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Association between recent internal travel and malaria in Ugandan highland and highland fringe areas

Caroline A. Lynch¹, Jane Bruce², Amit Bhasin², Cally Roper², Jonathan Cox² and Tarekegn A. Abeku^{2,3}

¹ Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK

² Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, UK

³ Malaria Consortium, London, UK

Abstract

OBJECTIVE To examine the association between travel (recency of travel, transmission intensity at destination compared to origin and duration of travel) and confirmed malaria in Uganda.

METHODS Health facility-based case-control study in highland (~2200 m), and highland fringe (~1500 m) areas with adjustment for other covariates.

RESULTS In the highland site, patients who had travelled to areas of higher transmission intensity than their home (origin) areas recently were nearly seven times more likely to have confirmed malaria than those who had not (OR 6.9; $P = 0.01$, 95% CI: 1.4–33.1). In the highland fringe site, there was also a statistically significant association between travel and malaria (OR 2.1; $P = 0.04$, 95% CI: 1.1–3.9).

CONCLUSIONS For highland areas, or areas of low malaria transmission, health authorities need to consider internal migrants when designing malaria control programs. Control interventions should include information campaigns reminding residents in these areas of the risk of malaria infection through travel and to provide additional mosquito nets for migrants to use during travel. Health authorities may wish to improve diagnosis in health facilities in highland areas by adding travel history to malaria case definitions. Where routine monitoring data are used to evaluate the impact of interventions on the malaria burden in highland areas, health authorities and donors need ensure that only cases from the local area and not ‘imported cases’ are counted.

keywords malaria, migration, Uganda, highland, elimination

Introduction

Migration is a key factor in the spread of antimalarial drug resistance [1, 2] and the maintenance, or increase of malaria transmission [3]. Yet it remains one of the least studied areas of malaria epidemiology mainly because there are many different types of migration making it difficult to measure in a standardised way [4]. While data are sparse, indications are that both international and internal migration have increased dramatically since the 1990s [4, 5] highlighting the urgent need to understand the role of travel in relation to malaria.

This study examines the association between travel (assessing recency of travel, and transmission intensity at origin and destination areas and duration of travel) and confirmed malaria, while adjusting for other possible covariates. Given the current global move towards malaria elimination, understanding the role of migration in increasing an areas ‘vulnerability’ through

the maintenance or re-introduction of malaria infections is critical.

Methods

In 2007, a health facility-based case-control design was used to determine the association between confirmed malaria among symptomatic patients and travel in the previous 4 weeks. Cases and controls were recruited in two districts, the highland site of Kabale (~2200 m above sea level) and a highland fringe site of Rukungiri (~1500 m above sea level). Patients were matched 1:1 for age in years, sex, village of residence and date of presentation. Individual travel histories during the month prior to presentation were recorded at health facilities at time of presentation. Patients were subsequently interviewed using structured questionnaires at their residence to verify reported travel patterns, and to collect additional information on socio-economic and environmental factors. Household locations and altitude

were captured using a Garmin™ (Garmin Ltd, Switzerland) Geographical Positioning System (GPS).

Background

Malaria (predominantly *P. falciparum*) is highly endemic in Uganda with an estimated 90% of the population at risk of infection and disease. However, unstable and epidemic-prone transmission areas are found in highland fringe, and highland areas, respectively (Figure 1), particularly in the south-west of the country.

The two study sites for this study were referral health centres. Bufundi health centre is located in a highland area of Kabale district (~2200 m above sea level), and Kebisoni health facility is located in a highland fringe area of Rukunigiri district at ~1500 m. Malaria in both sites is seasonal, with peaks in transmission occurring in December (short rains) and April (long rains). Malaria transmission is low in the highland site and unstable, bordering on hyperendemic, in the highland fringe site (Figure 1).

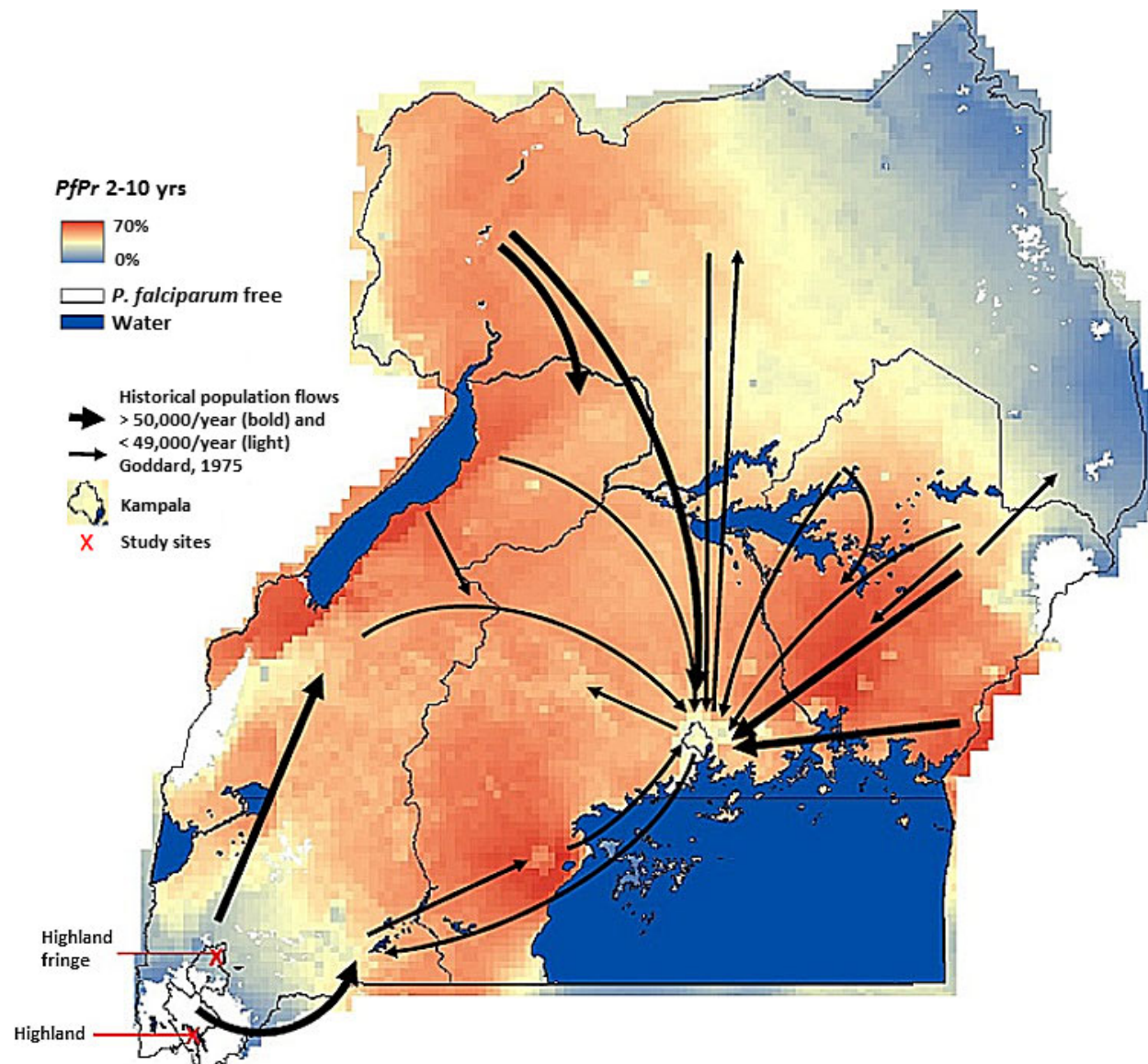


Figure 1 Study sites, historical migration flows, and estimated levels of *P. falciparum* malaria endemicity within the limits of stable transmission, Uganda. Adapted from Gething, P.W. *et al.* (2011)[6] and Lynch, C.A. & Roper, C. (2011) [7].

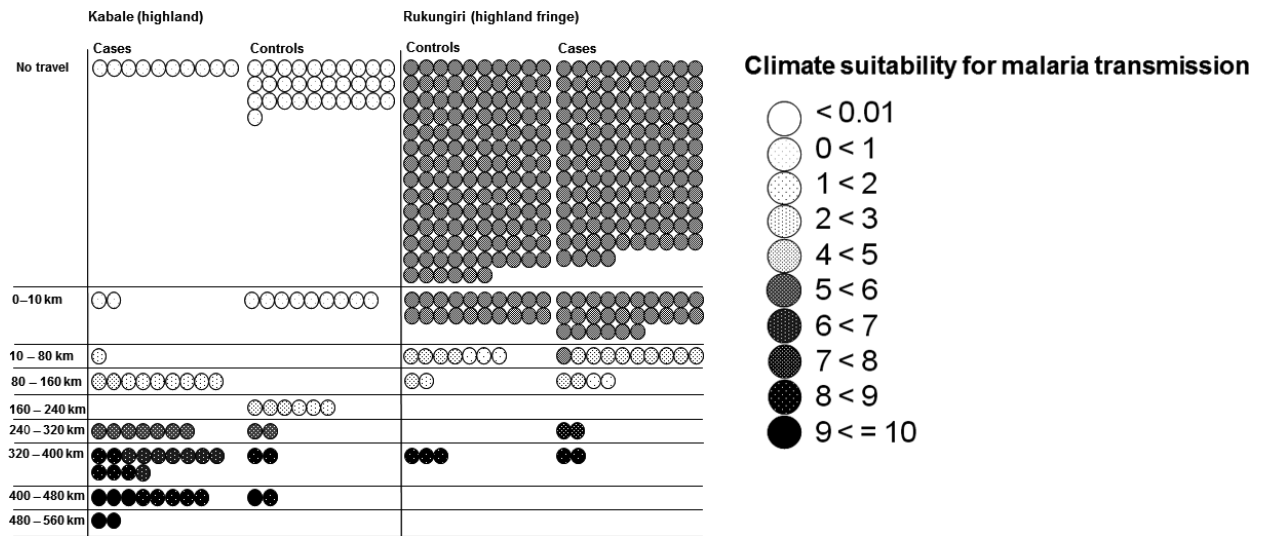


Figure 2 Migration streams in Kabale (highland) and Rukungiri (highland fringe).

Definitions

Cases and controls were defined as patients presenting to the health facility, who satisfied the following criteria: study area resident having lived in the subcounty for a year or more; having suspected malaria according to standard Uganda Ministry of Health case definitions; without symptoms or signs of another illness including complicated malaria. Furthermore, cases were rapid diagnostic test (RDT)-positive for *P. falciparum* while controls were RDT-negative; RDTs are histidine-rich protein (HRP)-2 antigen-based tests, which have high sensitivity (98%) and specificity (88%) in Uganda [8].

Travel exposure was measured using three variables: (i) any travel, for at least one night, in the last 4 weeks outside the patients' subcounty of residence; (ii) transmission intensity in destination areas compared to origin; and (iii) duration of travel. Patients' travel history, destination subcounty and district, and travel dates were recorded through interviews at the laboratory on first presentation.

Estimates of climate suitability for malaria transmission, derived from the malaria risk atlas for Africa (MARA) [9], were used as measures of transmission intensity or risk of malaria infection in origin and destination areas. MARA maps present modelled data of average malaria distribution derived from rainfall and temperature data, which supplement empirical data where they existed [10]. Using MARA estimates, each origin and destination subcounty (that is subdistrict level) was categorised as having low to high transmission intensity on a scale of 0–10, where 0 is no transmission and 10 was intense

transmission, according to the average estimated climate suitability for malaria transmission. According to the MARA model, malaria transmission intensity in an average year was zero in the subcounty of the highland site, and five in the highland fringe site. Thus, patients who travelled from the highland site to areas of zero malaria transmission risk were considered to have travelled to areas of equal risk. Patients from the highland site who travelled to areas with greater than zero transmission intensity were categorised as travellers to higher malaria risk areas. Patients from the fringe site were defined as having travelled to areas of lower or equal risk if they travelled to areas with a risk <5 and to areas of higher risk if they travelled to areas with transmission risk >5.

Excluded patients were those living outside the direct catchment area of the health facilities and visiting the area for <6 months because their home environments and exposures could not be measured and compared with those living in the study area.

Data management and analysis

Data were entered into Epi Info™ version 2000 (CDC, Atlanta), merged and cleaned before transferring to STATA version 10 (StataCorp, Texas). The associations between malaria and each of the travel variables as well as local potential confounding factors were estimated using a Mantel–Haenszel test. Multivariate conditional logistic regression models were used to test the association between malaria and each travel variable controlling

for local factors that were significant in the bivariate analysis at $P < 0.05$.

Results

In the highland site, 52 cases and 52 controls were recruited. The mean age of patients was 26 years (95% CI: 23.7–29.2), and most patients were male (80%). In the fringe site, 168 cases and controls were recruited. The mean age for cases was 17.5 years (95% CI: 15.8–19.1); more than half of patients were male (58%).

The proportion of patients travelling in the previous 4 weeks from the highland site was greater (46%; 95% CI: 36.4–55.9) than that for the fringe site (12.8%; 95% CI: 9.2–16.4). Most patients who travelled from highland villages went to areas of higher malaria transmission intensity, while a smaller proportion went to areas of equal malaria transmission intensity. Travellers who left the fringe site tended to go to destinations close by where transmission intensity was estimated to be equal or less than in their home areas. Figure 2 describes travel among cases and controls by transmission intensity and distance from home areas for both sites. A high proportion of controls travelled from the highland site (30.7, 95% CI: 17.8–43.7), however cases travelled far more (61.5%, 95% CI: 47.9–75.2). In addition, cases tended to travel further distances, to areas of higher transmission intensity than controls who travelled. In the fringe site, the difference between travel among cases and controls was not as stark as for the highland site with 19% of controls having travelled in the last 4 weeks compared to 26% of cases. Cases and controls had similar travel patterns in that they tended to travel to areas nearby.

For people who travelled from the highland site, the mean duration of travel was 15 weeks. Those who travelled from the fringe site did so for far less time, on average 1 week.

Association between travel and symptomatic malaria in the highland site ($n = 52$)

All three travel variables (assessing recency of travel, and transmission intensity at origin and destination areas and duration of travel) were significantly associated with confirmed malaria after both bivariate and multivariate analyses (Table 1). Confounding variables significant after the bivariate analysis were socio-economic factors (which reduced risk of malaria for the second wealth quintile category) and altitude (where living at a higher than average altitude had a protective effect). After multivariate conditional regression controlling for significant confounding factors, all travel variables remained significant for malaria. Overall, travellers were nearly five times (95% CI: 1.4–16.3) more likely to have malaria than non-travellers. Travel to areas of higher risk increased the odds of malaria to nearly seven times for travellers vs. non-travellers (95% CI: 1.4–33.1).

The risk of malaria for those who travelled for longer than the average period of time (duration of travel) was significantly higher in the bivariate analysis (OR 5.1). However, after controlling for confounding variables, altitude and socio-economic status, the risk of malaria was greater for people who travelled for less time (OR 6.1), nearly double the risk for people who travelled for longer periods (OR 3.2) compared to those who did not travel. The difference between those who travelled for less time compared to those who travelled for more was not significant given the overlap in confidence intervals.

Association between symptomatic malaria and travel in the highland fringe site ($n = 168$)

In the fringe site recent travellers had an increased risk of being a patient with confirmed malaria (OR 1.9). While travel remained significant after adjusting for confounding, the estimate seemed to be driven by an increased risk of

Table 1 Odds Ratios and Adjusted Odds Ratios after bivariate and conditional logistic regression, Kabale district (highland)

Travel outcomes	Cases	Controls	OR	95% CI		<i>P</i>	aOR*	95% CI		<i>P</i>
No travel	20	36	1				1			
Travel in the last 4 weeks	32	16	4.2	1.7	10.2	0.002	4.7	1.4	16.3	0.01
No travel	20	36	1				1			
Travel to areas of low or equal risk	2	7	1.2	0.3	4.7	0.8	1.5	0.3	7.9	0.7
Travel to areas of high risk	30	9	5.9	2.1	16.9	0.001	6.9	1.4	33.1	0.02
No travel	20	36	1				1			
Less than average time travelled	19	11	3.8	1.6	9.0	0.003	6.1	0.9	42.0	0.07
More than average time travelled	13	5	5.1	1.2	22.3	0.03	3.2	1.1	10.1	0.04

*Estimates are from conditional logistic regression models after adjusting for altitude and socio-economic status.

malaria for those who travelled to areas of the same or lower transmission intensity (Table 2). No association was detected between duration of travel and confirmed malaria.

Discussion

We report findings from a health facility-based case–control study undertaken in highland and highland fringe areas of south-west Uganda. In the highland site, patients who travelled in the last 4 weeks were at nearly five times the risk of malaria than those who did not travel, after controlling for local factors. Unsurprisingly, travel to areas of higher malaria transmission intensity was associated with an even greater (OR 6.9) risk of malaria. Travel for longer than average periods of time significantly increased risk of malaria three times over those who did not travel. However, patients who travelled for longer than the average 15 weeks tended to travel to higher transmission areas, as such this estimate probably reflects their greater exposure to risk over a longer period of time in the destination area.

Results from our highland site confirm findings from similar studies in South-East Asia [11–14] and South America [15–17], which have shown travel to be a significant risk factor for malaria and/or infection, and a study in Kenya, where there was an increased risk for malaria among well persons (OR 1.59; 95% CI: 1.2–2.1) and outpatients (OR 2.38; 95% CI: 2.17–2.6) who had travelled in the previous 8 weeks anywhere outside their highland residence [18, 19].

Our results go beyond these in looking at different aspects of travel such as assessing transmission intensity at origin and destination areas as well as duration of travel. A study in the Kenyan highlands [19] indicates the risk of asexual parasitaemia (confirmed malaria) was significantly associated with travel more than 20 km away within 6 weeks of the study (Pearson $\chi^2 = 58.28$; $P < 0.001$). We developed a more refined measure by assessing the change in transmission risk. This nuanced

approach may have allowed for more accurate categorisation of transmission intensity in areas to which people travelled. The magnitude of the estimates from our highland site indicates a much higher risk of malaria when patients travelled to areas of higher transmission than in previous studies. Confidence intervals for the highland site were wide; thus, the estimate is not very precise. However, the difference in estimated travel-associated risk in our Uganda site may be as a result of the higher altitude compared to the Kenyan site resulting in lower mean monthly temperature and lower transmission intensity at origin. In addition, transmission intensity at the destination area was estimated for smaller administrative (subcounty) areas than in either of the Kenyan studies, allowing for more spatial variability in transmission intensity to areas where patients had travelled.

In the highland site, pockets of higher transmission have been demonstrated in the past [20], but at the time of this study district-wide IRS campaigns could have reduced the risk of travellers acquiring infections if they were travelling within the district. However, travellers who left the highland district almost always travelled to areas of higher transmission intensity because of the overall low risk within the highland district.

The risk of malaria associated with duration of travel in the highland areas is puzzling. When duration of travel estimates are adjusted for significant local factors, the risk of malaria associated with shorter periods of travel increases to double that associated with longer periods of travel. This is due to the effect of altitude as a confounder. In general, people who lived in the highland site tended to travel further and for more time than those from the highland fringe site. However, people who lived at the highest altitudes (>2100 m) were at increased risk of symptomatic malaria after travelling, even when they travelled for shorter durations, indicating that those at the highest altitudes were at the greatest risk.

In the fringe site, travel to any area in the last 4 weeks doubled the risk of malaria. However, when travel is di-

Table 2 Odds Ratios and Adjusted Odds Ratios after bivariate and conditional logistic regression, Rukungiri district (highland fringe)

Travel outcomes	Cases	Controls	OR	95% CI		P	aOR*	95% CI		P
No travel	140	153	1				1			
Travel in the last 4 weeks	28	15	1.9	1.1	3.4	0.02	2.1	1.1	3.9	0.02
No travel	140	153	1				1			
Travel to areas of low or equal risk	24	9	2.6	1.6	4.4	<0.0001	2.9	1.6	5.2	<0.0001
Travel to areas of high risk	4	6	0.7	0.2	3.6	0.7	0.7	0.1	3.7	0.7
No travel	140	153	1				1			
Less than average time travelled	20	11	1.9	0.9	4.1	0.1	1.9	0.9	4.0	0.1
More than average time travelled	8	4	2.0	0.9	4.4	0.1	2.8	0.9	8.3	0.07

*Estimates are from conditional logistic regression models after adjusting for whether the household had an animal enclosure.

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saggregated by transmission intensity at destination, the risk of malaria is highest for those who travelled to areas of lower or equal transmission intensity. This finding is related to the relatively large number of highland fringe cases who reported travel in the last 4 weeks to areas of low or equal malaria risk. Compared to those who travelled to areas of higher risk (24 *vs.* 4). This result could be due to a combination of factors. Firstly, a high number of false-positive RDTs may have contributed to those who had travelled to lower transmission intensity sites as positive, when they were true negative cases. Second, results could be due to misclassification of malaria risk at destination areas. Our classification of malaria risk is based on a static risk map based on climate suitability. In reality, malaria transmission in south-west Uganda and in other areas of the country is variable with seasons. This study took place during the dry season in the highland and highland fringe sites of Uganda. However, there could have been rains in other areas of the country increasing risk – which would not have been captured in our categorisation. Third, residents who travelled from the highland fringe site did so for relatively short durations (average 1 week) increasing the likelihood that they may have been infected in their home areas. Finally, behaviour of highland fringe area residents moving to equal or lower transmission areas could have resulted in greater risk, albeit in a lower risk area. If people perceived that they were travelling to an area of equal or lower risk, it may be that they behaved differently in those areas for example, failing to use a net, staying outside later into the evening etc.

The study has several limitations. A major challenge of case-control design is the selection of control populations that are a relevant group to compare against cases. In this study, health facility-based controls were chosen, which may not be representative of the general population ‘at risk’. This choice was rationalised on the basis that controls would be comparable to cases having been drawn from the same population. However, infrequent use of public health facilities in the region [8] may have led to selection bias which could have led to either an over or underestimation of malaria risk associated with travel.

A second limitation to the study was the small number of patients who were recruited compared to initially estimated sample requirements. Originally the sample size for the highland site was estimated at 372, to be able to detect an OR of 2 or greater. For the fringe site, the sample size was estimated at 1500 to detect an OR 1.5. However, the number of confirmed malaria cases that presented during the study period was lower than originally estimated; due in part to the introduction of RDTs into the facilities, and it was not logistically or financially

possible to continue the study beyond the study period. The validity of assumptions made for the study was checked retrospectively using the true proportion of controls exposed in the samples. The final sample size for Kabale was estimated to have 80% power to detect an OR of 3.1 or greater, while in Rukungiri we would have 80% power to detect an OR of 2.55 or greater [21–23].

We used the HRP-2 antigen-based RDT to confirm malaria as opposed to the ‘gold standard’ microscopy. At the time of the study, HRP-2 manufacturers reported that these test kits could remain positive for up to a fortnight after effective treatment of malaria patients [24]. However, Hopkins *et al.* [25] demonstrated that the positive predictive value of HRP-2-based RDTs can decrease dramatically in low transmission sites. Conversely, Abeku *et al.* (2008) [26] showed the positive predictive value of RDTs to be higher in lower transmission sites. As a result, a number of cases, either travellers or non-travellers, could have been false positives the impact of which could be a differential misclassification leading to an over or underestimation of the true relationship between malaria and travel.

There are further limitations to categorising transmission intensity in both origin and destination areas using the MARA model. While there is strong evidence for the association between different climate factors (e.g. temperature) and malaria [27–29], there are also local factors, including seasonality, that can affect the distribution of malaria which are not accounted for in the MARA model. Thus, this method may lead to misclassification errors as may have been the case for the highland fringe site.

Nevertheless, the implications of the findings are important in the highland site, where the association between travel and malaria was significant. The relatively high rate of travel among the control group suggests that travel among the general population is a common phenomenon which needs attention from health planners and workers during the design of control programs or diagnosis of patients. Malaria control interventions in highland sites need to include information campaigns to remind people about the risk of malaria associated with travel in addition to perhaps providing single mosquito nets for migrants during travel. In terms of diagnosis and treatment, health authorities could consider the inclusion of travel history in the case definition for malaria and whether this increases positive predictive value.

Non-local malaria infection or disease could distort the epidemiological picture in the area, potentially leading to an overestimation of the malaria burden. Where routine malaria data are being used to forecast epidemics, ‘imported cases’ could introduce errors into the data, resulting in less efficient forecasting systems. Where the

same data are being used to evaluate an intervention (e.g. IRS), cases introduced from outside the area may lead to the intervention being classified as a failure when it has, in fact, reduced local transmission.

Non-local malaria infections could also change the malaria transmission patterns in the highland area. There is evidence that infected travellers have caused malaria outbreaks in low transmission and low receptivity areas in the past [30]. ‘Hotspots’ of malaria infection have been detected in the highlands [20] indicating that while overall transmission is low, there are areas that can sustain malaria transmission presumably as a result of local factors. In this situation, should travellers return home at the right time to the right place, it is possible that they could infect resident non-immune non-travellers potentially causing a malaria outbreak.

Extrapolating the role of travel further, it is possible to imagine, with recent documented evidence for increases in temperatures in East African highlands [31], that the ‘insidious creep of the disease into hitherto unaffected highlands’ described by Garnham in the pre-eradication era could become a reality.

Beyond the East African highland areas, these findings are significant in highlighting the relatively high rate of internal migration in an area not previously identified as one from which migration was a common occurrence. However, results also highlight the importance of understanding the underlying malaria epidemiology in areas from where, and to which, migrants travel irrespective of whether they cross a border or not. Unsurprisingly, residents from lowest transmission settings are at greatest risk of malaria when travelling to higher transmission areas. With interventions being scaled up nationally in many countries, it is likely that transmission intensity will become more variable over landscapes where it was once considered homogenous. Given this situation, the role of a migrant either as a ‘passive transmitter’ or ‘active acquirer’ is crucial not only at cross-border migration between countries of different endemicity but also within country boundaries.

Findings are of particular importance for areas where migration has been identified as a common event, for example, among large mobile populations in West Africa, and large streams of mobile and migrant populations in South-East Asia where travel occurs to and from areas where outdoor transmission occurs. In this latter area, artemisinin resistance has been detected in all six countries of the Greater Mekong Subregion, and thus the risk of its spread, facilitated through migration, is of particular concern. Finally, as the global malaria elimination strategy aims to ‘shrink the malaria map’ through elimination in

lower transmission areas first [32], the role of travel will be a constant and increasingly important issue that could jeopardise gains made over the last decade.

The implications of the study in fringe site are less clear in terms of design or monitoring of interventions. Results serve as a reminder that migration is not always a factor in the rise of malaria incidence in fringe highland sites. This may either be because travel is infrequent in the fringe highland sites, or because transmission in those areas is already too high to be affected by additional malaria cases brought into the area by travellers.

Further work is needed on the seasonality of travel to and from low transmission sites and the potential impact on routine malaria data and overall estimates of the burden of disease in those areas. The potential role of returning infected travellers to highland areas in spreading infection should also be investigated.

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Corresponding Author Caroline A. Lynch, Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK. E-mail: caroline.lynch@lshtm.ac.uk