Population dynamics and malaria occurrence in the main hotspot of the Brazilian Amazonia*

Igor Cavallini Johansen – Universidade Estadual de Campinas

Priscila Thihara Rodrigues – Universidade de São Paulo

Marcelo Urbano Ferreira – Universidade de São Paulo

Malaria in the Amazon is often perceived as an exclusively rural disease, but transmission has been increasingly documented within and near urban centers. Here we explore patterns and causes of urban-to-rural population mobility, which places travelers at risk of malaria in Mâncio Lima, the main malaria hotspot in northwestern Brazil. We also analyze rural-to-urban mobility caused by malaria treatment seeking, which poses an additional risk of infection to urban residents. We show that the rural localities most frequently visited by urban residents – typically farming settlements in the vicinity of the town – are those with the most intense malaria transmission and also the most frequent source localities of imported malaria cases diagnosed in the town. The most mobile urban residents are typically poor males 16 to 60-years old from multi-sited households who lack a formal job. Highly mobile residents represent a priority target for more intensive and effective malaria control interventions, that cannot be readily delivered to the entire community, in this and similar urbanized endemic settings across the Amazon.

Key words: Health and morbidity, Urbanization and urban populations, Demographic and social surveys, Policy.

* Paper presented in the session "Social and demographic factors influencing communicable and non-communicable diseases" at the 2021 IUSSP International Population Conference.

Introduction

Although the overall burden of malaria in Latin America and the Caribbean has decreased dramatically over the past two decades, transmission persists in 21 countries in the region, where 120 million people are estimated to be currently exposed to some risk of infection (WHO, 2019). The Amazon Basin, a vast territory that extends over Bolivia, Brazil, Colombia, Ecuador, Guyana, French Guiana, Peru, Suriname, and Venezuela, contributes approximately 90% of the region's malaria burden (Ferreira, Castro, 2019).

Malaria in the Amazon has traditionally been perceived as a disease affecting poor rural communities, with most reported infections acquired in remote riverine villages (Ladeia-Andrade et al., 2009), frontier farming settlements (Castro, Monte-Mór, Sawyer, 2006; Da Silva Nunes et al., 2008), gold mining (Pommier et al., 2016; Sánchez et al., 2017), and Amerindian reserves (Robortella et al., 2020). Indeed, malaria rates tend to be lower in cities and towns, compared to surrounding rural settings, due to multiple factors such as improved housing and access to healthcare and limited availability of mosquito vector habitats (Wilson et al., 2015). Nevertheless, since the mid-1990s malaria cases have been increasingly reported within and near urban centers in the Amazon, consistent with sustained transmission in or around towns across the region (Corder et al., 2019; Salla et al., 2020).

Urbanized spaces ranging from metropolitan areas to small towns sprawling into the rainforest gradually became more tightly articulated to the surrounding farming settlements, riverine villages, and even indigenous communities (Monte-Mór, 2004; Castriota, Tonucci, 2018). This process extends to rural spaces some socioeconomic and spatial relations that are typical of urban centers, blurring the traditional rural-urban boundary, and fosters human mobility across the rural-urban interface as a key component of new livelihood and income diversification strategies (Barbieri, Monte-Mór, Bilsborrow, 2009; Barbieri, Guedes, Dos Santos, 2019). Rural families typically travel to the nearest town or city at least once a month to sell their crops, purchase goods, and receive social benefits from conditional cash transfer programs and rural retirement programs (Eloy, Brondízio, Pateo, 2015).

Malaria transmission rates in Brazil are nowadays greatest in the upper Juruá Valley, next to the border with Peru (Ferreira, Castro, 2016). With <0.5% of the Amazon's population, the region contributes 18% of the overall country's malaria burden, estimated at 186,485 cases in 2018 (WHO, 2019).

Here we combine travel histories and epidemiological surveillance data to explore human mobility patterns in Mâncio Lima the main urban malaria hotspot of Brazil. We found that the localities that are most frequently visited by urban residents are typically those with the most intense malaria transmission. These localities also contribute the vast majority of imported malaria infections diagnosed in the urban area. Importantly, communities that drive most urban malaria risk are not hard-to-reach riverine villages; instead, they are situated in the vicinity of the town, where effective public health interventions are easier to implement.

Methods

In the urban area of Mâncio Lima (Fig. 1), located in the upper Juruá Valley, a population census performed by our field team between November 2015 and April 2016 enumerated 9,124 permanent residents, with ages ranging between <1 month and 105 years (mean, 27.0; median, 22.0; SD, 20.0 years) and distributed into 2,329 households (Corder et al., 2019). Structured questionnaires applied to a household-based random sample of approximately 20% of the urban residents were used to obtain sociodemographic data and travel histories. To this end, two consecutive cross-sectional surveys were carried out in the study site and targeted the same population sample. The first survey, between May and June 2019, comprised 2,015 subjects aged <1-105 years (mean, 28.2; median, 24.0; SD, 20.1 years) distributed into 522 households, while the second, between September and October 2019, comprised 2,130 subjects aged <1-105 years (mean, 28.4; median, 24.5; SD, 20.1 years) distributed into 562 households. Demographic, socioeconomic and occupational/behavioral information was obtained.

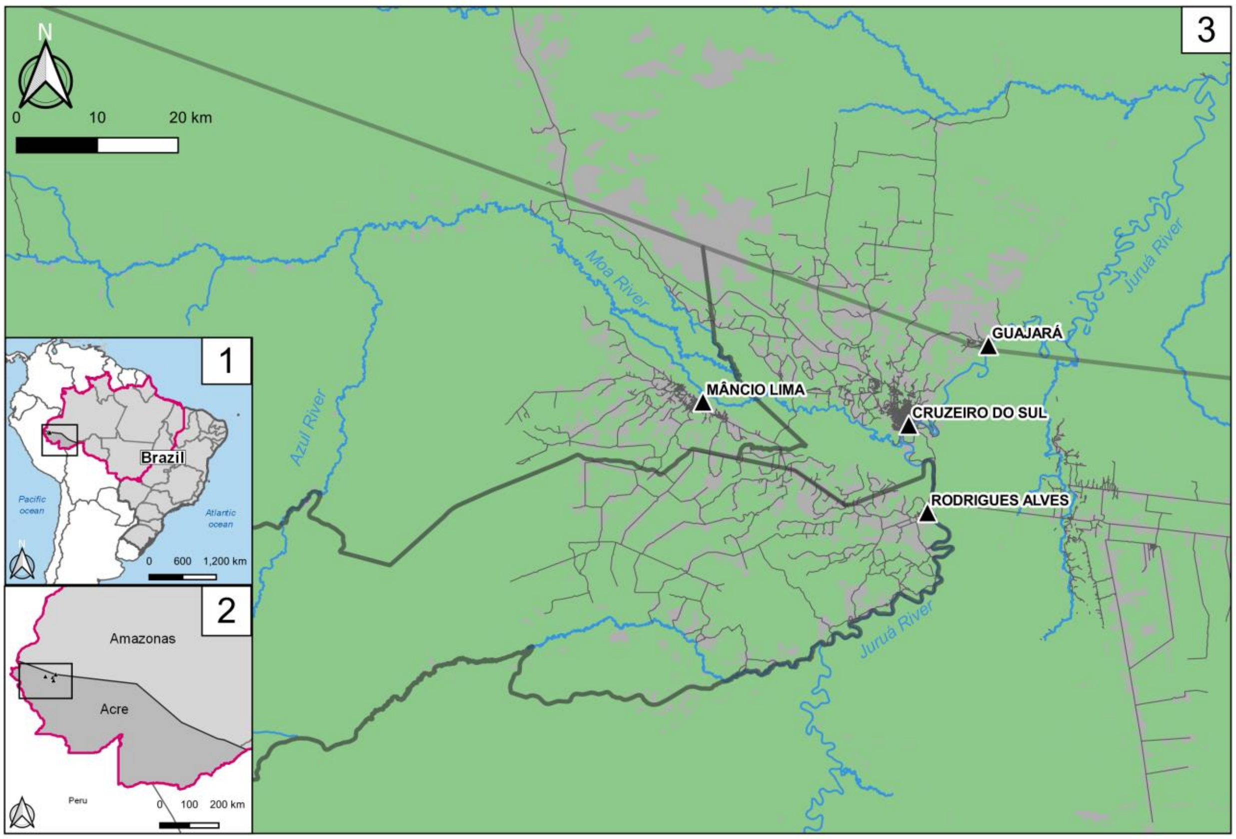
To measure the spatial mobility of urban residents, individual reports of overnight trips within the past 6 months were collected during two consecutive cross-sectional surveys carried out 6 months apart. Reports included the total duration of each trip and its destination, allowing us to calculate the total number of days each individual spent in each destination between September 2018 and August 2019.

We retrieved all malaria case notifications from the upper Juruá Valley region (combined 2020 population estimate, 144,671 inhabitants) that were entered into the electronic malaria notification system of the Ministry of Health of Brazil between January 2016 and December 2018. Because malaria is a notifiable disease in Brazil and diagnostic testing and treatment are not available outside the network of government-run health care facilities, the database comprises the vast majority of laboratory-confirmed malaria episodes countrywide (Daher et al., 2019).

From the electronic malaria notification system we retrieved the following locality-related information: (a) GPS coordinates, (b) population size, (c) number of locally acquired, laboratory-confirmed malaria episodes that were diagnosed and treated in the locality between 2016 and 2018, and (d) number of malaria episodes reportedly acquired in other localities that were diagnosed, treated and notified in the town of Mâncio Lima between 2016 and 2018 (i.e., imported infections – WHO, 2018).

From these data retrieved from the electronic malaria notification system we estimated the average Annual Parasite Index (API) between 2016 and 2018 for every locality in the region and quantified rural-to-urban mobility caused by malaria-treatment seeking during this period, which determines the frequency of influx of infected individuals into the town (i.e., its vulnerability – WHO, 2018).

Fig 1. Location of the study site, the municipality of Mâncio Lima, Acre state, Brazil. 1: Brazilian Federal Units and the Amazon, also known as Legal Amazonia (magenta line in the map); 2: Acre and Amazonas states in dark and light gray, respectively, with the municipalities covered in this study highlighted in the western area. 3: The municipalities of the upper Juruá Valley region: Mâncio Lima, Rodrigues Alves and Cruzeiro do Sul in Acre state and Guajará in Amazonas state. Dark thick lines represent the municipalities' borders. The triangles show the town of each municipality, and in light green the forest cover in contrast with gray representing mostly deforested areas. Roads and streets are represented.



Data analysis

Field-collected data, entered using tablets programed with REDCap (Harris et al., 2009), were cleaned and exported to Stata SE 15.0 (StataCorp, TX, USA) for statistical analysis. Proportions were compared with χ^2 tests and correlations were investigated using the Pearson's correlation test.

Multivariate regression models with either dichotomic or continuous outcome variables were run to identify correlates of urban-to-rural mobility. The dichotomic outcomes analyzed with logistic regression models were: (1) overnight trip outside the town within the past 12 months (no/yes) and (2) overnight trip to high-risk localities – i.e., those with an API greater than that of the town of Mâncio Lima (442 cases per 1,000 inhabitants) – within the past 12 months (no/yes). Given the nested structure of the data (individuals clustered into households), we used the "meqrlogit" STATA command to build mixed-effects logistic regression models that included the grouping variable "household" as a random factor. These models performed better than their Poisson counterparts, as judged by Akaike's and Bayesian information criteria; therefore, only logistic regression results are presented here. The continuous outcome variables analyzed with negative binomial models were: (3) total number of overnights outside the town within the past 12 months and (4) total number of overnights in high-risk localities. Models were built with the "menbreg" STATA command, including the grouping variable "household" as random factor.

Variable selection for the final models followed the hierarchical approach based on conceptual frameworks as suggested by Victora and colleagues (Victora et al., 1997). Variables available were: age group (0-5; 6-15; 16-40; 41-60; 41-60; > 60 years); gender (female, male); literacy (illiterate; literate); terciles of a household wealth index (poorest; intermediate; least poor) that considers housing characteristics and assets, such as vehicles and home appliances, and was computed as described by Filmer and Pritchett (Filmer, Pritchett, 2001); if anyone in the household receives benefits from the federal Bolsa Família conditional cash transfer program (Rasella et al., 2013) (no; yes); individual work status (does not work; formal employee; informal employee; employer); family head workstatus (does not work; formal employee; informal employee; employer); regular fishing (no/yes) and presence of a second residence outside the urban area (no, yes).

Ethics statement

The study protocol was approved by the Institutional Review Board of the Institute of Biomedical Sciences, University of São Paulo, Brazil, and by the National Committee of Ethics in Research (CONEP) of the Ministry of Health of Brazil (CAAE number 64767416.6.0000.5467). Written informed consent and assent were obtained from all study participants.

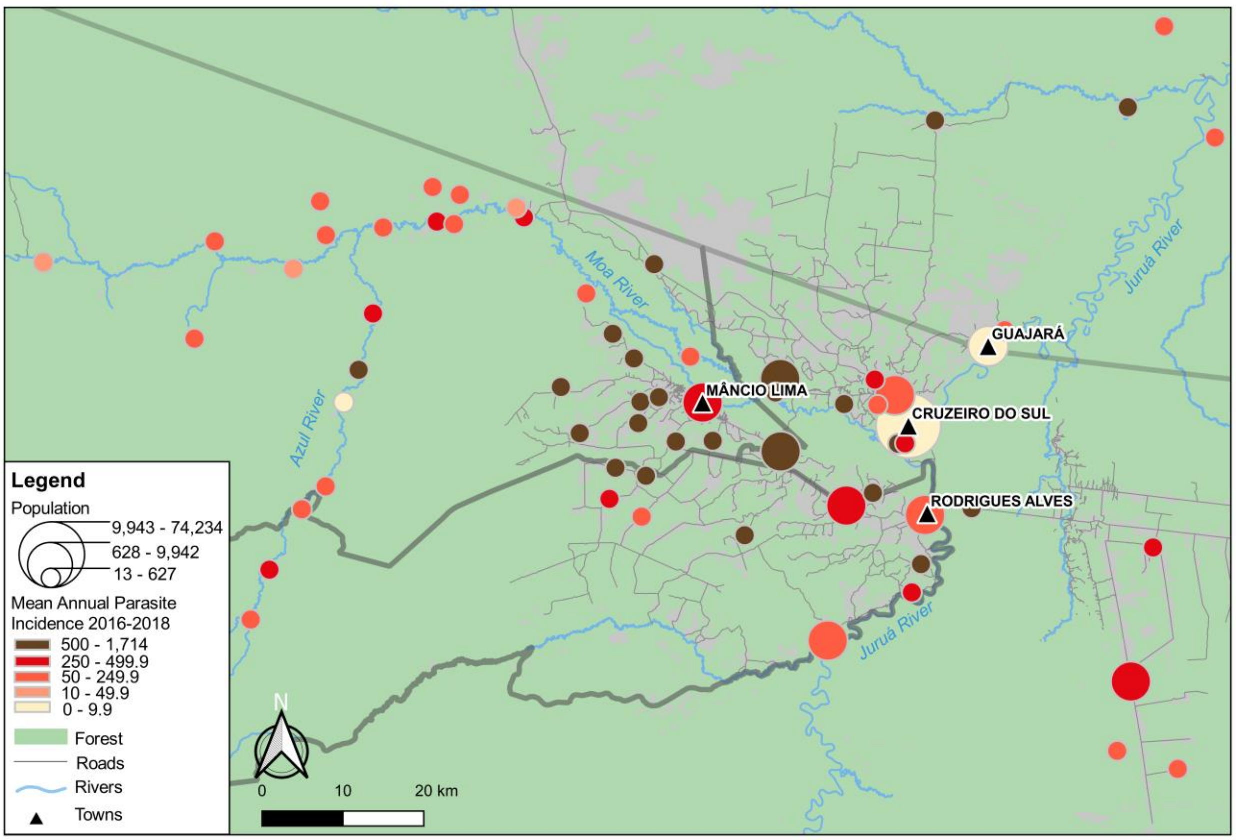
Results

Complete mobility information was available from 1,903 individuals, distributed into 504 households, who participated in both cross-sectional surveys. This total corresponds to 94.4% of individuals interviewed in May-June 2019 and 89.3% of those interviewed in September-October 2019. Participants have a mean age of 28.4 years, with a male:female ratio of 0.95. Adults ≥25 years old reported 7.3 years of schooling on average, which corresponds to incomplete elementary school; 19.2% of study participants ≥15 years old are illiterate. Only 53.0% of individuals ≥18 years old reported to be currently working; of those, 8.6% are formally employed and the majority (55.7%) are informal employees who engage in seasonal farming in the surroundings of the town. Multi-sited households are common in Mâncio Lima – 16.8% (85 out of 504) of the families maintain both urban and rural residences.

Malaria rates in the town of Mâncio Lima and surrounding localities

Fig. 2 shows that average APIs vary widely among the 65 localities in the upper Juruá Valley that were reported as destinations of overnight trips by urban residents in Mâncio Lima.

Fig 2. Map showing the location of the municipal seat of Mâncio Lima and the 65 localities in the upper Juruá Valley region that were mentioned as travel destinations by study participants. Georeferenced localities are represented by circles with size proportional to their population size and filled with tones from light yellow to dark brown that are proportional to malaria transmission intensity, using the average annual parasite incidences (APIs) for both *P. vivax* and *P. falciparum* between 2016 and 2018 as a proxy (higher APIs in darker tones).



Average API between 2016 and 2018 ranges across localities from 1 to 1,714 laboratory-confirmed malaria cases, regardless of the species, per 1,000 population per year. The average API for the town of Mâncio Lima during the same period was 442 cases per 1,000 population per year, which is surprisingly high for an urban setting. For comparison, the three other urban centers in the upper Juruá Valley region– namely, Cruzeiro do Sul (estimated urban population, 63,800 inhabitants), Rodrigues Alves (population, 13,200), and Guajará (population, 8,800), whose locations are indicated in Fig. 2 – sustain substantially lower malaria transmission compared with Mâncio Lima, with mean APIs of 1, 50, and 8 malaria cases per 1,000 population between 2016 and 1018, respectively. Of note, three fourths of the 24 localities with very intense malaria transmission (API ≥ 500) are periurban farming settlements situated within a 20-km radius of the town of Mâncio Lima. Only three high-risk localities are remote riverine villages along the main local rivers (Juruá, Moa, and Azul).

Contrary to the commonly held perception of malaria as a disease of isolated communities deep in the rainforest in the Amazon, periurban agricultural settlements contribute most of the malaria burden in the upper Juruá Valley, what is especially apparent for the municipality of Mâncio Lima. Somewhat surprisingly, this pattern is even more marked for *P. falciparum* infections, which mostly cluster in the vicinity of the town, being much less frequent in more remote sites. Locally transmitted malaria remains relatively infrequent in the towns of Rodrigues Alves and Guajará and the city of Cruzeiro do Sul (Table 1).

Table 1. Malaria cases according to most likely local of infection (either urban or rural) for all municipalities in the Amazon and selected municipalities in the Upper Juruá Valley of Brazil, 2016-2018.

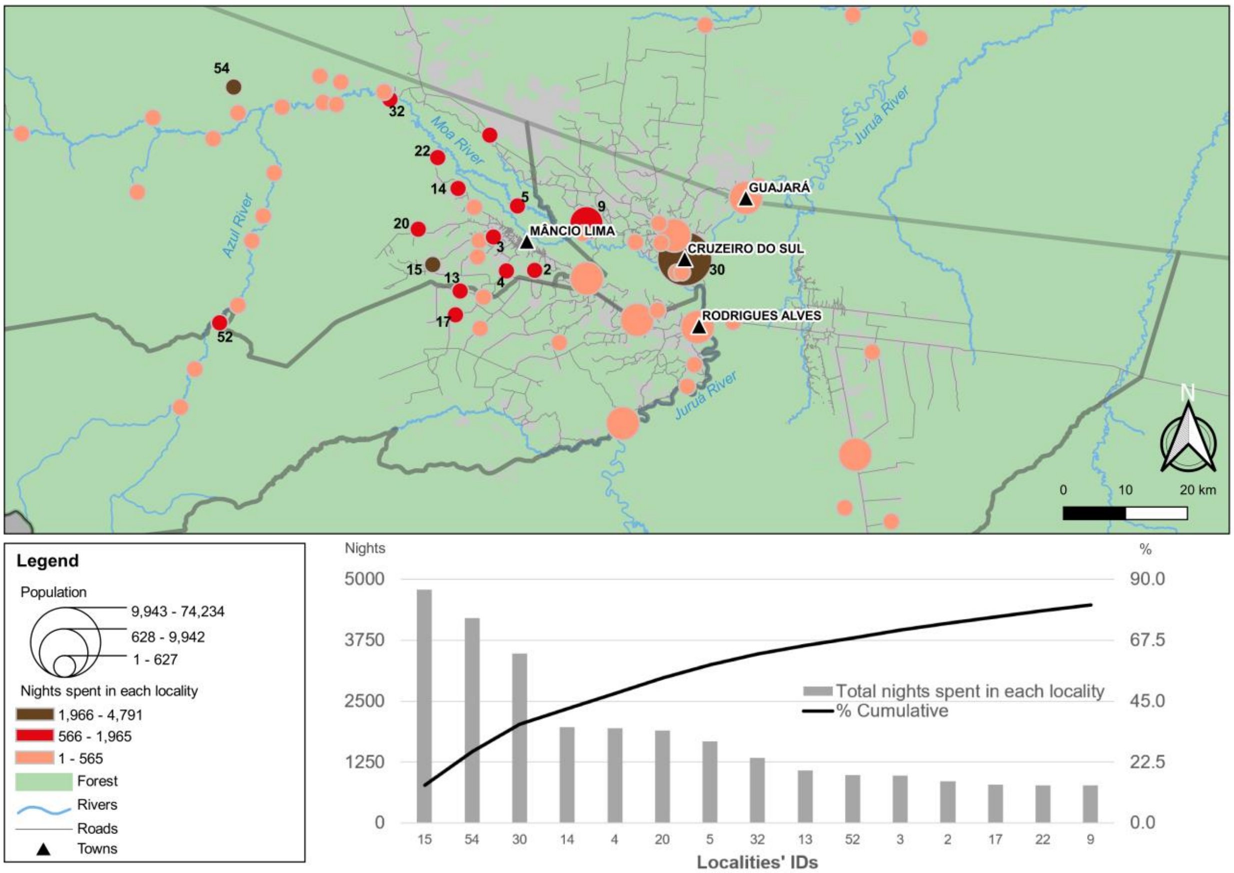
	Malaria cases			%	
Municipality	Urban	Rural	Total	Urban	Rural
All municipalities in the Amazon	67,700	383,479	451,179	15.0	85.0
Mâncio Lima	11,550	12,171	23,721	48.7	51.3
Cruzeiro do Sul	8,033	43,181	51,214	15.7	84.3
Rodrigues Alves	639	13,033	13,672	4.7	95.3
Guajará	669	5976	6645	10.1	89.9

Urban-to-rural mobility and its determinants

Over one third (35.5%) of the study participants reported at least one overnight trip between September 2018 and August 2019, with a total of 34,150 overnights outside the town, corresponding to approximately 5% of their nights during the study period. Nearly half (47.0%) of the study participants who reported overnights outside the town were away for ≥1 month during the study period (one or more trips); 24.4% of them were away for ≥3 months.

The three most frequent destinations are two small rural settlements (Tonico and Timbauba, #15 and #54 in Fig. 3, respectively) and the nearest city (Cruzeiro do Sul, #30 in Fig. 4). In contrast, the towns of Rodrigues Alves and Guajará attract relatively few visitors from Mâncio Lima. Tonico, the most visited locality, displays the highest API in the region, estimated at 1,714 cases per 1,000 inhabitants between 2016 and 2018.

Fig 3. Trip destinations of residents in the town of Mâncio Lima according to number of overnight stays. As in Fig 2, the map shows the location of the town of Mâncio Lima and the 65 localities in the upper Juruá Valley region with overnigths reported by study participants. Georeferenced localities are represented by circles with size proportional to their population size and filled with tones from light orange to dark brown that are proportional to the number of overnights in each locality between September 2018 and August 2019 (larger number of overnights in darker tones). The lower panel shows the cumulative number and proportion of overnights in the top-15 localities; their identification codes (IDs) are shown in the map.



Fifteen localities (14 of them rural) account for over 80% of overnights (Fig. 3, lower panel). Importantly, the localities within 20 km of Mâncio Lima (32.3% of those shown in Fig. 3) account for 58.1% of the total overnights outside the town. In addition, 48.7% of the reported overnights were in rural localities with API ≥ 500 (compare Fig. 2 and 3), exposing urban visitors to substantial malaria risk. In other words, during the study period participants reportedly spent, on average, 2.4% of their nights in high-risk localities, mostly in the vicinity of the town.

The number of overnights in each locality is not significantly correlated with its distance from the town of Mâncio Lima (Pearson's r = -0.22, P = 0.09). We note, however, that the three most visited localities (Tonico, Cruzeiro do Sul and Timbauba) are outliers in the regression analysis, being disproportionately more visited than expected from their distance from the town of Mâncio Lima. Because the city of Cruzeiro do Sul (4,204 overnights), situated at Euclidian distance of 26 km southeast from Mâncio Lima, is the largest urban center in the region, its attractiveness is easily understood. Moreover, as discussed below, Tonico and Timbauba are common sites for second residences of urban families. When these three outliers are removed from the regression analysis, a significant negative correlation is observed between the number of overnights and distance from the town (Pearson's r= -0.36, P = 0.004), suggesting that study participants tend to spend more overnights in proximate localities, with the exceptions noted above.

Not surprisingly, members of multi-sited households display increased mobility. Indeed, 55.4% of study participants whose families have a second residence reported at least one overnight trip in the previous 12 months, compared with only 30.7% of those with no second residence ($P < 0.01$, χ^2 test). The riverine village of Timbauba, along the Moa river (54 km northwest of the town in Euclidian distance), is the second most frequent site for a second residence and also the second most visited locality (4,204 overnights). Likewise, the farming settlement of Tonico (16 km west of the town by road), the most visited locality (4,791 overnights) and the highest API in the region, is among the top-five locations where study participants have a second residence.

Mixed-effects multiple logistic regression analysis identified five significant correlates of overall urban-to-rural mobility and four correlates of mobility to high-risk areas (Table 2). Common risk factors associated with both outcomes were: (a) male gender; (b) regular fishing; and (c) a second residence outside the urban area. Age between 16 and 40 years was a statistically significant risk factor for overall mobility, while people older than 60 years old were less likely to spend their nights in high-risk areas. Informal employees were more likely to travel, but not necessarily to high-risk localities.

Mixed-effects negative binomial regression models identified the following factors independently associated with increased number of overnights outside the town: (a) male gender, (b) age between 16 and 60 years, (c) informal employment, (d) regular fishing, and (e) second residence outside the urban area (Table 3). We note that the least poor study participants reported less overnights outside the town, compared with the lowest wealth stratum. Taken together, these results allow to identify high-mobility study participants as typically males aged 16 to 60 years old in the lowest wealth stratum, with informal jobs, who have a second residence outside the town and fish regularly.

Table 2. Mixed-effects logistic regression analysis of correlates of urban-to-rural overall mobility (left columns) and mobility to high-risk areas (right columns) in the study population of Mâncio Lima, northwestern Brazil (n=1,903)

	Overall mobility (overnight trip outside the town within the past 12 months)						**Mobility to high-risk areas (overnight trip outside the town within the past 12 months to localities with an API greater than that of the town of Mâncio Lima)**					
	Unadjusted model			**Adjusted model**			**Unadjusted model**			**Adjusted model**		
	OR[a]	**(95% CI)[b]**	***P***	**OR[a]**	**(95% CI)[b]**	***P***	**OR[a]**	**(95% CI)[b]**	***P***	**OR[a]**	**(95% CI)[b]**	***P***
Age												
0-5	Reference			Reference			Reference			Reference		
06-15	1.19	(0.7-2.0)	0.506	1.06	(0.6-1.8)	0.837	1.01	(0.5-2.0)	0.968	0.93	(0.5-1.9)	0.846
16-40	2.64	(1.6-4.2)	<0.0001	1.97	(1.2-3.3)	0.009	1.47	(0.8-2.7)	0.210	1.08	(0.5-2.1)	0.815
41-60	2.49	(1.4-4.4)	0.001	1.60	(0.8-3.0)	0.146	1.18	(0.6-2.5)	0.657	0.72	(0.3-1.7)	0.452
> 60	0.81	(0.4-1.6)	0.543	0.63	(0.3-1.3)	0.198	0.32	(0.1-0.9)	0.029	0.22	(0.1-0.6)	0.006
Gender												
Female	Reference			Reference			Reference			Reference		
Male	1.82	(1.4-2.4)	<0.0001	1.46	(1.1-2.0)	0.011	2.01	(1.4-2.9)	<0.0001	1.61	(1.1-2.4)	0.017
Work status												
Does not work	Reference			Reference			Reference			Reference		
Formal employee	1.38	(0.8-2.3)	0.198	0.90	(0.5-1.6)	0.709	1.38	(0.7-2.6)	0.312	1.15	(0.6-2.4)	0.695
Informal employee	3.13	(2.2-4.4)	<0.0001	1.61	(1.1-2.4)	0.022	2.21	(1.5-3.4)	<0.0001	1.44	0.8-2.5)	0.192
Employer	0.36	(0.0-4.2)	0.414	0.22	(0.0-2.6)	0.231	3.90	(0.1-105.5)	0.419	3.74	(0.1-108.8)	0.444
Wealth index[c]												
Poorest	Reference			Reference			Reference			Reference		
Intermediate	0.70	(0.4-1.2)	0.223	0.77	(0.43-1.4)	0.385	1.90	(0.8-4.4)	0.132	2.33	(1.0-5.5)	0.054
Least poor	0.76	(0.4-1.3)	0.336	0.75	(0.4-1.4)	0.368	1.29	(0.6-3.0)	0.554	1.35	(0.6-3.3)	0.515
Fishing												
No	Reference			Reference			Reference			Reference		
Yes	3.3	(2.3-4.7)	<0.0001	2.40	(1.6-3.5)	<0.0001	2.52	(1.58-4.0)	<0.0001	2.13	(1.3-3.6)	0.004
Second residence												
No	Reference			Reference			Reference			Reference		
Yes	5.05	(2.8-9.1)	<0.0001	5.59	(3.0-10.6)	<0.0001	6.8	(2.9-16.0)	<0.0001	7.58	(3.1-18.6)	<0.0001

[a]OR= odds ratio
[b]CI= confidence interval
[c]Wealth Index terciles

Table 3. Mixed-effects negative binomial regression analysis of correlates of urban-to-rural overall mobility (left columns) and mobility to high-risk areas (right columns), in the study population of Mâncio Lima, northwestern Brazil (n=1,903)

	Overall mobility (total number of overnights outside the town within the past 12 months)						**Mobility to high-risk areas (total number of overnights in localities with an API greater than that of the town of Mâncio Lima)**					
	Unadjusted model			**Adjusted model**			**Unadjusted model**			**Adjusted model**		
	IRR[a]	**(95% CI)[b]**	***P***	**IRR[a]**	**(95% CI)[b]**	***P***	**IRR[a]**	**(95% CI)[b]**	***P***	**IRR[a]**	**(95% CI)[b]**	***P***
Age												
0-5	Reference			Reference			Reference			Reference		
06-15	1.31	(0.7-2.3)	0.362	1.24	(0.7-2.2)	0.463	1.01	(0.4-2.3)	0.990	0.91	(0.4-2.0)	0.821
16-40	3.52	(2.1-6.0)	<0.0001	2.73	(1.5-4.8)	0.001	2.06	(1.0-4.3)	0.052	1.61	(0.7-3.6)	0.243
41-60	4.14	(2.2-7.8)	<0.0001	2.42	(1.2-4.9)	0.015	1.75	(0.7-4.4)	0.237	1.06	(0.4-2.9)	0.911
> 60	1.27	(0.6-2.8)	0.566	0.97	(0.4-2.2)	0.938	0.72	(0.2-2.4)	0.595	0.48	(0.1-1.7)	0.256
Gender												
Female	Reference			Reference			Reference			Reference		
Male	2.43	(1.8-3.3)	<0.0001	1.94	(1.4-2.7)	<0.0001	3.04	(2.00-4.7)	<0.0001	2.76	(1.7-4.6)	<0.0001
Work status												
Does not work	Reference			Reference			Reference			Reference		
Formal employee	1.59	(0.9-2.8)	0.114	0.97	(0.5-1.8)	0.917	1.87	(0.8-4.6)	0.175	1.55	(0.6-4.0)	0.363
Informal employee	4.26	(2.9-6.2)	<0.0001	1.70	(1.0-2.8)	0.031	3.32	(1.9-5.7)	<0.0001	1.46	(0.7-3.0)	0.302
Employer	1.66	(0.1-22.0)	0.702	0.65	(0.0-9.4)	0.751	4.65	(0.2-130.1)	0.366	2.85	(0.1-102.2)	0.566
Wealth index[c]												
Poorest	Reference			Reference			Reference			Reference		
Intermediate	0.53	(0.3-1.0)	0.041	0.60	(0.3-1.1)	0.103	3.03	(1.0-9.4)	0.056	2.76	(1.0-7.8)	0.055
Least poor	0.53	(0.3-1.0)	0.047	0.51	(0.3-1.0)	0.037	1.74	(0.6-5.4)	0.335	1.14	(0.4-3.2)	0.805
Fishing												
No	Reference			Reference			Reference			Reference		
Yes	3.60	(2.4-5.4)	<0.0001	1.93	(1.3-3.0)	0.003	2.62	(1.4-4.9)	0.003	1.39	(0.7-2.7)	0.322
Second residence												
No	Reference			Reference			Reference			Reference		
Yes	13.3	(7.3-24.4)	<0.0001	15.46	(8.3-28.8)	<0.0001	60.18	(18.3-197.8)	<0.0001	60.99	(19.7-188.4)	<0.0001

[a]IRR= incidence rate ratio. Note that “incidence” here refers to the total number of overnights over 12 months.
[b]CI= confidence interval
[c]Wealth Index terciles

Malaria treatment seeking and rural-to-urban mobility

Overall, 19,847 laboratory-confirmed malaria cases – including 16,347 *P. vivax* infections (82.4%) and 3,500 *P. falciparum* infections (17.6%) – were diagnosed, treated, and notified in the town of Mâncio Lima between January 2016 and December 2018. Of them, 5,389 (33.0%) *P. vivax* infections and 1,545 (44.1%) *P. falciparum* infections were classified as imported during routine case investigation. The ratio between locally transmitted and imported infections in the town is 2.0:1 for *P. vivax* and 1.3:1 for *P. falciparum*. These data indicate that a large number of subjects, either urban residents or not, who acquired malaria outside of the town regularly seek treatment in Mâncio Lima and expose their inhabitants to some risk of infection, given the malaria receptivity of the urban area.

We next investigated the geographic origin of imported malaria infections notified in Mâncio Lima. The vast majority of them (77.8% for *P. vivax* and 78.3% for *P. falciparum* infections) had one of the 65 localities shown in Fig. 2 recorded as the most likely origin during routine case investigation. Importantly, the top-10 source localities, none of them more than 20 km away from the urban area, account for 64.5% of *P. vivax* and 69.3% of *P. falciparum* infections imported into the town of Mâncio Lima. Permanent malaria diagnosis outposts are not available in these localities. Importantly, the number of imported cases correlates negatively with the distance between the putative source locality and the town (Pearson's r= -0.45, P = 0.001).

Discussion and Conclusion

The association between circular population movement and urban malaria risk has long been recognized in South America (Osorio et al., 2010). Although public health policies cannot prevent directly human mobility, which is "driven mostly by need rather than choice" (Martens et al., 2000), they can proactively address some of the underlying causes and consequences of movements that contribute to malaria transmission.

Here we show that surveillance data combined with additional sociodemographic and mobility information from population-based surveys provides valuable information that can be explored for evidence-based planning and deployment of interventions aimed to reduce urban malaria risk across the Amazon.

We characterize patterns of spatial mobility in the main urban malaria hotspot of Brazil and their main determinants. We focus on the urban-to-rural mobility that places travelers at risk for malaria and rural-to-urban mobility caused by treatment seeking that poses a risk to urban residents, especially if rural visitors extend their stay in the town for selling crops, purchasing goods, or fully recovering from the current malaria episode. Importantly, the most common travel destinations are typically those with the most intense malaria transmission – essentially farming settlements situated within 20 km of Mâncio Lima, accessible to public health interventions, rather than remote riverine communities. These findings have clear implications for implementing effective malaria control policies in potential source communities that may fuel urban malaria transmission. The most mobile urban residents are poor males 16 to 60-years old from multi-sited households who lack a formal job in the town. Likewise, the most frequent source localities of imported cases diagnosed in Mâncio Lima are also situated within 20 km radius of the town.

The presence of multi-sited households in the Amazon (Olson et al., 2010) is part of a broader process called extended urbanization (Monte-Mór, 2004; Barbieri, Monte-Mór, Bilsborrow, 2009; Castriota, Tonucci, 2018). The traditional rural-urban divide in the region has been gradually replaced by a continuous gradient of "urbanicity" – typically urban features are extended to rural communities while towns and cities retain some "rurality" (Dal'Asta et al., 2018). Our findings suggest that human mobility across the rural-urban gradient, mostly motivated by subsistence or commercial farming in peri-urban settlements, poses a continuous risk of malaria introduction into more urbanized and densely populated spaces.

These results can inform public health responses to prevent mobility-related urban and peri-urban malaria transmission across the Amazon, including large cities such as Manaus (Almeida et al., 2018) and Porto Velho (Tada et al, 2007) in Brazil and Iquitos in Peru (Brach et al., 2005). The first challenge consists in identifying the most mobile population strata who may contribute a large proportion of infections in the community (Corder et al., 2019). Once identified, mobile individuals may be targeted with more intensive and effective interventions that cannot be readily delivered to the entire community. Importantly, the high-risk individuals in Mâncio Lima will acquire clinical immunity faster, after repeated infections (Corder et al., 2020), and eventually constitute a large clinically silent reservoir that carries malaria parasites across the rural-urban interface. Delivering personal protection measures, such as bed nets, and adequate access to diagnosis and treatment are examples of strategies to mitigate mobility-associated malaria risk.

Second, human mobility fuels malaria transmission in urban centers in the Amazon that are receptive – i.e., whose environmental conditions allow for malaria transmission from a human through a vector mosquito to another human (WHO, 2018). Indeed, molecular analyses of parasite isolates provide evidence for sustained malaria transmission in the town of Mâncio Lima (Salla et al., 2020). Vectors are increasingly abundant in this and other urbanized spaces in the Amazon and can sustain local malaria transmission. Typical larval habitats are natural water bodies in unplanned peri-urban settlements adjacent to forested areas (Crowder, 2002) and natural and human-made fish farming ponds, now widespread in towns and cities across the region (Maheu-Giourx et al., 2010; Reis et al., 2015; Barros, Honório, 2015; Lana et al., 2017; Martins et al., 2018). Larval source management with biological larvicides represents a logical approach to malaria control in urbanized spaces where breeding sites are relatively few, easy to find and readily accessible. It has been successful in African cities (Fillinger, Lindsay, 2011;

Maheu-Giroux, Castro, 2013) and can drastically reduce anopheline larval density in fish farming ponds in the Amazon (Fontoura et al., 2020).

Third, imported infections diagnosed in urban communities across the Amazon do not necessarily originate in hard-to-reach traditional settlements. Instead, our results indicate that they are mostly acquired in farming settlements in the vicinity of the city or town, where farmers usually sell their crops and purchase goods. These findings imply that more intensive control interventions and better infrastructure for laboratory diagnosis and prompt treatment in nearby rural localities might drastically reduce the number of cases imported into the urban area.

This study has some limitations. One is the possible recall bias in travel histories obtained at approximately six-month intervals. Alternatives to travel histories include the use of mobile phone data, which have been increasingly used to track human movements over time (Wesolowski et al. 2016). To this end, individuals are assigned to a primary cell phone tower based on the most frequently used tower at night. Travel to another tower catchment area is inferred if their location is recorded at that tower for more than one night. However, this strategy depends on relatively good mobile phone coverage, typically found in cities and towns (Fornace et al., 2018) but absent in most rural sites in the Amazon. Recall bias may also affect the inference of the most likely site of infection, which was also self-reported, in the investigation of imported malaria cases. Finally, the use of routine malaria surveillance data, which are limited to clinical cases detected by conventional diagnostic methods such as microscopy or rapid diagnostic tests, is also a limitation. Routine surveillance typically overlooks chronic asymptomatic carriers of submicroscopic parasitemias who may seed infections in urban spaces over extended periods of time (Lindblade et al., 2013).

Despite these potential study limitations, we show that surveillance data combined with additional sociodemographic and mobility information from population-based surveys provides valuable information that can be explored for evidence-based planning and deployment of interventions aimed to reduce urban malaria risk across the Amazon.

References

Almeida ACG, Kuehn A, Castro AJM, Vitor-Silva S, Figueiredo EFG, Brasil LW, et al. High proportions of asymptomatic and submicroscopic *Plasmodium vivax* infections in a peri-urban area of low transmission in the Brazilian Amazon. Parasit Vectors. 2018;11:194.

Barbieri A, Guedes GR, dos Santos RO. Migration, livelihoods and development in the post-frontier: evidences from the Brazilian Amazonia. Paper presented at the Meeting of the Population Association of America, Austin, Texas, 2019. Available at: http://paa2019.populationassociation.org/uploads/192149.

Barbieri A, Monte-Mór R, Bilsborrow, R. Towns in the jungle: exploring linkages between rural-urban mobility, urbanization and development in the Amazon. In: de Sherbinin A, Rahman A, Barbieri A, Fotso JC, Zhu Y (eds.). Urban population-environment dynamics in the developing world: case studies and lessons learned. Paris, Committee for International Cooperation in National Research in Demography (CICRED), 2009. Available at http://www.populationenvironmentresearch.org/workshops.jsp#W2007

Barros FS, Honório NA. Deforestation and malaria on the Amazon frontier: larval clustering of *Anopheles darlingi* (Diptera: Culicidae) determines focal distribution of malaria. Am J Trop Med Hyg. 2015;93:939-953.

Branch O, Casapia WM, Gamboa DV, Hernandez JN, Alava FF, Roncal N, et al. Clustered local transmission and asymptomatic *Plasmodium falciparum* and *Plasmodium vivax* malaria infections in a recently emerged, hypoendemic Peruvian Amazon community. Malar J. 2005;4:27.

Browder JO. The urban-rural interface: urbanization and tropical forest cover change. Urban Ecosyst. 2002;6:21-41.

Castriota R, Tonucci J. Extended urbanization in and from Brazil. Environ Plan D Soc Space. 2018; 36:512-528.

Castro MC, Monte-Mór RL, Sawyer DO, Singer BH. Malaria risk on the Amazon frontier. Proc Natl Acad Sci USA. 2006;103:2452-2457.

Corder RM, Ferreira MU, Gomes MGM. Modelling the epidemiology of residual Plasmodium *vivax* malaria in a heterogeneous host population: A case study in the Amazon Basin. PLoS Comput Biol. 2020;16:e1007377.

Corder RM, Paula GA, Pincelli A, Ferreira MU. Statistical modeling of surveillance data to identify correlates of urban malaria risk: A population-based study in the Amazon Basin. PLoS One. 2019;14:e0220980.

Da Silva-Nunes M, Codeço CT, Malafronte RS, Da Silva NS, Juncansen C, Muniz PT, Ferreira MU. Malaria on the Amazonian frontier: transmission dynamics, risk factors, spatial distribution, and prospects for control. Am J Trop Med Hyg. 2008;79:624-635.

Daher A, Silva JCAL, Stevens A, Marchesini P, Fontes CJ, Ter Kuile FO, Lalloo DG. Evaluation of *Plasmodium vivax* malaria recurrence in Brazil. Malar J. 2019 Jan 22;18(1):18.

Dal'Asta AP, Lana RM, Amaral S, Codeço CT, Monteiro AMV. The urban gradient in malaria-endemic municipalities in Acre: Revisiting the role of locality. Int J Environ Res Publ Health. 2018;15:1254.

Eloy L, Brondízio E, Pateo R. New perspectives on mobility, urbanisation and resource management in riverine Amazonia. Bull Latin Am Res 2015;34:3-18.

Ferreira MU, Castro MC. Challenges for malaria elimination in Brazil. Malar J. 2016;15:284.

Ferreira MU, Castro MC. Malaria situation in Latin America and the Caribbean: residual and resurgent transmission and challenges for control and elimination. Methods Mol Biol. 2019;2013:57-70.

Fillinger U, Lindsay SW. Larval source management for malaria control in Africa: myths and reality. Malar J. 2011;10:353.

Filmer D, Pritchett LH. Estimating wealth effects without expenditure data — or tears: an application to educational enrollments in states of India. Demography. 2001;38:115-132.

Fontoura PS, da Costa AS, Ribeiro FS, Ferreira MS, Castro MC, Ferreira MU. Field efficacy of VectoMax FG and VectoLex CG biological larvicides for malaria vector control in northwestern Brazil. J Med Entomol. 2020;57:942-946.

Fornace KM, Surendra H, Abidin TR, Reyes R, Macalinao MLM, Stresman G, Luchavez J, Ahmad RA, Supargiyono S, Espino F, Drakeley CJ, Cook J. Use of mobile technology-based participatory mapping approaches to geolocate health facility attendees for disease surveillance in low resource settings. Int J Health Geogr. 2018;17:21.

Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) – A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42:377-381.

Ladeia-Andrade S, Ferreira MU, de Carvalho ME, Curado I, Coura JR. Age-dependent acquisition of protective immunity to malaria in riverine populations of the Amazon Basin of Brazil. Am J Trop Med Hyg. 2009;80:452-459.

Lana RM, Riback TIS, Lima TFM, da Silva-Nunes M, Cruz OG, Oliveira FGS, et al. Socioeconomic and demographic characterization of an endemic malaria region in Brazil by multiple correspondence analysis. Malar J. 2017;16:397.

Lindblade KA, Steinhardt L, Samuels A, Kachur SP, Slutsker L. The silent threat: asymptomatic parasitemia and malaria transmission. Expert Rev Anti Infect Ther. 2013;11:623-639.

Maheu-Giroux M, Casapía M, Sotto-Calle VE, Ford LB, Buckeridge DL, Coomes OT, et al. Risk of malaria transmission from fish ponds in the Peruvian Amazon. Acta Trop 2010; 115:112-118.

Maheu-Giroux M, Castro MC. Impact of community-based larviciding on the prevalence of malaria infection in Dar es Salaam, Tanzania. PLoS One. 2013;8:e71638.

Martens P, Hall L. Malaria on the move: human population movement and malaria transmission. Emerg Infect Dis. 2000;6:103-109.

Martins LMO, David MR, Maciel-de-Freitas R, Silva-do-Nascimento TF. Diversity of *Anopheles* mosquitoes from four landscapes in the highest endemic region of malaria transmission in Brazil. J. Vector Ecol. 2018;43: 235–244.

Monte-Mór R. Modernities in the jungle: extended urbanization in the Brazilian Amazon. Ph.D. thesis. Los Angeles, University of California, Los Angeles, 2004.

Olson SH, Gangnon R, Silveira GA, Patz JA. Deforestation and malaria in Mâncio Lima County, Brazil. Emerg Infect Dis. 2010;16:1108-1115.

Osorio L, Todd J, Bradley DJ. Travel histories as risk factors in the analysis of urban malaria in Colombia. Am J Trop Med Hyg. 2004;71:380–386.

Pommier de Santi V, Dia A, Adde A, Hyvert G, Galant J, Mazevet M, Nguyen C, Vezenegho SB, Dusfour I, Girod R, Briolant S. Malaria in French Guiana linked to illegal gold mining. Emerg Infect Dis. 2016;22:344-346.

Rasella D, Aquino R, Santos C, Paes-Sousa R, Barreto ML. Effect of a conditional cash transfer programme on childhood mortality: a nationwide analysis of Brazilian municipalities. Lancet 2013;382: 57-64.

Reis IC, Codeço CT, Degener CM, Keppeler EC, Muniz MM, de Oliveira FG et al. Contribution of fish farming ponds to the production of immature *Anopheles* spp. in a malaria-endemic Amazonian town. Malar J. 2015;14:452.

Robortella DR, Calvet AA, Amaral LC, Fantin RF, Guimarães LFF, França Dias MH, Brito CFA, Sousa TN, Herzog MM, Oliveira-Ferreira J, Carvalho LH. Prospective assessment of malaria infection in a semi-isolated Amazonian indigenous Yanomami community: Transmission heterogeneity and predominance of submicroscopic infection. PLoS One. 2020;15:e0230643.

Salla LC, Rodrigues PT, Corder RM, Johansen IC, Ladeia-Andrade S, Ferreira MU. Molecular evidence of sustained urban malaria transmission in Amazonian Brazil, 2014-2015. Epidemiol Infect. 2020;148:e47.

Sánchez JF, Carnero AM, Rivera E, Rosales LA, Baldeviano GC, Asencios JL, Edgel KA, Vinetz JM, Lescano AG. Unstable malaria transmission in the southern Peruvian Amazon and its association with gold mining, Madre de Dios, 2001-2012. Am J Trop Med Hyg. 2017;96:304-311.

Tada MS, Marques RP, Mesquita E, Dalla Martha RC, Rodrigues JA, Costa JD, et al. Urban malaria in the Brazilian Western Amazon Region I: high prevalence of asymptomatic carriers in an urban riverside district is associated with a high level of clinical malaria. Mem Inst Oswaldo Cruz. 2007;102:263-269.

Victora CG, Huttly SR, Fuchs SC, Olinto MT. The role of conceptual frameworks in epidemiological analysis: a hierarchical approach. Int J Epidemiol. 1997;26:224-227.

Wesolowski A, Buckee CO, Engø-Monsen K, Metcalf CJE. Connecting mobility to infectious diseases: the promise and limits of mobile phone data. J Infect Dis. 2016;214(suppl 4):S414-S420.

Wilson ML, Krogstad DJ, Arinaitwe E, Arevalo-Herrera M, Chery L, Ferreira MU, Ndiaye D, Mathanga DP, Eapen A. Urban malaria: Understanding its epidemiology, ecology, and transmission across seven diverse ICEMR network sites. Am J Trop Med Hyg. 2015;93(3 Suppl):110-123.

World Health Organization. WHO malaria terminology. Geneva, World Health Organization, 2018 (WHO reference number: WHO/HTM/GMP/2016.6). Available at: https://www.who.int/malaria/publications/atoz/malaria-terminology/en/

World Health Organization. World Malaria Report 2018. Geneva, World Health Organization, 2019. Available at: http://www.who.int/malaria/publications/world-malaria-report-2019/en/