



# Impact of Highland Topography Changes on Exposure to Malaria Vectors and Immunity in Western Kenya

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**Background:** It is almost an axiom that in the African highlands (above 1,500 m) transmission of *Plasmodium falciparum* is limited primarily by low ambient temperature and that small changes in temperature could result in temporary favorable conditions for unstable transmission within populations that have acquired little functional immunity. The pattern of malaria transmission in the highland plateau ecosystems is less distinct due to the flat topography and diffuse hydrology resulting from numerous streams. The non-homogeneous distribution of larval breeding habitats in east African highlands obviously affects *Anopheles* spatial distribution which, consequently, leads to heterogeneous human exposure to malaria. Another delicate parameter in the fragile transmission risk of malaria in the highlands is the rapid loss of primary forest due to subsistence agriculture. The implication of this change in land cover on malaria transmission is that deforestation can lead to changes in microclimate of both adult and larval habitats hence increase larvae survival, population density, and gametocytes development in adult mosquitoes. Deforestation has been documented to enhancing vectorial capacity of *Anopheles gambiae* by nearly 100% compared to forested areas.

**Method:** The study was conducted in five different ecosystems in the western Kenya highlands, two U-shaped valleys (Iguhu, Emutete), two V-shaped valleys (Marani, Fort Ternan), and one plateau (Shikondi) for 16 months among 6- to 15-year-old children. Exposure to malaria was tested using circumsporozoite protein (CSP) and merozoite surface protein immunochromatographic antibody tests. Malaria parasite was examined using different tools, which include microscopy based on blood smears, rapid diagnostic test based on HRP 2 proteins, and serology based on human immune response to parasite and vector antigens have been also examined in the highlands in comparison with different topographical systems of western Kenya.

**Results:** The results suggested that changes in the topography had implication on transmission in highlands of western Kenya and appropriate diagnosis, treatment, and control tool

**Abbreviations:** CSP, circumsporozoite protein; IgG, immuno globulin G; MSP, merozoite surface protein antibodies.

needed to be considered accordingly. Both plateau and U-shaped valley found to have higher parasite density than V-shaped valley. People in V-valley were less immune than in plateau and U-valley residents.

**Conclusion:** Topography diversity in western Kenya highlands has a significant impact on exposure rates of human to malaria vectors and parasite. The residents of V-shaped valleys are at risk of having explosive malaria outbreaks during hyper-transmission periods due to low exposure to malaria parasite; hence, they have low immune response to malaria, while the U-shaped valleys have stable malaria transmission, therefore, the human population has developed immunity to malaria due to continuous exposure to malaria.

**Keywords:** topography, V-valley, U-valley, immunity, exposure, rapid diagnostic kit, highland

## INTRODUCTION

Malaria is a major human health threat that occurs globally in tropical and sub-tropical regions. Though malaria has been declining from 1.5 million mortality cases to 438,000 cases in 2014 (1), efforts has to be made to investigate the underlying causes of these hundreds of death cases. The mounting threat is evidence witnessed by increased numbers of malaria outbreaks in the Kenyan highlands (elevation >1,500 m), where malaria was previously rare (2, 3). Malaria outbreaks occurred sporadically in the highlands of western Kenya from the 1920s to the 1950s (4, 5). Since 1988, however, malaria epidemics have occurred with heightened frequency throughout the Kenyan highlands, causing serious mortality and morbidity (2, 3). Malaria in the Western Kenya Highland is characterized by unstable and high-transmission variability (6, 7), which results into epidemics during periods of suitable climatic conditions. Depending on drainage characteristics of the highland vector ecosystems, different transmission intensities results into heterogeneous exposure and development of immunity (6, 8–10). The sensitivity of a site to malaria epidemics is dependent on the level of immunity of the human population. In the last two decades, malaria epidemics have increased in frequency and intensity in the East Africa highlands in populations that have little or no exposure to plasmodial infections (3, 11–13). Research indicates that the mechanisms leading to epidemic malaria in the highlands are complex and are probably due to the concerted effects of factors, such as topography, hydrology, climate variability, land-use/land-cover change, and drug resistance (6, 8–10, 14). Effective disease control calls for a clear understanding of the interaction between these epidemiologic factors (9).

In this study, the highlands topography was classified into three ecosystems these being the flat bottomed valleys (U-shaped), the narrow bottomed valley (V shaped), and the plateau. A longitudinal cohort study was carried out with a primary focus on a spatial-temporal qualitative assessment of exposure to infections using immunological markers in the different ecosystems. Parasitological surveys were carried out to provide baseline data on the effects of ecosystem characteristics on malaria prevalence. Malaria epidemics in western Kenya highlands are driven by climate variability. However, environmental terrain characteristics

can modify the level of malaria transmission and the rate of development of immunity (10). Immunity to severe malaria generally requires only a few infections at any level of endemicity (15–17). However, the long interval between infections and the spatial variability of transmission in areas of unstable endemicity fail to provide frequent enough challenge to sustain much disease-modulating immunity. Recent studies suggested that residents of highland areas generally lack immunity to *Plasmodium falciparum* and are particularly vulnerable to malaria infection (18–20). The proportion of asymptomatic individuals is usually lower in highlands than in high-transmission areas where there is small among-season variation in *P. falciparum* prevalence and parasite densities (21); thus, a small increase in the abundance of vectors may lead to a significant malaria outbreak in the highlands. At high altitudes in the highlands and on hilltops, where malaria transmission intensity is low, human populations have poorly developed immunity to malaria because exposures are infrequent, and persons are vulnerable to severe clinical illness and complications from *Plasmodium* infection (22). High risk for severe malaria is seen in persons living in areas with low-to-moderate transmission intensities (23). In such areas, the proportion of asymptomatic persons is usually lower than in high-transmission areas, where *P. falciparum* prevalence and parasite density varies little between seasons (24). As a consequence of low immunity in the human population of the highlands, malaria epidemics have caused significant human mortality (6). Compared to the malaria situation between the 1920s and 1950s, the current pattern of malaria epidemics in the highlands is characterized by increased frequencies (23), expanded geographic areas (8, 25), and increased case-fatality rates (3). The reemergence of epidemic malaria is likely due to local malaria transmission in the highlands (2, 7, 26, 27). In the late 1980s and early 1990s, a series of malaria epidemics were reported in the western highlands of Kenya and other communities at high altitude in Africa (28–30). Whereas substantial progress has been made on epidemiology and ecology of malaria in highlands, little is known on what proportion of human population exposed to malaria has mounted an immune response. This study was designed to identify how major environmental terrain characteristics that control the breeding of malaria vectors in the western Kenya highlands can influence exposure to transmission and the development of an immune response.

## MATERIALS AND METHODS

### Study Sites

Study sites were characterized into three topographical types.

#### “U”-Shaped Valleys

##### *Iguhu in Kakamega*

Iguhu village (00°17' N, 34°74' E and elevation 1,450–1,580 m above sea level) is located in Kakamega district, western Kenya, with population  $\approx$ 11,000 (**Figure 1**). This area experiences two rainy seasons and averages 2,000 mm rainfall per year. The long rainy season usually occurs between April and May, with an average monthly rainfall 150–260 mm, while the short rainy season usually occurs between September and October, with an average monthly rainfall 165 mm. Malaria prevalence peaks usually lag 1–2 months after the rain. The mean annual daily temperature is 20.8°C. The area has experienced extensive deforestation and swamp reclamation in recent years as a result of rapid human population growth and the demand for settlement and agricultural land; therefore, only patches of forest remain. Malaria vectors in the area are *Anopheles gambiae* sensu stricto and *Anopheles funestus* (31–33). Maize is the principal subsistence crop with vegetables grown on small irrigated plots in valley bottoms. The Yala River bisects the area; most mosquito larval habitats are found on riverbanks in the bottom of the valley and on the banks of streams during both dry and rainy seasons (34).

##### *Emutete in Emuhaya*

Emutete village (00°22' N, 34°64' E and elevation 1,463–1,603 m above the sea level) is located in Emuhaya district (**Figure 1**).

This area is hilly characterized by steep-sided valleys with flat bottoms and plateaus where most homes are built. Small streams run along the valley bottoms and papyrus swamps are common. The valleys are approximately 2.4 km<sup>2</sup> in area and at least 1 km apart. This area is densely populated, with malaria prevalence of 39.6% (35). This area experiences two rainy seasons and averages 2,500 mm rainfall per year. Malaria prevalence peaks usually lag 1–2 months after the rain. The mean annual daily temperature is 20.5°C.

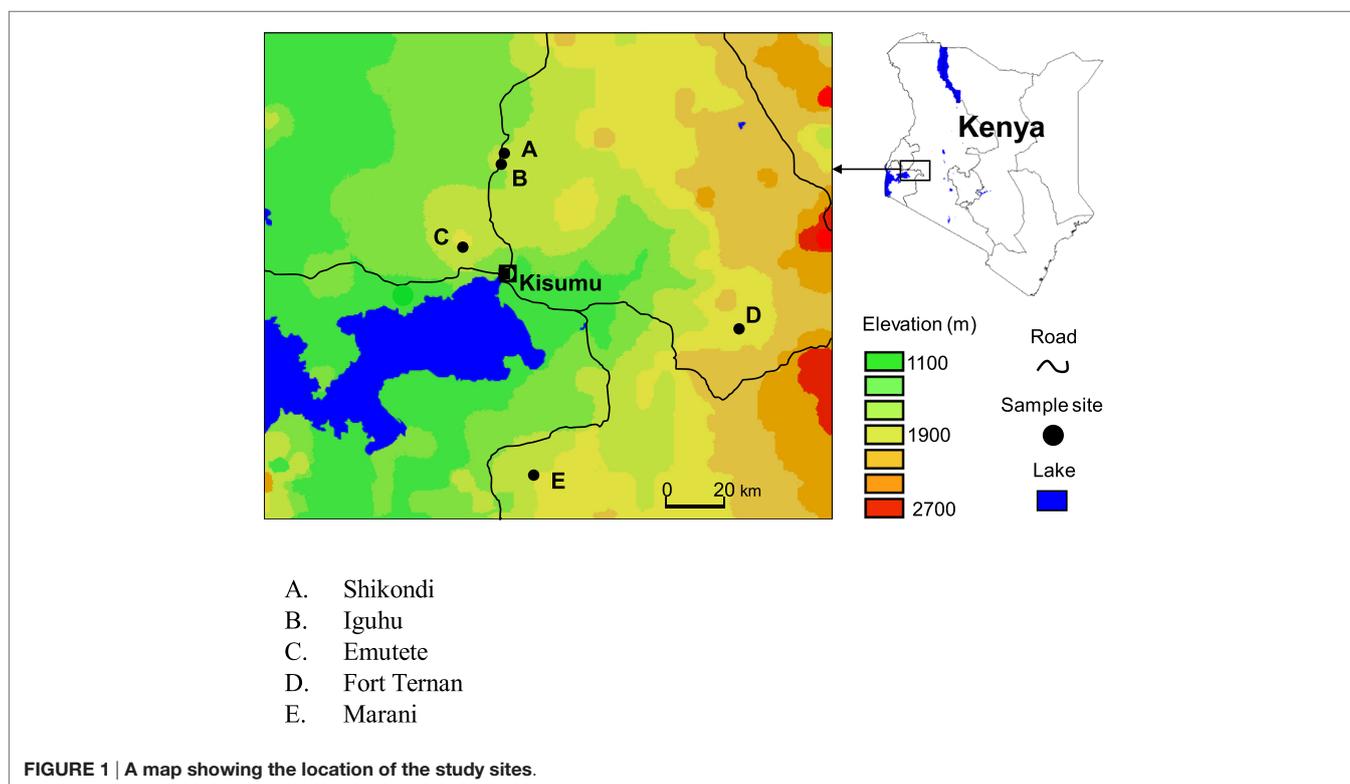
#### “V”-Shaped Valleys

##### *Marani in Kisii*

Marani (00°02' N, 34°48' E and elevation 1,520–1,700 m above the sea level) is located on the highland plateau adjacent to the Lake Victoria Basin and 17 km north of Kisii (**Figure 1**). This area is in a steep valley where the Marani River flows through a shallow gorge on the western side, and river banks are forested with *Eucalyptus* trees. Malaria epidemics have occurred frequently in this area in the last 15 years.

##### *Fort Ternan in Kericho*

Fort Ternan (00°12' S, 35°21' E and elevation 1,500–1,600 m above the sea level) is found in Kericho District (**Figure 1**). Malaria prevalence in this area is unstable varying annually between 10 and 60%, due to this instability, epidemics are common with a high morbidity and mortality rates. Depending on the temperature during a specific year, transmission risk in this area is either seasonal or sporadic (2). This area consists of a variety of land covers ranging from shore regions to hilly areas and from



rainy forests to tea plantations. Agricultural activities in these area are dominated by cash crops, e.g., sugarcane, tea, and coffee.

## Plateau

### *Shikondi in Kakamega*

Shikondi (00°19' N, 34°76' E, elevation 1,533–1,576 m above the sea level) is a plateau found in Kakamega district, Western Kenya (Figure 1). This area experiences two rainy seasons and averages 2,000 mm rainfall per year. The long rainy season usually occurs between April and May, with an average monthly rainfall 150–260 mm, while the short rainy season usually occurs between September and October, with an average monthly rainfall 165 mm. Malaria prevalence peaks usually lag 1–2 months after the rain. The mean annual daily temperature is 20.8°C.

## Laboratory Analysis

### Immunoassay for Exposure to Malaria

Exposure to malaria parasites is indicated by the presence of circumsporozoite proteins (CSPs) antibodies and the merozoite surface protein (MSP) antibodies in the serum. These antibodies persist even if the individual is cured of the parasite. Malaria P.f./P.v. 3 line test device consist of a sample window containing an absorbent pad where the serum/plasma are to be added. It contains a membrane strip, which is pre-coated with recombinant malaria P.f. capture antigens (MSP, CSP) on the test band P.f. region and with recombinant malaria P.v. capture antigens (MSP, CSP) on the test band P.v. region. The recombinant malaria P.v./P.f. antigen (MSP, CSP)-colloidal gold conjugate and serum sample moves along the membrane chromatographically to the test region (P.f., P.v.) and forms a visible line as antibody-antigen gold particle complex forms with high degree of sensitivity and specificity. Blood samples were collected by a standard finger prick and put in capillary tubes, then centrifuged at 1,800 rpm for 5 min to obtain the serum. After the test, kit had been brought to room temperature, the device was put on a flat surface and a drop of serum was added in to the sample window and allowed to soak in, then two drops of the diluent was added into the sample window. The positive results were read in 10 min and the negative results in 20 min.

### Microscopic Analysis of Malaria Parasites

Standard finger-prick method was used for blood samples collection and thick and thin smears prepared on well labeled slides. After smears were air dried, they were fixed in methanol and stained with 4% Giemsa for 30 min (36). The stained smears were then examined using the magnification of 1,000× oil immersions to identify and count the parasite species. Random checks were carried out on the slide counts by independent microscopists to ensure quality control. Parasite density was scored against leukocytes (8,000 cells/μl of blood) positive slide; otherwise, the whole slide was carefully scanned before being declared negative (37).

## Weather Data

Meteorological data collected were mean monthly rainfall, maximum, and minimum temperature for each study site. Data were obtained from the Kenya Department of Meteorology.

## Data Analysis

Malaria parasites site-specific prevalence rates were determined by expressing positive blood smears as a percentage of all the examined blood smears. Geometric mean parasite density was calculated for each site considering only true positive slides. The paired *t*-test was used to determine differences of the prevalence of antibody and malaria parasites infections among the sites at 0.05 significance level. *K* function was used to determine if spatial distribution of infections in the sites was significantly clustered or it was random. In this method, the distance interval is specified, and then the GIS calculates the average number of infections within the distance of each infection. Increasing distances at a specified interval shows at what distance the concentration of infections is the greatest. If the average number of infections found at a distance is greater than that for a random distribution throughout the study area, then the distribution is considered clustered. The GIS finds the distance from each point to every other point, and then, for each point, counts up the number of surrounding points within the given distance. *I* is a weight and is either 1 if the neighboring point is within the distance of the target point or 0 if it is not. To see if there is a pattern, the observed *K* values at each distance is compared to the expected values for a random distribution. This is done by plotting the values on the chart, with the *K* values on the *y*-axis against the distance on the *x*-axis. The *K* value gets very large as the distance increases to reduce the height of the *y*-axis and make the chart easier to read, log transformed values are plotted instead of the raw *K* values. *L* (*d*) is a variation of the *K* values. At any distance, if the line for the observed *L* values is above that of the expected values, the distribution is more clustered than expected for random distribution. If it is below the line for the expected values, the distribution is more dispersed. To determine if the pattern is statistically significant, the curve of the observed distribution is compared to the confidence limits for a random distribution. An observed *L* value that exceeds the upper confidence limit indicated statistically significant clustered pattern for that distance, while one that falls below the lower limit indicates a statistically significant dispersed pattern (38).

## RESULTS

### Malaria Parasite Prevalence

Both *P. falciparum* and *Plasmodium malariae* was found in Iguhu and Emute while only *P. falciparum* was found in the other sites. Malaria parasites prevalence varied significantly between the U-shaped and the V-shaped valleys ( $t = 12.036$ ,  $df = 12$ ,  $P < 0.05$ ), between U-shaped valley and the plateau ( $t = -11.65$ ,  $df = 12$ ,  $P < 0.05$ ) and between V-shaped valleys and the plateau ( $t = -2.76$ ,  $df = 12$ ,  $P < 0.05$ ). There was no significant difference in the parasite prevalence within the U-shaped valleys ( $t = 1.27$ ,  $df = 12$ ,  $P > 0.05$ ), and within the V-shaped valleys ( $t = -4.44$ ,  $df = 12$ ,  $P > 0.05$ ). The mean parasite prevalence in the U-shaped valleys was 22.12%, in the V-shaped valleys was 2.76% and at the plateau was 4.42% over the study period. There was 5.0-fold greater parasite prevalence in the U-shaped compared to the V-shaped valleys.

## Parasite Density

Population living in U-shaped valleys had higher parasite density compared to the V-shaped valleys but varied at the plateau. Geometric means varied significantly between the V-shaped valleys and the plateau ( $t = -2.72$ ,  $df = 12$ ,  $P < 0.05$ ) and between the V-shaped valleys and the U-shaped valleys ( $t = -7.03$ ,  $df = 12$ ,  $P < 0.05$ ). There was no significant difference in the geometric means within the V-shaped valleys ( $t = -2.1$ ,  $df = 12$ ,  $P > 0.05$ ), within the U-shaped valleys ( $t = -1.73$ ,  $df = 12$ ,  $P > 0.05$ ) and between the U-shaped valley and the plateau ( $t = 1.38$ ,  $df = 12$ ,  $P > 0.05$ ).

## Gametocyte Prevalence

The U-shaped valleys had higher *P. falciparum* gametocytes prevalence compared to the V-shaped valleys and at the plateau. Gametocytes prevalence varied significantly between the V-shaped valleys and the U-shaped valleys ( $t = 6.60$ ,  $df = 12$ ,  $P < 0.05$ ), between V-shaped valleys and the plateau ( $t = 3.13$ ,  $df = 12$ ,  $P < 0.05$ ) and between U-shaped valleys and the plateau ( $t = 3.34$ ,  $df = 12$ ,  $P < 0.05$ ). There was no significant difference in the gametocytes prevalence within the V-shaped valleys ( $t = 0.30$ ,  $df = 12$ ,  $P > 0.05$ ), within the U-shaped valleys ( $t = -0.20$ ,  $df = 12$ ,  $P > 0.05$ ). No gametocytes found in Marani during the period of the study (Figure 2).

## Antibodies Prevalence

The U-shaped and V-shaped valleys had significant variations on antibodies prevalence varied between them ( $t = 6.23$ ,

$df = 12$ ,  $P < 0.05$ ) and between the U-shaped valleys and the plateau ( $t = 6.18$ ,  $df = 12$ ,  $P < 0.05$ ). There was no significant difference in the antibodies prevalence within U-shaped valleys ( $t = -0.66$ ,  $df = 12$ ,  $P > 0.05$ ), within V-shaped valleys ( $t = 0.68$ ,  $df = 12$ ,  $P > 0.05$ ) and between V-shaped valleys and the plateau ( $t = -0.99$ ,  $df = 12$ ,  $P > 0.05$ ). The mean antibody prevalence in the U-shaped valley was 24.19%, in the V-shaped valley was 10.13% and at the plateau was 12.23% over the period of the study. There was 2.0-fold greater antibody prevalence in the U-shaped compared to the V-shaped valleys.

## Spatial Distribution of Malaria Infections

The global weighted  $K$  function,  $L(d)$ , was used to examine the spatial distribution of malaria infection by household over an interpoint distance of 100–1,400 m for all the sites. Figure 3 shows measures of the observed  $L(d)$  and the 95% CI plotted for various values of interpoint distance for the Surveys in Emutete and Iguhu, respectively. The spatial distribution of infections is considered evenly dispersed if the observed  $K$  function values are below the lower limit of the 95% CI, clustered if above the upper limit, or random if within the 95% CI. The weighted  $K$  function indicated that the malaria infection distribution pattern was significantly different than expected under complete spatial randomness in the U-shaped valley (Figure 4) but was random in the V-shaped valley (Figure 3) and the plateau (Figure 5). Spatial clustering occurred at the swamps in the U-shaped valleys (Figure 4), it was less clustered at the plateau at low altitude but random in the V-shaped valley (Figure 3). The majority of

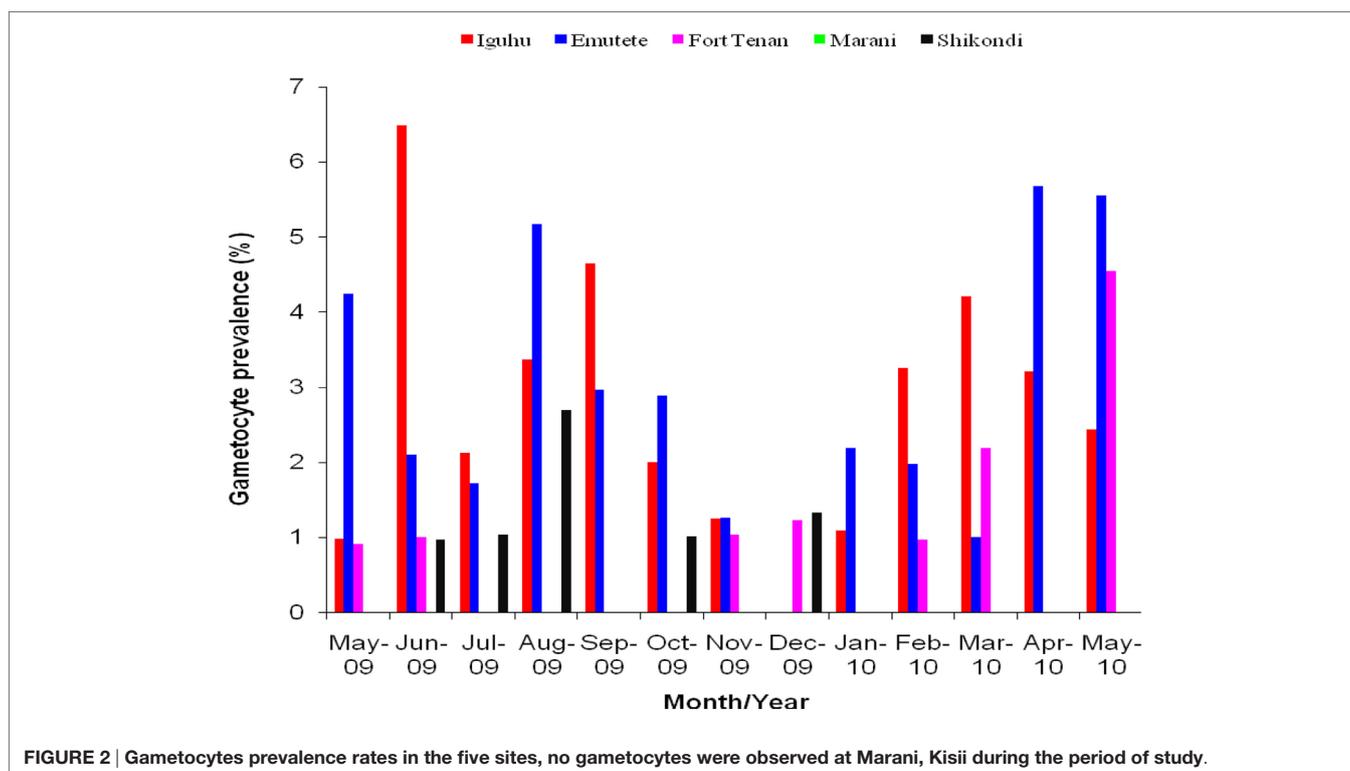
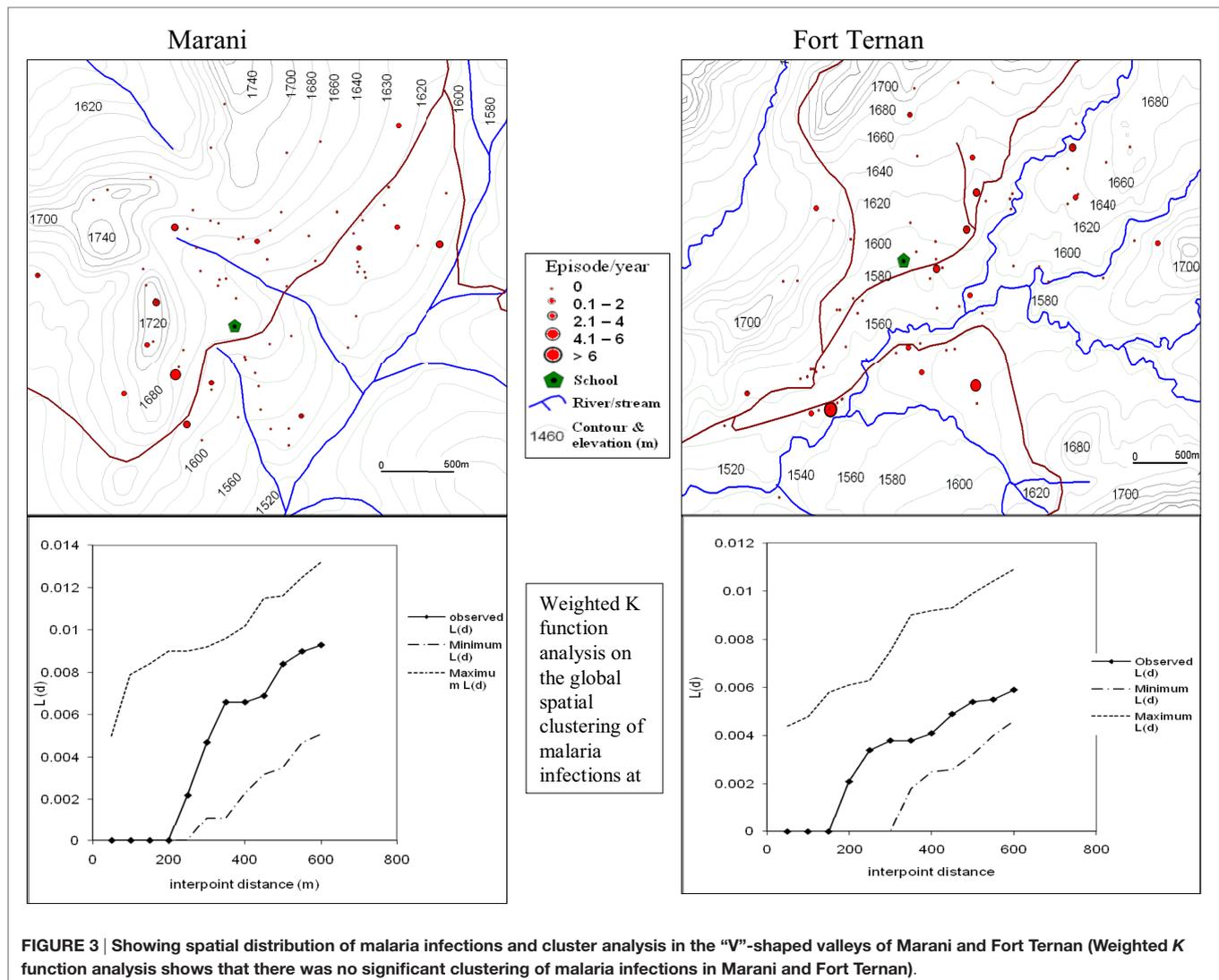


FIGURE 2 | Gametocytes prevalence rates in the five sites, no gametocytes were observed at Marani, Kisii during the period of study.

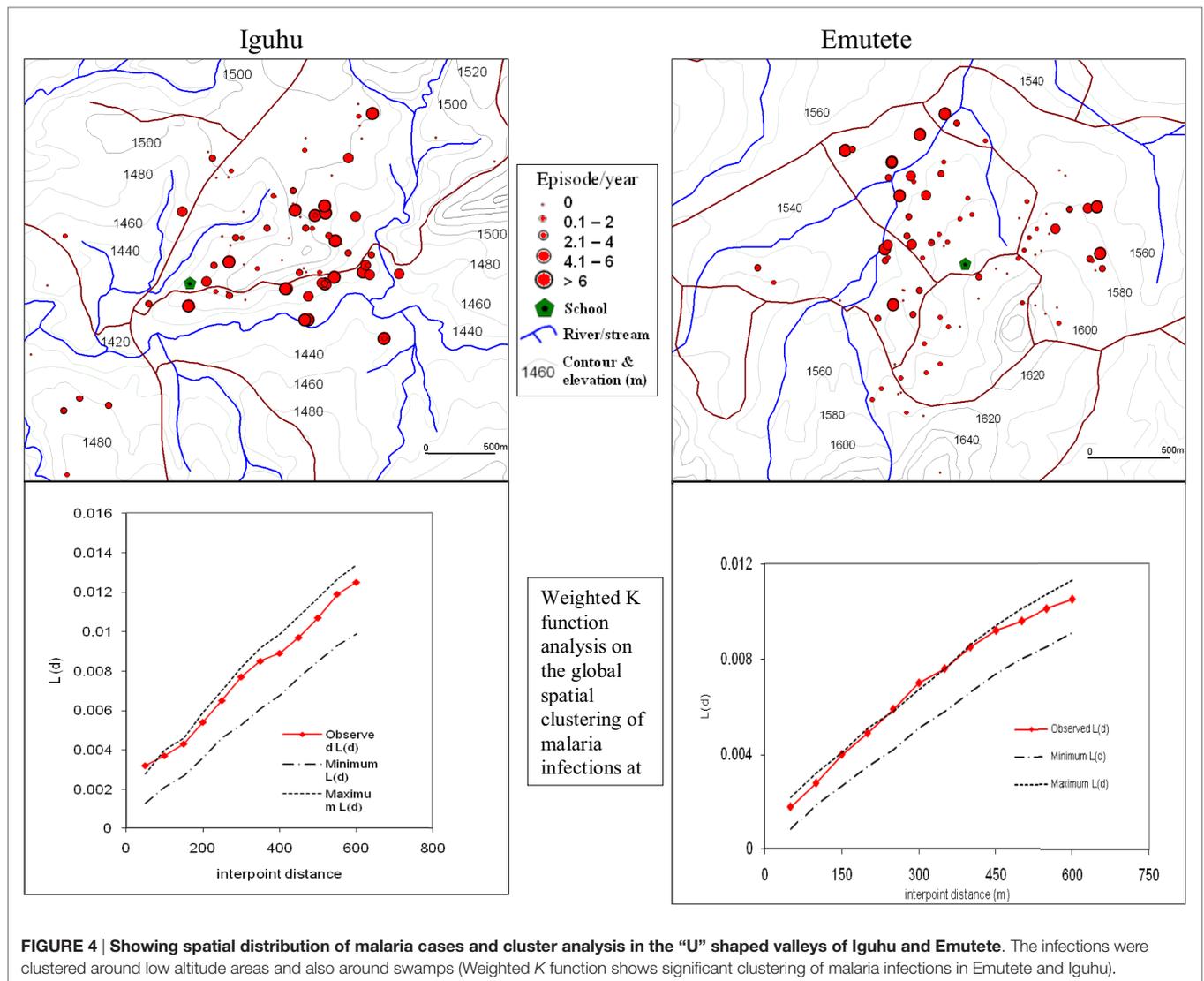


children with parasite positive blood smears in the U-shaped valleys were found infected 4–6 occasions during 12 months, while those in the V-shaped valleys and the plateau had 1–2 infections per year. Thus, the children in the U-shaped valleys were infected for a longer period (**Figures 3 and 4**).

## DISCUSSION

This study has revealed that the western Kenya highland topography is a complex ecosystem comprising of hills, plateaus, valleys, rivers, streams, and swamps. This ecosystem has profound effects on the level of malaria transmission. It has been shown that malaria transmission in the highlands is heterogeneous with the highest incidence being found at valley bottoms followed by hillsides and hilltops (9, 10, 14, 39). In this study, we found that the prevalence of malaria infections was fivefold higher in children living in the U-shaped valleys than in the children living in the V-shaped valleys and the prevalence of malaria infections

at the plateau was similar to that of the V-shaped valleys. Similar findings have been reported in different topography in highlands (10, 16, 40, 41). The prevalence of malaria parasites antibodies was twofold higher in the children living in the U-shaped valleys than in the children living in the V-shaped valleys. Similar findings have been shown in western Kenya highlands with serological markers, where the residents at the valley bottom are more exposed to mosquitoes infectious bites than those living in uphill's (42, 43). The gametocytes prevalence was also high in the children living in the U-shaped valleys compared to the V-shaped valleys and the plateau with no gametocytes observed at Kisii. The children population in U-valleys previously were found to have higher exposure to mosquitoes that subsequently have caused them to be in higher risk of *P. falciparum* gametocytes carriage (10, 16, 42, 43). Parasite densities were high in the children living in the U-shaped valley compared to the V-shaped valleys and varied greatly at the plateau. Similar findings were present previously with the human population in broad valleys having more

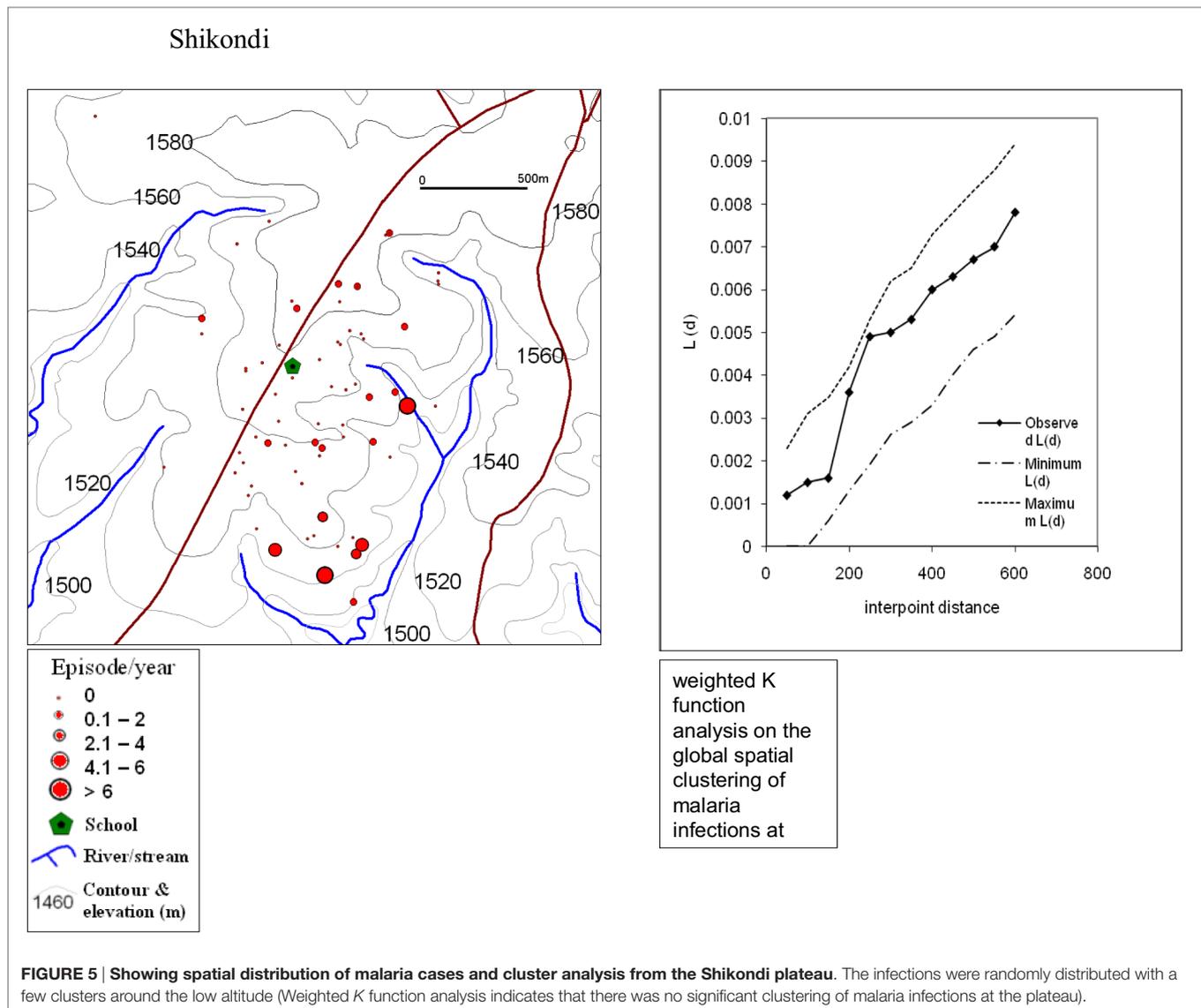


exposure to mosquitoes and higher infection rates (9, 10, 44, 45). We also found out that there was clustering of infections at the swamps in the U-shaped valleys but the infections were randomly distributed in the V-shaped valley and the plateau. Topographic features of the highlands restrict the spatial distribution of vector breeding habitats; this, ultimately, affects malaria transmission, exposure of the human population to malaria infection, and development of immunity of human populations to malaria (9, 43, 45).

In the highlands, most severe malaria cases during an epidemic come from uphill human populations that have not been regularly exposed to malaria infection (7, 10, 44, 46–48). Studies of malaria in highland areas have generally concentrated on malaria parasites densities and vector densities in malaria stable areas within the highlands. Literature searches did not reveal studies that have assessed the immune profile of the population in the highlands and whether topography especially the shape of the valleys in the highlands and plateaus are consistently associated

with malaria risk. Our study addresses this gap in knowledge and demonstrates that topography in this case the shape of the valley and plateaus affects exposure of the human population to malaria and immune response to malaria. These findings suggest that within the highlands some areas have stable malaria transmission and the human population in these areas has developed immunity to malaria; in low and unstable malaria transmission areas, the human population lack immunity to malaria and are likely to suffer severe clinical malaria and subsequently malaria epidemics.

High malaria parasites prevalence in the U-shaped valleys compared to the V-shaped valleys indicates that malaria transmission in the U-shaped valley is more stable. Our findings are similar to later studies which indicated that children in the malaria stable transmission areas have asymptomatic parasitemia and that children under this condition are able to suppress high parasitemia and presumably avoid severe disease (9, 45). The twofold higher mean antibodies prevalence than the



mean parasites prevalence in the V-shaped valleys may suggest that malaria in the V-shaped valley is symptomatic, most cases are treated and more antibodies are detected since the parasites are cleared by the drugs. Other studies have shown a log-linear relationship between exposure and child prevalence predicted by mathematical models assuming exposure-dependent immunity (49). The log-linear relationship between transmission intensity and prevalence of both infections and enlarged spleens, thus, support the existence of exposure-dependent acquired immunity (50). Our results also indicate that children in the U-shaped valley were able to maintain the same level of parasite densities throughout the study, but children in the V-shaped valley took long to achieve the same levels of parasite densities as those in the U-shaped valleys, this suggests that children in stable malaria transmission areas are able to control the numbers of parasites in the blood during a period of increased exposure to infected mosquitoes in the main transmission season

(10, 42, 43). Apart from *P. falciparum*, *P. malariae* was observed in the U-shaped valleys but only *P. falciparum* was observed in the V-shaped valleys and the plateau, this suggest that residents of malaria stable transmission areas often have mixed infections but only *Plasmodium* species is found in unstable malaria transmission areas (51).

There was also great variation of the parasites densities at the plateau that is indicated by the magnitude of the error bars, this can be explained by the flat topography and the more diffuse hydrology resulting from numerous streams at the plateau. Other studies have shown that malaria transmission at the plateau ranges from low on the hilltops to high to a level as high as that at the valley bottoms (10, 42, 44). According to the Ministry of Health in Burundi, malaria in the high plateau is hypo- to meso-endemic and prone to epidemics (52). Our results have shown clearly that malaria prevalence in the highland is greatly affected by the terrain characteristics of the highland, the dynamics of malaria

infections were significantly different among the two valley systems and the plateau indicating that malaria transmission in the highlands is heterogeneous due to its complex topographical features. The shape of the valley affects the availability of mosquito breeding habitats, thus affecting malaria transmission. U-shaped valleys have poor drainage and this causes accumulation of water during rainy seasons creating excellent breeding habitats for malaria vectors; by contrast, there is no accumulation of water in the V-shaped valleys due to good drainage.

The high gametocytes prevalence rates in the U-shaped valleys compared to the V-shaped valleys indicate that the reservoir of malaria infections in the U-shaped valleys is higher than in the V-shaped valleys and the plateau. While the population living in the U-shaped valley maintains a large reservoir of infectious gametocytes, the people living in the V-shaped valley comprise a high proportion of susceptible individuals. Under permissive climatic conditions, the infectious vector population could increase, leading to higher rates of malaria prevalence. In our study, the mean gametocyte density varied significantly between the V-shaped and the U-shaped valleys, and between each of the two valley systems and the plateau. The low prevalence of gametocytes in the V-shaped valleys with no gametocytes observed in Kisii indicates that there is a weak transmission system in the V-shaped valley (15, 16).

High antibody prevalence in the U-shaped valley compared to the V-shaped valleys and at the plateau indicates that children in the U-shaped valley are regularly exposed to malaria parasites due to stable malaria transmission in these areas and, therefore, they have developed immunity to malaria parasites. Majority of residents in the U-shaped valleys suffer 2–6 episodes of malaria per year or are continuously infected for 6 months whereas in the V-shaped valley and the plateau majority of the residents suffer 1–2 malaria episodes per year or are continuously infected for 2 months (42, 43). This shows that individuals in the U-shaped valleys have developed immunity to malaria due to continuous exposure to malaria parasites. Similar studies have shown that the majority of breeding habitats in the hilly highlands are confined to the valley bottoms because the hillside gradients provide efficient drainage, these areas are, therefore, characterized by well-established transmission, with the majority of children 6–13 years old maintaining asymptomatic parasitemia (9, 10, 40). Previous studies using human sera from individuals in malaria endemic populations have found evidence of association between total IgG levels MSP2 with a reduced subsequent risk of clinical malaria (3, 19, 42–44). Other studies have shown that in regions where malaria is hyperendemic, adults develop potent but non-sterile immunity against malaria in which individuals chronically harbor low-grade parasitemia and only occasionally suffer from mild clinical malaria (53). Soe and others also showed that there is an association between antigen-specific antibody responses and protection against clinical malaria in Southeast Asia (53). Segeja and colleagues in Tanzania showed that individuals with higher levels of IgG are partially protected from malaria infections (54). The findings of our study indicate

that the high prevalence of antibodies in the U-shaped valleys is responsible for asymptomatic malaria in these areas. In spite of high prevalence of malaria in the U-shaped valleys, individuals in the U-shaped valley have developed immunity to clinical malaria, individuals in the V-shaped valleys, on the other hand, have low prevalence of malaria but they also lack immunity to malaria and, therefore, they are more prone to malaria epidemics during hyper-transmission periods. Spatial analysis of the malaria antibodies and infections indicated that there was a significant positive clustering around swamps and marshes in the U-shaped valleys of western Kenya highlands.

## CONCLUSION

The findings of this study indicate that the topography characteristics of the highland valleys systems affect the exposure of the human population to malaria parasites and the immune response to malaria. The residents of V-shaped valleys are at risk of having explosive malaria outbreaks during hyper-transmission periods due to low exposure to malaria parasite; hence, they have low immune response to malaria, while the U-shaped valleys have stable malaria transmission; therefore, the human population has developed immunity to malaria due to continuous exposure to malaria. The spatial distribution maps have found clustering of malaria infections around the swamps and at low altitude in the U-shaped valleys and random distribution of malaria in the V-shaped valleys, implementation of malaria control treats the highlands as a homogeneous entity and does not take into consideration the high heterogeneity of transmission and incidence. Thus, the distribution of interventions does not take in care the different transmission intensities and disease incidence, topography maps can be reliably used to identify the affected areas and the scarce resources focused to these areas to control malaria.

## AUTHOR CONTRIBUTIONS

CW conceived and designed the study, did data collection, and analysis. EK drafted the manuscript. Both revised and agreed upon submission.

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