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Age Group Shift of Fever as a Predictor of Malaria as Transmission Decreases in Western Kenya

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ABSTRACT

Over 1 billion episodes of febrile infections occur each year, and they are the primary cause of medical visits among those living in underdeveloped areas. Most of these non-malarial febrile fevers are presumptively treated with antibiotics, and this could lead to long-term unwanted consequences such as drug resistance. We examined and determined the incidence and predictors of non-malarial febrile illnesses in a Kenyan area of unstable, low malaria transmission. A 5-year (2013–2017) retrospective study was carried out at two health facilities in the Kenyan highlands of Kipsamoite and Kapsisiywa, Nandi County. The patients who presented to any of the health facilities within the study area with fever were tested for clinical malaria and classified as having malarial fever or non-malarial febrile. Frequency distribution tables were generated to show the prevalence of non-malarial fever in the context of place, person, and time. A confidence interval (CI) of 95% was used to assess statistical significance. The incidence of non-malarial febrile illnesses remained relatively low in children under 5 years of age. During the 5-year period, there was a general drop in the cases of non-malarial fever in December of each year. A total of 644(50%) of participants presented with fever. Of these, 12 (2%) had febrile malaria. This means that 632 (50.1%) of the individuals were suffering from a non-malarial febrile illness. The prevalence and incidence of malaria were generally very low (2%) during the five-year period. The highest incidence for children under the age of 5 and those 5–15 years of age was recorded in July 2013, while individuals above 15 years had the highest incidence in May 2017. It was observed that there was no consistency in the incidence of fever, as shown by the peaks, over time. During the 5-year period, there is a general drop in the cases of non-malarial fever in December of each year. Only two peaks (May 2017 and September 2017) of the incidence of non – malarial fever match with incidence of fever for > 15 years. Only two peaks (July 2013 and May 2017) of the incidence of non – malarial fever match with incidence of fever for 5 – 15 years. None of the peaks for the incidence of non – malarial fever match with incidence of fever for < 5 years.

KEYWORDS: *Non-Malarial Febrile Illness*

INTRODUCTION

Since the inception of the "test before treat approach" and the rolling out of the mRDT there has been emerging evidence that a high proportion of febrile illnesses are non-malarial although such febrile illnesses have, in the past, been treated presumptively as malaria. This has been especially the case in malaria endemic areas with limited laboratory resources.

Furthermore, the implementation of malaria elimination protocols in low resource settings of sub-Saharan Africa such as the use of treaded bed nets and Artemisinin-based Combination Therapies (ACT) has resulted in a drastic decline in malaria transmission and hence reduced incidence and prevalence of malaria. it has however been noted that the prevalence and incidence of non – malarial fever still remains high in most malaria endemic areas.

A study conducted in a Kenyan area of unstable, low malaria transmission confirmed that this is the case. This study showed that out of the 3420 individuals who presented with fever during the five-year period of study (2007–2011), *Plasmodium falciparum* and *Plasmodium malariae* were confirmed in 224 (6.5%) and 3 (0.09%) individuals, respectively. Out of the 224, 36 (16.1%) were children under 5 years old, and 188 (83.9%) were ≥ 5 years of age. Even though these were treated using the appropriate standard of care, 93.4% of those who presented with non-malaria fever were unaccounted for. Despite the several cases of non-malarial fever, there is limited epidemiological data on the prevalence and incidence of Non-Malarial Febrile Illnesses (NMFIs) in low resource settings with limited research.

We conducted a study to determine the prevalence and incidence of NMFIs in an area of unstable low malaria transmission, Nandi County, Kenya. The prevalence of NMFIs was described in terms of person and place. The incidence was described in terms of person and time. This was done using data that was collected from the study sites between 2013 and 2017.

METHODS

Study Sites

The study was based in Kipsamoite and Kapsisiywa, Nandi County, from 2013 to 2017. These sites are at 2,132 m and 1,887 m above sea level, respectively. Both sites lie between 0º16`55.64ºN to 0º21`52.40ºN latitude and 34º59`7.17" E to 35º5`19.90" E longitude. A mountainous, rocky forest borders the western side of Kipsamoite, and a marsh encircles the eastern portion of this research area (Ernst *et al*., 2006). People living in these areas are predominantly Nandi, a Kalenjin sub-tribe. The major occupations of the residents in this study area are cash crop farming (sugarcane and tea), subsistence farming (maize, vegetables, and beans), and livestock farming (cattle and chicken). The area has **a history of previous malaria epidemics and an unstable, seasonal, and unpredictable malaria transmission**. In both sites, malaria incidence is highly seasonal. Heavy rains are usually experienced from late March to early May. This usually causes malaria cases to rise during June and July (Cohen et al., 2008). The most common vector of *P. falciparum* is *Anopheles gambiae s. l.* (Ernst *et al*., 2006). There are only two health centers within the study site, and patients are not charged for the services offered.

Study Design

A retrospective study encompassing the review of the demographic and clinical data collected from the study sites between 2013 and 2017 was done. The clinical data included medical symptoms while the demographic data included age and sex, displayed or reported by the visiting individuals.

Study Population and Recruitment

Study participants were drawn from the seven villages of Kipsamoite and the ten villages of Kapsisiywa. All those who had visited the health facilities at the study sites and were diagnosed with non-malarial febrile syndrome with or without a combination of other symptoms were included in the study.

Inclusion Criteria

All people of any age who are long-term residents of the two study sites and had no plans to relocate before the completion of the study were taken into consideration for participation.

Exclusion Criteria

Missing data cases were specifically omitted from the study if the sex, age, and clinical diagnosis were not available.

Sampling Procedure

This study used existing data (targeting those who visited the facilities with fever) collected from the study sites during the period from 2013 to 2017. Due to the low malaria transmission, a site-wide sampling approach was used to ensure that as many fever cases as possible were captured (Gibbons & Coleman, 2001). The data was filtered to include only cases of non-malarial febrile illnesses. Study participants were recruited into the study after a full introduction of the study to them and upon giving their full informed consent.

Sample Size

During the period 2013–2017, a total of 2,760 individuals reported to the facility. Out of these, 1,453 (52.6%) reported having a fever. Of those that reported that they had fever, clinical fever (axillary temperature ≥ 37.5^0) was confirmed in 463 (31.9%) individuals only. Furthermore, microscopic examination of the blood smears of the 463 individuals with clinical fever revealed that 155 (33.5%) individuals had *P. falciparum*, 2 (0.4%) individuals had *P. malariae*, while *P. ovale* and *P. vivax* were not detected in any of the patients. This implies that 306 (66.1%) individuals did not have clinical malaria, although they had confirmed clinical fever. However, of the 1,453 individuals who reported to have had fever when they reported to the clinic, 156 (10.7%) individuals had *P. falciparum*, 2 (0.4%) individuals had *P. malariae*, while *P. ovale* and *P. vivax* were not detected in any of the patients. This implies that 89% of those who reported having a fever did not have clinical malaria.

DATA COLLECTION METHODS

This study used secondary data collected by the clinicians in the two health centers within the study sites during the period 2013–2017. This includes demographic data and clinical symptoms. During data collection by the clinicians, a unique study number was assigned to each study participant.

Surveillance for Non-Malaria Fever with Combination of Symptoms

Demographic surveys and non-malaria fever surveillance were conducted in these locations during the data collection for this study. Every year, household demographics were conducted. The only medical facilities in the region are the dispensaries run by the Kenyan Ministry of Health, which were monitored for non-malarial fever at both locations. All local residents were given a free malaria test and treatment. By microscopic analysis of blood smears, individuals with malaria-like symptoms who lacked a clear alternative diagnosis were checked for Plasmodium species. Local clinical officers examined the following symptoms: fever, chills, headache, nausea, vomiting, loss of appetite, jaundice, diarrhea, backache, joint problems, and severe malaise.

Further to this, the following data on the participants were also collected: village of residence, household number, age, and gender. Artemether-lumefantrine (Coartem) was administered to all subjects who had positive blood tests for Plasmodium falciparum or Plasmodium malariae (the only Plasmodium species identified in this region)..

Keen attention was, however, paid to those patients with fever and negative blood smears for Plasmodium falciparum and Plasmodium malariae, the most common species in this area. These were mapped by age.

CLINICAL AND LABORATORY PROCEDURES

Blood Collection

Blood samples from the study participants were taken by the physicians as part of the data collection for this study in order to check for Plasmodium spp. in the blood. The procedure of finger-pricking was used for this. A microtainer tube was used to collect about 0.5 cc of blood. Field blood samples were collected, stored in a cold box, and transported to the lab. The blood samples were stored at -30ºC after being centrifuged at 10,000 rpm for five minutes on the same day they were collected.

Recording of Clinical Manifestation

Clinicians in the Kapsisiywa and Kipsamoite used special clinical forms to record all the clinical symptoms of all individuals presenting at the facilities. Fever was measured as an axillary temperature ≥37.5ºC using a thermometer.

Testing for *Plasmodium Spp.* using Microscopy

Giesma stain was used to stain dry, thick, and thin blood smears for 30 to 40 minutes. After that, clean water was used to clean and rinse the stained smears. After drying, the slides were placed under the microscope and inspected using oil immersion (X100) with the film pointing down.

Other Symptoms

Where a patient is not diagnosed with clinical malaria, Form C10 is filled out to establish and record the other symptoms the patient had. These symptoms included headache, jaundice, loss of appetite, vomiting, diarrhea, backache, chills, joint pains, nausea, and severe malaise.

Data Analysis

Data was analyzed using STATA (STATACORP, version 16, College Station, Texas, USA). A Chi-square test was used to determine the association between each symptom (headache, appetite loss, chills, joint pains, vomiting, malaise, backache, nausea, diarrhea, and jaundice) and non-malarial fever.

Bivariate and multivariate regression was used to evaluate the predictors associated with episodes of fever. Statistical significance was assessed using a confidence interval (CI) of 95%.

Data Management

All the study participants were assigned a unique study number. The data were entered as per the standard operating procedure.

ETHICAL CONSIDERATION

Ethical approval for the study was obtained from the Moi Teaching and Referral Hospital Institutional Research Ethics Committee (MTRH/MU-IIREC). A copy of the most recent approval has been attached as Appendix 3. Each participant in the study had to sign a consent form twice in order to participate voluntarily. The participant (a parent or guardian in cases involving children) kept one copy. Participants who were unable to sign the consent form left their thumbprints in the witness form, which was also signed by a literate witness. Participants in the study were informed and given the option to end participation at any time.

RESULTS

Demographic Characteristics

Between 2013 and 2017, we collected data from 651 (51% of participants) in Kipsamoite and 628 (49% of participants) in Kapsisiywa sites in Kenya. Of the 1279 participants, 583 (45.58%) were male and 696 (54.42%) were female. The age of the participants ranged from

0.15 to 92.55 years. The mean (SD) age was 25 (19.2) years. Table 1 shows the demographic characteristics of the study participants by age and site.

The experimental site is located in the drier sub-region of the Central Cropping Region, which is the central non-irrigated agricultural region of the country.

Data from the agro-meteorological station of Darkhan-Uul province in 2022 and 2023, where the experience research was conducted, was taken and used.

In 2022, when the research was carried out, the average monthly temperature during the growing season was 0.4 degrees lower than many years average, the sum of active heat was 108.3 degrees, and the amount of precipitation was 39.2 mm less, which indicates that there was a lot of drought. During the plant growth period of 2023, the sum of active heat above 10°C is 54.6°C higher than many years average, 147.9 mm more than many years average, and the distribution is 6.7 mm less than many years average in May, 19.4 mm in June, and 54.3 mm in July, with 24.1 mm in August and 56.8 mm in September, respectively.

The humus layer of the field is 35-40 cm, with 1.52% humus and a neutral. According to the level of nutrient supply for rapeseed cultivation determined by the agrochemical laboratory of the Institute, the nitrogen (NO3-N) in plant digestible form is 1.79 mg/100 g or very little, and it is a sufficient soil with phosphorus and potassium.

Planting was calculated at the rate of 2 million seed per hectare and was sown at a depth of 2-3 cm with the Omichka-SKP-2.1 seeder. The total experimental area was 0.25 ha, the size of 1 plot size was 105 m^2 (2.1 width, 50 m length) in 4 repetitions sowed on May 25.

Table 1. *Demographic characteristics*

Characteristic		**Overall**	**Kipsamoite (n=651)**	**Kapsisiywa (n=628)**
Age (yrs) mean(sd) median(range)		25 (19.2); 21.14 (0.15, 92.55)	25 (18.8); 20.36 (0.71, 90.91)	26 (19.6); 21.45 (0.15, 92.55)
Gender	Female n/N (%)	583/1279 (46%)	275/651 (42%)	308/628 (49%)
	Male n/N (%)	696/1279 (54%)	376/651 (58%)	320/628 (51%)
Age Category	>15Yrs n/N (%)	798/1279 (62%)	403/651 (62%)	395/628 (63%)
	5 - 15 Yrs n/N (%)	343/1279 (27%)	165/651 (25%)	178/628 (28%)
	<5 Yrs n/N (%)	138/1279 (11%)	83/651 (13%)	55/628 (9%)

Prevalence of of Malarial Fever and Non-Malarial Fever

Clinical fever was confirmed in a total of 632 (49% of participants). The prevalence of malarial fever was a shown below

Table 2*. Prevalence of Malarial Fever and Non-Malarial Fever by Site and characteristics*

Characteristic		**Overall**	**Kipsamoite (n=651)**	**Kapsisiywa (n=628)**
Malaria/Fever by age				
>15 Yrs	Malarial Fever n/N (%)	97/332 (29%)	20/104 (19%)	83/228 (36%)
	Non-Malarial Fevern/N (%)	235/332 (71%)	84/104 (81%)	145/228 (64%)
5 - 15 Yrs	Malarial Fevern/N (%)	86/192 (45%)	23/54 (43%)	65/141 (46%)
	Non-Malarial Fevern/N (%)	106/192 (55%)	31/54 (57%)	76/141 (54%)
<5 Yrs	Malarial Fevern/N (%)	13/105 (12%)	7/61 (11%)	6/44 (14%)
	Non-Malarial Fevern/N (%)	92/105 (88%)	54/61 (88%)	38/44 (86%)

Monthly Incidence of Malarial Fever and Non-Malarial Fever

The highest incidence of NMF for children under the age of 5 was recorded in March 2013, September 2013 and March 2014. The peaks of Malarial and NMF do not match. For 5–15 years of age the incidence of malarial fever had highest peaks in June 2013 and May 2017. The peaks of malarial and non-malarial fever show

similarities between May – August of each year. This was the case with participants aged > 15 years. During the 5-year period, there is a general drop in the cases of non-malarial fever in December of each year.

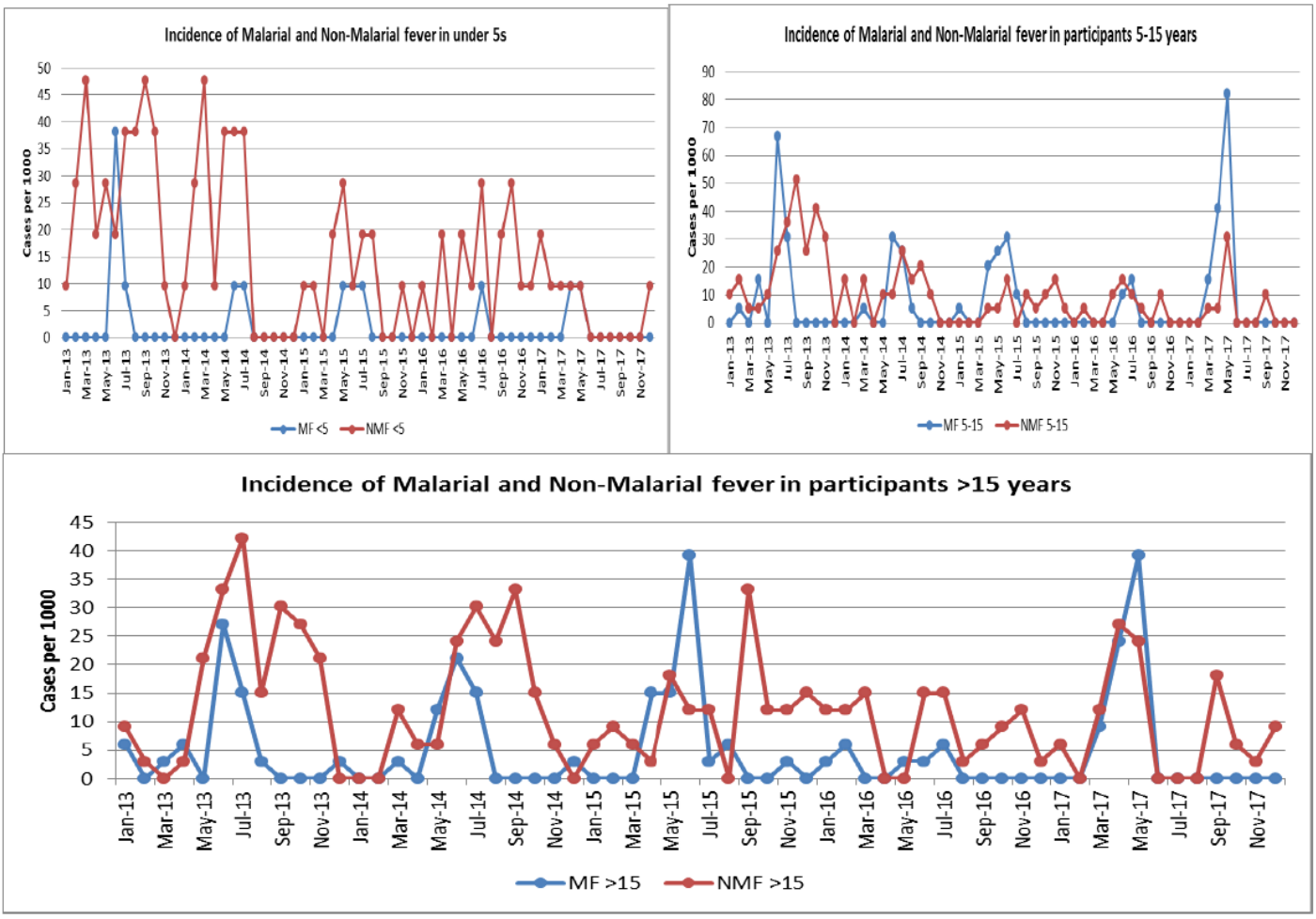

Figure 1. *Monthly Incidence of Fever and Non-Malarial Fever*

DISCUSSION

This study established that the incidence of non-malarial febrile illness had similar peaks during the five-year study period across all the age categories. The highest peak was observed in July 2013, and similar peaks were noted in April–May and July–September. This study area receives heavy rainfall during the April–May period, with a precipitation count of up to 285.09mm. It has been reported that precipitation alters natural and constructed ecosystems in ways that favor the spread of vector-borne and waterborne infectious illnesses, principally in relation to mosquito vectors (Aune et al., 2021). Even in locations where disease risk was previously low, the rates of mosquito-borne illnesses rise considerably because of the quantity of adequate breeding places following severe rainfall accompanied by floods (Waring & Brown, 2005). It has been documented that the monsoon season usually brings with it common monsoon diseases and infections, which include water-borne, air-borne, and bacterial and viral infections, including but not limited to Dengue, Chikungunya, Viral Fever, pneumonia, and the common cold and Flu (Chowdhury et al., 2018). This means that the vector transmitting the plasmodium bacteria could also be transmitting other pathogens within the population, or rather, there could be other vectors within the population transmitting fever-causing pathogens (Atkinson & Springer, 2010). For example, the female Aedes mosquito (*Aedes aegypti)* transmits the dengue fever to humans. Usually, the region experiences its highest rainfall beginning in April of every year. Thus, there is an upsurge in the quantity of vectors throughout this period due to increase in the number of breeding sites occasioned by stagnant waters and bushy areas. In addition, the increasing rate of growth in the population of the area has caused people to live in environmentally fragile places such as swamps and water catchment areas, further exposing them to disease vectors (Kenya, 2013).

Given the rising impacts of pollution, global warming, and climate change, the World Health Organization reports that unhealthy environments account for more than 12 million deaths annually (World Health Organization, 2016). The results in Chapter 4 above show a high prevalence of uncharacterized fever, which, if not addressed, may soon be a principal cause of ill

health and mortality in the area. Additionally, it is anticipated that climate change would have a direct impact on zoonotic infectious disease transmission by altering a vector's geographic range (Bezirtzoglou et al., 2011). Although several researchers have attempted to describe the epidemiology of highland malaria in Kenya, few have paid attention to the non-malarial cases of fever. For instance, Arness et al. (2003), in their study "**Epidemiology of highland malaria in western Kenya,**" attributed the new malaria cases to travel to holoendemic areas. Mutanda et al. (2014), on the other hand, focused on the association between fever and malaria in their study titled "**Sensitivity of fever for diagnosis of clinical malaria in a Kenyan area of unstable, low malaria transmission,**" thus ignoring the high cases of non-malarial fever.

Most children under the age of 5 have a high probability of developing fever as a result of an infection (Mutanda et al., 2014). This is evidenced by the high number of non-malarial febrile cases in children under the age of 5 years (84%). This also implies that people aged between 5 and 15 years and those aged > 15 years had a substantial protective effect against fever (Holtzclaw, 2020). The prevalence and incidence of malaria were generally very low (2%) during the five-year period. This is attributed to the fact that the area has a low transmission of malaria and standard procedures like insecticide-treated bed netting and indoor residual spraying are available in the area.

A comparison of the annual incidence of non-malarial fever by site revealed that the findings were not statistically significant. This is because the two areas are subjected to similar environmental conditions and have relatively similar populations.

The implementation of the malaria prevention protocols in the study area reduced malaria transmission. However, the peaks for fever and non – malarial fever in the 5 – 15 age group continue to agree over the study period. This implies that fever continues to predict malaria in this age group.

This study has shown that in a highland area of unstable low malaria transmission, there are numerous cases of non-malarial fever in children < 5 years, 5–15 years, and individuals > 15 years of age. The incidence of non-malarial febrile illness and the incidence of malarial fever are inconsistent over time suggesting that the causes are different. As such, clinicians should be advised accordingly.

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