Association between recent overnight travel and risk of malaria: a prospective cohort study at three sites in Uganda

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Summary: At three sites in Uganda, recent overnight travel was associated with an increased incidence of malaria in cohort participants followed for one year. Individuals who travel may represent a high-risk group that could be targeted for malaria control interventions.

Running title: Overnight travel and the risk of malaria

ABSTRACT

Background. Human movement can undermine malaria control efforts. However, understanding of the association between travel and malaria infection in Africa is limited. We evaluated the association between recent overnight travel and malaria incidence in Uganda.

Methods. All children aged 0.5-10 years and one adult living in 266 randomly selected households within 3 different regions of Uganda were followed prospectively. Information on overnight travel was collected in 2015 - 2016. Malaria, defined as fever with parasites detected by microscopy, was measured using passive surveillance.

Results. At least one overnight trip was reported by 64 of 275 (23.3%) participants in Walukuba, 37 of 317 (11.7%) in Nagongera, and 19 of 314 (6.1%) in Kihihi. Among individuals who traveled, the incidence of malaria was higher in the first 60 days after traveling, compared to periods without recent travel at all 3 sites (overall 1.15 vs 0.33 episodes per person-year, incidence rate ratio 3.53, 95% confidence interval [CI] 1.85-6.73, p<0.001). Risk factors for malaria within 60 days following overnight travel included young age (19.5% in children vs 4.9% in adults, odds ratio [OR] 5.29, 95% CI 1.34-21.0, p=0.02) and not using an insecticide treated net (ITN) during travel (18.0% for no use vs 4.1% for any use, OR 5.10, 95% CI 1.07-24.5, p=0.04).

Conclusions. Recent overnight travel was associated with a higher incidence of malaria. Individuals who travel may represent a high-risk group that could be targeted for malaria control interventions, particularly use of ITNs.

Key words: Travel, malaria, Uganda, ITNs

BACKGROUND

Over the past decade, substantial reductions in the burden of malaria have been documented worldwide, following heavy investment in control interventions [1]. Despite this success, malaria control remains a major challenge, and recent evidence suggests that progress has stalled or reversed in some regions [2]. In Uganda, the scale-up of long-lasting insecticide treated nets (ITNs), indoor residual spraying of insecticides (IRS), and treatment of symptomatic malaria cases with artemisinin-based combination therapies (ACTs) has been associated with reduced malaria incidence

and prevalence in some areas [3-5]. However, malaria control gains have been greatest in areas receiving IRS, and a dramatic resurgence of malaria occurred in Northern Uganda following the withdrawal of IRS [6-8]. To ensure that recent gains are not lost, strategic deployment of malaria control interventions is needed. In addition to widescale implementation of malaria control interventions, targeting individuals with major contributions to the infectious reservoir of parasites may be a valuable approach [9].

Human movement is an underappreciated risk factor for malaria transmission [10-12]. Individuals living in low-transmission areas, or in areas where malaria has been controlled, may be at increased risk of infection when traveling to areas of higher transmission intensity [13-15]. Infected travelers may return home with symptomatic malaria, or asymptomatic parasitemia, contributing to the burden of malaria cases, and serve as a reservoir of parasites for onward transmission [10, 13]. Furthermore, returning travelers may re-introduce parasites in areas where malaria has previously been eliminated, presenting a major challenge to control efforts. Although travel to endemic countries has been recognized as a risk factor for malaria [16-18], evidence on the risk posed by travel within endemic areas is less robust. Several studies from Africa [12-15, 19-21], and elsewhere [10, 11, 22, 23], suggest that recent travel (generally within the last month) is associated with an increased risk of malaria. However, our understanding of the causal association between travel and malaria infection, particularly in Africa, is limited by the design of prior studies, which have been either cross-sectional [13, 19, 20] or case-control studies [12, 14, 15, 21], and by heterogeneity in methods used to determine malaria outcomes [19, 24].

In Uganda, little information on the association between overnight travel and the risk of malaria exists. One case-control study conducted among children presenting to health facilities in western Uganda found that travel from highland areas with low-level malaria transmission to higher transmission areas was strongly associated with risk of malaria [21]. To further investigate travel as a

risk factor for malaria in Uganda, we analysed prospective data from cohorts in 3 different regions to evaluate the association between recent overnight travel and the incidence of malaria.

METHODS

Study area and site characteristics

The study was conducted at 3 sub-counties with varied malaria epidemiology (Figure 1). Walukuba sub-county in Jinja district is a peri-urban area in the south-central part of Uganda near Lake Victoria with relatively low malaria transmission intensity [25]. Nagongera sub-county in Tororo district is a rural area in south-eastern Uganda bordering Kenya. Prior to the introduction of indoor residual spraying (IRS), malaria transmission in Nagongera was intense, but following three rounds of IRS with bendiocarb at 6 months intervals, initiated in December 2014, malaria transmission reduced considerably [4]. A fourth round of IRS with pirimiphos-methyl was conducted in June-July 2016. Kihihi sub-county in Kanungu district is a rural area in the south-west part of the country bordering a national park, where malaria transmission intensity is classified as moderate (10 – 100 infectious bites per person per year). All study sites received ITNs between 2013 and 2014 as part of a national ITN distribution campaign [3].

Enrollment and follow up of study participants

The methods are described in detail elsewhere [26]. Briefly, all children aged 0.5-10 years and one adult from 100 randomly selected households per site were enrolled into the cohorts. Study participants were included if they 1) were full time residents of the selected household, 2) had no intention to move outside the sub-county for the next two years, 3) agreed to come to a dedicated study clinic located within the sub-county for any febrile illness, 4) agreed to avoid antimalarial medications administered outside the study, and 5) provided written informed consent, or consent was obtained from parents or guardians for children.

All participants were given an ITN (PermaNet®, Vestergaard Frandsen, Switzerland) at enrollment and were followed for all their healthcare needs at the study clinic, which was open 7 days a week. Participants were provided free health care, clinic travel expenses and an ITN, but received no other incentives to participate. Episodes of malaria were diagnosed by passive case detection and defined as a history of fever within the past 24 hours or an elevated temperature ($\geq$ 38.0° C tympanic) with a positive malaria blood smear. Episodes of malaria were treated with artemether-lumefantrine (uncomplicated malaria) or quinine (complicated malaria). In addition, participants were invited to make a routine visit to the study clinic every 3 months. At each of these visits, a thick blood smear was taken to assess for parasitemia. ITN use, defined as whether the participant reported sleeping under an ITN the previous night, was measured at the time of routine clinic visits. The cohorts were dynamic, such that all newly eligible children were enrolled, and participants were withdrawn when they reached 11 years of age. Additional criteria for withdrawal from the study included 1) permanent movement out of the sub-county, 2) inability to be located for >4 months, 3) withdrawal of informed consent, 4) withdrawal of all children under their care in the case of adults, and 5) inability to comply with the study schedule and procedures.

Recent overnight travel follow-up

As part of the scheduled 3-month visit assessment, study participants were asked about their travel history from July 2015 through June 2016 at every visit to the study clinic. Overnight travel was defined as spending at least one night away from the sub-county of residence. For study participants who reported any overnight travel, data on dates of travel, destination of travel, ITN use, and the reasons for travel were collected.

Estimation of entomological inoculation rates

Entomological inoculation rates were estimated using data from entomologic surveys carried out concurrently with the cohort study. Details on surveys, processing of mosquito specimens, and

identification of sporozoites have been described elsewhere [25]. Briefly, one CDC light trap collection was carried out monthly in the main sleeping room of each house. Light traps were positioned with the light 1.5 m from the floor near the foot of the bed and were left hanging to collect mosquitoes between 19.00 h and 07.00 h the following morning.

Laboratory procedures

Thick blood smears were stained with 2% Giemsa, allowed to dry for 30 minutes, and read by experienced laboratory technologists. Parasite densities were calculated by counting the number of asexual parasites per 200 leukocytes or per 500 leukocytes if the count was less than 10 asexual parasites per 200 leukocytes, assuming a leukocyte count of 8,000 per microliter. A blood smear was considered negative if the examination of 100 high power fields did not reveal any asexual parasites. For quality control, blood smears were read by a second microscopist, and discrepancies in malaria parasites detection or parasite density readings of $\geq$ 25% were resolved by a third microscopist. The third reading was assessed, and the final reading results selected according to whether they agreed with first or second reading. Mosquito specimens were sorted to species level and counted. Sporozoites were identified using an enzyme-linked immunosorbent assay, as previously described [25].

Statistical analysis

All data were recorded onto standardised case record forms, double-entered into Microsoft Access (Microsoft Corporation, Redmond, Washington, USA), and analysed using Stata 14 (STATA Corp., College Station, TX, USA). The observation period for this project covered July 1st 2015 through June 30th 2016, during which time data on travel were collected. For each cohort participant, person-time of follow-up was categorized according to the number of days since last overnight travel, dichotomized into ≤60 days or > 60 days since overnight travel. A cut-off of 60 days was determined after exploring thresholds of 14, 30, 60, and 120 days following overnight travel. Person-time of

follow-up while traveling was not included in the analyses since it was not possible to diagnose malaria while study participants were away. The outcome of interest was the incidence of malaria, defined as the number of new episodes of malaria per person time of follow up. Comparisons between the incidence of malaria during exposed and unexposed periods included only individuals with at least one overnight trip, such that each participant served as their own control. Associations between recent overnight travel and malaria incidence were expressed as incidence rate ratios (IRR) and estimated using generalized estimating equations with a Poisson family adjusting for seasonality and repeated measures in the same study participant. To determine seasonality, the follow-up period was stratified into January to February and May to June (dry seasons), and March to April and July to December (rainy seasons). Associations between risk factors and whether or not a person was diagnosed with malaria in the 60 days following each individual trip were expressed as odds ratios (OR) and estimated using generalized estimating equations with a binomial family adjusting for repeated measures in the same participant. A p-value < 0.05 was considered statistically significant.

Ethics considerations

The study obtained ethical approvals from the Makerere University School of Medicine Research and Ethics Committee, the Uganda National Council of Science and Technology, the London School of Hygiene and Tropical Medicine Ethics Committee, Durham University School of Biological and Biomedical Sciences Ethics Committee and the University of California, San Francisco Committee on Human Research.

RESULTS

Characteristics of the study sites, participants and travel histories

From July 2015 to June 2016, travel histories were taken from 906 participants living in 266 households across the 3 study sites (Table 1). Of these, 120 (13.3%) participants reported at least

one episode of recent overnight travel, resulting in a total of 138 individual trips. Most participants (86.7%) who traveled reported taking only one trip. The proportion of participants reporting any recent overnight travel, and the total number of trips taken, were highest in Walukuba, followed by Nagongera, and Kihihi. Overall, the median duration of each trip was 7 nights. Most participants reported traveling for pleasure or to attend a funeral; very few traveled for business. Reported use of ITNs during recent overnight trips was much lower than that reported at scheduled 3-monthly visits (35.5% vs 99.8%, p<0.001).

Association between recent overnight travel and risk of malaria

Among individuals who traveled, the incidence of malaria was over 3 times higher in the 1-60 days after traveling, as compared to periods without travel in the previous 60 days (1.15 vs. 0.33 episodes of malaria PPY, IRR=3.53, 95% CI 1.85-6.73, p<0.001) after adjustment for seasonality (Table 2). When the analysis was stratified by age, this finding was statistically significant only in children. Recent overnight travel was associated with a higher risk of malaria incidence in all 3 study sites, most notably in Nagongera, where the incidence of malaria was over 6-fold higher during the post-travel period.

Risk factors of any malaria following recent overnight travel

In an analysis adjusted for repeated measures in the same study participant, being a child less than 11 years of age, and not using an ITN during travel, were associated with an increased odds of being diagnosed with malaria within 60 days of return from overnight travel. The odds of malaria following travel was over 5 times greater in children than in adults. Similarly, the odds of malaria following travel in participants who did not use an ITN during travel was 5 times that of those who reported any ITN use (Table 3). Traveling during the rainy season and traveling for shorter durations were associated with an increased odds of being diagnosed with malaria, but these associations did not reach statistical significance in multivariate analyses (Table 3).

Blood smear results before and after recent overnight travel

Of the 138 overnight trips, 133 (96.4%) had at least one routine blood smear result available before and after travel (Figure 2). In most cases (93.2%), the pre-travel blood smear was negative. Of the 9 trips in which the pre-travel blood smear was positive, only 2 had symptomatic malaria; both cases were treated and had a negative blood smear after travel. Of the 7 cases of asymptomatic parasitemia before travel, only one had symptomatic malaria diagnosed after travel, 2 had asymptomatic parasitemia after travel, and 4 had a negative blood smear after travel. Of the 124 trips that were blood smear negative before travel, 17 (13.7%) were diagnosed with symptomatic malaria after travel, 6 (4.8%) had asymptomatic parasitemia after travel, and 101 (81.5%) had a negative blood smear after travel. Thus, of the 18 trips in which symptomatic malaria was diagnosed after travel, and for which a pre-travel blood smear result was available, 17 (94.4%) had a negative blood smear before traveling, suggesting that the infection was acquired during travel

DISCUSSION

Human movement plays an important role in the spread of malaria and other infectious diseases [15, 27, 28]. However, gaps remain in our understanding of associations between travel and malaria incidence in malaria endemic areas. To further investigate travel as a risk factor for malaria in Uganda, we analysed data from cohorts in 3 different epidemiological settings. Among individuals who traveled, the incidence of malaria was significantly higher in the first 2 months after traveling compared to periods without recent travel. Residents who traveled from Nagongera, a rural site where IRS has been successfully deployed, were at particularly high risk following travel, as were children and those participants who did not sleep under an ITN when traveling. These results suggest that individuals who travel within Uganda constitute a high-risk group that could be targeted for malaria control interventions.

Human movement has been shown to contribute to the rebound of malaria when programs fail, or control efforts are discontinued. In the 1960s, human mobility contributed to the resurgence of malaria in Africa after the World Health Organisation's Global Malaria Eradication Program collapsed and has been highlighted as a factor that received insufficient attention [29, 30]. A similar resurgence of malaria occurred more recently in southern Africa when the Joint Malaria Control Initiative ended due to lack of funding, fuelled by the reintroduction of parasites into South Africa and Swaziland from travelers from Mozambique [32, 33]. In another recent study from Zanzibar, individuals traveling to malaria endemic areas were found to be the most important source of imported infection, contributing up to 15 times more malaria cases than non-residents visiting the island [27]. In Equatorial Guinea, travel between Bioko Island and the mainland within the previous eight weeks was associated with an increased risk malaria infection; parasite prevalence was substantially higher in passengers arriving on Bioko Island than those departing [13]. Thus, evidence from across Africa highlights that human movement is an important but often underappreciated challenge for malaria control.

Our findings support those of prior studies that showed travel to be a risk factor for malaria in Africa and help to clarify the causal association between travel and malaria risk. Previous studies included cross-sectional surveys [13, 19, 20], which are limited to observations at a single point in time, and case-control studies [12, 14, 15, 21], which are susceptible to biases. Additional attempts to evaluate recent travel as a risk factor for malaria have been made using census data, [19, 34, 35] which is limited by the potential for recall bias, and inability to assess causal associations [19, 20]. In our study, participants were followed prospectively, and data on parasitemia and clinical symptoms were collected longitudinally, before and after travel. This robust study design allowed us to capture incident cases, and to track changes in parasitemia within individual travelers over time. However, most of the adults included in the cohort were females (93.6%), which limits our ability to generalize our findings to other populations at risk, including young male workers.

Our study had several limitations. First, we relied on microscopy for identification of parasitemia. By relying on microscopy for malaria diagnosis, which has limited sensitivity, we likely underestimated the number of malaria infections in our study. However, because our primary outcome was clinical incidence, which is typically associated with higher parasite densities within the level of detection by microscopy, this is unlikely to have impacted on our results. Second, the numbers of participants who traveled in our cohort study was small, limiting our ability to evaluate behavioral risk factors and activities associated with travel. In addition, these data were too sparse to make comparisons of the risk of malaria infection between adults and children who traveled together on the same trip. Third, we could not account for all potential risk factors for malaria infection in cohort members. However, the analysis was constructed such that each individual served as their own control, allowing us to adjust for potential unmeasured confounders. Finally, the destination of travel and level of malaria transmission relative to that where people were traveling from, was not considered in our analysis, limiting our ability to evaluate interactions between transmission intensity and seasonality of home compared to destination of travel.

Malaria control in Africa relies heavily on vector control applied at the population level. However, there is increasing awareness of the roles of high risk individuals in transmission of malaria. Our results showed that recent overnight travel was a significant risk factor for malaria. If travelers contribute significantly to the burden of malaria and to the infectious reservoir, they can be targeted for specific actions, including education on the risks of travel, emphasis on using ITNs while traveling, and possibly use of chemoprevention, as is routine for travelers from non-endemic countries. Future research should further explore travel-related behaviors to better identify individuals at greatest risk of malaria. To successfully control and eventually eliminate malaria in Africa, innovative methods directed at high risk individuals will be a valuable addition to complement population-level vector control.

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Conflict of interest

All authors declare no competing interests, and the funders of the project had no role in the study design, data collection, data analysis, data interpretation and writing of the report.

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Figure legends

Figure 1. Map of Uganda showing study sites (red): Walukuba sub-county located in south central part of Uganda, Kihihi in south-western part, and Nagongera in South-east Uganda.

Figure 2. Results of blood smears before and after recent overnight travel.

Table 1. Characteristics of study sites, participants, and travel history by study site

Characteristic	Study site			
	All sites	Walukuba	Nagongera	Kihihi
Entomological inoculation rate[1]	N/A	2.4	4.5	11.2
Total number assessed for overnight travel	906	275	317	314
Total number of children, n (% total)	687 (75.8%)	205 (74.6%)	242 (76.3%)	240 (76.4%)
Female children, n (% children)	339 (49.3%)	101 (49.3%)	116 (47.9%)	122 (50.8%)
Total number of adults, n (% total)	219 (24.2%)	70 (25.5%)	75 (23.7%)	74 (23.6%)
Female adults, n (% adults)	205 (93.6%)	66 (94.3%)	68 (90.7%)	71 (96.0%)
Participants reporting any overnight travel, n (% total)	120 (13.3%)	64 (23.3%)	37 (11.7%)	19 (6.1%)
Characteristics of participants reporting any recent overnight travel				
Total number of children, n (% total)	69 (57.5%)	38 (59.4%)	25 (67.6%)	6 (31.6%)
Female children, n (% children)	27(39.1%)	13(34.2%)	9 (36.0%)	5 (83.3%)
Total number of adults, n (% total)	51 (42.5%)	26 (40.6%)	12 (32.4%)	13 (68.4%)
Female adults, n (% adults)	48 (94.1%)	24 (92.3%)	11 (91.7%)	13 (100%)
Total duration of observation in days, median (IQR)	266 (223-280)	239 (208-267)	280 (263-284)	268 (260-283)
Total duration of overnight travel in days, median (IQR)	8 (4-19)	10 (6-21)	7 (3-13)	4 (2-16)
Number of overnight trips reported, n (%)				
1	104 (86.7%)	55 (85.9%)	31 (83.8%)	18 (94.7%)
2	14 (11.7%)	8 (12.5%)	5 (13.5%)	1 (5.3%)
3	2 (1.7%)	1 (1.6%)	1 (2.7%)	0
Characteristics of individual recent overnight trips taken by children				
Total number of overnight trips	77	42	29	6
Duration of each trip, median (range)	9 (1 – 39)	10 (1 – 39)	7 (2 – 33)	3 (2 – 16)
Reasons for travel, n (%)				
Pleasure / visiting relatives	60 (77.9%)	34 (81.0%)	21 (72.4%)	5 (83.3%)
Attending funeral	11 (14.3%)	7 (16.7%)	4 (13.8%)	0
Caring for sick relative	4 (5.2%)	0	4 (13.8%)	0
Business	0	0	0	0
Seeking medical care	1 (1.3%)	0	0	1 (16.7%)
Not specified	1 (1.3%)	1 (2.4%)	0	0
Any reported ITN use during travel, n (%)	26 (33.8%)	10 (23.8%)	14 (48.3%)	2 (33.3%)
Characteristics of individual recent overnight trips taken by adults				
Total number of overnight trips	61	32	15	14
Duration of each trip, median (range)	6 (1 - 79)	6 (1 - 34)	5 (1 - 33)	5 (1 - 79)
Reasons for travel, n (%)				
Pleasure / visiting relatives	28 (45.9%)	15 (46.9%)	9 (60.0%)	4 (28.6%)
Attending funeral	19 (31.2%)	14 (43.8%)	3 (20.0%)	2 (14.3%)
Caring for sick relative	9 (14.8%)	1 (3.1%)	3 (20.0%)	5 (35.7%)
Business	3 (4.9%)	2 (6.3%)	0	1 (7.1%)
Seeking medical care	2 (3.3%)	0	0	2 (14.3%)
Not specified	0	0	0	0
Any reported ITN use during travel, n (%)	23 (37.7%)	9 (28.1%)	9 (60.0%)	5 (35.7%)

[1] infective bites per person per year July 2015 – June 2016

Table 2. Associations between recent overnight travel and incidence of malaria among participants with any overnight travel

Age group	Study site	Time in relationship to overnight travel	Episodes of malaria	Person years of observation	Incidence of malaria[1]	Unadjusted IRR (95% CI)	Unadjusted p-value	Adjusted aIRR[2] (95% CI)	Adjusted p-value
All	All	No overnight travel in previous 60 days	20	60.1	0.33	reference		reference	
		1-60 days since overnight travel	21	18.3	1.15	3.61 (1.84-7.11)	<0.001	3.53 (1.85-6.73)	<0.001
Stratified by age group									
Children	All	No overnight travel in previous 60 days	16	32.9	0.49	reference		reference	
		1-60 days since overnight travel	18	10.1	1.78	3.93 (1.82-8.49)	<0.001	3.67 (1.77-7.61)	<0.001
Adults	All	No overnight travel in previous 60 days	4	27.2	0.15	reference		reference	
		1-60 days since overnight travel	3	8.2	0.37	2.51 (0.47-13.6)	0.28	2.28 (0.48-10.8)	0.30
Stratified by study site									
All	Walukuba	No overnight travel in previous 60 days	7	28.5	0.25	reference		reference	
		1-60 days since overnight travel	9	10.0	0.90	3.73 (1.26-11.0)	0.02	3.26 (1.12-9.48)	0.03
All	Nagongera	No overnight travel in previous 60 days	3	20.9	0.14	reference		reference	
		1-60 days since overnight travel	6	5.2	1.16	7.95 (1.78-35.5)	0.007	6.54 (1.65-26.0)	0.008
All	Kihihi	No overnight travel in previous 60 days	10	10.8	0.93	reference		reference	
		1-60 days since overnight travel	6	3.1	1.91	2.02 (0.93-4.35)	0.07	2.84 (1.32-6.13)	0.008

[1] per person years
[2] adjusted for seasonality

Table 3: Risk factors for malaria following recent overnight travel

Risk factor	Categories	Proportion of participants diagnosed with malaria 1-60 days following overnight travel	Univariate*		Multivariate*	
			OR (95% CI)	p-value	OR (95% CI)	p-value
Age group	Adult	3/61 (4.9%)	reference		reference	
	Child	15/77 (19.5%)	4.62 (1.27-16.8)	0.02	5.29 (1.34-21.0)	0.02
Report ITN use during travel	Any	2/49 (4.1%)	reference		reference	
	None	16/89 (18.0%)	5.06 (1.12-22.7)	0.04	5.10 (1.07-24.5)	0.04
Season when traveling	Dry season[¥]	6/80 (7.5%)	reference		reference	
	Rainy season	12/58 (20.7%)	3.19 (1.13-9.04)	0.03	2.94 (0.97-8.92)	0.06
Duration of travel	9-79 days	6/60 (10.0%)	reference		reference	
	< 9 days	12/78 (15.4%)	1.61 (0.58-4.50)	0.36	2.30 (0.72-7.33)	0.16

*adjusted for repeated measures in the same participant

[¥]January to February and May to June

Figure 1.

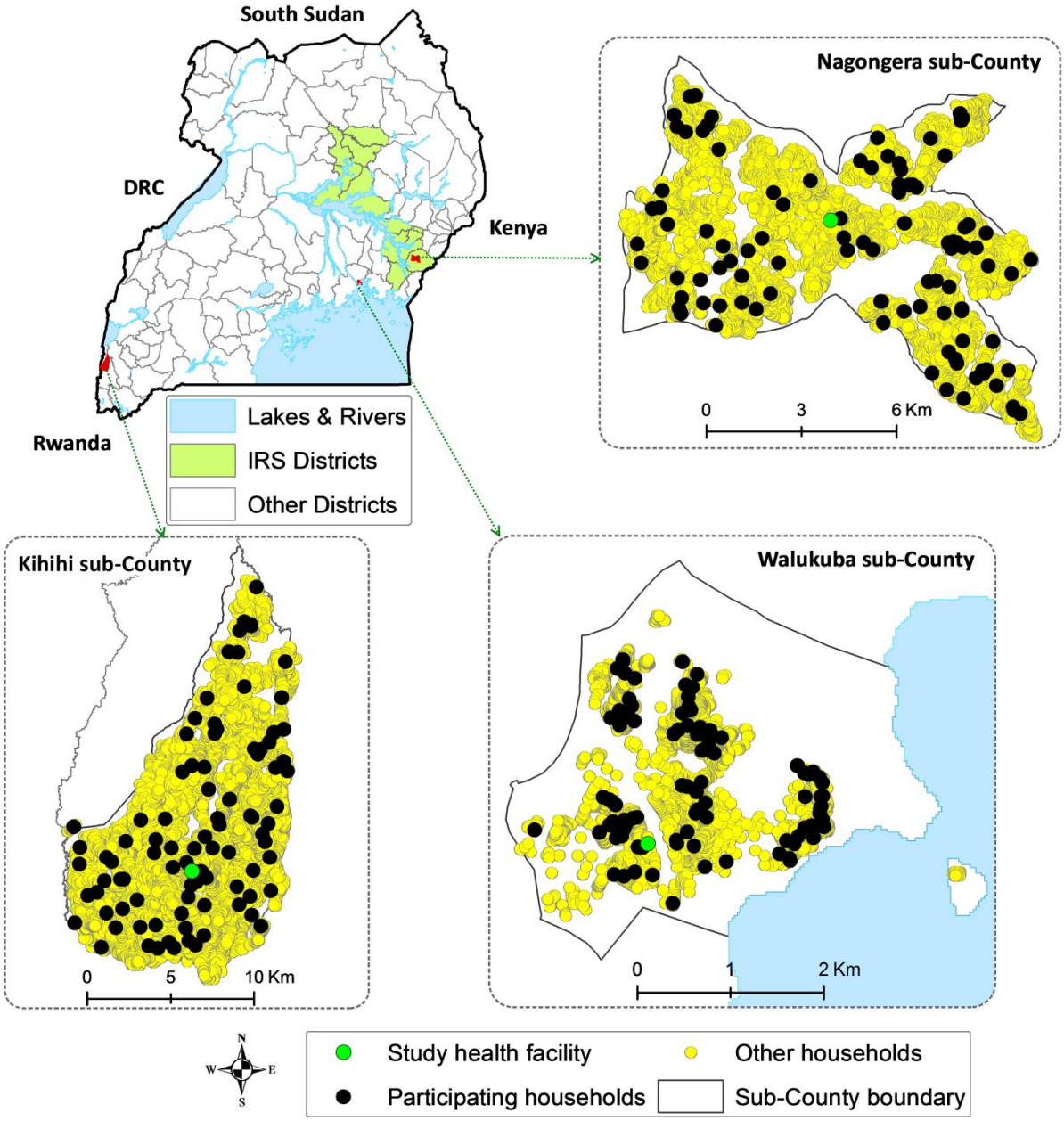

Figure 2