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The role of disease-driven human mobility changes in dengue transmission

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The role of disease-driven human mobility changes in dengue transmission

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Abstract

The role of disease-driven human mobility changes in dengue transmission
By Kathryn L. Schaber

Human mobility plays a central role in shaping pathogen transmission by generating spatial and/or individual variability in potential pathogen-transmitting contacts. Fine-scale, daily mobility patterns are of particular importance for viruses spread by *Aedes aegypti*, a day-biting mosquito with a limited flight range and a propensity for residential locations. Indeed, house-to-house human movement has been shown to underlie spatial patterns of dengue incidence. Recent research has shown, however, that symptomatic infection can influence human mobility and pathogen transmission dynamics. While the mobility changes of a symptomatic individual and their social contacts can significantly influence the spread of directly transmitted pathogens, they have not yet been included in theoretical models of dengue virus (DENV) transmission. This dissertation aims to determine the importance of dynamic human mobility patterns for human-mosquito contact networks that lead to DENV transmission heterogeneity. Data were analyzed on the mobility of symptomatic dengue cases and their social contacts, then the impact of these disease-driven mobility changes on human-mosquito contacts and onward DENV transmission was determined. I found that presence and magnitude of mobility change depended on the day of illness and the individual's sense of well-being, with the largest decrease in mobility occurring on the first three days of symptoms when infectiousness is peaking. Almost all symptomatic individuals received help from their housemates throughout illness and continued to receive visits from their 'routine visitors', most of whom were aware of the illness. Those who did help symptomatic individuals only made mobility changes drastic enough to affect their work in 28% of cases. When accounting for symptomatic mobility change, there were significant changes in the number of expected mosquito bites an infectious individual received, the location the bites occurred, and the individual's predicted onward transmission. I also found that the role of biting suitability in determining an individual's onward transmission can be dependent on the density of mosquitoes in the individual's home. Broadly, these results display a variety of ways symptomatic dengue illness can impact human mobility patterns, further affecting an individual's exposure to human-mosquito contacts and their overall contribution to DENV transmission.

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Chapter 1: Introduction

The force of infection, or the rate at which individuals get infected with a pathogen, for a vector-borne disease is composed of three terms: probability of contact between a susceptible individual and a mosquito, probability that the mosquito is infected with the pathogen, probability that contact between the susceptible human and infected mosquito results in successful transmission [1]. Each of these rates/probabilities can vary between individuals or locations, causing transmission heterogeneity, where certain individuals or locations contribute disproportionately to pathogen transmission and epidemic spread [2-4]. Traditionally for vector-borne diseases, mosquito movement and spatial variation of mosquito densities are the primary factors that cause differing probabilities of human-mosquito contact, thereby generating spatial transmission heterogeneity [5].

Human movement, social contacts, and vector-borne disease

These spatial factors of mosquitoes can be outweighed, however, when human mobility occurs at a broader spatial scale. Human mobility can drive transmission across multiple spatial and temporal scales, shaping the structure of transmission networks and influencing epidemiologic processes such as pathogen introduction, epidemic transmission, and endemic persistence [6-10]. While fine scale (daily, intra-urban) human mobility patterns may not have an effect for pathogens spread by widely dispersed vectors with large movement ranges, it has been shown to play an important role with vectors such as *Aedes aegypti*, a day-biting mosquito that has a limited flight range (<100m) and a propensity for the indoors [11].

Daily human movement plays a more significant role in transmission of *Aedes aegypti*'s pathogens, because it works on a broader scale, dispersing virus into multiple locations where mosquitos are present and able to bite susceptible individuals. Spatially, mosquito densities vary between households and an individual's daily movement patterns determine the number of mosquitoes contacted per day. Within a population, susceptible individuals will have different routine movements, contact different numbers of mosquitoes, and have varying probabilities of contacting an infected mosquito. While mosquitoes can be present at any/all locations an individual routinely visits, studies have shown that residential areas have a higher prevalence of *Aedes aegypti* mosquitoes and are the primary locations of human-mosquito exposure [12, 13].

Routine movements between *households* are likely to be shaped by social connections between individuals in the population, where two people with a strong connection will likely visit each other's houses frequently. Therefore, routine movement can cause two individuals with strong social ties to have *frequent, daytime contact with the same mosquitoes* in a location where human-mosquito exposure occurs [12]. Consequently, a susceptible individual's probability of contacting an *infected* mosquito will vary depending on the infection status and social tie strength of individuals in their contact network. Conversely, an infected individual's contribution to transmission can be influenced by not only how many bites they receive, but also which vectors the bites are from and whom those vectors encounter next [16].

The presence of symptomatic infection may, however, influence routine mobility patterns, in turn influencing onward virus transmission and the structure of transmission chains. Research on directly transmitted diseases has demonstrated disease-driven behavior changes (namely isolation, avoidance, and caregiving) [14] and the significant influence they can have on predictions of pathogen spread [15-18]. The effects of these behavioral changes on transmission

should also be considered for certain vector-borne diseases, particularly those spread by *Aedes aegypti*, or a similar vector. The impact of movement changes on an individual's mosquito contacts and onward transmission will likely depend on the distribution of mosquitoes at their home and across the rest of their activity space (routinely visited locations) [8, 19, 20]. At a population level, human mobility changes could affect pathogen spread in a variety of ways depending upon which individuals in the population experience symptoms and change their mobility and potential exposure to *Aedes aegypti* mosquitoes. One *Aedes*-borne illness where human movements have been shown as key to explaining transmission dynamics is dengue [21-25].

Dengue as a study system

Dengue is the most important mosquito-borne viral disease of humans worldwide, affecting approximately 390 million people a year and endemic in over 100 countries [26]. Prevalent in the tropics and subtropics, the acute illness is caused by any of four immunologically related viruses in the family *Flaviviridae* and is transmitted by *Aedes* spp. mosquitoes (primarily *Aedes aegypti*). Symptoms associated with dengue (acute fever, headache, musculoskeletal pain, and rash) occur in a small proportion of cases, while the other 70% of cases experience either very mild symptoms (inapparent) or no symptoms (asymptomatic) [27-29]. For those individuals who are infected with dengue virus (DENV) and experience symptoms, infectiousness tends to peak during the first few days after onset of symptoms and lasts for 4-5 days [30-32]. There are, however, a few days before symptom onset when individuals have sufficient viremia levels to be infectious [30, 32].

House-to-house human movement has been shown to significantly influence DENV transmission [33-35], with an individual's risk of DENV infection significantly increasing when he or she routinely visited the same residential locations as DENV-infected people [34]. Further, when mobility-driven contact structure has been included in theoretical models, the effect on DENV epidemic transmission is dramatic. Overlapping movement patterns within social groups drive the fine-scale heterogeneity in DENV transmission rates [33].

Furthermore, variations in movement patterns occur during a dengue epidemic, with symptomatically DENV-infected individuals visiting fewer houses and staying at home more [3, 36, 37]. This variation in mobility has not yet been taken into account for theoretical DENV models; however, it will likely impact human-mosquito contacts and onward transmission. There may not be population-level effects on epidemic size and length, given the prevalence of asymptomatic infections, which are not associated with mobility reduction. The pattern of transmission may be affected by asymptomatic (and susceptible) individuals changing their movement patterns to act as caregivers for their symptomatic social contacts. It is necessary to account for these socially structured mobility changes in dengue transmission in order to better understand the impact on human-mosquito contacts and transmission heterogeneity. Inclusion of dynamic mobility also elucidates the important role asymptomatically and pre-symptomatically infected individuals may have in maintaining onward DENV transmission.

Study Area

A unique location to study the role of human mobility on DENV transmission is the Amazon city of Iquitos, Peru. Iquitos is a geographically isolated, tropical urban environment with approximately 430,000 inhabitants located along the margin of the Amazon River [38]. The

city's economic structure is highly informal and dynamic, with one-third of economically active individuals either unemployed or informally employed [39]. Iquitos has been the home of extensive, long-term arboviral research led by the University of California, Davis and U.S. Naval Medical Research Unit 6 since 1999 [8, 29, 34, 35, 40-42]. Extensive human mobility studies paired with detailed epidemiological data have made Iquitos an informative site for understanding the dynamics of arbovirus transmission. All four serotypes of DENV have been introduced in Iquitos; however, at any particular time virus transmission is usually dominated by a single serotype [29, 43]. Previous research [35] demonstrated that inhabitants visit an average of 5.8 (±3.6 SD) locations over a two-week period. While most movement (~80%) occurs within 1 km of their home, inhabitants have highly irregular and temporally unstructured routines that are not dominated by a single location, such as a workplace [35].

Dissertation Summary

In this dissertation, I aim to determine the importance of dynamic human mobility patterns on human-mosquito contact networks that lead to DENV transmission heterogeneity. I will accomplish this by analyzing detailed data on the mobility of symptomatic dengue cases and their social contacts, then determining the impact of these changes on both human-mosquito contacts and onward DENV transmission using a mathematical framework that accounts for house-to-house movement and stochastic DENV transmission.

I hypothesize that the dynamic human movement patterns of symptomatic individuals will drastically reduce the overall connectedness of the DENV transmission network; however, increased contact of symptomatic cases with caregivers and the sustained mobility of pre-symptomatic and asymptomatic hosts will continue to drive onward DENV transmission.

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Chapter 2: Dengue illness impacts daily human mobility patterns in Iquitos, Peru

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Introduction

Human mobility plays a central role in shaping the structure of transmission networks and in influencing epidemiologic processes such as pathogen introduction, epidemic transmission, and endemic persistence [1-4]. While human mobility can drive transmission across multiple spatial and temporal scales [3, 5], it is at the finest scales (daily, intra-urban human movements) where epidemic processes occur and emergency public health interventions are usually implemented. Evidence from theoretical models and empirical studies show that individual and/or spatial variability in number and frequency of contacts can lead to transmission heterogeneity, where certain individuals or locations contribute disproportionately to pathogen transmission and epidemic spread [6-8]. Thus, identifying social and behavioral characteristics (e.g., mobility patterns, occupations, age classes) most responsible for such disproportionate contributions has become a public health priority, with significant potential for leveraging the power of public health surveillance programs and targeted disease control [9-11].

Dengue, an acute illness caused by four immunologically related viruses in the family *Flaviviridae* and transmitted by *Aedes* spp. mosquitoes (primarily *Aedes aegypti*), is the most important mosquito-borne viral disease of humans worldwide [12]. Because *Aedes aegypti* seldom disperse beyond 100 meters, have a propensity for resting and biting inside residential buildings, and bite during the day [13-16], human movements are key to explaining the urban transmission dynamics of dengue virus (DENV) [17-21]. Individual movement patterns can also

expand the spatial scale of transmission and lead to significant heterogeneity in transmission patterns by connecting otherwise discrete subpopulations of mosquitoes [3, 22, 23]. Extensive movement studies performed in the upper Amazon city of Iquitos, Peru, have shown that while human mobility within a resource-poor urban center is highly unstructured (with only 38% of participants having regular mobility routines), the majority of locations visited are either residential or commercial, with most movements (81%) occurring within 1 km of an individual's home [24-28]. Moreover, an individual's risk of DENV infection significantly increased when he or she routinely visited the same residential locations as DENV-infected people, whereas the distance the individual lived from a DENV-infected case was not significant [26].

Such empirical characterizations of fine-scale human mobility patterns and risk of DENV infection have informed complex simulation models that explore the theoretical role of human movement on the spatial and temporal patterns of disease dynamics [18, 23, 29]. When mobility-driven contact structure is included in theoretical models, the effect on DENV epidemic transmission is dramatic. Overlapping movement patterns within social groups drive the fine-scale heterogeneity in DENV transmission rates; however, the presence of a mosquito vector can hide the effect of socially structured movements if only spatially aggregated infection dynamics are considered [23]. Such models do not take into account the fact that symptomatic infection may influence mobility, which in turn can influence onward virus transmission and the structure of transmission chains. Research on directly transmitted diseases has demonstrated disease-driven behavior changes [30] and the significant influence they can have on predictions of pathogen spread [31-34]. For DENV, mobility data have been captured for febrile symptomatic individuals and healthy individuals using either retrospective movement surveys [35] or GPS trackers [36]. Febrile DENV-infected individuals visited significantly fewer places, traveled

shorter distances, and spent more time at home [35, 36]. These patterns reveal particularly important information for understanding the complex relationship between symptom severity and human mobility, and to ultimately determine if there is an association between human mobility and infectiousness to mosquitoes. However, because DENV infectiousness peaks at 0-2 days after onset of symptoms and lasts for 4-5 days after onset of symptoms [37-39], human mobility during the first few days of symptoms could be key to better understand transmission dynamics. The goal of this study, therefore, was to conduct detailed, daily retrospective interviews to measure the mobility behavior of clinically apparent DENV-infected individuals throughout their illness, with the goal of generating mobility metrics that can be used to characterize the absolute and relative impacts of disease on potential exposure to *Aedes aegypti* mosquitoes.

Methods

Study Area

This study was performed in the Amazon city of Iquitos, Peru. Iquitos is a geographically isolated, tropical urban environment with approximately 430,000 inhabitants located along the margin of the Amazon River [40]. The city's economic structure is highly informal and dynamic, with one-third of economically active individuals either unemployed or informally employed [41]. Iquitos has been the home of extensive, long-term arboviral research led by the University of California, Davis and U.S. Naval Medical Research Unit 6 since 1999 [3, 24-28, 42]. Extensive human mobility studies paired with detailed epidemiological data have made Iquitos an informative site for understanding the dynamics of arbovirus transmission. All four serotypes of DENV have been introduced in Iquitos; however, at any particular time virus transmission is usually dominated by a single serotype [42, 43]. Previous research [27] demonstrated that

inhabitants visit an average of 5.8 (±3.6 SD) locations over a two-week period. While most movement (~80%) occurs within 1 km of their home, inhabitants have highly irregular and temporally unstructured routines that are not dominated by a single location, such as a workplace [27].

Study Design

The study followed a contact-cluster design in which reverse transcription polymerase chain reaction (RT-PCR) positive, or viral nucleic acid test positive, DENV-infected individuals (index cases) were captured through community or clinic-based febrile surveillance systems, as described previously [26]. At the time of the initial blood sample, a 15-day retrospective semi-structured movement survey (RMS) was administered to the index case to identify the locations they visited in the 15 days prior to diagnosis (characterizing the "pre-illness" period). Consenting individuals (contacts) from the index cases' home and residential locations visited by the index case were then screened for DENV infection using RT-PCR [26] [44]. The RMS was administered to DENV PCR-positive contacts to quantify mobility behavior associated with potential virus exposure.

RMSs were developed based on findings of focus groups and validated by comparison with data from people wearing GPS tracking devices [24, 25]. RMSs capture positional, temporal and behavioral information of routine human mobility. Questions focus on the amount of time an individual spent at home, the visitors they received, and the places they visited. For time spent at home, individuals were asked about the average number of hours spent at home each day of the week, specifically focusing on the period from 5 a.m. to 10 p.m., which includes the peak landing and biting times for *Aedes aegypti* [45]. For places visited, information was collected on the type of place visited, when, for how long, and how often in the 15-day period.

Trained, local Iquitos residents (the 'Movement Team') verbally administered electronic RMSs and recorded the information on tablets in the CommCare application [46].

To track movements of DENV positive participants during their illness, daily interviews using a modified daily RMS (DRMS) were conducted in person or by telephone for 7 days following the initial RT-PCR-positive blood test. Where participants were not available for daily interviews, information about movements on several days was collected at a single interview. The DRMS asks about the amount of time spent at home the previous day(s) and the following information about each place visited during the previous day(s): day visited, place type, location, time of day visited, and time spent. For residential places visited, the DRMS asks whom they were visiting, their reason for visiting, if anyone in the home was ill during the preceding 15 days, and (for routinely visited houses) if/why there was any change in the time of visitation, as compared to the "pre-illness" period. During this seven-day period, DENV positive individuals were also administered two Quality of Well-Being surveys (QWB) by the Movement Team, one 2-3 days and one 7 days after the initial PCR-positive blood test. The QWB survey is a validated instrument used to measure an individual's quality of life during chronic illness [47]. Our study was a novel application of the QWB survey to an acute illness. The survey responses were sent to the developers at University of California, San Diego, who used a weighted algorithm to produce one well-being score between 0.0 (death) and 1.0 (asymptomatic and fully-functioning) covering the three days prior to each survey date [47].

At a follow-up visit scheduled 30 days after the initial PCR-positive blood test, individuals were given a 15-day ("post-illness") RMS and QWB survey in an effort to record their "baseline" mobility behavior and well-being in the absence of illness.

Data Processing

For each study participant, the following variables were computed from the "pre-illness" and "post-illness" 15-day RMS: (1) total number of locations visited, (2) proportion of visits to each location type, (3) total number of houses visited, (4) proportion of visits to houses of family members vs. houses of friends, and (5) average proportion of time spent at home per day. Equivalent daily values of these variables were collected for each participant from the DRMSs. Rather than referring to values as occurring on a certain number of days after the PCR-positive blood test, a standardized "day after symptom onset" variable was calculated. Because blood tests were not done on the same day of illness for all participants, DRMSs captured a range of 1-15 days after symptom onset. We focused our analysis on days 1-9 after symptom onset; few individuals had data for days 10-15 after symptom onset.

Data Analysis

Analysis of mobility data had two main objectives: (1) comparing healthy (pre- and post-illness) mobility to mobility during illness, and (2) determining if mobility patterns changed during the 9 days after symptom onset.

For the first objective, mobility during illness was calculated by averaging a participant's DRMS for all available time points up to day 9 after symptom onset. Comparisons were done for the following mobility metrics: daily number of locations visited, daily number of houses visited, and proportion of time spent at home. When a metric followed a normal distribution (assessed via the Shapiro-Wilk test), pairwise comparisons were performed with paired t-tests followed by Holm-Bonferroni corrections. When the variable was not normally distributed, the non-parametric Kruskall-Wallis Rank Sum Test and pairwise Wilcoxon Signed Rank Test for paired data were utilized. As many individuals would stop visiting other locations during their illness period [35], we also analyzed the number of locations, number of houses, and time at home as

binary variables, asking if any locations/houses were visited and if any time was spent away from home. These binary outcomes were compared between all possible pairs of time points (pre-during, during-post, and pre-post illness) using McNemar's χ^2 test.

If locations were visited, further analyses determined what type of locations they were. While these data were subject-correlated across time points, they could not be analyzed as paired data because not all participants visited locations at every time point. Generalized logistic mixed-effects models (GLMMs) determined the association between the probability of a location type being visited and the time period being considered (pre-during-post illness), while accounting for repeated measures by using participant ID as the random intercept. Location type was separated into four groups: (1) house, (2) health, (3) education/work, and (4) other (e.g., recreation, church, market, port). Similarly, logistic GLMMs determined the association between time period (pre-during-post symptoms) and the probability of a specific house type being visited (e.g., family versus friend).

For the second objective, aiming to determine whether mobility patterns changed during the illness period, we calculated mobility metrics for 3-day groups (days 1-3, 4-6, and 7-9 after onset of symptoms). Daily data were aggregated into 3-day groups to allow for robust analyses, while also controlling for the dearth of data points on certain days. In particular, the first two days after symptom onset had incomplete information for some participants due to the time required to capture individuals with symptoms, run RT-PCR tests, and obtain confirmed test results. To make pre/post and during-illness data comparable, 15-day RMS values were condensed to give movements over an average 3-day period. Analysis of the number of locations/houses, proportion of location/house types, and time spent at home followed the same steps described above. Comparisons were made between the 3-day groups to determine whether

significant changes occur in movement patterns during illness. Further, movements within the 3-day groups were each compared to post-illness mobility.

The associations between daily (DRMS) mobility patterns and possible predictor variables were examined using Generalized Linear Mixed Models (GLMMs), Generalized Additive Mixed Models (GAMMs), and Generalized Additive Models for Location Scale and Shape (GAMLSSs) [48-50]. Best-fit models were determined for each of the following mobility outcomes: total number of locations visited (count variable), relative number of locations visited (compared to when healthy) (continuous variable), total number of houses visited (count), relative number of houses visited (continuous), total proportion of time spent time at home (continuous), and relative amount of time spent at home (continuous). For both the total number of locations visited and total number of houses visited, GLMMs and GAMMs with underlying Poisson distributions were compared. An individual's age, occupation, gender, QWB score, and the "day after symptom onset" were considered as predictor variables, with the best-fit model determined using an AIC and a Chi-square test comparing reduction in residual deviance. The response variable proportion of time spent at home was best characterized by a one-inflated beta distribution, so analysis was done with GAMLSS, as detailed below.

Although GLMM and GAMM regressions model the mean (μ) value of the distribution of the response variable, GAMLSS allows other distribution parameters to be modeled as a function of explanatory variables. A one-inflated beta distribution has possible values $0<y\leq1$ and is defined in two parts: the probability that $y=1$ (modeled by the η parameter) and the probability for $0<y<1$, which is shaped by a traditional beta distribution with parameters mean (μ) and shape (σ). Here, the η parameter was the probability an individual stayed at home 100% of the time

(y=1). If an individual did not stay at home the entire day, the proportion of time that was spent at home (0<y<1) was determined by a beta distribution with μ and σ.

We also considered response variables as relative values in order to control for the individual variation in mobility levels. The number of locations (houses) an individual visited on each day during illness was considered relative to the average number of locations (houses) they visited pre-illness. Similarly, the number of hours a participant spent at home during each day of illness was compared to the average number of hours that individual spent at home pre-illness. While relative number of houses could not be well explained by a set distribution, both relative number of locations visited and relative amount of time spent at home were best characterized by the logistic distribution. Analysis of these response variables was done with GAMLSS, where both the mean (μ) and the standard deviation (σ) parameters of the logistic distribution could be modeled as a function of explanatory variables. Best-fit GAMLSS models were chosen using forward and backward selection for each of the explanatory variables. All statistical analyses were performed in R 3.3.0 statistical computing software [48-51].

Ethics Statement

The procedures for enrollment of participants, dengue diagnosis, semi-structured interviews, and participant follow-up were approved by the Institutional Review Board (IRB) of the United States Naval Medical Research Center Unit No. 6 (NAMRU-6) (NAMRU6.2014.0021) in compliance with all applicable federal regulations governing the protection of human subjects. IRB relying agreements were established between NAMRU-6 and Emory University, Tulane University, University of California Davis, University of Rhode Island, San Diego State University, and University of Notre Dame. In addition to IRB approval, investigators obtained host country approval from the Loreto Regional Health Department,

which oversees health research in Iquitos. Adult study participants provided written informed consent and a parent or guardian provided informed consent on behalf of child study participants.

Results

Detailed mobility data were collected from a total of 62 DENV+ participants. Descriptions of participant demographics and data completeness appear in the Supplemental Text (**Text S2.1**). The most commonly reported symptoms were general malaise (100%), weakness (96.61%), fever (93.22%), headache (91.53%), anorexia (89.83%), and musculoskeletal pain (84.75%). During days 1-9 post-onset of symptoms, the average maximum malaise intensity of participants was 7.5 on a scale of 10 (range: 0-10), as compared to a mean intensity of 0.28 out of 10 (range: 0-6) during the post-illness time period. While all participants reported some level of malaise and dengue-related symptoms, the vast majority of participants (88.7%) received only outpatient care.

For the 34 participants with QWB scores collected at all time points (2-3 days post blood test, a week post blood test, and post-illness), scores were considered in terms of "days after symptom onset". The mean QWB score of those reported in the nine days after symptom onset was 0.61 (range: 0.25-1.0). The median QWB score was less than 0.70 all nine days after symptom onset; however, a few individuals had scores of 1.0 ("asymptomatic") as early as day 4. While the DRMS may have captured mobility on days when individuals were asymptomatic, the vast majority of individuals retained symptoms throughout the nine days after symptom onset (**Figure S2.3**). Therefore, that period will be referred to as "during illness" in the remaining sections.

The mean QWB score at the post-illness time point was 0.88 (range: 0.48-1.0, median 1.0). While the post-illness survey may contain data from a few individuals who were still symptomatic, in general we considered it a suitable approximation of healthy mobility. Another proxy for healthy mobility, the "pre-illness" RMS, may have also captured some symptomatic movements because the 15-day retrospective survey could not be given until DENV cases were captured a median of 3 days after symptom onset.

Healthy vs. Symptomatic Mobility Patterns

When comparing healthy (pre-/post-illness) and symptomatic time points, there was a significant difference in both the proportion of time spent at home and the average number of locations visited (**Figure 2.1A-2.1B**). Healthy participants spent 60% of their time at home and visited an average of 1.3/1.1 (pre-/post-illness) locations per day, whereas ill participants spent 74% of their time at home (Wilcoxon test: $p < 0.001$) and visited an average of 0.73 locations (Wilcoxon test: pre-illness: $p < 0.001$; post-illness: $p=0.010$) (**Table S2.2**). Participants were also significantly less likely to visit other houses during illness, as compared to pre-illness (McNemar's χ^2: $p < 0.001$) and post-illness (McNemar's χ^2: $p = 0.043$) (**Table S2.3**).

The odds (adjusted odds ratio/AOR) of an individual visiting an education/work location during healthy time points (AOR pre-/post-illness: 2.0/4.4) were significantly greater than during illness (GLMM: $p < 0.001$; **Table 2.1, Figure 2.2**). Similar significant differences were seen for visits to "other" place types (GLMM: $p<0.001$; **Table 2.1, Figure 2.2**). Conversely, the odds of participants going to a health-related place pre- or post-illness were significantly lower than during illness (AOR: pre-/post-illness: 0.019/0.002; **Table 2.1, Figure 2.2**). Although individuals were more likely to visit a house during the pre-illness time period as compared to during illness (AOR: 1.684; GLMM: $p=0.013$), there was no significant difference for post-illness (AOR:

0.872; GLMM: p=0.64), where individuals were predicted to visit houses with a mean probability of 21% (**Table 2.1, Table S2.4**).

Mobility Patterns During Illness

During days 1-3 and 4-6 after symptom onset, individuals were significantly more likely to spend all of their time at home, compared to both days 7-9 after symptom onset (McNemar's χ^2: p = 0.046) and post-illness (McNemar's χ^2: days 1-3: p = 0.008; days 4-6: p = 0.008) (**Table S2.6**). There was also a significant difference in the average proportion of time spent for days 1-3 and 4-6 (76%) when compared to both days 7-9 (69%) (Wilcoxon test: days 1-3: p = 0.014; days 4-6: p = 0.008) and post-illness (59%) (Wilcoxon test: days 1-3: p = 0.005; days 4-6: p < 0.001; **Figure 2.3B, Table S2.5**). Individuals were significantly less likely to visit any locations during illness compared to post-illness (McNemar's χ^2: days 1-3: p = 0.001; days 4-6: p < 0.001; days 7-9: p = 0.008; **Table S2.6**). Accordingly, the average number of locations visited was significantly lower on days 1-3 (paired t-test: p = 0.017) and 4-6 after symptom onset (paired t-test: p < 0.001) when compared to the mean 3.4 places visited every 3 days at post-illness (**Figure 2.3A**). The average number of locations visited on days 1-3 (1.5 places/3-days) was also significantly less than the average number of locations visited on days 7-9 after symptom onset (2.2 places/3-days) (Wilcoxon test: p = 0.047; **Table S2.5**).

When considering the type of location visited (**Figure 2.4**), the three during-illness time points (days 1-3/4-6/7-9) were compared to the post-illness period. Post-illness, the participants were predicted to visit education/work places with a 48% probability, "other" places with a 32% probability, houses with a 20% probability, and health-related places with only a 0.2% probability (**Table S2.7**). Compared to post-illness, the odds of an individual visiting an education/work place were significantly lower for days 1-3 (AOR: 0.08), days 4-6 (AOR: 0.22),

and days 7-9 after symptom onset (AOR: 0.26) (GLMM: $p < 0.001$; **Table 2.2**). Conversely, the odds of visiting a health-related place during illness were significantly higher compared to post-illness (AOR: days 1-3: 3826; days 4-6: 1041; days 7-9: 365), likely due to the very low probability of a health-related location being visited post-illness when healthy (GLMM: $p < 0.001$). The likelihood of visiting a house during illness was not significantly different than the likelihood post-illness (AOR: days 1-3: 1.08; days 4-6: 1.20; days 7-9: 1.64; GLMM: $p > 0.05$). There were also no significant correlations between the illness time point and the odds of visiting a family member's (versus friend's) house (**Table 2.2, Table S2.7**).

Daily Mobility Patterns During Symptomatic Illness

The best-fitting model to describe the relative number of locations visited was a GAMLSS with a logistic distribution. The μ parameter (mean) was best explained by a positive effect of day after symptom onset ($p < 0.001$) and a random intercept for participants, which allowed the mean relative number of locations to vary by participant. The σ parameter (standard deviation) was best explained by QWB score ($p < 0.001$), day after symptom onset ($p < 0.001$), and an interaction between the two ($p < 0.001$) (**Table 2.3**). For relative amount of time spent at home, the best-fit model was a GAMLSS with underlying logistic distribution, where the μ parameter was best explained by a negative effect of day ($p = 0.0011$) and a random intercept for participants. The σ parameter was best explained by a positive effect of day after symptom onset ($p < 0.001$) (**Table 2.4**).

With proportion of time spent at home as the response variable, the best-fit model explains the η parameter as a function of age (<18 or >18) ($p = 0.005$) and an interaction between age and day after symptom onset ($p = 0.018$). The μ parameter was explained by a random slope of participants over time and the σ parameter was explained by the QWB score and

a smoothed function of the day of illness (**Table 2.5**). This suggests that whether an individual spent all (100%) of their time at home was dependent on both their age and the day of illness, whereas the proportion of time spent at home (when less than 100%) depended on the day of illness ($p = 0.005$) and how they were feeling (QWB score) ($p = 0.094$; **Table 2.5**). While the day of illness did not have an overall effect on the mean proportion of time spent at home (when less than 100%), the random slope for participants suggests that day of illness had a varying effect across participants.

Discussion

We found that dengue illness affects almost all aspects of an individual's mobility behavior. During mild symptomatic illness, individuals visited significantly fewer locations and houses and spent significantly more time at home. Further, symptomatic participants visited education/work and "other" locations less often than when they were healthy and visited health locations more often. These results (1) are consistent with and expand prior evidence indicating that individuals with symptomatic illness move less than healthy individuals [31, 35, 52]; (2) refine estimates of the effects of mild symptomatic dengue illness on movement by quantifying changes before, during and after the symptomatic phase of infection; and (3) suggest the need to better account for disease-driven mobility behavior changes in DENV transmission models [31, 53].

The most dramatic changes in mobility occurred during the first 3 days after symptom onset, when significantly fewer locations were visited and significantly more time was spent at home. During days 4-6 and 7-9 after symptom onset, the number of locations visited increased and the proportion of time spent at home decreased. By days 7-9 after symptom onset, the

number of locations visited and the time spent at home were no longer significantly different from healthy behaviors. This reduction in mobility during illness, particularly on days 1-3 after symptom onset, could affect an individual's contribution to onwards DENV transmission. For DENV, viremia reaches levels infectious to mosquitoes a few days prior to symptom onset and peaks at 0-2 days after symptom onset, with titers then lowering by days 4-5 (although some individuals are still capable of infecting mosquitoes) (37-39). During peak infectiousness, most individuals are spending more time at home and visiting fewer places, thereby reducing the number of distinct *Aedes aegypti* mosquitoes with whom potential virus-spreading contacts occur. This may allow those few individuals who do not alter their movements to have a more significant role in pathogen transmission during peak infectiousness. During the pre-symptomatic period, however, almost all individuals have high mobility and a viremia level sufficient for virus transmission to mosquitoes [38]. Recent theoretical models of within-host viral dynamics for symptomatic individuals estimate that 24% of onward transmission results from mosquitoes biting during the pre-symptomatic period [54]. When also accounting for mobility changes throughout viremia, many individuals may have their greatest contribution to transmission be during the pre-symptomatic stage. Ten Bosch et. al. also estimated that asymptomatic individuals had only 80% the net infectiousness of symptomatic individuals [54]. This reduction in net infectiousness may be counteracted by the hypothetically unaltered mobility patterns exhibited by asymptomatic (and minimally symptomatic) individuals, further increasing the overall contribution of silent transmission. Such potential dynamics emerging from the coupling between individual infectiousness, movement, and disease severity deserve further investigation [55], because they may help explain the explosive nature of DENV outbreaks and the limitations of vector control in containing virus transmission.

Throughout an individual's illness period, we found that day of illness and the participant's subjective sense of well-being (QWB score) were significant predictors for the relative number of locations visited, as compared to pre-illness. When considering the proportion of time spent at home, an individual's age and their day of illness were significant in predicting whether they chose to stay at home 100% of the day or not, with children being more likely to stay home all day compared to adults. When an individual chose to spend some amount of time outside their house, the day of illness and the QWB score significantly predicted the proportion of time. Further, the relative amount of time participants spent at home compared to pre-illness was also significantly predicted by the day of illness. Individuals with more severe symptoms and those at the beginning of their illness were more likely to be spending more time at home (both absolute proportion of time and amount of time relative to pre-illness values). Further, when compared to pre-illness, individuals at the beginning of their illness have lower values of relatively visited locations compared to toward the end of illness.

One limitation of our study is the reliance on participant recall, which can be subject to recall bias. However, the retrospective semi-structured interview we utilized was previously tested in Iquitos and was found to obtain superior data on activity space, as compared to wearable GPS data-loggers [24]. Further, in the DRMS participants only needed to recall movements over the past 24 hours, making bias less likely. Our study also faced limitations with the number of participants and the ability to measure movement on the first two days after symptom onset. Nevertheless, our study is one of the first to collect human mobility data at a daily scale during symptomatic infection. Future studies could build on our study by collecting detailed mobility data from more individuals with a wider spectrum of symptom severity,

including across a wider range of diseases. Future studies should also seek to make coupled measurements of an individual's infectiousness throughout the course of mobility data collection.

Human mobility patterns have played an important role in recent vector-borne disease transmission models [56]. There is, however, an increasing need to include differing mobility patterns when modeling individuals that are ill versus healthy. We demonstrate that individuals with dengue spend significantly more time at home, particularly during the first days after symptom onset when they are most infectious, potentially limiting contact with *Ae. aegypti* outside their home. When looking at the locations being visited during illness, however, the proportion of houses was consistent throughout and remained similar to the post-illness level. This may be of particular importance for onward transmission given the propensity for *Ae. aegypti* to bite inside houses [13, 14, 57]. The abundance of mosquitoes in both an individual's home and the houses/locations they visit when infectious will likely determine the effect that reduced mobility has on their overall contribution to DENV transmission. Reduction in mobility patterns when symptomatic could also affect the amount of overlap a social group has in the places they frequent. Given the significant role of socially structured human mobility in determining fine-scale DENV transmission rates [23], accounting for the dynamic nature of social contacts during a symptomatic DENV infection could allow for more accurate modeling of disease transmission and the design of more efficient disease prevention strategies.

Tables

Table 2.1: Adjusted Odds Ratios (and 95% Confidence Intervals) for location type throughout illness, derived from logistic GLMMs.

	Pre-Illness (Day 0)	Post-Illness (Day 30)
Education/Work	1.884 (CI: 1.317-2.725) ***	4.429 (CI: 2.964-6.695) ***
Health	0.019 (CI: 0.009-0.037) ***	0.002 (CI: 0.001-0.008) ***
Other	2.144 (CI: 1.496-3.110) ***	1.660 (CI: 1.109-2.508) *
House	1.684 (CI: 1.110-2.585) *	0.872 (CI: 0.539-1.419)
Family's House	0.348 (CI: 0.078-1.360)	0.509 (CI: 0.125-1.855)

Odds Ratios are for pre- and post-illness time periods, compared to the period during illness (daily interview period) based on logistic GLMMs. For houses, the odds ratios are given for family member's houses (vs. friend's houses). Significant associations between time period and location visitation are denoted with red asterisks (* $p<0.05$, ** $p<0.01$, ***$p<0.001$).

Table 2.2: Adjusted Odds Ratios (and 95% Confidence Intervals) for location type during illness, derived from logistic GLMMs.

	Days 1-3	Days 4-6	Days 7-9
Education/Work	0.08 (CI: 0.03-0.18) ***	0.22 (CI: 0.11-0.43) ***	0.26 (CI: 0.14-0.45) ***
Health	3826 (CI: 585-42793) ***	1041 (CI: 205-9101) ***	365 (CI: 72-3175) ***
Other	0.51 (CI: 0.22-1.08)	0.29 (CI: 0.14-0.56) ***	0.86 (CI: 0.47-1.52)
House	1.08 (CI: 0.39-2.80)	1.20 (CI: 0.52-2.73)	1.64 (CI: 0.76-3.42)
Family's House	21.15 (CI: 0.16-1.48×10^{23})	1.48 (CI: 0.22-12.35)	0.97 (CI: 0.15-6.40)

Odds ratios are for days 1-3, 4-6, and 7-9 after symptom onset, as compared to the post-illness time period, based on logistic GLMMs. For houses, the odds ratios are given for family member's houses (vs. friend's houses). Significant associations between time period and location visitation are denoted with red asterisks (* $p<0.05$, ** $p<0.01$, ***$p<0.001$).

Table 2.3: Fixed effects of a GAMLSS predicting relative number of locations visited, as compared to pre-illness.

Parameter		Estimate	Std. Error	z value	p-value
μ	Intercept	-1.07	0.023	-46.79	< 0.001 ***
μ	Day	0.063	0.0132	4.81	< 0.001 ***
σ	Intercept	-7.001	0.914	14.85	< 0.001 ***
σ	Day	1.086	0.157	-2.85	0.001 ***
σ	QWB score	7.371	5.07	1.70	0.001 ***
σ	Day*QWB score	-1.252	-5.56	1.70	0.001 ***

Each distribution parameter (μ, σ) has distinct explanatory variables.

Table 2.4: Fixed effects of a GAMLSS predicting relative amount of time spent at home, as compared to pre-illness.

Parameter		Estimate	Std. Error	z value	p-value
μ	Intercept	4.974	0.385	12.91	< 0.001 ***
μ	Day	-0.295	0.088	-3.37	0.0011 **
σ	Intercept	-0.133	0.164	-0.81	0.421
σ	Day	0.107	0.029	3.69	< 0.001 ***

Each distribution parameter (μ, σ) has distinct explanatory variables.

Table 2.5: Fixed effects of a GAMLSS predicting proportion of time spent at home.

Parameter		Estimate	Std. Error	z value	p-value
μ	Intercept	0.599	1.02e-05	58426	< 0.001 ***
σ	Intercept	9.147	0.616	14.85	< 0.001 ***
σ	pb(Day)	-0.332	0.116	-2.85	0.006 **
σ	QWB score	1.754	1.034	1.70	0.094
η	Intercept	-1.995	0.930	-2.15	0.035 *
η	Age: (<18)	2.992	1.044	2.87	0.005 **
η	Day	0.215	0.154	1.40	0.166
η	Age: (<18)*Day	-0.425	0.176	-2.42	0.018 *

Each distribution parameter (μ, σ, η) has distinct explanatory variables.

Figures

Figure 2.1: Mobility Values Throughout Illness.
(A) Average number of locations visited during each time period (B) Average proportion of time spent at home during each time period. Significant differences, denoted by letters, were detected using pairwise paired Wilcoxon Sign Rank tests with Bonferroni's correction to account for a family-wise error-rate of 0.05. All significant differences had p-values < 0.01.

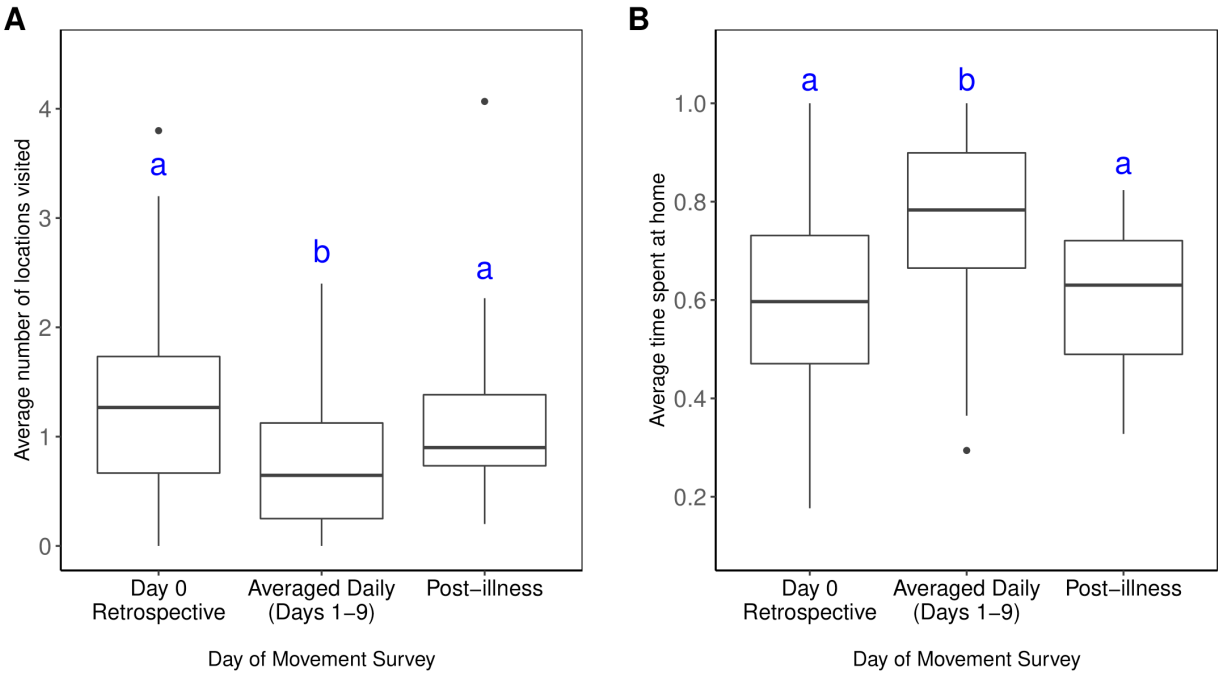


Figure 2.2: Place Types Visited Throughout Illness.
Expressed as the percent of locations being visited of each location type. Other location type includes: markets, restaurants, ports, churches, cemeteries, recreational places, internet cafes, and all else. The number of participants who visited places is listed above each time point.

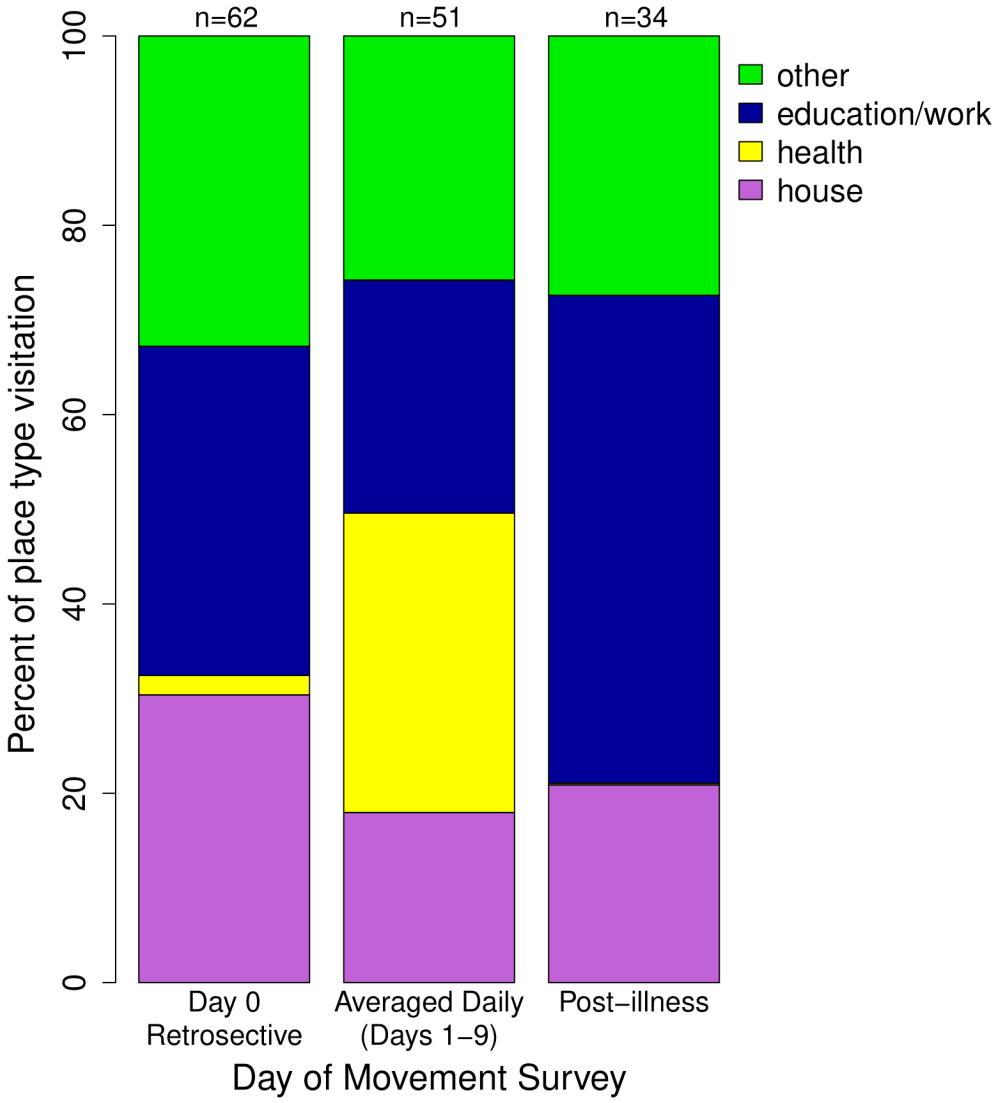


Figure 2.3: Mobility Values During Illness (in 3-day intervals).
(A) Average number of locations visited per 3-day period. (B) Average proportion of time spent at home per 3-day period. Significant differences, denoted by letters, were detected using pairwise paired Wilcoxon Sign Rank tests with Bonferroni's correction to account for a family-wise error-rate of 0.05. All significant differences had p-values < 0.05.

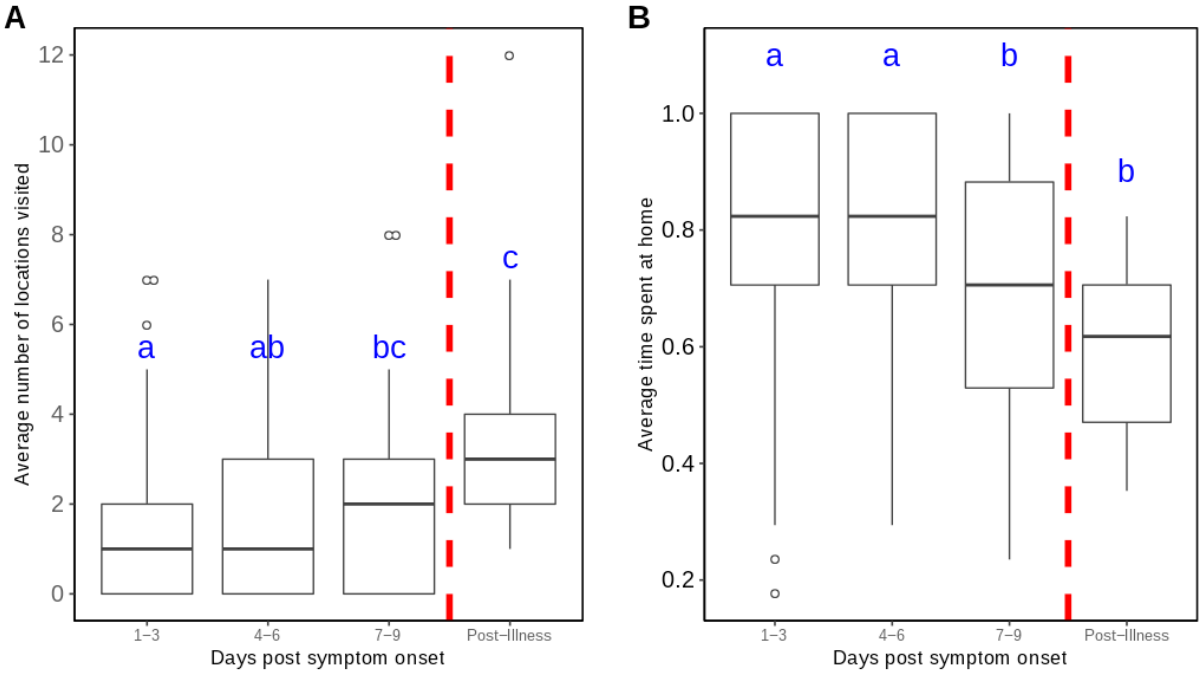
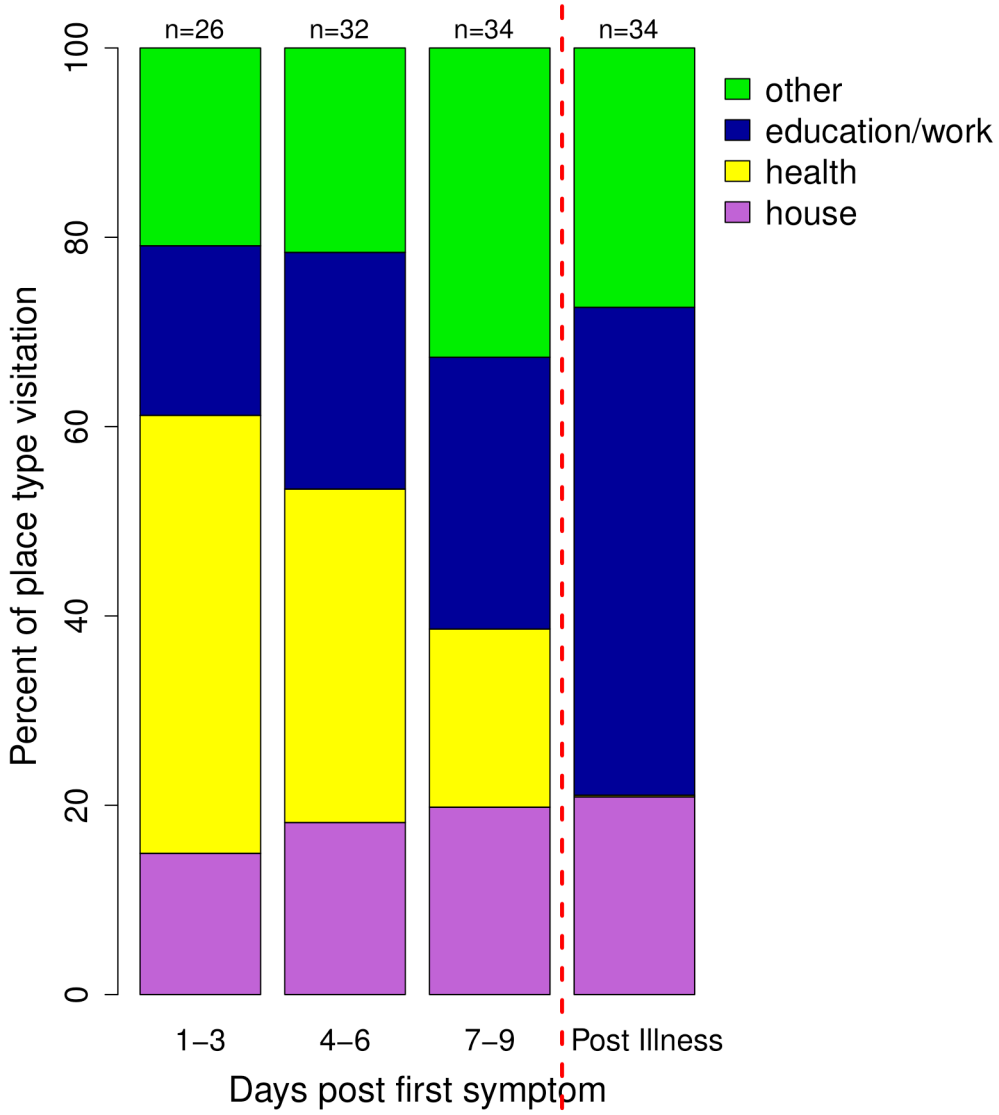


Figure 2.4: Place Types Visited During Illness (in 3-day intervals).
Expressed as the percent of locations being visited of each location type. Other location type includes: markets, restaurants, ports, churches, cemeteries, recreational places, internet cafes, and all else. The number of participants who visited places is listed above each time point.



Supplementary materials

Text S2.1: Participant Description.

Detailed mobility data were collected from a total of 62 DENV+ participants. The median age of participants was 17 years old, with 35 (57%) participants being under 18 years old. Thirty-nine (63%) participants were students. Other participants were housewives (13%) or worked in unskilled labor (10%), in construction (6%), as vendors (5%), in healthcare (2%), or as self-employed (2%). Of the 62 participants, 35 (60%) were male and 27 (40%) were female. DENV positive participants were administered the pre-illness RMS, a median of 3 days after symptom onset. Of these 62 participants, 34 completed a post-illness mobility survey a range of 30-127 days after initial PCR+ blood test. Daily mobility data was collected from an average of 40 participants on days 1-9 after symptom onset; however, on days 1, 2, and 9, only 21, 33, and 28 participants, respectively, provided data (Table S1). By merging DRMS results into 3-day groups, we had data for 46, 54, and 49 participants on days 1-3, 4-6, and 7-9 after symptom onset, respectively.

Table S2.1: Number of participants with data on each day post-symptom onset. In the bottom section, the number of participants for each 3-day group is given.

Day post symptom onset	1	2	3	4	5	6	7	8	9	Post-illness
Number of participants with data	21	33	45	51	48	47	45	45	28	34
Day post symptom onset	1-3			4-6			7-9			Post-illness
Number of participants with data	46			54			49			34

Table S2.2: Results of pairwise Wilcoxon Sign Rank tests of paired data for time points pre-, during, and post-illness. Tests were performed for number of locations visited, number of houses visited, and proportion of time spent at home, comparing between three time points: pre-, during, and post-illness. (* $p<0.05$, ** $p<0.01$, ***$p<0.001$).

Outcome Variable	Time point 1	Time point 2	p-value
Locations visited	During Illness (Days 1-9)	Pre-illness	< 0.001 ***
Locations visited	During Illness (Days 1-9)	Post-illness	0.010 *
Locations visited	Pre-illness	Post-illness	1.000
Houses visited	During Illness (Days 1-9)	Pre-illness	< 0.001 ***
Houses visited	During Illness (Days 1-9)	Post-illness	0.093
Houses visited	Pre-illness	Post-illness	1.000
Time spent at home	During Illness (Days 1-9)	Pre-illness	< 0.001 ***
Time spent at home	During Illness (Days 1-9)	Post-illness	< 0.001 ***
Time spent at home	Pre-illness	Post-illness	1.000

Table S2.3: Results of McNemar's χ^2 test for time points pre-, during, and post-illness. Tests were performed for number of locations visited, number of houses visited, and proportion of time spent at home, comparing between three time points: pre-,during, and post-illness. (* $p<0.05$, ** $p<0.01$, ***$p<0.001$).

Outcome Variable	Time point 1	Time point 2	χ^2 score	p-value
Locations visited	During Illness (Days 1-9)	Pre-illness	5.82	0.016 *
Locations visited	During Illness (Days 1-9)	Post-illness	3.2	0.074
Locations visited	Pre-illness	Post-illness	0.5	0.480
Houses visited	During Illness (Days 1-9)	Pre-illness	20.35	< 0.001 ***
Houses visited	During Illness (Days 1-9)	Post-illness	4.08	0.043 *
Houses visited	Pre-illness	Post-illness	0.1	0.752
Time spent at home	During Illness (Days 1-9)	Pre-illness	5.82	0.016 *
Time spent at home	During Illness (Days 1-9)	Post-illness	3.2	0.074
Time spent at home	Pre-illness	Post-illness	0	1

Table S2.4: Mean predicted probability of a specific location type being visited throughout illness. Probabilities are predicted for pre-, during, and post-illness time periods, based on logistic GLMMs. For houses, the probabilities are predicted for visiting family member's houses (vs friend's houses) (Table 2.1).

	Pre-illness (Day 0)	Post-illness (Day 30)	During Illness (Daily)
Education/Work	0.345	0.517	0.243
Health	0.017	0.001	0.316
Other	0.326	0.273	0.255
House	0.304	0.207	0.178
Family's House	0.55	0.46	0.67

Table S2.5: Results of pairwise Wilcoxon Sign Rank tests of paired data for time points during illness. Tests were performed for number of locations visited, number of houses visited, and proportion of time spent at home, comparing between post-illness and three time points during illness (days 1-3, 4-6, 7-9). (* $p<0.05$, ** $p<0.01$, ***$p<0.001$).

Outcome Variable	Time point 1	Time point 2	p-value
Locations visited	Days 1-3	Post-illness	0.0170 *
Locations visited	Days 4-6	Post-illness	< 0.001 ***
Locations visited	Days 7-9	Post-illness	0.123
Locations visited	Days 1-3	Days 4-6	1.000
Locations visited	Days 1-3	Days 7-9	0.047 *
Locations visited	Days 4-6	Days 7-9	0.871
Houses visited	Days 1-3	Post-illness	0.628
Houses visited	Days 4-6	Post-illness	0.148
Houses visited	Days 7-9	Post-illness	0.722
Houses visited	Days 1-3	Days 4-6	1.000
Houses visited	Days 1-3	Days 7-9	0.289
Houses visited	Days 4-6	Days 7-9	1.000
Time spent at home	Days 1-3	Post-illness	0.005 **
Time spent at home	Days 4-6	Post-illness	< 0.001 ***
Time spent at home	Days 7-9	Post-illness	0.308
Time spent at home	Days 1-3	Days 4-6	1.000
Time spent at home	Days 1-3	Days 7-9	0.014 *
Time spent at home	Days 4-6	Days 7-9	0.008 **

Table S2.6: Results of McNemar's χ^2 test for time points during illness. Tests were performed for number of locations visited, number of houses visited, and proportion of time spent at home, comparing between four time points: days 1-3, 4-6, 7-9, and post-illness. (* p<0.05, ** p<0.01, ***p<0.001).

Outcome Variable	Time point 1	Time point 2	χ^2 score	p-value
Locations visited	Days 1-3	Post-illness	10.08	0.001 **
Locations visited	Days 4-6	Post-illness	11.08	< 0.001 ***
Locations visited	Days 7-9	Post-illness	7.11	0.008 **
Locations visited	Days 1-3	Days 4-6	0	1.000
Locations visited	Days 1-3	Days 7-9	3.06	0.080
Locations visited	Days 4-6	Days 7-9	2.08	0.149
Houses visited	Days 1-3	Post-illness	2.29	0.131
Houses visited	Days 4-6	Post-illness	2.5	0.114
Houses visited	Days 7-9	Post-illness	0.44	0.505
Houses visited	Days 1-3	Days 4-6	0	1.000
Houses visited	Days 1-3	Days 7-9	5.14	0.023 *
Houses visited	Days 4-6	Days 7-9	3.2	0.074
Time spent at home	Days 1-3	Post-illness	7.11	0.008 **
Time spent at home	Days 4-6	Post-illness	7.11	0.008 **
Time spent at home	Days 7-9	Post-illness	3.2	0.074
Time spent at home	Days 1-3	Days 4-6	0	1.000
Time spent at home	Days 1-3	Days 7-9	4	0.046 *
Time spent at home	Days 4-6	Days 7-9	2.5	0.114

Table S2.7: Mean predicted probability of a specific location type being visited during illness. Probabilities are predicted for time points during illness and post-illness, based on logistic GLMMs. For houses, the probabilities are predicted for visiting family member's houses (vs friend's houses) (Table 2).

	Days 1-3	Days 4-6	Days 7-9	Post-Illness (Day 30)
Education/Work	0.165	0.244	0.278	0.479
Health	0.467	0.353	0.177	0.002
Other	0.200	0.208	0.323	0.315
House	0.138	0.175	0.193	0.200
Family's House	0.71	0.67	0.65	0.46

Table S2.8: Results from likelihood ratio tests between pairs of GLMMs of total number of locations visited with various explanatory variables. The Chi square test statistic is looking at the reduction in deviance for each model as compared to GLMM(day). AICs are also provided for each model. The best-fit model is highlighted in red.

MODEL	DF	AIC	Deviance	Chisq	Pr(>Chi)
GLMM(day)	3	368	362.25		
GLMM(qwb_score)	3	372	365.72	0	1
GLMM(day, qwb_score)	4	369	360.71	1.55	0.21
GLMM(day*qwb_score)	5	370	360.45	1.81	0.41

Table S2.9: Table comparing additive regression models for total number of locations visited with various explanatory variables. AIC values, degrees of freedom (DF), and amount of deviance explained (%) are provided for each model. The best-fit model is highlighted in red.

MODEL	DF	AIC	Deviance Explained (%)
GAMM(day)	3	532	1.26 %
GAMM(s(day),s(qwb_score), ti(qwb_score,day))	7	538	2.65%
GAMM(te(qwb_score,day))	7	538	3.87%

Table S2.10: Fixed effects of the best-fit model for total number of locations visited: GLMM "Total Locations ~ day".

	Estimate	Std. Error	t value	p-value
Intercept	-0.898	0.274	-3.28	0.001 **
day	0.077	0.041	1.86	0.063

Table S2.11: Results from likelihood ratio tests between pairs of GLMMs of total number of houses visited with various explanatory variables. The Chi square test statistic is looking at the reduction in deviance for each model as compared to GLMM(day). AICs are also provided for each model. The best-fit model is highlighted in red.

MODEL	DF	AIC	Deviance	Chisq	Pr(>Chi)
GLMM(day)	3	103	96.72		
GLMM(qwb_score)	3	104	97.91	0	1
GLMM(day, qwb_score)	4	105	96.59	0.133	0.715
GLMM(day*qwb_score)	5	105	94.65	2.067	0.356

Table S2.12: Table comparing additive regression models for total number of houses visited with various explanatory variables. AIC values, degrees of freedom (DF), and amount of deviance explained (%) are provided for each model. The best-fit model is highlighted in red.

MODEL	DF	AIC	Deviance Explained (%)
MODEL	DF	AIC	Deviance Explained (%)
GAMM(day)	3	841	1.26 %
GAMM(te(qwb_score,day))	7	853	2.52%

Table S2.13: Fixed effects of the best-fit model for total number of houses visited: GLMM "Total Houses ~ day".

	Estimate	Std. Error	z value	p-value
Intercept	-8.457	2.083	-4.061	< 0.001 ***
day	0.171	0.010	1.718	0.086

Figure S2.1: Average Number of Houses Visited Throughout Illness. Expressed as the average number of houses visited during each time period. Significant differences, denoted by letter, were found using pairwise paired t-tests with Holm's correction to account for a family-wise error-rate of 0.05.

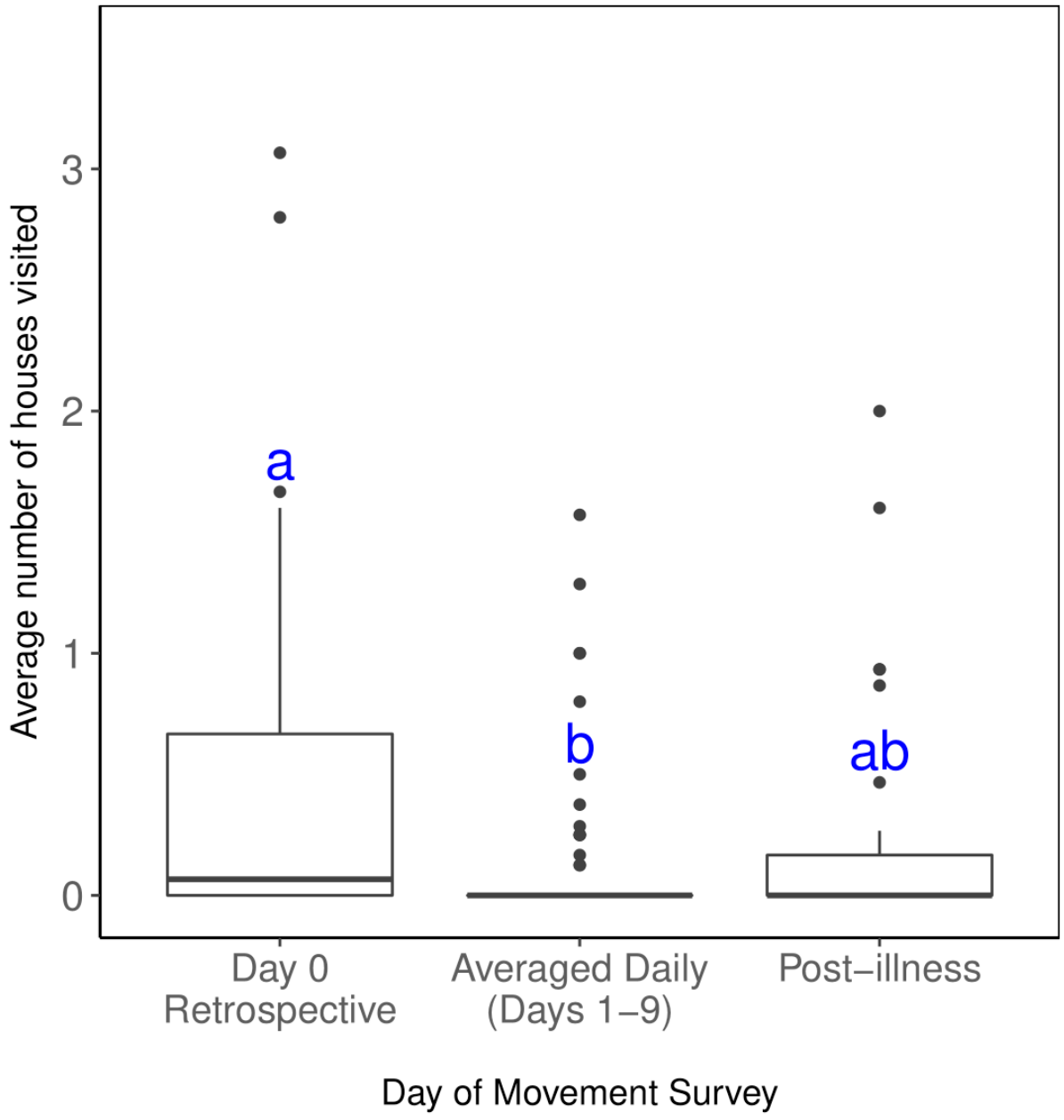


Figure S2.2: Average Number of Houses Visited During Illness (in 3-day intervals). Expressed as the average number of locations visited per 3-day period for time point. Significant differences, denoted by letter, were found using pairwise paired t-tests with Holm's correction to account for a family-wise error-rate of 0.05.

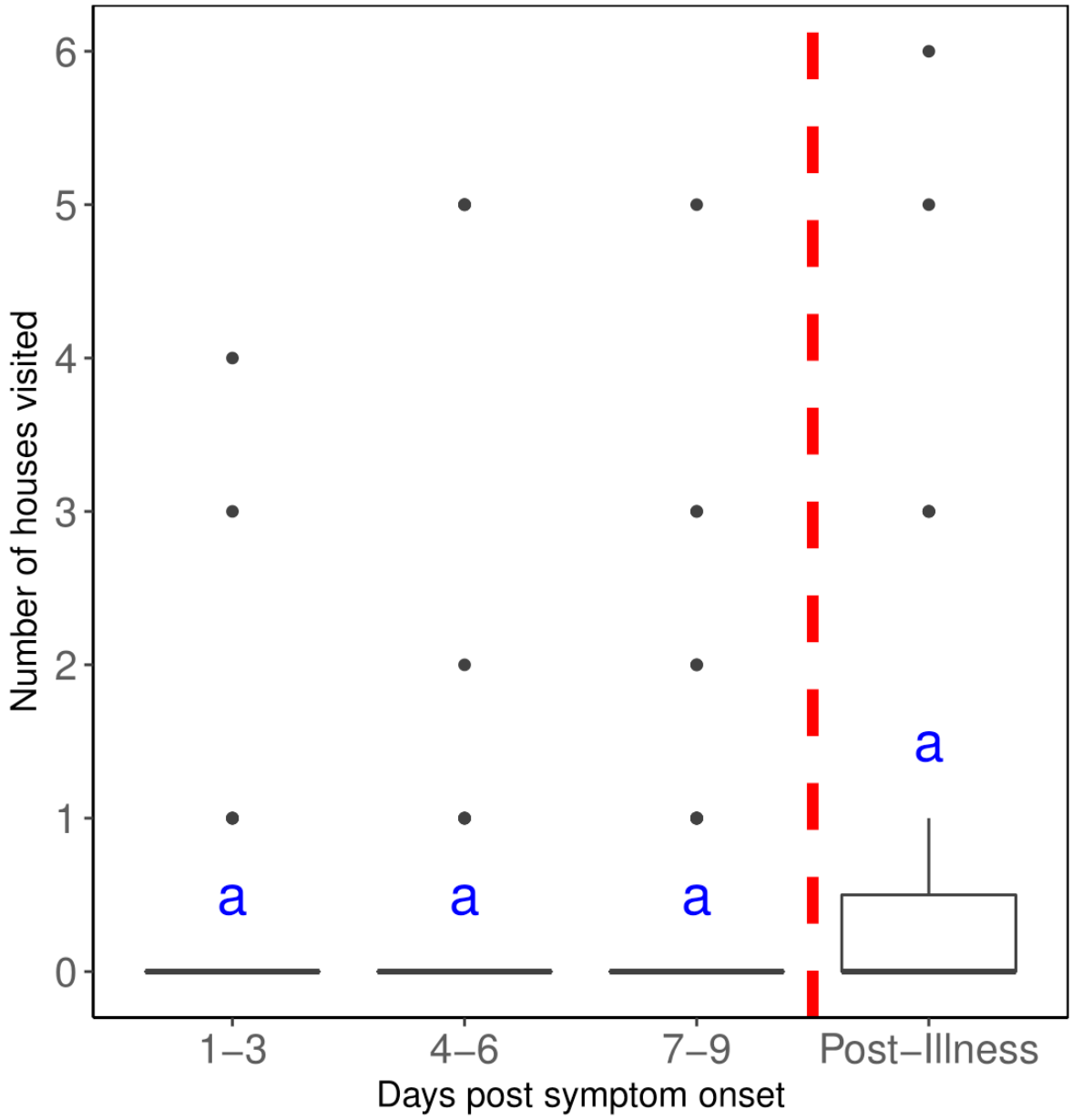
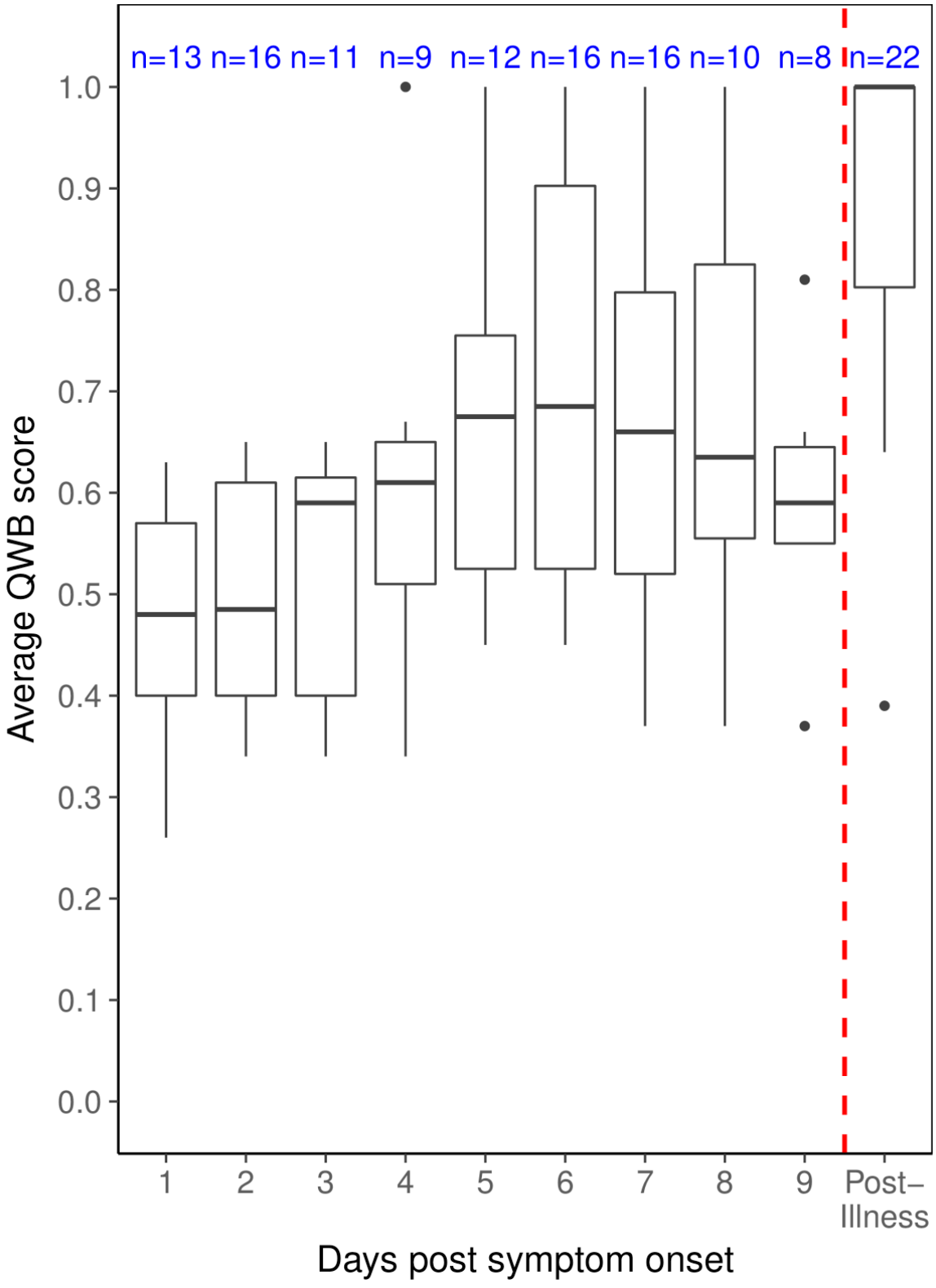


Figure S2.3: Median (interquartile range) QWB-score as a function of day of illness. Numbers on top indicate number of surveys that included paired movement and QWB data.



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Chapter 3: The unexpected cost of caregiving for symptomatic dengue cases

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Introduction

Dengue fever, an acute illness caused by four immunologically related viruses, is the most important mosquito-borne viral disease of humans [1]. Due to the sedentary, day-biting behavior of the primary vector, *Aedes aegypti*, and its propensity for residential locations [2-5], human mobility and visitation patterns to other residential locations shape human-mosquito contacts and dengue virus (DENV) transmission dynamics [6-11]. Indeed, an individual's risk of DENV infection increases when they routinely visited the same residential locations as other DENV-infected people [12]. Recently, studies have shown that individuals with symptomatic dengue infection have significant changes in their mobility patterns during illness, spending more time at home and visiting fewer locations during the first six days of illness [13, 14]. These disease-driven mobility changes are predicted to lead to a large proportion of primary infectious bites occurring at the home of an infectious individual, causing an increase in the risk of acquiring infection for those living in or visiting the residence (as seen in Chapter 4). During the outbreak of another *Aedes*-borne disease, chikungunya, the probability of transmission between household members was 12%, compared to 0.3% for those living more than 50 meters away. Further, females, who spent significantly more time in or around the home, were 1.5 times more likely than males to become infected [15].

Often symptomatic individuals have family members or friends help take care of them during illness. Estimations of this disease-driven change in social connections have been limited due to difficulties in obtaining accurate information about household dynamics during illness. Frequently, partial information about caregiving behavior in response to dengue illness has been obtained from surveys aimed at quantifying the 'indirect' costs of dengue [16, 17]. Specifically, some studies have separated lost days at work/school for caregivers/housemates [17-21], leading to rough estimates showing that those caring for dengue patients may miss an average of 4-5 days at work, with one study reporting 52% of those in the household being workers [17, 20]. Similarly, for children in Thailand, approximately half of caregivers worked, with the most common caregivers being female, specifically the child's mother [22]. As most studies focus on caregiving for everyone or children specifically, it is unclear how common caregiving is for adults and whether the person providing care is a housemate or an outside visitor, a factor that could determine how much of an effect their mobility changes have on shaping the structure of DENV transmission networks.

We capitalized on an established contact-cluster design to monitor the social support received by symptomatic DENV-infected individuals throughout their illness period, focusing on the frequency with which individuals receive home-based care from housemates and/or visitors, as well as the number of caregivers, how they helped, and if their work was affected by this activity. We hypothesize that caregiving behavior will be common, with the majority of caregivers being adult housemates of the sick individual. We further hypothesize that the type of help given and the impact on the caregiver's work will depend on symptom severity and the relation of the caregiver to the DENV-infected individual.

Methods

Study Area

This study was performed in the Amazon city of Iquitos, Peru. Iquitos is a geographically isolated, tropical urban environment with approximately 430,000 inhabitants located along the margin of the Amazon River [23]. The city's economic structure is highly informal and dynamic, with one-third of economically active individuals either unemployed or informally employed [24]. Iquitos has been the home of extensive, long-term arboviral research led by the University of California, Davis and U.S. Naval Medical Research Unit 6 since 1999 [11, 25-30]. Extensive human mobility studies paired with detailed epidemiological data have made Iquitos an informative site for understanding the dynamics of arbovirus transmission. All four serotypes of DENV have been introduced in Iquitos; however, at any particular time virus transmission is usually dominated by a single serotype [29, 31]. Previous research [27] demonstrated that the majority of individual's movement (~80%) occurs within 1 km of their home; however, mobility is highly irregular and temporally unstructured, rarely centering around a single location, such as a workplace [27].

Study Design

Iquitos residents with a laboratory-confirmed DENV infection (by PCR) were recruited into the study through clinic- and community-based longitudinal febrile surveillance, as previously described [26]. At the time of initial case capture (blood sample), a retrospective semi-structured movement survey (RMS) was verbally administered by trained nurses (the 'Movement Team') to identify the locations an individual had visited in the 15 days prior to diagnosis (to identify behaviors during the exposure period) as well as the visitors they received at home in the previous three days. A modified, daily RMS (DRMS) was conducted for the

following seven days [14], which included a small subset of questions about the individual's quality of life (QOL). These questions, which focused on an individual's ability to complete normal activities, were taken from a larger QOL survey administered only twice during illness. The QOL questions were, however, added to the DRMS partway through data collection, so only a portion of respondents have answers recorded. There was also a daily survey regarding the symptoms an individual experienced [Paz-Soldan, in review]. During this seven-day period, DENV positive individuals were also administered two Quality of Well-Being surveys (QWB) by the Movement Team, one 2-3 days and one seven days after the initial PCR-positive blood test. The QWB survey is a validated instrument used to measure an individual's quality of life during chronic illness [32][Elson, in review] that uses a weighted algorithm to produce one well-being score between 0.0 (death) and 1.0 (asymptomatic and fully-functioning)[32]. On the seventh day after the initial blood test, individuals were administered a survey about the expenses incurred during dengue illness, for both the symptomatic individual and possible caretakers.

At a follow-up visit scheduled 30 days after the initial PCR-positive blood test, individuals were given "post-illness" RMS and QWB surveys in an effort to record their "baseline" mobility behavior and well-being in the absence of illness. Individuals were also given another 'Expenses' survey in case any expenses were accrued after the day-7 survey was administered. **Table S3.1** provides a description of each survey, including when it was administered and the number of respondents, as well as listing the particular questions we will be analyzing.

Data Processing

For each study participant, rather than referring to daily survey values as occurring on a certain number of days after the PCR-positive blood test, a standardized "day after symptom onset" variable was calculated. Because blood tests were not done on the same day of illness for all participants, daily surveys captured a range of 1-14 days after symptom onset. We focused our analysis on days 1-10 after symptom onset; few individuals (12/71) had data for days 11-13 after symptom onset.

For each day after symptom onset, DRMS data were utilized to record (1) how many visitors an individual had at their home (if any), (2) their relation of the visitor, (3) why they were visiting, (4) if they knew the person was sick at the time of visit, and (5) whether they visit at least once a week in the absence of illness (self-reported 'routineness' of the visitor). Further, the QOL questions on the DRMS gave daily data on whether individuals felt they had the *ability to do* daily, physical, and self-care activities. Pre- and post-illness RMS provided the "baseline" number of visitors an individual received.

The QWB survey provided two data points within the symptomatic period, which were combined into an overall value of whether individuals felt they *needed help* with daily activities or personal care at any point throughout symptoms. Similarly, the two time points in the 'Expenses' data were combined to provide information on (1) if an individual had someone help care for them, (2) how many people helped, (3) the relation of the helpers, (4) what they helped with, and (5) whether the helper's work was affected.

While the symptom survey provided data on 36 symptoms, we focused on six groups of symptoms that are often associated with dengue illness (malaise/weakness, fever/chills, headache/retro-orbital pain, body/muscle pain, bone/join pain, and abdominal pain). For each symptom group, the presence (0/1) and intensity level (0-1) were analyzed for each day of

illness, as was the number of symptom groups experienced on each day (out of six) and the total intensity score for all symptom groups (out of six). For the entire illness period, variables were calculated for overall presence of each symptom, maximum intensity score for each symptom, maximum number of daily symptom groups experienced, and maximum daily intensity score.

Data Analysis

Analysis of the data had two main goals: (1) examining the home visits and caregiving received by individuals with a symptomatic dengue infection, and (2) determining whether these behaviors could be predicted by characteristics of the symptomatic individuals and their illness. For the first objective, caregiving behaviors were examined for the following variables: (1) presence of caregivers, (2) number of caregivers, (3) relation of caregiver, (4) days help was provided, (5) whether the caregiver helped take care of the sick individual, (6) whether they helped around the house, (7) whether they helped by providing money or items, and (8) whether their work was affected. For each variable of interest, overall values were provided and comparisons were made based on the gender (male/female) and age (adult/child) of the symptomatic individual, as well as the gender/age combination of the individual (male adult/male child/female adult/female child). These comparisons were conducted using Fisher's Exact test.

Comparisons were also conducted to determine whether gender or age (or a combination of the two) were associated with receiving visitors at some point during illness. Visitor behaviors were also summarized for the entire illness period using variables: (1) presence of visitors, (2) number of unique visitors, (3) relation of visitors, (4) number of unique visits by each visitor, (5) whether they were 'routine visitors', (6) whether they knew about the illness, and (7) the reason for the visit. Characteristics of an individual's visit were compared based on whether the

individual was a ‘routine visitor’ or not (as self-reported by the symptomatic person). We also examined whether there were any significant differences in visitor behavior if caregiving was or was not present and vice versa (if visitor presence affected caregiving behaviors).

For the second objective, possible predictors for receiving caregiving behavior were examined using Generalized Linear Models (GLMs). Best-fit models were determined for the logistic response variables of: presence of caregiving, number of caregivers (one versus two), relationship of caregiver (housemate or not), if helped around the house (yes/no), if helped with buying things or giving money (yes/no), and if the caregiver’s work was affected (yes/no). Possible predictor variables included the age (child vs. adult) and gender (male vs. female) of the sick individual (as well as an interaction variable for age and gender), whether the sick individual had a high or low number of housemates (split into a binary variable around the median number of housemates), whether they needed help with personal care activities or daily activities at some point during illness (QWB), overall presence of each symptom group during illness, maximum daily symptom groups experienced, and maximum daily symptom intensity score. Best-fit models were determined using the corrected AIC (AICc) and the relative likelihood of the model (weight).

Whether or not a symptomatic individual received visitors was examined as a logistic response variable in two ways: for the entire illness period and for each day of illness. When the entire illness period was considered, GLM models were examined with the same predictor variables as above. When the response variable was the presence of visitors on each day of illness, Generalized Linear Mixed Models (GLMMs) were used, with the participant ID as a random effect to account for repeated observations [33]. Day of illness was included as a possible predictor variable to determine whether visitor presence changes throughout illness.

Daily values were also provided for the possible predictor variables of symptom presence and the ability to complete activities (QOL). Variables with set values that did not change during illness (i.e., gender, age, number of housemates, whether help was needed to complete daily or personal care activities) were also considered as possible predictors. All statistical analyses were performed in R 3.3.0 statistical computing software [33, 34].

Results

Detailed data were collected from 71 DENV+ participants about daily visitors received, 67 of who also provided data on caregiving behavior. The age group and gender of these participants, as well as the number of participants when both datasets were combined, can be found in the supplemental information (**Table S3.2**). The majority of participants surveyed reported having an illness lasting five or more days (76.9%).

Overall, the percent of individuals who reported experiencing a symptom class at some point during illness was 98.7% (malaise/weakness), 93.7% (fever/chills), 93.7% (headache/retro-orbital pain), 79.8% (body/muscle pain), 68.4% (bone/joint pain), and 59.5% (abdominal pain). The presence of symptoms at each day after symptom onset was also calculated (**Table S3.3**). of the 70 individuals who responded to the QWB survey, the percent of individuals who reported *needing help* with daily activities and personal care at some point during illness were 52.9% and 14.3%, respectively. Comparatively, a large proportion of participants reported having some limitation in their ability to complete physical (72.7%), daily (69.7%), and self-care (60.6%) activities when asked on each day of illness (QOL) (**Table S3.3**).

Who is Receiving Help

During symptomatic dengue illness, 89.5% of participants had someone help care for them. Visitors were received by 32.3% of sick individuals, with 87.1% of visitors knowing the individual was sick and 80.0% of visits being related to their illness (**Table 3.1**). Of the 60 individuals who had someone help them, 33.3% also had visitors at some point during their illness. A total of four individuals (6.0%) had no caregiving help and received no visitors during illness. Of the seven individuals who did not receive help, five were adult females. Accordingly, children were significantly more likely than adults to have someone helping them (97.5% vs. 77.8%) (Fisher's Exact test, p=0.01) and female children (100%) were significantly more likely than female adults (68.8%) (Fisher's Exact test, p=0.02) (**Table 3.2, S3.4**). Female children also received significantly more visitors during illness (50%) compared to male children (13.0%) (Fisher's Exact test, p=0.02), with females (45.7%) having an overall higher rate of visitors than males (19.4%) (Fisher's Exact test, p=0.02) (**Table 3.2, S3.4**). Accordingly, the events of receiving caregiving and visitors during illness were most associated with the age and sex of the ill person, respectively (**Table S3.5, S3.6**). Children had a higher expected probability of receiving help compared to adults (97.4% vs. 76.9%) and females had a higher predicted probability of receiving visitors compared to males (50% vs. 20%).

When examining whether or not visitors were received on each day of illness, the best-fit GLMM by AICc score included the interaction between age and sex (after accounting for participant ID as a random effect), where female children had the highest predicted probability of receiving visitors on each day of illness (13.5%) and male children had the lowest (0.6%) (**Table S3.7**) (**Figure 3.2**). This model, however, was not significantly better than the GLMM including only sex (and random effect of participant) when looking at reduction in deviance (χ^2 Analysis of

Deviance, p=0.09) (**Table S3.7**). In this model, males and females had predicted probabilities of 1.2% and 7.8% for receiving visitors on each day of illness.

During illness, individuals tended to receive either one (47.8%) or two (26.1%) visitors, the majority of whom (69.6%) only visited once during the illness period (**Table 3.1**). It was most common for sick individuals to receive help from one person (88.7%) who helped for the length of the illness (94.1%). There was a significant association between number of people helping an ill individual and whether they reported needing help with personal care at some point during illness (from the QWB survey) (**Table S3.8**). Those who needed personal care help had a 33.3% predicted probability of receiving help from two people, compared to only 6.1% for those who didn't need help.

Who is Giving Help

In 91.2% of cases, the sick individual received help from a relative that lived with them. According to the best-fit model for relation of the caregiver, children had a higher predicted probability of receiving help from a housemate (97.6%) compared to adults (86.4%) (**Table S3.9**). Of the visitors received during illness, half (49.9%) were family members, 35.3% were friends, and 15.3% were other individuals, with 87.1% of visitors being reported as 'routine visitors' (visited at least once a week pre-illness) by the ill participant (**Table 3.1**). Those who weren't routine visitors were mostly friends (54.5%) or other individuals (36.4%). Sixty-three percent of 'non-routine visitors' were aware that the participant was sick, compared to 90.5% of routine visitors (**Table 3.1**).

What Help is Being Given

The majority (83.8%) of visits a symptomatic individual received from a 'routine visitor' were for reasons related to the illness, 66.2% were for emotional support, 6.8% were for logistic

support, and 8.1% for some other illness related reason (**Table 3.1**). Comparatively, 45.5% of visits from 'non-routine visitors' were not disease related, and those that were related to the illness were for something other than emotional support (9.1%) or logistic support (9.1%) (**Table 3.1**). When the symptomatic individuals received help from caregivers, the most common way of helping was by taking care of them (95.6%), with 47.1% of caregivers helping around the house (taking care of children, cooking, cleaning) and 38.2% helping by buying things for the sick individual or giving them money (**Table 3.3**). The largest proportion of people (34.3%) helped only with taking care of the sick person; however, 20.9% of people helped in all three ways (**Table 3.3**). There were no significant differences between gender or age class in whether each type of help was provided, although getting help around the house was quite common for adult males (75%) compared to adult females (41.67%) (Fisher's Exact test, p=0.2) and children (40.91%) (Fisher's Exact test, p=0.08) (**Table S3.4**). There was no significant difference in the way the caregivers helped or the reason for a visitor's visit when looking at the 20 individuals who received both visitors and caregivers during illness. The best-fit model for whether or not an individual received help in the form of money or things accounted for how many house members they had (less than or greater than median of 8) and whether they needed personal care help during their illness (**Table S3.10**). Individuals who needed help with personal care and had a large number of housemates had a higher predicted probability of receiving money and things than those who didn't need personal care help and/or live with fewer housemates (**Figure 3.3**). The best-fit model for predicting whether or not help was received around the house included the maximum symptom intensity score (**Table S3.11**).

What is the Impact for the Person Giving Help

Of all the people helping symptomatically ill individuals, only 28.4% had their work affected. It was significantly more common for work to be affected when helping sick adults (41.7%) compared to sick children (18.2%) (Fisher's Exact test, p=0.05) (**Table 3.2**). In particular, 58.3% of those helping adult females had their work affected, as compared to 25% helping adult males (Fisher's Exact test, p=0.2), 22.7% helping female children (Fisher's Exact test, p=0.06), and 13.6% helping male children (Fisher's Exact test, p=0.02) (**Table S3.4**). The best-fit model (based on AICc score) predicting whether a helper's work would be affected accounted for presence of bone/joint or abdominal pain during illness (**Table S3.12**), where the predicted probability of work being affected was higher both when helping those with bone/joint and abdominal pain versus those who didn't experience these symptoms (**Figure 3.4**). This model was, however, not significantly better than the GLM based on only maximum symptom intensity score during illness (χ^2 Analysis of Deviance, p=0.13), where a higher maximum intensity was associated with an increased probability that the person helping would have their work affected.

Discussion

Almost all individuals with symptomatic dengue received some form of help during their illness, whether through caregiving or illness-related visits. Caregiving was most associated with the sick individual's age group, where children were most likely to receive help and for that help to be from a relative they live with, which is consistent with previous results that the majority of child caregivers are the mother [22]. Visiting behaviors differed most between genders, with females more likely than males to receive visitors overall and on each day of illness.

Interestingly, however, female children seemed to be significantly more likely to receive both caregiving and visitors during illness.

Previous social support research found that most long-term assistance is received from family members, whereas short-term aid is mostly provided by friends and neighbors [35]. While our study was on a much shorter timescale, we see similar trends with 91% of caregiving coming from relatives in the same household and 95% of caregivers helping for the length of the illness. Comparatively, other family members and friends made up the majority of visitors during illness, 70% of whom only visited once during the illness period. Our data also agrees with previous findings that patients most often want emotional support from family and friends (rather than logistic support) [36], with almost all caregivers helping to take care of the ill individuals and 66% of visitors coming to give emotional support.

The likelihood of receiving other forms of help, around the house or through material aid/money, was most associated with the magnitude of the disease, whether symptom intensity or the need for personal care. Likely once an individual's symptoms become very intense (enough so to need personal care help) they become unable to get housework done or make it to the store to buy things needed for their illness. Giving things/money was more likely when a sick individual had a large number of housemates. This could be due to the correlation with a lower socioeconomic status (although we did not find a significant effect when we ran a model with a composite SES score) or it could be more likely that housemates get housework done when there are more of them present.

It was also found that providing money or material aid was the least common way caregivers helped sick individuals. This could be due in part to the relatively low cost of ambulatory dengue illness. Indeed, in a previous study, direct costs made up just 10.2% of the

total cost of a single dengue case [17]. The majority of the cost burden for dengue infection was indirect, based on days lost at school and work for the patient and their caregiver. This high cost of lost workdays is particularly interesting given that we found only 28% of caregivers had their work affected, although the effect would likely last the length of the symptomatic illness. It was most common for those helping female adults to have their work affected, possibly because children and male adults already had their mother/spouse (female adult) acting as a caregiver before illness, whereas when the mother was sick, a working adult would have to take days off to help take care of them.

The mobility behavior of a susceptible individual can determine their exposure to infectious mosquitoes and subsequent risk of DENV infection. If members of a frequently visited house become DENV+, an individual's probability of exposure may increase, assuming they don't change their movements. The presence of symptomatic cases may, however, cause social contacts to practice avoidance (stop visiting) or caregiving (visit more frequently/longer), which could cause decreases or larger increases in infection risk for the susceptible individual, respectively. These mobility changes could also decrease the connectivity of the infectious individual's home and stunt the onward transmission potential, given that house-to-house human movements drive DENV transmission [26].

One important factor to consider for dengue is the prevalence of infections that progress with mild or no symptoms (~70%) [29, 37, 38]. Recent evidence has demonstrated that these individuals can be infectious to mosquitoes [22, 39]. This study also documented DENV viremia reaching infectious levels a few days prior to symptom onset. Further, recent theoretical models estimated that 24% of onward transmission can result from mosquito bites during the presymptomatic period [41]. In both of these cases, individuals could be infectious to mosquitoes

without having their routine mobility patterns impacted by symptomatic illness [42, 43]. If individuals with presymptomatic or asymptomatic infectiousness acted as caregivers/visitors, however, their mobility could change to spend more time at the home of the symptomatically ill individual and less time at other locations, impacting expected onward transmission. As predicted with symptomatic cases in Schaber et.al., infectious individuals limiting their mobility could cause either increases or decreases in onward transmission depending partially on the distribution of mosquitoes across their activity space [in progress].

We hypothesized that the majority of a symptomatic individual's social contacts would stop visiting to protect themselves from infection while one or two housemates of the individual would act as caregivers, spending more time at home. We found that caregiving, while very common for housemates, did not affect the helper's mobility patterns in the majority (72%) of cases. Mobility patterns of visitors were also surprisingly unaffected, with 'routine visitors' still visiting the symptomatic person at least once during their illness. This continuation of routine mobility patterns in the presence of a symptomatic dengue case may not have an effect for the onward transmission of presymptomatic/asymptomatic individuals, but it could increase a susceptible individual's exposure to infectious mosquitoes and allow the sustained spatial transmission potential of DENV.

Tables

Table 3.1: Summary of Visitors Received During Illness by Ambulatory DENV infected individuals in Iquitos, Peru.
Data on the visits individuals received when ill is provided overall, and split into groups of visits based on if made by routine visitors (self reported).

		By Routine Visitor? (self reported)	
	All Visits (n=85)	Yes (87% visits)	No (13% visits)
Relationship of Visitor?			
Family	49.91%	55.41%	9.09%
Friend	35.29%	32.43%	54.55%
Other	15.29%	12.16%	36.36%
Know of Illness?			
Yes	87.06%*	90.54%*	63.64%
Reason for Visit?			
Emotional Support	58.82%	66.22%	9.09%
Logistical Support	7.06%	6.76%	9.09%
Other Disease Support	11.77%	8.11%	36.36%
Not Related to Disease	20.00%*	16.22%*	45.46%
Routine Visitor?			
Yes	87.06%	---	---

*2 visits had NA values

Table 3.2: Results of Fisher's Exact Test for Sex/Age Comparisons of Caregiving and Visitor Behaviors Experienced by Ambulatory DENV infected individuals in Iquitos, Peru. Tests were performed for whether caregiving was received, if the person who helped was their housemate, if the person who helped had their work affected, whether the type of help was taking care of the individual, helping around the house, or helping with money and buying things. Tests were also performed for whether or not visitors were received during the illness period (*p<0.05, ** p<0.01, ***p<0.001).

Outcome Variable	Group 1	Group 2	p-value
Someone Helped	Female	Male	0.4
Someone Helped	Adult	Child	0.01**
Helped by Housemate	Female	Male	0.2
Helped by Housemate	Adult	Child	0.7
Helper's Work Affected	Female	Male	0.2
Helper's Work Affected	Adult	Child	0.05*
Helped Take Care of Me	Female	Male	1.0
Helped Take Care of Me	Adult	Child	1.0
Helped Around House	Female	Male	0.5
Helped Around House	Adult	Child	0.2
Helped with Money/Things	Female	Male	0.8
Helped with Money/Things	Adult	Child	0.8
Received Visitors	Female	Male	0.02*
Received Visitors	Adult	Child	0.6

Table 3.3: Frequency of Different In-Home Caregiving Behaviors Provided to Ambulatory DENV Infected Individuals in Iquitos, Peru. Given as the number and percent of helpers (out of 67).

Help Take Care of Person	Help Around House*	Help with Money/Buying Things	Number of Helpers
Yes	Yes	Yes	14 (20.9%)
Yes	Yes	No	17 (25.4%)
Yes	No	Yes	11 (16.4%)
Yes	No	No	23 (34.3%)
No	Yes	Yes	0 (0%)
No	Yes	No	0 (0%)
No	No	Yes	2 (3.0%)
No	No	No	0 (0%)

* Includes help with taking care of kids, cooking, and cleaning

Figures

Figure 3.1: Percent of the Population with Symptoms Present, Abilities Limited (Physical, Daily, Self-care), and Visitors Received on each Day after Symptom Onset During Ambulatory DENV infection in Iquitos, Peru. Symptoms are split into six groups. Each type of event (presence of symptoms, limited abilities) is presented in a separate facet, both of which have a line for percent of the population that received visitors.

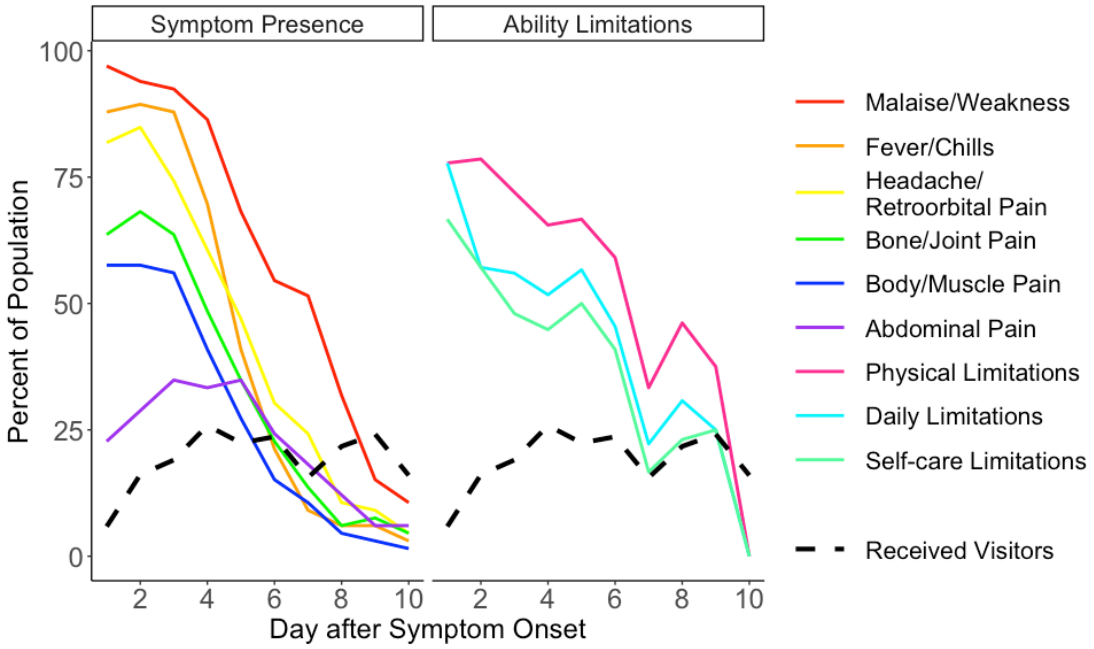


Figure 3.2: Predicted Probability of Receiving a Visitor on Each Day of Illness, Based on a GLMM Fitted to Data of DENV Infected Individuals in Iquitos, Peru. Given in terms of age group and sex. Error bars represent 95% Confidence Intervals.

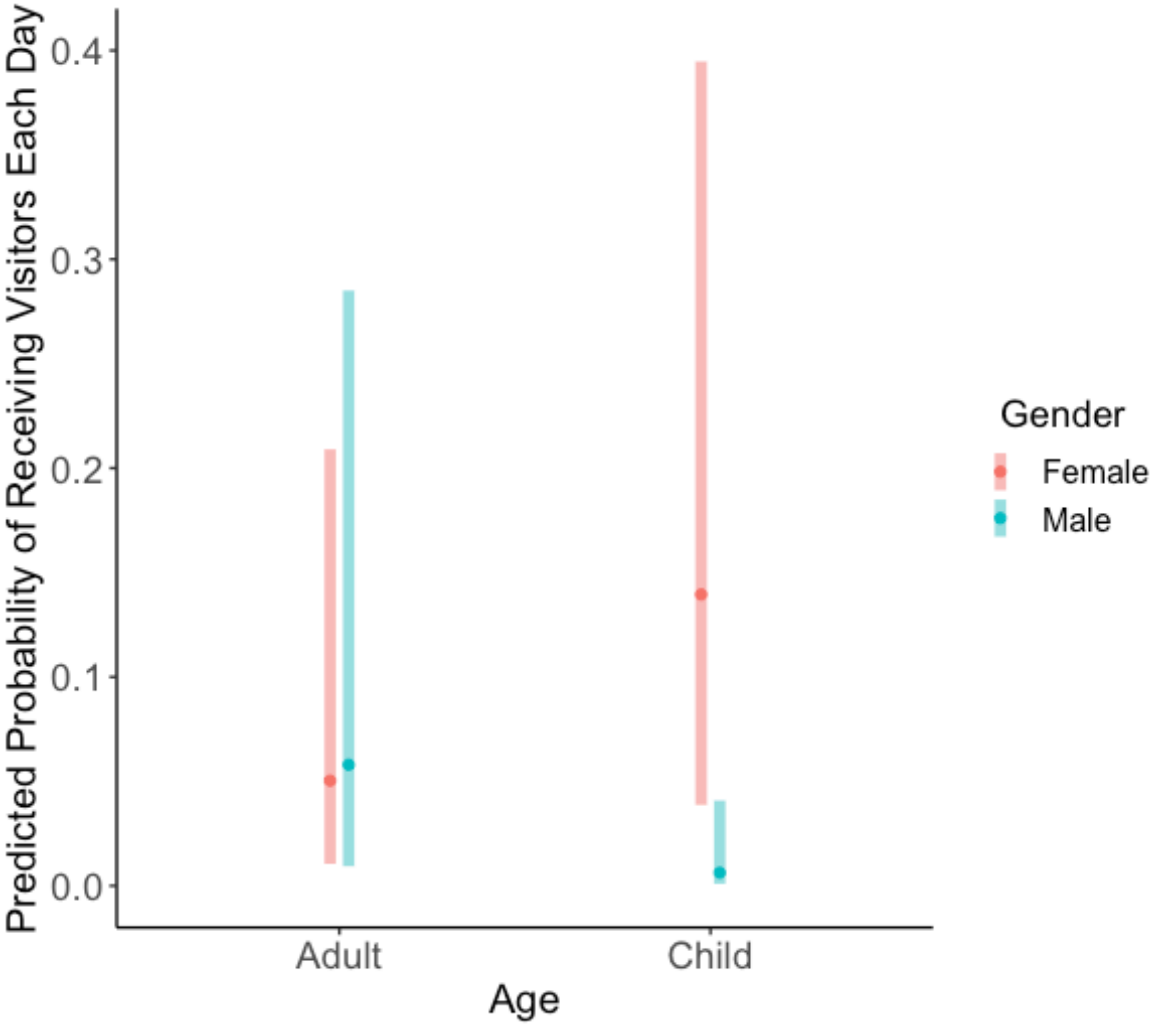


Figure 3.3: Predicted Probability of Receiving Money or Things as a Form of Caregiving During Ambulatory DENV Infection, Based on a GLM Fitted to Data From Iquitos, Peru. Given in terms of number of housemates and whether the individual reported needed personal care during illness. Error bars represent 95% Confidence Intervals.

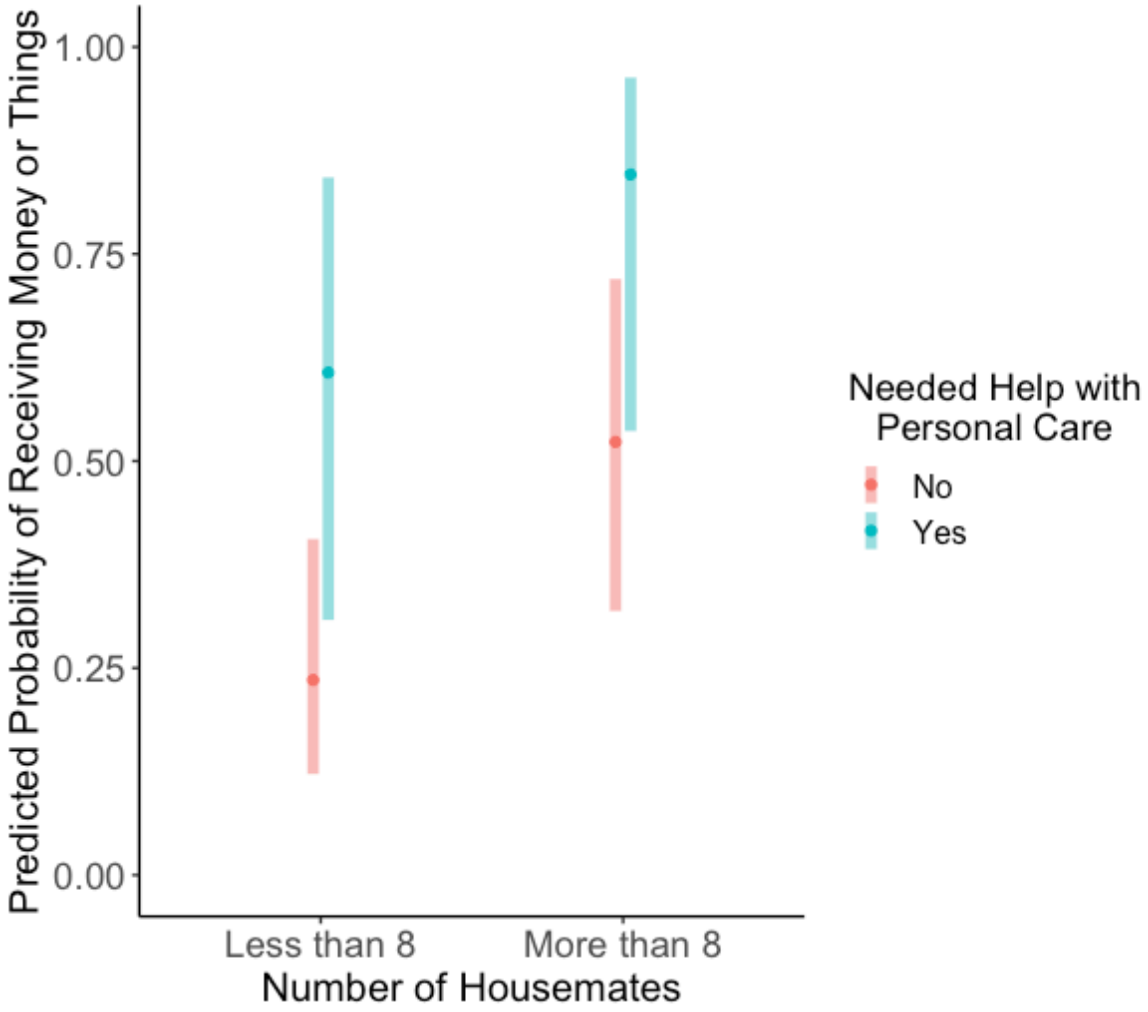
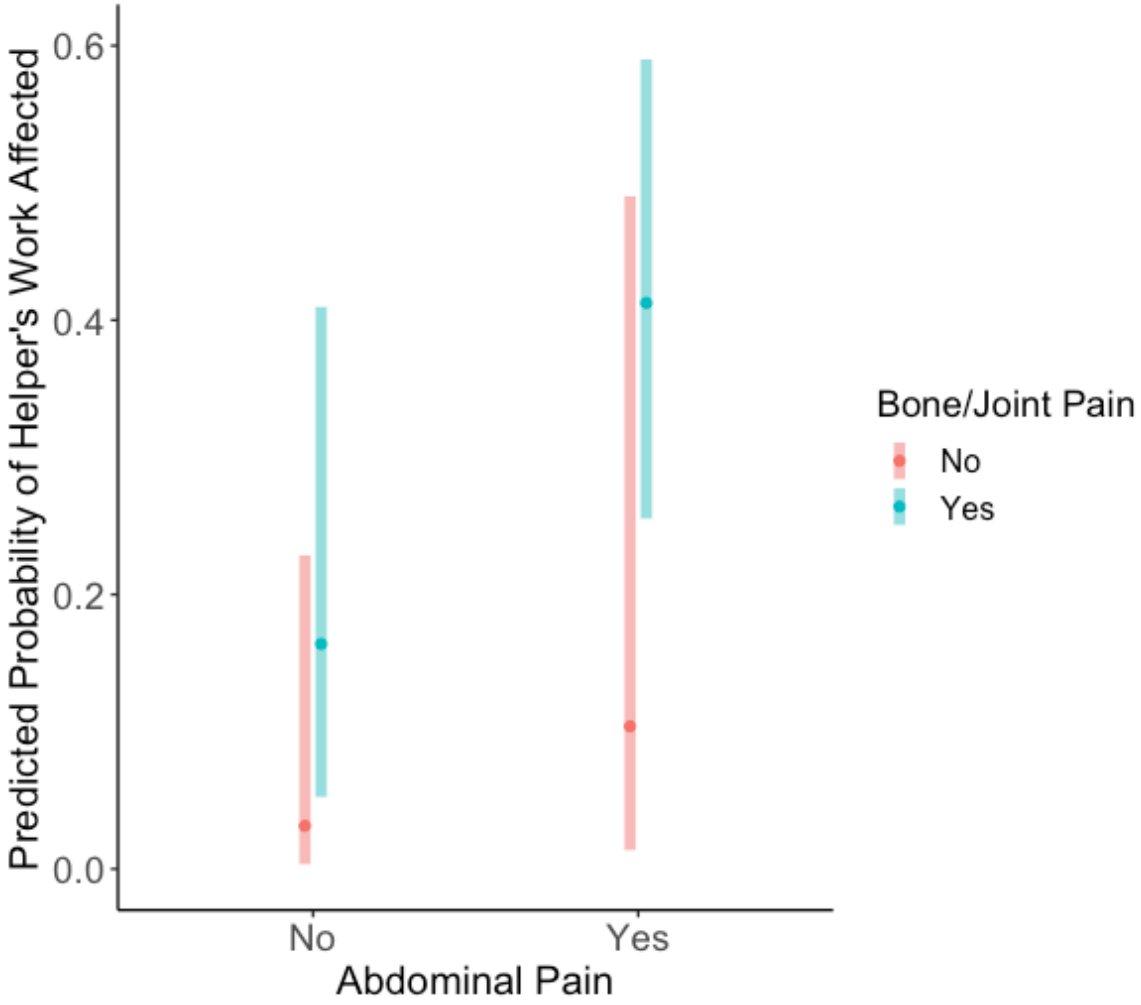


Figure 3.4: Predicted Probability of Caregiver's Work Being Affected During Ambulatory DENV Infection, Based on a GLM Fitted to Data From Iquitos, Peru. Given in terms of if abdominal pain is present and if bone/joint pain is present at any point during illness. Error bars represent 95% Confidence Intervals.



Supplemental materials

Table S3.1: Description of Surveys. Provides descriptions of each survey and questions of interest on the survey, as well as the time point when each survey was administered to individuals, how the data were aggregated for analysis, the number of respondents total, and the number of respondents who also have data on 'Expenses' and 'Daily Visitors'.

Questions of Interest	When Administered (days after blood test)	Survey Description	Number of Respondents Total:	Survey Name
• Did anyone help take care of you during illness? • How many people? • What was their relationship to you? • How did they help you? • Was their work affected by helping you?	Day 7 Day 30	To look at the direct costs (money spent on medication, etc.) and indirect (lost income due to absence at work) costs incurred during illness for the ill individual and possible caretakers.	67 (67)	Expenses
• Did you have visitors? • What was their relationship to you? • Why were they visiting? • Did they know you were ill at the time of the visit? • Do these individuals routinely visit you (without illness)?	Days 1-7	To determine whether visitors were received at an individual's home. (Part of a larger retrospective movement survey modified to identify locations visited, time spent at home, and visitors received in the previous 24 hours of illness.)	71 (67)	Daily Visitors subsection of the Daily Retrospective Movement Survey (DRMS)
• Did you have the *ability to do* daily activities? • Did you have the *ability to do* physical activities? • Did you have the *ability to do* self-care activities?	Days 1-7	To assess an an individual's ability to complete their normal activities (taken from a larger QOL survey)	33 (31)	Daily 'Quality of Life' (QOL) subsection of the Daily Retrospective Movement Survey (DRMS)*
• Did you *need help* with daily activities? • Did you *need help* with personal care activities?	Day 2-3 Day 7 Day 30	To measure an individual's quality of life as a well-being score ranging between 0.0 (death) and 1.0 (asymptomatic and fully-functioning).	70 (67)	Quality of Well-Being (QWB)

• For each symptom:
  • Were symptoms present?
  • Rate the symptom intensity(1-10)
	Days 1-7	To assess presence and intensity of 36 different symptom types associated with dengue illness, and whether alleviating measures were taken/worked.	79 (66)	Illness Perception and Response (IPR)

* QOL questions were added to the end of DRMS surveys partway through data collection, hence the low number of respondents.

Table S3.2: Age and sex distribution for of participants with (A) expenses (caregiving) and (B) daily visitor data.

Expenses (n=67)

A)	Children (<18)	Adult (>= 18)	
Male	22 (32.84%)	11 (16.42%)	33 (49.25%)
Female	18 (26.87%)	16 (23.88%)	34 (50.75%)
	40 (59.70%)	27 (40.30%)	

Daily Visitors (n=71)

B)	Children (<18)	Adult (>= 18)	
Male	23 (32.39%)	13 (18.31%)	36 (50.70%)
Female	18 (25.35%)	17 (23.94%)	35 (49.30%)
	41 (57.75%)	30 (42.25%)	

Table S3.3: Daily frequencies of individuals experiencing symptoms, activity limitations, and receiving visitors. Symptoms are split into six groups. Numbers represent the total number of individuals experiencing the symptom/limitation/visitors on that day, where the total number of respondents for each day is listed at the top of each section. Colors represent the percent of the population affected. Different color scales are used for symptom, limitation, and visitor presence in order to easily visualize the patterns.

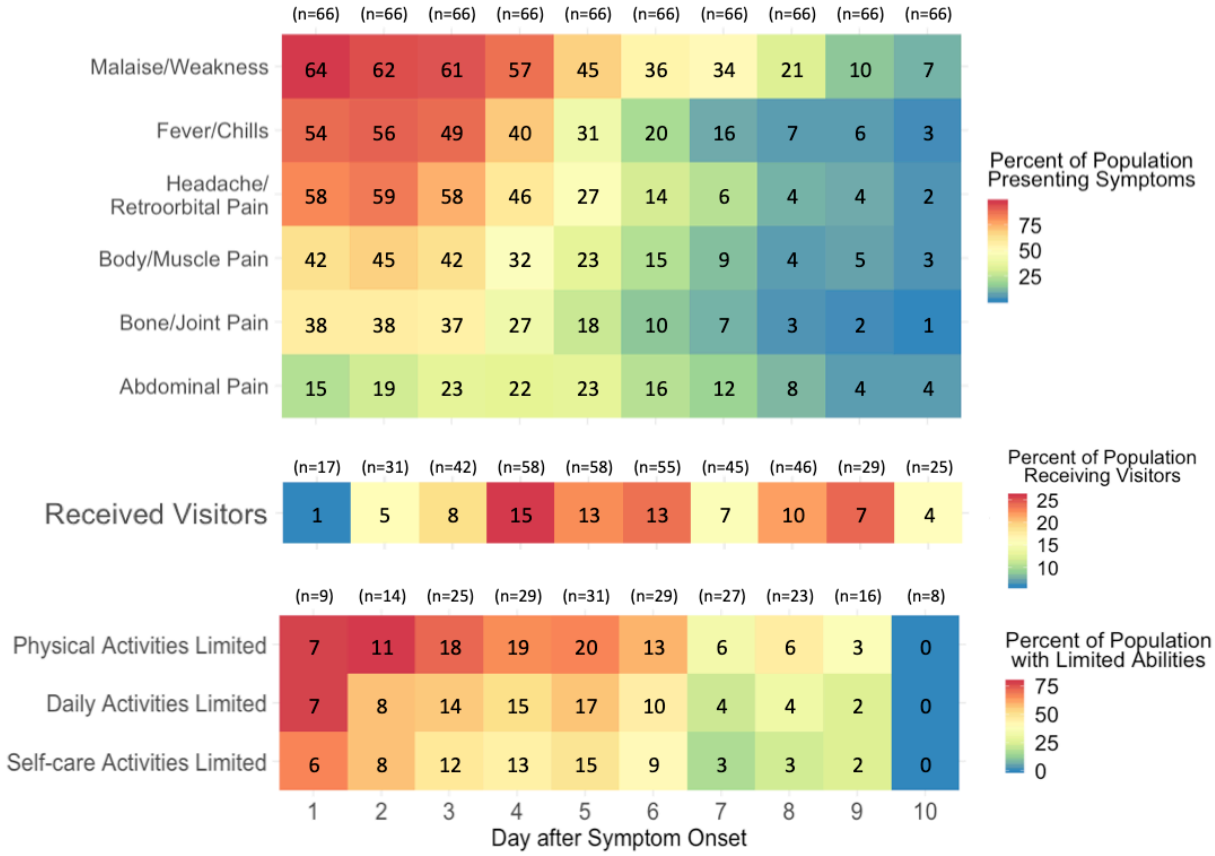


Table S3.4: Results of Fisher's Exact test for sex and age combinations. Tests were performed for whether caregiving was received, if the person who helped had their work affected, and whether helped around the house. Tests were also performed for whether or not visitors were received at some point during illness (* $p<0.05$, ** $p<0.01$, ***$p<0.001$).

Outcome Variable	Group 1	Group 2	p-value
Someone Helped	Female Adult	Male Adult	0.3
Someone Helped	Female Adult	Female Child	0.02*
Someone Helped	Female Adult	Male Child	0.06
Helper's Work Affected	Female Adult	Male Adult	0.2
Helper's Work Affected	Female Adult	Female Child	0.06
Helper's Work Affected	Female Adult	Male Child	0.02*
Helped Around House	Male Adult	Female Adult	0.2
Helped Around House	Male Adult	Male Child	0.08
Helped Around House	Male Adult	Female Child	0.08
Received Visitors	Male Child	Female Child	0.02*
Received Visitors	Male Child	Male Adult	0.2
Received Visitors	Male Child	Female Adult	0.07

Table S3.5: Results from likelihood ratio tests between pairs of logistic GLMs with various explanatory variables and response variable of whether or not caregiving was received. For each model, values are provided for the reduction in deviance compared to the null model, corrected AIC (AICc), change in AICc compared to the best fit model (ΔAICc), and model weight. The best-fit model is highlighted in red.

Predictor Variable(s)	Deviance	df	AICc	Δ AICc	Weight
Intercept		1	46.5	4.9	0.038
Sex	1.59	2	47.0	5.4	0.029
Age (<18)	7.02	2	41.6	0.0	0.442
Sex * Age	10.5	4	42.6	1.0	0.266
Maximum Number of Symptom Groups Present	7.87	6	50.0	8.4	0.007
Maximum Symptom Intensity Score	2.81	2	45.8	4.2	0.054
Number Housemates (<8)	3.18	2	45.4	3.8	0.065
Presence of Headache/Retro-orbital Pain	1.17	2	47.4	5.9	0.024
Presence of Body/Muscle Pain	0.333	2	48.3	6.7	0.016
Presence of Bone/Joint Pain	0.662	2	47.9	6.4	0.018
Presence of Abdominal Pain	0.010	2	48.6	7.0	0.013
Needed Help with Personal Care (QWB)	0.007	2	48.6	7.0	0.013
Needed Help with Daily Activities (QWB)	0.38	2	48.2	6.6	0.016

Table S3.6: Results from likelihood ratio tests between pairs of logistic GLMs with various explanatory variables and response variable of whether or not visitors were received. For each model, values are provided for the reduction in deviance compared to the null model, corrected AIC (AICc), change in AICc compared to the best fit model (ΔAICc), and model weight. The best-fit model is highlighted in red.

Predictor Variable(s)	Deviance	df	AICc	Δ AICc	Weight
Intercept		1	88.2	4.7	0.045
Sex	6.8	2	83.6	0.0	0.462
Age (<18)	0.522	2	89.9	6.3	0.020
Sex * Age	8.38	4	86.5	2.9	0.110
Maximum Number of Symptom Groups Present	0.06	2	90.3	6.7	0.016
Maximum Symptom Intensity Score	0.36	2	90.0	6.4	0.019
Number Housemates (<8)	0.32	2	90.1	6.5	0.018
Presence of Headache/Retro-orbital Pain	0.001	2	90.4	6.8	0.015
Presence of Body/Muscle Pain	0.121	2	90.3	6.7	0.016
Presence of Bone/Joint Pain	0.699	2	89.7	6.1	0.022
Presence of Abdominal Pain	1.04	2	89.3	5.8	0.026
Needed Help with Personal Care (QWB)	0.100	2	90.3	6.7	0.016
Needed Help with Daily Activities (QWB)	0.11	2	90.3	6.7	0.016
Visitors Received on Original (Day 0) survey	0.808	3	89.6	6.0	0.023

Table S3.7: Results from likelihood ratio tests between pairs of logistic GLMMs with various explanatory variables and response variable of whether or not visitors were received for each day of illness. For each model, values are provided for the reduction in deviance compared to the null model, corrected AIC (AICc), change in AICc compared to the best fit model (ΔAICc), and model weight. The best-fit model is highlighted in red.

Predictor Variable(s)	Deviance	df	AICc	Δ AICc	Weight
Intercept	226	2	229.9	4.0	0.053
Day of Illness	225	3	231.5	5.6	0.023
Sex	220	3	226.5	0.7	0.279
Age (<18)	225	3	231.5	5.6	0.024
Sex * Age	216	5	225.8	0.0	0.390
Number of Symptom Groups Present on Day	226	3	231.6	5.8	0.021
Symptom Intensity Score on Day	226	3	231.9	6.0	0.019
Number Housemates (<8)	226	3	231.9	6.0	0.019
Presence of Malaise/Weakness on Day of Illness	226	3	231.7	5.9	0.021
Presence of Fever/Chills on Day of Illness	226	3	231.9	6.0	0.019
Presence of Headache/Retro-orbital Pain on Day of Illness	226	3	231.6	5.7	0.022
Presence of Body/Muscle Pain on Day of Illness	225	3	231.4	5.6	0.024
Presence of Bone/Joint Pain on Day of Illness	225	3	231.5	5.6	0.023
Presence of Abdominal Pain on Day of Illness	226	3	231.9	6.0	0.019
Needed Help with Personal Care (QWB)	226	3	231.9	6.0	0.019
Needed Help with Daily Activities (QWB)	225	3	231.3	5.5	0.025

Table S3.8: Results from likelihood ratio tests between pairs of logistic GLMs with various explanatory variables and response variable of whether the ill individual had one or two caregivers. For each model, values are provided for the reduction in deviance compared to the null model, corrected AIC (AICc), change in AICc compared to the best fit model (ΔAICc), and model weight. The best-fit model is highlighted in red.

Predictor Variable(s)	Deviance	df	AICc	Δ AICc	Weight
Intercept		1	40.7	2.4	0.1159
Sex	0.032	2	42.8	4.5	0.040
Age (<18)	0.004	2	42.8	4.5	0.040
Sex * Age	4.69	4	42.6	4.4	0.043
Maximum Number of Symptom Groups Present	2.03	5	47.7	9.5	0.003
Maximum Symptom Intensity Score	0.78	2	42.0	3.8	0.059
Number Housemates (<8)	0.024	2	42.8	4..5	0.040
Presence of Headache/Retro-orbital Pain	0.445	2	42.4	4.1	0.050
Presence of Body/Muscle Pain	0.79	2	42.0	3.8	0.059
Presence of Bone/Joint Pain	0.107	2	42.47	4.4	0.042
Presence of Abdominal Pain	0.366	2	42.4	4.2	0.048
Needed Help with Personal Care (QWB)	4.55	2	38.2	0.0	0.386
Needed Help with Daily Activities (QWB)	1.29	2	41.5	3.3	0.076

Table S3.9: Results from likelihood ratio tests between pairs of logistic GLMs with various explanatory variables and response variable of whether the caregiver was a housemate or not. For each model, values are provided for the reduction in deviance compared to the null model, corrected AIC (AICc), change in AICc compared to the best fit model (ΔAICc), and model weight. The best-fit model is highlighted in red.

Predictor Variable(s)	Deviance	df	AICc	Δ AICc	Weight
Intercept		1	32.0	0.8	0.130
Sex	1.4	2	32.7	1.6	0.090
Age (<18)	2.95	2	31.2	0.0	0.196
Sex * Age	5.09	4	33.5	2.3	0.061
Maximum Number of Symptom Groups Present	5.90	5	35.1	3.9	0.028
Maximum Symptom Intensity Score	0.38	2	33.7	2.6	0.054
Number Housemates (<8)	0.353	2	33.8	2.6	0.054
Presence of Headache/Retro-orbital Pain	0.262	2	33.9	2.7	0.051
Presence of Body/Muscle Pain	0.055	2	34.1	2.9	0.046
Presence of Bone/Joint Pain	0.021	2	34.1	2.9	0.045
Presence of Abdominal Pain	1.72	2	32.4	1.2	0.106
Needed Help with Personal Care (QWB)	0.102	2	34.0	2.8	0.047
Needed Help with Daily Activities (QWB)	1.4	2	32.7	1.6	0.090

Table S3.10: Results from likelihood ratio tests between pairs of logistic GLMs with various explanatory variables and response variable of whether or not help was received in the form of money and things. For each model, values are provided for the reduction in deviance compared to the null model, corrected AIC (AICc), change in AICc compared to the best fit model (ΔAICc), and model weight. The best-fit model is highlighted in red.

Predictor Variable(s)	Deviance	df	AICc	Δ AICc	Weight
Intercept		1	88.5	4.9	0.048
Sex	0.855	2	89.8	6.1	0.025
Age (<18)	0.323	2	90.3	6.7	0.019
Sex * Age	1.25	4	93.9	10.2	0.003
Maximum Number of Symptom Groups Present	3.38	5	94.1	10.5	0.003
Maximum Symptom Intensity Score	0.04	2	90.6	7.0	0.017
Number Housemates (<8)	3.75	2	86.9	3.2	0.107
Presence of Headache/Retro-orbital Pain	0.074	2	90.6	6.9	0.017
Presence of Body/Muscle Pain	0.674	2	90.0	6.3	0.023
Presence of Bone/Joint Pain	0.031	2	90.6	7.0	0.017
Presence of Abdominal Pain	0.103	2	90.6	6.9	0.017
Needed Help with Personal Care (QWB)	4.1	2	86.6	2.9	0.128
Needed Help with Daily Activities (QWB)	1.25	2	89.4	5.7	0.031
Number Housemates (<8) + Needed Help with Personal Care (QWB)	9.2	3	83.7	0.0	0.544

Table S3.11: Results from likelihood ratio tests between pairs of logistic GLMs with various explanatory variables and response variable of whether or not help was received around the house. For each model, values are provided for the reduction in deviance compared to the null model, corrected AIC (AICc), change in AICc compared to the best fit model (ΔAICc), and model weight. The best-fit model is highlighted in red.

Predictor Variable(s)	Deviance	df	AICc	Δ AICc	Weight
Intercept		1	90.8	1.1	0.117
Sex	0.251	2	92.7	3.0	0.046
Age (<18)	2.52	2	90.4	0.7	0.142
Sex * Age	4.07	4	93.3	0.7	0.033
Maximum Number of Symptom Groups Present	3.48	5	96.3	6.6	0.008
Maximum Symptom Intensity Score	3.26	2	89.7	0.0	0.206
Number Housemates (<8)	0.612	2	92.3	2.6	0.055
Presence of Headache/Retro-orbital Pain	0	2	92.79	3.3	0.040
Presence of Body/Muscle Pain	0.875	2	92.0	2.4	0.063
Presence of Bone/Joint Pain	1.25	2	91.7	2.0	0.075
Presence of Abdominal Pain	0	2	92.9	3.3	0.040
Needed Help with Personal Care (QWB)	0.412	2	92.5	2.8	0.050
Needed Help with Daily Activities (QWB)	2.27	2	90.6	1.0	0.126

Table S3.12: Results from likelihood ratio tests between pairs of logistic GLMs with various explanatory variables and response variable of whether or not the helper's work was affected. For each model, values are provided for the reduction in deviance compared to the null model, corrected AIC (AICc), change in AICc compared to the best fit model (ΔAICc), and model weight. The best-fit model is highlighted in red.

Predictor Variable(s)	Deviance	df	AICc	Δ A5.4ICc	Weight
Intercept		1	74.0	5.3	0.021
Sex	2.1	2	74.1	5.4	0.020
Age (<18)	2.24	2	73.9	5.2	0.022
Sex * Age	4.6	4	76.1	7.4	0.008
Maximum Number of Symptom Groups Present	6.63	5	756.4	7.7	0.006
Maximum Symptom Intensity Score	7.37	2	68.8	0.1	0.283
Number Housemates (<8)	0.023	2	76.2	7.5	0.007
Presence of Headache/Retro-orbital Pain	1.17	2	75.0	6.3	0.013
Presence of Body/Muscle Pain	0.872	2	75.3	6.6	0.011
Presence of Bone/Joint Pain	6.17	2	70.0	1.3	0.155
Presence of Abdominal Pain	5.82	2	70.4	1.7	0.130
Needed Help with Personal Care (QWB)	2.02	2	74.2	5.5	0.019
Needed Help with Daily Activities (QWB)	0.084	2	76.1	7.4	0.007
Presence of Bone/Joint Pain + Presence of Abdominal Pain	9.68	3	68.7	0.0	0.298

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Chapter 4: The impact of symptomatic mobility change on dengue virus transmission

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Introduction

The rate at which humans encounter vectors (mosquitoes, ticks, bugs) is a driver of vector-borne disease transmission dynamics [1, 2]. Human-vector contacts can be influenced by myriad of factors, including the vector's host-seeking behavior [3, 4], the host's biting attractiveness [5-8], and the spatial distribution/density of both hosts and vectors [9-12]. Variations in some or all of these factors can lead to heterogeneous exposure, where certain individuals have higher contact rates with vectors than others [13-15]. The epidemiological consequence of such uneven distribution of human-vector contacts could be significant, as long as it results in key encounters where a large number of vectors are infected [2]. Therefore, individual contribution to transmission is influenced by not only how many bites are received, but also which vectors the bites are from and whom those vectors encounter next [16].

Given the central epidemiological role of mixing between hosts and vectors, there is a need for better quantification of its frequency and temporal variability, as its epidemiological role depends on the coupling among human (behavior, immunity, etc.), vector (dispersal, longevity, etc.), and environmental heterogeneities [17]. Theoretical and simulation models have been used to assess the role of such factors. One such model focuses on how heterogeneous exposure to vectors, poor mixing, and finite host numbers can determine the spatial scale of transmission [16]. Poor mixing can lead to infections being clustered in groups of closely

connected individuals, as observed in the clustering of infections among socially connected individuals [18-20]. This association between human behavior and mixing is of particular relevance for dengue and other *Aedes*-borne viruses (dengue, chikungunya, Zika) [1, 21-23], for which house-to-house human movement has been shown to underlie spatial patterns of incidence [18, 20, 24].

Dengue is an acute illness caused by any of four immunologically related viruses in the family *Flaviviridae* and transmitted by *Aedes* spp. mosquitoes (primarily *Aedes aegypti*). Prevalent in the tropics and subtropics, it is the most important mosquito-borne viral disease of humans worldwide [25]. Symptoms associated with dengue (acute fever, headache, musculoskeletal pain, and rash) occur in a small proportion of cases, while the other 70% of cases experience either very mild symptoms (inapparent) or no symptoms (asymptomatic) [26-28]. Recently, it was empirically shown that human mobility patterns change throughout symptomatic (febrile) dengue infection, with individuals visiting fewer locations and staying at home more [29-31]. While disease-driven mobility changes significantly influence the spread of directly transmitted pathogens, they have not yet been included in theoretical models of dengue virus (DENV) transmission [32, 33]. For DENV, the impact of movement changes on an individual's mosquito contacts and onward transmission will likely depend on the distribution of mosquitoes at their home and across the rest of their activity space [17, 21, 34]. At a population level, human mobility changes could affect pathogen spread in a variety of ways depending upon which individuals in the population experience symptoms and change their mobility and potential exposure to *Aedes aegypti* mosquitoes.

For those DENV-infected individuals who experience symptoms, infectiousness tends to peak during the first few days after symptom onset when mobility is restricted and most human-

mosquito contacts are occurring at the individual's home [35-37]. There are, however, a few days before symptom onset when individuals have sufficient viremia levels to be infectious and have not yet changed their movement patterns [35, 37]. A recent theoretical model of within-host viral dynamics estimated that 24% of an individual's onward transmission results from mosquito bites during this presymptomatic phase [38]. We hypothesize that the presymptomatic period could have a significant change in its contribution to transmission when accounting for the decreased mobility levels during the rest of the infectiousness period. To test this hypothesis, we examined the role of disease-driven mobility change in DENV transmission by theoretically exploring how day-to-day changes in a symptomatic individual's mobility and human-mosquito contacts, combined with heterogeneous attractiveness to mosquitoes, may impact population-level dynamics of DENV transmission.

Methods

Original Model Framework

Our model builds on a previously published mathematical framework that describes where and when human-mosquito contacts occur based on fine-scale human and mosquito mobility [16]. In the original framework, a set of houses, {f}, and larval sites, {l}, were arranged on a disc. Each house was assigned a number of residents equal to 2 plus a Poisson random variable ($\lambda = 3.5$), creating a two-person minimum per household. In order to assign the numbers of mosquitoes/larvae at each house/larval site, mosquito movement and reproduction were simulated for a total of 200 time steps, with the first 100 acting as a burn-in period. Counts of mosquitoes and larvae at each location were averaged over the second 100 time steps, providing the 'equilibrium' values. Poorly mixed mosquito movement was characterized by matrices L and

F, giving the distance-based probabilities of an adult female mosquito moving from any house to any larval site, and vice versa [16]. Human mobility was also determined using distance-based probabilities, with the proportion of time each individual spent at each household documented in the H matrix. Each row of the H matrix described where a single host spent time and each column detailed all of the individuals spending time at a single household. Each individual was also assigned a biting suitability score (which accounts for biting attractiveness, avoidance behavior, and defensive behavior) using a random exponential draw with rate based on empirical biting data [39]. Based on the mobility matrix, H, and biting suitability scores, a U matrix was calculated to be the distribution of mosquito bites on all individuals at each house, where each row gave the distribution of bites on all hosts at a single household and each column depicted the bites distributed on a single individual across all households. A stochastic transmission model was layered on top of this framework, which included a household-level SEI model for mosquitoes and an individual-based SEIR model for hosts (**Figure S4.1**). Individuals transitioned through multiple exposed (E) sub-stages, totaling the duration of pathogen latency in terms of feeding-cycle-length time steps. Hosts also transitioned through multiple infectious (I) sub-stages, until a random number draw from a probability distribution transitions them into the recovered (R) stage. Transmission was initiated by moving a single human into the first infectious (I) stage.

Model simulations had discrete time steps to capture the length of a mosquito feeding cycle (~3 days). During each time step, hosts would allocate their time at houses based on H. The mosquitoes at each house would take blood meals from possible hosts based on U matrix probabilities and move to a larval site based on L probabilities. Eggs were laid based on a Poisson distribution with mean equal to number of adult females at the site multiplied by average

egg batch size. Adult mosquitoes then moved to a house searching for their next blood meal based on F probabilities. During each time step, mosquito larvae also progressed through a set number of stages based on site-specific density dependence until emerging into adult mosquitoes. For both mosquitoes and humans, each time step also accounted for progression through illness.

Updated Model Description

Our model was set up in a similar manner as the original model with a few modifications to enable us to address our motivating questions. Parameters with set values were defined (Table 1), then houses and larval sites were placed on a disc, humans and mosquitoes were assigned locations, and mosquito movement probabilities were determined (**Figure 4.1a**) (**Table 4.2**). Rather than defining human mobility patterns based on distance, we generated a socially structured human mobility matrix for each of 200 simulation runs (**Figure 4.1b**). First, a random social network with household structure was constructed using the "configuration model" [40]. Each individual was assigned a number of "half-edges" (their degree) from a Poisson distribution with rate $\lambda = 2.8$, the mean number of residential locations visited in a data set described by Perkins et al. [34]. Fifteen percent of individuals were given no half-edges and did not move from their home [20]. Half-edges were then paired uniformly at random to form the edges of the social network, making sure there were no self-loops, multiple edges, or loops within houses (**Figure 4.1b**). This random network was represented as an |h|-by-|h| adjacency matrix SN, where |h| is the size of the set of hosts {h}. A separate |h|-by-|f| presence/absence matrix, Homes, is constructed, where $Homes_{i,j}$ denotes whether or not the i^{th} host lives at the j^{th} residential site.

Multiplying the SN and Homes matrices produced an |h|-by-|f| matrix, HM, denoting which residential sites an individual will visit based on their social network (note that this matrix

was not presence/absence, as when the i^{th} host was socially connected to multiple individuals at the j^{th} residential site, $HM_{ij} > 1$) (**Figure 4.1b**). This matrix was used to populate the human mobility matrix, H, which calculated the proportion of time each host spent at each household in the same way as the original model (**Figure 4.2**). Each host, i, spent 50% of their time at home, j, ($H_{ij} = 0.5$) and divided the remaining 50% of their time into the houses visited in HM (When $HM_{ij} > 1$, as mentioned above, a proportionally larger amount of time was allocated at that residential location). For the 15% of individuals, i, who had no mobility outside their home*, j,* $H_{ij} = 1$. Based on this implicit mobility matrix and each individual's biting suitability, the |f|-by-|h| matrix U was created to describe the distribution of mosquito bites on all individuals at each house, as in the original model [16].

The overlaid transmission model was similar to the original version; however, only one exposed (E) stage was included (based on pathogen latency of DENV) and the maximum number of infectious sub-stages was 5 ($I_1 – I_5$). Rather than use a single set value for human infectiousness, values were chosen for each of these sub-stage ($I_1 – I_5$) based on data of mean daily probability of mosquito infection for individuals with primary infections [38] (**Figure 4.3**). For each 3-day infection time point in our model, we averaged these mean infectiousness values (Table 3). The updated transmission model also defined the first time step in the human infectiousness stage (I_1) as the "presymptomatic period" and all subsequent infectious time steps ($I_2 – I_5$) as the "symptomatic" period, where the presymptomatic period contributed to 25% of infectiousness for individuals who progressed through all five infectiousness stage ($I_1 – I_5$) before recovery.

After the model framework was set-up, at each time step of the simulation: hosts allocated their time at houses based on H; mosquitoes moved to larval sites, laid eggs, had

advancement in larval stages, moved back to houses, and took blood meals in the same format as the original model. Both hosts and mosquitoes progressed through incubation (E), infectiousness (I), and (for hosts) recovery (R) (**Figure 4.3**). Virus transmission occurred from infectious hosts to susceptible mosquitoes and from infectious mosquitoes to susceptible hosts. At the end of each time point, host mobility was changed for those hosts who were symptomatically infectiousness.

Host Mobility Changes**:** Two different scenarios were considered to examine mobility changes: (1) no symptomatic movement change and (2) movement change throughout symptomatic infection. For scenario (1) no changes were made to the mobility matrix. For scenario (2), host mobility changes occurred at each 3-day time step of symptomatic infection based on recently published data on human mobility throughout symptomatic infection [31] (**Table 4.3**) (**Figure S4.2**). As data from Schaber et al. [31] were grouped as days 1-3, 4-6, and 7-9 after symptom onset, they corresponded to the I_2, I_3, and I_4 stages here. When individuals were in the first three days after symptom onset, they were significantly more likely to spend *all* of their time at home and visit *no* places. Accordingly, when an individual transitioned into symptomatic infection in the simulation (I_2), their movement was completely stopped (HM[i,] = 0) and all time was spent at home (HM[i, home] = 1). During days 4-6 after symptom onset (sub-stage I_3), individuals spent an average of 76% of time at home and visited approximately 1/3 of normally frequented places. On days 7-9 after symptom onset (sub-stage I_4) time at home and fraction of places being visited averaged 69% and 2/3, respectively. Therefore, we set the time at home to be 80% (70%) for the I_3 (I_4) stage and had individuals visiting 1/3 (2/3) of their originally frequented houses (**Table 4.3**). The order in which houses were added back into an individual's movements in stages I_3 and I_4 was determined by random sample where a house's probability of being chosen

was weighted by its original HM value. This made it more likely that individuals would resume visiting houses where they were socially connected to multiple residents. When individuals reached the I_5 stage (days 10-12 after symptom onset), movement patterns and time at home were reset to original values (**Table 4.3**). At the end of each time step, once these movement changes were updated for all symptomatic individuals in the HM matrix, the H and U matrices were recalculated as described above. We also considered a scenario where only 30% of individuals (chosen from a random binomial draw) had symptomatic infection with mobility change in order to determine whether the presence of asymptomatic infections had an impact on symptomatic mobility changes.

Two other scenarios of interest that we accounted for were (1b) no movement change with no presymptomatic period and (2b) movement change throughout symptomatic infection with no presymptomatic period. For these scenarios the first stage of infectiousness (I_1), the presymptomatic period, was removed and individuals became immediately symptomatic with infectiousness and movements corresponding to the $I_2 – I_5$ stages.

Model Outputs**:** Previously, multiple metrics were created to explore how mobile hosts and mosquitoes contribute to pathogen dispersal [16]. Of particular interest was the matrix R, which corresponded to the concept of effective reproductive number. This matrix gave the probability that a primary infection in one host will result in a secondary infection in some other host, where summing each row provided the number of expected secondary infections arising from a single individual. The B matrix was also utilized to measure the expected number of bites per time step on each host at each blood-feeding habitat (house). Each row of B provided the number of expected bites on a single individual at all households and each column gave the expected number of bites occurring on all individuals at a single household during one time step. At the

population level, dynamics were examined using the simulation outputs of cumulative number of infections at each time step and number of infectious hosts at each time step. We utilized these original metrics and created versions that accounted for mobility change.

The B matrix could be used as a way to examine heterogeneity in human-mosquito contact rates, not only across hosts/locations, but also throughout an individual's infectiousness period. As this metric was based on the distribution of bites across hosts at each site (U), and therefore affected by the human mobility matrix (H), a list of B matrices was created to measure biting pre-epidemic (with normal movements) and during each time step of infectiousness. Within each simulation, B_{norm} was calculated for all individuals before infection spread began. During disease spread, B_i[k,] was recorded for each host, k, at each infectiousness sub-stage (I_1 – I_5), i. This set of matrices gave us the expected number of mosquito bites on each host at each house throughout infectiousness/mobility changes.

The previously-derived version of the R matrix, referred to as R_{norm}, measured the probability of host l receiving one or more secondary infectious bites arising from primary infectious host, k. This accounts for the primary infectious host transmitting the virus to a susceptible mosquito (the primary infectious bite) and that newly infectious mosquito then transmitting the virus to a susceptible host (the secondary infectious bite). The R metric was slightly adjusted to account for time-step-specific infectiousness where

$$R_{k,l} = 1 - e^{-bV(c_1 + c_2 + c_3 + c_4 + c_5)}$$

with c_i values representing an individual's time-step-specific infectiousness values. The V matrix gave the number of expected secondary bites on each host arising from primary bites on all other hosts over one time step, where each row described the number of expected secondary bites on all hosts from primary bites on a single individual and each column provides the number of

expected secondary bites received by a single individual from primary bites on all other hosts during one time step. Because the U matrix affected the V matrix, host mobility change was accounted for by creating a set of matrices, V_i, for each sub-stage of infectiousness ($I_1 – I_5$). When host k was infectious in the simulation, their V_i[k,] values were recorded for each I sub-stage ($I_1 – I_5$). At the end of the simulation run a matrix referred to as $R_{movement}$ was created, where

$$R_{movement} = 1 - e^{-b(V_1c_1 + V_2c_2 + V_3c_3 + V_4c_4 + V_5c_5)}.$$

In order to examine the importance of where the primary infectious bite occurs on host k, we also divided $R_{movement}$ into two separate matrices, $R_{movement}$ (home), and $R_{movement}$ (other houses). This was done by calculating V_i(home) and V_i(other houses), which derived the number of expected secondary bites on each host arising from primary bites that occur at each time point of infectiousness, i, on all other hosts *at their home* and *everywhere but their home*. These V_i (home) and V_i (other houses) matrices were then used to derive $R_{movement}$ (home) and $R_{movement}$ (other houses), respectively. Similarly, R_{norm} was divided into R_{norm} (home) and R_{norm} (other houses) in order to compare the effect of where a primary infectious bite occurred when not accounting for mobility.

A new metric that focused on the number of mosquitoes present in each individual's home was also considered. The number of mosquitoes in each individual's home was recorded at the beginning of the simulation run (pre-epidemic) and at each time point of infectiousness for that individual. For each scenario a list was output with all of these metrics for each of 200 simulation runs.

Data Analysis:

Analysis of simulation outputs had three main objectives: Determining the effects of disease-driven mobility changes on (1) population-level outbreak dynamics, (2) onward transmission, and (3) human-mosquito contacts.

For the first objective, determining the effects of mobility change on population-level disease dynamics, we compared four scenarios: no mobility change; no mobility change and no presymptomatic period; mobility change; mobility change and no presymptomatic period. The effect of mobility changes could be determined by comparing the "no mobility change" and "mobility change" scenarios. To determine the role of the presymptomatic period when mobility changes occur, we compared the difference in 'mobility change, presymptomatic' and 'mobility change, no presymptomatic' to the difference in 'no mobility change, presymptomatic' and 'no mobility change, no presymptomatic' in order to account for the baseline effect of removing one period of infectiousness (the presymptomatic period).

The number of infectious hosts at each time step was used to calculate the maximum infection prevalence, the time to maximum prevalence, and the length of the epidemic (when the number of infectious hosts was 0 without increasing again). The cumulative number of infections at each time step was utilized to record the total percent of the population infected in an epidemic, as well the time point when the percent of cumulative infections reached 10% and 65%. For the remaining two objectives, we focused our analysis on the scenario were a presymptomatic period is present and mobility changes were occurring. In order to determine the effect of these mobility changes on onward transmission, the R_{norm} and $R_{movment}$ matrices were utilized. Row sums of $R_{movement}$ and R_{norm} gave the expected number of secondary infectious bites arising from all primary bites on an individual host either with or without accounting for movement changes. Similarly, row sums of $R_{movement}$(home), $R_{movement}$(other houses),

R_{norm}(home), and R_{norm}(other houses) determined the expected secondary bites arising from an individual due to only primary bites at their home or only primary bites at other houses (with and without movement changes). The distributions of $R_{movement}$ and R_{norm} values were compared and R_{change} was calculated to examine how accounting for mobility affects an individual's R-value.

Possible predictor variables for onward transmission were examined using generalized additive models (GAMs) [41]. Best-fit models were determined for $R_{movement}$, $R_{movement}$(home), R_{change}, and R_{change}(home). R_{change} values were analyzed both as raw numbers and as percent change relative to R_{norm} values. The variables considered as predictors were an individual's biting suitability score, the number of mosquitoes in their home, the percent of expected mosquito bites that occur at their home pre-exposure, and the number of places they visit pre-exposure. Best-fit was determined with ΔAICc and the percent of deviance explained by each model.

For the third objective, we calculated the expected number of mosquito contacts for each individual pre-exposure and at each stage of infectiousness (I_1 – I_5). Expected counts were calculated as row sums of B_{norm} and each B_i matrix. For all individuals that experienced infection, the change in number of expected mosquito contacts was calculated for each infectiousness stage, as compared to pre-exposure. Percent change was also calculated to account for variation in healthy mosquito contact counts

$$\frac{B_i - B_{norm}}{B_{norm}}.$$

We examined the importance of these variations in healthy mosquito contacts by comparing those with the top 20% of expected contacts pre-exposure to the rest of the population (bottom 80%). B matrices were also used to determine the percent of an individual's mosquito contacts that occurred at their home. Generalized additive models (GAMs) were examined for

change in expected mosquitoes contacts, both as a number and a percent. Predictors and methods for finding best-fit models are as mentioned above. All statistical analyses were performed in R 3.3.0 statistical computing software.

Results

Epidemic Dynamics

Among the 200 simulations run for each scenario, outbreaks occurred in 76% and 53.5% when mobility changes were and were not considered, respectively (**Table 4.2**). When the presymptomatic period was removed, only 55% and 39.5% of simulation led to outbreaks with and without mobility change. In the simulations where outbreaks did not occur, the infection only spread to a few people (maximum of 20) before leaving the population. For simulations leading to epidemics, the inclusion of symptomatic mobility change increased the time to peak infection by 8% (9 days) and increased the length of the epidemic by 5% (13.5 days) to reach the epidemic's end (**Table 4.2**) (**Figure 4.3**). These delays had minimal effects on the percent of the population infected at peak prevalence and overall, with average changes of -0.7% and 0.2%, respectively (**Table 4.2, S4.1**). Removing the presymptomatic period had minimal effects on epidemic timing regardless of whether mobility changes were included, with epidemic length decreasing by less than 3 days, on average (**Table 4.2**) (**Figure 4.3**). Without mobility change, peak prevalence decreased by an average of 0.9% and total percent of individuals infected decreased by an average 2.4% (**Table 4.2, S4.3**). In the presence of symptomatic mobility changes, removal of the presymptomatic period caused a 5.7% decrease at peak prevalence and a 4% decrease in the percent of population infected, on average (**Table 4.2, S4.3**) (**Figure 4.3**).

Onward Transmission

At a population level, the distributions of onward transmission (R) values were 5.4 (± 5.1 SD) and 5.9 (± 4.8 SD) without and with mobility change, respectively (**Table 4.3**) (**Figure S4.3**). At an individual level, however, the average change in onward transmission when mobility changes were considered (R_{change}) was -15.1% (± 29.9 SD) and the average change in onward transmission for only primary bites at home (R_{change}(home)) was 39.7% (± 22.7 SD) (**Table 4.3**) (**Figure S4.4**). Further, while R_{norm} and $R_{movement}$ had similar values, primary bites at home and at other locations seemed to contribute an equal amount to onward transmission for R_{norm}, whereas primary bites at home had a much larger contribution for $R_{movement}$ (**Table 4.3**) (**Figure 4.4a**). The majority of secondary infectious bites contributing to transmission occurred at other houses for both R_{norm} and $R_{movement}$ (**Table 4.3**) (**Figure 4.4b**).

The best-fit model for all of the onward transmission response variables was one accounting for an individual's biting suitability score, the number of mosquitoes in their home, the percent of bites expected to occur at home pre-exposure, and all possible interactions between these three (**Table S4.4-S4.7, S4.9**). There were, however, reduced models that provided more straightforward trends to examine. For example, for models of onward transmission ($R_{movement}$) with single predictor variables, biting suitability score and number of mosquitoes at home pre-exposure explained 32.3% and 27.7% of deviance, respectively, whereas percent of bites expected at home pre-exposure only explained 9.3% of deviance (**Table S4.5**). Further, 74.8% of deviance is explained in a model containing biting suitability, number of mosquitoes at home, and their interaction, which is only 2.9% less than the best-fit model. Independently, larger numbers of mosquitoes at home and higher biting suitability score both increased the expected onward transmission value (**Figure 4.5**). Those individuals with larger values of both saw an extra increase in expected onward transmission due to the interaction term,

whereas those with high mosquito numbers and a low biting suitability score saw a decrease in their expected effect (**Figure 4.5**). The effect was visible in the predicted values of onward transmission, where increasing biting suitability score from 0 to 1 only increased predicted onward transmission by 5 when there was a low mosquito count at home, compared to an increase of 30 for those with high mosquito density at home (**Figure 4.5**).

Predictions of onward transmission without mobility change included (R_{norm}) were also dependent on the interactions between biting suitability, number of mosquitoes present at home, and percent of bites expected at home. Including a variable for the total number of mosquitoes in all the houses an individual visited pre-exposure did not increase the fit of models (**Table S4.4**). When an individual's R_{norm} value was accounted for, the percent change in onward transmission due to mobility inclusion (R_{change}) could be predicted by the percent of bites expected to occur at home pre-exposure with 80.50% of deviance explained (**Table S4.7**). Accounting for the other two variables and the interaction terms only increased explained deviance by 3.4% (**Table S4.7**). When the percent of bites expected to occur at home pre-exposure was below 42%, there was a predicted decrease in onward transmission, whereas those with greater than 42% of bites expected at home pre-exposure saw increases in onward transmission when mobility was accounted for (**Figure 4.6a**). The notable exception to this monotonically increasing effect was the tempered increase in onward transmission for those who received their pre-exposure bites almost exclusively at home (**Figure 4.6a**). When examining the change in onward transmission only from primary bites at home (R_{change}(home)), a majority of the deviance was explained in a model with percent bites expected at home pre-exposure as well as biting suitability score, where individuals with low biting suitability scores were predicted to have the biggest percent increases in onward transmission when accounting for mobility (**Table S4.7**) (**Figure 4.6b**). When both

variables were considered, the change in onward transmission from primary bites at home only was predicted to be positive for all individuals, with the biggest percent increase for those with low biting suitability scores and a small percent of bites at home pre-exposure and the most tempered increase for those with almost all of their expected bites occurring at home pre-exposure (**Figure 4.6b**). If R_{change} was examined as a raw number rather than a percent change, all three variables and their interaction terms were needed to achieve a good model fit (**Table S4.6**).

Human-Mosquito Contacts During Illness

At the population level, the distribution of expected mosquito contacts appeared to be similar throughout symptomatic mobility (**Table S4.8**) (**Figure S4.5**). When examining the change in an individual's expected contacts at each time point of symptoms, however, 57% of individuals had a decrease in expected contact and 38% had an increased (**Table 4.4**) (**Figure S4.7-S4.8**). Further, of those individuals who received the top 20% of expected mosquito contacts pre-exposure, 24% had a large enough decrease in mosquito contacts on the first three days after symptom onset to no longer be in the top 20% when symptomatic (**Figure S4.6**).

The percent change in expected mosquito contacts from pre-exposure to the first three days after symptom onset was best explained by a GAM including biting suitability score, number of mosquitoes at home pre-exposure, and percent of bites expected at home pre-exposure, as well as their interactions, which explained 93% of deviance (**Table S4.9**). The model with only a term for percent of bites expected at home pre-exposure, however, was able to explain 92% of the deviance (**Table S4.9**). The effect of percent bites at home on percent change in expected mosquito contacts was very similar to the effect on percent change in onward transmission. Those with less than 42% of bites at home pre-exposure were predicted to have

decreases in expected contacts on the first three days of symptoms while those with greater than 42% of bites at home pre-exposure were predicted to see increases in expected contacts (**Figure 4.7**). Individuals who received none of their bites at home pre-exposure were expected to have the largest percent decrease, whereas those who received around 90% of their bites at home pre-exposure had the largest percent increase (**Figure 4.7**). If change in expected mosquito contacts was examined as a raw value rather than a percent change, all three variables and their interactions were needed to provide an accurate prediction and explain a large amount of the deviance (**Table S4.9**).

For the scenario where only 30% of cases experienced symptoms (and symptomatic mobility change), the expected values and relative changes for onward transmission and human-mosquito contacts had similar dynamics as in the case above where all individuals were symptomatic (**Table S4.10-S4.17, Figure S4.9-S4.15**).

Discussion

Transmission of DENV is highly focal at the household level, likely due to the mobility and biting behaviors of *Ae. aegypti* [23, 42-44]. Fine-scale human mobility has been shown to expand this spatial scale and cause transmission to be characterized by human-mosquito contacts at an individual's home as well as the other houses they routinely visit (their activity space), generating variation in exposure to mosquitoes [18, 20, 21, 30, 45]. This importance of both primary bites at home and at other houses in contributing to onward transmission can be seen in the distribution of R_{norm} values when mobility changes are not included. While this may hold true for the 70% of cases with inapparent infection, individuals with symptomatic infection drastically change their movements during infectiousness [31]. These changes in mobility make

an individual's household mosquitoes contacts significantly more important for determining their onward transmission potential, with the activity space playing a severely diminished role. This shift in where mosquito contacts occur when an individual is infectious can lead to either increased or decreased contact rates and onward transmission, largely based on what percent of mosquito contacts were already expected to occur at home before mobility change.

An individual's biting suitability has been previously identified as an important determinant of their onward transmission potential [1]. While this held true in our analysis, we found the effect to be dependent on the density of mosquitoes in an individual's home. Those with only a few mosquitoes in their home could go from lowest to highest biting suitability score and cause 5 more secondary infections, whereas those with many mosquitoes in their home could cause 30 more secondary cases. Indeed, individuals with low values in either biting suitability score or number of mosquitoes at home were predicted to have low onward transmission, partially due to the interaction effect of these two variables (**Figure 4.5**).

While an individual's biting suitability cannot be changed, the number of mosquitoes in their home can, which has significant implications for disease control. While reducing household mosquitoes would be predicted to decrease onward transmission for all individuals, the effect could be particularly drastic for those with high biting suitability given the synergistic effect of the two factors on expected transmission. Further, those with a small number of mosquito bites expected in their homes are predicted to see a decrease in onward transmission potential when symptomatic mobility changes are accounted for.

One limitation of our study was the lack of an empirical social network to accurately parameterize our model framework. However, using a random graph accounted for the inhomogeneous nature of social interactions while still allowing conclusions to be generalized to

multiple locations. Further, by wiring a new random social network at the beginning of each simulation, it's unlikely that outcomes will be caused by specific artifacts of the network structure. The model was also limited by its size, being representative of a neighborhood rather than an entire city. However, given that the most significant effects were seen at the individual level (rather than the population-level), increasing the number of houses in the framework would likely not have a drastic impact. While this model framework allowed for many different metrics to be examined, there were limitations in what could be calculated from simulations due to the stochastic nature. Further research should focus on possible advancements of the model and the methods used to analyze the simulations.

There are numerous factors that can contribute an individual's onward transmission potential. In order to better understand the complex dynamics of disease transmission, we developed a framework that examines the contribution of multiple heterogeneous factors, both individually and in relation to each other. In particular, the coupling between mobility and symptom severity was empirically parameterized to better understand its role in disease dynamics. Symptomatic mobility change can have a significant impact on the relationship between biting suitability, density of mosquitoes, and location where the majority of mosquito contacts are occurring, leading to a spectrum of changes in expected mosquito contacts and onward transmission potential. The interconnectedness of these factors may have an effect on the relative contribution of symptomatic individuals to overall epidemic transmission dynamics.

Tables

Table 4.1: Parameters that Vary by Infectiousness Stage. Values provided for individuals when susceptible, and at each sub-stage of infectiousness based on data from [31, 38].

Stage of infectiousness	S	I_1	I_2	I_3	I_4	I_5
Day of Symptoms	– – –	Presymptomatic	Days 1-3	Days 4-6	Days 7-9	Days 10-12
Infectiousness	– – –	0.4	0.7	0.4	0.1	0.01
Time at home (%)	50%	50%	100%	80%	70%	50%
Fraction of original houses being visited	1	1	0/3	1/3	2/3	1

Table 4.2: Infection Prevalence Based on Presence of Presymptomatic Period and/or Mobility Changes. Infection prevalence data were analyzed from four scenarios: (1) no mobility change occurred and the presymptomatic period was present, (2) no mobility change occurred and no presymptomatic period was present, (3) mobility change occurred and the presymptomatic period was present, and (4) mobility change occurred and no presymptomatic period was present. For each scenario, the average time point was listed for when infection prevalence reaches its maximum and reaches 0% at the end of epidemic. The percent of the population infected during maximum infection prevalence was also listed, as well as the number of simulations where an outbreak occurred. Time steps values were converted to days (1 time step = 3 days).

	Simulations Where Outbreak Occurred (of 200)	Maximum Infection Prevalence (%)	When Maximum Prevalence Occurred (days)	Length of Epidemic (days)
No Changes	107 (53.5%)	19.8 (0.8)	112.5 (11.1)	252.9 (24.3)
No Changes, No Presymptomatic	79 (39.5%)	18.9 (0.8)	112.2 (14.1)	255.9 (26.4)
Mobility Changes	152 (76%)	19.1 (0.7)	121.5 (13.8)	266.4 (26.1)
Mobility Changes, No Presymptomatic	110 (55%)	13.4 (0.7)	124.2 (13.5)	268.8 (25.2)

Table 4.3: Average R Values With and Without Mobility Change and Change in R due to Mobility Change Inclusion. R_{norm} values were calculated using an individual's healthy movement patterns, while $R_{movement}$ values accounted for changes in mobility throughout infectiousness. Changes in R-values due to mobility inclusion were calculated for each individual as a raw number and as a percent of R_{norm} value. Overall R-values were listed, as well as R-values based on only primary bites occurring at home or at other houses.

	Mean (sd) Onward Transmission		Mean (sd) Change in Onward Transmission with Movement Changes	
	R_{norm}	$R_{movement}$	(#)	(%)
1° bites at home	2.3 (2.7)	4.3 (4.2)	1.0 (1.1)	39.74 (22.67)
1° bites at other houses	2.2 (2.6)	1.1 (1.2)	-1.9 (1.9)	-62.28 (9.13)
2° bites at infectious individual's home	0.3 (0.4)	0.6 (0.7)	0.1 (0.2)	31.86 (35.59)
2° bites elsewhere	5.0 (4.7)	5.2 (4.2)	-1.5 (3.2)	-17.1 (28.97)
Total	5.4 (5.1)	5.9 (4.8)	-1.1 (2.5)	-15.14 (29.94)

Table 4.4: **Average Change in Expected Mosquito Bites for Each Infectiousness Sub-stage When Symptomatic Mobility Change is Occurring ($I_2 - I_4$), Separated Based on Expected Bite Values Pre-exposure.** Average changes are given both as raw numbers and percent change relative to number of expected bites pre-exposure.

	Top 20% bites pre-exposure		Bottom 80% bites pre-exposure	
	(#)	(%)	(#)	(%)
Days 1-3 after symptom Onset	-0.9 (3.8)	-13.0 (48.9)	-0.2 (0.7)	-17.5 (51.0)
Days 4-6 after symptom Onset	-0.3 (2.7)	-5.6 (37.1)	-0.1 (0.5)	-8.7 (38.1)
Days 7-9 after symptom Onset	-0.1 (1.6)	-1.6 (22.1)	-0.1 (0.3)	-4.9 (23.2)

Figures

Figure 4.1: Diagram with Setup of Model Framework for Each Scenario and Each Simulation Run. (a) For each scenario, (i) houses and larval sites are placed on a disc, humans are assigned to each house, and mosquitoes are assigned to each house/larval site. (ii) Then, distance-based mosquito mobility matrices are created with the probabilities of mosquitoes moving from any house to any larval site (L) and any larval site to any house (F). (b) For each of 200 simulation runs, (i) a random social network (SN) is generated for humans by assigning each person a degree (where 15% spend all of their time at home and have a degree of 0), then randomly matching humans to each other while avoiding connections between members of the same household. (ii) Using information on social network contacts and where each individual lives, (iii) a human movement matrix, HM defines which houses individuals visit, weighted by the number of social network contacts that live there. Using this mobility data, a matrix H is created, which defines the proportion of time an individual spends at each house. Fifty percent of time is spent at home and 50% of time is split between social contacts' houses based on the edge weights in HM. (c) Example of the human mobility network (H) configured for 50 houses is provided. The top is the sub-network containing only connections between an individual and their own home. The bottom is the sub-network containing only connections between an individual and other houses. Blue square nodes represent houses and orange circle nodes represent individuals. Edges between an individual and their own home are black and edges connecting to other houses are gray. Edges are weighted by H matrix values, where thicker edges reflect more time spent at a place.

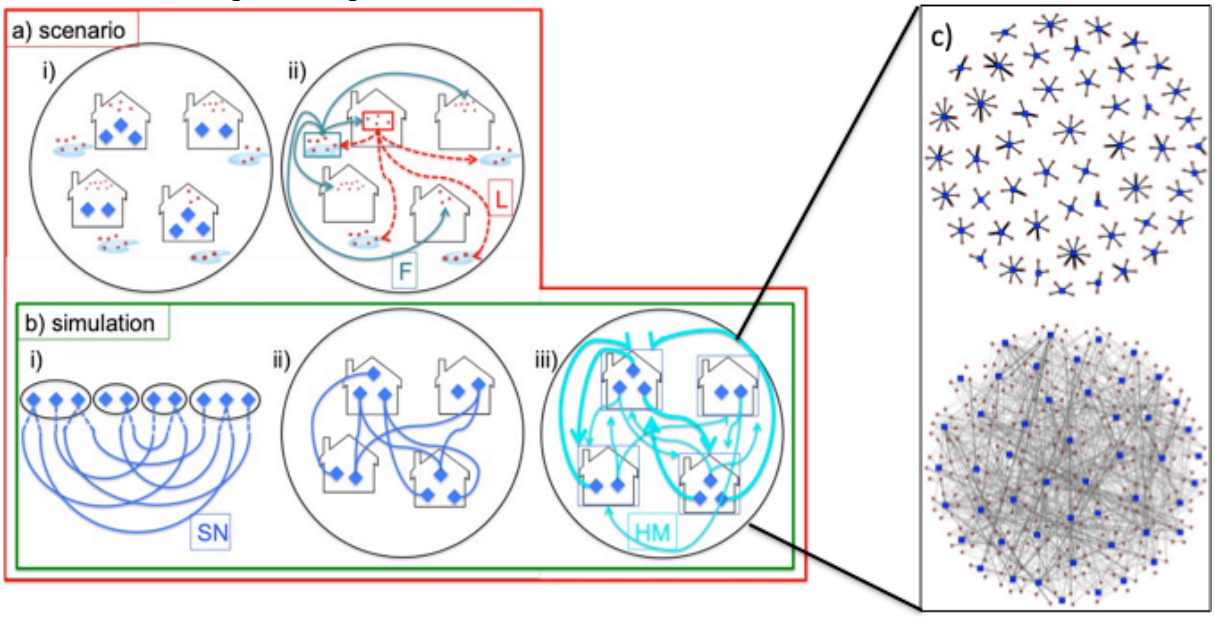


Figure 4.2: Diagram of Stochastic DENV Transmission Model. A household-level SEI model is used for mosquitoes. For humans, an individual-based SEIR model is used. The I (infectious) stage is divided into five sub-stages, each with their infectiousness value, shown here with weighted arrows (shown in Table 3). Individuals can either progress to the next (I) infectious sub-stage or move straight to the (R) recovered stage based on a probability function. The probability of moving to the recovered stage is shown with weighted arrows.

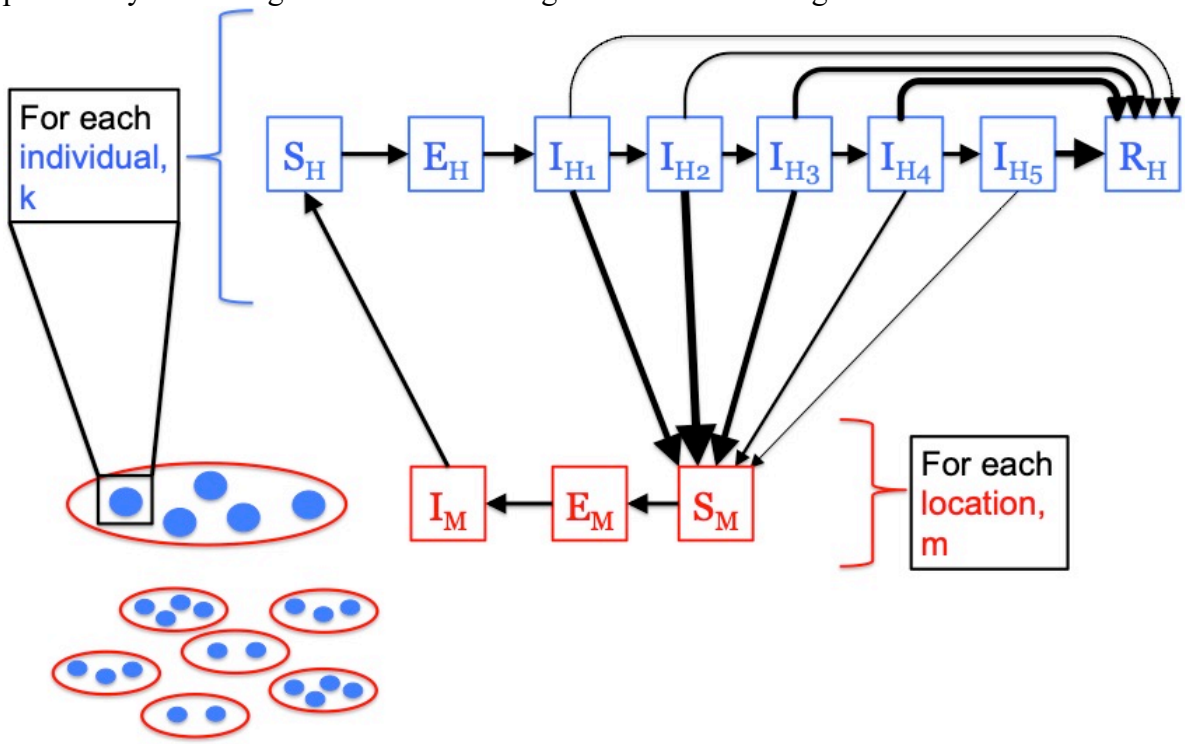


Figure 4.3: Proportion of Population Infected During Epidemic Simulations, by Scenario. For each scenario and for each time step, the average proportion of infected hosts is calculated across all simulation runs where an outbreak occurred. Standard deviations are included in the shaded ribbons.

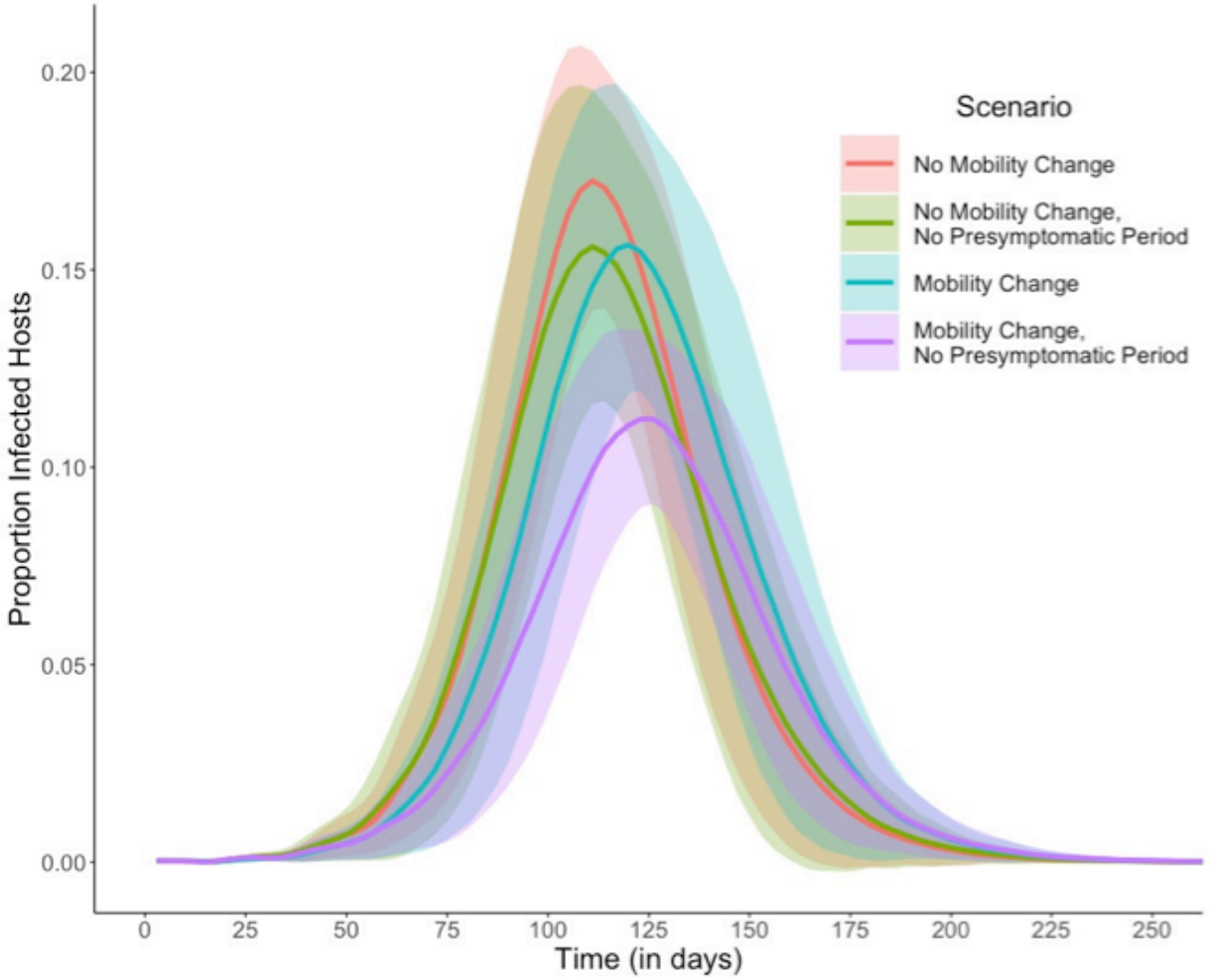


Figure 4.4: Expected Onward Transmission Values With and Without Movement Changes Accounted For, Separated by Where Primary Bites Occur and Where Secondary Bites Occur. (a) gives onward transmission for primary bites occurring at home (red) and at other houses (blue) both without (left) and with (right) movement change included. (from left to right: R_{norm}(home), R_{norm}(other houses), $R_{movement}$(home), and $R_{movement}$(other houses)) (b) gives onward transmission for secondary bites at the home of the primary infected individual (red) and at other houses (blue).

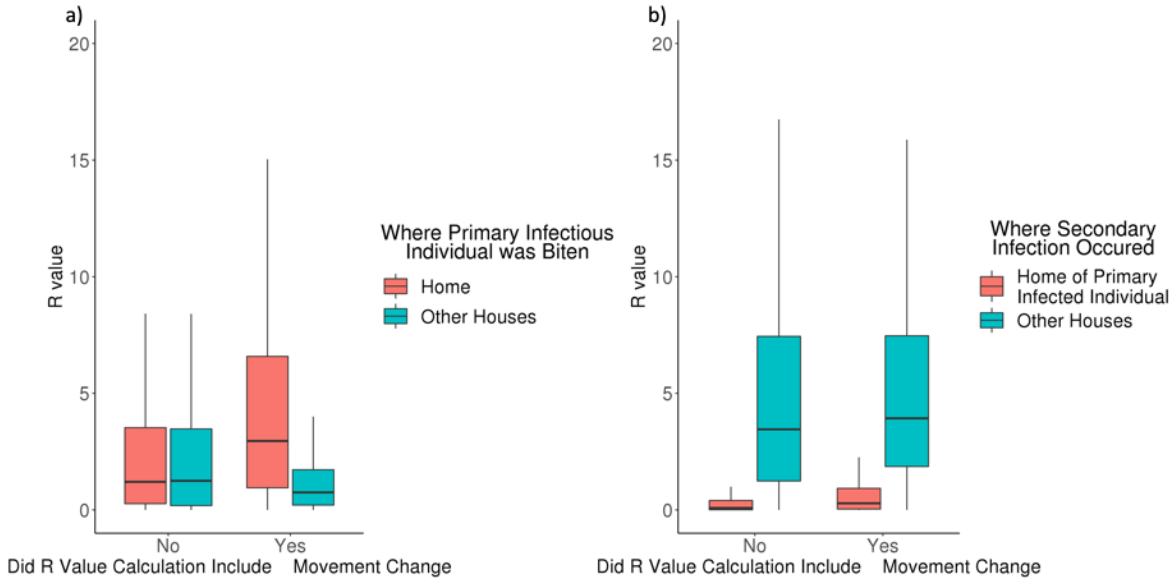


Figure 4.5: Smooth Functions and Predictions for $R_{movement}$ Based on a GAM Model Containing Number of Mosquitoes in Home Pre-exposure, Biting Suitability Score, and Their Interaction. On the left (i, ii, iii), the component smooths for each predictor variable are provided. For the 1-d smooths (i, ii), the y-axis is the contribution of the predictor variable to the fitted response, centered around 0 (with 0 denoted by a red dashed line). For the 2-d smooth for the interaction term (iii), a heatmap with overlaid contours is provided. The values of the contours represent the contribution of the interaction term to the fitted response. Positive values are in red and negative values are in blue. On the right (iv) is the predicted values of onward transmission based on biting suitability and number of mosquitoes at home pre-exposure, presented as a heatmap with contours.

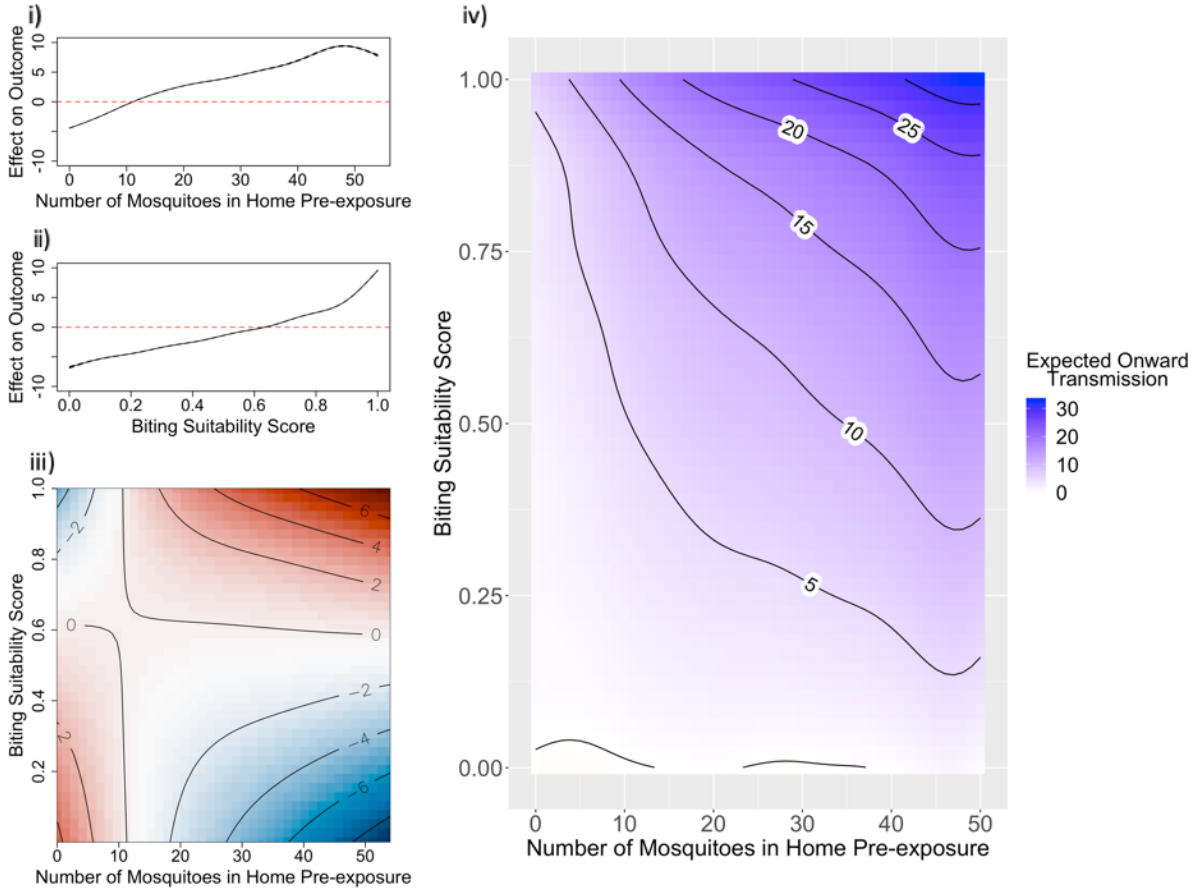


Figure 4.6: Smooth Functions and Predictions for Percent Change in $R_{movement}$ and $R_{movement}$(home) Based on GAM Models. (a) The smooth value for percent change in $R_{movement}$, predicted by percent of bites expected at home pre-exposure. As there is only one predictor variable in this model, the y-axis represents the fitted response based on the predictor variable. (b) Smooth values for percent change in $R_{movement}$(home), predicted by biting suitability score and percent of bites expected at home pre-exposure. On the left (i, ii), the component smooths for each predictor variable are provided. The y-axis is the contribution of the predictor variable to the fitted response, centered around 0 (with 0 denoted by a red dashed line). On the right (iii) is the predicted percent change in onward transmission from primary bites at home based on biting suitability and percent of bites expected at home pre-exposure, presented as a heatmap with contours.

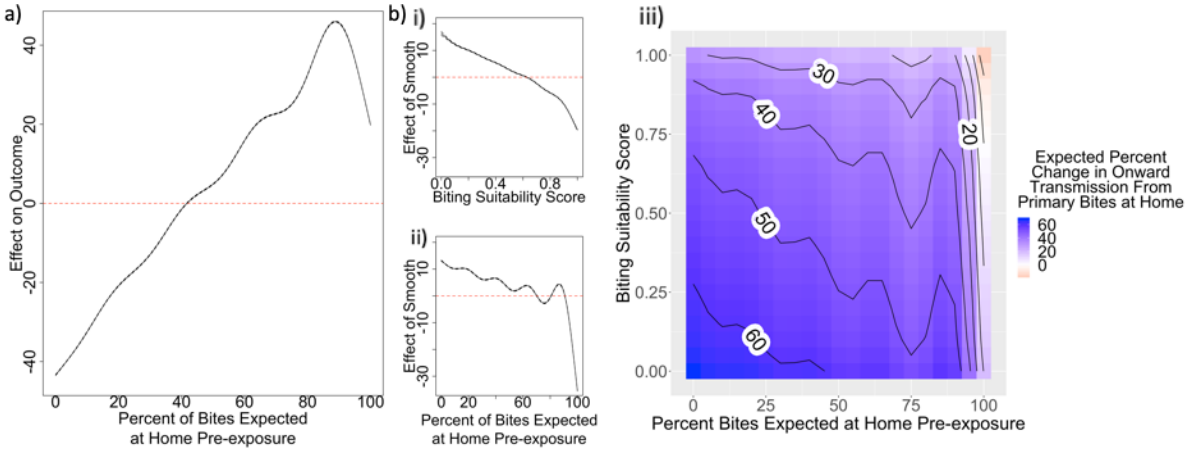
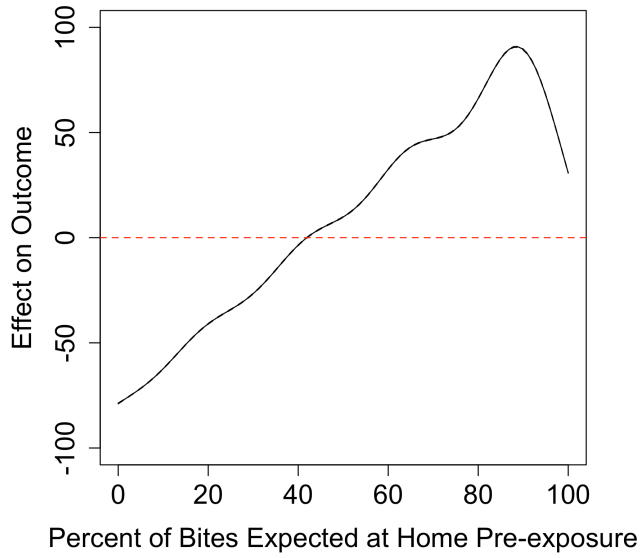


Figure 4.7: Smooth Functions and Predictions for Percent Change in Expected Mosquito Contacts Based on GAM Model Containing Percent of Bites Expected at Home Pre-exposure. The smooth function for the predictor variable. As there is only one predictor variable in this model, the y-axis represents the fitted response based on the predictor variable.



Supplemental materials

Table S4.1: Simulation Parameters with Set Values for All Scenarios.

Symbol	Value	Definition
T	200	Number of time steps in simulation
ν	10	Number of mosquito eggs per capita per feeding cycle
$\lvert f \rvert$	600	Number of houses
$\lvert l \rvert$	600	Number of aquatic habitats
ξ	4	Length of the larval stage (in feeding cycles)
s_L	0.9	Mosquito survival between blood feeding (houses) and egg laying
s_F	0.9	Mosquito survival between egg laying and blood feeding (houses)
σ	3	Pathogen incubation period in hosts
τ	1	Pathogen incubation period in mosquitoes
ρ_{max}	5	Maximum number of time steps for host infectiousness (I)
c(i)		Host-to-mosquito transmission efficiency for infectiousness stage I_i
b	0.75	Mosquito-to-host transmission efficiency

Table S4.2: Simulation Parameters Set for Each Scenario.

Symbol	Definition
α	Strength of density dependence on larval mosquitoes
Hh	Number of hosts per house
L	Probability of mosquito movement from house to larval site
F	Probability of mosquito movement from larval site to house
M_{larvae}	Number of larvae in each stage at each larval site
Smf	Number of susceptible adult mosquitoes at each house
Sml	Number of susceptible adult mosquitoes at each larval site
ρ_i	Probability of host recovery at each stage of infectiousness
γ	Host biting suitability

Table S4.3: Cumulative New Infections Based on Presence of Presymptomatic Period and/or Mobility Changes. Average time points when cumulative percent of new infections reached 10%, 65%, and total percent infection. Average percent of the population infected was also listed. Data were averaged across simulation runs for four scenarios: (1) no mobility change occurred and the presymptomatic period was present, (2) no mobility change occurred and no presymptomatic period was present, (3) mobility change occurred and the presymptomatic period was present, and (4) mobility change occurred and no presymptomatic period was present. Time steps values were converted to days (1 time step = 3 days).

	Time When Cumulative Percent of Population Infected (days):		
	> 10%	> 65%	Total Percent of Population Infected
No Changes	81.6 (10.8)	128.7 (10.8)	76.5 (0.8)
No Changes, No Presymptomatic	82.8 (13.5)	132.9 (13.8)	74.1 (0.9)
Mobility Changes	89.1 (13.2)	137.7 (13.8)	76.7 (0.9)
Mobility Changes, No Presymptomatic	90.9 (12.9)	150.9 (13.5)	72.7 (0.9)

Table S4.4: Comparison of GAMs for Expected Onward Transmission Without Mobility Change, R_{norm}. Amount of deviance explained (%),degrees of freedom (DF), change in AICc compared to the best fit model (ΔAICc), and model weight are provided for each model. The best-fit model is highlighted in red.

	Total Onward Transmission Without Mobility Changes Included			
Factors	Deviance Explained (%)	df	Δ AICc	Weight
Percent bites at home	0.54%	10.915	5.47×10^5	<0.001
Number of mosquitoes at home	13.57%	10.949	4.95×10^5	<0.001
Number of mosquitoes in activity space	2.97%	10.999	5.38×10^5	<0.001
Biting suitability score	37.69%	10.973	3.74×10^5	<0.001
Biting suitability score, Number of mosquitoes at home, Number of mosquitoes in activity space, Percent bites at home	64.60%	37.925	1.65×10^5	<0.001
Biting suitability score, Number of mosquitoes at home, Number of mosquitoes in activity space, Percent bites at home, (Biting suitability score) X (Number of mosquitoes at home)	69.13%	52.782	1.14×10^5	<0.001
Biting suitability score, Number of mosquitoes at home, Number of mosquitoes in activity space, Percent bites at home, (Biting suitability score) X (Percent bites at home)	65.40%	53.754	1.56×10^5	<0.001
Biting suitability score, Number of mosquitoes at home, Number of mosquitoes in activity space, Percent bites at home, (Number of mosquitoes at home) X (Percent bites at home)	67.25%	53.898	1.36×10^5	<0.001
Biting suitability score, Number of mosquitoes at home, Percent bites at home, (Biting suitability score) X (Number of mosquitoes at home) X (Percent bites at home)	77.35%	148.876	0.0	1.0

Table S4.5: Comparison of GAMs for Expected Onward Transmission. Models are Compared for Response Variables $R_{movement}$ and $R_{movement}$(home). Amount of deviance explained (%),degrees of freedom (DF), change in AICc compared to the best fit model (ΔAICc), and model weight are provided for each model. The best-fit model is highlighted in red.

	Total Onward Transmission				Onward Transmission from 1° bites at home			
Factors	Deviance Explained (%)	df	Δ AICc	Weight	Deviance Explained (%)	df	Δ AICc	Weight
Percent bites at home	9.31%	10.960	4.22×10^5	<0.001	28.66%	10.997	5.09×10^5	<0.001
Number of mosquitoes at home	27.73%	10.955	3.53×10^5	<0.001	42.98%	10.974	4.26×10^5	<0.001
Biting suitability score	32.33%	10.949	3.33×10^5	<0.001	20.02%	10.873	5.52×10^5	<0.001
Biting suitability score, Number of mosquitoes at home, Percent bites at home	67.19%	28.742	1.16×10^5	<0.001	69.44%	28.872	1.95×10^5	<0.001
Biting suitability score, Number of mosquitoes at home, Percent bites at home, (Biting suitability score) X (Number of mosquitoes at home)	74.82%	43.336	3.59×10^4	<0.001	81.19%	44.528	1.55×10^4	<0.001
Biting suitability score, Number of mosquitoes at home, Percent bites at home, (Biting suitability score) X (Percent bites at home)	69.41%	44.384	9.45×10^4	<0.001	76.21%	44.737	1.02×10^5	<0.001
Biting suitability score, Number of mosquitoes at home, Percent bites at home, (Number of mosquitoes at home) X (Percent bites at home)	67.98%	44.901	1.08×10^5	<0.001	70.04%	44.207	1.88×10^5	<0.001
Biting suitability score, Number of mosquitoes at home, Percent bites at home, (Biting suitability score) X (Number of mosquitoes at home) X (Percent bites at home)	77.67%	133.940	0.0	1.0	81.97%	120.327	0.0	1.0

Table S4.6: Comparison of GAMs for Change in Expected Onward Transmission When Mobility is Included. Models are Compared for Response Variables R_{change} and R_{change}(home). Amount of deviance explained (%),degrees of freedom (DF), change in AICc compared to the best fit model (ΔAICc), and model weight are provided for each model. The best-fit model is highlighted in red.

	Change in Total Onward Transmission				Change in Onward Transmission from 1° bites at home			
Factors	Deviance Explained (%)	df	Δ AICc	Weight	Deviance Explained (%)	df	Δ AICc	Weight
Percent bites at home	32.10%	10.987	2.57×10^5	<0.001	32.78%	10.999	1.62×10^5	<0.001
Number of mosquitoes at home	8.74%	10.639	3.46×10^5	<0.001	26.46%	10.954	1.96×10^5	<0.001
Biting suitability score	17.59%	10.960	3.16×10^5	<0.001	6.34%	10.576	2.85×10^5	<0.001
Biting suitability score, Number of mosquitoes at home, Percent bites at home	54.48%	28.970	1.37×10^5	<0.001	49.99%	28.692	5.27×10^4	<0.001
Biting suitability score, Number of mosquitoes at home, Percent bites at home, (Biting suitability score) X (Number of mosquitoes at home)	55.54%	43.868	1.30×10^5	<0.001	52.48%	43.806	3.38×10^4	<0.001
Biting suitability score, Number of mosquitoes at home, Percent bites at home, (Biting suitability score) X (Percent bites at home)	61.33%	44.781	8.79×10^4	<0.001	53.39%	44.521	2.67×10^4	<0.001
Biting suitability score, Number of mosquitoes at home, Percent bites at home, (Number of mosquitoes at home) X (Percent bites at home)	59.28%	44.905	1.03×10^5	<0.001	51.37%	44.580	4.24×10^4	<0.001
Biting suitability score, Number of mosquitoes at home, Percent bites at home, (Biting suitability score) X (Number of mosquitoes at home) X (Percent bites at home)	71.14%	140.400	0.0	1.0	56.65%	121.847	0.0	1.0

Table S4.7: Comparison of GAMs for Percent Change in Expected Onward Transmission When Mobility is Included. Models are Compared for Response Variables R_{change} and R_{change}(home) as Percentages. Amount of deviance explained (%),degrees of freedom (DF), change in AICc compared to the best fit model (ΔAICc), and model weight are provided for each model. The best-fit model is highlighted in red.

	Percent Change in Total Onward Transmission				Percent Change in Onward Transmission from 1° bites at home			
Factors	Deviance Explained (%)	df	Δ AICc	Weight	Deviance Explained (%)	df	Δ AICc	Weight
Percent bites at home	80.50%	10.999	5.70×10^4	<0.001	40.24%	10.999	9.91×10^4	<0.001
Number of mosquitoes at home	46.61%	10.955	3.60×10^5	<0.001	4.78%	10.810	2.72×10^5	<0.001
Biting suitability score	2.47%	10.243	5.41×10^5	<0.001	11.65%	10.825	2.44×10^5	<0.001
Biting suitability score, Number of mosquitoes at home, Percent bites at home	82.03%	28.689	3.24×10^4	<0.001	52.63%	28.846	1.31×10^4	<0.001
Biting suitability score, Number of mosquitoes at home, Percent bites at home, (Biting suitability score) X (Number of mosquitoes at home)	82.86%	42.705	1.82×10^4	<0.001	52.83%	38.762	1.15×10^4	<0.001
Biting suitability score, Number of mosquitoes at home, Percent bites at home, (Biting suitability score) X (Percent bites at home)	83.58%	44.142	5.18×10^3	<0.001	53.93%	44.231	2.78×10^3	<0.001
Biting suitability score, Number of mosquitoes at home, Percent bites at home, (Number of mosquitoes at home) X (Percent bites at home)	82.16%	44.092	3.01×10^4	<0.001	52.79%	44.416	1.19×10^4	<0.001
Biting suitability score, Number of mosquitoes at home, Percent bites at home, (Biting suitability score) X (Number of mosquitoes at home) X (Percent bites at home)	83.87%	94.979	0.0	1.0	54.29%	95.766	0.0	1.0

Table S4.8: Average Expected Mosquito Bites for Each Sub-stage of Infectiousness After Symptom Onset ($I_2 - I_5$), Separated Based on Expected Bite Values Pre-exposure.

	Top 20% bites pre-exposure	Bottom 80% bites pre-exposure
Pre-exposure	7.6 (3.2)	1.6 (1.1)
Days 1-3 after symptom Onset	6.1 (4.4)	1.2 (1.1)
Days 4-6 after symptom Onset	6.7 (4.0)	1.3 (1.1)
Days 7-9 after symptom Onset	7.2 (3.5)	1.5 (1.1)
Days 10-12 after symptom Onset	7.6 (3.3)	1.6 (1.1)

Table S4.9: Comparison of GAMs for Change in Expected Mosquito Contacts in the First Three Days After Symptom Onset When All Time is Spent at Home (sub-stage I_2). Models are Compared for Response Variable as a Raw Number and a Percentage. Amount of deviance explained (%),degrees of freedom (DF), change in AICc compared to the best fit model (ΔAICc), and model weight are provided for each model. The best-fit model is highlighted in red.

	Change in Expected Mosquito Contacts				Percent Change in Expected Mosquito Contacts			
Factors	Deviance Explained (%)	df	Δ AICc	Weight	Deviance Explained (%)	df	Δ AICc	Weight
Percent bites at home	24.58%	10.998	3.04×10^4	<0.001	92.08%	11.000	7.05×10^4	<0.001
Number of mosquitoes at home	8.53%	10.053	3.75×10^5	<0.001	53.82%	10.958	7.21×10^5	<0.001
Biting suitability score	7.21%	10.956	3.80×10^5	<0.001	1.66%	10.141	1.00×10^6	<0.001
Biting suitability score, Number of mosquitoes at home, Percent bites at home	37.17%	28.962	2.36×10^4	<0.001	92.97%	28.646	2.66×10^4	<0.001
Biting suitability score, Number of mosquitoes at home, Percent bites at home, (Biting suitability score) X (Number of mosquitoes at home)	39.72%	42.620	2.21×10^4	<0.001	93.16%	43.992	1.62×10^4	<0.001
Biting suitability score, Number of mosquitoes at home, Percent bites at home, (Biting suitability score) X (Percent bites at home)	46.37%	44.832	1.78×10^3	<0.001	93.38%	44.317	4.25×10^3	<0.001
Biting suitability score, Number of mosquitoes at home, Percent bites at home, (Number of mosquitoes at home) X (Percent bites at home)	46.69%	44.778	1.76×10^4	<0.001	93.02%	43.086	2.40×10^4	<0.001
Biting suitability score, Number of mosquitoes at home, Percent bites at home, (Biting suitability score) X (Number of mosquitoes at home) X (Percent bites at home)	66.90%	139.163	0.0	1.0	93.46%	110.269	0.0	1.0

Table 4.10: Average R Values With and Without Mobility Change and Change in R due to Mobility Change Inclusion for Only Symptomatic Individuals in the Scenario with 70% Asymptomatic Cases and 30% Symptomatic Cases. R_{norm} values were calculated using an individual's healthy movement patterns, while $R_{movement}$ values accounted for changes in mobility throughout infectiousness. Changes in R-values due to mobility inclusion were calculated for each individual as a raw number and as a percent of R_{norm} value. Overall R-values were listed, as well as R-values based on only primary bites occurring at home or at other houses.

	Mean (sd) Onward Transmission		Mean (sd) Change in Onward Transmission with Movement Changes	
	R_{norm}	$R_{movement}$	(#)	(%)
1° bites at home	3.3 (3.3)	4.4 (4.2)	1.0 (1.1)	38.8 (21.0)
1° bites at other houses	3.1 (3.1)	1.2 (1.2)	-1.9 (1.9)	-62.3 (8.8)
2° bites at infectious individual's home	0.3 (0.4)	0.5 (0.6)	0.0 (0.1)	31.9 (35.6)
2° bites elsewhere	4.6 (4.3)	5.5 (4.3)	-0.6 (1.8)	-17.1 (29.0)
Total	7.2 (5.5)	6.0 (4.8)	-1.1 (2.4)	-15.3 (29.2)

Table S4.11: Comparison of GAMs for Expected Onward Transmission Without Mobility Change, R_{norm}, for Only Symptomatic Individuals in the Scenario With 70% Asymptomatic Cases and 30% Symptomatic Cases. Amount of deviance explained (%),degrees of freedom (DF), change in AICc compared to the best fit model (ΔAICc), and model weight are provided for each model. The best-fit model is highlighted in red.

	Total Onward Transmission Without Mobility Changes Included			
Factors	Deviance Explained (%)	df	Δ AICc	Weight
Percent bites at home	1.11%	10.849	4.96×10^5	<0.001
Number of mosquitoes at home	14.12%	10.976	4.51×10^5	<0.001
Number of mosquitoes in activity space	2.78%	10.694	4.91×10^5	<0.001
Biting suitability score	41.31%	10.969	3.29×10^5	<0.001
Biting suitability score, Number of mosquitoes at home, Number of mosquitoes in activity space, Percent bites at home	67.43%	37.909	1.41×10^5	<0.001
Biting suitability score, Number of mosquitoes at home, Number of mosquitoes in activity space, Percent bites at home, (Biting suitability score) X (Number of mosquitoes at home)	72.53%	52.877	8.63×10^4	<0.001
Biting suitability score, Number of mosquitoes at home, Number of mosquitoes in activity space, Percent bites at home, (Biting suitability score) X (Percent bites at home)	38.56%	53.765	1.30×10^5	<0.001
Biting suitability score, Number of mosquitoes at home, Number of mosquitoes in activity space, Percent bites at home, (Number of mosquitoes at home) X (Percent bites at home)	69.26%	53.764	1.22×10^5	<0.001
Biting suitability score, Number of mosquitoes at home, Percent bites at home, (Biting suitability score) X (Number of mosquitoes at home) X (Percent bites at home)	79.04%	142.323	0.0	1.0

Table S4.12: Comparison of GAMs for Expected Onward Transmission for Only Symptomatic Individuals in the Scenario With 70% Asymptomatic Cases and 30% Symptomatic Cases. Models are Compared for Response Variables $R_{movement}$ and $R_{movement}$(home). Amount of deviance explained (%),degrees of freedom (DF), change in AICc compared to the best fit model (ΔAICc), and model weight are provided for each model. The best-fit model is highlighted in red.

	Total Onward Transmission				Onward Transmission from 1° bites at home			
Factors	Deviance Explained (%)	df	Δ AICc	Weight	Deviance Explained (%)	df	Δ AICc	Weight
Percent bites at home	10.57%	10.863	1.45×10^5	<0.001	29.22%	10.924	1.42×10^5	<0.001
Number of mosquitoes at home	29.11%	10.784	1.22×10^5	<0.001	43.93%	10.841	1.20×10^5	<0.001
Biting suitability score	34.15%	10.823	1.15×10^5	<0.001	20.96%	10.156	1.52×10^5	<0.001
Biting suitability score, Number of mosquitoes at home, Percent bites at home	70.12%	28.580	3.99×10^4	<0.001	71.25%	28.480	5.56×10^4	<0.001
Biting suitability score, Number of mosquitoes at home, Percent bites at home, (Biting suitability score) X (Number of mosquitoes at home)	78.15%	41.359	9.96×10^3	<0.001	83.20%	42.973	4.27×10^3	<0.001
Biting suitability score, Number of mosquitoes at home, Percent bites at home, (Biting suitability score) X (Percent bites at home)	72.73%	43.812	3.12×10^4	<0.001	78.19%	44.119	2.92×10^4	<0.001
Biting suitability score, Number of mosquitoes at home, Percent bites at home, (Number of mosquitoes at home) X (Percent bites at home)	70.63%	44.508	3.82×10^4	<0.001	71.75%	41.929	5.40×10^4	<0.001
Biting suitability score, Number of mosquitoes at home, Percent bites at home, (Biting suitability score) X (Number of mosquitoes at home) X (Percent bites at home)	80.34%	119.280	0.0	1.0	83.95%	89.401	0.0	1.0

Table S4.13: Comparison of GAMs for Change in Expected Onward Transmission When Mobility is Included for Only Symptomatic Individuals in the Scenario with 70% Asymptomatic Cases and 30% Symptomatic Cases. Models are Compared for Response Variables R_{change} and R_{change}(home). Amount of deviance explained (%),degrees of freedom (DF), change in AICc compared to the best fit model (ΔAICc), and model weight are provided for each model. The best-fit model is highlighted in red.

	Change in Total Onward Transmission				Change in Onward Transmission from 1° bites at home			
Factors	Deviance Explained (%)	df	Δ AICc	Weight	Deviance Explained (%)	df	Δ AICc	Weight
Percent bites at home	35.47%	10.970	8.35×10^4	<0.001	36.18%	10.999	5.44×10^4	<0.001
Number of mosquitoes at home	10.79%	10.444	1.15×10^5	<0.001	30.81%	10.337	6.21×10^4	<0.001
Biting suitability score	20.24%	10.903	1.04×10^5	<0.001	7.84%	8.761	8.96×10^4	<0.001
Biting suitability score, Number of mosquitoes at home, Percent bites at home	59.00%	28.916	4.02×10^4	<0.001	56.72%	27.218	1.73×10^4	<0.001
Biting suitability score, Number of mosquitoes at home, Percent bites at home, (Biting suitability score) X (Number of mosquitoes at home)	60.35%	41.236	3.70×10^4	<0.001	60.03%	41.357	9.73×10^3	<0.001
Biting suitability score, Number of mosquitoes at home, Percent bites at home, (Biting suitability score) X (Percent bites at home)	66.63%	44.367	2.05×10^4	<0.001	60.39%	42.660	8.86×10^3	<0.001
Biting suitability score, Number of mosquitoes at home, Percent bites at home, (Number of mosquitoes at home) X (Percent bites at home)	61.99%	44.797	3.30×10^4	<0.001	58.10%	40.703	1.42×10^4	<0.001
Biting suitability score, Number of mosquitoes at home, Percent bites at home, (Biting suitability score) X (Number of mosquitoes at home) X (Percent bites at home)	73.12%	132.449	0.0	1.0	63.93%	94.946	0.0	1.0

Table S4.14: Comparison of GAMs for Percent Change in Expected Onward Transmission When Mobility is Included for Only Symptomatic Individuals in the Scenario with 70% Asymptomatic Cases and 30% Symptomatic Cases. Models are Compared for Response Variables R_{change} and R_{change}(home) as Percentages. Amount of deviance explained (%),degrees of freedom (DF), change in AICc compared to the best fit model (ΔAICc), and model weight are provided for each model. The best-fit model is highlighted in red.

	Percent Change in Total Onward Transmission				Percent Change in Onward Transmission from 1° bites at home			
Factors	Deviance Explained (%)	df	Δ AICc	Weight	Deviance Explained (%)	df	Δ AICc	Weight
Percent bites at home	82.38%	10.999	2.01×10^4	<0.001	44.05%	10.995	3.02×10^4	<0.001
Number of mosquitoes at home	49.45%	10.956	1.21×10^5	<0.001	4.84%	10.422	8.10×10^4	<0.001
Biting suitability score	2.50%	7.769	1.84×10^5	<0.001	12.48%	9.630	7.30×10^4	<0.001
Biting suitability score, Number of mosquitoes at home, Percent bites at home	83.83%	25.628	1.18×10^4	<0.001	57.44%	28.521	4.08×10^3	<0.001
Biting suitability score, Number of mosquitoes at home, Percent bites at home, (Biting suitability score) X (Number of mosquitoes at home)	84.60%	38.348	7.21×10^3	<0.001	57.58%	35.900	3.78×10^3	<0.001
Biting suitability score, Number of mosquitoes at home, Percent bites at home, (Biting suitability score) X (Percent bites at home)	85.38%	41.127	2.26×10^3	<0.001	58.95%	41.963	6.47×10^2	<0.001
Biting suitability score, Number of mosquitoes at home, Percent bites at home, (Number of mosquitoes at home) X (Percent bites at home)	84.04%	39.580	1.06×10^4	<0.001	57.57%	42.877	3.81×10^3	<0.001
Biting suitability score, Number of mosquitoes at home, Percent bites at home, (Biting suitability score) X (Number of mosquitoes at home) X (Percent bites at home)	85.73%	87.289	0.0	1.0	59.25%	70.557	0.0	1.0

Table S4.15: Average Expected Mosquito Bites for Each Sub-stage of Infectiousness After Symptom Onset ($I_2 – I_5$) for Only Symptomatic Individuals in the Scenario with 70% Asymptomatic Cases and 30% Symptomatic Cases, Separated Based on Expected Bite Values Pre-exposure.

	Top 20% bites pre-exposure	Bottom 80% bites pre-exposure
Pre-exposure	7.4 (3.1)	1.6 (1.1)
Days 1-3 after symptom Onset	6.1 (4.2)	1.2 (1.1)
Days 4-6 after symptom Onset	6.6 (3.8)	1.4 (1.1)
Days 7-9 after symptom Onset	7.1 (3.3)	1.5 (1.1)
Days 10-12 after symptom Onset	7.5 (3.1)	1.6 (1.1)

Table 4.16: Average Change in Expected Mosquito Bites for Each Infectiousness Sub-stage When Symptomatic Mobility Change is Occurring ($I_2 – I_4$), for Only Symptomatic Individuals in the Scenario with 70% Asymptomatic Cases and 30% Symptomatic Cases, Separated Based on Expected Bite Values Pre-exposure. Average changes are given both as raw numbers and percent change relative to number of expected bites pre-exposure.

	Top 20% bites pre-exposure		Bottom 80% bites pre-exposure	
	(#)	(%)	(#)	(%)
Days 1-3 after symptom Onset	-0.8 (3.6)	-12.6 (47.2)	-0.2 (0.7)	-17.3 (49.9)
Days 4-6 after symptom Onset	-0.3 (2.5)	-5.9 (35.5)	-0.1 (0.5)	-9.0 (36.9)
Days 7-9 after symptom Onset	-0.09 (1.5)	-2.0 (20.7)	-0.05 (0.3)	-5.0 (22.5)

Table S4.17: Comparison of GAMs for Change in Expected Mosquito Contacts in the First Three Days After Symptom Onset When All Time is Spent at Home (sub-stage I_2) for Only Symptomatic Individuals in the Scenario with 70% Asymptomatic Cases and 30% Symptomatic Cases. Models are Compared for Response Variable as a Raw Number and a Percentage. Amount of deviance explained (%),degrees of freedom (DF), change in AICc compared to the best fit model (ΔAICc), and model weight are provided for each model. The best-fit model is highlighted in red.

	Change in Expected Mosquito Contacts				Percent Change in Expected Mosquito Contacts			
Factors	Deviance Explained (%)	df	Δ AICc	Weight	Deviance Explained (%)	df	Δ AICc	Weight
Percent bites at home	23.54%	10.962	7.95×10^4	<0.001	93.59%	11.000	2.12×10^4	<0.001
Number of mosquitoes at home	8.31%	10.402	9.68×10^4	<0.001	56.03%	10.951	2.05×10^5	<0.001
Biting suitability score	7.38%	10.886	9.78×10^4	<0.001	1.71%	8.392	2.81×10^6	<0.001
Biting suitability score, Number of mosquitoes at home, Percent bites at home	36.54%	28.872	6.18×10^4	<0.001	94.43%	25.907	7.86×10^3	<0.001
Biting suitability score, Number of mosquitoes at home, Percent bites at home, (Biting suitability score) X (Number of mosquitoes at home)	39.14%	40.747	5.78×10^4	<0.001	94.60%	39.624	5.01×10^3	<0.001
Biting suitability score, Number of mosquitoes at home, Percent bites at home, (Biting suitability score) X (Percent bites at home)	45.56%	44.163	4.72×10^4	<0.001	94.82%	41.467	1.00×10^3	<0.001
Biting suitability score, Number of mosquitoes at home, Percent bites at home, (Number of mosquitoes at home) X (Percent bites at home)	46.96%	44.717	4.47×10^4	<0.001	94.47%	39.000	7.25×10^3	<0.001
Biting suitability score, Number of mosquitoes at home, Percent bites at home, (Biting suitability score) X (Number of mosquitoes at home) X (Percent bites at home)	66.90%	124.530	0.0	1.0	94.49%	73.152	0.0	1.0

Figure S4.1: Equations for human and mosquito transmission models, as seen in [16].
(A)Stochastic, individual-based SEIR dynamics for hosts. ρ_{fail} is a failure distribution that defines the probability of recovering after i time steps. (B)Stochastic, household-level SEI dynamics for mosquitoes. Bernoulli, Binomial, and Multinomial functions generate random numbers from those distributions with the supplied parameters. See **Tables S4.1-4.2** for parameter definitions.

A

$$S(t+1) = \text{Bernoulli}\left(S(t), (1-b)^{\sum_{\{I\}} \text{Multinomial}(I'(t),U)}\right)$$

$$E_0(t+1) = S(t) - S(t+1)$$

$$E_e(t+1) = E_{e-1}(t)$$

$$I_0(t+1) = E_{\sigma-1}(t)$$

$$I_i(t+1) = \text{Bernoulli}(I_{i-1}(t), 1-\rho_{fail}(i-1))$$

$$R(t+1) = R(t) + \left(\sum I_i(t) + E_{\sigma-1}(t) - \sum I_i(t+1)\right)$$

B

$$S'(t+1) = \text{Multinomial}(A_\xi(t+1), F) + \text{Multinomial}(S''(t), LF)$$

$$S''(t+1) = S'(t+1) - \text{Binomial}(\text{Multinomial}(S'(t+1), U), cI(t))$$

$$E'_0(t+1) = S'(t+1) - S''(t+1)$$

$$E'_e(t+1) = \text{Multinomial}(E'_{e-1}(t), LF)$$

$$I'(t+1) = \text{Multinomial}(I'(t) + E'_{\tau-1}(t), LF)$$

Figure S4.2: Mobility Values During Illness (in 3-day Intervals).
(A) Average number of locations visited per 3-day period. (B) Average proportion of time spent at home per 3-day period. Significant differences, denoted by letters, were detected using pairwise paired Wilcoxon Sign Rank tests with Bonferroni's correction to account for a family-wise error-rate of 0.05. All significant differences had p-values < 0.05.

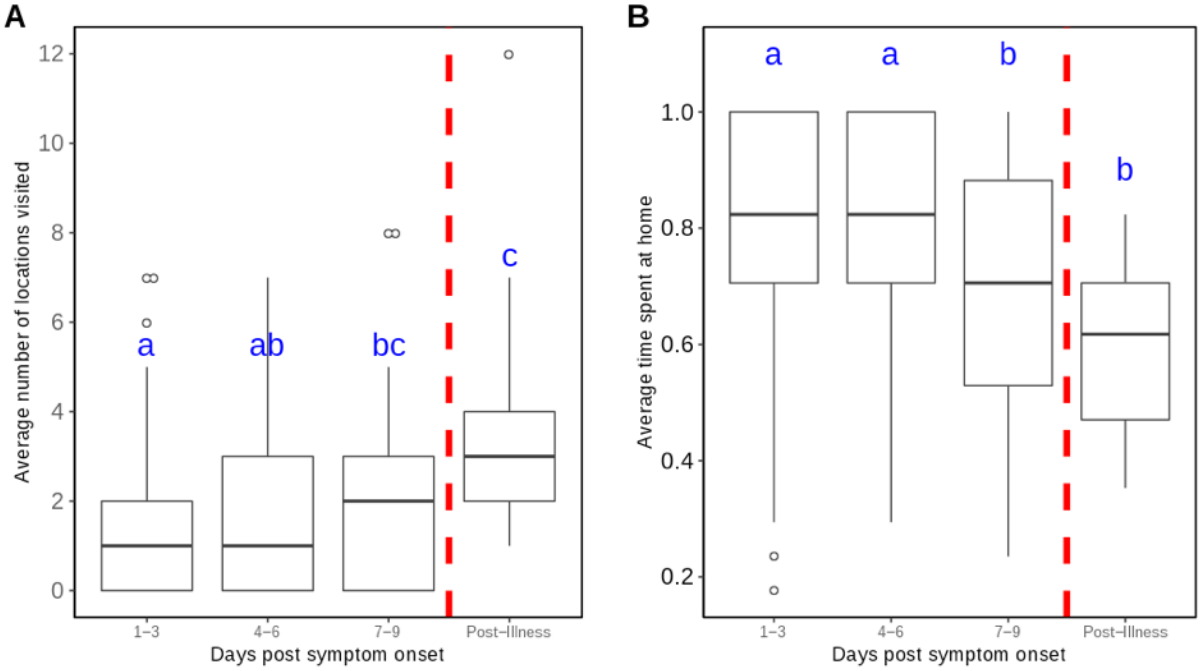


Figure S4.3: Distribution of R_{norm} and $R_{movement}$ Values. Outliers were removed.

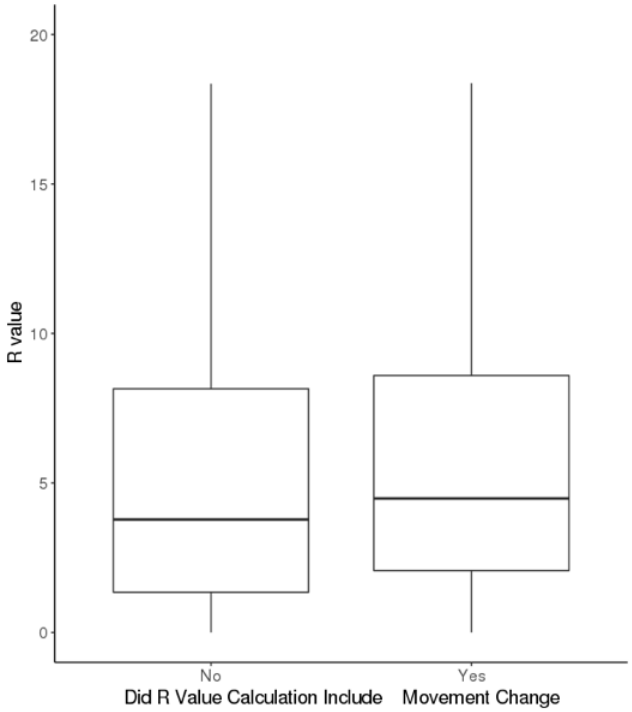


Figure S4.4: Distribution of R_{change}, R_{change}(home), and R_{change}(other houses) Values. Outliers were removed. The red line represents no change.

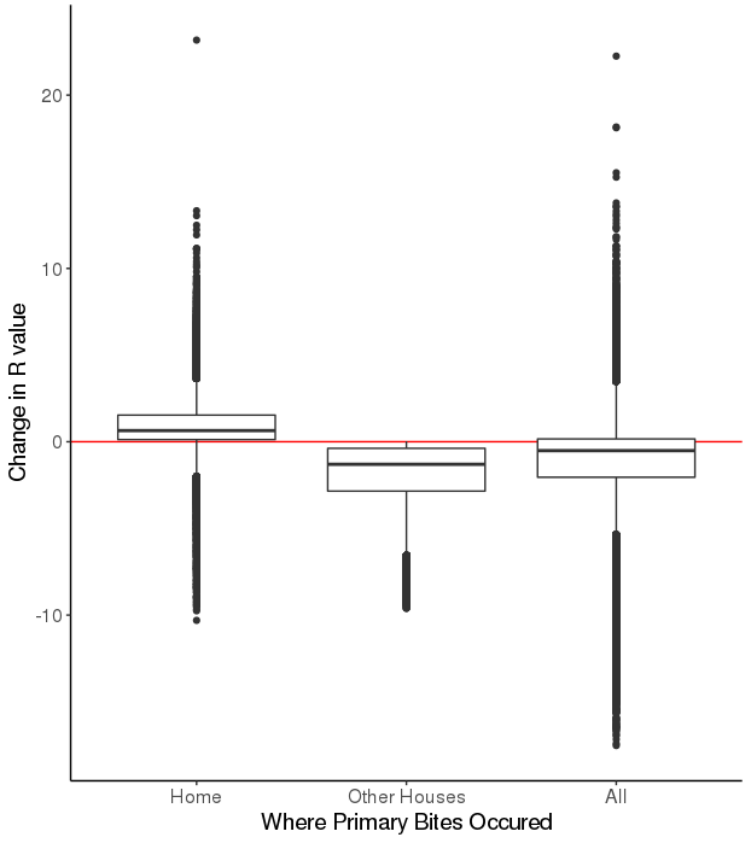


Figure S4.5: Distribution of Expected Mosquito Contacts at Each Infectiousness Sub-stage.

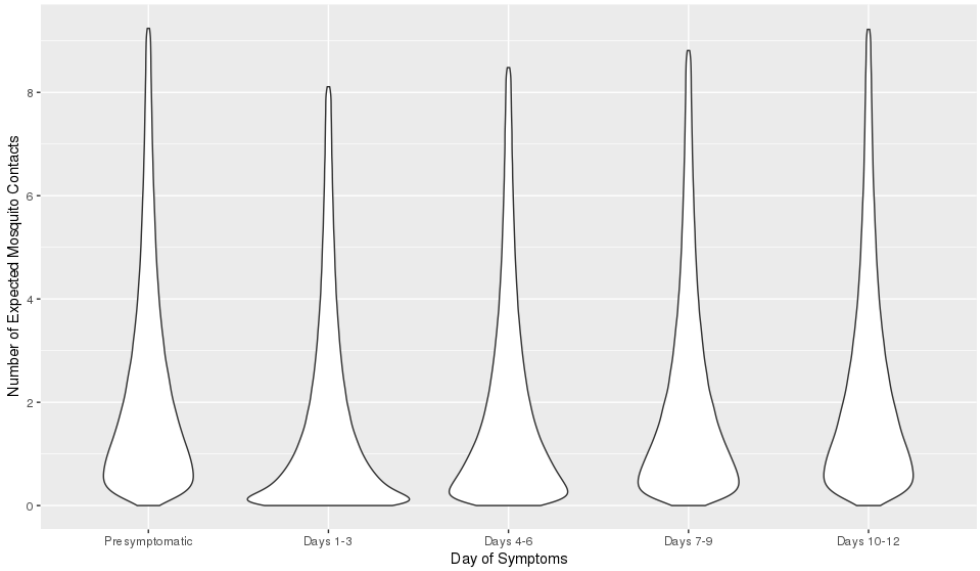


Figure S4.6: Distribution of Expected Mosquito Contacts at Each Infectiousness Sub-stage, Separated Based on Top 20/Bottom 80% of Expected Bites Pre-exposure.

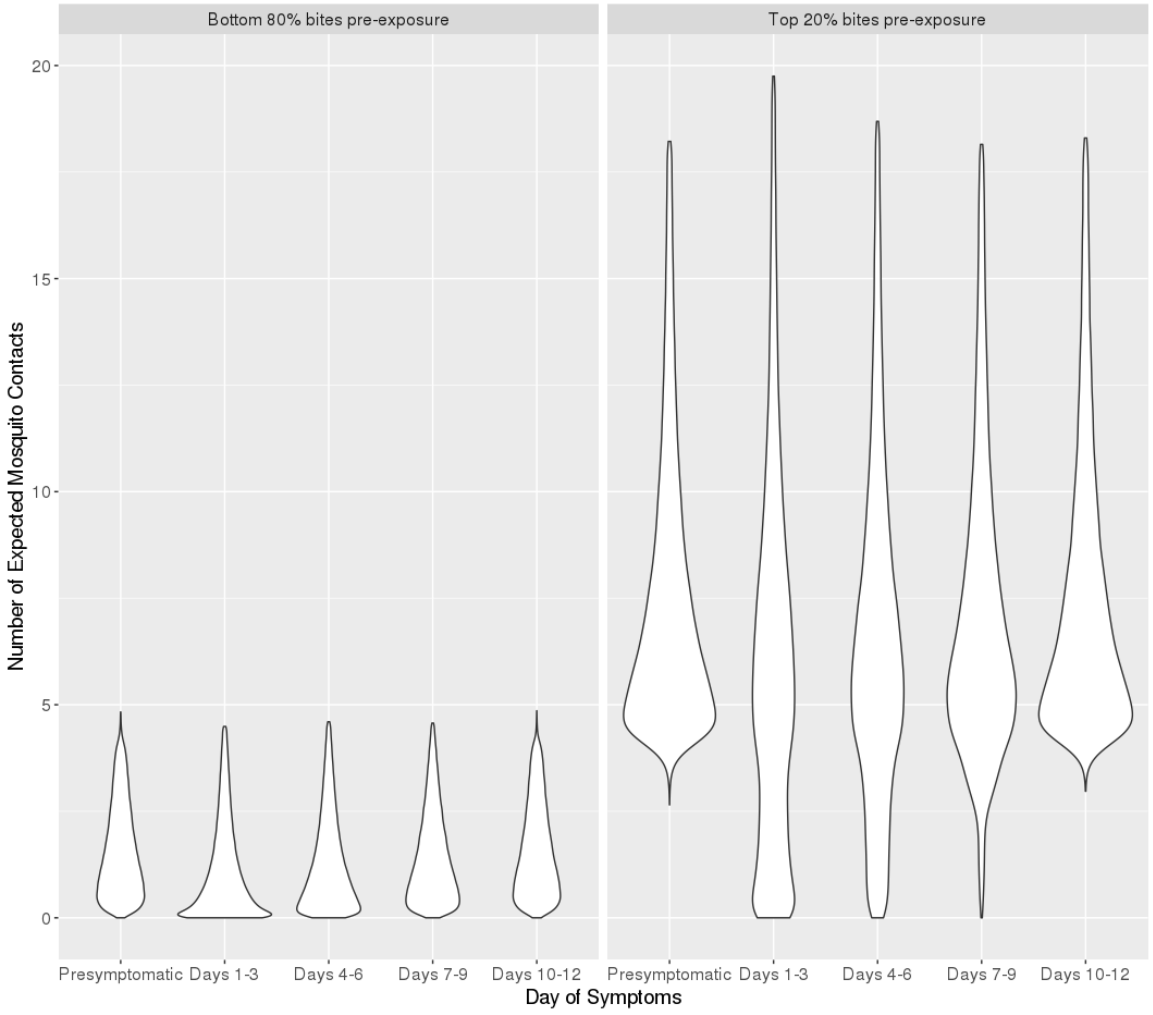


Figure S4.7: Distribution of Change in Expected Mosquito Contacts at Each Infectious Sub-stage Relative to Pre-exposure Values, Separated Based on Top 20/Bottom 80% of Expected Bites Pre-exposure.

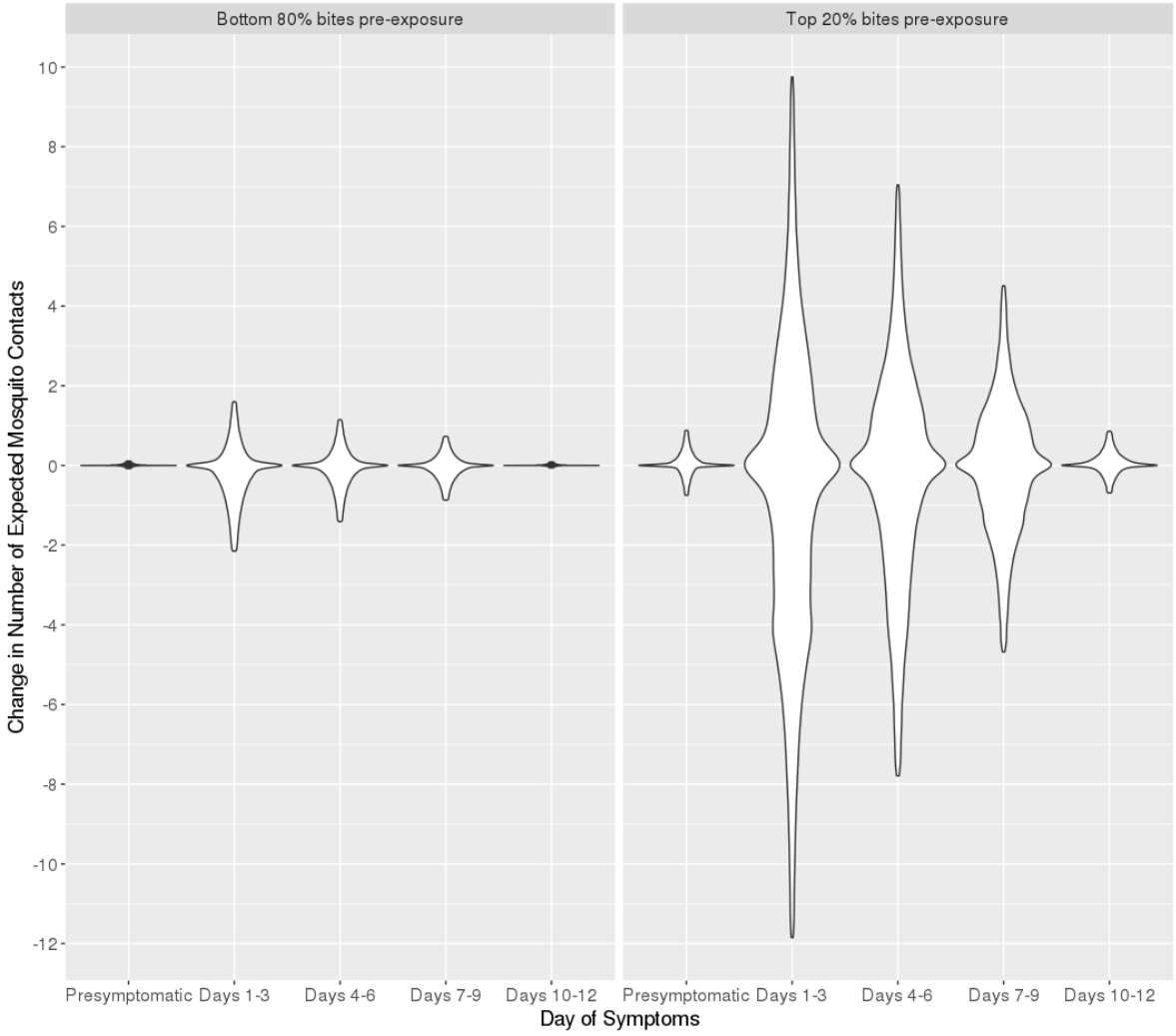


Figure S4.8: Distribution of Percent Change in Expected Mosquito Contacts at Each Infectious Sub-stage Relative to Pre-exposure Values, Separated Based on Top 20/Bottom 80% of Expected Bites Pre-exposure.

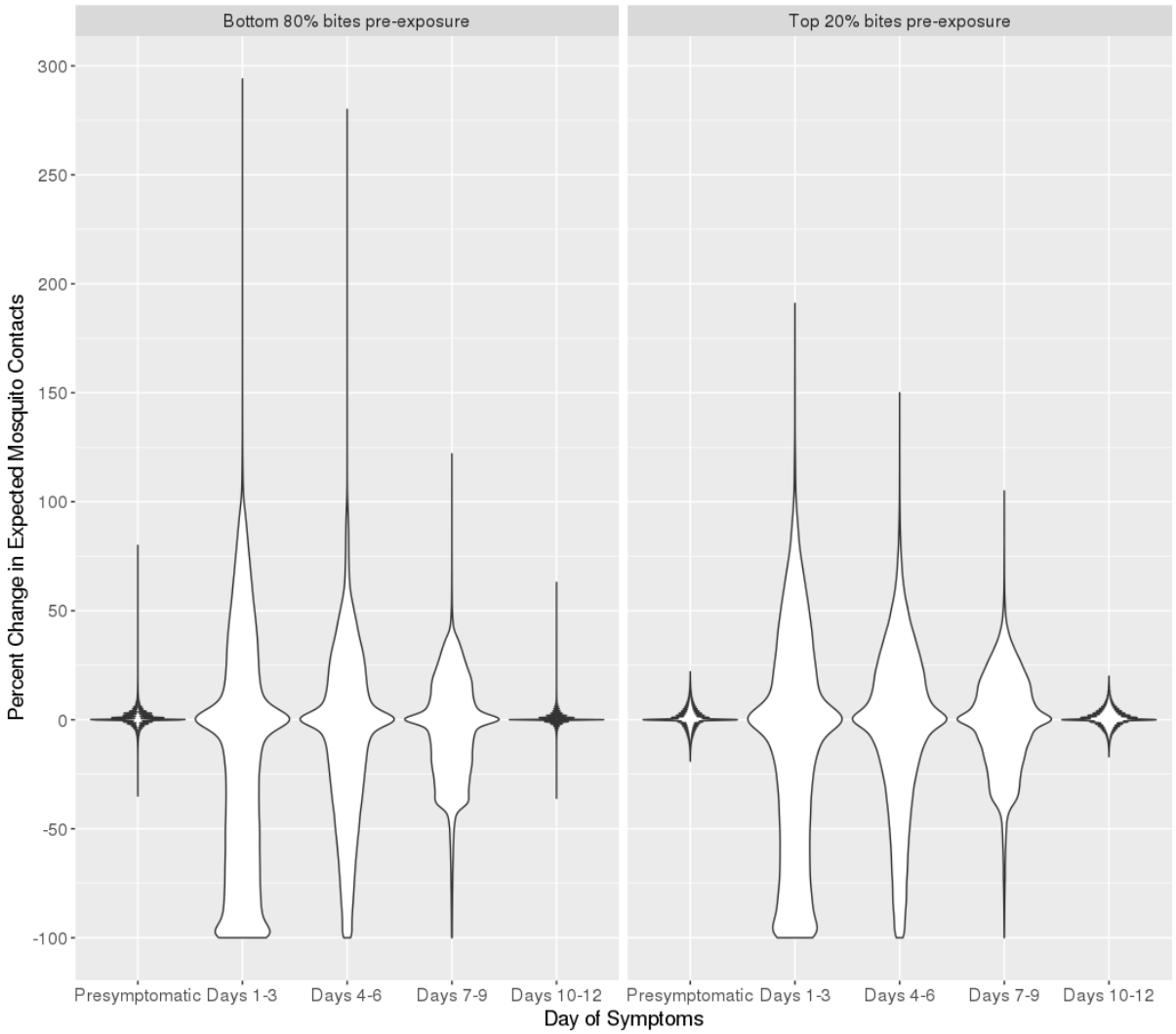


Figure S4.9: Distribution of R_{norm} and $R_{movement}$ values for Only Symptomatic Individuals in the Scenario With 70% Asymptomatic Cases and 30% Symptomatic Cases. Outliers were removed.

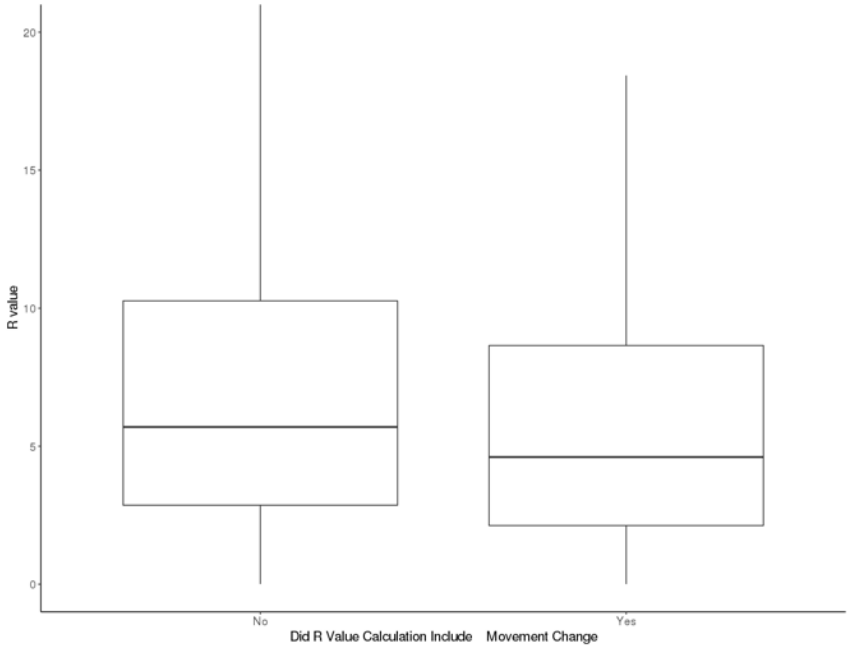


Figure S4.10: Distribution of R_{change}, R_{change}(home), and R_{change}(other houses) values for Only Symptomatic Individuals in the Scenario With 70% Asymptomatic Cases and 30% Symptomatic Cases. Outliers were removed. The red line represents no change.

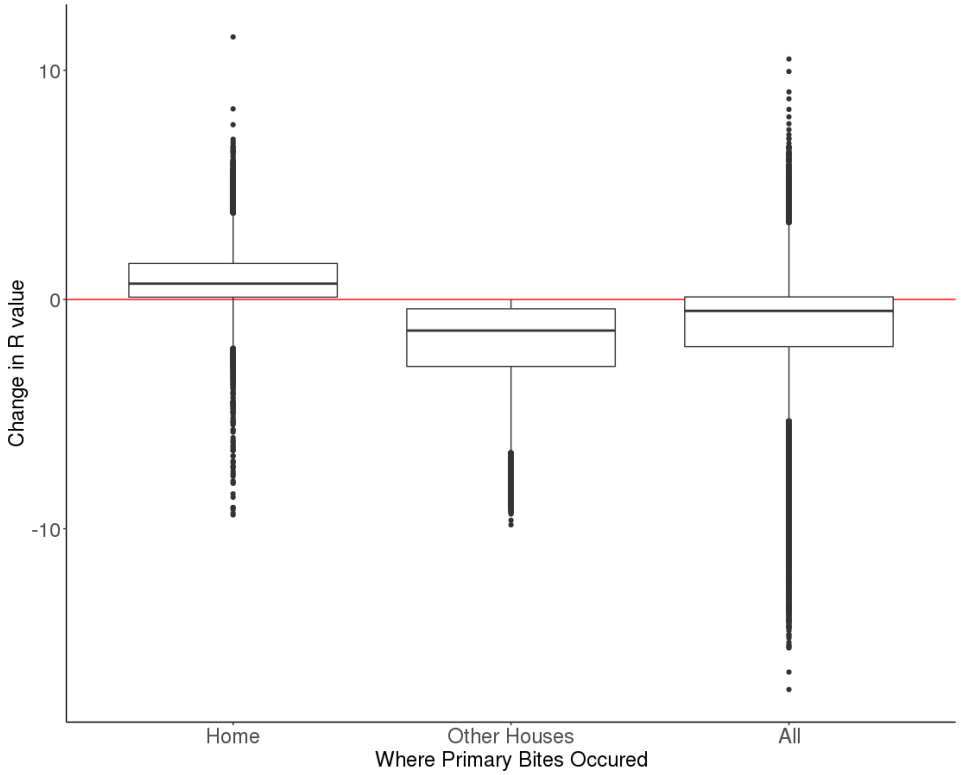


Figure S4.11: Expected Onward Transmission Values With and Without Movement Changes Accounted For, Separated by Where Primary Bites Occur and Where Secondary Bites Occur, for Only Symptomatic Individuals in the Scenario With 70% Asymptomatic Cases and 30% Symptomatic Cases. (a) gives onward transmission for primary bites occurring at home (red) and at other houses (blue) both without (left) and with (right) movement change included. (from left to right: R_{norm}(home), R_{norm}(other houses), $R_{movement}$(home), and $R_{movement}$(other houses)) (b) gives onward transmission for secondary bites at the home of the primary infected individual (red) and at other houses (blue).

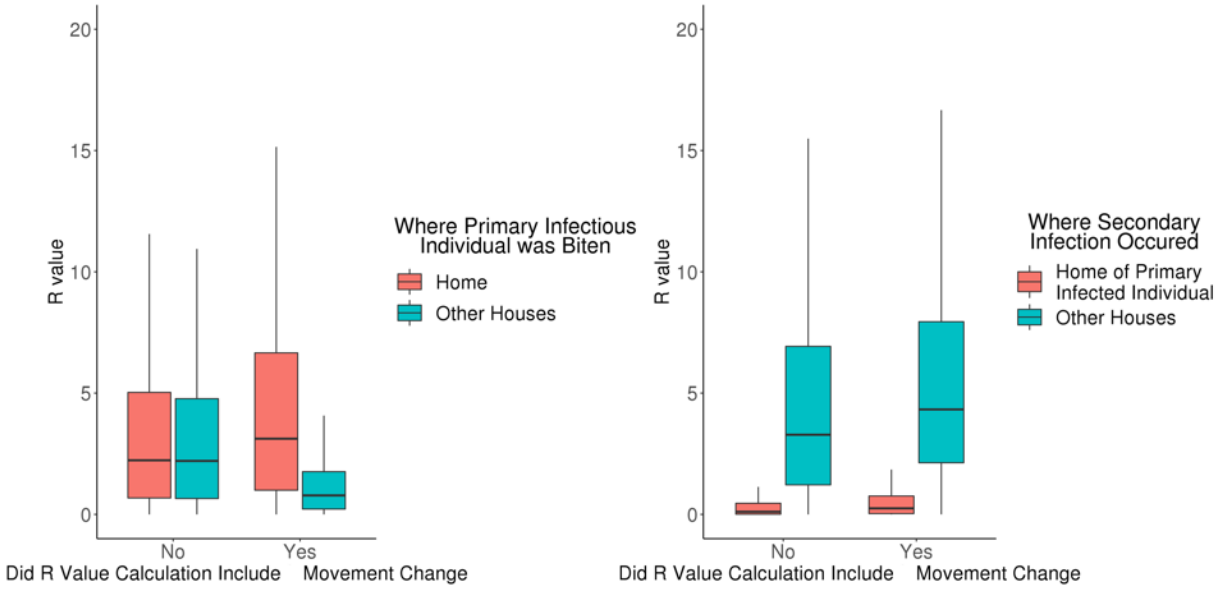


Figure S4.12: Distribution of Expected Mosquito Contacts at Each Infectiousness Sub-stage for Only Symptomatic Individuals in the Scenario With 70% Asymptomatic Cases and 30% Symptomatic Cases.

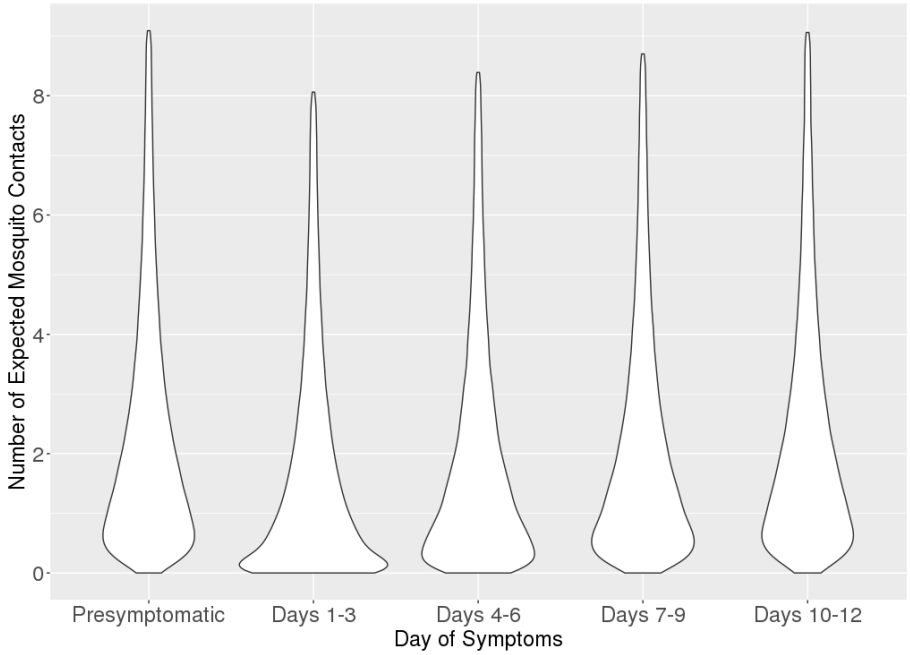


Figure S4.13: Distribution of Expected Mosquito Contacts at Each Infectiousness Sub-stage, for Only Symptomatic Individuals in the Scenario With 70% Asymptomatic Cases and 30% Symptomatic Cases, Separated Based on Top 20/Bottom 80% of Expected Bites Pre-exposure.

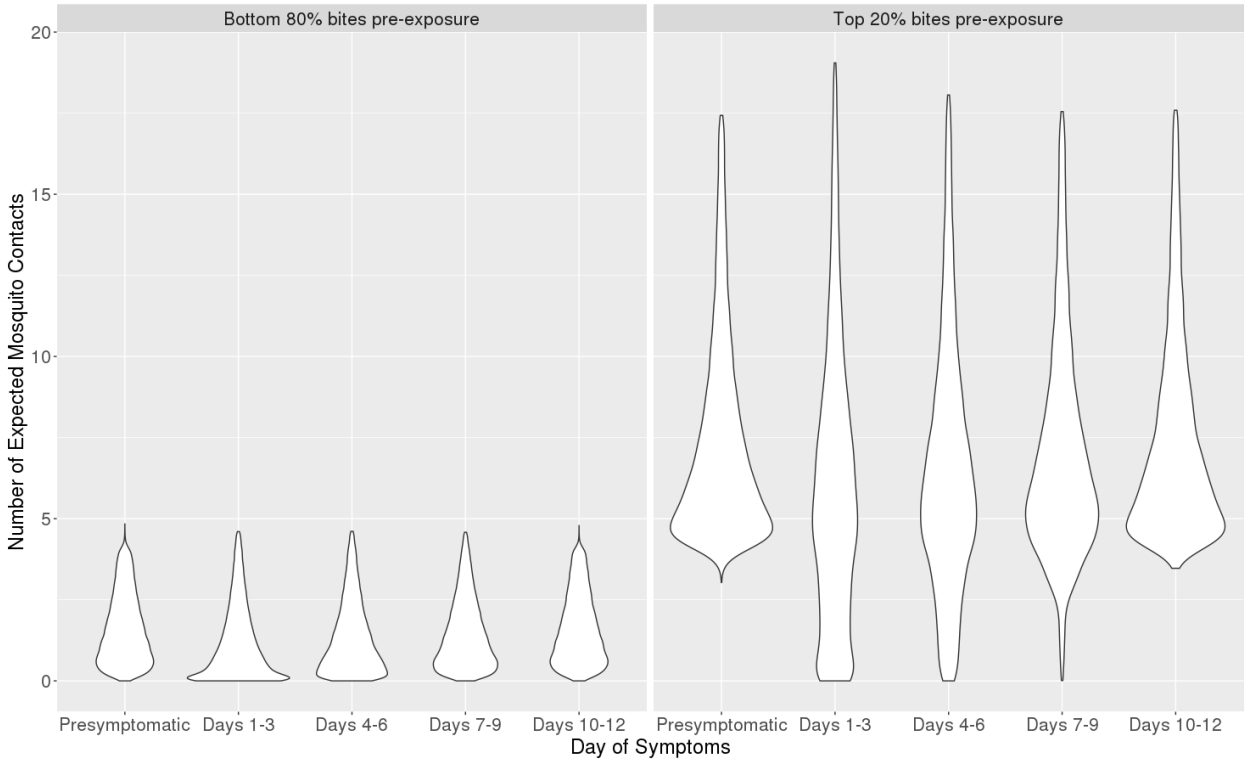


Figure S4.14: Distribution of Change in Expected Mosquito Contacts at Each Infectious Sub-stage Relative to Pre-exposure Values, for Only Symptomatic Individuals in the Scenario With 70% Asymptomatic Cases and 30% Symptomatic Cases, Separated Based on Top 20/Bottom 80% of Expected Bites Pre-exposure.

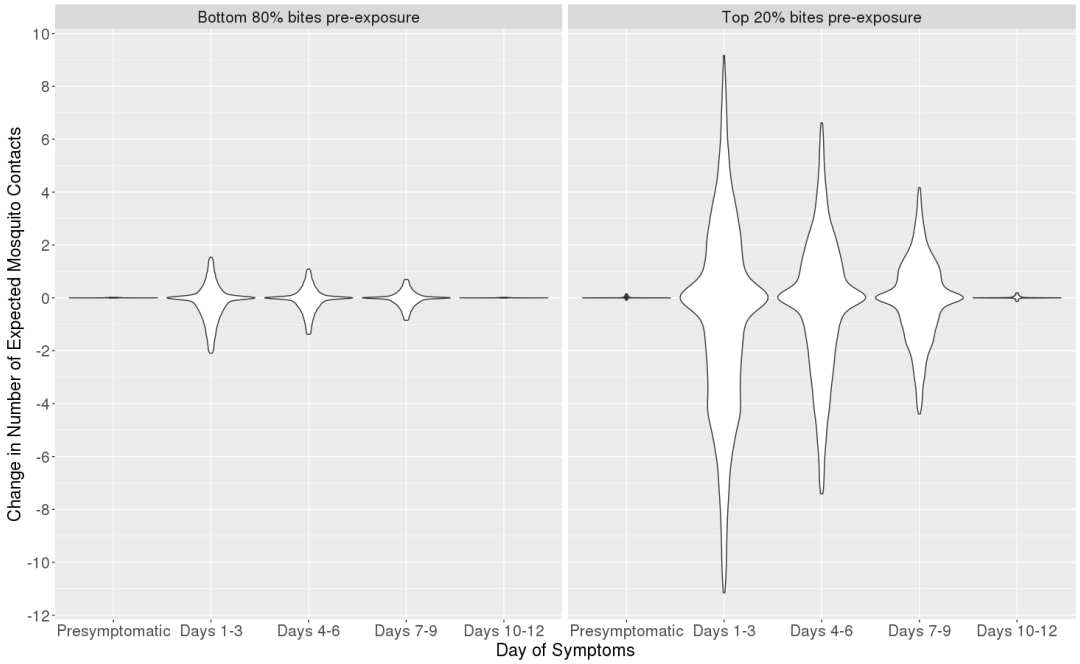
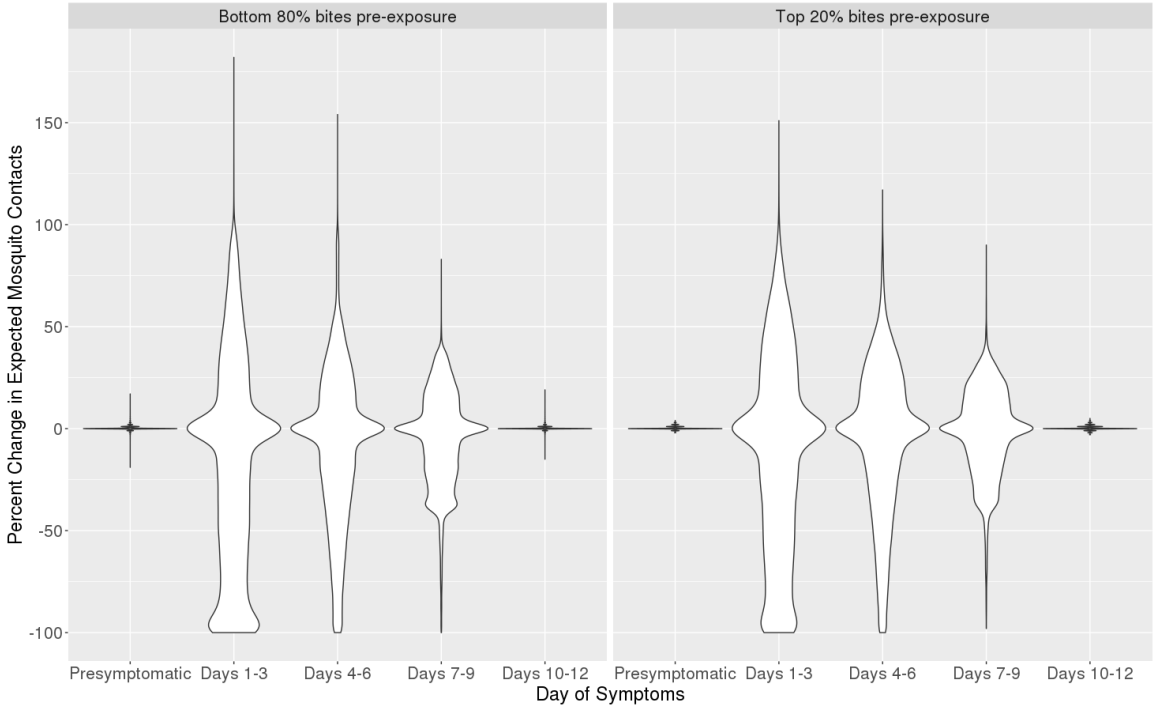


Figure S4.15: Distribution of Percent Change in Expected Mosquito Contacts at Each Infectious Sub-stage Relative to Pre-exposure Values, for Only Symptomatic Individuals in the Scenario With 70% Asymptomatic Cases and 30% Symptomatic Cases, Separated Based on Top 20/Bottom 80% of Expected Bites Pre-exposure.



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Chapter 5: Conclusion

Summary of Results

The overall goal of this research was to determine the importance of dynamic human mobility on human-mosquito contact networks that lead to DENV transmission heterogeneity. Chapters 2 and 3 describe the mobility changes seen for individuals with symptomatic dengue infection in Iquitos, Peru and for their social network contacts. In Chapter 2, I found empirical evidence of the coupling between human mobility and symptom severity, with symptomatic dengue cases experiencing mobility changes throughout their illness period, dependent on both the day of illness and their subjective sense of well-being. The largest decrease in mobility occurred during the first three days of symptoms, which is also the time when infectiousness peaks for dengue infection. Further, while individuals experienced changes in the types of locations they visited, the proportion of residential location being visited stayed consistent throughout illness.

In Chapter 3, I describe how symptomatic dengue infection can also cause mobility changes for the social network contacts of the ill individual. These changes were, however, much less common than expected. Contacts designated as “routine visitors” continued to visit the symptomatic individual during illness, most with awareness of the illness. While the vast majority of symptomatic individuals received help, most caregivers were housemates of the individual and while they may have made slight mobility changes, only 28% made changes drastic enough for their work to be affected. The largest effect was seen when female adults were ill, likely because they acted as the caregiver of the house for their children and/or spouse, whereas when they were ill the working spouse would have to change their schedule to help.

Chapter 4 examines the impact that symptomatic mobility change can have on human-mosquito contacts and onward transmission of DENV. When accounting for dynamic mobility change throughout the illness period (parameterized based on Chapter 2), there were significant changes in the number of expected mosquito bites an infectious individual would receive and the location they would occur. Consequently, the vast majority of primary infectious bites (bites where an infectious individual transmits DENV to a susceptible mosquito) contributing to an individual's expected onward transmission occurred in their home, with the rest of their activity space playing a severely diminished role. Comparatively, when an individual was susceptible the home and the activity space contributed equally to infectious mosquito exposure. Therefore, accounting for mobility change when symptomatic leads to a disconnect between the exposure and onward transmission processes.

This distinction between exposure and onward transmission is particularly important in the lens of dengue prevention and control. A common control method is reactive insecticide spraying, focusing on homes of reported dengue cases. This approach may help decrease onward transmission of the virus by symptomatic individuals, due to the amplified role of the home; however, it may only be marginally successful in preventing exposure to DENV, given the role of the activity space. Further, the importance of the activity space for presymptomatic and asymptomatic infectiousness will likely cause reactive spraying to fail in controlling an epidemic. The best strategy for preventing an epidemic may be limiting exposure by practicing avoidance behavior: susceptible individuals (or those without symptoms) not visiting houses with infectious individuals (and likely infectious mosquitoes). We found in Chapter 3, however, that this prevention practice was not very common for the social contacts of symptomatic dengue cases.

In this dissertation, I found empirical evidence of a coupling between human mobility and symptom severity. This coupling, and other heterogeneous factors, were included in a model of disease transmission in order to better understand how each factor impacts disease dynamics, both individually and in relation to the other heterogeneities. The results emphasized the importance of couplings in determining the people and places that drive disease transmission.

Future Work

The results of this research lead to multiple avenues for future exploration. Future studies on the mobility changes of caregivers should also be considered. While only 28% of caregivers have large enough changes for their work to be affected, there are likely smaller changes in mobility that are occurring to accommodate the ill individual. While previous studies have been done on caregiving behavior, they focus on the monetary effect of caregiving, rather than the effect on daily patterns. Studies on the mobility changes of those living with symptomatically ill individuals could provide more robust data to accurately predict the effect of mobility on DENV transmission [1-6].

Further, given the predicted impacts of symptomatic mobility change on heterogeneous DENV transmission (seen in Chapter 4), it is imperative to also examine the possible effects of mobility changes by the social network contacts of the ill individuals. In Chapter 4 our model assumed the social contacts of a symptomatic individual stop visiting during the illness period. In Chapter 3, however, routine visitors continued to visit throughout the individual's illness. Accounting for this could have a large effect on DENV transmission, as susceptible individuals could be exposed to the infectious mosquitoes in the ill person's home. Further, caregiving behavior was shown to affect the work of approximately a third of helpers, the vast majority of

whom were housemates. This is another mobility behavior that could affect DENV transmission and should be further explored.

Another important line of research that should be considered is the role of presymptomatic and asymptomatic individuals. Approximately 70% of dengue infections are characterized by mild or no symptoms [7-9]. Further, DENV viremia reaches levels infectious to mosquitoes a few days prior to symptom onset, leading to a pre-symptomatic infectious period during which individuals' routine is not impacted by illness [10, 11]. If individuals with presymptomatic or asymptomatic infectiousness act as caregivers/visitors, spending time at the home of the symptomatically ill individual and possibly decreasing time at other locations could impact their expected onward transmission.

Human mobility patterns can be impacted in a variety of ways in the presence of symptomatic dengue transmission, all of which have the ability to affect exposure to human-mosquito contacts and onward DENV transmission. Here, we described the mobility changes of the symptomatically ill individual and their social network contacts and examined the possible impacts of symptomatic mobility changes. Further research can focus on the impact of social network contacts changing their mobility, the importance of "hidden" infectiousness (presymptomatic and asymptomatic infection), and the efficacy of reactive vector control in order to better understand the complex interaction of symptoms, mobility, and infectiousness.

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participation. JRC has also received funding for scientific research from Sanofi Pasteur. JGLY is an employee of Sanofi Pasteur. This does not alter our adherence to all PLOS policies on sharing data and materials.
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