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An abstract of
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Abstract

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Dengue virus, the most prevalent mosquito-borne virus in the world, has been re-emerging and propagating in recent years across the world through increased host, pathogen, and vector interactions. Because the vector, Aedes aegypti, moves relatively short distances and feeds during the day, movement patterns of humans may play an important role in disease propagation. The current study is an assessment of some of the contributions of human movement to transmission of dengue in the economically disadvantaged urban environment (EDUE) of Iquitos, Peru. Demographics of study participants as well as entomological indices at the household level were included in the analysis.

The current study drew on methods from the literature of time geography as well as novel metrics to quantify the study participants' "activity spaces." An activity space is defined by the locations visited and paths used. Activity space metrics as well as entomological and demographic variables were tested for significance in explaining rates of seroprevalence and seroincidence of dengue virus (DENV) using univariate logistic regression. Full multivariate models for seroprevalence and seroincidence of DENV included both fixed effects (demographic, entomologic, and activity space variables) and random effects (individual participants and neighborhoods). These mixed-models were ranked using the Deviation Information Criterion (DIC) for model comparison.

The results of the study indicate that most movements are within 500 m of a house, which may be important in predicting risk and defining areas for control and surveillance. We conclude that there is no "best" model for explaining seroprevalence and seroincidence of DENV. Age of the participant and sum of routinely visited locations' distance from home, were significant variables for DENV prevalence. Number of residents in house was significantly associated with dengue incidence and there were no significant variables explaining DENV-4 incidence. We discuss the limitations of the study as well as future directions and conclude that more studies are needed to explore the role of human movement in dengue propagation.

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Introduction

In recent years, infectious diseases have been propagating at an increasing rate, and disease emergence and re-emergence has been on the rise (Morse 1995; Gubler 1998; Jones 2008). Scientists have attributed patterns of disease emergence to increased exposure, or contact between host and pathogen, among other factors (Anderson and May 1991; Morse 1995; Kuno 1997; Jones 2008). For vector-borne diseases (i.e., malaria, West Nile virus, dengue virus), an interdisciplinary approach to studying exposure requires an understanding of pathogen and vector ecology as well as human behavior (Gubler 1998; Weaver and Barrett 2004; Kilpatrick, Kramer et al. 2006).

Within the context of vector-borne diseases, mosquito-borne diseases are the main cause of substantial global morbidity and mortality. Many mosquito-borne diseases are concentrated in tropical regions, which house the world's most economically disadvantaged nations, and approximately 32 percent of the world's population (Gallup, Sachs et al. 1999).

The human behavioral and socio-demographic dimensions of vector-borne and particularly mosquito-borne diseases have been examined at a coarse spatio-temporal scale to include factors such as global population growth, associated unplanned and uncontrolled urbanization, substandard housing, crowding, deterioration in water, sewer and waste management systems, lack of effective mosquito control, air travel, and decay of public health infrastructures (Gubler 2002, Hales et al. 2002, Morse 1995, Knudsen 1992, Martens 2000, Rappole et al. 2000, Sutherst 2004.) In particular, human mobility, an important factor in determining host-pathogen interaction, has been studied from the long range perspective of international travel and migration (Hall 2000; Wilder-Smith and Gubler 2008). While these types of movement are effective in describing coarse spatial and temporal patterns of emergence and re-emergence of major vector-borne diseases (Cosner, Beier et al. 2009), human behavior at the scale of daily host-pathogen interaction is a poorly understood element of vector-borne disease propagation (Adams and Kapan 2009; Stoddard, Morrison et al. 2009).

Dengue virus is the most prevalent mosquito-transmitted virus in the world and causes more morbidity and mortality than any other arthropod-borne virus. Dengue infection can be asymptomatic, mildly asymptomatic or can cause severe clinical outcomes in the form of dengue fever (DF) or dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS), when exposed to a second strain (Guzman and Kouri 2003). Dengue occurs in mostly tropical countries where 2.5 - 3.0 billion people are at risk (Gubler 1997; Gubler 1998; Halstead 2007). Dengue is endemic in more than 100 tropical countries, and dengue hemorrhagic fever has been documented in more than 60 of these countries (WHO, 2000). At present, there are an estimated 50-100 million cases of DF and 250,000-500,000 cases of DHF/DSS a year (WHO, 1999).

The principal mosquito vector for dengue transmission is *Aedes aegypti* with *Aedes albopictus* acting as a secondary vector in some areas. Dengue is caused by four closely related, antigenically distinct single-stranded RNA viruses (DENV-1, DENV-2, DENV-3, and DENV-4) in the genus Flavivirus, family Flaviridae (Matthias Kalitzky 2006). Horizontal transmission occurs between *Ae. aegypti* mosquitoes and humans, with an incubation period ranging from 3-7 days in the human host (intrinsic incubation period) and 8-11 days in the mosquito vectors (Slosek 1986; Halstead 2007). The immature forms of the vector mainly develop in standing water often found in man-made containers, and adult females rarely fly more than 100m (Getis et al. 2003). Dispersal therefore is largely dependent on the movement of viremic human hosts and occurs even when vector populations are low (Harrington, Scott et al. 2005; Stoddard, Morrison et al. 2009). Immunity induced by infection with one serotype is protective and affords transient cross-protection against the others. However, this transient protection does not effectively protect from sequential infections with different serotypes (Morrison et al. 2010). Secondary infections are often more severe and can lead to dengue hemorrhagic fever (DHF) (Neal S. Young 2005). There is no vaccine for dengue virus, so prevention relies on virological surveillance and vector control (Morrison et al. 2010).

Ae. aegypti adults feed during the day, have a limited flight range (~100m) and are abundant in densely populated urban areas (Stoddard, Morrison et al. 2009). These factors, along with human movement in and out of zones of infection, allow heterogeneity in exposure and infection rates (Teixeira, Barreto et al. 2002). Other vector-borne diseases, such as malaria, have different patterns of exposure, since the anopheline vectors feed at night, and exposure is mostly limited to the home or area of rest (Martens and Hall 2000). Therefore, movement of human hosts during the day does not play a significant role in exposure.

In Iquitos, a city located in the Amazonian region of Peru, the history of dengue virus transmission has been documented by the US Naval Medical Research Center Detachment (NMRCD) since the early 1990s when Dengue Virus (DENV) was presumably reintroduced into Peru (Phillips et al. 1992). There have been five recorded epidemics of febrile disease caused by sequential invasions: DENV-1 in 1990-1991, an American strain of DENV-2 in 1995 (Watts et al. 1999, Hayes et al. 1996), DENV-3 in 2001 (Kochel et al. 2008), an Asian strain of DENV-2 in 2002, and DENV-4 in 2008 (Forshey et al. 2008). The current study was carried out from 2008 to 2010, toward the beginning of the DENV-4 epidemic invasion.

Exposure to vector-borne disease is measured through a variety of metrics and methods. Quantifications of vector density and abundance are common measures of exposure, although these do not always predict exposure accurately (Morrison, Zielinski-Gutierrez et al. 2008).

Traditional entomological surveillance techniques used to measure exposure to *Ae. aegypti* are based on the assumption that exposure occurs at the home. The premise/house index (HI; percentage of houses infested with larvae and/or pupae), container index (CI; percentage of water-holding containers infested with larvae and/or pupae), and Breteau index (BI; number containers infested with larvae and/or pupae per 100 houses) were designed to detect the presence or absence of *Ae. aegypti* larvae and/or pupae. Many investigators have raised questions as to the effectiveness of such methods since they fail to account for larval mortality, heterogeneity in container productivity, and temporal differences in *Ae. aegypti* life stages. Particularly, the presence of larvae is not always strongly correlated with the presence of adult female mosquitoes in a household (Morrison, Astete et al. 2004). Factors impacting larval mortality and development such as container size, crowding, and availability of nutrients in aquatic larval habitats must also be taken into account (Scott and Morrison 2010). Even with improved entomologic surveillance techniques, incorporating interaction with the host and a consideration of space and time are needed to strengthen estimates of exposure and analyses of risk. To address this need, we build on Stoddard et al.'s conceptual model that incorporates human movement into risk of exposure. They estimated a transmission rate (R_0) of 1.3 when exposure is assumed to occur only in the home versus 3.75 when exposure at multiple locations due to movement is considered (Stoddard, Morrison et al. 2009).

To better assess exposure, we borrowed from the theoretical framework of the field of time geography, which aims to understand constraints on human activity participation in space and time (Miller 2005). The "activity space model" (Hägerstrand 1970) provides a conceptualization of dynamics of human movement, locations used and paths between them (Stoddard, Morrison et al. 2009). Understanding the contribution of daily human mobility to epidemiologic risk to dengue will be a crucial step in understanding the impact of human behavior on exposure risk at a local scale. Movement has never been used as a risk factor for dengue infection (Stoddard, Morrison et al. 2009). Iquitos, Peru, offers unique conditions for studying such dynamics. As an economically disadvantaged urban environment, Iquitos represents a novel socio-demographic context which has not been the focus of human mobility studies to date.

The present study was undertaken to investigate the relative contributions of entomologic, socio-demographic variables and activity space (AS) measurements to DENV prevalence and incidence for residents of Iquitos between the years 2008 and 2010. We calculated AS measurements derived from transportation and movement literature as well as novel metrics for each participant. We tested these through univariate and multivariate analysis and examined their relative strength as parameters predicting seroprevalence and seroincidence of dengue among study participants.

Aims

The overall goal of this work is to evaluate epidemiologic risk of dengue virus transmission as a function of entomologic, socio-demographic and human movement risk factors in the context of an economically disadvantaged urban environment. We explored the following questions: 1) Does human movement help predict incidence and prevalence of dengue within Iquitos? 2) What determines an individual’s risk of exposure to dengue within Iquitos and which populations are at a higher risk? 3) What measures of AS are most relevant to the study of dengue within Iquitos? We aimed to test the following hypotheses:

1) Exposure at the home will remain most important for the majority of participants, but including movement metrics will strengthen the explanatory power of the regression model of seroprevalence and seroincidence of dengue.

2) Mobile populations will exhibit AS patterns correlated with high risk of exposure.

3) Measures of AS that give weight to epidemiologically relevant locations will be better predictors of exposure than measures of AS that take all visits into account, including those to public spaces.

The results of this work are relevant for vector and disease surveillance and may have implications for vector control and vaccine strategies. Understanding the role of human movement is important for determining possible patterns of transmission, populations that have higher rates of mobility and therefore play important roles in disease transmission, areas of potential human-vector infective contacts, and areas that can be targeted for increased vector control (Scott and Morrison 2008).

Materials and methods

Study Area

The study area consists of two neighborhoods in the Amazonian city of Iquitos (73.2° W, 3.7° S, 120 m above sea level) in the Department of Loreto, northeastern Peru. Iquitos is a geographically isolated city due to the three rivers (Amazon, Nanay and Itaya) that surround it on all sides and allow access to the city only by air or water. The population is ~400,000 people and employment is highly dynamic, with 33.4% of the economically active urban population unemployed or informally employed (*Instituto Nacional de Estadística e Informática* of Peru, 2007). The major industries in the area are small commercial enterprises, fishing, oil, lumber, tourism, and some agriculture. Iquitos consists of four districts: San Juan, Maynas, and Punchana, running from south to north and Belen on the east. The two neighborhoods chosen for the study, Maynas in the north central part of the city, and Tupac Amaru to the southwest (Figure 1), have been characterized in previous studies as areas of high (Maynas) and low (Tupac Amaru) prevalence of human dengue infection (Morrison 2004). Maynas is the wealthier and older of the two neighborhoods, although both areas are heterogeneous with regards to socioeconomic status. Well-constructed households with piped water and poorly constructed households with no water or sewer services also occur in both neighborhoods. Maynas has a higher proportion of permanent houses constructed with bricks and concrete than Tupac Amaru. Conversely, Tupac Amaru is a community in transition from predominantly temporary wood houses with palm roofs to houses constructed with brick and concrete. Even though Maynas has a better-developed sewer system than Tupac Amaru, the Maynas water supply is less consistent. Consequently, Maynas residents are more likely than those in Tupac Amaru to store water in containers that are potential development sites for immature *Ae. aegypti*. In contrast, Tupac Amaru has many open sewers but because of close proximity to the city water plant most houses have a sTable water supply and are less likely to store water than in Maynas (Getis et al., 2003).

Study Design

Background

Data for this study came from a NIH-funded project in Iquitos, Peru (NIH/NIAID R01 AI069341-01) involving collaborators from UC Davis, Emory University, the Naval Medical Research Center Detachment in Lima, Peru (NMRCD) and the Loreto Department of Health. Many of the same investigators have been collaborating in Iquitos since 1998. From 1998 to

2003, a 5 year longitudinal cohort study titled “Entomologic Assumptions of Dengue Control,” was conducted, a Geographic Information System (GIS) for the study area was developed, and data were gathered from clinic-based and school-based febrile surveillance, serological studies, cluster investigations, and DNA profiling of *Ae. aegypti* blood meals. The current project is focused on entomological factors and risk of dengue across a person’s AS. Extensive data on human demography, *Ae. aegypti* entomological indices, and dengue epidemiology were collected from 2008 to 2010, with measures of human movement incorporated through a variety of methods. To track human movement, the research team in Iquitos employed a combination of structured interviews and GPS data loggers worn by participants to quantify AS (Vazquez-Prokopec, Stoddard et al. 2009). A study was performed to test the social acceptability of the GPS data loggers. The GPS units were shown to be acceptable by all focus group participants. Main concerns included caring properly for the unit, whether the unit would audio/videotape them, health effects of prolonged use, responsibility for units, and confidentiality of information (Paz-Soldan, Stoddard et al. 2010). For the purposes of the current study, only the prospective interview data were used for quantifying AS metrics since this enabled us to use a larger set of participants for our analysis.

Prospective Activity Space study

Participants in the prospective AS studies come from a subset of the larger febrile surveillance study. There are 2,400 participants in the surveillance study, with 1,200 from Tupac Amaru and 1,200 from Maynas. These participants are visited three times a week, and have blood drawn when febrile. Adult mosquitoes are collected from households and identified in the lab every four months. Participants involved in the longitudinal cohort comprise a subset of the surveillance study participants, and, in addition to febrile surveillance, these participants have annual blood draws to define their infection status using Plaque Reduction Neutralization Assays (PRNTs). Participants in the prospective AS study were selected from the longitudinal cohort. These individuals agreed to participate in semi-structured interviews administered to identify places visited on a routine basis. These locations are geo-referenced, verified by field workers and added to the Iquitos geo-referenced database for analysis.

Entomology

Entomologic variables for this study include average numbers of pupae and adult *Ae. aegypti*, as well as numbers of water-storing containers and containers infested with immature mosquitoes per household. Water-storing containers are simple and practical to count and give some indication of the number of available larval habitats. Pupae are more practical to count than other life stages and pupal mortality is slight and well characterized. Adults are difficult to capture using traditional methods such as human bait, indoor sweeps with hand nets and other manual methods. The most effective device for collecting *Ae. aegypti* adults is the battery-powered backpack aspirator, which was used to collect data for our study.

Serostatus

Prevalence and incidence of dengue virus infection were determined through measures of seropositivity, for which human blood was assayed for evidence of infection with all four DENV serotypes. Standard NMRCD ELISAS were used to assay human sera for anti-DENV IgM. Standard NMRCD PRNT was followed for detection of neutralizing antibody against DENV. The value reported for the PRNT was the serum dilution that reduced 70% of plaques compared to normal human serum in the same dilution. For the purposes of this study, the first blood draw served as an indication of infection prevalence, and each subsequent change in anti-DENV IgM indicated seroconversion and was used to estimate incidence of DENV or DENV-4 infection.

Data Management and Processing

All entomological and human data collected in surveys were joined to geographic coordinates via a spatially specific house or location code using GIS. All data from the NIH-funded project were managed in Microsoft ACCESS (Redmond, WA) database files. Data were entered daily by field teams and managed and corrected by investigators. Databases were shared electronically among key project personnel for analyses, publications, oral presentations, and project development. The final database used for the current study included participant codes, demographic variables for each participant (such as neighborhood, age, sex, and occupation), entomological variables for each household (including numbers of pupae, adult females, water-storing containers, and containers infested with immature mosquitoes) location of residence and coordinates, locations visited and coordinates, and seroconversion status as well as dates of serology testing. AS metrics were processed for each participant using excel pivot Tables, access queries, and functions in arcGIS.

Activity Space metrics

AS metrics included spatial and non-spatial metrics. These were first calculated for all sites and later re-calculated for “epidemiologically-important” sites alone. “Epidemiologically-important” or “epi sites” refer mainly to locations where infective contacts (between mosquitos and hosts) are assumed to be high. This assumption is based on previous entomological studies and surveillance data from Iquitos, Peru, that suggest that infected female *Aa. Aegypti* are mainly found in residential settings (Morrison, Gray et al. 2004). Therefore these sites exclude public spaces such as churches, cemeteries, schools, markets, parks, etc. where infective contacts are assumed to be low. “Epi sites” include residential locations such as houses, the airport, stores, banks, bars, “bodegas” (storage areas for food), prisons, clinics, factories, hospitals, hotels, restaurants, and government offices.

A total of ten metrics were calculated for each participant (five with all sites, five with “epi sites.”) Figure 2 gives a visual representation of each of the five metrics calculated with all routinely visited locations (RVLs). Some of the metrics were based on theoretical and applied literature mainly in the fields of time geography and transportation. Other metrics were unique to the current study. Two non-spatial (NS) metrics were determined for each participant. The first, number of routinely visited locations (RVLs), was calculated in Microsoft Excel using the following formula:

$$NS1 = \sum RVLs \tag{1}$$

The second NS metric, number of routinely visited locations by relative time outside home, was calculated using the following formula:

$$NS2 = \sum RVLs \times t_{ro} \tag{2}$$

Where t_{ro} is the relative time outside home calculated by the equation

$$t_{ro} = \frac{(t_{total} - t_{home})}{t_{total}} \tag{3}$$

Where t_{total} is the total time spent at all RVLs as reported by the interviews and t_{home} is the time spent at the household.

Spatial metrics include the sum of the distance of RVLs to the home (S1A):

$$S1A = \sum d_i \tag{4}$$

Where d_i is the distance from location i to home calculated by the Pythagorean theorem when setting longitude as x and latitude as y:

$$d_i = \sqrt{[\![(y]\!]_i - y_{home})^2 + (x_i - x_{home})^2} \tag{5}$$

The sum of distances by relative time spent at each location (S1B) was also calculated in Microsoft Excel using the following formula:

$$S1B = \sum_{i=1}^{n} (d_i \; x \; t_{ri}) \tag{6}$$

Where t_{ri} is the relative time calculated by

$$t_{ri} = \frac{t_i}{t_{total}} \tag{7}$$

Other spatial AS metrics computed using ArcGIS (ESRI, Redlands CA) included area of minimum convex polygons (MCPs) (S2), area of standard deviation ellipse (SDE) (S3A) and ratio of SDE axes (S3B). MCPs were developed for estimating animal home ranges (Worton 1987; White 1990; Kie 1996) but apply well to the human AS we are trying to capture here. Standard deviation ellipses are also used extensively as measures of AS in transportation, healthcare access and other studies (Nemet ; Newsome, Walcott et al. 1998; Arcury, Gesler et al. 2005; Sherman, Spencer et al. 2005).

MCPs were calculated in ArcGIS using Hawth's Tools. The MCP tool creates convex polygons for each unique value that completely encloses all input data points by connecting the outer locations. Therefore, using RVLs as input points and participant code as unique values creates a unique polygon for each participant with all RVLs enclosed within it. The formula used by the software to calculate the area of MCPs is the following:

$$A = \frac{x_1 \, (y_n - y_2) + \sum_{i=2}^{n-1} x_i (y_{i-1} - y_{i+1}) + x_n (y_{n-1} - y_1)}{2} \tag{8}$$

Where (x,y_i), i = 1, 2,…, n are the coordinates of the RVLs. A number of locations in the semi-structured interviews did not include coordinates because they could not be located and geoprocessed by field workers. Since MCPs cannot be created with less than three input points, participants with less than three routinely visited locations with recorded coordinates were not included in the analysis. Figure 3 shows an example of a MCP calculated in ArcGIS.

Standard deviation ellipses (SDEs) were calculated in ArcGIS using Spatial Analyst, with RVLs as input points and participant code as unique values, using two standard deviations. The standard deviation ellipse tool creates a feature class containing elliptical polygons for each case. If the underlying spatial pattern of the features is concentrated in the center with fewer features toward the periphery (spatial normal distribution), a two standard deviation ellipse contains approximately 95 percent of the features. Figure 3 shows an example of a SDE calculated in arcGIS.

Data Analysis

We chose multi-level mixed effects statistical models as the method of analysis for this study. Explanatory variables in mixed effects models are a mixture of fixed effects and random effects. Fixed effects are those that influence only the mean of y (seroprevalence, seroincidence, etc.) and random effects influence only the variance of y. The purpose of random effects is to quantify the variation among units, which can include blocks (block random effects) or individuals (i.e. blocks of 1, individual random effects). We computed random effects with each neighborhood (Maynas vs. Tupac Amaru) representing a block and each participant code representing an individual. We used the framework of generalize linear mixed models (GLMMs) which combine the properties of linear mixed models (which incorporate random effects) and generalized linear models (which handle nonnormal data by using link functions and exponential family distributions). For our analysis, we defined the family distribution as binomial since we are interested in two outcomes: infected or not infected. Bolker et al. state that “GLMMs are the best tool for analyzing nonnormal data that involve random effects” (2009).

The approach of model comparison was chosen over hypothesis testing to avoid dichotomies of “significant” vs. “insignificant,” and for a more critical analysis of results. Analysis was conducted not to determine the “true model” but rather to select a model that would prove most useful and offer insights, given the limited data and parameters as well as the complexity of an epidemic invasion. Model development involved careful *a priori* thinking to avoid pitfalls of a “shotgun strategy” (Anderson 2002) in which variables are merely collected and tested to “find the variables that are significant.” After a careful consideration of the literature and background information on the study question, variables of interest were selected and tested for relative significance through univariate logistic regression using the logit command in STATA 11.1 with prevalence (infection at any point of study period), incidence (seroconversion between July 2009 and July 2010), and incidence of DENV-4 (seroconversion to DENV-4 between July 2009 and July 2010) as binary outcome variables. Variables with $p<0.20$ were included in the multivariate mixed effects models. Entomological variables were also included although they did not yield p-values<0.20, based on prior knowledge of the epidemiology of dengue transmission and the association of these variables with dengue virus infection in previous studies (Scott and Morrison 2003). Table 1 shows a summary of variables selected through univariate logistic regression, and prior information for inclusion in the multi-level mixed effects models.

Results of univariate logistic regressions for each outcome variable produced a number of full models. In cases where there were two or more AS metrics with $p<0.20$, each AS metric was used in a separate full model. All full models included random effects for both participant code and neighborhood. Once the full models were constructed, candidate models could be extracted by excluding different combinations of the remaining variables. The 10 candidate model combinations for each outcome were selected *a priori*. Once the candidate models were selected, they were tested in R 2.12.0 using the INLA package. The deviance information criterion (DIC) was recorded for each model and used for model comparison. Models with $\Delta DIC \leq 2.0$ $(\Delta DIC = DIC\ of\ model - minimum\ DIC)$ were considered to be top models.

Results

Demographics and Human Movement Patterns

Demographics and human movement patterns for the 712 participants analyzed in this study were obtained through semi-structured interviews. A summary of key demographic attributes of the 712 study participants is included in Table 2. Of the total 712 participants 53.0% were from Maynas and 47.1% were from Tupac Amaru. For these 712 study participants, the average sex ratio was 1.23 (F:M), with a large proportion of the participants belonging to the 6-18 age group (40.5% of the total participants). The 712 study participants came from 284 households, and account for ~ 12% of total household members.

A large portion of the sites recorded in the surveys/semi-structured interviews were located, with only ~ 4% not found or outside the study area. A total of 4822 routine locations were recorded in Maynas and 4765 in Tupac Amaru, with 3% of routine locations in Maynas and 5% in Tupac Amaru missing.

Regardless of the area of residence, study participants spent on average 70% of their overall day time outside the home. Participants from Tupac Amaru tended to visit on average more locations than participants in Maynas ($t = -4.3$, d.f. $=710$, $p<0.001$). Participants from Tupac Amaru also visited on average more epidemiologically relevant sites ($t = -3.9$, d.f. $= 720$, $p<0.001$).

Figure 4 shows a comparison of AS metrics for all participants combining Maynas and Tupac Amaru. Figure 4f) and 4g demonstrate that S1A is significantly higher for all sites than for epi-sites alone ($t=-37.1$, d.f.$=1422$, $p<0.001$) indicating that nonresidential sites that are less important epidemiologically are further away, exaggerating AS metrics without increasing predictive power.

Residential locations had the highest frequency of routine visits for residents from both neighborhoods (Maynas = 34.6% of all locations visited, Tupac Amaru = 35.5%). Figure 5 shows location types by frequency of routine visits. Participants from Maynas visited markets more than shops and participants from Tupac Amaru visited shops more than markets, perhaps as a result of the fact that the closest major market is farther away for Tupac Amaru residents than it is for Maynas residents. Maynas residents mostly visited the "Mercado Modelo" market (accounted for 219 routine visits in our study) which is on average 1,194 m away from their homes. They also visited "Mercado Clavero" (182 routine visits, average of 255 m away) and "Mercado Belen" (147 routine visits, average of 2,923 m away). Tupac Amaru residents mostly visited "Mercado Belen" which is further away on average (2,279m) than "Mercado Modelo" is to Maynas residents.

Maynas residents are more likely to visit locations within their own neighborhood than Tupac Amaru residents. 39.3% of locations visited by Maynas residents were in Maynas and 18.2% were in Tupac Amaru whereas 24.7% of locations visited by Tupac Amaru residents were in Tupac Amaru and only 0.86% were in Maynas (Figure 6).

As can be seen in Figures 7 and 8, the locations most frequently visited are those closest to the household. 42.8% of locations visited by Maynas residents and 39.7% of locations visited by Tupac Amaru residents fall within 500m of the home. 50% of locations (excluding the home) occur within 732m of the home for Maynas residents and within 1401m of the home for Tupac Amaru residents. Tupac Amaru residents appear to have two peaks of activity: one near the home and one about 2300m away from the household (Figure 7). This second peak of activity can be attributed to visits to Mercado Belen. For “epi-sites” only (Figure 9), 50% of RVLs visited by Maynas residents fall within 243m of the home, while 50% of those visited by Tupac Amaru residents fall within 195m.

Ae. aegypti occurrence and DENV Infection Patterns

Ae. aegypti pupae abundance differed between the two neighborhoods with significantly higher numbers of pupae in Maynas ($t=-2.0$, d.f.=710, $p<0.05$). Abundance of adult mosquitoes did not differ between neighborhoods ($t=0.76$, d.f.=710, $p>0.4$).

The data for our study were collected during and immediately following the introduction of Dengue Virus 4 to Iquitos as a novel serotype, resulting in a large outbreak. The force of transmission was very high with epidemic peaks in Fall, 2009 and Spring, 2010 (Figure 10). Figure 11 shows clinical DENV isolates during the study period and the introduction of the DENV-4 serotype in 2008.

Determinants of Dengue Infection

Univariate Analysis

According to chi-squared tests of homogeneity, both prevalence and incidence of dengue as well as prevalence of DENV-4 were significantly different between the two neighborhoods and between males and females. Maynas residents had significantly higher rates of baseline dengue incidence (Maynas = 48.3%, Tupac Amaru = 40.6%, Chi2=4.23, $p<0.05$) and incidence of DENV-4 (Maynas = 43.0%, Tupac Amaru = 34.9%, Chi2=4.82, $p<0.05$), but not of overall dengue prevalence. Females had significantly higher rates of dengue incidence (Female = 48.0%, Male = 40.6%, Chi2=3.90, $p<0.05$), but not of incidence of DENV-4 or overall dengue prevalence.

The results of univariate logistic regressions (Table 4) indicate that for dengue prevalence, dengue incidence and DENV-4 prevalence, age, sex, neighborhood and distance from home had p-values<0.20 and could be included in the multivariate regressions. Additional variables included occupation, interaction of distance from home with proportion of time outside the home, and area of SDEs for epi-sites for dengue prevalence; number of residents, number of containers, and area of SDEs for epi-sites for dengue incidence; and time at home for DENV-4 prevalence.

Multivariate analysis

All top five mixed-effects models for DENV prevalence (Table 5) have similar predictive power ($\Delta \mathrm{DIC} \leq 2.0$ for all five models). However, of the variables included in these five models, age and S1A (sum of distances from home) have the greatest predictive power in explaining seroprevalence. Age has a significant positive coefficient (0.0176 to 0.0182, depending on model), meaning that the higher the age, the greater the probability of seroprevalence. The AS metric (S1A) has a significant negative coefficient (-2.14E-5 to -2.03E-5, depending on model), meaning that the lower the sum of distances from home, the higher the probability of seroprevalence.

Models 1-4 of DENV incidence (Table 6) have similar predictive power $(\Delta\mathrm{DIC} \leq 2.0)$. Number of residents was the only variable that appeared significant. The coefficient was negatively significant (-0.0439 to -0.0416), meaning that the fewer residents a participant lived with, the higher the chance of DENV incidence.

For DENV-4 incidence, none of the candidate or full models had significant variables (Table 7). The lack of fit could be related to the epidemic invasion of DENV-4 at the time of the study.

Discussion

Studies of vector-borne disease and dengue studies in particular, have often neglected the human behavioral component of exposure risk. There is a need for understanding risk of exposure to dengue in economically disadvantaged urban environments, and understanding risk of exposure will lead to improved vector surveillance and control. Our study attempts to fill this gap by including the component of human mobility, which has not been studied in economically disadvantaged urban environments to date. Thus, our study is a contribution to an exploration of differences in movement patterns of economically disadvantaged populations who experience the greatest dengue disease burden.

We aimed to address three questions in our study: 1) Does human movement help predict incidence and prevalence of dengue within Iquitos? 2) What determines an individual’s risk of exposure to dengue within Iquitos and which populations are at a higher risk? 3) What measures of activity space (AS) are most relevant to the study of dengue within Iquitos?

Our prediction for question 1) was that including movement metrics would strengthen the explanatory power of the regression model of dengue seroprevalence and seroincidence. All top models of seroprevalence, seroincidence and DENV4 seroprevalence included some measure of AS, conforming to our predictions. However, our initial hypothesis was that AS metrics that indicated increased movement (for example, greater sum of distance from home) would be associated with greater risk of exposure. Our results show an inverse relationship between sum of distance to home and dengue prevalence and incidence, indicating that movement further from the home is associated with lower incidence and prevalence of dengue. This finding indicates that although AS matters because it appeared in all top models, movement near the household may have the greatest impact on risk of exposure. Additional studies are needed to test this new hypothesis.

Our prediction for question 2) was that mobile populations would exhibit AS patterns correlated with high risk of exposure. We were not able to distinguish AS patterns between populations, and therefore cannot draw conclusion about the exposure risk of mobile populations. This may be due to available activity space metrics that do not give a good indication of differences in AS among differing age, sex and occupation groups. Alternatively, modes of transportation, and thus restrictions to daily mobility, may be uniform for all population groups in Iquitos, which would result in relatively uniform activity spaces.

However, we did find that sex, neighborhood, and number of residents in household were important univariate determinants of dengue incidence and that being a student was an important univariate determinant of DENV-4 prevalence. In the multivariate models, neighborhood acted as a random effect, and occupation and sex were not significant predictors. Therefore, we conclude that students and females are not high risk populations when other factors are taken into account. Number of residents in household continued to be an important predictor in top multivariate seroincidence models. This result does not support our prediction that mobile populations with greater AS would be at a higher risk of exposure.

Our prediction for question 3) was that AS metrics that only accounted for locations of highly likely exposure (epi-sites) would be better predictors of exposure than AS metrics that accounted for all sites. Our results did not support this prediction. The AS metric that contributed most to top seroprevalence and seroincidence models was the sum of distances of RVLs from the home, and this metric took into account all sites. We conclude that the assumption of what constitutes an epi-site must be revisited in order to fully determine whether AS metrics that take this assumption into account are indeed better predictors of risk. For example, it is possible that schools (Garcia-Rejon, Lorono-Pino et al. 2011) and cemeteries (Abe, McCall et al. 2005; Vezzani 2007) are epidemiologically important locations and that including them as epi-sites would strengthen the predictive power of regression models for dengue incidence and prevalence.

Our main findings indicate that movement patterns occur within 500m of the house, and that participants with local AS closest to the home have higher seroprevalence for all dengue serotypes. We also concluded that age is positively associated with seroprevalence and that number of residents in a household is negatively associated with seroincidence. No predictors were found significant for seroincidence of DENV-4, possibly due to the complex dynamics of novel serotypes, a topic which requires additional attention.

Age and sum of distances from home were the two significant predictors for seroprevalence. For age, the longer one has lived, the greater is their probability of infection by any serotype of dengue. Sum of distances from home for routinely visited locations was included in the strongest models, which is an indicator that human movement at a level closer to the household may be playing some role in risk of infection.

Number of residents in a household was the only significant predictor for seroincidence, with an inverse association. The reason for this is not clear. If we assume transmission at the household level, a lower number of residents occupying a household may increase the mosquito-human ratio, potentially increasing each resident's probability of being bitten by an infected mosquito. Taking into account transmission occurring outside the household, an individual with fewer shared residents will have fewer networks and therefore a lower probability of being linked to an infected individual who may cause a household vector to also become infected. Since our seroincidence model indicated a significantly negative association of the number of residents with infection, our study may indicate that transmission at the household level is indeed most significant, however, there are many complicating factors, and more studies are needed to further explain this result.

Exposure has been measured at various scales, with most entomologic indices collected at the household level. Indices such as the Breteau Index at the level of the block (on average about 50 houses) have been used as predictors of dengue transmission (Sanchez, Cortinas et al. 2010). Sanchez et al. (2010) defined a neighborhood as a house plus the surrounding blocks within a radius of 100 m. They found a Breteau index of four to be the threshold level for transmission in neighborhood blocks. Health departments commonly control and contain dengue through perifocal spraying, which consists of the spraying of actual or potential breeding sites and the surrounding areas. This practice has been very effective in reducing DENV transmission (Scott and Morrison 2003). Historically, the World Health Organization (WHO) recommended perifocal spraying for dengue control, and later increased the extent of coverage to a radius of 100 m around the house. Most recently WHO has recognized the limitation of treatment even at the 400m level stating that “by the time a case is detected and a response mounted, the infection is likely to have spread to a wider area.” (WHO 2009). Our study did not define the spatial scale at which movement influences risk of exposure. Nevertheless, we expect that interventions will need to go beyond a 100 m radius of the home and propose that future studies examine AS at the neighborhood level to determine the scale at which movement impacts exposure.

Limitations

Results from this study were limited by 1) the quality and quantity of entomologic data, 2) exclusion of participants due to missing data, 3) epidemic invasion of DENV-4, 4) a lack of developed AS metrics for epidemiologic purposes, 5) data availability, and 6) assumptions concerning rates of infective contacts in public spaces. Entomologic data are being revised and corrected for gaps in the data and for other possible errors. In the current study, averages of entomologic variables such as number of pupae, adults and containers were taken for the entire study period. Entomologic data were not available for most routinely visited locations outside the home, so analyses incorporating risk across the individual’s AS using entomologic variables were not possible.

Of the original 1280 participants in the prospective AS study for which survey data and sero-status were available, only 712 were used in the current study. The remaining participants were excluded from analysis due to missing values in one or more fields; 29 participants were excluded because they were missing household data such as entomological variables and number of residents; 255 additional participants with <3 epi-relevant sites were excluded because their MCPs and SDEs were given empty values (a polygon cannot be constructed with two or less points); additional participants were excluded because demographic variables from the survey were missing.

In 2008, during the current study, DENV-4 invaded Iquitos, causing an epidemic and introducing added complexity to the situation. Whereas a large proportion of the population was immune to DENV-3, DENV-4 was a novel serotype with less predictable epidemic patterns of infection. More studies will need to explore the dynamics of epidemic invasion of novel serotypes to better understand complexities of epidemic disease transmission.

In this study we explored human movement using AS metrics from the literature as well as novel metrics. AS metrics, especially those addressing patterns of disease transmission or exposure to disease agents, are lacking, as most metrics have been developed within the field of transportation or to determine home ranges for animal movement.

We examined entomologic, demographic and movement variables using a regression analysis of seroprevalence and seroincidence of dengue. Due to data limitations, we were not able to include additional variables that may be strong predictors in the model. Entomologic data were limited to the household, and entomologic indices for each site visited within the AS were not available. It is possible that entomologic variables used in this study, such as number of adult females, pupae, containers and positive containers were not significant because our study lacked other essential interacting considerations such as threshold density, feeding behavior, extrinsic incubation period and vector competence (Kuno 1997). Among the demographic variables, we did not have an indicator of socio-economic status, which has been shown previously to be important (Teixeira, Barreto et al. 2002).

Future Directions

This study is an initial contribution to quantifying human mobility in the context of dengue exposure risk. Both mosquito-associated and human-associated factors must be considered to determine the contact rate for dengue transmission, yet human activities are unquestionably more difficult to quantify (Kuno 1997). Kuno states that “adoption of techniques that consider the impact of human movement and probability of contact with virus may improve the quantification of the impact of human movement and related activities” and “infection does not necessarily take place at the residence of persons under study, since the number of infective female mosquitoes found per house during an epidemic has generally been less than one… since both humans and vectors are mobile, the locations where susceptible human, virus and vector meet must be analyzed in a dynamic context.” This study attempts to fill this gap by contributing to the quantification of human movement related to dengue exposure risk.

New metrics that will distinguish movement patterns of individuals within a disease setting must be developed. Studies of human movement have been conducted in economically advanced urban centers and there is a need to explore questions of movement within economically disadvantaged urban environments. Differences in economy oftentimes translate into differences in movement patterns (Hillier 1996), and these have a potential to contribute to the understanding of exposure to dengue.

Assumptions concerning epidemiologically important or “epi-sites” will need to be explored in more detail. We excluded public spaces such as schools, markets, cemeteries, ports, parks, etc. from our epi-sites, assuming that, in general, infective contact is very low in such spaces. Studies indicate, however, that some of these spaces such as schools (Garcia-Rejon, Lorono-Pino et al. 2011) and cemeteries (Vezzani 2007) may be viable locations for transmission of dengue. Hence, this assumption must be revisited to create a new classification of epi-sites that will be taken into account when constructing AS metrics. A study to be conducted this summer will explore the relative contributions of public spaces such as markets, schools, churches, cemeteries and ports to infection with dengue. Entomological and human behavioral data will be collected to determine the likelihood of infective contact in such spaces, and will be incorporated into our Iquitos field studies.

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Figures and Tables

Table*s*

Table 1. Summary of fixed and random effects used to construct 10 models *a priori* to predict dengue virus prevalence and incidence among study participants in Iquitos, Peru.

Fixed effects	**Description**
Demographics	
Sex	Sex of participant
Age	Age of participant
Res	Number of residents that share participants' household
Entomology	
Aa_fem	Average number of adult female *Ae. aegypti* collected at the participant's household throughout study period
Pupae	Average number of *Ae. aegypti* pupae collected at the participant's household throughout study period
Cont	Average number of containers found at the participant's household throughout study period
Pos_cont	Average number of containers infested with *Ae. aegypti* larvae or pupae found at the participant's household throughout study period
Occupation	
Hswf	1=housewife
Stdnt	1=student
Child	1=child (includes primary school students ages 5 to 12)
Trade	1=vendor (includes those who work at stores, restaurants, and retail)
Other	1=other (includes government workers, teachers, police, guards, unemployed, etc.)
Activity Space	
Rel_time_home	Relative time spent inside house
S1A	Sum of RVLs' distances from house
S1B	Sum of RVLs' distances from house by relative time spent outside house
S3A epi	Area of standard deviation ellipse for "epi-relevant" sites
Random effects	
Part_code	Random effects associated with participant code
Neighborhood	Random effects associated with neighborhood

Table 2. Key demographic attributes for the 712 participants involved in the study.

	Neighborhood		
	Maynas	**Tupac Amaru**	**Total**
Number of participants	377	335	712
Number of households	133	151	284
Number of residents per household	7.37 (3.50)	6.98 (3.58)	7.19 (3.54)
Sex Ratio (F:M)	1:0.79	1:0.83	1:0.81
Age group			
6 to 18	157	131	288
19 to 30	96	84	180
31 to 45	66	59	125
46 to 59	58	61	119
Occupation			
Child	62	71	133
Housewife	61	70	131
Trade	14	18	32
Student	161	113	274
Other*	79	63	142

*"Other" represents domestic worker, factory or construction worker, food services, guard or soldier, police, office job, retired, teacher, trade or craft, transportation, unemployed and self-employed. There is no significant difference for number of residents per household between Maynas and Tupac Amaru residents (t=1.63, d.f.=710, p>0.1)

Table 3. Prevalence and Incidence by demographics.

	Prevalence (Seroconverted at any point before July 2010)	Incidence (Seroconverted July 2009-July 2010)	Prevalence of DENV-4 (Seroconverted at any point before July 2010)
Neighborhood			
Maynas	203 (53.9%)	182 (48.3%)	162 (43.0%)
Tupac Amaru	158 (47.2%)	136 (40.6%)	117 (34.9%)
Sex			
Female	212 (53.8%)	189 (48.0%)	164 (41.6%)
Male	149 (46.9%)	129 (40.6%)	115 (36.2%)
Age group			
3-8	4 (26.7%)	4 (26.7%)	3 (20.0%)
8-18	140 (51.3%)	119 (43.6%)	110 (40.3%)
18-34	88 (50.4%)	77 (42.8%)	70 (38.4%)
35-45	63 (50.4%)	55 (44.0%)	48 (38.4%)
45-59	52 (56.5%)	50 (54.4%)	41 (44.6%)
59+	14 (51.9%)	13 (48.2%)	7 (25.9%)
Occupation			
Child	53 (39.9%)	44 (33.1%)	42 (31.6%)
Housewife	70 (53.4%)	62 (47.3%)	53 (40.5%)
Trade	13 (40.6%)	13 (40.6%)	13 (40.6%)
Other	69 (48.6%)	62 (43.7%)	47 (33.1%)
Student	156 (56.9%)	137 (50.0%)	124 45.3%)
Total	361 (50.7%)	318 (44.7%)	279 (39.2%)

Table 4. Results of univariate logistic regression reporting odds ratios for prevalence/incidence and demographic, entomologic and activity space variables. Significant variables (p<0.05) are marked in red. *Variables with p<0.20.

	Dengue Prevalence odds ratio	**Dengue Incidence** odds ratio	**DENV4 Prevalence** odds ratio
	Demographics		
Age			
6 to 18	0.80	0.66*	0.96
19 to 30	0.77	0.66*	0.94
31 to 45	0.82	0.70*	0.92
46 +		Omitted	
Occupation			
Child	0.70*	0.64*	0.93
Housewife	1.21	1.16	1.37
Merchant	0.72	0.88	1.38
Student	1.40*	1.29	**1.67**
Other		Omitted	
Sex	0.20*	**1.35**	1.26*
Neighborhood	0.77*	**0.73**	**0.71**
Number of Residents	0.98	**0.96**	0.98
	Entomology		
Adult females	0.96	0.98	0.93
Containers	0.97	**0.90**	0.98
Positive Containers	1.18	1.06	1.05
Pupae	0.99	0.99	0.99
	Activity Space Metrics		
Time at home	1.00	1.00	1.00*
NS1	0.99	1.00	0.99
NS1 epi	1.00	1.01	1.00
NS2	0.99	0.99	1.00
NS2 epi	0.97	0.96	0.97
S1A	**1.00**	1.00*	1.00*
S1A epi	1.00	1.00*	1.00
S1B	1.00*	1.00*	1.00
S1B epi	1.00	1.00	1.00
S2	1.00	1.00	1.00
S2 epi	1.00	1.00	1.00
S3A	1.00	1.00	1.00
S3A epi	1.04*	1.04*	1.01
S3B	0.97	0.96*	0.98
S3B epi	1.00	1.00	1.00

Table 5. Summary of top 5 mixed-effects models for DENV prevalence.

	Demographics			Occupation					Entomology				Activity Space Metrics					
Model	sex	age	res	hswife	stdnt	child	other	trade	pupae	*Aa* fem	cont.	pos. cont.	S1A	S1B	S3A epi	intrcpt	DIC	ΔDIC
1	0.3038	**0.0180**	-----	0.1777	0.9313	0.3783	0.2112	-0.2231	-----	-----	-----	-----	**-2.06E-05**	-----	-----	-0.1931	979.15	0
2	0.3129	**0.0182**	-0.0258	0.1737	0.9341	0.3899	0.2192	-0.2415	-----	-----	-----	-----	**-2.14E-05**	-----	-----	0.0178	979.21	0.06
3	0.3179	0.0171	-----	0.1793	0.9321	0.3667	0.2216	-0.2242	-----	-----	-----	0.1676	**-2.03E-05**	-----	-----	-0.2164	980	0.85
4	0.2955	0.0174	-----	0.2018	0.9246	0.3628	0.2183	-0.2320	-----	-----	-----	-----	-----	-2.06E-05	-----	-0.2679	980.25	1.1
5	0.3042	**0.0176**	-0.0254	0.1988	0.9272	0.3734	0.2267	-0.2507	-----	-----	-----	-----	-----	-2.14E-05	-----	-0.0626	980.37	1.22

Significant variables (p<0.05) are marked in red.

Table 6. Summary of top 5 mixed-effects models for DENV incidence.

	Demographics			Entomology				Activity Space Metrics					
Model	sex	age	res	pupae	*Aa* fem	cont.	pos. cont.	S1A	S3A epi	Rel t_home	intrcpt	DIC	ΔDIC
1	0.2664	0.0087	**-0.0435**	-----	-----	-----	-----	-1.68E-05	-----	-----	0.0262	973.98	0
2	0.2936	0.0069	**-0.0419**	-----	-----	-----	-----	-----	0.0396	-----	-0.2806	975.03	1.05
3	0.2705	0.0087	**-0.0437**	-----	-----	-----	-----	-1.91E-05	-----	-0.3535	0.1779	975.54	1.56
4	0.2706	0.0085	**-0.0439**	-----	-----	-----	0.0555	-1.67E-05	-----	-----	0.0202	975.83	1.85
5	0.2709	0.0085	**-0.0416**	-----	-----	-----	-----	-----	-----	-0.0073	-0.2463	976.88	2.9

Significant variables (p<0.05) are marked in red.

Table 7. Summary of top 5 mixed-effects models for DENV-4 prevalence.

	Demographics		Occupation					Entomology				Activity Space Metrics				
Model	sex	age	hswf	stdnt	child	other	trade	pupae	*Aa* fem	cont.	pos. cont.	S1A	Rel t_home	intrcpt	DIC	ΔDIC
1	0.2393	-----	0.2766	0.6267	0.0457	0.1404	0.3860	-----	-----	-----	-----	-1.95E-05	-0.9475	0.2717	953.43	0
2	0.2405	0.0110	0.1463	0.7684	0.2767	0.0162	0.2678	-----	-----	-----	-----	-2.03E-05	-0.9945	-0.0351	953.96	0.53
3	0.2326	-----	0.2828	0.6232	0.0461	0.1356	0.3877	-0.0058	-----	-----	-----	-1.89E-05	-0.9335	0.2772	953.99	0.56
4	0.2456	-----	0.2722	0.6319	0.0485	0.1405	0.3822	-----	-----	-----	0.0755	-1.94E-05	-0.9519	0.2518	955.17	1.74
5	0.2461	-----	0.2738	0.6342	0.0538	0.1344	0.3792	-0.0073	-----	-----	0.1823	-1.84E-05	-0.9382	0.2286	955.19	1.76

Significant variables (p<0.05) are marked in red.

Figures

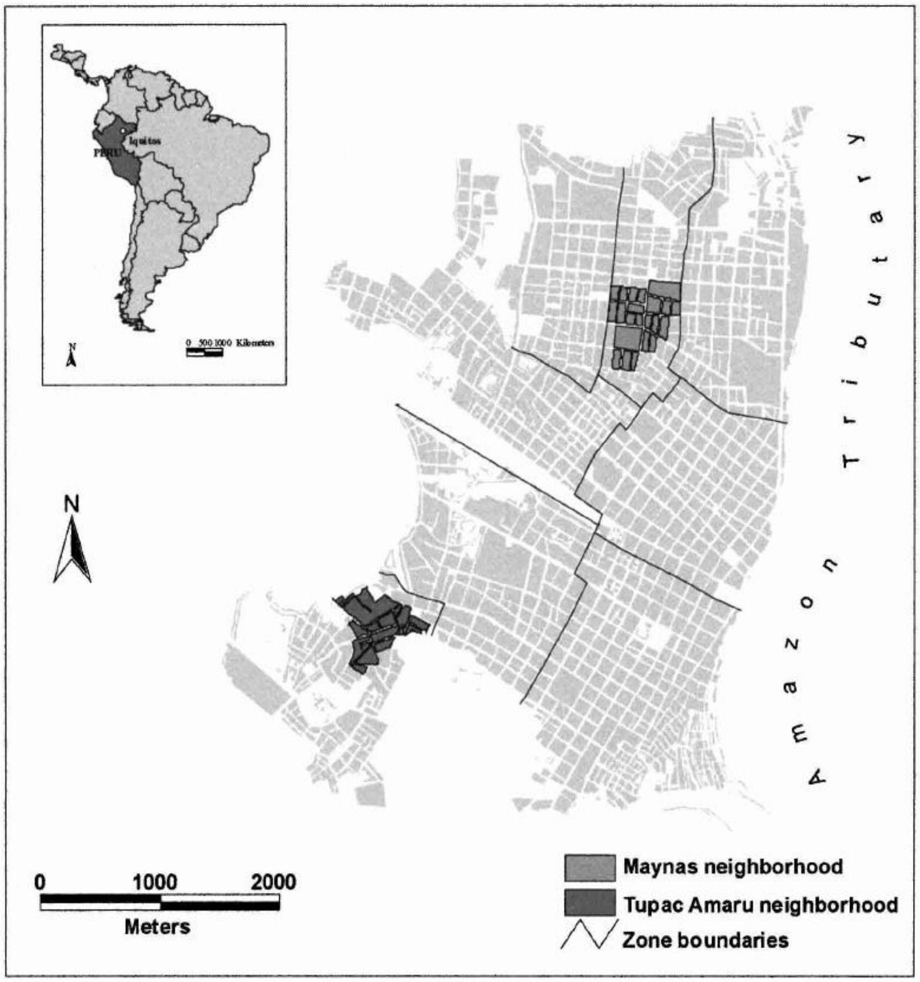


Figure 1. Map of Iquitos, Peru and location of the Maynas and Tupac Amaru study areas. (Morrison, 2005).

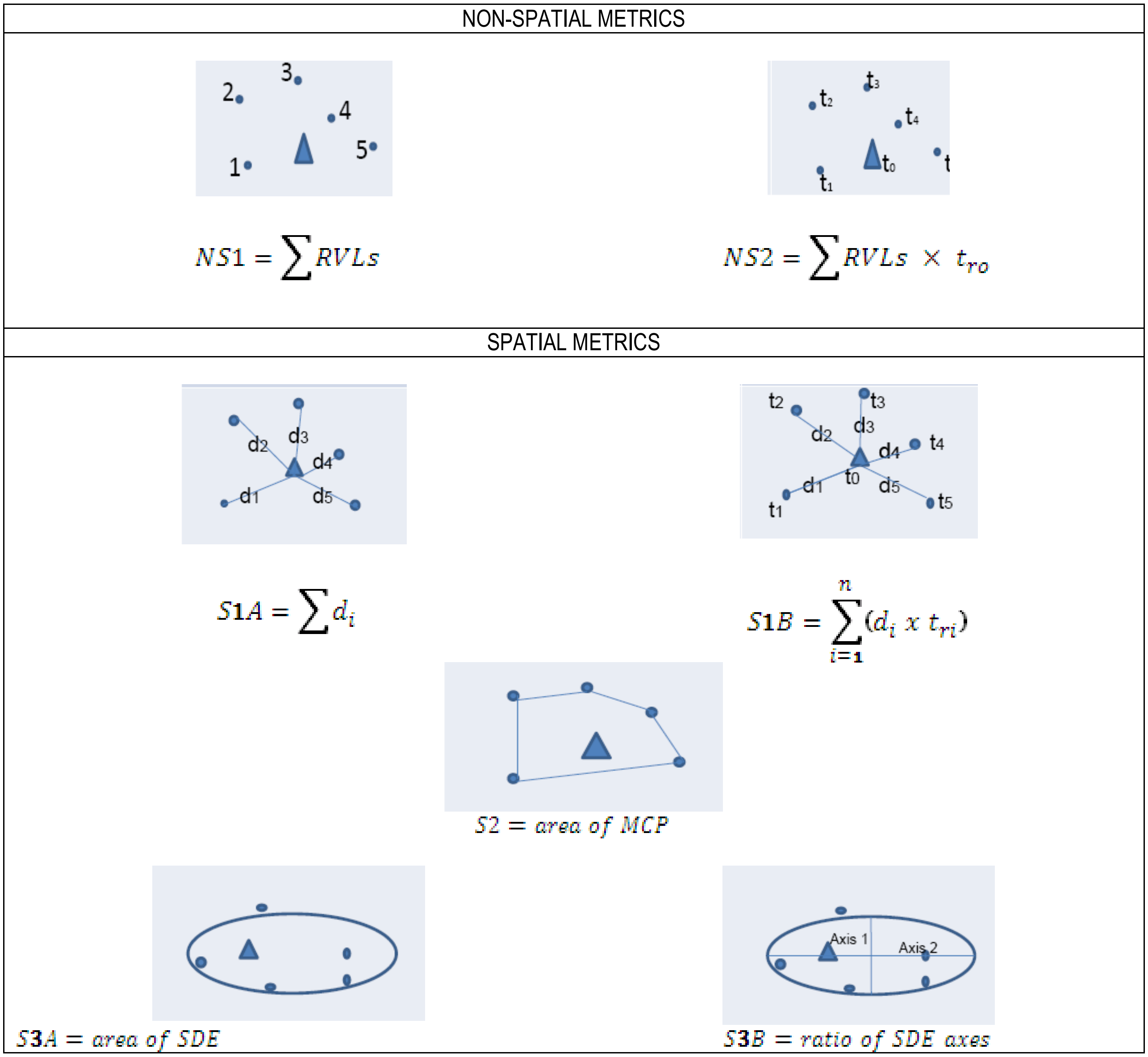


Figure 2. Illustration of spatial and non-spatial activity space metrics. Non-spatial (NS) metrics include number of routinely visited locations (RVLs) (NS1) and the interaction of NS1 with the relative time spent outside the home (t_{ro}) (NS2). Spatial (S) metrics include the sum of distance to home for each RVL (S1A), the interaction of S1A with the relative time spent at each location (tri) (S1B), the area of minimum convex polygons (MCPs) (S2), the area of standard deviation ellipses (SDE) (3A) and the ratio of SDE axes (S3B).

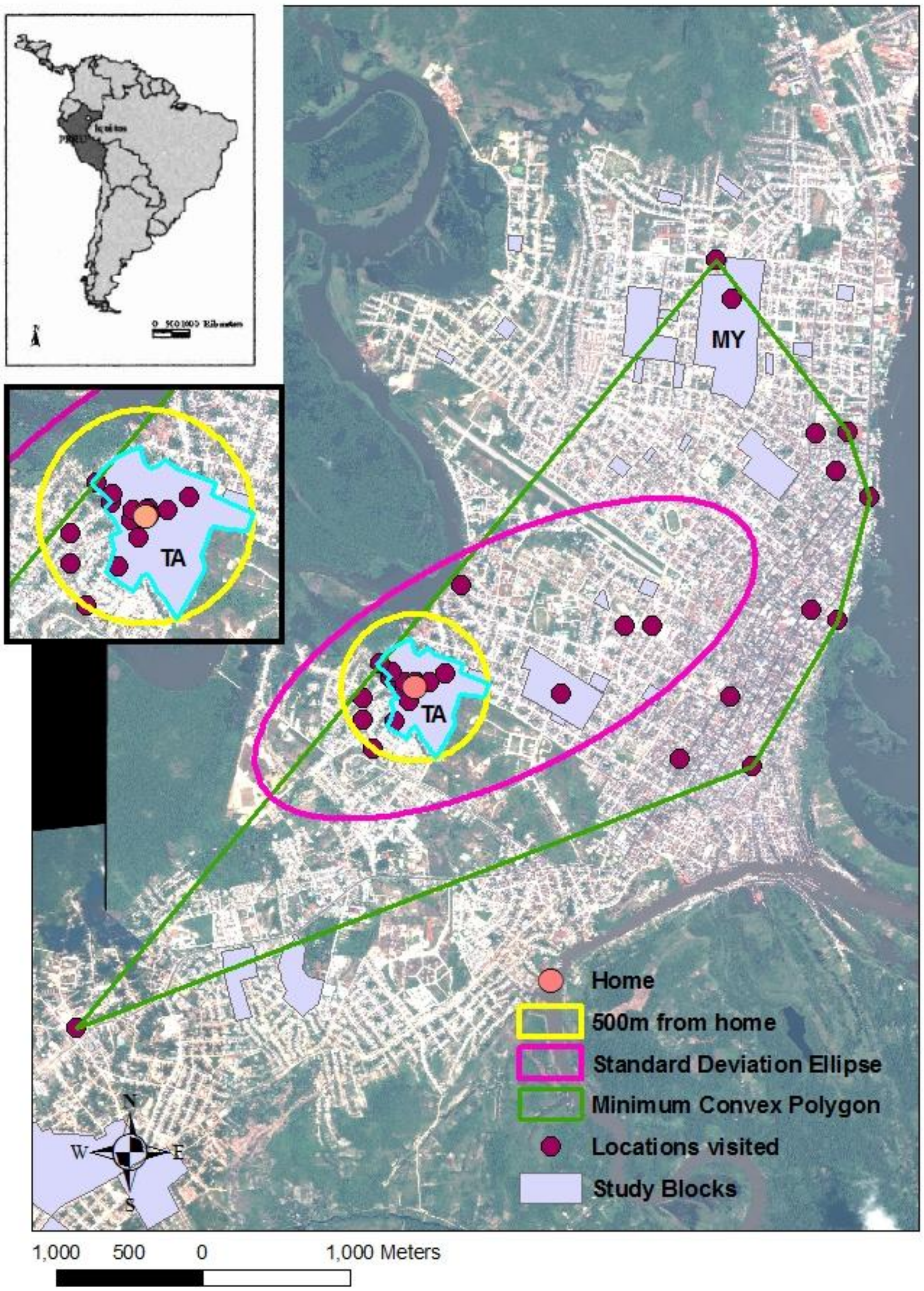
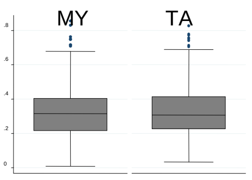
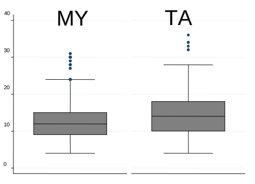
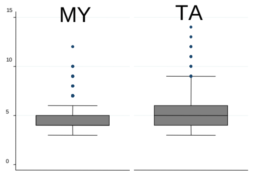
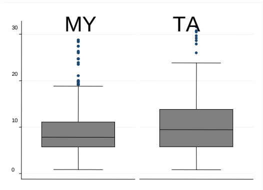
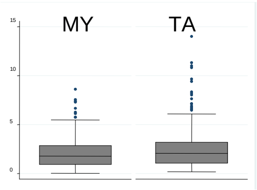
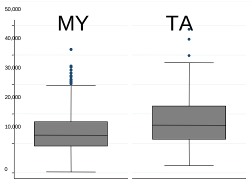
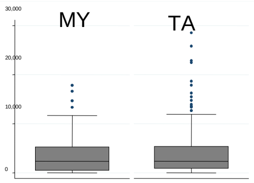
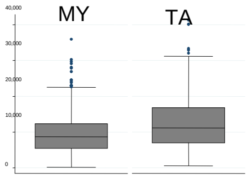
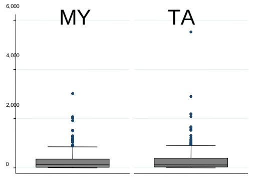
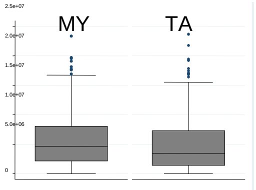
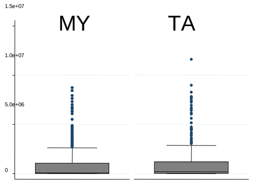
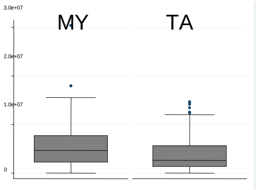
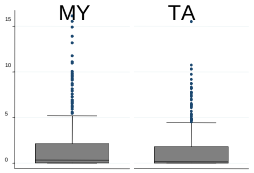
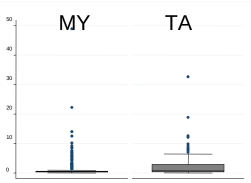
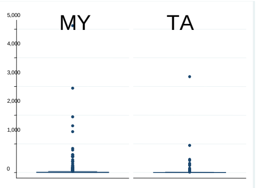


Figure 3. Example of a Minimum Convex Polygon and Standard Deviation Ellipse for a participant from Tupac Amaru.

Non-Spatial Movement Parameters	**All**	**Epi-Locations**
Relative time spent at home	**a)**  	
Number of locations visited (NS1)	**b)***  	**c)*** 
Number of locations by proportion of time outside house (NS2)	**d)***  	**e)** 

Figures 4a) through e). Non-spatial human movement patterns of the 712 participants involved in the study.
* indicates significant difference in means of AS metrics between Maynas and Tupac Amaru residents. ($p<0.05$)

Spatial Movement Parameters	**All**	**Epi-Locations**
Distance from home (m) (S1A)	**f)*** 	**g)*** 
Distance from home by proportion of time outside house (S1B)	**h)*** 	**i)** 
Area of Minimum Convex Polygons for all locations (m^2) (S2)	**j)*** 	**k)** 
Area of Standard Deviation Ellipse (m^2) (S3A)	**l)*** 	**m)** 
Ratio of axes of Standard Deviation Ellipse (m^2) (S3B)	**n)*** 	**o)** 

Figures 4f) through 4o). Spatial human movement patterns of the 712 participants involved in the study.
* indicates significant difference in means of AS metrics between Maynas and Tupac Amaru residents (p<0.05)

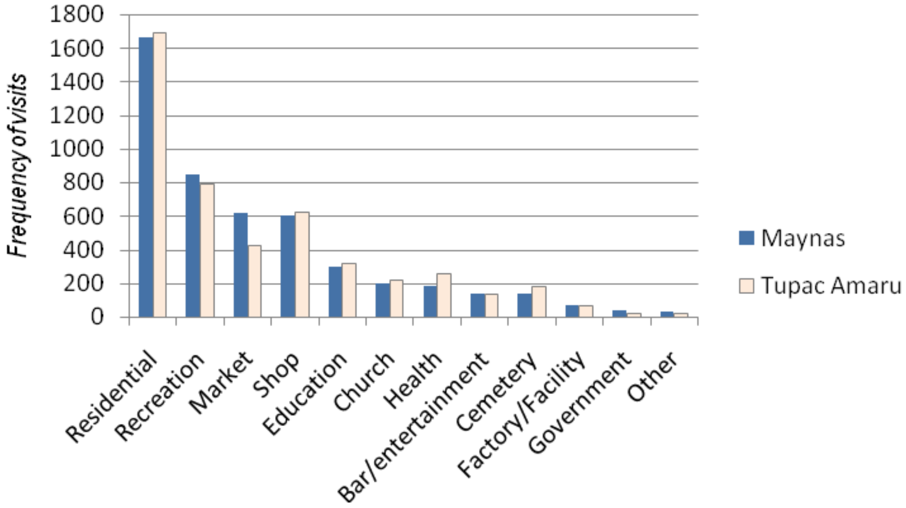


Figure 5. Frequency and location types visited by neighborhood.

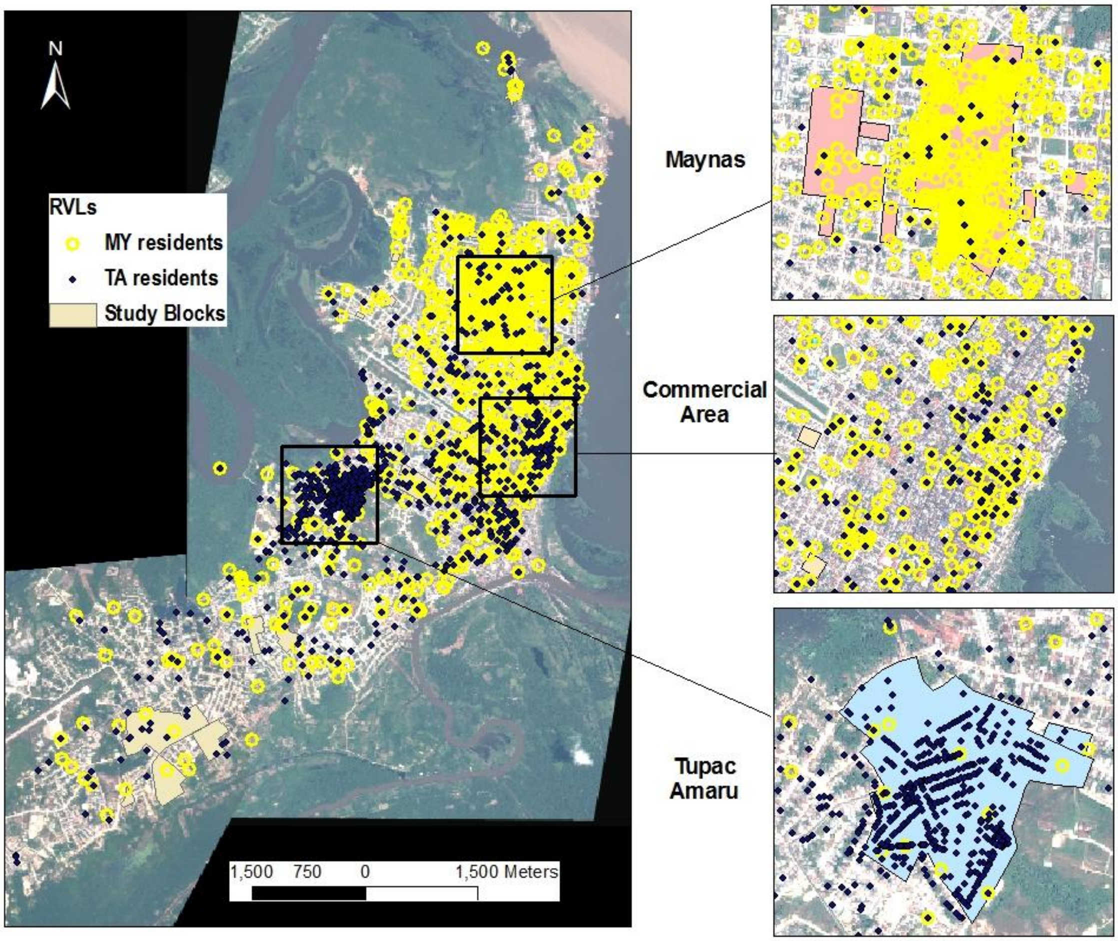


Figure 6. Routinely visited locations (RVLs) visited by Maynas (MY) and Tupac Amaru (TA) residents with close ups in the two study blocks and commercial area in Iquitos, Peru.

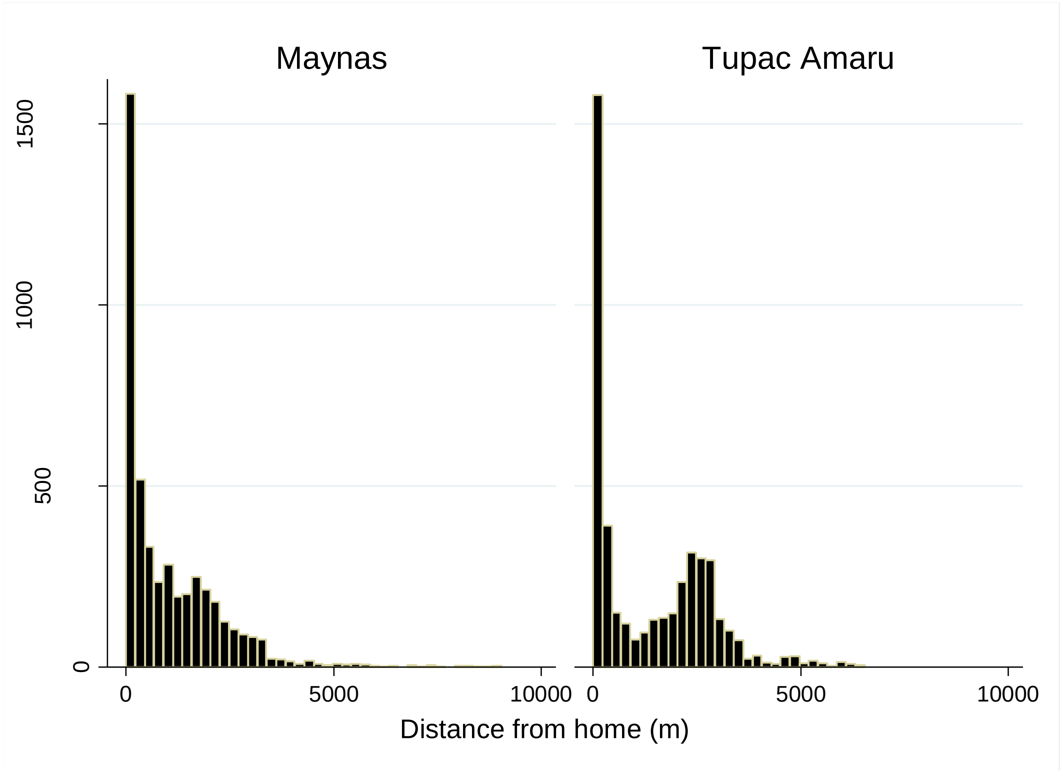


Figure 7. Frequency of locations visited and distance from home (excluding the home itself).

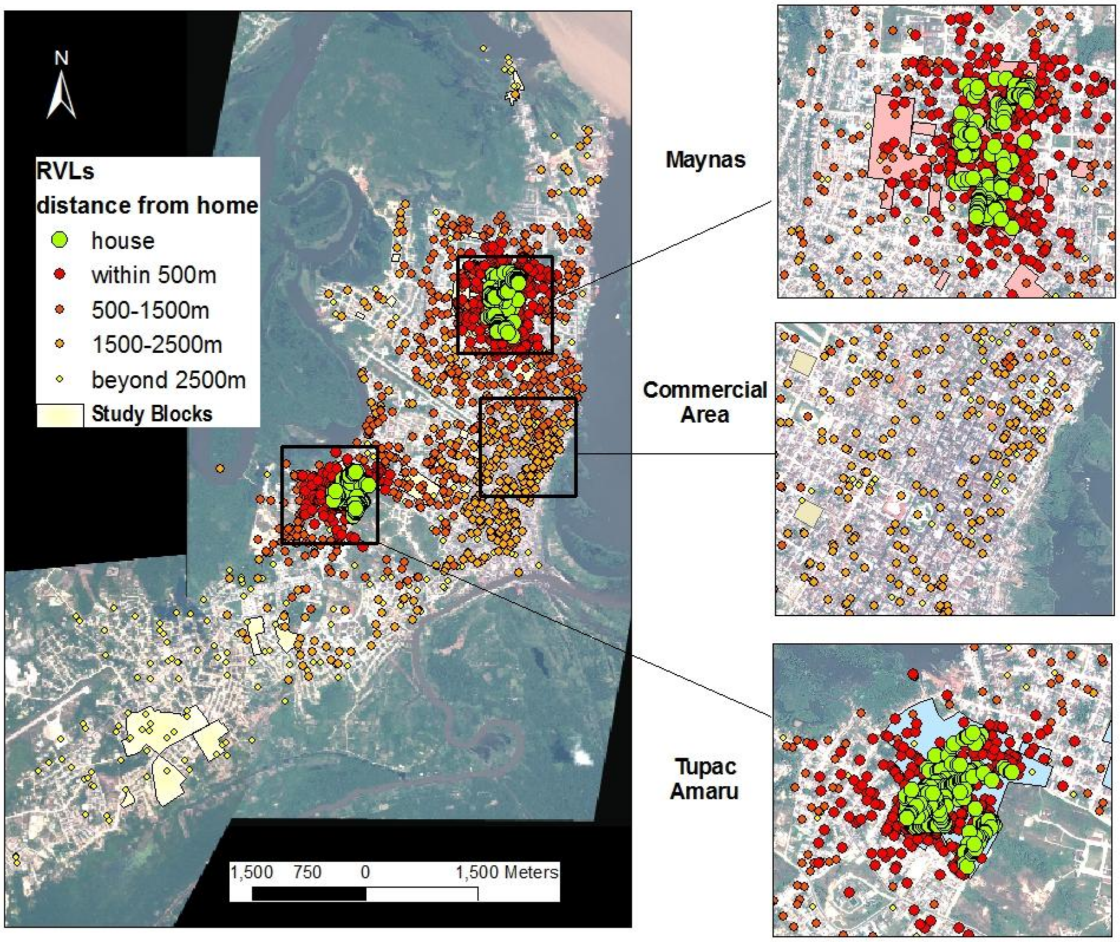


Figure 8. Map of routinely visited locations (RVLs) coded by distance from home with close-ups of Maynas, Tupac Amaru, and the commercial area of Iquitos, Peru

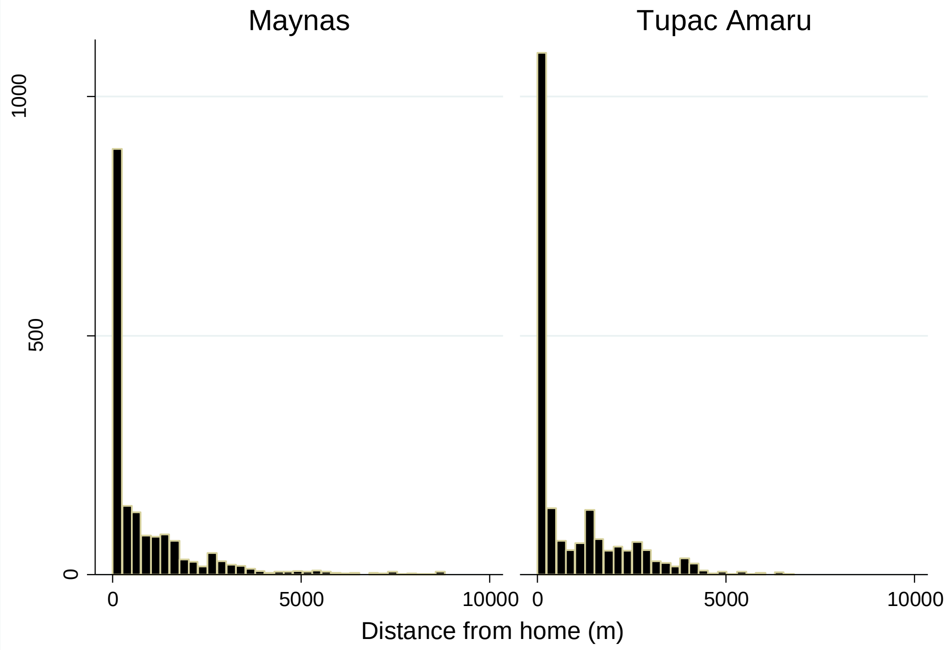


Figure 9. Frequency of “epi – locations” visited and distance from home (excluding the home itself).

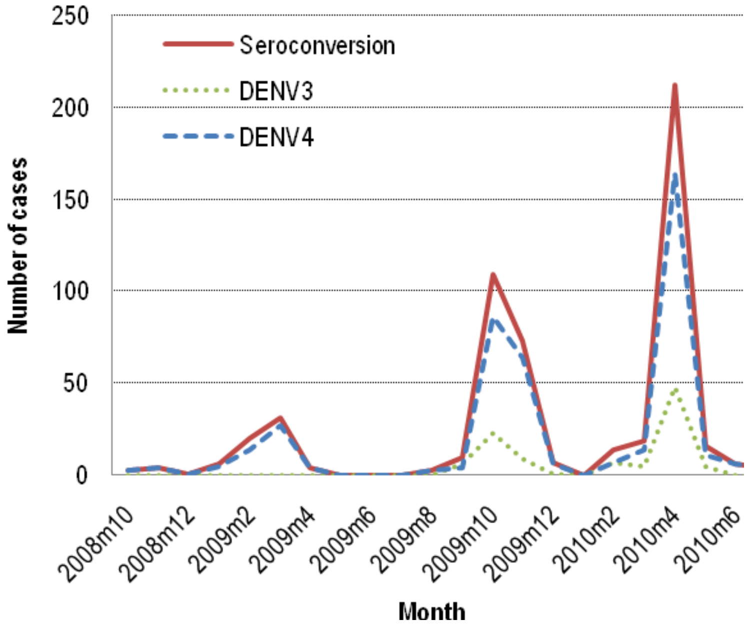


Figure 10. Number of Dengue Virus Cases in Iquitos, Peru by Serotype and Month. From 1281 participants. Seroconversion refers to infection by both DENV3 and DENV4 serotypes.

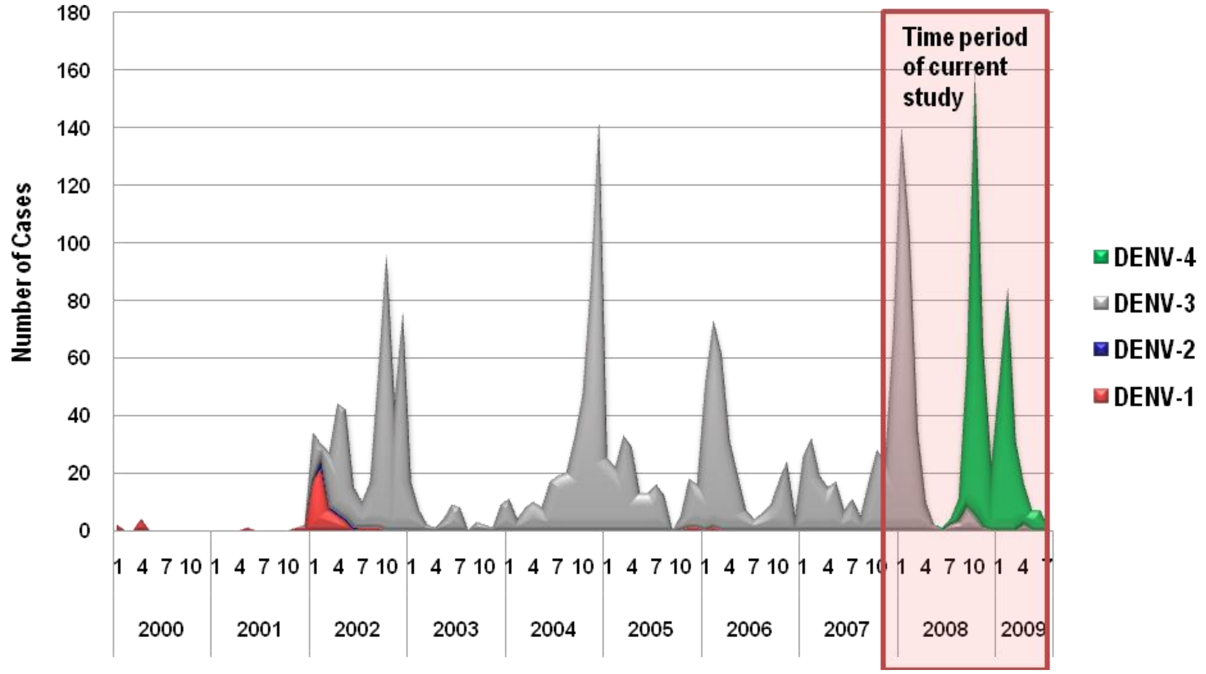


Figure 11. Dengue Virus Isolates from Iquitos, Peru Clinics (Stoddard et al. in preparation). Time period of current study is highlighted.