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Epidemic Malaria in a Protracted Refugee Situation:
Implications for Prevention and Control

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Epidemic Malaria in a Protracted Refugee Situation: Implications for Prevention and Control

By

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B.S.
University of Arkansas
2015

Thesis Committee Chair: Jorge Vidal, PhD

An abstract of
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Abstract

Epidemic Malaria in a Protracted Refugee Situation:
Implications for Prevention and Control
By Griffin Sonaty

Background: Malaria is a risk to many in refugee settlements in sub-Saharan Africa. Population movement, food insecurity, and lack of sustained preventive measures can coalesce with environmental factors suitable for malaria transmission to enable epidemics in semi-arid regions. Displacement crises present challenges in epidemic detection and response, and few studies have examined the morbidity, mortality, and case management of malaria in refugee settlements. The purpose of this assessment was to describe the epidemiology of malaria in Kakuma refugee camp in the context of an upsurge in late 2015 following El Niño rains to inform recommendations for prevention and control.

Results: Malaria incidence rate for December 2015 and January 2016 exceeded a 5-year C-SUM epidemic threshold. From January 2010 to July 2016, monthly malaria incidence rate increased, on average, by 0.0165 cases per 1,000 persons per month, ($R2 = 0.134$, $p < 0.0001$). A census of clinic registers from December 2015 and January 2016 revealed heterogeneities in confirmed malaria burden across age, sex, and location of residence: those aged 12–17 were at the highest risk compared to adults aged 18–59, OR=2.57 (95% CI: 2.47-2.67). Males were at higher risk compared to females, OR=1.16 (95% CI: 1.12-1.19). Hot spots of malaria incidence among refugees under five were detected in Kakuma I sub-camp using Anselin Moran's I at a fixed-distance band value of 585 m. Differential management of malaria cases was observed across the six outpatient clinics in Kakuma.

Conclusions: Epidemic malaria was detected in a semi-arid protracted displacement crisis following climatic abnormalities and reports of food insecurity. Geographic and demographic heterogeneities were detected, but incidence was high throughout the camp. Intervention measures should include universal coverage and community promotion of long-lasting insecticidal nets; clinician refresher training on malaria case management; monitoring of malaria diagnostic and therapeutic stocks; and vector control, such as indoor residual spraying, to decrease the baseline malaria incidence**.**

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Chapter 1. Introduction

Overview

Malaria is a persistent threat in many refugee camps in sub-Saharan Africa. Malnutrition, ongoing population movement, and chronic underfunding for preventive measures can promote conditions suitable for malaria transmission [1]. Although many refugee settlements are located in areas with high malaria risk, there is a dearth of evidence in the literature on malaria-associated morbidity, mortality, and environmental risk factors in camp settings, especially in semi-arid regions with epidemic potential. Although epidemics of malaria have been described in settings with displaced populations, the comparative magnitude is often difficult to assess when historical data are unavailable or not presented. There is also little evidence on the quality of case management during epidemics in these settings. In addition, while geographic and demographic heterogeneities in malaria morbidity and mortality are known to occur across a variety of settings, very few studies have described the epidemiology of malaria in refugee settlements [2].

In late 2015, an upsurge in malaria cases was noted in Kakuma refugee camp following heavy *El Niño* rains. Located in semi-arid northwestern Kenya, the camp has previously experienced epidemic malaria, and entomological surveys have identified *Anopheles arabiensis* larvae year-round in drainage pits associated with tap-stands [3]. However, it was unclear whether changing case burden in late 2015 to early 2016 reflected seasonal transmission, a true epidemic, or a transition to a higher baseline level of endemicity. To answer this question, trends in malaria incidence over the previous six years were evaluated to determine whether an outbreak occurred in late 2015 and early 2016. Data collected from a census of clinic registers during the upsurge were analyzed to describe demographic characteristics of cases and to evaluate clinical practices and malaria case management in the camp. Geospatial analysis of incident malaria cases was

undertaken to identify potential malaria hot spots and risk factors, including differential coverage of control measures. To provide recommendations for future epidemic preparedness and response, these factors are assessed in the context of a malaria upsurge from December 2015 to January 2016 in Kakuma refugee camp.

Situation in South Sudan and Somalia

According to the United Nations High Commissioner for Refugees (UNHCR), the displacement crisis affecting the people of South Sudan is currently the worst in Africa, with over 1.4 million South Sudanese refugees in neighboring countries and 1.8 million internally displaced people at the end of 2016 [4]. Prior to December 2013, there were already over 120,000 South Sudanese refugees in neighboring countries. Reignited conflict and food insecurity beginning in December 2013 prompted an efflux of 645,000 refugees out of South Sudan to neighboring countries through 2015 [5]. Continued armed conflict drove over 750,000 additional South Sudanese people into neighboring countries in 2016 [4]. Most have fled from the eastern lowland states of Jonglei, Unity, Upper Nile, Central Equitoria, and Eastern Equitoria [6, 7]. The major reception countries around East Africa include Uganda, Ethiopia, Sudan, Kenya, and the Democratic Republic of the Congo [5]. Despite attempts to provide diplomatic solutions to the conflict—such as the formation of the Transitional Government of National Unity in early 2016—rising inflation and continued instability are expected to displace an additional half million people from South Sudan through 2017 [8].

Elsewhere in eastern Africa, Somalia continues to be one of the highest-ranking countries-of-origin for refugees, with almost one million in neighboring countries in mid-2016 [9]. This protracted crisis continues to displace Somalis to Kenya, Yemen, Ethiopia and Uganda, with reports of further conflict and famine in rural areas through 2016 [10]. However, the predicted

number of Somali refugees in Kenya for 2017 is unstable due to efforts to encourage voluntary repatriation of Somali refugees from Dadaab, with pledges from UNHCR and partners to support the repatriation process following appeals from the government of Kenya to close the camp [10, 11]. In addition to voluntary repatriation of Somalis, UNHCR plans to help relocate non-Somali refugees—and those awaiting resettlement to a third country—to Kakuma refugee camp in northwestern Kenya [12]. These influxes of refugees from South Sudan and Somalia have continued to grow Kakuma camp beyond its capacity.

Kakuma Refugee Camp

UNHCR established Kakuma refugee camp in 1992 in response to the influx of adolescents fleeing southern Sudan and settling in Turkana county along the East African Rift in northwestern Kenya [13]. This semi-arid district is characterized by extended periods of dry, hot weather, with brief periods of rainfall around April and November—annual mean rainfall is limited to 200mm [14]. Originally developed to host 80,000 refugees, Kakuma has grown over the years: the camp hosted more than 185,000 refugees at the beginning of 2016, 51% of whom were from South Sudan, 30% from Somalia, and most the remainder from Sudan, Democratic Republic of Congo, Ethiopia, Burundi, Uganda, Rwanda, and Eritrea [15]. While there are typically 10,000-15,000 newly registered refugees per year, there were 45,627 new arrivals in 2014, primarily from South Sudan [16]. Of note, global acute malnutrition was 11.4% among children under five in November 2015, up from 7% in November 2014 [17].

Kakuma is organized into sub-camps, zones, and blocks which consist of households. Of the four sub-camps, the newest is Kakuma IV, where 70% of those arriving after December 2013 are settled, and 91% of the population are from South Sudan, according to a 2014 livelihood survey [18]. Half of those living in both Kakuma II and III are from Somalia, while the oldest section,

Kakuma I, is demographically heterogeneous. The average length of stay in the camp is 10 years. Around 8.2% of households owned at least one business in 2014, and over 20% of households had at least one member working, although refugees in Kenya are not legally permitted to work in the formal sector [18]. Much of the informal sector is involved in trade with the host Turkana community in nearby Kakuma town, where refugees can travel without a permit [19]. Some members of the host community also attend schools in Kakuma camp.

Health services in the camp are provided by International Rescue Committee (IRC), which administers two inpatient hospitals and six outpatient clinics. However, the clinics are often understaffed, with the number of consultations per clinician per day regularly exceeding the standard of 50 [20]. Essential medicines on the WHO-Kenya MOH list are procured by UNHCR [13]. IRC also supports a cadre of community health workers who conduct community mobilization activities. Water, sanitation, and vector control activities are implemented by Norwegian Refugee Council, while the National Council of Churches of Kenya is responsible for shelter construction. Long-lasting insecticide-treated nets (LLINs) are distributed by UNCHR to pregnant women and children under five at prenatal and child wellness visits.

Malaria Clinical Presentation

Malaria is an acute febrile illness caused by parasitic infection with protozoan Plasmodium species. The most common of these, *Plasmodium falciparum*, is associated with increased risk of complications, particularly cerebral malaria, severe anemia, renal failure, and death [1]. It was identified as the species in 99% of malaria infections in the 2006 assessment at Kakuma [3]. Uncomplicated malaria with *P. falciparum* can be characterized by any combination of fever, chills, headache, myalgia, fatigue, vomiting, cough, diarrhea, and abdominal pain. Progression to severe malaria is indicated by convulsions, pulmonary edema, circulatory collapse, and coma.

Those at highest risk of complications include children under five years of age, pregnant women, and immunocompromised individuals [1]. Since repeated infection with *P. falciparum* can eventually lead to diminished clinical sequelae, an age-profile of clinical presentation for malaria is typically present in highly endemic settings [2].

Malaria Epidemiology

Malaria is endemic in 91 countries, with 91% of cases occurring in sub-Saharan Africa [21]. While worldwide incidence and mortality rates have decreased by 41% and 62%, respectively, since 2000, there is still a considerable burden: there were an estimated 212 million cases and 429,000 deaths due to malaria worldwide in 2015 [21]. With some of the largest displacement crises occurring in malaria endemic areas of Africa, malaria is a substantial health risk to millions of refugees and internally displaced persons in the region [1]. In an analysis of UNHCR health information systems from 90 camps from 2006-2010, Hershey and colleagues found that malaria was the largest contributor to morbidity and mortality in refugees under five years old across Africa [22]. High burdens of global acute malnutrition, which can be much higher than surrounding host communities, contribute to this increased risk of malaria complications in African refugee camps due to the increased susceptibility and subsequent parasite density in hosts [22, 23].

Malaria Vectors

The primary vectors for transmission of malaria-causing parasites to humans are female Anopheles mosquitoes. Species of the *An. gambiae* complex constitute the most efficient *P. falciparum* vectors and are the dominant vector species across most of Africa [24]. In northwestern Kenya, the dominant vector is *An. arabiensis*, which thrives in semi-arid environments [24, 25]. It transmits *P. falciparum* to humans during the time from sunset to sunrise [24]. *An. arabiensis* has

also been described as exhibiting more exophilic, zoophilic, and exophagic activity than *An. gambiae s.s.*; though heterogeneity in preference is observed across environments [26, 27]. It has been observed that *An. arabiensis* may also adapt feeding and resting behavior in response to vector control strategies like indoor residual spraying [28]. The larval stage of *An. arabiensis* can survive a broader array of habitats than other *An. gambiae* species, including small and large man-made reservoirs and turbid pools [24, 29]. Larval reproduction persists through dry seasons if man-made reservoirs are present in arid regions—otherwise adults may enter aestivation or migrate without habitats for oviposition [29-31]. The cyclical density of vectors through dry and wet periods typically reflects the incidence of malaria over these periods in semi-arid regions.

Chapter 2. Review of Literature

Malaria in Kenya

Malaria endemicity throughout Kenya is dictated primarily by environmental factors. The semi-arid regions of the North and East are classified as seasonal low-transmission zones, which typically have malaria parasite prevalence estimates of less than 10% in children, consistent with the Malaria Atlas Project classification of intermediate risk [32]. Modelled *P. falciparum* prevalence in children 2-10 years old ($Pf\text{PR}_{2\text{-}10}$) for Rift Valley Province, where Kakuma is located, was 8.98% (UI: 3.16 - 21.92%) in 2015 [33]. In contrast, the lake endemic region of Kenya, in the Western Province, had $Pf\text{PR}_{2\text{-}10}$ of 21.81% (5.39 - 49.37), characteristic of an intermediate transition region [33]. These differences in prevalence guide the strategy of the National Malaria Control Programme [34]. The Kenya plan for malaria control in semi-arid seasonal transmission zones focuses on case management, epidemic preparedness and response, surveillance, and behavior change. Vector control and intermittent preventive treatment during pregnancy are added priorities in endemic and highland epidemic zones [34]. LLINs are distributed by the National Malaria Control Programme in endemic and highland epidemic zones through periodic mass distribution, antenatal care, social marketing, and private sector shops. Indoor residual spraying (IRS) is not routinely conducted in Kenya, and larval source management is restricted to areas with easily identifiable habitats [34]. Despite this regional targeting, the 2015 Kenya Malaria Indicator Survey showed that 52.4% of households surveyed in semi-arid seasonal transmission zones owned at least one LLIN, most of which were obtained at health facilities or private shops [34]. Of existing LLINs in semi-arid zones, 82.7% were used on the night before the survey, the highest utilization of any epidemiologic zone. Even though malaria parasite prevalence is low in the semi-arid zones, the community is aware of malaria and takes precautions to prevent

it when possible. However, 36% of those surveyed responded that malaria is only a risk during the rainy season [34].

Malaria in South Sudan and Somalia

In eastern South Sudan, malaria parasite prevalence was estimated to be near 20%, or intermediate risk, in the 2009 Malaria Indicator Survey [35]. LLIN usage was low, with around 25% of children under five and 35% of pregnant women sleeping under LLINs. Driving this low usage was a lack of knowledge of malaria prevention: only 30% of respondents knew that sleeping under an LLIN can reduce the risk of malaria [35]. Similarly low levels of LLIN usage were reported by Somalis in a 2008 survey in South-Central Somalia. Only 12% of respondents reported sleeping under an LLIN, even though the *Pf*PR was 19.6% for children under five and 20.5% for children 5-14, suggesting intermediate transmission [36]. A 2009 National Micronutrient Survey that incorporated malaria indicators reported low transmission *Pf*PR in other districts of Somalia: 2.1% and 1.3% in the North West and North East, respectively [32, 37].

Epidemics in Humanitarian Emergencies

Protracted humanitarian emergencies present unique challenges in malaria epidemic prevention and control. These are often mediated by extended periods of food scarcity and a lack of sustained funding for chronically displaced populations [1]. Epidemics of malaria often occur in regions where endemicity is low and vector density is dependent on variable climatic factors *[38]*. Since those with limited exposure to the parasite do not develop clinical immunity, increased vector density and subsequent transmission of the parasite can result in exceptional increases in cases across the entire population *[39, 40]*. In populations where clinical immunity is present, epidemic transmission can primarily occur through those with subclinical infection while increased morbidity and mortality are mostly observed in children, pregnant women, and

immunocompromised individuals *[41]*. Epidemics can also occur in endemic areas where mass population movements result in high numbers of malaria-naïve individuals moving into areas of high risk *[38]*. Mass population movements can also facilitate re-introduction of malaria from endemic to non-endemic areas if there is an available vector, resulting in epidemics in the host community *[38]*.

Epidemic Detection

Detection of epidemics, however, is complicated in emergency settings where numerous factors can contribute to the number of patients seeking care for malaria at clinics where surveillance is conducted. Changing population denominators, varying levels of food security, supply stock-outs, clinical staff capacity, and transmission intensity can all affect the number of patients diagnosed with malaria *[1, 42]*. While a technical declaration of an epidemic may not be necessary to implement malaria control measures when an upsurge in cases is observed, larger-scale control strategies require a clear determination of burden.

In the highlands of Western Kenya, which the MOH classifies as epidemic-prone, Hay and colleagues explored the sensitivity of three epidemic threshold methods to retrospectively detect epidemics using surveillance data from three inpatient hospitals *[43]*. Using reported malaria cases in children under 15 years of age, they constructed thresholds first based on the quartile method described by WHO *[44]*. Monthly case counts from the five previous years were placed in quartiles and monthly case counts from the present year were classified as epidemic if exceeding the third quartile for a given month *[44]*. Next Hay *et al.* used a method developed by Cullen and colleagues in Thailand with a monthly mean case count plus 95% confidence limit for the previous five years (n=5) *[45]*. These methods are predicated on the assumption that malaria transmission should be similar across years in the same month. To normalize the distribution of monthly case counts,

which were skewed by unstable peaks across years, they adapted the Cullen method by log-transforming the counts *[43]*. They adapted an additional technique developed by CDC to account for yearly variation in seasonal peaks, the C-SUM method *[46]*. Means for each month from the five previous years, along with each surrounding month (n=15), were calculated and used with a 95% confidence limit to set a monthly threshold. They also applied log-transformations with the C-SUM method. This resulted in the most restrictive definition of an epidemic, establishing a comparatively high threshold due to wide confidence intervals on monthly means *[43]*. Using untransformed data for each method resulted in comparatively low thresholds leading to many months being classified as epidemic. The WHO method was the most sensitive, leading to more than a third of months over the 10-year period to be classified as epidemic. Regardless of the specific method used, a threshold should serve as an indicator of increased case burden that requires more effort and resources than typical to control.

For protracted situations where longitudinal data have been collected, monthly case counts may not be sufficient to strictly define an epidemic, since the population denominator can change drastically across years. To determine if case burden is greater than what would be expected at a given place at a given time, the incidence rate of clinical malaria can be used to estimate the population burden in comparison to the same month over five previous years, analogous to the processes used by Hay *et al. [1, 43]*. Since the camp population in Kakuma has more than doubled in the past five years, it would be more appropriate to adapt these methods for use with incidence rates instead of case counts.

Case Management

Case management is the primary malaria control strategy in semi-arid environments, epidemics, and humanitarian emergencies. UNHCR recommends that implementing partners at

Kakuma follow the guidelines of the Kenya Ministry of Health and Sanitation (MOH) in malaria case management protocol. Patients presenting to clinic with fever should be screened for signs of severe malaria. If signs of severe malaria are present, the patient should immediately start therapy with intramuscular quinine and be transferred to a referral facility. Otherwise, patients should be tested for parasitological evidence of malaria using a rapid diagnostic test (RDT) or light microscopy. If the patient has uncomplicated malaria with parasitological confirmation, the patient should begin three-day therapy with artemether-lumefantrine (AL). If parasitological confirmation is not possible and uncomplicated malaria is suspected, the patient should be presumptively treated with AL. In addition to an antimalarial, patients should be treated with paracetamol to manage fever [47]. Other strategies recommended by the MOH during epidemics include social mobilization, active surveillance by health workers, preparation of referral facilities, IRS campaigns, and LLIN campaigns if appropriate.

In response to reported epidemics of malaria in Kenya, Burundi, Ethiopia, and southern Sudan in the early 2000s, Médecins Sans Frontières (MSF) attempted to rapidly scale up case management by testing and treatment with antimalarial therapies *[48]*. Checchi and colleagues emphasized consistent themes from the experiences of MSF in these case studies: climatic abnormalities (usually drought in a preceding year and excessive rainfall in preceding months); displacement or conflict; rapid upsurges in cases; delayed detection of upsurges; overwhelmed health facilities; and disorganized replenishment of antimalarial therapies *[48]*. Nevertheless, MSF substantially increased treatment of cases during the epidemics, although the impact of these interventions on reducing transmission was unknown due to the delays in both detection and intervention. Minimal attack rates for each epidemic were estimated to vary from 22.2 to 86.5%, while case fatality ratios for children under five with complicated malaria were all below 9% *[48]*.

In addition, the high proportion of complicated cases that were children under five years of age (20-78%) led Checchi *et al.* to conclude that adults in these areas may possess some degree of clinical immunity, despite previous assumptions about transmission classification *[48]*. They recommended continued investment in access to care and vector control alongside epidemic preparedness and detection in each situation.

Vector Control

Several strategies for vector control have been assessed in the context of epidemic malaria in emergencies. Charlwood and colleagues conducted a randomized trial of IRS with malathion (an organothiophosphate) in a protracted refugee crisis in eastern Sudan—a semi-arid region with seasonal malaria transmission facilitated by *An. arabiensis* [49]. Fourteen isolated camps were randomized to either spray every structure with malathion or spray none. Most structures were thatched-roof, mud-walled *turkels*, constructed by the refugees who had resided there for up to 20 years. Antimalarial treatment was made available to all cases in both control and intervention camps. Incidence and mortality rates in children under five for the two months following rainy season spray campaigns were the main outcomes. The rate ratio for clinical incidence of malaria was 0.9 (95% CI: 0.7 - 1.2), while that of all-cause mortality was 0.0 (no deaths were reported in intervention camps, while six were reported in control camps). The authors concluded that resources used for IRS would be better utilized on larval source management after observing few habitats for breeding. However, no inquiry was made into the possibility of insecticide resistance, despite previously documented malathion resistance in *An. arabiensis* in Sudan [50]. Additionally, the spray campaigns took place in September, after the beginning of the rainy season and onset of typical malaria upsurges [49]. Given the similarity of environment and vector to Kakuma, this study may suggest that IRS is not an effective strategy to prevent malaria upsurges; although the

weaknesses of the study could invalidate this. Additionally, IRS has been shown to be effective at reducing baseline levels of malaria transmission outside of epidemics in both stable and unstable transmission settings [51].

Maes and colleagues assessed the effect of timely vector control strategies to prevent epidemic malaria in a semi-arid environment in Northeastern Kenya using an ecologic study design [52]. They compared a sequence of exceptional drought and flooding in Wajir town in 1998 and 2007—both accompanied by Rift Valley Fever outbreaks mediated by similar environmental conditions—using incidence of malaria hospital admissions in children under 15 as the primary outcome. In 1998, an IRS campaign was initiated five months after peak rains and two months after peak malaria incidence (up to 50 per 1,000 person-weeks). In contrast, IRS, LLIN distribution, and larval source management were initiated in 2007 less than three months after peak rains, before malaria incidence increased. The vector control campaign was followed by only a small upsurge in incidence (up to 0.4 per 1,000 person-weeks). Both campaigns achieved near full coverage with IRS in roughly one month. While there are substantial limitations to the design of the study, it is apparent that timely vector control intervention could be related to decreased likelihood of malaria upsurges in semi-arid environments after climatic abnormalities. Substantiating the study results, nearby Garissa county did not receive immediate vector control interventions in 2007 following similar climatic abnormalities and reported an epidemic of malaria in the same timeframe of this study [52]. Since Kakuma experiences similar periods of aridity followed by flooding, timely intervention with IRS, LLINs, and larval source management following exceptional rains could aid in preventing malaria upsurges.

Although mass LLIN distribution has proven to be effective in reducing malaria burden, multiple studies have demonstrated that coverage is heterogeneous across age groups throughout

Africa. Noor *et al.* showed from Demographic and Health Surveys and Malaria Indicator Surveys that school-aged children (5-19) are consistently the least covered age group following mass LLIN distribution campaigns, despite having the highest parasite prevalence [53]. Similarly, Vanden Eng and colleagues reported that the highest proportion of those not sleeping under nets—with at least one hung in the household—are children aged 5-15 [54]. Polec *et al.* concluded with moderate certainty in a 2015 Cochrane review that education on net usage can increase net usage in those over five [55]. Given the large proportion of school-aged children in Kakuma, special consideration must be taken in LLIN distribution if universal coverage is to be achieved.

A less common vector control strategy to prevent malaria in emergencies is insecticide-treated plastic sheeting (ITPS) for shelter construction. Burns and colleagues assessed the effectiveness of plastic sheeting extruded with deltamethrin to prevent malaria in a phase III double blind study in newly established refugee camps in Sierra Leone [56]. Outer sections of two stratified camps were each randomly allocated to either receive the ITPS or normal polyethylene sheeting for covering the walls and/or ceiling of thatch-roof, mud-walled huts. The small study assessed parasite prevalence and incidence rate of reinfection in children 4-36 months of age after an initial mass treatment campaign and sheeting distribution. For the camp where sheeting was placed on both ceilings and walls, the incidence rate ratio was 0.39 (95% CI: 0.36 - 0.41), while that of the camp with sheeting on only ceilings was 0.85 (0.81 - 0.89). The adjusted odds ratio for parasite prevalence roughly five months after the intervention was 0.57 (0.41 - 0.78) for the ceiling-and-wall arm and 1.09 (0.80 - 1.48) for the ceiling-only arm. It is evident that the use of insecticide-treated plastic sheeting on walls and ceilings of shelters reduced malaria burden in this setting. However, this study was conducted in a high transmission zone where malaria transmission is perennial [56]. In addition, plastic sheeting is intended for construction of shelters in acute-phase

emergencies and may not be practical for retrofitting existing structures [1]. The sheer number of long-standing structures in Kakuma precludes this type of intervention.

The final type of vector control strategy possible in semi-arid environments is larval source management. Shililu and colleagues concluded in 2007 that managing habitats by draining or depositing *Bacillus thuringiensis israelensis*, *B. sphaericus*, or an organophosphate larvicide effectively reduced *An. arabiensis* density for at least 24 months in a randomized study in rural Eritrea [29]. In addition, Tusting *et al.* concluded in a 2013 Cochrane review with moderate certainty that larval source management can reduce malaria prevalence and incidence in environments where habitats are few enough to achieve high coverage [57]. Since Kakuma has similar environmental and vector characteristics as Eritrea, it is possible that larval source management could aid in malaria control.

Considerations for Control

Responsive interventions to control epidemic malaria require extensive planning and coordination. Early detection of epidemics has been used to initiate response activities, though the trend is moving toward early warning based on climatic cues, before malaria incidence increases [58]. Hay and colleagues suggest that early warning for semi-arid environments could be based on rainfall alone, where control activities are initiated directly following a rainfall event [40]. To intervene in the highest-risk populations first, it has been suggested to target hot spots of malaria transmission to minimize the impact of an upsurge in epidemic-prone regions [59]. Spatial hot spots of malaria transmission have been detected at scales from half a kilometer to three kilometers in both densely populated and rural settings [60, 61]. These can be detected through spatial analysis of malaria incidence in children, as it is suspected they may provide the most accurate representation of transmission, since few develop subclinical infection [62]. Despite the

established methods to detect hot spots, it is unclear whether implementing control strategies in hot spots can reduce malaria incidence outside of the hot spot or have a lasting impact within the hot spot [63]. Heterogeneities in transmission may be more important to identify in Kakuma so that gaps in control coverage can be addressed.

Malaria in Kakuma Camp

Kakuma experienced an epidemic of malaria in June-August 2005 following an abbreviated rainy season, prompting an entomological investigation and rapid assessment of malaria prevalence [3]. Bayoh and colleagues reported that there were approximately 11,000 cases of malaria seen at camp clinics in July, when the population was near 90,000 [3]. A malaria prevalence survey among febrile patients presenting to clinics in August showed an age-dependent prevalence profile: 13.4% (95% CI: 6.3 - 24.0) of febrile children aged 0-1 years in clinic were positive for *P. falciparum* parasites by blood smear microscopy; 55.2% (41.5 - 68.3) for children 2-4; 62.4% (53.0 - 71.2) for children 5-17; and 38.0% (27.3 - 49.6) for those 18 and over [3]. Despite this, the estimated three-day malaria attack rate during the prevalence survey was highest among children aged 2-4, at ~5 per 1,000, compared to 1.4 per 1,000 overall [3]. This could simply mean that there were more children aged 2-4 years with other febrile illnesses in addition to the high malaria burden, since the survey was only among those presenting to clinic. Estimated attack rates were also geographically heterogeneous: Zone 3 of Kakuma I had the highest three-day incidence at ~4.5 per 1,000 population. This was related to the heterogeneity of vector density. Zone 3 of Kakuma I had the highest larvae density on the wet season larval habitat survey, and the second-highest in the dry season at 5.4 and 1.9 larvae per dip, respectively. While vector density throughout the camp varied significantly between the wet and dry season, tap-stand pits facilitated oviposition through the dry season and accounted for almost 90% of all larval habitats in the camp

in both seasons. All non-*culex* mosquitos captured in wet and dry season household surveys were identified as *An. arabiensis* by PCR [3]. The proportion of houses containing *Anopheles* and indoor resting density did not differ between wet and dry seasons. This supports Bayoh and colleagues' conclusions that the tap-stand pits were responsible for ongoing malaria transmission through the dry season. Though they suggest that the prevalence estimates are indicative of hyperendemic transmission, the estimates are among febrile clinic patients and are not comparable to community-based prevalence surveys from which endemicity classification is derived. More longitudinal, clinical, and geospatial analyses are necessary to describe malaria epidemiology in Kakuma camp.

Summary of Current Problem and Study Relevance

Malaria presents a considerable challenge to those residing in refugee camps and the agencies responsible for their health. While established interventions to prevent malaria epidemics are available, their effectiveness depends on the epidemiologic and environmental context. Though several methods for epidemic detection have been proposed, few have been used successfully to provide timely warning for implementation of control interventions. A better understanding of the epidemiology of malaria in semi-arid camp settings is needed to provide recommendations for long-term control. Through analyzing the upsurge of malaria in Kakuma refugee camp in early 2016, recommendations for control can be provided.

Chapter 3. Manuscript

Epidemic malaria in a semi-arid protracted displacement crisis: implications for prevention and control

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Keywords: epidemic malaria, *El Niño*, refugee, epidemic detection

Running title: Epidemic malaria in Kakuma

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Contribution of the Student

The student participated in the analysis of data and writing of the manuscript. Data collection was carried out by epidemiologists from the Malaria Branch of the Centers for Disease Control and Prevention / Kenya Medical Research Institute (CDC/KEMRI) with the assistance of program staff for International Rescue Committee. Data entry was completed by program staff at CDC/KEMRI.

Fulfilling the formatting requirements of the *Malaria Journal* of BioMed Central.

Abstract

Background: Malaria is a risk to many in refugee settlements in sub-Saharan Africa. Population movement, food insecurity, and lack of sustained preventive measures can coalesce with environmental factors suitable for malaria transmission to enable epidemics in semi-arid regions. Displacement crises present challenges in epidemic detection and response, and few studies have examined the morbidity, mortality, and case management of malaria in refugee settlements. The purpose of this assessment was to describe the epidemiology of malaria in Kakuma refugee camp in the context of an upsurge in late 2015 following *El Niño* rains to inform recommendations for prevention and control.

Results: Malaria incidence rate for December 2015 and January 2016 exceeded a 5-year C-SUM epidemic threshold. From January 2010 to July 2016, monthly malaria incidence rate increased, on average, by 0.0165 cases per 1,000 persons per month, ($R^2 = 0.134$, $p < 0.0001$). A census of clinic registers from December 2015 and January 2016 revealed heterogeneities in confirmed malaria burden across age, sex, and location of residence: those aged 12–17 were at the highest risk compared to adults aged 18–59, OR=2.57 (95% CI: 2.47-2.67). Males were at higher risk compared to females, OR=1.16 (95% CI: 1.12-1.19). Hot spots of malaria incidence among refugees under five were detected in Kakuma I sub-camp using Anselin Moran's I at a fixed-distance band value of 585 m. Differential management of malaria cases was observed across the six outpatient clinics in Kakuma.

Conclusions: Epidemic malaria was detected in a semi-arid protracted displacement crisis following climatic abnormalities and reports of food insecurity. Geographic and demographic heterogeneities were detected, but incidence was high throughout the camp. Intervention measures should include universal coverage and community promotion of long-lasting insecticidal nets; clinician refresher training on malaria case management; monitoring of malaria diagnostic and therapeutic stocks; and vector control, such as indoor residual spraying, to decrease the baseline malaria incidence.

Background

Malaria is a persistent threat in many refugee camps in sub-Saharan Africa. Malnutrition, ongoing population movement, and chronic underfunding for preventive measures can promote conditions suitable for malaria transmission [1]. While many refugee settlements are located in areas with high malaria risk, there is a dearth of evidence in the literature on malaria-associated morbidity, mortality, and environmental risk factors in camp settings, especially in semi-arid regions with epidemic potential. Although epidemics of malaria have been described in settings with displaced populations, the comparative magnitude is often difficult to assess when historical data are unavailable or not presented [1, 3, 48, 52]. There is also little evidence on the quality of case management during epidemics in these settings. In addition, while geographic and demographic heterogeneities in malaria morbidity and mortality are known to occur in confined areas, very few studies have rigorously described the epidemiology of malaria in refugee settlements [2, 60, 62].

In late 2015, an upsurge in malaria cases was observed in Kakuma refugee camp following heavy *El Niño* rains. Located in semi-arid northwestern Kenya, the camp had previously experienced epidemic malaria, and entomological surveys in 2006 identified *Anopheles arabiensis* larvae year-round in drainage pits associated with tap-stands [64]. In the context of the 2015-2016 upsurge, it was unclear whether increased case burden reflected typical seasonal transmission, a true epidemic, or a transition to a higher baseline of malaria endemicity. The purpose of this assessment was to describe the upsurge in person, place, and time; assess case management and clinical burden; explore potential causes; and provide recommendations for malaria prevention and control following the increased number of cases seen in clinics at Kakuma from December 2015 to January 2016.

Methods

Assessment site and population

Kakuma refugee camp lies in the semi-arid Turkana region along the Tarach river of northwestern Kenya. It was established by the United Nations High Commissioner on Refugees (UNHCR) in 1992 following a displacement crisis during a Sudanese civil war, but has recently grown considerably. The camp hosted 60,000 refugees in 2010, but grew to host more than 185,000 at the beginning of 2016—51% of whom were from South Sudan, 30% from Somalia, and the majority of the remainder from Sudan, Democratic Republic of Congo, Ethiopia, Burundi, Uganda, Rwanda, and Eritrea. Kakuma refugee camp is organized into four sub-camps divided into zones, which are further divided into blocks that consist of households (Appendix 1, Suppl. Figure 1). These 130 blocks have an average population of 1,478 (range: 76 – 5,601). New sub-camps are added as the population grows, and the number of the camp represents the order in which it was built.

Camp residents rely on UNHCR and implementing partners for provision of basic needs. Livelihood activities are primarily limited to the informal sector, though trade occurs with the local pastoralist Turkana community in nearby Kakuma town. The surrounding host community is able to access education and health facilities within the camp. Health services in the camp are overseen by UNHCR and provided by International Rescue Committee (IRC), which administers two inpatient hospitals and six outpatient clinics, along with a cadre of community health volunteers who conduct community mobilization activities. Clinics are primarily accessed by those in the sub-camp where the clinic is located, and the host community primarily access clinics in Kakuma I (Appendix 1, Suppl. Figure 1.)

Turkana has a climate characterized by persistent dry periods and high temperatures,

interrupted by brief seasons of rain near April and November—mean annual rainfall is limited to 200 mm [14]. While the Tarach is typically a dry riverbed, flash flooding during the dry season has been reported by camp staff due to rains at the highland headwaters along the Ugandan border. The Norwegian Refugee Council, under the guidance of UNHCR, is responsible for water, sanitation, and vector control activities. Indoor residual spraying with pyrethroids was typically conducted before the April and November rains, though there was no record of IRS campaigns in 2015. LLINs were historically distributed to pregnant women and children under five at prenatal and child clinic visits. While upsurges in malaria cases have been previously described, it was not clear whether malaria burden in Kakuma reflects perennial low-transmission with seasonal peaks or high risk transmission, as suggested by the age-profile of parasite prevalence in previous surveys [64].

To address this question, morbidity and mortality from January 2010 to November 2015 were analyzed and compared to that of December 2015 through early 2016. It was also unclear whether geospatial and demographic differences in malaria burden were present in Kakuma. A census of clinic registers from December 2015 to January 2016 was conducted in order to identify differences in the burden of malaria by location of residence and patient demographics, and to assess clinical management of patients with malaria. Findings were used to provide recommendations for malaria prevention and control in Kakuma.

Historical trends, clinical burden, and geospatial heterogeneity were assessed in the context of a malaria upsurge in Kakuma from December 2015 to January 2016 to characterize the epidemiology of malaria in this semi-arid protracted displacement situation. Case management and patient characteristics were also assessed to guide recommendations for prevention and control of malaria.

Temporal trends

Malaria-specific morbidity and malaria mortality, as well as all-cause mortality counts for each month from December 2009 to July 2016 were abstracted from the UNHCR Health Information System (HIS). Counts were stratified by age group (under or over five years), by refugee status (refugee or host community), and by case definition (confirmed or suspected). Suspected malaria was defined as acute febrile illness with no other etiology indicated. Confirmed malaria was defined as having a positive parasitological test. Age-stratified monthly population census data for refugees were abstracted from the UNHCR ProGres database for the same period. Monthly malaria counts and population denominators were used to generate incidence rates among refugees. Monthly case fatality rates were determined by dividing the number of malaria-attributable deaths by the number of confirmed malaria cases. The monthly proportion of deaths attributed to malaria was calculated by dividing malaria-attributable mortality by all-cause mortality.

Climatic data abstraction

Monthly rainfall totals at Lodwar meteorological station, 100 km southeast of Kakuma, were accessed from the National Climatic Data Center database for January 2010 to July 2016 [65]. The sum of rainfall over three months prior to each month was calculated as a proxy for possible environmental conditions suitable for increased vector density and malaria transmission [40].

Clinical and geospatial factors

Case demographic and clinical data were abstracted from IRC clinic registers for the period with highest clinical burden: 1 December 2015 to 31 January 2016. Included in the registers were date, age, sex, refugee status, residential block, first or return visit (for the same illness), axillary temperature, symptoms, malaria parasitological test result, diagnoses, and treatment. Population

denominator data as of 31 January 2016 were abstracted from UNHCR monthly population summaries for age- and sex-stratified analyses. Spatial data for camp blocks, clinics, and environmental features were provided by the UNHCR planning office. Population and long-lasting insecticidal bed net (LLIN) ownership data for spatial analyses were abstracted from the July 2016 camp census conducted by IRC.

Data analysis

Clinical and longitudinal surveillance data were abstracted in Excel version 15.3 (Microsoft Corp, Redmond, WA) and imported to SAS® software version 9.4 (SAS Institute, Cary, NC) for statistical analysis, then visualized using Tableau® software version 10.1 (Tableau Software, Seattle, WA). ArcGIS® version 10.3 (ESRI, Redlands, CA) was used to perform spatial analyses and visualization. Temporal trends in malaria incidence were analyzed using linear regression, with month of year as the predictor ($df = 2$, $n = 158$). Correlation of monthly incidence with the sum of rainfall at Lodwar in the previous three months was assessed using Pearson correlation. A monthly epidemic threshold was developed using a modified C-SUM method [43, 46]. Incidence rates over the five preceding years were averaged for each month and the two adjacent months ($n=15$); the upper 95% confidence limit of this measure was used as the threshold for each month. Pearson correlation of case counts by refugee status was conducted to determine if malaria case burden in the host community correlated with that of refugees in the camp.

To identify where incidence rate was higher or lower than what would be expected from a random spatial distribution, cumulative incidence rate by block over the two-month period was assessed using Anselin Local Moran's I cluster analysis for both children under five and total population, adjusted for multiple comparisons and spatial dependence [66]. Incremental spatial autocorrelation was used to determine a fixed-distance band value for spatial relationships, since block size varied throughout the camp. Incident case data were analyzed at the block level to

protect patient confidentiality.

To analyze clinical burden of malaria, frequency tables were generated in SAS software, stratified by sex and age group. Parasitological test positivity rate, proportion of febrile patients tested for malaria, and antimalarial prescribing rate among febrile patients with missing tests were plotted over time and stratified by clinic to identify potential stock-outs or changing clinician response to case burden. Test positivity rate was also assessed by age group to determine if possible under-detection of clinical cases occurred.

Ethical consideration

This rapid assessment was conducted in response to a public health emergency, and was therefore exempted from IRB review by both CDC and Emory University. UNHCR and the Kenya National Malaria Control Program gave permission for the evaluation to proceed. Only non-identifiable case characteristics were abstracted from clinic registers.

Results

Temporal trends

A total of 53,928 confirmed cases of malaria were reported in the UNHCR HIS from December 2015 to February 2016. The clinical incidence of malaria among refugees for December 2015, January, and February 2016 was 91.3, 125.4, and 61.8 cases per 1,000 persons, respectively—the highest in the six-year period analyzed. The incidence rate exceeded the epidemic threshold of 53.0, 53.8, and 44.4 cases per 1,000 persons in December 2015, January, and February 2016, respectively (Figure 1). From January 2010 to July 2016, monthly malaria incidence rate increased, on average, by 0.0165 cases per 1,000 persons per month, ($R^2 = 0.134$, $p < 0.0001$) (Figure 2a). Surges in incidence occurred each year, though the relative timing of the surge varied across years (Figure 3). Sum of rainfall in the previous three months recorded at

Lodwar station was correlated with malaria incidence ($r = 0.38$, $p = 0.0007$).

[Figure 1]

[Figure 2]

Case counts among the host community reflected those among refugees over the same six-year period, though at a much smaller scale, ($r = 0.72$, $p < 0.0001$) (Figure 2b). Population denominator data were not available for the host community, as the catchment area outside the camp was undefined. Malaria-attributable mortality rates among refugees in January 2016 exceeded the 95% upper confidence limit (UCL) of the 2010 – 2015 January average. The proportion of all-cause mortality attributed to malaria for January 2016 was 41.8, 36.8, and 33.3% among refugees under-five, refugees over-five, and the host community, respectively. This exceeded the 95% UCL for the 2010 – 2015 January average for host community and refugees under-five. Case fatality rates among the host community, refugees under-five, and refugees over-five all remained below 0.5% and within the 95% UCL of the 2010 – 2015 January average. All-cause mortality rates among refugees both over- and under-five remained below respective humanitarian emergency Sphere standards of 0.8 and 1.5 per 1,000 person-months through the peak transmission period, though they exceeded the 95% UCL of the 2010 – 2015 December and January averages [67].

[Figure 3]

Geospatial heterogeneities

Cumulative incidence per 1,000 persons per block over the two-month peak transmission period were plotted on the camp layout. Spatial trends were identified at a range of 585 m using incremental spatial autocorrelation. Clustering was detected using with 95% confidence in Zone 3 of Kakuma I for incidence among refugees under-five and incidence among all refugees (Figure 4a). Zone 3 of Kakuma III was also identified as a cluster of high incidence among all refugees

(Figure 4b). Insecticide-treated net ownership from the July 2016 census showed that 88.5% of blocks met the UNHCR recommendation of one net per two pregnant women and children under five; however, 4.6% of blocks met the recommendation for universal coverage—one net per two persons. Net coverage by block among all refugees was inversely correlated to cumulative incidence by block among all refugees ($r = -0.23$, $p = 0.0073$), with an overall average of one net per five persons (Appendix 1, Suppl. Table 1).

[Figure 4]

Case management

Data from all six outpatient clinics in Kakuma refugee camp were accessed for 1 December 2015 to 31 January 2016. Of 49,946 patient encounters recorded in outpatient clinic registers over this period, 25,165 (50.4%) included a malaria diagnosis (Table 1). The proportion of visits involving malaria differed by clinic, ranging from 27.4% of visits at Clinic 4 in Kakuma I to 63.0% at Clinic 6 in Kakuma III. Of 35,246 febrile cases, 24,190 (68.6%) received a parasitological test for malaria, which also differed by clinic. Proportion of febrile cases tested for malaria also differed by under- and over-five age groups, ($\chi^2 = 4145.3$, $p < 0.0001$). The type of parasitological test was not consistently recorded in clinic registers. Parasitological test positivity rates differed by age group and clinic, ranging from 65.5% in those under five at Clinic 6 to 99.8% in those aged 12 – 17 at Clinic 4, excluding the few tested aged 60 and over. Among all patients with positive parasitological tests, antimalarial (artemether-lumefantrine or quinine) prescription rates ranged from 77.1% at the outpatient department (OPD) of the General Hospital in Kakuma IV to 99.6% at Clinic 4. Among febrile patients without parasitological test results, the rate of antimalarial prescription ranged from 2.9% at Clinic 4 to 35.0% at Clinic 6.

Table 1. Management of outpatient malaria cases by age group and clinic in Kakuma refugee camp, Turkana, Kenya: 1 December 2015 - 31 January 2016.

Variable	Main Hospital		Clinic 2		Clinic 4		Clinic 5		Clinic 6		General Hospital	
	No.	%*	No.	%	No.	%	No.	%	No.	%	No.	%
Patient encounters	13,334		3,289		6,453		6,861		16,434		3,575	
Reported malaria visits	6,867	51.5	1,559	47.4	1,764	27.3	2,997	43.5	10,345	63.0	1,633	45.7
Confirmed malaria visits	6,816	51.1	1,525	46.4	1,693	26.2	2,944	42.9	9,539	58.0	1,577	44.1
Prescribed antimalarial	5,951	87.3	1,483	97.2	1,686	99.6	2,815	95.6	9,276	97.2	1,216	77.1
Febrile patients[†]	8,574	64.3	2,291	69.7	4,042	62.6	4,739	69.1	12,804	77.9	2,796	78.2
Age < 5	1,767	73.8	1,042	81.7	1,699	80.5	1,765	71.5	2,770	77.3	763	85.5
Age ≥ 5	6,807	62.2	1,249	62.0	2,343	54.0	2,974	67.7	10,034	78.1	2,033	75.8
Febrile patients not tested[a]	2,153	25.1	779	34.0	2,407	59.6	2,071	43.7	2,447	19.1	1,199	42.9
Age < 5	961	54.4	457	43.9	1,503	88.5	1,085	61.5	984	35.5	397	52.0
Age ≥ 5	1,192	17.5	322	25.8	904	38.6	986	33.2	1,463	14.6	802	39.5
Prescribed antimalarial	144	6.7	27	3.5	70	2.9	83	4.0	857	35.0	89	7.4
Age < 5	32	3.3	19	4.2	6	0.4	20	1.8	166	16.9	4	1.0
Age ≥ 5	112	9.4	8	2.5	64	7.1	63	6.4	691	47.2	85	10.6
Test positivity rate by age group												
< 5	637	73.3	468	76.7	187	91.7	664	83.6	1,360	65.5	322	83.6
5 - 11	1,840	92.7	492	94.5	477	99.6	788	96.2	2,579	84.5	495	94.7
12 - 17	2,221	95.0	372	97.3	553	99.8	672	97.8	2,639	83.0	395	95.4
18 - 59	2,084	88.6	185	87.7	466	99.8	801	96.4	2,911	75.6	359	92.1
60 +	34	85.0	8	88.9	10	100.0	19	82.6	50	59.5	6	54.6

†Febrile defined as reporting fever, hotness of body, or axillary temperature ≥ 38˚C.

[a]Testing includes either blood smear microscopy or rapid diagnostic test.

*Other than test positivity rate, percentages reflect proportion among parent group, one level up indentation hierarchy.

Malaria incidence differed by age group and sex through peak transmission. Clinical incidence was higher among males than females, with an odds ratio (OR) of 1.16 (95% CI: 1.12-1.19) (Figure 5). The highest 2-month cumulative incidence was in adolescents aged 12 – 17 years, OR = 2.57 (95% CI: 2.47-2.67) (Table 2). School-aged children (5 – 17 years of age) accounted for 56.2% of cases but only 41.6% of the population (Appendix 1, Suppl. Table 2). The proportion of visits classified as a return visit for malaria did not differ meaningfully across age group or sex at 9.72% overall, but was substantially different across clinics (χ^2 = 7,004.4.3, p < 0.0001) (Figure 6). Clinic 2 in Kakuma I classified over half of visits related to malaria as return visits, while the

OPD of the Main Hospital in Kakuma I recorded no return malaria visits. Clinics 5, 6, and the OPD of the General Hospital in Kakuma IV each had over 20% of malaria visits not classified.

Table 2. Unadjusted estimated attack rate (AR), incidence odds ratios (OR), and 95% confidence intervals (CI) for the risk of malaria by sex and age in Kakuma refugee camp: 1 December 2015 - 31 January 2016.*

	Confirmed Malaria No.	Population No.	AR	OR	95% CI	
Patient Age Group						
< 5	2,946	25,027	0.12	**1.62**	**1.55**	**1.70**
5 - 11	5,815	42,825	0.14	**1.91**	**1.84**	**1.98**
12 - 17	6,092	34,621	0.18	**2.57**	**2.47**	**2.67**
18 - 59	6,144	80,700	0.08	1.00		
60 +	112	2,811	0.04	**0.50**	**0.42**	**0.61**
Patient Sex						
Female	9,070	85,828	0.11	1.00		
Male	12,039	100,156	0.12	**1.12**	**1.05**	**1.19**

*Significant values in bold.

[Figure 5]

[Figure 6]

Plotting febrile cases without a parasitological test, confirmed cases without an antimalarial prescription, and antimalarial prescribing among febrile cases without a parasitological test over time revealed multiple time points of acute increases in proportion of febrile cases without a parasitological test, proportion of malaria patients not receiving an antimalarial, and proportion of febrile cases missing a test but receiving an antimalarial. (Appendix 1, Suppl. Fig. 2-4). Antimalarial stock-outs may have occurred in the OPD of the Main Hospital during the week of 13 December and in the OPD of the General Hospital during the week of 3 January. Stock-outs of diagnostics may have occurred in the OPD of the General Hospital during the weeks of 13 December and 17 January, in Clinic 4 during the week of 27 December, and in Clinic 2 during the week of 3 January.

Discussion

This is the first time that malaria burden has been described longitudinally in the published literature in Kakuma camp. Using historical case data and population figures, incidence rates were analyzed from 2010 to 2016. Based on these historical data, clinical incidence of malaria in Kakuma from December 2015 to February 2016 was higher than what should be expected based on a C-SUM threshold—and the highest in the six-year period assessed—constituting an epidemic. After the epidemic, incidence rates receded below the threshold until exceeding it again briefly in June 2016.

Longitudinal trends suggest that the baseline incidence may also have increased over the six-year period, leading to a higher baseline endemicity than elsewhere in Rift Valley Province. Classification of transmission intensity can be defined by parasite prevalence rate: low risk transmission occurs where parasite prevalence is under 5% in children aged 2-10 years; intermediate when 5-40%; and high when above 40% [32]. Since the low *Pf*PR_{2-10} for the Turkana region in 2015 suggests lower intermediate transmission, it would be expected that an epidemic would lead to relatively equal clinical incidence across age groups, due to infection naivety and subsequent lack of clinical immunity [2, 33]. However, the age-profile of clinical incidence tapered in adults during the 2015-2016 epidemic at Kakuma camp. Therefore, a level of endemicity consistent with some level of infection regularity and subsequent clinical immunity in adults in the camp is likely. However, clinical incidence during the epidemic was highest in adolescents, unlike high transmission settings where the highest clinical incidence is observed in children under five [68]. This suggests that Kakuma could have a baseline level of intermediate transmission, somewhere between low and high risk [32]. This level of endemicity reflects that of eastern South Sudan and South-central Somalia—the regions of origin for the two largest demographic groups

in Kakuma [35, 36]. To maintain levels of clinical immunity acquired prior to displacement, adults would have to be continually exposed to similar rates of infection [68]. Given that the average length of stay in Kakuma is 10 years, an intermediate transmission level may be necessary for this.

Surges within years and correlation with rainfall preclude simple classification as stable intermediate transmission [32, 69]. Correlation of case counts between refugees and the host community also suggests some environmental determinants may be related to incidence. A lack of consistency in incidence across years for the same month complicates the epidemiology and subsequent epidemic preparedness and detection. The only months with consistently low incidence (10-15 cases per 1,000 person-months) from 2010 to 2016 were March and April. All other months differed considerably across the six years.

Spatial heterogeneities of incidence within the camp were detected both among children under five and among all refugees. These clusters of high incidence indicate a non-random distribution of malaria throughout the camp. Some possible explanations for this could include variation in vector exposure by proximity to vector breeding sites or in construction of shelters with mud walls [2]. Other explanations could include variation in susceptibility to clinical sequelae of infection due to different longitudinal exposure to infection based on region of origin or age [68]. Differential detection of cases could also be related to variation in sensitization of the community or diagnosing practices by clinic, where under-diagnosing could lead to artificially low incidence estimates in some areas of the camp. While the reasons for this clustering are unclear, it should be noted that cumulative incidence was high throughout most of the camp, and interventions focusing only on areas of clustering would not likely affect transmission in other areas of the camp [63]. Additionally, net coverage was low throughout the camp, with only four blocks meeting the criteria for universal coverage in July of 2016 (Appendix 1, Suppl. Table 1).

Due to the low proportion of febrile cases tested for malaria parasites and the high test positivity rates, it is possible that clinical malaria cases were under-detected during the epidemic period analyzed. The low number of suspected cases also suggests under-detection. This is most evident in Clinic 4, in Kakuma I, where the high proportion of febrile cases not receiving a parasitological test could have deflated the reported number of malaria cases, with test positivity rates nearing 100%. In a 2014 national survey during the short rains, Githinji and colleagues reported test positivity rates among febrile cases of only 3.8% in the seasonal low transmission zones of Kenya, which include the Turkana region [70]. Comparatively, in the lake endemic region, test positivity rates among febrile patients did not exceed 50%. In an analysis of test positivity rates over 2010 to 2015 in Madagascar, seasonal peaks of transmission during epidemic years resulted in test positivity rates up to 70% [71]. Test positivity rates in Clinic 6, in Kakuma III, were closer to this, with a higher proportion of febrile patients tested, suggesting that varying diagnostic practices could influence reported malaria incidence. The variation in proportion of reported return visits for malaria across clinics also suggests differential understanding or use of the revisit criteria: a patient that returns to the clinic for the same case of malaria within one week. It should be noted that rapid diagnostic tests are not useful if repeated at a revisit, since the antigen can remain in the blood for over two weeks after clinical cure [72].

Incidence through the epidemic was consistently higher in school-aged children than in other age groups, and higher in males than in females. This same trend was observed in North-east Tanzania with seasonal malaria incidence [73]. This could be related to the policy of targeting LLIN distribution to children under five and pregnant women, or to risk-associated behavior. Variable use of LLINs across sex and age groups has also been reported across Africa, resulting

in differential exposure to malaria vectors [53]. Nocturnal outdoor behavior, which could also differ across sex and age groups, could also increase exposure to *An. arabiensis* [26, 73].

The 2015–2016 epidemic was characterized by a rapid upsurge in cases following climatic abnormalities related to the *El Niño* Southern Oscillation and reports of food insecurity. These enablers could have affected the basic reproductive number by increasing the ratio of vectors to humans and decreasing the recovery rate, respectively [74]. Factors related to malaria control interventions could also have had an impact during the 2015–2016 epidemic: lack of LLIN universal coverage and technical challenges such as pyrethroid resistance (results of the entomological survey described elsewhere) could be related to higher incidence. Increased malaria-attributable mortality and proportion of all-cause mortality attributed to malaria reflects the exceptional case burden. Despite this large case burden, case fatality rates remained low. This demonstrates the resilience of the health system in Kakuma, though improvements in case management and malaria control are possible.

Evidence of stock-outs and lag time of initiating testing for febrile cases among some clinics exhibits potential unpreparedness. Acute increases of febrile cases not receiving parasitological testing suggest stock-outs, while the chronically high proportion of untested febrile cases in Clinic 4 suggest a lack of sensitization to malaria risk. The high proportion of untested febrile cases in Clinic 6 may be attributed to operating at night, when laboratory testing is unavailable, and presumptive diagnosis of malaria was indicated by a high proportion of untested febrile cases receiving an antimalarial. Acute peaks in the proportion of confirmed malaria cases without an antimalarial at the Main and General Hospital OPD suggest stock-outs of antimalarials.

Conclusions

An epidemic of malaria in a semi-arid protracted displacement crisis occurred from December 2015 to February 2016. Geographic and demographic heterogeneities were detected, but incidence was high throughout the camp. Immediate control measures should include mass distribution of LLINs to achieve universal coverage; sensitization of the community to the importance of consistently sleeping under the nets regardless of age; and clinician refresher training on malaria testing, prescribing, and case definition protocol. Intermediate interventions should include maintaining an alert system for sensitizing both clinicians and the community to malaria following rains or when significant increases in malaria incidence are detected in the HIS. Commodity management systems should be developed to monitor stocks of diagnostic supplies and antimalarial medications to avoid stock outs. Longer term control strategies, such as IRS campaigns with non-pyrethroid insecticides, should be planned during periods of consistently low incidence before the onset of April or November rains, which could help to reduce the baseline endemicity of malaria in the camp.

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Figures

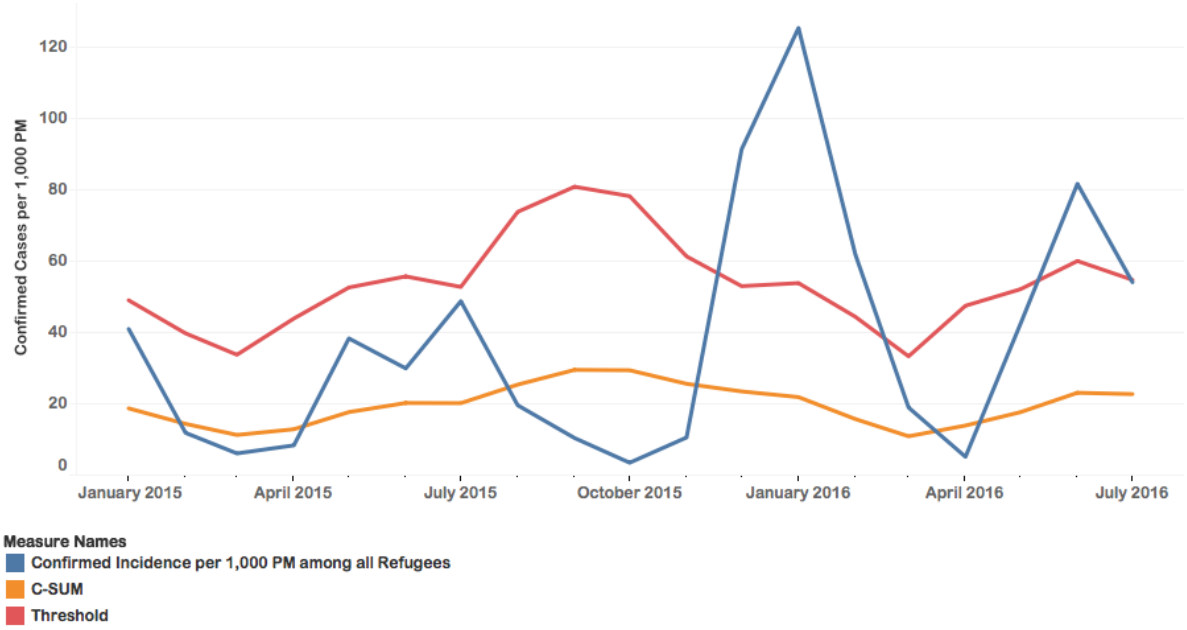


Figure 1. Incidence rate of confirmed malaria among refugees at Kakuma: January 2015 – July 2016. Rate is cases per 1,000 person-months (PM). C-SUM represents the average incidence rate for each month and its adjacent months over the five previous years. The threshold is the upper 95th percent confidence limit of the C-SUM. Monthly population denominator is derived from UNHCR records in ProGres.

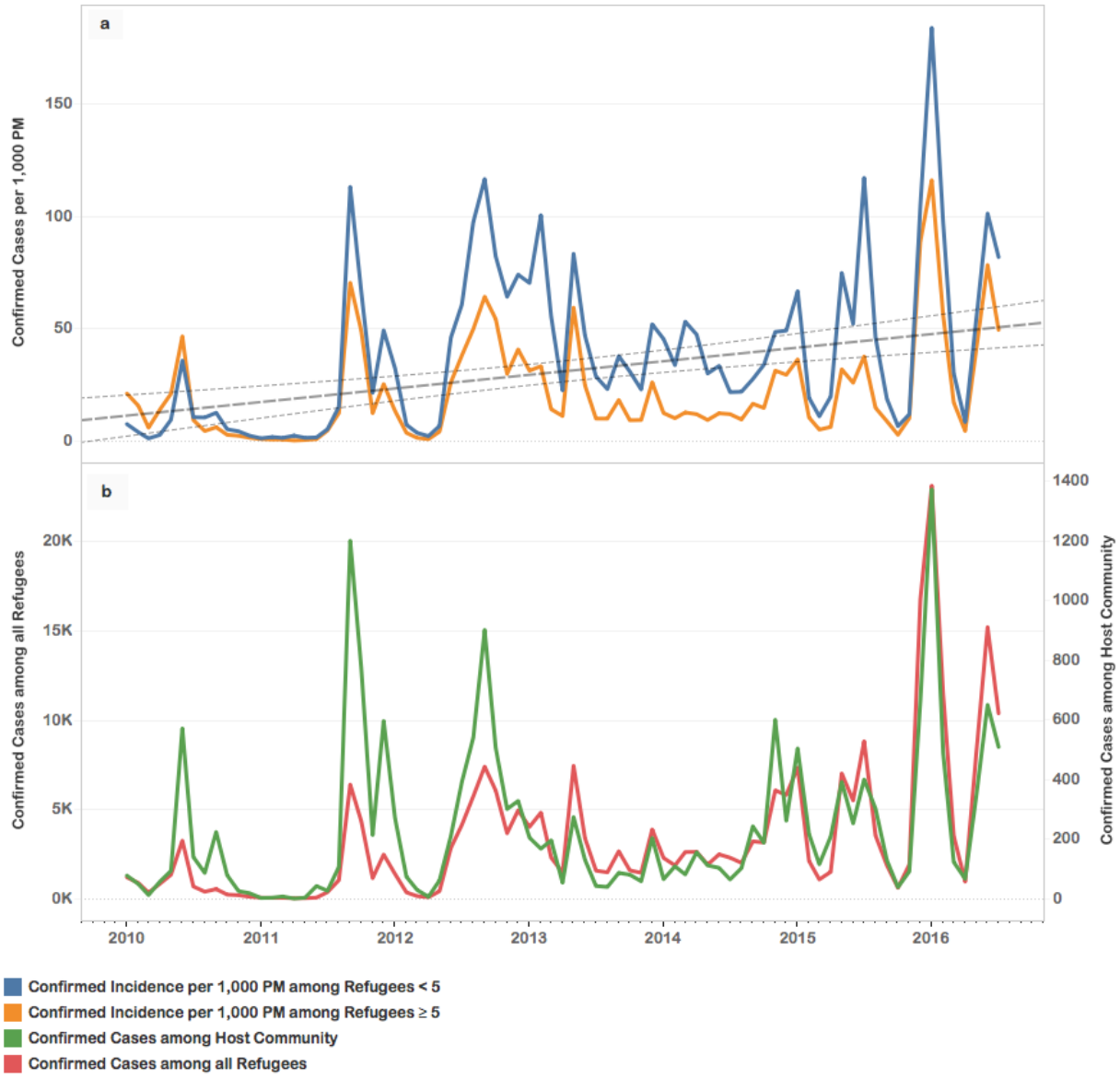


Figure 2. Incidence rates and case counts of confirmed malaria at Kakuma: 2010 – 2016. (a) Rate is per 1,000 person-months (PM). Simple linear regression with 95% confidence intervals is shown as dashed line. Incidence rate is consistently higher in children under five. (b) Confirmed cases per month. Axes differ markedly in scale, but surges occur at same time points.

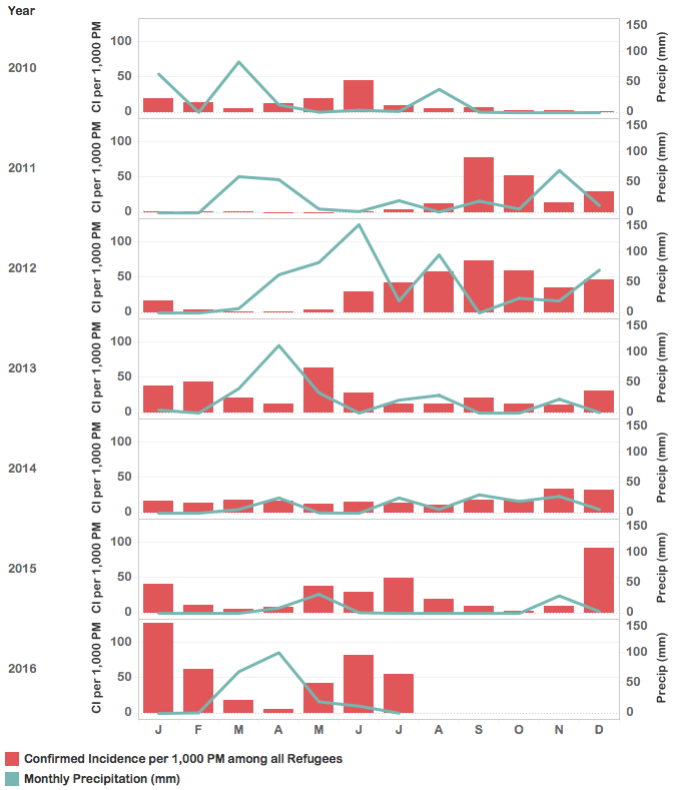


Figure 3. Yearly trends in malaria incidence and rainfall at Kakuma: 2010 – 2016. Monthly cumulative incidence is per 1,000 person-months (PM). Monthly precipitation totals are summarized from Lodwar meteorological station (HKLO), 100 km southeast of Kakuma. Surges in incidence are not consistent across years, but typically follow surges in rainfall.

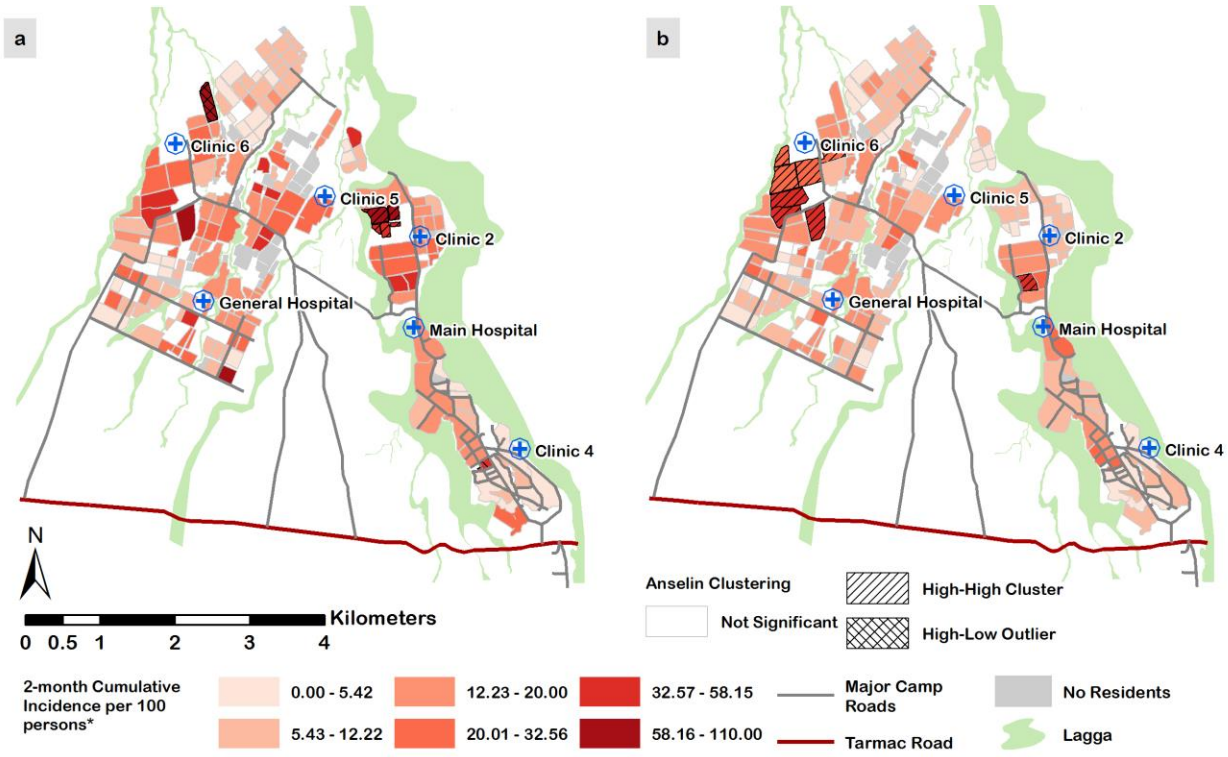


Figure 4. Spatial clustering of malaria incidence in Kakuma: December 2015 – January 2016. 2-month cumulative incidence of clinical malaria among refugees under five (a) and among all refugees (b). Row-standardized Anselin Local Moran's I high-high clusters and high-low outliers at a Euclidean fixed-distance band value of 586m are shown at the 95% confidence level, corrected for multiple comparisons. Kakuma I, Zone 3 contains clusters in (a) and (b), while Kakuma III, Zone 3 contains a cluster among all refugees (b). Block 4 of Zone 2 in Kakuma III and Block 1 of Zone 2 in Kakuma I are high-low outliers of incidence among refugees under five (a). Coordinate system: WGS 1984 UTM Zone 36N. Data courtesy UNHCR Kakuma Planning Office and IRC. *Block population based on July 2016 census.

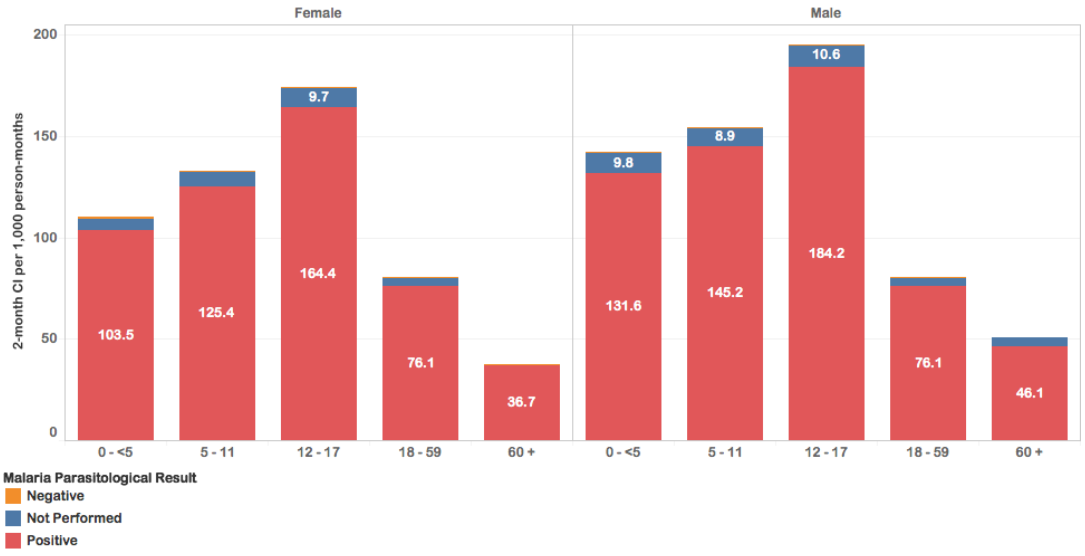


Figure 5. Incidence of reported clinical malaria by sex and age group at Kakuma: December 2015 – January 2016. 2-month cumulative incidence per 1,000 persons, disaggregated by confirmed and suspected cases for each sex and age group. Population denominators for each sex and age group are as of 31 January 2016.

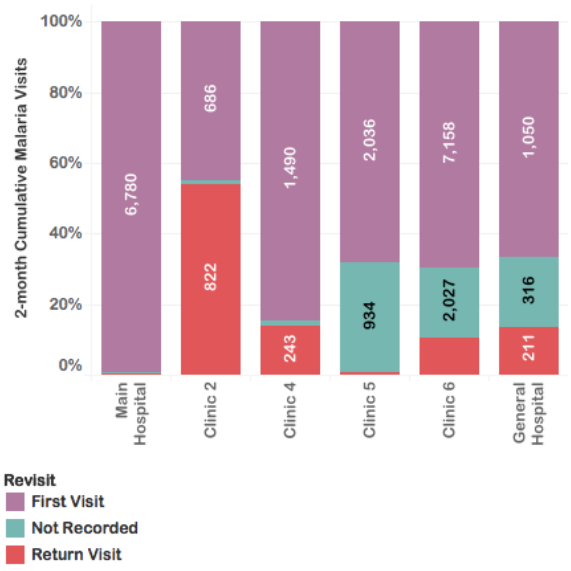


Figure 6. Proportion of return visits among malaria-related clinic visits by clinic at Kakuma: December 2015 – January 2016. Proportion is among visits for patients with a malaria diagnosis. The number of visits is shown inside bars.

Chapter 4. Conclusion and Recommendations

This is the first time that malaria burden has been described longitudinally in Kakuma camp. Longitudinal analyses are not often possible in displacement crises, since population denominators rapidly change and historical case data are not often available. With the incorporation of UNHCR HIS and ProGres databases, case data and population figures were available from 2010 for Kakuma. Using these sources, incidence rates were analyzed from 2010 to 2016. Based on this historical data, clinical incidence of malaria in Kakuma from December 2015 to February 2016 was higher than what should be expected based on a C-SUM threshold—and the highest in the six-year period assessed—constituting an epidemic. After the epidemic, incidence rates receded below the threshold until exceeding it again briefly in June 2016.

Longitudinal trends suggest that the baseline incidence may also have increased over the six-year period, leading to a higher baseline endemicity than elsewhere in Rift Valley Province. Classification of transmission intensity can be defined by parasite prevalence rate: low risk transmission occurs where parasite prevalence is under 5% in children aged 2-10 years; intermediate when 5-40%; and high when above 40% [32]. Since the low *Pf*PR_{2-10} for the Turkana region in 2015 suggests lower intermediate transmission, it would be expected that an epidemic would lead to relatively equal clinical incidence across age groups, due to infection naivety and subsequent lack of clinical immunity [2, 33]. However, the age-profile of clinical incidence tapered in adults during the 2015-2016 epidemic at Kakuma camp. Therefore, a level of endemicity consistent with some level of infection regularity and subsequent clinical immunity in adults in the camp is likely. However, clinical incidence during the epidemic was highest in adolescents, unlike high transmission settings where the highest clinical incidence is observed in children under five [68]. This suggests that Kakuma could have a baseline level of intermediate transmission,

somewhere between low and high risk [32]. This level of endemicity reflects that of eastern South Sudan and South-central Somalia—the regions of origin for the two largest demographic groups in Kakuma [35, 36]. To maintain levels of clinical immunity acquired prior to displacement, adults would have to be continually exposed to similar rates of infection [68]. Given that the average length of stay in Kakuma is 10 years, an intermediate transmission level would likely be necessary for this.

Surges within years and correlation with rainfall preclude simple classification as stable intermediate transmission [32, 69]. Correlation of case counts between refugees and the host community also suggests some environmental determinants may be related to incidence. A lack of consistency in incidence across years for the same month complicates the epidemiology and subsequent epidemic preparedness and detection. The only months with consistently low incidence (10-15 cases per 1,000 person-months) from 2010 to 2016 were March and April. All other months differed considerably across the six years.

Spatial heterogeneities of incidence within the camp were detected both among children under five and among all refugees. These clusters of high incidence indicate a non-random distribution of malaria throughout the camp. Some possible explanations for this could include variation in vector exposure by proximity to vector breeding sites or in construction of shelters with mud walls [2]. Other explanations could include variation in susceptibility to clinical sequelae of infection due to different longitudinal exposure to infection based on region of origin or age [68]. Differential detection of cases could also be related to variation in sensitization of the community or diagnosing practices by clinic, where under-diagnosing could lead to artificially low incidence estimates in some areas of the camp. While the reasons for this clustering are unclear, it should be noted that cumulative incidence was high throughout most of the camp, and

interventions focusing only on areas of clustering would not likely affect transmission in other areas of the camp [63]. Additionally, net coverage was low throughout the camp, with only four blocks meeting the criteria for universal coverage in July of 2016 (Appendix 1, Suppl. Table 1).

Due to the low proportion of febrile cases tested for malaria parasites and the high test positivity rates, it is possible that clinical malaria cases were under-detected during the epidemic period analyzed. The low number of suspected cases also suggests under-detection. This is most evident in Clinic 4, in Kakuma I, where the high proportion of febrile cases not receiving a parasitological test could have deflated the reported number of malaria cases, with test positivity rates nearing 100%. In a 2014 national survey during the short rains, Githinji and colleagues reported test positivity rates among febrile cases of only 3.8% in the seasonal low transmission zones of Kenya, which include the Turkana region [70]. Comparatively, in the lake endemic region, test positivity rates among febrile patients did not exceed 50%. In an analysis of test positivity rates over 2010 to 2015 in Madagascar, seasonal peaks of transmission during epidemic years resulted in test positivity rates up to 70% [71]. Test positivity rates in Clinic 6, in Kakuma III, were closer to this, with a higher proportion of febrile patients tested, suggesting that varying diagnostic practices could influence reported malaria incidence. The variation in proportion of reported return visits for malaria across clinics also suggests differential understanding or use of the revisit criteria: a patient that returns to the clinic for the same case of malaria within one week. It should be noted that rapid diagnostic tests are not useful if repeated at a revisit, since the antigen can remain in the blood for over two weeks after clinical cure [72].

Incidence through the epidemic was consistently higher in school-aged children than in other age groups, and higher in male children than in female children. This same trend was observed in North-east Tanzania with seasonal malaria incidence [73]. This could be related to

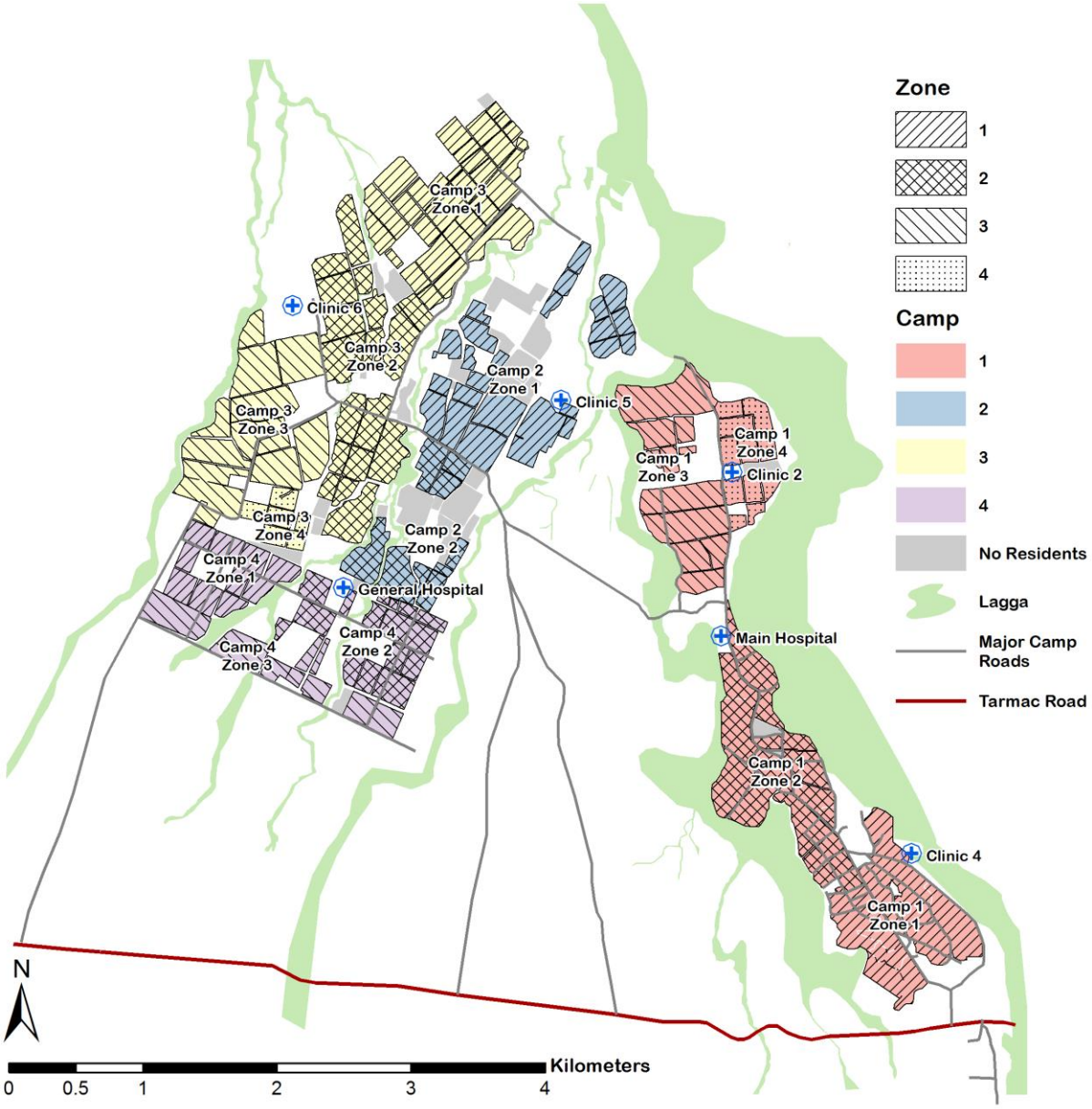
decreased risk in children under five and pregnant women since LLIN distribution is targeted to these groups. Variable use of LLINs across sex and age groups has also been reported across Africa, resulting in differential exposure to malaria vectors [53]. Nocturnal outdoor behavior, which could also differ across sex and age groups, could also increase exposure to *An. arabiensis* [26, 73].

The 2015-2016 epidemic was characterized by a rapid upsurge in cases following climatic abnormalities related to the *El Niño* Southern Oscillation and reports of food insecurity. These enablers could have affected the basic reproduction number by increasing the ratio of vectors to humans and decreasing the recovery rate, respectively [74]. Factors related to malaria control interventions could also have had an impact during the 2015-2016 epidemic: lack of LLIN universal coverage and technical challenges such as pyrethroid resistance (results of the entomological survey described elsewhere) could be related to higher incidence. Increased malaria-attributable mortality and proportion of all-cause mortality attributed to malaria reflects the exceptional case burden. Despite this large case burden, case fatality rates remained low. This demonstrates the resilience of the health system in Kakuma, though improvements in case management and malaria control are possible. Evidence of stock-outs and lag time of initiating testing for febrile cases among some clinics exhibits potential unpreparedness.

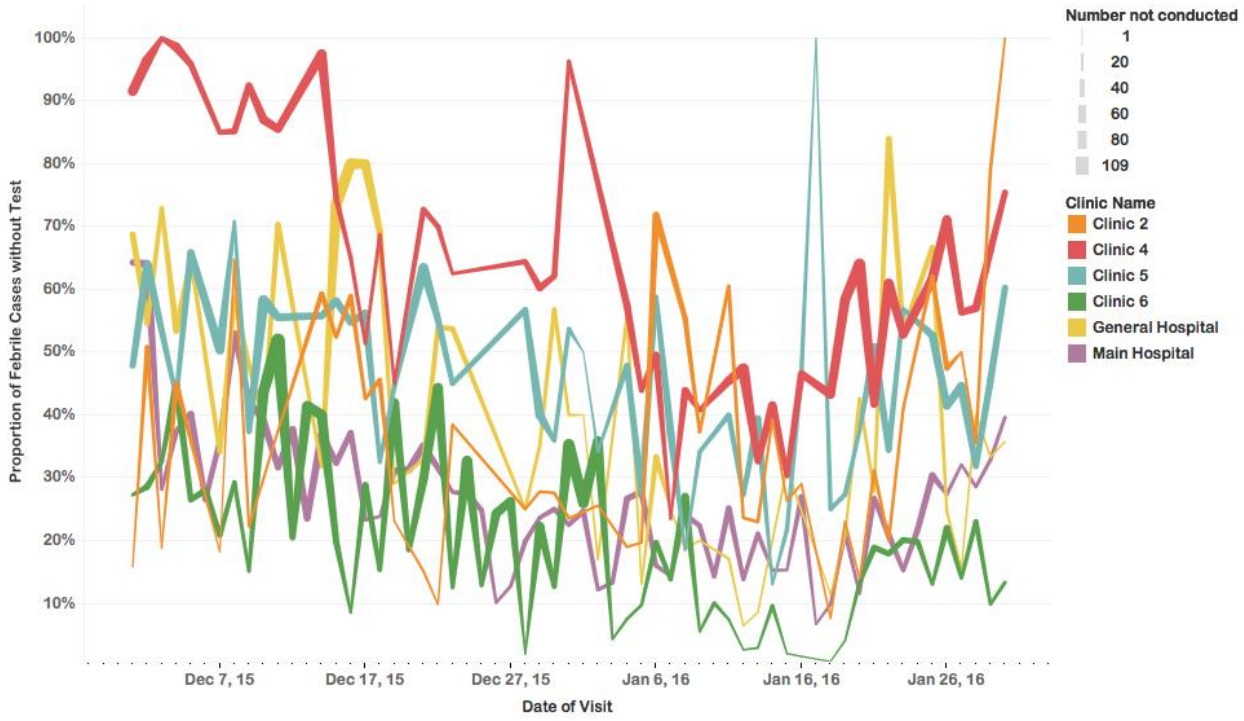
An epidemic of malaria in a semi-arid protracted displacement crisis occurred from December 2015 to February 2016. Geographic and demographic heterogeneities were detected, but incidence was high throughout the camp. Immediate control measures should include mass distribution of LLINs to achieve universal coverage; sensitization of the community to the importance of consistently sleeping under the nets regardless of age; and clinician refresher training on malaria testing, prescribing, and case definition protocol. Intermediate interventions

should include maintaining an alert system for sensitizing both clinicians and the community to malaria following rains or when significant increases in malaria incidence are detected in the HIS. Commodity management systems should be developed to monitor stocks of diagnostic supplies and antimalarial medications to avoid stock outs. Longer term control strategies, such as IRS campaigns, should be planned during periods of consistently low incidence before the onset of April rains, which could help to reduce the baseline endemicity of malaria in the camp.

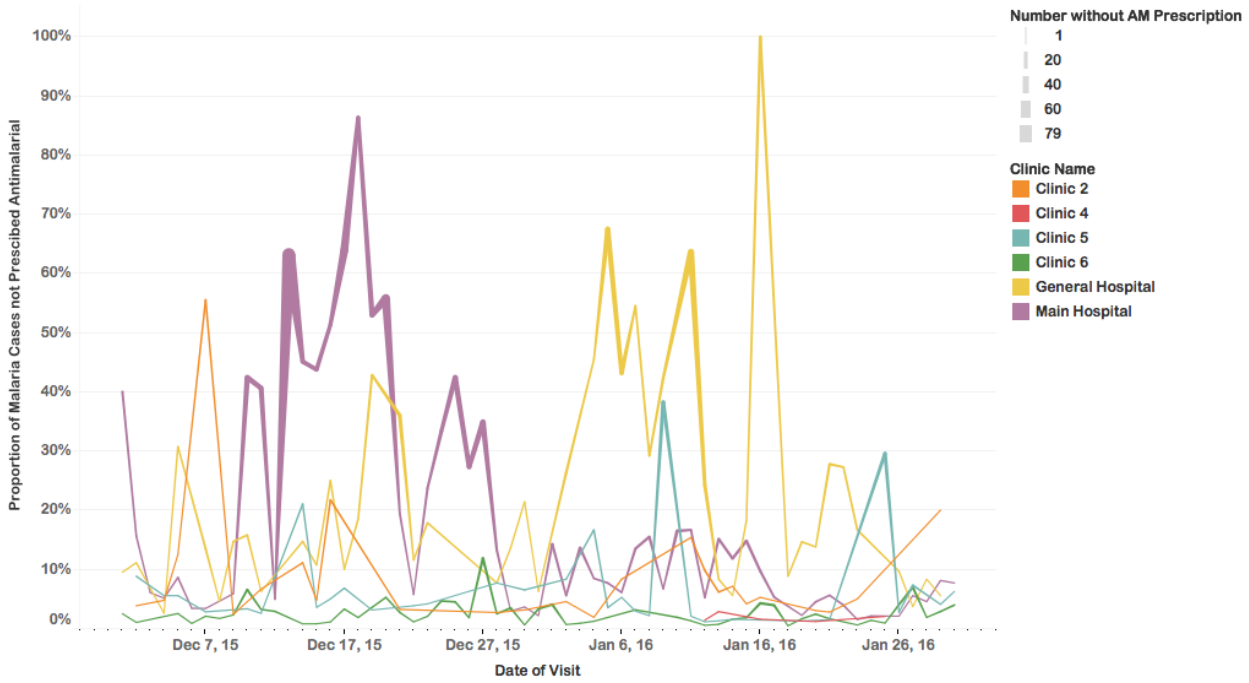
Appendix 1



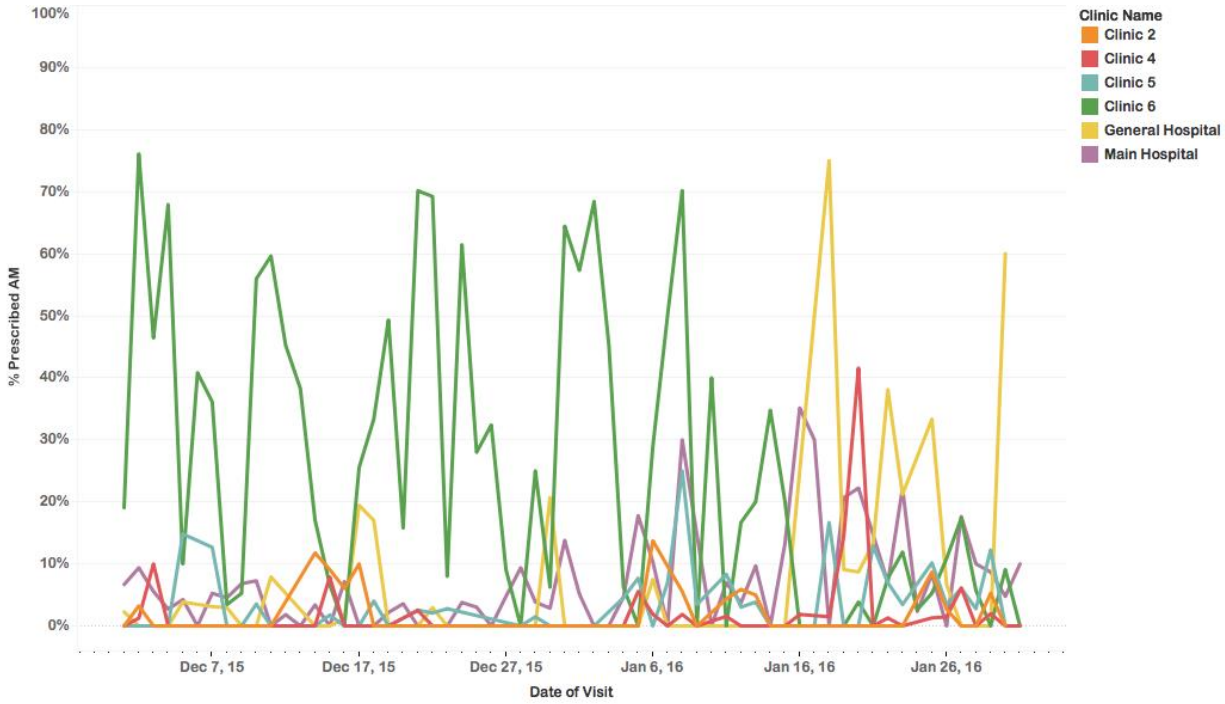
Supplemental Figure 1. Layout of Kakuma refugee camp, Turkana, Kenya: January 2016. Individual polygons represent blocks, which each consist of a mean 232 (range: 11 to 725) households. *Lagga* is the Tarach, a seasonal river that only has water during flash floods or rains. Coordinate system: WGS 1984 UTM Zone 36N. Data courtesy UNHCR Kakuma Planning Office.



Supplemental Figure 2. Proportion of febrile patients without a parasitological test, by clinic, at Kakuma: December 2015 – January 2016. Changes over time could represent changing clinician behavior, while acute peaks could represent stock-outs of rapid diagnostic tests or materials for slide microscopy. Lines are weighted by number of observations.



Supplemental Figure 3. Proportion of confirmed malaria cases without prescription for antimalarial, by clinic, at Kakuma: December 2015 – January 2016. Acute peaks could represent stock outs of antimalarial. Lines are weighted by number of observations.



Supplemental Figure 4. Proportion of febrile cases missing a parasitological test that were prescribed an antimalarial, by clinic, at Kakuma: December 2015 – January 2016. Antimalarial (AM) includes either quinine or artemether-lumefantrine. Acute peaks could represent increased presumptive treatment, potentially related to stock-outs of diagnostics. Clinic 6 remains open through the night when the laboratory is closed.

Supplemental Table 1. Population and ITN ownership by zone, Kakuma refugee camp, Turkana, Kenya: July 2016 Census.

Variable	Kakuma I				Kakuma II		Kakuma III				Kakuma IV		
	Zone 1	Zone 2	Zone 3	Zone 4	Zone 1	Zone 2	Zone 1	Zone 2	Zone 3	Zone 4	Zone 1	Zone 2	Zone 3
Total Population	21,649	25,145	24,269	11,673	17,918	6,768	25,577	17,180	14,453	2,359	10,281	9,622	5,344
Pregnant Women & Children < 5	3,192	3,762	1,947	1,549	2,818	1,281	4,781	2,884	2,876	431	1,664	1,733	936
Number of Households	3,481	3,891	3,156	1,610	2,966	1,185	4,864	2,628	2,293	369	1,449	1,488	733
ITNs Owned	4,820	4,474	4,672	2,239	5,140	1,463	8,123	3,858	1,455	993	1,710	2,014	665
Persons per ITN[†]	4.5	5.6	5.2	5.2	3.5	4.6	3.1	4.5	9.9	2.4	6.0	4.8	8.0
Pregnant Women & Children < 5 per ITN[◊]	0.7	0.8	0.4	0.7	0.5	0.9	0.6	0.7	2.0	0.4	1.0	0.9	1.4

[†]Universal coverage standard is no more than 2 persons per ITN.

[◊]UNHCR standard for emergencies is no more than 2 pregnant women & children < 5 per ITN.

Supplemental Table 2. Population by age group and sex, Kakuma refugee camp, Turkana, Kenya: 31 January 2016.

	Sex		Total
	Male	Female	
Age Group			
< 5	12,677	12,350	25,027
5 - 11	22,539	20,286	42,825
12 - 17	20,191	14,430	34,621
18 - 59	43,817	36,883	80,700
60 +	932	1,879	2,811
Total	100,156	85,828	185,984