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Socioeconomic and Environmental Factors Associated with the Risk of Dengue Fever Incidence in Guatemala (2017-2018)



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# Socioeconomic and Environmental Factors Associated with the Risk of Dengue Fever Incidence in Guatemala (2017-2018)

A Thesis submitted in partial satisfaction of the requirements for the degree of Master of Science

in

Public Health

by

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Professor Andrea Joyce, Chair
Professor Alec Chan-Golston
Professor Ricardo Cisneros
Professor Colleen Naughton

2022

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# ABSTRACT

Kasem Umer Salim
Master of Science in Public Health
University of California Merced, 2022
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Dengue fever is a mosquito-borne illness that infects 390 million people annually. Dengue outbreaks in Guatemala have been occurring more often and at increased rates since the first dengue outbreak in Guatemala in the 1970s. This study will examine environmental and socioeconomic factors associated with dengue in Guatemala at the municipality (county) level. Socioeconomic factors included population density, literacy, use of cellphones, computers, and the internet (CCI), Mayan language speakers, economic activity, and attending school. Environmental factors included elevation, temperature, and precipitation. The relationship between our environmental and socioeconomic predictor variables and the Dengue cases outcome variable was initially evaluated through chi-square tests of independence and one-way ANOVA, and then again through three zero-inflated negative binomial regression models (Socioeconomic, Environmental, and Combined). For all models, temperature and elevation were concerned as predictors of zero-inflation. Predicted rates of Dengue Fever incidence and adjusted confidence intervals were calculated after increasing mean yearly temperature by 1°C. In the combined model the significant variables included population density, use of CCI, attending school, and Mayan language speakers. There was a positive relationship between use of CCI and Dengue Fever and negative relationships between population density, attending school, and Mayan language speakers and Dengue Fever. Elevation was significant as a predictor of zero-inflation for all three regression models. The Ayutla, Ocós and Champerico, three municipalities with the highest mean yearly temperature, all had increased rates of Dengue Fever incidence following a 1°C increase in temperature, while the municipality of Guatemala had a decreased rate. This research suggests that socioeconomic factors may play a larger role in predicting risk of Dengue incidence in Guatemala when compared to environmental factors. The predicted rates of Dengue Fever also highlight the potential effect climate change (in the form of increasing temperature) can have on Dengue Fever incidence in Guatemala.

# Introduction

## Global Burden of Dengue

Dengue Fever is one of the most prevalent mosquito-borne diseases impacting about half of the world's population with populations from 129 countries at risk of Dengue virus infection (WHO, 2022). The actual number of Dengue cases is underreported due to many asymptomatic or self-managed cases (WHO, 2022). Bhatt et al. (2013) estimated 96 million Dengue virus infections being diagnosed clinically and 390 million total Dengue virus infections per year (Bhatt et al. 2013). Additionally, Zeng et al. (2021) approximated the number of deaths due to Dengue fever increased from 16,957 in 1990 to 40,467 in 2017 and 2,922,630 disability adjusted life years (DALYs) globally attributable to Dengue Fever in 2017 (Zeng et al. 2021). Although Dengue incidence and deaths appear to have decreased for 2020 and 2021, COVID-19 most likely limited case reporting in many countries (WHO, 2022).

## *Aedes aegypti* and Dengue

*Aedes aegypti* are the primary vector of Dengue virus transmission to humans. The *Aedes aegypti* life cycle begins with female *Aedes aegypti* laying eggs near or inside pools of water as small as a teaspoon of water. Eggs then hatch into larvae which undergo four larval stages until developing into pupae. Pupae then undergo metamorphosis and change their organs and exoskeleton to prepare for the next stage, the adult mosquito. Adult *Aedes aegypti* can act as a vector for transmission of diseases with Dengue being one of the most prominently transmitted (CDC 2020, Rodhain et al. 2001, Ramchurn et al. 2009). *Ae. aegypti* prefer their larval habitats to be in containers near areas with a high building density (Tedjou et al. 2019). *Ae. aegypti* favor tropical and subtropical areas of the world; however, *Ae. aegypti* distribution will only increase over time as climate change will result in higher global temperature leading to currently unfavorable areas being slowly transformed into more tropical or subtropical areas (Khormi et al., 2014).

Dengue is characterized by four serotypes, all of which are transmitted to humans through a mosquito vector, such as *Aedes aegypti*. When a person is bit by an *Ae. aegypti* mosquito and infected with Dengue, they can develop mild or severe symptoms. Mild symptoms include fever, aches, and pains, nausea, and vomiting, and/or a rash which can be confused for the symptoms of common illnesses (CDC, 2019). Once an individual has had Dengue, infection with a different strain can result in Hemorrhagic Dengue (also called severe dengue). Severe Dengue can result in life-threatening symptoms in only a few hours after infection and requires hospitalization.

In order to diagnose Dengue, clinicians consider whether a symptomatic patient has recently traveled to a Dengue-endemic area in the two weeks prior to symptom occurrence. After determining if a patient possibly has Dengue, the patient undergoes diagnostic testing in the form of nucleic acid amplification tests (NAATs), serologic tests, or cross-reactive flaviviruses. People that are infected with Dengue contain viral genomic sequences. Tests such as rRT-PCR or Dengue nonstructural protein 1 (NS1), NAATs, use a single acute-phase serum specimen that was obtained from a symptomatic patient within 7 days since symptom occurrence and identify the presence of either the rRT-PCR or NS1. Presence of either can be considered as a confirmation of Dengue infection as long as the symptoms and travel history also indicate Dengue infection. Serologic testing can be done through IgM Antibody Capture Enzyme-Linked Immunosorbent Assay (MAC-ELISA). IgM antibodies can be detected in Dengue-infected patients approximately 4 days after symptom onset. Detection of IgM antibodies becomes more useful than NAATs if it has been over a week since symptom occurrence. MAC-ELISA results can become complicated if there is cross-reactivity with other flaviviruses such as Zika. In cases with cross-reactive flaviviruses present, a combination of NAATs and MAC-ELISA is recommended to diagnose Dengue (CDC, 2019).

Dengue infections are the result of four viruses/serotypes: DEN-1, DEN-2, DEN-3, and DEN-4. Each of the four serotypes can cause the same clinical manifestations after infection, including asymptomatic Dengue and Dengue Hemorrhagic Fever (Whitehead et al. 2007). Additionally, antibodies created from infection from one serotype will not prevent repeat infection from one of the other three serotypes; therefore, it is possible to be infected with the Dengue virus up to four times with each consecutive infection having a higher risk of severe Dengue (Yung et al. 2015). DEN-2 makes up approximately 57% of all Dengue infections with DEN-1 making up 22%, DEN-3 making up 17% and DEN-4 making up 4% of all Dengue infections. Yung et al. (2015) conducted a study on clinical differences between the four Dengue serotypes and concluded that patients infected with the DEN-1 serotype have a higher risk of developing Dengue Hemorrhagic Fever when compared to DEN-2 and DEN-3 (there were not enough samples of DEN-4 infections for conclusive results) (Yung et al. 2015).

**Climate and Dengue**

Naish et al (2014) conducted a systematic review of Dengue and found that climate change will result in increased climatic suitability for Dengue transmission as well as a geographical expansion of the regions at risk of Dengue. Climate change will also increase the rate of mosquito development, reduce virus incubation time, and create more breeding sites for *Ae. aegypti* (Naish et al. 2014). *Ae. aegypti* distribution, and thus inherently Dengue distribution, will expand as climate change will result in higher global temperature leading to currently unfavorable areas being slowly transformed into more tropical or subtropical areas (Khormi et al., 2014). Patz et al. (1998) examined the potential risk of increased disease transmission posed by climate change using computer-based simulation analysis. They found the largest increase in global epidemic potential in temperate regions. They also found that at increased temperatures, less mosquitoes will be needed to maintain the endemicity of regions where Dengue already is endemic (Patz et al. 1998). Hales et al. (2002) concluded that climate change occurring would result in an increase in land that is suitable for Dengue transmission which will lead to Dengue affecting a larger percentage of the population (Hales et al. 2002). Tran et al. (2020) studied the potential threshold effects of climatic factors on Dengue vector indices and found that an increase in 1°C in regions with an average warmer temperature (30.17 °C) resulted in a larger increase in Dengue infection rates than a 1°C increase in regions with an average colder temperature (27.21 °C) (Tran et al. 2020).

### *Aedes aegypti* and Dengue in California

*Ae. aegypti* first appeared in California in the summer of 2013 in the coastal county of San Mateo as well as the Central Valley counties of Fresno and Madera (Gloria-Soria et al. 2014). These migrating mosquitoes likely originated from the southeastern United States of America where Dengue and *Ae. aegypti* has long been established (Gloria-Soria et al. 2014). *Ae. aegypti* are currently present in 22 out of 58 counties in California including the following counties: Butte, Fresno, Imperial, Kern, Kings, Los Angeles, Madera, Merced, Orange, Placer, Riverside, Sacramento, San Bernardino, San Diego, San Joaquin, Santa Barbara, Shasta, Stanislaus, Sutter, Tulare, Ventura, and Yolo. Notable cities that have *Ae. aegypti* present are Sacramento, Merced, Madera, Atwater, and Los Angeles (CDPH 2021). Los Angeles, in particular, might be at risk of *Aedes aegypti* outbreak. Donelley et al. (2020) conducted a cross-sectional study on 162 households in Los Angeles County. They found that *Aedes aegypti* abundance was higher in lower-income neighborhoods and around households with larger outdoor areas, greater densities of containers with standing water, less frequent yard maintenance, greater air-conditioner use, more rain-exposed containers in the home, and more plotted plants indoors (Donelley et al. 2020).

There have been zero locally acquired Dengue infections in California as of 2022 (CDPH 2022). The presence of Dengue in California is fully due to travel-associated infections. Rivera et al. (2020) approximate that 16% of all travel-associated Dengue virus infections in the US are attributable to California (Rivera et al. 2020). Rivera et al. (2020) concluded California, New York, Hawaii, and Texas were the US states that best demonstrated the ongoing risk for local Dengue virus transmission after the subsequent introduction of travelers infected with travel-associated Dengue Fever. CDPH tracks the reported travel-associated Dengue infections for all California counties since 2016. Los Angeles, Alameda, Orange, San Diego, and Santa Clara counties have had the highest counts of travel-associated Dengue infections since 2016; however, in the last few years there have been COVID-19 related travel restrictions which have resulted in only 28 travel-associated infections in all of California for 2021 and currently only seven reported cases for 2022 (CDPH 2022). Conversely, a recent Dengue outbreak in Florida resulted in 413 cases of Dengue fever (most of whom were travel-associated infections from Cuba) and this increase in travel-associated infections lead to 18 locally acquired cases from which one woman died (Sharp et al. 2021). Travel-related Dengue infections do need to be carefully monitored as they can sire locally acquired Dengue infections if left unchecked.

### Factors Associated with Dengue in Guatemala, Central America

Guatemala is located in Central America. It is a small country, approximately the size of Kentucky (One World Nations Online 2022), on the Pacific Coast south of Mexico. Generally, the terrain has a low-lying coastal zone, and interior highlands with altitudes up to 4,211 meters. Dengue is widespread in Central America including in Guatemala (Castillo Signor et al. 2020). The mosquito *Aedes aegypti* was considered eradicated from Guatemala in 1959 (PAHO&WHO 1973) but has been reintroduced and since then Dengue outbreaks have occurred. Dengue fever outbreaks first reemerged in Guatemala in the late 1970s. The second outbreak did not occur until 1987 in the rainy season of Southern Guatemala's Escuintla. Since then, outbreaks have been occurring more often and at increased incidence rates with the largest Dengue outbreak occurring in 2010 (Ponciano et al. 2019, Signor et al 2020).

Signor et al. (2020) studied 17 years of Dengue fever surveillance data in Guatemala (from 2000 to 2016) in order to describe and identify epidemiological trends. They found that DEN1 was detected in 39.5% of cases while DEN2 was detected in 45.9%, DEN3 was detected in 10.5% and DEN4 in 4.1% of cases. They also found that immediately following Dengue epidemics, adults had a lower Dengue incidence which was likely due to increased immunity (Signor et al. 2020). Edwards et al. (2016) screened serum samples and found that 46 (32%) of 144 samples taken from the national reference laboratory in Guatemala had arbovirus coinfections of chikungunya virus and Dengue virus (Edwards et al. 2016).

Socioeconomic risk factors present in Guatemala including rapid growth of the population density, increased population mobility, increased poverty, and lack of basic services have contributed towards the spread of Dengue's epidemiological impact (Kuno 1995, Ponciano et al 2019). Wilson et al. (2002) discussed how Dengue is spreading across North, South and Central America and how vector control programs have had limited success due to human population growth. The increased use of air travel results in Dengue serotypes reaching areas they otherwise would not have, lack of diagnostic testing in poorer areas such as Guatemala, and misdiagnosis of Dengue fever for common illnesses (Wilson et al 2002). Joyce et al. (2021) conducted negative binomial regressions on Dengue cases from 262 municipalities in El Salvador and found several significant variables that can be used to predict Dengue cases in future studies and to inform prevention strategies. Dengue transmission was significantly associated with environmental factors (temperature, precipitation, and non-forested area), socioeconomic factors (poverty rate, illiteracy rate, and school attendance), infrastructure factors (percent of homes with sanitary service, municipal trash service, electricity, and cement brick flooring) and population density (Joyce et al. 2021).

Hotez et al. (2020) analyzed neglected tropical disease (NTD) control and malaria control to determine physical and social determinants of NTD's in Central Latin America. They discuss the steep rise in Dengue cases in Central Latin America with an incidence of 0.93 million in 2000 which increased to 3.57 million in 2017; this steep increase in Dengue was the most prevalent in Venezuela and the Northern Triangle countries of Guatemala, El Salvador, and Honduras. A possible social determinant discussed by Hotez et al. (2020) was the rise of illegal drug production and trafficking in the Northern Triangle countries which halts public health and vector control activities. Gangs that control drug trade control neighborhoods making it unsafe to perform vector control activities which results in continued Dengue spread.

Another possible social determinant discussed was the Central Latin American dry corridor, developed due to five years of drought (with occasional heavy rain) and Central America's inherent vulnerability to climate change, which has caused malnutrition, food insecurity, urbanization, and human displacements. The Indigenous populations in the Northern Triangle countries are also at a disproportionate risk of Dengue infection due to poor access to healthcare and severe poverty (Hotez et al. 2020).

Environmental risk factors have also been studied in Guatemala. Ponciano et al (2019) conducted a study using statistical analysis and mathematical modeling to conclude that, in Guatemala where temperature and humidity are favorable for *Aedes aegypti* proliferation, rainfall/precipitation can be an effective weather covariate to predict Dengue activity (Ponciano et al. 2019). Rizzo et al (2012) conducted a study analyzing Dengue vector management techniques in Guatemala. They discovered that the combination of insecticide treated materials and targeted interventions in productive container types was an effective strategy to reduce the number of adult *Aedes aegypti* in the town of Poptun in Guatemala (Rizzo et al. 2012). Other climatic factors that can affect Dengue transmission in Central America are extreme anomaly phenomena such as El Niño Southern Oscillation (ENSO). ENSO is a periodic change in the ocean and atmosphere that results in changes in air pressure in the atmosphere and by warming or cooling of the sea surface for the ocean of the tropical Pacific region. ENSO is split into two phases: El Niño, the phase when the water in the Pacific Ocean is warmer than it previously was, and La Niña, the phase when the water in the Pacific Ocean is colder than it previously was. Zambrano et al. (2010) tested the relationship between ENSO and Dengue incidence and found that the La Niña phase was significantly associated with Dengue incidence as La Niña in Honduras results in increased rainfall thereby increasing the collections of water at water-holding containers which are the favorable habitats for *Aedes aegypti* to breed (Zambrano et al. 2010).

Zambrano et al. (2019) used surveillance data of Dengue and census data to identify the spatial distribution of Dengue in Honduras from 2016 to 2019. They found that Dengue primarily involved the North and Central portions of Honduras with municipalities in these regions having >1000 cases/100,000 people (Zambrano et al. 2019). Hayes et al. (2003) studied potential risk factors that contribute to Dengue infections in El Salvador. They conducted a seroepidemiological survey in 106 randomly selected houses from the Las Pampitas community which was undergoing a Dengue outbreak. They found that 9.8% (95% CI: 5.8-13.7) of the households had recent infections, with 44% of those households being infected for the second time, and only 33% of the 106 households had acted against larval habitats around their houses. They concluded that recent infections were associated with infested discarded cans (OR=4.30), infested discarded plastic containers (OR=3.98), and discarded tire casing (OR=2.57) which had population attributable fractions of 4%, 13%, and 31%, respectively (Hayes et al. 2003). Troyo et al (2009) conducted a study using satellite imagery and ground-based data to identify urban structure and ecological characteristics correlated with Dengue incidence in Puntarenas, Costa Rica. They also found that tree cover was directly correlated with Dengue incidence and built area was inversely correlated with Dengue incidence (Troyo et al. 2009).

The objectives of this study were to investigate socioeconomic and environmental variables associated with Dengue in Guatemala. Few studies have been conducted on Dengue in Guatemala, yet there are typically tens of thousands of cases per year. This study differentiates itself from previous studies by exploring the interplay of climatic factors (temperature, elevation, precipitation) and socioeconomic factors (Mayan language speakers, economic activity, literacy, attending school, population density, urban population, indoor plumbing, and use of cellphones, computers, and internet) as risk factors of Dengue Fever in Guatemala at the population level. Specifically, the relationships between Mayan language speakers and Dengue Fever incidence as well as between use of cellphones, computers, and the internet and Dengue Fever incidence have not been explored in the literature. Consequently, the interaction between Mayan language speakers and education on the risk of Dengue Fever incidence has also not been explored. Additionally, this study was the first to consider average yearly temperature and elevation both as predictors of zero-inflation in Dengue Fever incidence. Central American countries are relatively close to the United States, and understanding factors associated with the Dengue cases in a country in geographic proximity can help us prevent Dengue from occurring in California. We currently have the *Aedes aegypti* mosquito present in California, but do not have endemic cases of Dengue Fever. Understanding which socioeconomic and environmental factors influence Dengue incidence may help us prevent cases in the United States. We hypothesized that population density, use of cellphones, computers and the internet, absence of indoor plumbing, urban population, temperature, and precipitation would be positively associated with Dengue cases, while school attendance, literacy, Mayan language speakers, economic activity, and elevation would be negatively associated with Dengue cases. We also hypothesized that modeling an increase in temperature of Guatemalan municipalities, specifically Ayutla, Ocós, and Champerico, by 1°C will increase Dengue Fever incidence in those municipalities.

## **Materials and Methods**

### Socioeconomic and Environmental Variables

The socioeconomic data came from the Guatemala census from 2018, the most recent census. The previous census was in 2002. In 2018, the population of Guatemala was 14,901,286. Guatemala is composed of 22 departments and 340 municipalities (UNFPA 2018). Municipalities are akin to counties in California. Some census variables were available at the department (state) level, while others were available at the municipality. Variables used in this study were all at the municipality level and are found on Table 1. Additional variables available from the Guatemala census of 2018 are listed in Appendix 1.

Socioeconomic variables considered for analysis were based on previous findings in the literature (Table 1). Literacy/knowledge (Hairi et al 2003) has been associated with *Aedes* control practices and school attendance has been found to impact Dengue-related knowledge, attitudes, and practices (Diaz-Quijano et al. 2018, AbhiRami et al. 2020). Income which has been associated with *Aedes aegypti* spread (David et al 2009). However, the Guatemala Census of 2018 did not contain an income variable, thus the economically active population variable was chosen as a rough estimate for income. Having access to cellphones, computers, and the internet can provide access to real-time health information for public health professional and thus contributes toward infectious disease prevention attributed to quicker surveillance and more rapid application of control strategies (Marques-Toledo et al. 2017), urban population has been found to be positively associated with the number of Dengue cases (Kolimenakis et al. 2021), and language barriers (assessed as Mayan language speakers) were found to acutely affect Dengue-related information needs and information-seeking behaviors of people who are illiterate and medically underserved (Ahmad et al. 2021). Finally, homes without indoor plumbing were found to be associated with increased risk of Dengue Fever (Trevino et al. 2020), and population density was found to be associated with *Aedes aegypti* prevalence (Kalra et al. 2017) and Dengue incidence (Schmidt et al 2011, Tsuzuki et al 2009). Population density was measured as the total population of a municipality over the area ($km^2$) of the municipality.

**Table 1**. Variables included which were available at the municipality level

| Variable Name |
|---|
| Population density (Total population/area ($km^2$) |
| Urban population |
| Population Mayan |
| Population attending School |
| Literate population |
| Population using cellphone, computer, or internet (CCI) |
| Population Economically active |
| Homes without indoor plumbing |
| Elevation (m) |
| Precipitation (mm) |
| Temperature (ºC) |

Environmental variables included the elevation at the head of the municipality (county seat), mean yearly temperature (ºC), and total annual precipitation (mm). Data available for the average minimum and average maximum yearly temperature for each municipality was averaged to determine the average mean yearly temperature for each municipality (Hernandez et al. 2019, Grainger et al. 2022). Latitude and longitude of the county seat were also obtained. Environmental variables were considered for analysis based on previous findings in the literature: mean yearly temperature has been found to be significantly associated with Dengue fever incidence (Gui et al. 2021), elevation was associated with *Aedes aegypti* prevalence (Kalra et al. 2017), as was precipitation/high rainfall (Kalra et al. 2017).

## Dengue Cases

Total Dengue cases were obtained from the Ministry of Health of Guatemala for each of the 340 municipalities for 2017 and 2018 were combined. Data available for Dengue cases did not distinguish cases as type 1, 2, 3, or 4. Cases were classified as mild (Dengue sin signos de alarma) or severe (Dengue grave, hemorrhagic). Only Dengue sin signos de alarma (not hemorrhagic) were used as the aim of this paper was to assess classic Dengue (not hemorrhagic). Also, Dengue hemorrhagic fever was excluded due to concerns of an individual being overrepresented in the data, or pseudoreplication. Cases were reported from small clinics and hospitals and made available for each municipality for the years of 2017 and 2018.

## Statistical Methods

### Descriptive Statistics

Univariate plots of all variables were constructed to examine their distributions and identify potential outliers. Bivariate plots of all variables with the Dengue cases over the two-year period (2017-2018) variable were used to visually assess the relationship between the health outcome and these variables. A binary variable for Dengue cases over the two-year period (2017-2018) was created which has “No cases” and “Yes cases” as categories and summary statistics were calculated for all variables by our binary Dengue cases variable. In addition, a categorical variable with 3 categories for Dengue cases over the two-year period (2017-2018) was created which has “No cases”, “Low cases”, and “High cases” as categories and summary statistics were calculated for all variables.

### Calculation of Incidence Rate of Dengue for Each Municipality

The incidence rate of Dengue in each municipality was calculated. The number of Dengue cases in the municipality was divided by the population in the municipality and the result was multiplied by 100,000. The rate is the cases per 100,000 people living in a municipality. The total Dengue cases per year was also determined for 2017 and 2018 for the entire country.

### Chi-Square tests of independence for Dengue Cases

Chi-square tests of independence were used to answer the general question of if each predictor variable was associated with Dengue cases for the two-year period (2017-2018) (Sokal et al. 1981). All predictor variables were standardized by the population. Data for each variable was used to create two categories, one with data lower than the median, and one with data higher than the median. First, the data for urban population, Mayan populations, populations attending school, literate population, population using computers, cellphones, and internet (CCI), population economically active, and homes without indoor plumbing were converted into percentages. Once the median was obtained for each category, the data for all municipalities were classified for each variable into the percent below the median (<50% than the median) or percent above the median (>50% than the median). Data for temperature, precipitation, and elevation were similarly classified into two categories. Chi square tests of independence were run using Stata 17.0

One-way Analysis of Variance and Covariance (ANOVA) was used to determine if there was a significant difference in the mean of each predictor variables among the three categories of Dengue cases (2017-2018), which were no dengue, low dengue, and high dengue (Sokal et al. 1981). The no dengue case category was defined as 0 cases, the low dengue case category was defined as 1 case to 10 cases, and the high dengue cases category was defined as 11+ cases. This grouping divided municipalities into two relatively equal groups with low dengue cases (103 municipalities) and high dengue cases (110 municipalities)

Tests were run at an alpha level of 0.05. If a variable was significant in a one-way ANOVA, Tukey's post-hoc tests were run between categories. All tests were implemented using Stata/BE 17.0.

**Modeling Municipality Rates of Dengue Cases**

Dengue cases were available as count data, and the distribution was found to have a Poisson-like (skewed) distribution. The Poisson distribution and Negative Binomial regression models were considered. We fit two models, Poisson regression model and Negative Binomial regression model, and ran a Likelihood Ratio test to determine whether the data were overdispersed (not normally distributed). The Likelihood Ratio test had an p-value of less than 0.001, which suggested that the data were overdispersed and indicated that Negative Binomial regression models were more appropriate for the data (Sokal et al. 1981). Upon examining data from the 340 municipalities, we determined that 127/340 had 0 Dengue cases. Due to the number of zeros in 127/340 municipalities, a consideration was made as to whether to use Negative Binomial Regression (which is for a dependent count variable), or to consider using a Zero-Inflated Negative binomial regression which accounts for the many municipalities with zero Dengue cases (Sokal et al. 1981). Model fit indices, including the Akaike information criterion (AIC) and the Bayesian information criterion (BIC), were used to compare the two regression types, and we found that the AIC and BIC were lower for the Zero-inflated negative binomial regression. Thus, the zero-inflated negative binomial regression was used instead of the Negative Binomial regression. Zero inflated negative binomial regression models were used to assess if the rate of Dengue cases per municipality over the 2017 to 2018 period was associated with the socioeconomic or environmental variables above.

Zero inflated negative binomial regressions were run separately for three groups of data, 1) socioeconomic variables (2) the environmental variables, and 3) a combined model which included the significant socioeconomic and environmental variables from both two models above. The socioeconomic variables included percent of the population attending school, percent of the population that are economically active, percent of the population that speak the Mayan language, population density, percent of the population that use cellphones, computers and internet, percent without indoor plumbing. Environmental variables included temperature, precipitation, and elevation. For each model, the predictor variables used in the regression models were population standardized and standardized at the mean. The population variable was used as the offset variable. Prior to running regressions, data were checked for correlation. Correlation matrices were created between the predictor variables. The literate individuals and urban population variables were highly correlated with other covariates in the model and thus omitted from the regressions. Two interaction terms were considered in the zero-inflated negative binomial regression model. The interaction considered were between population density and elevation, and attending school and Mayan language speakers, and their model fit data was examined to determine the best model.

For all models, temperature and elevation were concerned as predictors of zero-inflation. A categorical temperature variable was created with the categories ‘Favorable’, which contained municipalities with average temperatures less than 15°C and above 34°C, and ‘Unfavorable’, which contained municipalities with average yearly temperature between 16°C-33°C. Zero-inflated negative binomial regression models were created using temperature alone as an inflate variable and are included in the Appendix (Appendix 2, 3, 4). Coefficients with p-values less than 0.05 were considered significant. The incident rate ratios (IRRs) were obtained for all predictor variables in a model.

**Prediction Values and Adjusted Confidence Intervals**

Seven representative municipalities of the final model were evaluated by increasing the temperature of those municipalities 1°C and then performing predictions in Stata/BE version 17.0 and constructing the confidence intervals based on the seven newly constructed observations: percent economically active, percent Mayan language speakers, population density, percent attending school, and the percent using cellphones, computers, and internet, elevation, temperature, and precipitation. The previously mentioned variables were all fixed at the sample values, except for temperature which was increased by 1°C. The municipality of Guatemala was chosen as it contains the capital of Guatemala, Guatemala City. The three municipalities, San Jose Ojetenam, Concepción Tutuapa, and Todos Santos Cuchumatán, were chosen as they were the municipalities with the three lowest average temperatures (11.8°C, 11.9°C, 12°C). Ayutla, Ocós, and Champerico were chosen as they were the three municipalities with the highest average temperature (28.4°C, 28.4°C, 28.5°C). The ideal temperature for *Ae. Aegypti* survival has been identified as 20°C to 30°C (Tun-Lin et al., 2000), while other studies have specified steep increases in Dengue incidence from 22°C to 29°C (Fan et al. 2015) and high development rates for *Aedes aegypti* in the 28˚-33˚C temperature range (Dickerson 2007). San Jose Ojetenam, Concepción Tutuapa, and Todos Santos Cuchumatán all have mean temperatures far below the ranges of temperatures ideal for mosquito development, thus it is expected that the predicted rates of Dengue Fever incidence will be nonsignificant for these municipalities. The three municipalities with the highest mean yearly temperatures (Ayutla, Ocós, and Champerico) were all within the optimum temperature range (28˚-33˚C) for the development rate of *Aedes aegypti* (Dickerson 2007), thus we expected that a 1˚C increase in temperature would likely lead to a higher predicted rate of Dengue Fever incidence.

## Results

### Descriptive overview of Dengue in Guatemala

There were a total of 4,210 Dengue cases for the year of 2017, 7,414 Dengue cases for the year of 2018, and 11,624 Dengue cases for the two-year combined period in Guatemala.

### Incidence rate of Dengue in Guatemala (2017-2018)

The incidence rate of Dengue in the municipalities of Guatemala for the two-year period (2017-2018) ranges from a low of 0 cases/ 100,000 to a high of 1,923 cases/ 100,000 people. Figure 1 illustrates the spatial pattern in the incidence rates of Dengue. The municipalities with higher rates were more common on the periphery of the country. The inland portion of the country has higher elevation and had lower incidence rates. The municipalities with the top 10 incidence rates are shown in Table 2 alongside their population densities.

**Table 2**: Municipalities with the highest Incidence Rates per 100,000

| Municipality | Incidence Rate per 100,000 | Population Density |
|---|---|---|
| Pachalum | 644.87 | 211.27 |
| Guastatoya | 680.88 | 113.81 |
| Zacapa | 691.78 | 147.07 |
| Catarina | 716.33 | 368.12 |
| Antigua Guatemala | 790.38 | 667.59 |
| Cabanas | 872.37 | 98.42 |
| Teculutan | 931.71 | 83.04 |
| Genova | 1245.43 | 222.42 |
| Estanzuela | 1469.84 | 102.52 |
| Coatepeque | 1923.82 | 251.47 |

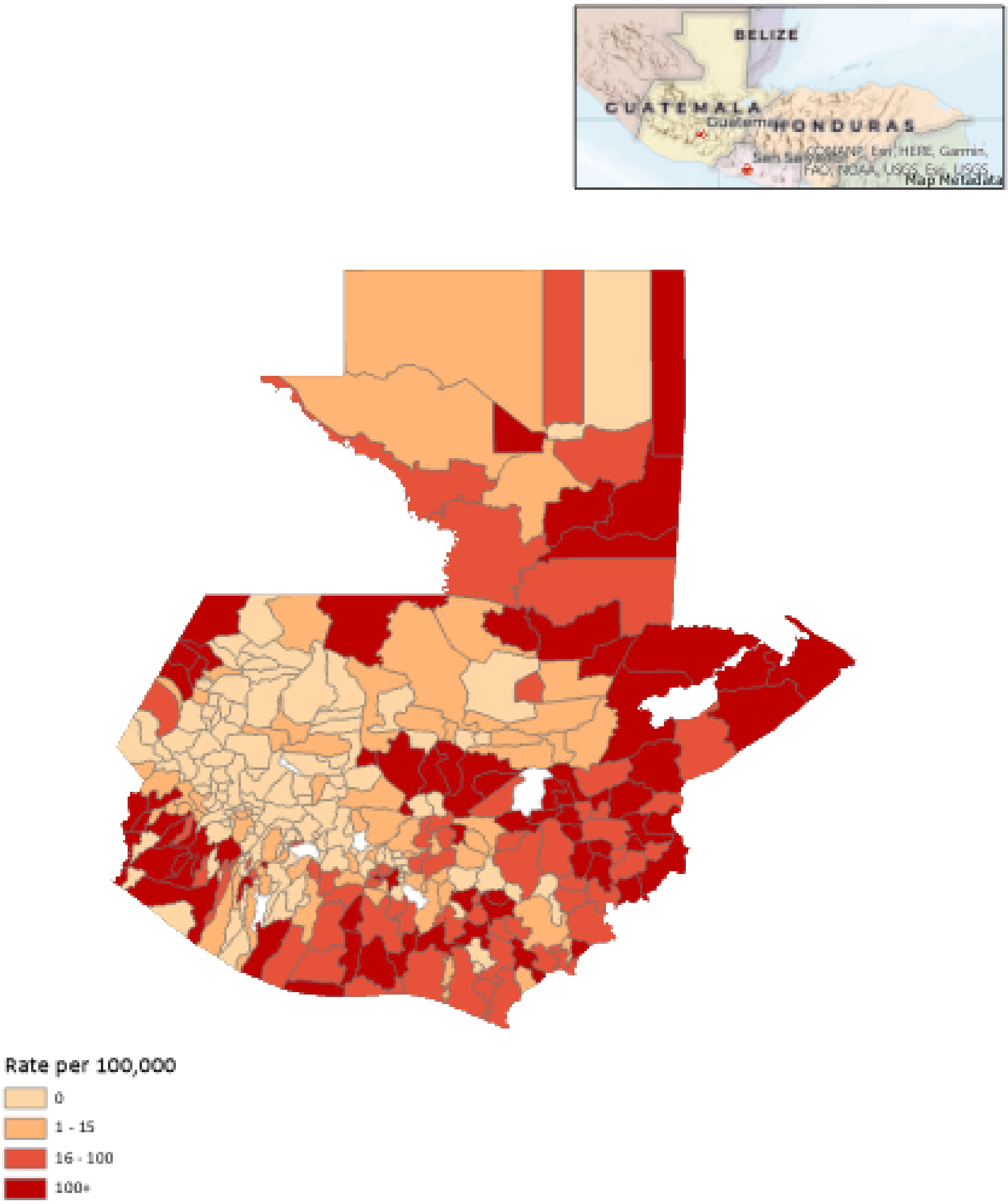


Figure 1: Dengue Fever Incidence rates per 100,000 people in Guatemala by municipality.

## Sample Characteristics and Bivariate Testing

**Table 3**. Characteristics of the Sample of Dengue Cases over the 2017-2018 Period for Municipalities with and without Dengue cases. Chi-square tests of independence were used to examine whether there was an association between Dengue cases and a predictor variable. There were 340 total municipalities. Municipalities with and without Dengue cases are shown for each variable. Significant differences are indicated as follows; * p < 0.05, ** p < 0.01, *** p<0.001

| | Municipalities with Dengue (N=213) Percent (n) | Municipalities without dengue (N=127) Percent (n) | Chi- Value |
|---|---|---|---|
| **Variable** | | | |
| % Literate Individuals | | | 15.40*** |
| % Above Median | 58.22 (124) | 36.22 (46) | |
| % Below Median | 41.78 (89) | 63.78 (81) | |
| % Attending School | | | 10.57** |
| % Above Median | 56.81 (121) | 38.58 (49) | |
| % Below Median | 43.19 (92) | 62.42 (78) | |
| % Economically Active | | | 5.54* |
| % Above Median | 54.93 (117) | 41.73 (53) | |
| % Below Median | 45.07 (96) | 58.27 (74) | |
| % Use of Cellphones, Computers, and Internet | | | 10.57** |
| % Above Median | 56.81 (121) | 38.58 (49) | |
| % Below Median | 43.19 (92) | 61.42 (78) | |
| % Urban Population | | | 2.12 |
| % Above Median | 53.05 (113) | 44.88 (57) | |
| % Below Median | 46.95 (100) | 55.12 (70) | |
| % Homes w/o Indoor Plumbing | | | 2.12 |
| % Above Median | 46.95 (100) | 55.12 (70) | |
| % Below Median | 53.05 (113) | 44.88 (57) | |
| % Mayan Speakers | | | 46.77*** |
| % Above Median | 35.68 (137) | 74.02 (94) | |
| % Below Median | 64.32 (76) | 25.98 (33) | |
| Population Density | | | 13.69*** |
| % Above Median | 42.25 (90) | 62.99 (80) | |

| | | | |
|---|---|---|---|
| % Below Median | 57.75 (123) | 37.01 (47) | |
| Elevation | | | 82.46*** |
| % Above Median | 30.99 (66) | 81.89 (104) | |
| % Below Median | 69.01 (147) | 18.11 (23) | |
| Temperature | | | 86.59*** |
| % Above Median | 69.48 (148) | 17.32 (22) | |
| % Below Median | 30.52 (65) | 82.68 (1050 | |
| Precipitation | | | 5.54* |
| % Above Median | 54.93 (117) | 41.73 (53) | |
| % Below Median | 45.07 (96) | 58.27 (74) | |

Chi-square tests of independence found that the socioeconomic variables population density ($\chi_2$=13.69, p<0.001), economically active ($\chi_2$=5.54, p=0.019), attending school ($\chi_2$=10.57, p=0.001), use of cellphones, computers, and the internet ($\chi_2$=10.57, p=0.001), Mayan language speakers ($\chi_2$=46.77, p<0.001), and literate individuals ($\chi_2$=15.40, p<0.001) were all significant (Table 3). Several variables were not significant, urban population ($\chi_2$=2.12, p=0.145) and homes without indoor plumbing ($\chi_2$=2.12, p=0.145). For environmental variables, all three variables were significant: elevation at the county seat ($\chi_2$=82.46, p<0.001), mean yearly temperature ($\chi_2$=86.59, p<0.001), and mean total precipitation ($\chi_2$=5.54, p=0.019).

**Table 4**. One-way ANOVA used to test for difference in each variable between three levels of Dengue, which were no dengue, low dengue cases, and high dengue cases. Significant differences are indicated as follows; * p < 0.05, ** p < 0.01, *** p<0.001

| | Variable Mean ± SE (n=340) | No Dengue Cases (N=127) Mean ± SE | Low Dengue Cases (N=103) Mean ± SE | High Dengue Cases (N=110) Mean ± SE | P-value |
|---|---|---|---|---|---|
| **Characteristics** | | | | | |
| % Literate Individuals | 66.78 ± 0.51 | 63.81 ± 0.89a | 67.86 ± 0.95b | 69.18 ± 0.71b | <0.001 |
| % Attending School | 23.39 ± 0.15 | 22.90 ± 0.27a | 24.10 ± 0.25ab | 23.31 ± 0.23b | 0.004 |
| % Economically Active | 31.48 ± 0.39 | 29.59 ± 0.73a | 31.48 ± 0.71b | 32.49 ± 0.53b | <0.001 |
| % Use of CCI | 11.48 ± 0.47 | 9.99 ± 0.73a | 12.70 ± 0.90ab | 12.06 ± 0.81b | 0.042 |
| % Urban Population | 42.99 ± 1.62 | 39.19 ± 2.60a | 45.61 ± 2.91a | 44.91 ± 2.93a | ns |
| % Homes w/o Indoor Plumbing | 91.54 ± 0.36 | 91.63 ± 0.62a | 91.38 ± 0.66a | 91.60 ± 0.61a | ns |
| % Mayan Speakers | 44.73 ± 2.23 | 67.00 ± 3.40a | 42.05 ± 3.97b | 21.54 ± 2.85c | <0.001 |
| Population Density | 392.14 ± 34.17 | 368.27 ± 25.77a | 444.97 ± 52.09a | 370.23 ± 89.03a | ns |
| Elevation (m) | 1246.09 ± 44.46 | 1828.59 ± 66.18a | 1162.57 ± 68.98b | 651.75 ± 45.77c | <0.001 |
| Temperature (C) | 20.92 ± 0.26 | 17.44 ± 0.39a | 21.39 ± 0.42b | 24.50 ± 0.26c | <0.001 |
| Precipitation (mm) | 1857.30 ± 38.79 | 1715.20 ± 47.01a | 1916.69 ± 73.33ab | 1965.74 ± 80.32b | 0.016 |

One-way ANOVAs were run for each predictor variable, to compare the means of the variables in with municipalities having no dengue cases, low dengue cases, or high dengue cases (Table 4). For socioeconomic variables, one-way ANOVAs revealed that there was a statistically significant difference in the variables economically active ($p<0.001$), attending school ($p=0.004$), use of cellphones, computers, and the internet ($p=0.042$),Mayan language speakers ($p<0.001$), and literate individuals ($p<0.001$). Several variables were not significant, population density ($p=0.596$), urban population ($p=0.1932$) and % homes without indoor plumbing ($p=0.9582$).

For environmental variables, all three variables had a statistically significant difference for each variable; elevation at the county seat ($p<0.001$), mean yearly temperature ($p<0.001$), and mean total precipitation ($p=0.016$). Pairwise comparison of the means (Tukey's method) was conducted for each significant variable by the Dengue three-category variable.

## Zero-Inflated Negative Binomial Regression

All socioeconomic variables were included in the zero-inflated negative binomial regression model. Population density ($p<0.001$), use of cellphones, computers, and the internet ($p=0.012$), and Mayan-speaking individuals ($p<0.001$) were found to be significantly associated with the rate of Dengue fever cases from 2017 to 2018 outcome variable (Table 5). The use of cellphones, computers, and the internet, in particular, had a high positive incidence rate ratio. An increase of one percent in the percent of people in a municipality using a cellphone, a computer and the internet increases the risk of Dengue fever incidence by a factor of 2.11 (Table 5). The zero-inflated negative binomial regression model found that of the environmental variables only temperature ($p<0.027$) was found to be a significant predictor of the rate of Dengue fever cases from 2017 to 2018 (Table 6).

**Table 5**. Socioeconomic Variables included in the Zero-Inflated Negative Binomial Regression Model Predicting Incidence Rate Ratios of the Dengue Cases of Each Municipality in 2017 and 2018 (N = 340)

| **Coefficients** | **IRR (95% CI)** |
|---|---|
| Population Density | 0.57 (0.45, 0.72) *** |
| % Attending School | 0.76 (0.56, 1.04) |
| % Use of Cellphones, Computers, and Internet | 2.11 (1.18, 3.77) * |
| % Economically Active | 0.72 (0.47, 1.09) |
| % Homes without Indoor Plumbing | 0.92 (0.74, 1.13) |
| % Mayan Language Speakers | 0.57 (0.45, 0.73) *** |
| Intercept | 0.0007 (0.0006, 0.0009) *** |
| **Inflate** | **OR (95% CI)** |
| Temperature | 0.76 (0.18, 3.32) |
| Elevation | 18.72 (4.51, 77.63) *** |
| Intercept | 0.089 (0.012, 0.65) * |

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

**Table 6**. Environmental Variables Only Zero-Inflated Negative Binomial Regression Model Predicting Incidence Rate Ratios of the Dengue Cases of Each Municipality in 2017 and 2018 (N = 340)

| **Coefficients** | **IRR (95% CI)** |
|---|---|
| Population Density | 0.92 (0.77, 1.09) |
| Elevation | 1.18 (0.31, 4.45) |
| Temperature | 4.07 (1.17, 14.14) * |
| Precipitation | 0.88 (0.74, 1.04) |
| Intercept | 0.0005 (0.0004, 0.0006) *** |
| **Inflate** | **OR (95% CI)** |
| Temperature | 0.71 (0.11, 4.84) |
| Elevation | 16.33 (2.91, 91.61) ** |
| Intercept | 0.067 (0.0057, 0.77) * |

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

The main effects zero-inflated negative binomial regression model is shown in Table 7. Population density (p<0.001), individuals attending school (p=0.006), use of cellphones, computers, and the internet (p<0.001), and Mayan-speaking individuals (p=0.009) were found to be significantly associated with the rate of Dengue fever cases from 2017 to 2018. For each of the following coefficient interpretations all other variables will be controlled for. An increase of one person/km$^2$ in population density in a municipality reduces the risk of Dengue fever incidence by a factor of 0.61. An increase of one percent in the percent of people using a cellphone, computer and the internet in a municipality increases the risk of Dengue fever incidence in the municipality by a factor pf 2.76. The risk of Dengue incidence in a municipality decreases by a factor of 0.69 for every percent increase in the percent of people attending schools in a municipality. For every percent increase in the percent of Mayan-speaking individuals in a municipality, the risk of Dengue fever incidence in that municipality is reduced by a factor of 0.72.

**Table 7**. Main Effects Zero-Inflated Negative Binomial Regression Model Predicting Incidence Rate Ratios of the Dengue Cases of Each Municipality in 2017 and 2018 (N = 340)

| **Coefficients** | **IRR (95% CI)** |
|---|---|
| Population Density | 0.61 (0.48, 0.76) *** |
| Elevation | 0.78 (0.24, 2.51) |
| Temperature | 2.90 (0.90, 9.32) |
| Precipitation | 1.06 (0.89, 1.27) |
| % Attending School | 0.69 (0.53, 0.90) ** |
| % Use of Cellphones, Computers, and Internet | 2.76 (1.65, 4.63) *** |
| % Economically Active | 0.86 (0.60, 1.24) |
| % Homes without Indoor Plumbing | 0.98 (0.79, 1.21) |
| % Mayan Language Speakers | 0.72 (0.57, 0.92) ** |
| Intercept | 0.0003 (0.0002, 0.0004) *** |
| **Inflate** | **OR (95% CI)** |
| Temperature | 0.41 (0.030, 5.80) |
| Elevation | 9.59 (1.05, 87.94) * |
| Intercept | 0.096 (0.004, 2.16) |

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

**Predicted Values and Adjusted Confidence Intervals**

Predicted rates and corresponding confidence intervals were calculated for seven representative municipalities of the final model by increasing the temperature of those municipalities based on the seven newly constructed observations of economically active individuals, elevation, average mean temperature, precipitation, Mayan-speaking individuals, population density, school attendance, economically active population, and the population using cellphones, computers, and internet (Table 8). Predicted values and their corresponding confidence intervals were also calculated for when the above-mentioned observations had all the variables (including temperature) fixed at their sample values. The municipalities of San Jose Ojetenam, Concepción Tutuapa, and Todos Santos Cuchumatán all had an incidence rate ratio (IRR) of 0 for Dengue Fever currently and for the fixed temperature scenario; similarly, there was a <1 IRR afterwards temperature adjustment. Champerico currently has an IRR of 0 for Dengue Fever from the 2017-2018; however, Champerico's Dengue fever IRR increased to 255.74 (95% CI: -67.41, 578.89) for the fixed temperature scenario and became 322.50 (95% CI: -158.48, 803.48) after the 1°C temperature increase. Likewise, Ayutla and Ocós, which had current IRRs of 356.28 and 276.73 respectfully, both had higher rates of Dengue fever from 2017 to 2018 predicting for the fixed temperature scenario and even higher IRRs after increasing temperature by 1°C [(668.92 (95% CI: 294.25, 1043.59) and (439.79 (95% CI: 5142.97, 736.61)]. Conversely, the municipality of Guatemala, which has a mean yearly temperature of 20.0°C, had an 87.84 Dengue fever incidence rate per 100,000 currently; however, both the IRRs for the fixed temperature scenario (26.44 (95% CI: 2.39, 50.49) and the 1°C temperature increase scenario [32.88 (95% CI: -158.48, 803.48)] were lower than the current IRR.

**Table 8**. Prediction Values and Adjusted Confidence Intervals

| Municipality | Current Dengue Fever (DF) IR (Incidence Rate) per 100,000 | Current Average Temperature | DF IR per 100,000 with Fixed Temperature IR (95% CI) | DF IR per 100,000 After 1°C Increase IR (95% CI) |
|---|---|---|---|---|
| Guatemala | 87.84 | 20.0°C | 26.44 (2.39, 50.49) | 32.88 (-158.48, 803.48) |
| San Jose Ojetenam | 0 | 11.8°C | 0.147 (-0.22, 0.51) | 0.183 (-0.28, 0.64) |
| Concepción Tutuapa | 0 | 11.9°C | 0.128 (-0.12, 0.37) | 0.159 (-0.15, 0.47) |
| Todos Santos Cuchumatán | 0 | 12.0°C | 0.762 (-0.04, 1.57) | 0.95 (.029,1.86) |
| Ayutla | 356.28 | 28.4°C | 537.10 (267.95, 806.25) | 668.92 (294.25, 1043.59) |
| Ocós | 276.73 | 28.4°C | 353.16 (126.37, 579.95) | 439.79 (142.97, 736.61) |
| Champerico | 0 | 28.5°C | 255.74 (-67.41, 578.89) | 322.50 (-158.48, 803.48) |

**Discussion**

The aim of this paper was to contribute to understanding how environmental and socioeconomic factors influence the distribution of Dengue in Guatemala. This was initially evaluated through chi-square tests of independence and one-way ANOVA between our environmental and socioeconomic predictor variables and the Dengue cases outcome variable, and then again through three zero-inflated negative binomial regression models.

Chi-square tests of independence found that literate individuals, attending school, economically active, use of CCI, homes without indoor plumbing, Mayan language speakers, population density, elevation, temperature, and precipitation were significant. For the one-way ANOVAs literate individuals, attending school, economically active, use of CCI, homes without indoor plumbing, Mayan language speakers, elevation, temperature, and precipitation were found to be significant. In the socioeconomic variable model, Mayan language speakers, use of CCI, and population density were significant, while in the environmental variable model we found temperature was significant. However, when all variables where combined, the significant socioeconomic variables in the regression model included population density, use of computer, cellphone, and the internet, attending school, and Mayan-speaking individuals. Notably, in the combined model, all three environmental variables, elevation, temperature, and precipitation, were found to not be significantly associated with the Dengue cases variable, which is inconsistent with past literature (Kalra et al 1997, Patz et al. 1998, Ponciano et al. 2019).

A significant finding from our study is the association between population density and Dengue fever incidence. Population density has also been found to be associated with Dengue incidence in previous studies (Kalra et al. 1997, Schmidt et al. 2011, Tsuzuki et al. 2009). Kalra et al. (1997) explored the prevalence of *Ae. aegypti* and *Ae. albopictus* populations in North, North-East and Central India. They found that the *Aedes* species were widespread in towns that were densely populated while the rural areas (less densely populated) were free of *Ae. aegypti* and *Ae. albopictus*. Tsuzuki et al. (2009) found comparable results at the household level in their study exploring the peridomestic environmental effects on repeated infestation by preadult *Ae. aegypti* in urban households. They discovered that premises with six or more residents had significantly higher odds of repeated *Ae. aegypti* infestation when compared to households with 1-3 residents. Both studies (Kalra et al. 1997, Tsuzuki et al. 2009) found positive relationships between population density and Dengue incidence and *Ae. aegypti* prevalence; however, this study found the relationship between population density and Dengue fever was negative and had an IRR of 0.61 (95% CI: 0.48, 0.76). This negative relationship might be explained by Schmidt et al. (2011) who also found a significantly negative association between population density and Dengue incidence. They found that human population densities ranging between ~3000 to 7000 people/km$^2$ in Vietnam were prone to Dengue outbreaks. These population densities were usually attributable to villages and peri-urban areas that did not have an adequate piped water supply (tap water). Our study found a negative relationship of population density and risk of Dengue fever incidence. These low population density municipalities could have villages that lack tap water and instead use water storage vessels that can be potential breeding sites for *Ae. aegypti*. We also considered whether the most densely populated areas are at higher elevation since the highest incidence areas on the map appear to be on the coast (low elevation). This interaction is discussed later in the paper.

In the past few years, technology has progressed to the point where smartphones are commonplace among the general population in both the global south and global north (Glushkova et al. 2019, Raento et al. 2009). This technological advancement can offer an opportunity to collect real-time health and geographical information for infected individuals both in and outside of the healthcare setting (Paolotti et al. 2014). This real-time data collection is an avenue that will allow public health professionals to identify infectious diseases and create mitigation strategies more quickly than ever before leading to overall fewer cases than there would have been without access to real-time health information. Having access to cellphones, computers, and the internet can provide access to real-time health information for public health professional and thus contributes toward infectious disease prevention attributed to quicker surveillance and thus quicker application of control strategies (Marques-Toledo et al. 2017). The previously discussed logic dictates that higher use of cellphones, computers, and the internet should be associated with a decreased incidence of Dengue cases as there is theoretically better surveillance and thus quicker implementation of vector controls which was our expectation. However, this study of Guatemala depicted a significantly positive association between the use of cellphones, computers, and the internet and Dengue fever cases at the municipality level (municipalities with higher number of users have increased risk of Dengue fever incidence).

A reason this positive relationship might be observed, as opposed to the expected negative relationship, is that the percent of people using of cellphones, computers or the internet can serve as an indicator for an urbanization setting. Pew Research Center (2014) conducted studies showing that smartphone ownership varies among urban and rural areas. Moreover, they found 60% of people living in urban and suburban areas owned smartphones while only 43% of people living in rural areas own smartphones, this can be due to their sociodemographic characteristics or better infrastructures (4G and Wi-Fi services) (Pew Research Center 2014, Hong et al. 2018). Thus, the Guatemalan municipalities that had high percentage of people using cellphones, computers and the internet might be linked with urbanization setting. The process of urbanization in tropical low-income countries can drive Dengue transmission via *Aedes aegypti* due to population growth, overcrowding, and manufactured larval habitats (Struchiner et al. 2015, Hong et al. 2018). Information and communication technologies (ICT), such as cellphones and computers, has also been linked with increased travel (Hong et al. 2018, Mokhtarian 2009). ICT might save time and money and give access to real-time travel information which can then be used to facilitate traveling or other activities. Urban areas are full of breeding areas for mosquitoes who will then infect humans with any number of mosquito-borne diseases, including Dengue. Additionally, these infected people might travel to other cities in the municipality, made easier due to smartphone use, furthering the spread of Dengue fever in that municipality. Therefore, vector-control officials and policy makers should consider the relationship between ICT, urbanization, and travel to understand the risk and spread of Dengue fever in Guatemala.

A notable finding of our study was the significant association between Mayan language speakers and Dengue incidence. Guatemala's official language is Spanish with 69.9% of the Guatemalan population being Spanish speakers; however, the other 31% speak one of any number of Maya (29.7%), Xinca, and Garifuna (combined 0.4%) languages (CIA 2022). Ethnic Mayans speak over 22 languages with different dialects which makes monolingualism (ethnic Mayans speaking only a Mayan language) a challenge for health promotion and health services as they are often only targeted at Spanish-speaking audiences (Instituto Nacional de Estadística 2016, PAHO 2017). Multiple studies have found Spanish fluency to be a significant predictor of health services utilization in Guatemala (Chomat et al. 2014; Ishida et al. 2012). Delayed utilization of healthcare services and information-seeking behaviors by Dengue-infected patients will delay the recording of Dengue incidence by health care facilities which will in turn lead to a slower application of vector control strategies by public health officials which will then result in increased Dengue fever incidence.

Our significant association between Mayan language and Dengue incidence might be indicative of the language barrier caused by this Mayan monolingualism on the part of Guatemalan health providers/organizations (speaking only Spanish) and on the part of ethnic Mayans (speaking only local Mayan language). For every percent increase in the percent of Mayan-speaking individuals in a municipality, the risk of Dengue fever incidence in that municipality is reduced by a factor of 0.72. Increasing the percentage of Mayan language speaking individuals in a municipality might make it more likely that healthcare workers and public health officials are also Mayan language speakers or have an interpreter; thus, limiting the language barrier during health education interventions and health care utilization.

Although this is the first study to examine the relationship between % Mayan language speakers and risk of Dengue fever incidence at the municipality level in Guatemala, several studies have examined the role of language barriers in the health education and healthcare access. Tai et al. (2022) conducted structured interviews to assess the factors that prevent mosquito-borne diseases among migrant workers in Taiwan before and after health education interventions. One of the questions asked migrant workers' perception on whether they lacked access to Dengue prevention information due to a language barrier which was not significantly different before and after the health education intervention, indicating that migrant worker's perception on the language barrier did not change due to the health education intervention. Agyemang-Duah et al. (2020) found that language barriers are one of the major factors preventing older, low-income adults from acquiring health information, while Ahmad et al. (2021) found that language barriers may acutely affect Dengue-related information needs and information-seeking behaviors of people who are illiterate and medically underserved. Wolz et al. (2014) conducted in-depth surveys of 39 immigrant Somali women and found that presence of a translator alone is not enough. Trust, accessibility, and quality of translation are crucial factors to ensure quality healthcare access. This significant association between Mayan language speakers and Dengue incidence will contribute to understanding the involvement of language barriers in Dengue-related health education, healthcare access, and information-seeking behaviors.

The final significant finding of our study was the negative relationship between school attendance and Dengue incidence (IRR=0.69 (95% CI: 0.57, 0.92)). This finding is consistent with several studies that have explored how school attendance/education has impacted Dengue-related knowledge, attitudes, and practices (Diaz-Quijano et al. 2018, AbhiRami et al. 2020). Diaz-Quijano et al. (2018) compared the knowledge, attitudes, and practices of people of different education levels in the Caribbean region of Columbia. They found that high school graduates had a higher frequency of correct answers for questions related to knowledge on Dengue symptoms and treatments. Diaz-Quijano et al. (2018) also found that graduates had a higher probability of engaging in Dengue control-related practices and attitudes when compared to other education levels. Furthermore, AbhiRami et al. (2020) conducted a Dengue-related health education program after a flood in Kelantan, Malaysia to assess the effect of health education interventions on student's Dengue-related knowledge, practices, and attitudes. They found that the health education intervention significantly improved knowledge and control-related practices in the flooded areas of Kelantan. Additionally, Ahmad et al. (2021) explored the relationship between education level and Dengue information-seeking behaviors and found that people with higher academic qualifications reported higher Dengue-related information needs when compared to people with not as high academic qualifications. This study's finding may be showing that higher percent of people attending school in a municipality might lead to more people in the municipality having Dengue-related knowledge, control-related practices and attitudes, and Dengue information-seeking behaviors which will then result in fewer Dengue cases (i.e., IRR of 0.69). Our findings will contribute towards the understanding of the role education plays in obtaining Dengue-related knowledge and guiding control-related practices and attitudes and Dengue information-seeking behaviors.

In contrast with the variables discussed previously, temperature and precipitation were not found to be associated in the combined model with the Dengue 2017-2018 cases. This result is inconsistent with most studies previously done which have found temperature and precipitation to be significantly associated with Dengue vector reproduction and transmission (Watts et al. 1987, Jansen et al. 2010, Alto et al. 2013, Morin et al. 2013); however, there are several studies that argue that there is no significant association between temperature and rainfall and Dengue incidence. Average mean temperature from 2017 to 2018 was not found to be significantly associated with Dengue fever cases from 2017 to 2018 in this study. Su et al. (2008) found a similar non-significant association between temperature and Dengue incidence over a ten-year period in Metro Manilla, Philippines. Goto et al. (2013) analyzed the effects of meteorological factors on Dengue incidence in Sri Lanka and, likewise, found that average maximum temperature and total weekly rainfall were not significantly associated with Dengue fever incidence in multiple locations in Sri Lanka. Precipitation has previously been associated with Dengue spread in combination with manufactured containers (Morin et al. 2013). Precipitation provides the water in manufactured containers, thereby creating essential breeding site for mosquito vectors.

One explanation for not finding a relationship with precipitation and Dengue in Guatemala is that in a country with Dengue as common as it is, people might be incorporating preventative strategies and removing the containers and potential breeding sites with them. These preventative actions will limit the role precipitation can have in Dengue reproduction, thereby limiting Dengue cases attributable to precipitation and possibly making socioeconomic factors greater predictors for Dengue incidence. Gui et al. (2021) offered a similar explanation after also not finding a significant association between precipitation and Dengue cases in their study looking at weather factors associated with reduced risk of Dengue transmission in Singapore. They suggested that outdoor environmental changes do not affect indoor breeding sites (domestic containers) which, according to Singapore's Ministry of Health's 2018 report on vector surveillance, accounts for 32% of potential breeding habitats (Ministry of Health 2018, Gui et al. 2021). These indoor breeding sites will be unaffected by precipitation thus possibly leading to a non-significant result. The inconsistent results of temperature and precipitation make it clear that further research is necessary to further the understanding of the relationships between temperature and precipitation and Dengue Fever incidence, especially as it pertains to indoor breeding habitats.

The interaction between population density and elevation as well as the interaction between percent Mayan language speakers and percent attending school were considered for this analysis; however, neither were found to be significantly associated with the rate of Dengue fever from 2017 to 2018. The interaction term between elevation and population density was considered due to Rijal et al. (2021) having found that the interaction between elevation and population density was significantly associated with Dengue fever incidence. Having said that, Tai et al. (2022) conducted structured interviews to assess the factors that prevent mosquito-borne diseases among migrant workers in Taiwan before and after health education interventions thus the interaction between Mayan language speakers (as a form of language barrier) and attending school (health education) might affect Dengue incidence and Dengue awareness. These interaction terms should be explored in future studies as they might provide further avenues to combatting Dengue fever.

We wanted to estimate the impact that climate change (in the form of rising temperature) might have on Dengue incidence in the municipalities of Guatemala and hypothesized that the three municipalities with the highest mean temperatures (Ayutla, Ocós, and Champerico) would have an increase in their rates of Dengue incidence. The three municipalities with the lowest average mean temperature (San Jose Ojetenam, Concepción Tutuapa, and Todos Santos Cuchumatán) had little to no change in the rate of Dengue fever incidence after increasing temperature by 1°C or for fixed temperature. The ideal temperature for *Ae. Aegypti* survival has been identified as 20°C to 30°C (Tun-Lin et al., 2000), while other studies have specified steep increases in Dengue incidence from 22°C to 29°C (Fan et al. 2015). San Jose Ojetenam, Concepción Tutuapa, and Todos Santos Cuchumatán all had mean temperatures below the ranges of temperatures ideal for mosquito development, so it is reasonable that there were no changes in Dengue incidence. On the other hand, the municipality of Guatemala had lower rates of Dengue fever incidence following the

1°C increase and fixed temperature when compared to the current rate of Dengue fever incidence from 2017 to 2018. Conversely, Ayutla, Ocós, and Champerico had higher rates of Dengue incidence for the fixed scenario when compared to current IRRs and even higher IRRs after the temperature adjustment which was consistent with our hypothesis. Tran et al. (2020) conducted a similar study assessing the potential threshold effects of climatic factors on Dengue vector indices which found that an increase in 1°C did result in an increase in Dengue infection rates, though there were variations in the magnitude of the increase depending on the temperature of the region (Tran et al. 2020). Ayutla, Ocós, and Champerico's increased rates after increasing temperature by 1°C might lend credence to 28˚-33˚C being the optimum temperature range for the development rate of *Aedes aegypti* (Dickerson 2007) since increasing those municipalities' current temperatures (28.4, 28.4, 28.5 respectfully) put them more firmly in the 28˚-33˚C range. Although, our mixed results might further indicate the interplay of climatic and socioeconomic factors influencing Dengue incidence in Guatemala.

Temperature and elevation were concerned as a predictor of zero-inflation thus were used as inflate variables for the zero-inflated negative binomial regressions. Chaves et al. (2021) has previously considered water temperature as a predictor of zero inflation for the abundance of *Ae. albopictus* (another vector for Dengue transmission). Furthermore, several studies have explored temperatures below 15°C being associated with reduced adult *Aedes aegypti* survival (Reuda et al. 1990), *Aedes aegypti* ceasing biting (Connor et al. 1924), and unsustainable flying for *Aedes aegypti* females (Rowley et al. 1968). Temperatures over 34°C have shown to be insufficient for aggregate survivals of all *Aedes aegypti* stages (Focks et al. 2000) and had a negative effect on the percentage of hatched *Aedes aegypti* eggs (Dickerson 2007). Additionally, Guatemalan land areas with elevations above 2000 meters have been modeled to have *Aedes aegypti* in only 0.90% of their land areas (Watts et al. 2017). In all zero-inflated negative binomial regression models (Table 5, Table 6, Table 7) elevation was significant as an inflate variable while temperature was not. This provides credence to the possibility that elevation is behind the zero-inflation in the data. However, there is still much to explore for temperature as an inflate variable. As mentioned earlier, several studies (Gui et al. 2021, Fan et al. 2015) have found that risk for Dengue fever incidence increases steeply from the 22°C-29°C temperature range, while other studies identified 20°C to 30°C as the ideal temperature for *Ae. aegypti* survival. Future studies might consider 20°C as the lower limit threshold.

The present study had some limitations. Income is a prominent socioeconomic factor linked with increased Dengue fever incidence (Mulligan et al. 2015, Lee et al. 2017); however, income was not included in the Guatemala census of 2018 and thus it can be a confounding variable in this study. Additionally, the school attendance variable in the Guatemala census did not specify the level of education and only signified that there was school attendance. This is a notable exclusion because several studies, as mentioned previously, have assessed varying levels of Dengue-related knowledge, practices, attitudes, and behaviors at different education levels (Diaz-Quijano et al. 2018, Ahmad et al. 2021). Temperature and elevation were used as the inflate variable as it was believed that they are the variables most attributable to the numerous zero Dengue cases, although it is possible that there is another variable not included in the model that is primarily responsible for the zero Dengue cases. Also, average mean temperature from 2017 to 2018 was used for this study; the association might be significantly associated if average minimum or maximum temperature was used in the study instead. Additionally, the temperature data we had available was a yearly average for each municipality; however, monthly data would be more useful in tracking changes and duration of dengue incidences. The Dengue fever cases data obtained from the Ministry of Health of Guatemala did not specify the serotype, which might have varying rates of incidence and transmission.

This study will contribute to understanding how environmental and socioeconomic factors interact to influence the distribution of Dengue in Guatemala. This research suggests that socioeconomic factors may play a larger role in predicting risk of Dengue incidence in Guatemala when compared to environmental factors. Future studies should continue to explore the interaction between environmental and socioeconomic factors and their effect on Dengue incidence while also including income and other environmental/climatic factors (humidity, wind speed) and addressing our limitations. Future studies should also consider exploring temperature and elevation as predictors of zero-inflation in Dengue Fever incidence. Future studies can explore how lifestyles in distinct cultures in countries apart from Guatemala influences Dengue fever, possibly Honduras or El Salvador (the rest of the Northern Triangle of Central America). Future studies should use adjusted confidence intervals to examine temperature threshold effects on Dengue incidence. Our findings should highlight the necessity to include the surveillance of socioeconomic factors, such as population density, CCI, Mayan language speaking individuals, and school attendance, by Dengue vector control agencies in Guatemala or risk compromising Dengue surveillance strategies.

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**Appendix 1. All Variables Related to Dengue Available at the Municipality Level**

| Variable Name Spanish | Variable Name in English | Variables to Include |
|---|---|---|
| A1. Población total por sexo, grupos quinquenales de edad y área, según municipio | Total population by gender, five-year age groups and area, by municipality. | Total population, urban vs rural, gender, age group. |
| A2. Población según parentesco con el jefe(a) del hogar, según municipio | Population according to kinship with the head of the household, by municipality | Population in collective or homeless dwellings |
| A3. Población de 10 años y más por estado conyugal, según departamento | Population aged 10 years and over by marital status, by department | None. |
| A4. Población total por lugar de nacimiento y lugar de residencia en abril del 2013, según departamento | Total population by place of birth and place of residence in April 2013, by department | Place of Residence in April 2013 |
| A5. Población total por pueblos, según departamento | Percent population in Ethnic groups | Percent population in Ethnic groups |
| A6. Población Maya por Unidad lingüística | Percent speaking each of 22 Mayan dialects | None. |
| A7. Población de 4 años o más, idioma materno | Population of 4 years or older, native language | None |
| A8. Poblacion de 4 o mas, con una dificultidad para ver, oir, caminar, concentrar, vertirse, comunicar | Population of 4 or older, with at least one disability (visión, hearing, mobility, more) | None |
| A9. Poblacion de 4 o mas, porcentaje por nivel de education | Population of 4 or older, with percent with no education and by education level | None. |
| A10. Poblacion de 4 o mas, que no assisti un establecimiento educativo, y por cual razon | Population from 4 to 29 who did not attend an educational institution, and for which reason | None. |
| A11.Poblacion de 7 anos o mas por analfabetismo, y asistencia escolar | Population 7 or older with illiteracy or no school attendance | Literacy, Attends School, Place of Study |
| A12. Población de 7 años o más por uso de celular, computadora y/o internet, según departamento | Population aged 7 years or more by use of cell phone, computer and / or internet, by department | Use of cell phone, computer and / or internet |
| A13. Población de 15 años y más, económicamente activa e inactiva, condición de inactividad y lugar de trabajo, según departamento | Population aged 15 years and over, economically active, and inactive, inactivity status and workplace, by department | economically active and inactive, inactivity status and workplace |
| A14. Mujeres de 15 años y más, número de hijos nacidos vivos, número de hijos vivos, y edad de la mujer al nacimiento de su primer hijo, según municipio | Women aged 15 years and over, number of children born alive, number of children alive, and age of the woman at the birth of her first child, by municipality | None. |
| B1. Hogares por tipo de tenencia de la vivienda, sexo del propietario de la vivienda, y sexo | Households by type of home ownership, sex of the homeowner, and sex of the | None. |

| | | |
|---|---|---|
| de la persona que toma las principales decisiones en el hogar, según departamento | person who makes the main decisions in the household, by department | |
| B2. Hogares por fuente principal de agua para consumo, según departamento | Households by main source of drinking water, according to department | Total Household, main source of drinking water |
| B3. Hogares por tipo y uso de servicio sanitario, según departamento | Households by type and use of health service, according to department | Health service and type of sanitary service |
| B4. Hogares según tipo de alumbrado, fuente principal de energía para cocinar y disponibilidad de cuarto exclusivo para cocinar, según departamento | Households according to type of lighting, main source of energy for cooking and availability of exclusive room for cooking, according to department | None. |
| B5. Equipamiento del hogar, según departamento | Household equipment, by department | Type of communication, Electronics in the house, water and hygiene, mode of transportation |
| B6. Hogares por forma principal de eliminación de la basura, según departamento | Households by main form of garbage disposal, according to department | Main form of garbage disposal |
| B7. Hogares por número de cuartos y dormitorios, según departamento | Households by number of rooms and bedrooms, according to department | Number of rooms and bedrooms |
| B8. Tipología de hogar, según departamento | Type of household, according to department | None. |
| C1. Tipo de vivienda y condición de ocupación, según departamento | Type of dwelling and occupation condition, by department | None. |
| C2. Viviendas particulares por material predominante en las paredes exteriores y en el techo, según departamento | Private dwellings by predominant material on the exterior walls and on the roof, according to department | Material on exterior walls of the homes |
| C3. Viviendas particulares por material predominante en el piso, según departamento | Private dwellings by predominant material on the floor, according to department | Materials predominantly on the floor |

Appendix 2. Socioeconomic Variables included in the Zero-Inflated Negative Binomial Regression Model Predicting Incidence Rate Ratios of the Dengue Cases of Each Municipality in 2017 and 2018 (N = 340)

| **Coefficients** | **IRR (95% CI)** |
|---|---|
| Population Density | 0.57 (0.45, 0.72) *** |
| Attending School | 0.77 (0.56, 1.04) |
| Use of Cellphones, Computers, and Internet | 2.07 (1.16, 3.71) * |
| Economically Active | 0.73 (0.48, 1.11) |
| Homes without Indoor Plumbing | 0.91 (0.74, 1.13) |
| Mayan Individuals | 0.57 (0.45, 0.73) *** |

| | |
|---|---|
| Intercept | 0.0008 (0.0006, 0.0009) *** |
| **Inflate** | |
| Temperature | -3.14 (-4.18, -2.11) *** |
| Intercept | -2.78 (-3.87, -1.70) *** |

* p < 0.05, ** p < 0.01, *** p < 0.001

Appendix 3. Environmental Variables Only Zero-Inflated Negative Binomial Regression Model Predicting Incidence Rate Ratios of the Dengue Cases of Each Municipality in 2017 and 2018 (N = 340)

| **Coefficients** | **IRR (95% CI)** |
|---|---|
| Population Density | 0.92 (0.77, 1.10) |
| Elevation | 0.90 (0.24, 1.10) |
| Temperature | 3.14 (0.91, 10.83) |
| Precipitation | 0.88 (0.74, 1.05) |
| Intercept | 0.0005 (0.0004, 0.0006) *** |
| **Inflate** | |
| Temperature | -3.03 (-4.18, -1.87) *** |
| Intercept | -3.11 (-4.42, -1.80) *** |

* p < 0.05, ** p < 0.01, *** p < 0.001

Appendix 4. Main Effects Zero-Inflated Negative Binomial Regression Model Predicting Incidence Rate Ratios of the Dengue Cases of Each Municipality in 2017 and 2018 (N = 340)

| **Coefficients** | **IRR (95% CI)** |
|---|---|
| Population Density | 0.61 (0.49, 0.76) *** |
| Elevation | 0.67 (0.21, 2.11) |
| Temperature | 2.47 (0.78, 7.90) |
| Precipitation | 1.06 (0.89, 1.27) |
| Attending School | 0.69 (0.53, 0.90) ** |
| Use of Cellphones, Computers, and Internet | 2.73 (1.62, 4.57) *** |
| Economically Active | 0.87 (0.61, 1.26) |
| Homes without Indoor Plumbing | 0.98 (0.79, 1.20) |
| Mayan Individuals | 0.72 (0.56, 0.92) ** |
| Intercept | 0.0003 (0.0002, 0.0004) *** |
| **Inflate** | |
| Temperature | -2.91 (-4.25, -1.57) *** |
| Intercept | -3.38 (-4.98, -1.78) *** |

* p < 0.05, ** p < 0.01, *** p < 0.001