receive this diagnosis (95% CI: 9.42, 13.22) (Table 5). At the same time, a malaria diagnosis reduced the likelihood of receiving an antibiotic (R: 0.07, 95% CI: 0.05, 0.12). Patients who had no diagnosis had a smaller likelihood of being treated with an antimalarial (RR: 0.20, 95% CI: 0.16, 0.23), as did patients who had a symptom listed as their diagnosis (RR: 0.11, 95% CI: 0.03, 0.44). These two diagnoses categories increased the likelihood of receiving an antibiotic (undiagnosed RR: 2.42, 95% CI: 2.12, 2.76; symptom listed as diagnosis RR: 1.57, 95% CI: 1.35, 1.84). Antihistamines were another treatment commonly prescribed to patients who remained undiagnosed (RR: 2.34, 95% CI: 1.02, 5.37). A fungal infection diagnosis was associated with no treatment (RR: 3.55, 95% CI: 18.53, 376.66), whereas receiving dermatitis as a diagnosis resulted in a RR of 15.97 for receiving an anti-fungal treatment (95% CI: 3.83, 66.55). Anemia was significantly associated with receiving a vitamin or supplement (RR: 17.98, 95% CI: 5.53, 58.49), while those with a malaria diagnosis were not as likely to receive them (RR: 0.10, 95% CI: 0.01, 0.74).

Several patterns were observed when comparing the relative risk of receiving one treatment based on having received another, different treatment (Table 6). Receiving an antimalarial was associated with a reduced likelihood of receiving an antibiotic (RR: 0.09, 95% CI: 0.06, 0.13), and, to a lesser extent, an antipyretic (RR: 0.71, 95% CI: 0.63, 0.80). Mirroring this finding, patients who received an antibiotic were at a lower risk for receiving an antimalarial (RR: 0.07, 95% CI: 0.05, 0.10). Treatment with an antipyretic resulted in a higher likelihood of receiving an antibiotic (RR: 1.5, 95% CI: 1.35, 1.65), and the reverse was true as well- receiving an antibiotic resulted in a higher likelihood of receiving an antipyretic (RR: 1.44, 95% CI: 1.32, 1.58). Several treatments showed an association with an increased risk of prescription for a vitamin/supplement, including anti-fungals (RR: 7.67, 95% CI: 2.04, 28.88), antihistamines (RR: 6.84, 95% CI: 2.57, 18.25), antihypertensives (RR: 26.26, 95% CI: 6.32, 109.09), and rehydration treatments (RR: 17.3, 95% CI: 7.66, 39.07).

For both febrile and non-febrile patients, antibiotic prescription was more common when patients were RDT-negative or reported not having a RDT performed (Table 7). Among febrile patients, 66.8% of RDT-negative patients and 67.5% of patients who did not have an RDT performed received an antibiotic, whereas only 5.8% of RDT-positive patients received this prescription. Results were similar among non-febrile patients, with 68.5% of RDT-negative patients, 54.1% of no-RDT patients, and 3.6% of RDT-positive patients prescribed an antibiotic. In contrast, antimalarial prescription was considerably more frequent for the RDT-positive patients. 98.1% of febrile patients with a positive RDT received an antimalarial, whereas only about 5.4% of those febrile patients with a negative RDT were given this prescription. 3.8% of febrile patients for whom a RDT was not performed received an antimalarial. A similar pattern can be seen in non-febrile patients (Table 7). Antipyretics were prescribed to larger proportions

of febrile patients than to non-febrile patients, and in both groups the frequency of prescription was higher for RDT-negative patients and for those who were not tested. Among febrile patients, 69.7% of RDT-negative patients and 60.5% of no-RDT patients received an antipyretic. Among non-febrile patients, these values were 48.7% and 45.7%, respectively. For RDT-positive patients, antipyretic prescription rates were lower at 42.2% among febrile patients and 23.2% among non-febrile patients.

Considering all surveyed outpatients, the average number of unique treatment types received by outpatients was 1.37 (S.D: 0.76) (Table 8). When looked at separately, febrile patients received an average of 1.47 (S.D: 0.74) different treatment types, while non-febrile patients received 1.20 (S.D: 0.78). For non-febrile patients, those who did not have an RDT performed received 1.16 (S.D: 0.80) treatment types on average, while those patients who had a definitive negative or positive test received 1.30 (S.D: 0.73) and 1.23 (S.D: 0.57) types, respectively. Febrile patients with a positive RDT received 1.48 (S.D: 0.61) treatments on average, and RDT-negative febrile patients received 1.49 (S.D: 0.68). Among febrile patients for whom no RDT was performed, an average of 1.46 (S.D: 0.84) treatments was prescribed.

The multivariate logistic regression produced crude and adjusted odds ratios for associations between antibiotic prescription and four variables: age, sex, fever status, and RDT status (Table 10). In the full model, only RDT status was significantly associated with receiving an antibiotic. The adjusted OR of 0.03 shows that for patients with a positive RDT, the odds of receiving an antibiotic are lower than for those who test negative ($p<0.01$). Patients five years and older, as well as febrile patients, appeared to have slightly decreased odds of antibiotic prescription, but these associations were not significant.

Chapter 4: Discussion and Public Health Implications

Surveyed outpatients at health facilities in Mozambique reported a variety of symptom presentations. While fever was the most common symptom for both CU5 and patients 5-and-older, there was a wide spectrum of symptoms and these frequently differed significantly by age group. Reporting no diagnosis from a consult was common, and malaria was a frequent diagnosis when one could be reported. Most patients left their consult with a prescription for at least one medication, with antipyretics being the most widely prescribed. The results indicate that previously described patterns of illness presentation and case management from across sub-Saharan Africa are reflected in the outpatient setting in Mozambique, but setting-specific findings can also be identified.

Literature suggests that in the same geographic setting, members of different age groups may present with different proportions of symptoms (Ndhlovu et al., 2015). The results of the present analysis reflect this pattern, with the frequency of several symptoms differing significantly between CU5 and older children and adults. “Cough” has been cited by some studies as the most common presenting symptom in younger and older outpatients at health facilities in eastern and southern-Africa, once fever status is accounted for (Hildenwall et al., 2016; Ndhlovu et al., 2015). This was the case for both a study focused on febrile patients with suspected malaria (Ndhlovu et al., 2015) and in a separate study that considered only febrile patients with a negative malaria test (Hildenwall et al., 2016). Aside from fever, the present analysis likewise found cough to be the most common symptom in CU5 (42.9%), although the same was not true for the older age group (26.5%). However, as the present study did not stratify symptom frequency by fever status, the results are not directly comparable.

A wealth of etiology studies from across the continent of Africa have revealed the diversity of diagnoses that may be applicable to patients presenting to health facilities in these settings (Crump et al., 2013; D'Acremont et al., 2014; Guillebaud et al., 2018; Hildenwall et al., 2016; Kibuuka et al., 2015; Kiemde et al., 2018; Sigauque et al., 2009). Such studies, which bring in additional diagnostic tools not usually available in a low-resource health facility, help us to understand what diagnoses and treatment frequency *should* look like for non-malaria outpatients. On the other hand, this methodology is not designed to reflect the reality of case management of non-malaria illness at these facilities. In truth, many patients who test negative for malaria via RDT or microscopy may leave their consult without a specific diagnosis guiding their treatment. The data presented here showed that over 50% of patients in both age groups left their consult without being able to report what their diagnosis was. While in some cases this may be a reflection of the clinician not explicitly sharing their diagnosis with the patient, other cases may represent a situation in which no diagnosis was reached.

With or without a definitive diagnosis, the majority of surveyed patients reported having at least one treatment prescribed to them, with patients receiving 1.37 different treatment types on average. Antipyretic treatments, antimalarials, and antibiotics were among the most common treatments received by surveyed outpatients of all ages in this data set. Similar results were seen in a 2006 study of CU5 outpatients in Nigeria that compiled prescription data from consult records (Nwolisa et al., 2006). Details of antimalarial prescription from the data set used in the present study have been previously described in detail by Candrinho et al. (2019).

High rates of antibiotic prescription in health facilities in sub-Saharan Africa have been noted in other investigations, and there is concern that improper or overuse may contribute to antibiotic resistance (D'Acremont et al., 2011; Prah et al., 2017). The literature also indicates that

frequency of antibiotic prescription is particularly high for patients who have a negative RDT for malaria (Batwala et al., 2011; D'Acremont et al., 2011; Ndhlovu et al., 2015). In the present data, 48% of all surveyed patients received at least one antibiotic. The effects of a negative RDT were also confirmed, as for both febrile and non-febrile patients frequency of antibiotic prescription differed significantly by RDT status, with substantially more RDT-negative patients receiving this medication than did RDT-positive patients. Among febrile patients, only 5.8% of RDT-positive patients received an antibiotic, while 66.8% of RDT-negative patients received one. The results of the logistic regression corroborated this- the odds ratio for RDT-positive patients receiving an antibiotic was small, at 0.03. However, in contrast to a study in Uganda which found antibiotic use to be more common in CU5 (Batwala et al., 2011), the present analysis showed that a higher proportion of adults and children older-than-5 received an antibiotic compared to CU5 (50.29% compared to 43.72%, $p<0.01$).

At least in some cases, prescription of an antibiotic would be the understandable next step following a bacterial infection diagnosis. The results of the crosstabulations from the current study offer information about the clinical presentations associated with augmented relative risk for a bacterial infection diagnosis- these included gastro-intestinal symptoms and genitourinary symptoms. Encouragingly, a malaria diagnosis lowered the relative risk of being prescribed an antibiotic. It was expected that a viral infection diagnosis would also result in a lower relative risk of receiving an antibiotic, but the results showed no significant association. However, the increased risk for antibiotic prescription for patients receiving no diagnosis highlights the importance of providing clinicians with the necessary tools, training, and algorithms to reach conclusions regarding the ailments of their patients and the correct course of action.

As in many parts of the world, indeterminate antibiotic use and the implications for possible resistance are of concern in Mozambique. A study of bacteremia in children admitted to rural health facilities in Mozambique determined that many of the pathogens showed resistance to commonly used antibiotics (Sigauque et al., 2009). The results from this analysis demonstrate the continued reliance on antibiotics to treat non-malaria patients in an outpatient setting and highlight the importance of providing additional point-of-care diagnostic tools to clinicians. Provision of these resources would allow for more accurate diagnoses and, consequently, more effective, appropriate, and targeted treatment. In the absence of these tools, clinicians in settings of declining malaria prevalence must continue to rely on purely clinical presentations in order to guess at any number of etiologies behind the non-malaria illnesses affecting their patients.

Public Health Implication

The results of this analysis are specific to the geography and population included in the original survey data- outpatients presenting to primary, secondary, and tertiary health facilities in three provinces of Mozambique. Other researchers have noted that suites of pathogens, illnesses, and their presentations are unique to each temporal and spatial setting (D'Acremont et al., 2014; Maze et al., 2018; Prasad et al., 2015), and therefore the results presented here reflect only what is true in the study setting. Nevertheless, this information provides clinicians practicing in this specific geography with a detailed overview of the types and frequencies of symptoms that they might encounter, and offers an opportunity for reflection on common diagnoses and treatment combinations. Routine surveillance systems that rely on consult records and logbooks do not always offer this same level of detail. Thus, the results from the present study may be useful for improving treatment algorithms for non-malaria illness so that they better reflect the conditions that clinicians are seeing in outpatients at health facilities in Mozambique.

This secondary analysis of a large survey data set also serves to inform the design of future health facility-based surveys. The original study for which the data were collected used the survey results to describe the quality of malaria case management in health facilities (Candrinho et al., 2019). The survey allowed interviewers to enumerate symptoms, diagnoses, and treatments in an "other" free-response option, and this revealed the diversity of responses received. Future surveys with similar target populations could be made more efficient and user-friendly through the inclusion of some of the most common "other" responses as pre-programmed select-multiple options. Specifically, dermatologic complaints and ear, eye, neck, and throat symptoms were common and could be added to the list of symptom options. Viral infections, such as influenza, and vascular conditions, including hyper- or hypotension, were reported frequently enough as diagnoses that adding these programmed options would also be beneficial. Furthermore, a closer look at the data revealed that several treatments were common but not included in the original survey options. These included vitamins and supplements, antihistamines, anti-parasitic medications, and rehydration treatments.

The categorization process also revealed that it was common for a symptom to be listed as a diagnosis, and vice-versa, suggesting that interviewers conducting health-facility surveys may benefit from additional training that focuses on differentiating the two categories. This issue is confounded by the fact that patients may be receiving a symptom as a diagnosis from their clinician. Improved algorithms and trainings that allow health care workers to distinguish these categories could be helpful. Designing future surveys for this specific geography with these changes in mind would allow data collection and analysis to more easily and efficiently incorporate the full range of responses, without requiring the time-intensive process of post-survey categorization of written-in answers.

Limitations

Several limitations exist for this study. One such limitation is that the quality of case management of the various symptom presentations cannot be judged. Aside from RDTs and microscopy for malaria, no additional diagnostics were performed as part of the exit interview of surveyed outpatients. Thus, information regarding the true etiology underlying patient complaints is unknown, and case management for conditions other than malaria cannot be deemed correct or incorrect. Our understanding of case management of non-malaria illness could be improved by future studies that combine outpatient exit interviews with additional diagnostic tests so that alignment of clinically-based diagnoses and prescribing practices with illness etiology can be ascertained.

Additionally, the categorization process for the written-in symptom, diagnosis, and treatment responses was limited by the nature of the available data. Data quality of written-in survey responses presented issues, as some responses were unintelligible or unidentifiable as a particular symptom, diagnosis, or treatment, even after consultation with an epidemiologist and physician familiar with outpatient health care in this setting. This further highlights the importance of designing future surveys to more easily capture the range of possible responses. Furthermore, this process was performed by considering data captured by surveys performed in three sub-Saharan African countries (Mozambique, Angola, and Guinea) so that eventual comparisons between data sets would be possible. In order to develop a scheme that captured the diversity of data from all countries, some categories have very few or no responses for Mozambique. Small values may limit the usefulness of produced risk ratios and odds ratios. To account for these small values when testing for association between variables, Fisher's exact test was used in place of a Chi-square test.

Finally, the results presenting the average number of treatments prescribed per outpatient considered this at the level of unique treatment types rather than total number of medications. The format of the data did not allow for the latter method to be used. That is, a patient who was prescribed two different antibiotics and two antipyretics would only be considered as having received two treatment types. For this reason, these results may not completely capture the magnitude of treatment combinations and polypharmacy- an issue that has been identified by other treatment-focused studies in sub-Saharan Africa (Nwolisa et al., 2006).

Conclusion

Over the past several decades, remarkable strides have been made towards reducing malaria prevalence in sub-Saharan Africa (Feachem et al., 2010; WHO, 2019). As efforts to work towards reduction and elimination of malaria continue, it is important to consider the variety of non-malaria illnesses afflicting communities across the continent. This study provides a detailed description of the symptoms, diagnoses, and treatments experienced and received by outpatients reporting to health facilities in three provinces of Mozambique. The results will serve to enhance surveillance, improve algorithms, and guide surveys in similar settings. Future research could combine etiology investigations with assessment of clinically-based consults in low-resource health facilities, in order to improve case management of non-malaria illness, reduce morbidity and mortality, and strengthen the ability of health systems to care for the unique populations that they serve.

Tables

Table 1. Frequency of Symptoms Reported from Survey Data of Outpatients at Public Health Facilities in Mozambique by Age Group

	<5 (N = 629)		>=5 (N= 1211)		
Symptom Category	n	**%**	n	**%**	Fisher's P-Value
Fever	469	74.56	731	60.36	<0.01
Chills	75	11.92	193	15.94	0.02
Weakness	166	26.39	314	25.93	0.87
Joint pain	52	8.27	411	33.94	<0.01
Seizures	28	4.45	14	1.16	<0.01
Headache	150	23.85	647	53.43	<0.01
Cough	270	42.93	321	26.51	<0.01
Breathlessness	55	8.74	60	4.95	<0.01
Vomiting	174	27.66	128	10.57	<0.01
Lack of appetite	136	21.62	159	13.13	<0.01
Stomachache	116	18.44	206	17.01	0.4
Diarrhea	131	20.83	98	8.09	<0.01
Diagnosis listed as symptom	6	0.95	11	0.91	1
Miscellaneous complaint	0	0.00	1	0.08	1
Musculo-skeletal pain	2	0.32	43	3.55	<0.01
Injury	3	0.48	13	1.07	0.29
Heart and chest symptoms	0	0.00	25	2.06	<0.01
Dermatologic symptoms	21	3.34	38	3.14	0.89
Ears, eyes, neck, and throat symptoms	45	7.15	68	5.62	0.22
Respiratory symptoms	2	0.32	4	0.33	1
Neuro-psychiatric symptoms	1	0.16	10	0.83	0.11
Genitourinary symptoms	2	0.32	33	2.73	<0.01
Gastro-intestinal symptoms	1	0.16	7	0.58	0.28

Shaded symptoms are original survey options.

Table 2. Frequency of Diagnoses Reported from Survey Data of Outpatients at Public Health Facilities in Mozambique by Age Group

	<5 (N = 629)		**>=5 (N= 1211)**		
Diagnosis Category	n	%	n	%	Fisher's P-Value
Malaria	208	33.07	195	16.10	<0.01
Pneumonia	17	2.70	29	2.39	0.75
Enteric Disease	1	0.16	1	0.08	1
Anemia	0	0	6	0.50	0.1
Ear Infection	2	0.32	3	0.25	1
Eye Infection	1	0.16	5	0.41	0.67
Urinary Tract Infection	0	0	8	0.66	0.06
Dermatitis	6	0.95	13	1.07	1
Trauma	1	0.16	4	0.33	0.67
Undiagnosed	334	53.10	794	65.57	<0.01
Symptom listed as diagnosis	25	3.97	37	3.06	0.34
Bacterial infections	0	0	4	0.33	0.31
Fungal infections	1	0.16	1	0.08	1
Parasitic infections	2	0.32	4	0.33	1
Viral infections	14	2.23	30	2.48	0.87
General respiratory diagnosis	1	0.16	2	0.17	1
Other Injury	0	0	3	0.25	0.56
Other Gastro-intestinal diagnosis	0	0	3	0.25	0.56
Neuro-psychiatric diagnosis	0	0	5	0.41	0.17
Other Skin/mucosal diagnosis	4	0.64	8	0.66	1
Miscellaneous diagnosis	2	0.32	25	2.06	<0.01

Shaded diagnoses are original survey options.

Table 3. Frequency of Treatments Reported from Survey Data of Outpatients at Public Health Facilities in Mozambique by Age Group

	<5 (N = 629)		>=5 (N= 1211)		
Treatment Category	n	%	n	%	Fisher's P-Value
Antimalarial[a]	250	39.75	262	21.64	<0.01
Antibiotic[b]	275	43.72	609	50.29	<0.01
Antipyretic[c]	331	52.62	624	51.53	0.66
No Treatment	6	0.95	6	0.50	0.36
Anti-convulsants	0	0	2	0.17	0.55
Anti-fungals	5	0.79	9	0.74	1
Anti-histamines	13	2.07	20	1.65	0.58
Anti-hypertenisves	0	0	2	0.17	0.55
Anti-parasitics	11	1.75	17	1.40	0.55
Psychiatric medications	0	0	1	0.08	1
Antiretrovirals	0	0	6	0.50	0.10
Diabetes Treatments	0	0	0	0	1
Treatments for gastro-intestinal issues	0	0	11	0.91	0.02
Other pain medications (not NSAIDs)	0	0	0	0	1
Rehydration treatments	10	1.59	7	0.58	0.04
Reproductive health treatments	0	0	0	0	1
Respiratory treatments	5	0.79	7	0.58	0.56
Skin and mucosal topical treatments	3	0.48	0	0	0.04
Steroids	0	0	9	0.74	0.03
Vaccines	0	0	1	0.08	1
Vitamins and Supplements	11	1.75	25	2.06	0.72
Miscellaneous treatments	0	0	0	0	1

Shaded treatments are original survey options.

[a] Antimalarial category includes the following options from original survey: Artemether Lumefantrine, Artesuante-Amodiaquine, Dihydroartemisinin-piperaquine, Sulfadoxine-pyrimethamine, Quinine tablets, Chloroquine, Primaquine, Artesunate Injection, Rectal Artesunate, Intramuscular Artemether, and "other anti-malarial".

[b] Antibiotic category includes written-in antibiotics from the "other" response option and two categories from original survey: 1.) Cotrimoxizole 2.) 'other antibiotic'

[c] Antipyretic category includes written-in antipyretics and one category from original survey: 1). Antipyretic

Table 4. Significant associations (Risk Ratios, RR) between symptoms and diagnoses from survey data of outpatients at public health facilities in Mozambique (p≤0.05)

		Diagnoses																				
		Malaria	Pneumonia	Enteric Disease	Anemia	Ear Infection	Eye Infection	Urinary Tract Infection	Dermatitis	Trauma	Undiagnosed	Symptom listed as diagnosis	Bacterial infections	Fungal infections	Parasitic infections	Viral infections	General respiratory diagnosis	Other Injury	Other Gastro-intestinal diagnosis	Neuro-psychiatric diagnosis	Other Skin/mucosal diagnosis	Miscellaneous diagnosis
Symptoms	Fever	2.88	3.56	-	-	-	-	0.18	-	-	0.77	-	-	-	-	-	-	0.00	-	-	-	-
	Chills	1.88	-	-	-	-	-	-	-	-	0.84	0.20	-	-	-	0.14	-	-	-	-	-	-
	Weakness	1.75	-	-	-	-	-	-	-	-	0.86	-	-	-	-	-	-	-	-	-	-	-
	Joint pain	-	-	-	-	-	-	-	-	-	1.10	0.44	-	-	-	-	-	-	-	-	-	-
	Seizures	2.24	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Headache	1.25	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Cough	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2.54	-	-	-	-	-	-
	Breathlessness	1.93	-	-	-	-	-	-	-	-	-	0.00	-	-	-	-	-	-	-	-	-	-
	Vomiting	2.06	-	-	-	-	-	-	-	-	0.85	-	-	-	-	0.24	-	-	-	-	-	-
	Lack of appetite	1.44	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Stomachache	-	0.21	-	-	-	-	-	-	-	1.12	-	-	-	-	-	-	-	-	-	-	-
	Diarrhea	-	-	-	-	-	-	-	-	-	-	2.45	-	-	-	0.16	-	-	-	-	-	-
	Diagnosis listed as symptom	-	-	-	-	-	-	-	-	-	-	-	-	-	> 100	-	-	-	-	-	-	-
	Miscellaneous complaint	-	-	-	-	-	-	-	-	-	-	-	-	-	-	42.77	-	-	-	-	-	-
	Musculo-skeletal pain	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	26.59	-	6.94
	Injury	0.00	-	-	-	-	-	-	-	28.50	-	-	-	-	-	-	-	-	-	-	-	-
	Heart and chest symptoms	0.18	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	12.63
	Dermatologic symptoms	0.30	-	-	-	-	-	-	41.51	-	-	-	-	-	-	-	-	-	-	-	-	-
	Ears, eyes, neck, and throat symptoms	0.31	-	-	-	22.92	30.57	-	-	-	-	-	-	-	-	4.50	-	-	-	-	15.28	-
	Respiratory symptoms	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	> 100	-	-	-	-	-
	Neuro-psychiatric symptoms	-	-	-	33.25	-	-	-	-	-	-	11.47	-	-	-	-	-	-	-	-	-	-
	Genitourinary symptoms	-	-	-	-	-	-	17.19	-	-	-	-	51.57	-	-	-	-	-	-	-	-	-
	Gastro-intestinal symptoms	-	-	> 100	-	-	-	-	-	-	-	-	76.33	-	-	-	-	-	> 100	-	-	-

Shaded symptoms and diagnoses are original survey options.

Cells shaded in orange indicate increased risk of outcome (diagnosis).

Cells shaded in green indicate decreased risk of outcome (diagnosis).

Table 5. Significant associations (Risk Ratios, RR) between diagnoses and treatments from survey data of outpatients at public health facilities in Mozambique (p≤0.05)

Diagnosis	Treatment																					
	Anti-malarial[a]	Antibiotic[b]	Antipyretic[c]	No Treatment	Anti-convulsants	Anti-fungals	Anti-histamines	Anti-hypertenisves	Anti-parasitics	Psychiatric medications	Anti-retrovirals	Diabetes Treatments	Treatments for gastro-intestinal issues	Other pain medications (not NSAIDs)	Rehydration treatments	Reproductive health treatments	Respiratory treatments	Skin and mucosal topical treatments	Steroids	Vaccines	Vitamins and Supplements	Miscellaneous treatments
Malaria	11.16	0.07	0.71	-	-	0.00	0.00	-	-	-	-	-	-	-	-	-	-	-	-	-	0.10	-
Pneumonia	0.00	1.56	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Enteric Disease	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Anemia	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	17.98	-
Ear Infection	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Eye Infection	-	-	-	27.79	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Urinary Tract Infection	-	2.09	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	28.63	-	-	-
Dermatitis	0.19	-	-	-	-	15.97	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Trauma	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Undiagnosed	0.20	2.42	1.43	-	-	-	2.34	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Symptom listed as diagnosis	0.11	1.57	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Bacterial infections	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Fungal infections	-	-	-	83.55	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Parasitic infections	-	-	-	-	-	-	-	-	23.51	-	-	-	-	-	-	-	-	-	-	-	-	-
Viral infections	0.00	-	1.37	-	-	-	-	-	-	-	40.82	-	-	-	-	-	-	-	-	-	-	-
General respiratory diagnosis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	55.67	-	-	-	-	-
Other Injury	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Other Gastro-intestinal diagnosis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Neuro-psychiatric diagnosis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Other Skin/mucosal diagnosis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Miscellaneous diagnosis	0.00	-	-	-	-	-	-	67.15	-	-	-	-	-	-	-	-	-	-	-	-	8.39	-

Shaded treatments are original survey options.

Cells shaded in orange indicate increased risk of outcome (Treatment)

Cells shaded in green indicate decreased risk of outcome (Treatment).

[a] Antimalarial category includes the following options from original survey: Artemether Lumefantrine, Artesuante-Amodiaquine, Dihydroartemisinin-piperaquine, Sulfadoxine-pyrimethamine, Quinine tablets, Chloroquine, Primaquine, Artesunate Injection, Rectal Artesunate, Intramuscular Artemether, and "other anti-malarial".

[b] Antibiotic category includes written-in antibiotics from the "other" response option and two categories from original survey: 1.) Cotrimoxizole 2.) 'other antibiotic'

[c] Antipyretic category includes written-in antipyretics and one category from original survey: 1). Antipyretic

Table 6. Significant associations (Risk Ratios, RR) between treatments from survey data of outpatients at public health facilities in Mozambique (p≤0.05)

Treatment A	Treatment B: Anti-malarial[a]	Antibiotic[b]	Antipyretic[c]	No Treatment	Anti-convulsants	Anti-fungals	Anti-histamines	Anti-hypertenisves	Anti-parasitics	Psychiatric medications	Anti-retrovirals	Diabetes Treatments	Treatments for gastro-intestinal issues	Other pain medications (not NSAIDs)	Rehydration treatments	Reproductive health treatments	Respiratory treatments	Skin and mucosal topical treatments	Steroids	Vaccines	Vitamins and Supplements	Miscellaneous treatments
Anti-malarial[a]	-	0.09	0.71	0	-	-	0	-	-	-	-	-	0	-	-	-	0	-	-	-	0.15	-
Antibiotic[b]	0.07	-	1.44	0	-	-	-	-	-	-	0	-	-	-	-	-	-	-	-	-	-	-
Antipyretic	0.62	1.5	-	0	-	-	2.13	-	2.32	-	0	-	-	-	4.32	-	-	-	7.41	-	3.84	-
No Treatment	0	0	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Anti-convulsants	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Anti-fungals	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	65.21	-	-	7.67	-
Anti-histamines	0	-	1.35	-	-	-	-	-	-	-	-	-	-	-	7.3	-	10.95	-	-	-	6.84	-
Anti-hypertenisves	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	26.26	-
Anti-parasitics	-	-	1.38	-	-	-	-	-	-	-	-	-	-	-	8.63	-	-	-	-	-	-	-
Psychiatric medications	-	-	-	-	>100	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Anti-retrovirals	-	0	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Diabetes Treatments	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Treatments for gastro-intestinal issues	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Other pain medications (not NSAIDs)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Rehydration treatments	-	-	1.6	-	-	-	6.92	-	8.25	-	-	-	-	-	-	-	-	-	-	-	17.3	-
Reproductive health treatments	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Respiratory treatments	0	-	-	-	-	-	9.83	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Skin and mucosal topical treatments	-	-	-	-	-	47.1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Steroids	-	-	1.72	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Vaccines	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Vitamins and Supplements	0.2	-	1.57	-	-	8.35	6.91	50.11	-	-	-	-	-	-	20.88	-	-	-	-	-	-	-
Miscellaneous treatments	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Shaded treatments are original survey options.

Cells shaded in orange indicate increased risk of outcome (Treatment B)

Cells shaded in green indicate decreased risk of outcome (Treatment B).

[a] Antimalarial category includes the following options from original survey: Artemether Lumefantrine, Artesuante-Amodiaquine, Dihydroartemisinin-piperaquine, Sulfadoxine-pyrimethamine, Quinine tablets, Chloroquine, Primaquine, Artesunate Injection, Rectal Artesunate, Intramuscular Artemether, and "other anti-malarial".

[b] Antibiotic category includes written-in antibiotics from the "other" response option and two categories from original survey: 1.) Cotrimoxizole 2.) 'other antibiotic'

[c] Antipyretic category includes written-in antipyretics and one category from original survey: 1). Antipyretic

Table 7. Treatment frequency by fever status and RDT status, from survey data of outpatients at public health facilities in Mozambique.

	Febrile Patients						Non-Febrile Patients					
	RDT+ N= 379 n (%)		RDT- N= 241 n (%)		No RDT N= 443 n (%)	Fisher's p-value	RDT+ N= 56 n (%)		RDT- N= 111 n (%)		No RDT N= 481 n (%)	Fisher's p-value
Anti-malarial[a]	372	(98.15)	13	(5.39)	17 (3.84)	<0.01	53	(94.64)	3	(2.70)	10 (2.08)	<0.01
Antibiotic[b]	22	(5.80)	161	(66.80)	299 (67.49)	<0.01	2	(3.57)	76	(68.47)	260 (54.05)	<0.01
Antipyretic[c]	160	(42.22)	168	(69.71)	268 (60.50)	<0.01	13	(23.21)	54	(48.65)	220 (45.74)	<0.01
No Treatment	0	(0.0)	1	(0.41)	6 (1.35)	0.05	0	(0.0)	0	(0.0)	5 (1.04)	0.74
Anti-convulsants	0	(0.0)	0	(0.0)	0 (0.0)	1	0	(0.0)	0	(0.0)	2 (0.42)	1
Anti-fungals	0	(0.0)	1	(0.41)	5 (1.13)	0.11	0	(0.0)	1	(0.90)	7 (1.46)	1
Anti-histamines	0	(0.0)	4	(1.66)	17 (3.84)	<0.01	0	(0.0)	2	(1.80)	7 (1.46)	0.72
Anti-hypertenisves	0	(0.0)	1	(0.41)	0 (0.0)	0.23	0	(0.0)	0	(0.0)	1 (0.21)	1
Anti-parasitics	3	(0.79)	1	0.41)	11 (2.48)	0.06	1	(1.79)	3	(2.70)	7 (1.46)	0.49
Psychiatric medications	0	(0.0)	0	(0.0)	0 (0.0)	1	0	(0.0)	0	(0.0)	1 (0.21)	1
Anti-retrovirals	0	(0.0)	0	(0.0)	0 (0.0)	1	0	(0.0)	0	(0.0)	6 (1.25)	0.77
Diabetes Treatments	0	(0.0)	0	(0.0)	0 (0.0)	1	0	(0.0)	0	(0.0)	0 (0.0)	1
Treatments for gastro-intestinal issues	0	(0.0)	1	(0.41)	2 (0.45)	0.45	0	(0.0)	2	(1.80)	5 (1.04)	0.66
Other pain medications (not NSAIDs)	0	(0.0)	0	(0.0)	0 (0.0)	1	0	(0.0)	0	(0.0)	0 (0.0)	1
Rehydration treatments	3	(0.79)	2	(0.83)	6 (1.35)	0.74	0	(0.0)	1	(0.90)	5 (1.04)	1
Reproductive health treatments	0	(0.0)	0	(0.0)	0 (0.0)	1	0	(0.0)	0	(0.0)	0 (0.0)	1
Respiratory treatments	0	(0.0)	2	(0.83)	6 (1.35)	0.05	0	(0.0)	0	(0.0)	4 (0.83)	1
Skin and mucosal topical treatments	0	(0.0)	0	(0.0)	2 (0.45)	0.51	0	(0.0)	0	(0.0)	1 (0.21)	1
Steroids	0	(0.0)	1	(0.41)	2 (0.45)	0.45	0	(0.0)	0	(0.0)	6 (1.25)	0.77
Vaccines	0	(0.0)	0	(0.0)	0 (0.0)	1	0	(0.0)	0	(0.0)	1 (0.21)	1
Vitamins and Supplements	1	(0.26)	3	(1.24)	10 (2.26)	0.04	0	(0.0)	2	(1.80)	15 (3.12)	0.49
Miscellaneous treatments	0	(0.0)	0	(0.0)	0 (0.0)	1	0	(0.0)	0	(0.0)	0 (0.0)	1

Shaded treatments are original survey options.

[a] Antimalarial category includes the following options from original survey: Artemether Lumefantrine, Artesuante-Amodiaquine, Dihydroartemisinin-piperaquine, Sulfadoxine-pyrimethamine, Quinine tablets, Chloroquine, Primaquine, Artesunate Injection, Rectal Artesunate, Intramuscular Artemether, and "other anti-malarial".

[b] Antibiotic category includes written-in antibiotics from the "other" response option and two categories from original survey: 1.) Cotrimoxizole 2.) 'other antibiotic'

[c] Antipyretic category includes written-in antipyretics and one category from original survey: 1). Antipyretic

Table 8. Mean number of treatments prescribed per outpatient in Mozambique, by fever status and RDT status

	Mean	S.D.
All outpatients	1.37	0.76
All febrile patients	1.47	0.74
Febrile, RDT+	1.48	0.61
Febrile, RDT-	1.49	0.68
Febrile, no RDT performed	1.46	0.84
All non-febrile patients	1.20	0.78
Non-febrile, RDT+	1.23	0.57
Non-febrile, RDT-	1.30	0.73
Non-febrile, no RDT performed	1.16	0.8

Table 9. Multivariate logistic regression showing correlates of receiving an antibiotic among surveyed outpatients in public health facilities in Mozambique.

	Crude Odds Ratio	P-value	Adjusted Odds Ratio	P-Value
Age				
*CU5	Ref	-	-	-
≥ 5 years	1.30	<0.01	0.76	0.23
Sex				
*Male	Ref	-	-	-
Female	1.24	0.02	1.05	0.82
Fever Status				
*Non-febrile	Ref	-	-	-
Febrile	0.76	<0.01	0.93	0.77
RDT Status				
*RDT-	Ref	-	-	-
RDT+	0.03	<0.01	0.03	<0.01

[b] Antibiotic category includes written-in antibiotics from the "other" response option and two categories from original survey: 1.) Cotrimoxizole 2.) 'other antibiotic'

[*] Asterisk indicates reference level within each variable

Appendices

Appendix 1. List of original and added survey categories for symptoms, diagnoses, and treatments

	Original survey categories	Added categories
Symptom Categories:		
	Fever	Diagnosis listed as symptom
	Chills	Miscellaneous complaint
	Weakness	Musculo-skeletal pain
	Joint Pain	Injury
	Seizures	Heart and chest symptoms
	Headache	Dermatologic symptoms
	Cough	Ears, eyes, neck, and throat symptoms
	Breathlessness	Respiratory symptoms
	Vomiting	Neuro-psychiatric symptoms
	Lack of Appetite	Genitourinary symptoms
	Stomachache	Gastro-intestinal symptoms
	Diarrhea	
	Other	
Diagnosis Categories:		
	Malaria	Symptom listed as diagnosis
	Pneumonia	Bacterial infections
	Enteric Disease	Fungal infections
	Anemia	Parasitic infections
	Ear Infection	Viral infections
	Eye Infection	General respiratory diagnosis
	Urinary Tract Infection	Other Injury
	Dermatitis	Other Gastro-intestinal diagnosis
	Trauma	Neuro-psychiatric diagnosis
	Undiagnosed	Other Skin/mucosal diagnosis
	Other (Please Specify)	Miscellaneous diagnosis
Treatment Categories:		
	Artemether-lumefantrine[AM]	Anti-convulsants
	Artesunate-amodiaquine[AM]	Anti-fungals
	Dihydroartemisinin-piperaquine[AM]	Anti-histamines
	Sulfadoxine-pyrimethamine[AM]	Anti-hypertenisves
	Quinine Tablets[AM]	Anti-parasitics
	Quinine Injection[AM]	Psychiatric medications
	Chloroquine[AM]	Anti-retrovirals
	Primaquine[AM]	Diabetes Treatments
	Artesunate Injection[AM]	Treatments for gastro-intestinal issues
	Rectal Artesunate[AM]	Other pain medications (not NSAIDs)
	Intramuscular Artemether[AM]	Rehydration treatments
	Other Antimalarial[AM]	Reproductive health treatments
	Cotrimoxazole[AB]	Respiratory treatments
	Other Antibiotic[AB]	Skin and mucosal topical treatments
	Antipyretic (Paracetamol, Aspirin etc)	Steroids
	Other	Vaccines
	No Treatment	Vitamins and Supplements
		Miscellaneous treatments

[AM] Indicates treatments condensed into "antimalarial" category for analysis

[AB] Indicates treatments condensed into "antibiotic" category for analysis

Appendix 2. Categorization of written-in symptom responses

Symptom Category	Included Responses	
Diagnosis listed as symptom	Candidiase oral	Infeccao urinaria
	Cardiopatia	Mastite
	Cárie dentario	Micose
	Gripe	Sarna
	Hernia	Sifilis
Miscellaneous complaint	Doente crónico	
Musculo-skeletal pain	Coluna vertebral/ dor de coluna vertebral	Dor de pés
	Dor e aquecimento dos pes	Dor na região cervical
	Dor de braco	Dor da regiao cervical esquerda
	Dor na coluna	Dor na regiao ingunal direita
	Dor das costela	Inch. Na nadega
	Dor lombar	Lombalgia
	Dor do membro inferior direito	
	Dor de pernas	
Injury	Acidente de trabalho	Ferida na regiao ocipital
	Dor do pe por picada de espinho de peixe	Queda
	Ferida	Traumatismo digital
	Fratura do braco direito	
	Ferida na perna	
Heart and chest symptoms	Control de Tensão	Hipertensão / HTA
	Dor toraxica / Dor torácica	Palpitacoes
	Dor da caixa toraxica	Palpitações cardíacas
	Dor do peito	Toracalgias
Dermatologic symptoms	Abcesso	Infecção na pele
	Aftas	Larva migrante cutânea
	Amargura na boca	Múltiplas pustulas e rash cutânea
	Borbulhas na cabeca	Múltiplas pustulas pruriginosas com erupção cutânea
	Borbulhas nas nadegas	
	Bolhas	Papula(s)
	Comichao / Comunchao	Piodermite
	Dermatite	Placas esbranquiçadas no assoalho da boca
	Dor de dente	
	Dor na lingua	Problema de pele
	Erupção cutânea	Prurido
	Ferida na boca	Rash cutânea com manchas hipercromicas pruriginosas
	Feridas na pele	
	Feridas no corpo	Sensacao de queimadura
	Feridas no assoalho da boca	Ulcerações orais
	Furunculo	Vesículas na pele

Appendix 2 cont. Categorization of written-in symptom responses

Symptom Category	Included Responses	
Ears, eyes, neck, and throat symptoms	Amidgalite	Dor de olhos
	Conjuntivite	Dor de pesc. E borbulha
	Constip. / Constipa. /	dor do pescoço
	Constipação / Constipaxao	Dor e verimelhidao dos olhos
	Coriza	Dor da vista
	Corrimento	Hematoma dos olhos
	Dificuldade de deglutir	Inchaço no pescoço
	Disfagia / Disfagia a solidos	Odinofagia
	Dor a engolir	Otite
	Dor d garganta	Pescoço
	Dor e inflamação dos olhos	Problemas oculares
	Dor da orelha	Rinorreia
	Dor de ouvido	Vista
Respiratory symptoms	Asma	
	Problemas respiratorio	
Neuro-psychiatric symptoms	Delírio	Sustos
	Ontura	Tontura
	Formigueiro nos pés e mãos	Tremores e sustos
Genitourinary symptoms	Aminorreia	Massa ma mama
	Corrimento uretral	Prurido vaginal
	Desmenoreia	Prurido escrotal
	Disuria	Sangramento vaginal
	Dor ao urinar.	Secrecoes na vagina
	Feridas no sexo	Úlceras genitais
	Hematuria terminal	Urina com sangue
Gastro-intestinal symptoms	Diarreia cm sangue	Náuseas
	Dor de baixo ventre	Orn a regiao umbilical

Appendix 3. Categorization of written-in diagnoses

Diagnosis Category	Included Responses	
Symptom listed as diagnosis	Anorexia	Febre / Febres
	Aumento do volume abdominal	Inchaço no pescoço
	Cefaleia	Leucorreia
	Colicas Abdominais	Lombalgia
	Constipação	Problemas da pele
	Diarreia	Problemas de visao
	Disturbios abdomens	Renite
	Dor abdominal	S febril / Sind febril
	Dor da barriga	Tontura
	Dor de cabeça	Tosse
	Dor ao urinar	
Bacterial infections	Dip.	Infeccao urinaria
	Sífilis	
Fungal infections	Candidiase oral	
Parasitic infections	Larva migrante cutânea	Sarna
	Micose	Shistossomiase
	Parasitose intestinal	
Viral infections	Amigdalite	Seropositivo em Tarv
	Gripe	Sida
	Herpez zoster	Sp em tarv
	HIV	Vinha na consulta tarv
	IVRS	
General respiratory diagnosis	Asma	
Other Injury	Ferida	Fratura do radio direito
Other Gastro-intestinal diagnosis	Desinteria / dinsetaria	Hernia
Neuro-psychiatric diagnosis	Enxaqueca	Sind reumatico neuropatia - periferica
	Epilepsia	
	Neuropatias perifericas	
Other Skin/mucosal diagnosis	Abcesso	Cojutivite / Conjuntivinte/ Conjuntivite
	Aftas	
	Borbulhas	Hematoma peri orbital
	Carie dentario	

Appendix 3 cont. Categorization of written-in diagnoses

Diagnosis Category	Included Responses	
Miscellaneous diagnosis	Acrtrite	Hipertensão arterial
	Alergia	HTA
	Aminorreia	Infecção tecidos moles
	Anemia moderada	Mastite
	Artrite	Massa nas mamas
	Capite	Suspeita de gravidez
	Gea	Tensão
	Hipertensão	Tensao alta

Appendix 4. Categorization of written-in treatments

Treatment Category	Included Responses	
Antibiotics (written-in)	Acido naldixico/	Fenoximetilpenicilina
	Amoxicilina/Amoxic/Amixicilina susp	Fenoximetil (comp, cp)
	Amoxacilina xarop	Fenoximetil penic comp
	Azitromicina / Acido Nalidicico	Fenox xarop
	Ciproflaxacina	Metronidazol
	Clorafenivol cps	Penicilina Procaina
	Clorafenicol susp 1f	Smocicilina caps (misspelling)
	Clorafenicol pomade oftalmica	Tetraciclina
	Conjuntivente	Tetraciclina pomade
	Cotrimoxazol	Tetraciclina pomade oftalmica
	Doxiclina	
	Eritrimicina/Eritromicina/Eritromicina/ Erkitromicina	
Anti-convulsants	Carbamazepina	
Anti-fungals	Clotrimazol	Nistatina susp.
	Clotrimazol crème	Nistantina
	Griseofluvina	Tiabendazol pomada
	Ketoconazol	
Anti-histamines	Clorfeniramina / Clorafeniramina / Clorafeniramina xarop	Prometazina xarop
Anti-hypertenisves	Co amilorido	
Anti-parasitics	Albendazole / Albandazol	Benzil benzeto de sódio
	Mebendazol	
Psychiatric medications	Tiorizina	
Anti-retrovirals	Antiretroviral / ARVs/MARVs	Arvs tenofovir compost

Appendix 4 cont. Categorization of written-in treatments

Treatment Category	Included Responses	
Diabetes Treatments	(None in Mozambique data set)	
Treatments for gastro-intestinal issues	Buscopam	Omeprazol
	Butilescoplamina/butilescopolamina	Ranitidina
	Hidroxido de aluminio	
Antipyretics/NSAIDs (written-in)	Ácido acetilsalicilico	Iboprofeno / Ibuprofeno
	Acido acitil salicilico	Ibuprofen susp.
	Aspirina	Paracetamol
	Diclofenac comp	Paracetamol xarop
	Diclofenac injetavel	
Other pain medications (not NSAIDs)	(None in Mozambique data set)	
Rehydration treatments	Sro	Soro fisiologico
Reproductive health treatments	(None in Mozambique data set)	
Respiratory treatments	Ambruxul	Hidrocortizona xarop
	Aminofilina	Salbutamol / Salbtamol
	Cloridrato de Ambroxul	Sminofilina
Skin and mucosal topical treatments	Soro fisiologico gotas nasais	Fisan po com axido de zinco
Steroids	Prednisolona	Predinizelona ampola
Vaccines	Vacina anti tetanica	
Vitamins and Supplements	Acido ascorbico	Salferoso acido folico
	Acido folico	sf+af comp
	Complexo B	Sulfato ferroso
	Multivitamina	Sulfato de zinco
	Sal ferrosol	
Miscellaneous treatments	(None in Mozambique data set)	

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