# Endemic-Dengue Infection in South America

## The Impact of Community Risk Factors on Regional Endemic Dengue Infection in South America:

## A Literature Review

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**Table of Contents**

**Research Question**

What are the community risk factors for endemic-dengue infection in South American metropolitan cities?

**Introduction**

Mosquito-borne disease incidence has increased worldwide. Dengue has recently seen an abrupt incline in cases specifically in South America. In 1947, Pan American Health Organization (PAHO) recommended an *A. aegypti* eradication program that contributed to South America's status as a dengue-free zone from 1952 to 1965 (Tapia-Conyer, Betancourt-Cravioto, & Méndez-Galván, 2012). That has since changed as globalization and urbanization have introduced new diseases into the population. The WHO states that mosquito-borne disease rates are currently on the rise, worldwide incidence of Dengue has risen 30-fold in the past 30 years (World Health Organization, 2020b). Environmental scientists expect this number to increases as global temperatures continue to rise, thus expanding mosquito's habitat (Colón-González et al., 2018).

Dengue is a flavivirus transmitted by the *Aedes* mosquito *(Ae. aegypti and Ae. Albopictus*). The cycle begins when a dengue infected mosquito takes a blood meal from a susceptible human and transmits the virus to the human (European Centre for Disease Prevention and Control, 2020). Human to mosquito transmission takes place 4-7 days after infection if a susceptible mosquito bites the infectious host, continuing the cycle to dengue transmission. Prevention of dengue relies on both ecological and educational prevention efforts (Messina et al., 2015). *Aedes* mosquitos often bite during the daytime and are most active outdoors but can breed and adapt to indoor environments. Dengue's primary mosquito vector is *Ae. aegypti*, a more ferocious biter than its counterpart *Ae. albopictus. Ae. aegypti* is well adapted to urban areas and primarily breeds in areas with stagnant or standing water like flowerpots or tires (World Health Organization, 2020a). For this reason, *Aedes* mosquitos and their prospective diseases are often found in cities with high population density (Ferede et al., 2018).

Dengue prevention has a rich history in the Americas. Pioneered by the Pan-American Health Organization (PANHO) in 1947, aggressive *Ae. aegypti* mosquito eradication programs found partial success in many countries (Brathwaite Dick et al., 2012). Due to waning political support, DDT resistant mosquitos, and high labor costs, the eradication program began to lose its traction, resulting in *Ae. aegypti* mosquito re-infestation in the 1980's. By the early 1990's almost all countries were back to pre-eradication dengue infection incidence rates (Brathwaite Dick et al., 2012). Furthermore, dengue cases were detected in countries that historically did not have endemic dengue like Peru, Bolivia, Paraguay, and Ecuador (Brathwaite Dick et al., 2012).

Dengue prevention started out with a focused effort on mosquito eradication effort via the spraying of pesticides' (larvicides and adulticides), specifically DDT, temephos and deltamethrin, both indoors and outdoors. While this has shown to have the most immediate success, many mosquitos have developed a resistance to this constant spraying, rendering them ineffective in some countries (Guedes, Beins, Navarro Costa, Coelho, & Bezerra, 2020). Other successful interventions like the dispersal of insecticide-treated bed nets, curtains and net screens have been proven to reduce the overall number of mosquito-borne infections as well as dengue. Local public health interventions like general population health education and container management and reduction efforts have been proven successful in mobilizing a more community- wide effort to reduce the possible breeding sites of mosquitos (Bardach et al., 2019). Many countries have put forth great effort in community education and media campaigns (Bardach et al., 2019).

There are currently four identified serotypes of dengue (DENV-1, -2, -3 or -4). Clinical infection of dengue is almost always seen after the second time an individual is infected. Clinicians classify dengue infection into two groups: uncomplicated and severe. About 40-80% of all infections are asymptomatic, only after initial infection if someone is re-infected than they are then met with clinical symptoms that can range anywhere from muscle aches to fever (World Health Organization, 2020a). This is a problem when documenting all cases of dengue as only those who are bitten twice end up seeking medical attention. Severe symptoms can manifest into hemorrhagic fever or dengue shock syndrome, but are only found in 5% of all

cases (Hasan, Jamdar, Alalowi, & Al Ageel Al Beaiji, 2016). There is no specific medication or clinical treatment for those infected, however early detection of severe dengue and proper medical care lowers the death rate to less than 1% (World Health Organization, 2020a). As of 2013, most countries in South America have reported DENV-1, -2 & -3 strains, and about half have also reported DENV-4 circulation. There is no proven cross immunity between strains (European Centre for Disease Prevention and Control, 2020). Brazil has reported the highest prevalence of all dengue serotypes in 2017. While this does vary by region and even city, the more serotypes circulating increases the chances for severe dengue and further clinical manifestations (Ramos-Castañeda et al., 2017).

Recent vaccine Dengvaxia has entered phase III clinical trials in 2020. Population level benefits of the vaccine have proven to be effective. The main problem with this new vaccine is that it has different effects on people depending on their serostatus. In those who are seropositive before vaccination, the vaccine was 74% effective, vs. those with no prior immunity or seronegative, the vaccine is 38.1% effective (World Health Organization, 2018). Because the vaccine performs differently in populations based on serostatus, serology testing and population seroprevalence of individual cities is important if this vaccine were to be implemented into country specific dengue prevention efforts (World Health Organization, 2018).

Those most affected by dengue in South America would be individuals that live in or around urban areas, as that is where *Ae. aegypti* and *Ae. Albopictus* thrive (Gubler, 2011). The geographic distribution of *Ae. aegypti* and *Ae. Albopictus* mosquito tends to circulate around the equatorial region of South America however cases have been found in all countries (Gubler, 2011). *Ae. Aegypti* and dengue have found a certain proclivity for Brazil's densely populated cities, causing Brazil and its territories to have the highest incidence density rate (452 of 100,000) and highest mortality rate starting in 2002 (Brathwaite Dick et al., 2012). The most recent dengue outbreak was in 2010 and affected almost every country. After the 2010 outbreak there has been a higher reported spread of all DENV serotypes, thus increasing the susceptible population at risk for new infection (Brathwaite Dick et al., 2012).

Understanding the risk factors for cities that experience a higher dengue related morbidity is the first step in assessing possible interventions and understanding transmission dynamics on a social and cultural level. While not all cities are alike and each face unique challenges, comparing the influencing variables of each may provide information for cities facing similar problems. The primary purpose of this literature review is to identify seroprevalence, cross sectional or ecological studies done in dengue endemic cities in South America to examine community risk factors that contribute to the persistence or spread of dengue.

**Methods**

A search conducted through PubMed advanced search for peer-reviewed articles in a range of ten years (2010-2020). The literature search looked for cross-sectional or ecological studies. Preference was given to studies that performed seroprevalence testing. The PubMed search addressed the following question; What are the main community risk factors of dengue infection in South American cities?

*Initial inclusion criteria*

i. Scholarly, Peer-reviewed

ii. Published within the last ten years (2010-2020)

iii. Information about dengue or *Aedes*. Mosquito transmission

iv. Study done in South America

*Initial exclusion criteria*

*i.* Literature reviews or Systematic reviews

*ii.* Articles in Spanish or Portuguese

Since the primary area of study is South America, many studies were originally written in either Spanish or Portuguese. While most had English translations, those that either only had translated abstracts or no English translation at all had to be excluded. The area of study was kept to South America and excluded Central America primarily because there are different breeding habits, mosquito control and climate that

further affect dengue transmission. Analyzing studies done in Central America could possibly weaken the internal validity of the study.

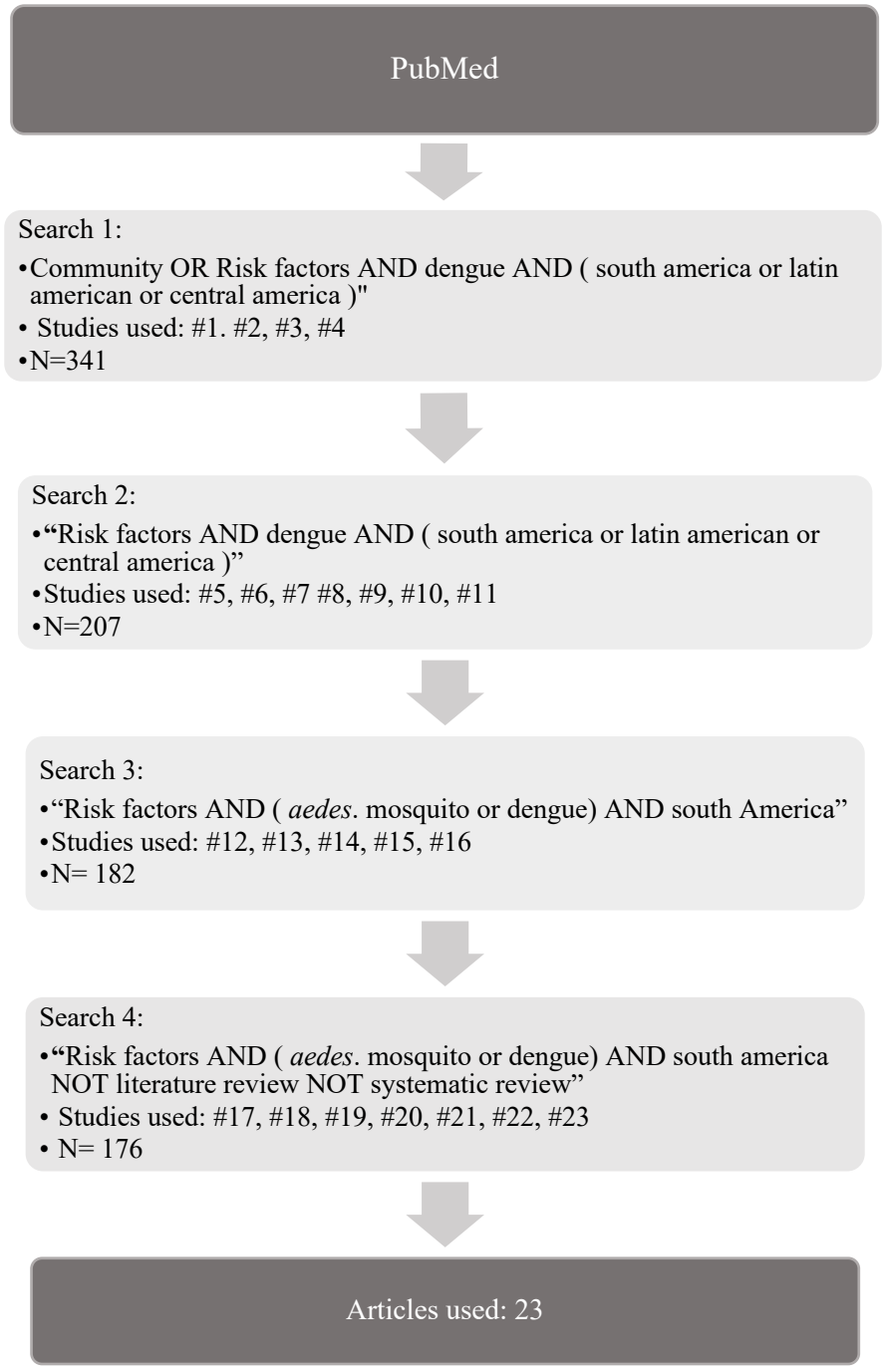
After initial inclusion and exclusion criteria could be identified, each selected publication's abstract was analyzed further. Preference was given to studies that included a serological component to the study, as this is the best way to capture the true prevalence of dengue and allows for a more in-depth analysis of serotype ranges. Studies were also vetted to ensure at least 2+ community risk factors were assessed, especially in ecological and spatial analysis studies. Studies that focused on a narrow subpopulation (pregnant women, children, elderly) were excluded as they only analyzed limited community risk factors. Clinical evaluations of dengue serotypes or dengue infection were vetted as well.

*Advanced Inclusion Criteria searched for in Abstract:*

i. Preference for studies with serological testing
ii. Knowledge and attitudes about prevention
iii. Demographic information of overall community
iv. Spatial analysis of cities and dengue infection
v. Excluded information on severity of disease and clinical evaluations

Out of 341 initial articles reviewed, 23 were identified that met both initial and advanced inclusion and exclusion criteria. After further reading and examination of all articles, three were excluded. Two articles primarily focused on a population subgroup, thus not providing an accurate portrayal of dengue morbidity in the prospective city's population. One article included comparison analysis of dengue infection in Southeast Asia and therefore could not be included either. Figure 1 shows study selection process.

Figure 1: Search terms and results



**Results**

The articles chosen spanned across most countries in South America. More than half of all studies took place in a Brazilian city. This is because Brazil is affected the most by dengue infection compared to other countries in South America and is also the largest country in South America. Sample size varied depending on the type of study and data source. Studies that included a serological testing component often included a smaller sample size. Ecological studies that utilized census data were larger and therefore able to analyze more variables. The most common community risk factors analyzed were socio-economic status, residence type, human migration patterns and education and prevention efforts.

*Socio- Economic Status and Employment*

Areas with lower SES or other measures of poverty like literacy rate and household median income are associated with higher dengue seroprevalence or prevalence. While there are many different evaluations of poverty or low income, positive association between lower SES and household median income and dengue infection is the most commonly cited risk factor out of all reviewed articles (de Castro et al., 2018; Farinelli, Baquero, Stephan, & Chiaravalloti-Neto, 2018; Kikuti et al., 2015). In studies that relied on hospital reporting over serological assays, those who reported severe dengue or clinical infection were more likely to live in area associated with lower SES as well as closer proximity to healthcare location (Kikuti et al., 2015). Illiteracy rate was found to be as high as 21% in the Amazonas state in Brazil, possibly indicating a public health failure of local education on mosquito breeding prevention (de Castro et al., 2018). Another study done in Brazil used employment, schooling, health history and drug usage to create a familiar vulnerability scale and found those classified as familiarly vulnerable had 55% greater odds of being infected with dengue (Nádia Cristina Pinheiro Rodrigues et al., 2018).

Employment type was also measured in a couple studies, specifically those who were either unemployed or working as domestic workers or day laborers were more likely to have dengue infection (Velasco-Salas et al., 2014; Vincenti-Gonzalez et al., 2017). Two studies actually reported higher OR's in

women being infected with dengue than men (N. C. P. Rodrigues et al., 2018; Velasco-Salas et al., 2014). This is most likely due the role women play in households and further association with unemployment.

*Residence Type*

Residence types may vary in key features such as plumbing, number of residents, and house type. In a high seroprevalence community, those who lived in an apartment had a lower risk of infection versus those who live in houses (Chiaravalloti-Neto et al., 2019). Informal housing, "rancheros" (shack or shanty in English) were positively associated with dengue infection.

One of the most predictive features of household dengue incidence was modern plumbing and sanitation services. Households with bathrooms and piped water had a negative association with dengue seroprevalence (de Castro et al., 2018; Kenneson et al., 2017; Lippi et al., 2018). One study specifically found garbage collection services associated with lesser spatial dengue prevalence (Lippi et al., 2018). Physical proximity to risk factors like tire shops or abandoned properties were measures and found to be significant predictors (Delmelle, Hagenlocher, Kienberger, & Casas, 2016; Kenneson et al., 2017). Closer geographical analysis of areas homogeneity affected by poverty found that there is variability of dengue risk, which mostly relate to residence or environmental differences or risk factors (Nádia Cristina Pinheiro Rodrigues et al., 2018). Improper waste control, whether it be sewage or trash, all provide *Aedes* mosquito ideal breeding habitats. A study done in Niterói, Southeastern Brazil found a that those who lived below the poverty line were more likely to not be serviced by proper sewage systems. Further association was found between primitive sewage systems and dengue mosquito transmission (Resendes, Silveira, Sabroza, & Souza-Santos, 2010).

Number of people per household or household crowding is also a positive association brought up in many studies (J. P. C. d. Santos, N. A. Honório, & A. A. Nobre, 2019; Velasco-Salas et al., 2014; Vincenti-Gonzalez et al., 2017). Household density or inhabitants per household may just be another marker of low SES or may present as an effect modifier to low SES. Residence variables are a good reflection of the effect a built environment has on mosquito breeding patterns. Closed and efficient plumbing systems, garbage collection

and sealed housing all limit the amount of opportunities a mosquito has to reproduce. It is important to remember that *Aedes* mosquito reproduces both indoors and outdoors, meaning that breeding sites inside houses are just as big of a threat as outdoor breeding sites. Residence type and geographical distribution may also influence the proximity on households to breeding grounds.

*Human Migration Patterns*

Human migration patterns are classified as movement between communities or populations and can be associated with international travel or a broad and robust public transportation system. These differences are not applicable to all cities as their source of human migration differs depending on the country or city location. A retrospective study found that the 2009 dengue outbreak in Argentina could be traced back to international travel (Gil et al., 2016). Local transmission in areas with increased recent population growth via mass migration are also associated with increased dengue prevalence (Salmón-Mulanovich et al., 2018). In an indigenous population with lower seroprevalence, those who were seropositive we more likely to make frequent trips to the city, further increasing their risk or exposure (Sacramento et al., 2018). While rural populations do not face as high of a disease burden as urban populations, social mixing between groups makes the rural population more susceptible to infection. While transportation networks effect on dengue transmission cannot as easily be studied, a retrospective 15 year study that analyzed both dengue cases and transportation networks found the revitalization of roads to be the most effective at broadening *Aedes* mosquito breeding territories and dengue infection (Lana, Gomes, Lima, Honório, & Codeço, 2017).

Changing population density was also found as a descriptor and consequence of human migration. Padmanabha et al. paper that included and entomological analysis of dengue carrying pupae, found that 92% of all pupae was found in 5% of the sample population, stating that population density and local human movement alone was how the general population came into contact with the 5% “super-producers” (Padmanabha, Durham, Correa, Diuk-Wasser, & Galvani, 2012).

*Education and Prevention Efforts*

Education and prevention efforts are measurement of population knowledge and perception about dengue infection and prevention. The differences are seen geographically as different countries have different prevention efforts and systems put in place. Most studies tend to measure local knowledge about mosquito breeding prevention. Removing open water collection containers is one of the most basic proven prevention techniques locals can employ, as one study shows an association between residence distance and sources of water collection breeding sites (Schafrick, Milbrath, Berrocal, Wilson, & Eisenberg, 2013). Knowledge of these dengue prevention techniques may not be present depending on local information sources. In estimates of local efforts for mosquito control, 81% reported using at least one form of prevention, however entomological data found 58% of houses we found to have local *Aedes*. mosquito breeding sites (Elsinga et al., 2018). This disconnect shows there may be a barrier between knowledge of prevention techniques and employment of said techniques. Indigenous rural communities who had an overall lower seroprevalence reported all dengue prevention and management information from either television or community health workers (Sacramento et al., 2018). Knowledge about the complete cycle of the disease itself is important to measure as some population might be unaware the asymptomatic nature of their first infection. Out of all persons who claims to have never been infected by Dengue, 68.4% were seropositive (Chiaravalloti-Neto et al., 2019).

**Discussion**

*Socio- Economic Status and Employment*

Characteristics of cities with high seroprevalence and reported dengue prevalence often have higher levels of poverty and low SES. It could be hypothesized that this is because of the lack of mosquito control prevention efforts put forth by the government or general degradation of infrastructure. This is also attributed to poor housing conditions and development, which as discussed, also increases chances for dengue incidence. Poverty and dengue prevalence association have been noted in many other papers (Mulligan, Dixon, Joanna Sinn, & Elliott, 2015).

*Residence type*

Residence types may vary in key features such as plumbing, number of residences, and house type. Housing issues such as improper sanitation services and well as inadequate plumbing systems are the most obvious risk factor measured in studies to have an association with dengue. This could be because untreated sewage or incomplete systems not only attract Ades mosquito but also provide favorable breeding habitats as well. Other housing issues there were noted were increased household density, this could be further confounding with poverty however it could be speculated that those who live in a denser household are more likely to spend time working outside the home, further exposing themselves to the outdoors. Housing issues within certain Latin American countries could be related to the overall lack of housing code or regulation.

Number of inhabitants per household or household density would count as both an indicator of low SES, especially in more urban sprawled cities. The number of inhabitants per household may increase when there are more children or elderly people under the same roof. As discussed in the results section, this has a positive association on dengue transmission. What also may be contributing to this association is the fact that children are often more likely to be infected by dengue than middle-aged adults. An ecological study done in Rio de Janeiro looking at household density and age demographics found clusters of dengue infected children under the age of 5 (J. Santos, N. A. Honório, & A. A. Nobre, 2019; J. P. C. d. Santos et al., 2019). Since children often contribute to increased household density and do not have acquired immunity to the region's endemic dengue serotype, they were the best indicator for understanding circulating dengue strains and population immunity. This is particularly important because it points out the flaw in only relying on reported dengue cases in determining the regions dominating dengue serotypes. None of the other chosen articles have further studied this correlation, however it is an important aspect when determining the population risk of contracting dengue.

of susceptible individuals when designing territory-based dengue studies

*Human migration patterns*

Human migration patterns are closely studied when talking about preventing either a higher rate of dengue carrying Ades mosquito or protecting against the introduction of new dengue serotypes into a population. This is mainly applied to rural areas where multiple dengue serotypes are less common, as seen in the study regarding a Brazilian indigenous population (Sacramento et al., 2018). Knowing that human travel and increased population density could be a causative factor for dengue cases might also be important when city planning and understand city growth dynamics as seen in Puerto Maldonado, Peru (Salmón-Mulanovich et al., 2018). It is important to note that while many cities in South America already have endemic levels of all four dengue serotypes, there are still many that are only affected by DENV-1 and DENV-3 (Hasan et al., 2016). Limiting the spread of other serotypes into the population could prevent an increase in severe dengue infection in neighboring cities (Hasan et al., 2016). With the Dengue Vaxia emergence in the global marketplace, countries affect by dengue have more of a reason to understand the transmission dynamics of circulating dengue serotypes in the population in order to appropriately assess how effective the vaccine will be if the population is already immune to the local serotype. Interestingly enough, one study particularly examined the relationship with a younger population and earlier detection of DENV serotypes (J. Santos et al., 2019; J. P. C. d. Santos et al., 2019). This is because the older an individual is, the more time they have to develop immunity. Other studies look at the length of residence in a particular city as a coefficient to determine population immunity to a specific dengue serotype.

*Education and prevention efforts*

Education and prevention efforts have shown varying effectiveness depending on location and country. Studies show conflicting evidence on individual based mosquito control efforts knowledge. While almost all reported have knowledge of *Aedes* mosquito dynamics, not all prevention efforts were practiced when properties were inspected (Elsinga et al., 2018). From the studies analyzed, it could be inferenced that the general population is familiar with how mosquito breeding intervention and control but not understand the dengue infection dynamic. Since are large population underestimates their dengue seroprevalences status of

infection, perception could skew control efforts if the individual thinks they have never been bit or infected by a dengue carrying mosquito (Chiaravalloti-Neto et al., 2019).

The assertion that a small portion of households in a dense population with higher transmission rates can be responsible for unknowingly cultivating favorable breeding sites for mosquitos despite public education efforts is expressed in a study done in Armenia, Colombia (Padmanabha et al., 2012). This makes the case that educating the majority of a dense population is not effective enough to prevent "super-producer" mosquito reproduction locations. This calls upon greater regulatory efforts, either put forth by local governments or city-wide programs that focus on ecological prevention solutions rather than media campaigns or community.

This paper along with many others has described the characteristics and identifiers of dengue endemic cities across South America. Historically, dengue and other arboviral disease transmission has been successfully reduced using a variety of ecological mosquito host prevention techniques' and public education. The disintegration of the PANHO mosquito eradication program left many public health gaps to be filled by county or city government. Industrialization and urban sprawl have also contributed to the increase on dengue morbidity. In order to create effective prevention plans weather that be in the form of vaccine or mosquito eradication, one must be able to identify the populations that are most affected by the disease in the first place.

*Limitations*

This literature review is limited by the broad scope of the study geographically. This means specific features or associations found may not apply to every city or population in South America. It is important to note that each country has dealt with mosquito control differently in the past and this history as well as current regime might have a greater effect on mosquito prevention efforts than household mosquito prevention ability and incentive. Weather patterns and altitude were not factored when analyzing cities, location and papers however this a significant effector of *Aedes* mosquito distribution. This review only provided evidence from 20 articles. In the time this review was written, other research may have been conducted, some research is waiting on publication, etc. The topic is much broader and more complicated than can be addressed by these

20 articles. All studies that were chosen were either cross-sectional or ecological except for one cohort study, meaning no causality can be established from risk factors and dengue outcome. Sample sizes were large in non -seroprevalence studies giving statistically significant OR more power and smaller confidence intervals.

*Implications*

More research is needed to investigate the actual magnitude of each community risk factor discussed above. Understanding the intricacies of poverty, migration patterns and urban development might lead to a better understanding of these factors within individual cities and not just in South America as a whole. More concrete information can also aid in future prevention efforts and policy.

As seen from many of the individual studies analyzed, seroprevalence assays are critical to understanding the scope of dengue in South America. Relying on reported clinical infection from hospital networks does not give rise to the preluding asymptomatic infections. For this reason, serological testing and understanding the distribution of DENV serotype within individual population could be one of the greatest factors when preventing infection as well as implementation of the DENV vaccine. Due to the obscure pathology of dengue, seroprevalence assays are the only indication that can accurately inform further policy in regard to government funded prevention.

This research analyzing community risk factors of cities affected by endemic dengue is to ultimately analyze more population-based indicators of dengue infection. This is important because while seroprevalence studies have much information to offer in regard to the distribution of disease, not all countries or research agencies have the means and ability to perform these serological assays on the general population. When recommending prevention strategies, the large amount of community risk factors that have been shown to be associated with dengue infection might be best alleviated by alternative prevention strategies, like city planning and agricultural landscaping. Primary investment in basic sanitation and plumbing services may yield a greater reduction on mosquito breeding grounds than public education efforts.

Furthermore, prevention of mosquito breeding and human to mosquito transmission does not only reduce the amount of dengue infection in a city, but presumably other mosquito born infections as well. Zika, West Nile, Chikungunya are all transmitted by *Ae. aegypti* and are only increasing in case numbers. Climate change is predicted to increase *Aedes* mosquito geographic range, thus increasing the susceptible population size for mosquito- borne disease (Reiter, 2001). Future cities that may find themselves in this situation may be able to identify or predict areas that are more likely to be affected by dengue,

**Conclusion**

Dengue is very relevant to the future of all countries in South America, and the number of infections are only projected to increase. An increase in severe dengue cases can be expected, as well as consistent circulation of DENV-4 serotype. More research is needed to fit the demand for serological backed studies to further inform individual countries' public health decisions. Research on reducing *Aedes* mosquito distributions can translate into a reduction of other arboviral diseases spread by *Aedes* mosquito as well. Investment in alternative prevention in the forms of public services, infrastructure and vaccination should be encourages to reduce transmission in dengue-endemic cities.

## References

Bardach, A. E., García-Perdomo, H. A., Alcaraz, A., Tapia López, E., Gándara, R. A. R., Ruvinsky, S., & Ciapponi, A. (2019). Interventions for the control of Aedes aegypti in Latin America and the Caribbean: systematic review and meta-analysis. *Tropical Medicine & International Health, 24*(5), 530-552. doi:https://doi.org/10.1111/tmi.13217

Brathwaite Dick, O., San Martín, J. L., Montoya, R. H., del Diego, J., Zambrano, B., & Dayan, G. H. (2012). The history of dengue outbreaks in the Americas. *The American journal of tropical medicine and hygiene, 87*(4), 584-593. doi:10.4269/ajtmh.2012.11-0770

Chiaravalloti-Neto, F., da Silva, R. A., Zini, N., da Silva, G. C. D., da Silva, N. S., Parra, M. C. P., . . . Nogueira, M. L. (2019). Seroprevalence for dengue virus in a hyperendemic area and associated socioeconomic and demographic factors using a cross-sectional design and a geostatistical approach, state of São Paulo, Brazil. *BMC Infectious Diseases, 19*(1), 441. doi:10.1186/s12879-019-4074-4

Colón-González, F. J., Harris, I., Osborn, T. J., Steiner São Bernardo, C., Peres, C. A., Hunter, P. R., . . . Lake, I. R. (2018). Limiting global-mean temperature increase to 1.5–2 °C could reduce the incidence and spatial spread of dengue fever in Latin America. *Proceedings of the National Academy of Sciences, 115*(24), 6243-6248. doi:10.1073/pnas.1718945115

de Castro, D. B., Sampaio, V. S., de Albuquerque, B. C., Pinto, R. C., Sadahiro, M., Dos Passos, R. A., . . . Braga, J. U. (2018). Dengue epidemic typology and risk factors for extensive epidemic in Amazonas state, Brazil, 2010-2011. *BMC Public Health, 18*(1), 356. doi:10.1186/s12889-018-5251-x

Delmelle, E., Hagenlocher, M., Kienberger, S., & Casas, I. (2016). A spatial model of socioeconomic and environmental determinants of dengue fever in Cali, Colombia. *Acta Trop, 164*, 169-176. doi:10.1016/j.actatropica.2016.08.028

Elsinga, J., Schmidt, M., Lizarazo, E. F., Vincenti-Gonzalez, M. F., Velasco-Salas, Z. I., Arias, L., . . . Tami, A. (2018). Knowledge, Attitudes, and Preventive Practices Regarding Dengue in Maracay, Venezuela. *Am J Trop Med Hyg, 99*(1), 195-203. doi:10.4269/ajtmh.17-0528

European Centre for Disease Prevention and Control. (2020). Factsheet about dengue. Retrieved from https://www.ecdc.europa.eu/en/dengue-fever/facts/factsheet

Farinelli, E. C., Baquero, O. S., Stephan, C., & Chiaravalloti-Neto, F. (2018). Low socioeconomic condition and the risk of dengue fever: A direct relationship. *Acta Trop, 180*, 47-57. doi:10.1016/j.actatropica.2018.01.005

Ferede, G., Tiruneh, M., Abate, E., Kassa, W. J., Wondimeneh, Y., Damtie, D., & Tessema, B. (2018). Distribution and larval breeding habitats of Aedes mosquito species in residential areas of northwest Ethiopia. *Epidemiology and health, 40*, e2018015-e2018015. doi:10.4178/epih.e2018015

Gil, J. F., Palacios, M., Krolewiecki, A. J., Cortada, P., Flores, R., Jaime, C., . . . Aparicio, J. P. (2016). Spatial spread of dengue in a non-endemic tropical city in northern Argentina. *Acta Trop, 158*, 24-31. doi:10.1016/j.actatropica.2016.02.003

Gubler, D. J. (2011). Dengue, Urbanization and Globalization: The Unholy Trinity of the 21(st) Century. *Tropical medicine and health, 39*(4 Suppl), 3-11. doi:10.2149/tmh.2011-S05

Guedes, R. N. C., Beins, K., Navarro Costa, D., Coelho, G. E., & Bezerra, H. (2020). Patterns of insecticide resistance in Aedes aegypti: meta-analyses of surveys in Latin America and the Caribbean. *Pest Manag Sci, 76*(6), 2144-2157. doi:10.1002/ps.5752

Hasan, S., Jamdar, S. F., Alalowi, M., & Al Ageel Al Beaiji, S. M. (2016). Dengue virus: A global human threat: Review of literature. *J Int Soc Prev Community Dent, 6*(1), 1-6. doi:10.4103/2231-0762.175416

Kenneson, A., Beltrán-Ayala, E., Borbor-Cordova, M. J., Polhemus, M. E., Ryan, S. J., Endy, T. P., & Stewart-Ibarra, A. M. (2017). Social-ecological factors and preventive actions decrease the risk of dengue infection at the household-level: Results from a prospective dengue surveillance study in Machala, Ecuador. *PLoS Negl Trop Dis, 11*(12), e0006150. doi:10.1371/journal.pntd.0006150

Kikuti, M., Cunha, G. M., Paploski, I. A., Kasper, A. M., Silva, M. M., Tavares, A. S., . . . Ribeiro, G. S. (2015). Spatial Distribution of Dengue in a Brazilian Urban Slum Setting: Role of Socioeconomic Gradient in Disease Risk. *PLoS Negl Trop Dis, 9*(7), e0003937. doi:10.1371/journal.pntd.0003937

Lana, R. M., Gomes, M., Lima, T. F. M., Honório, N. A., & Codeço, C. T. (2017). The introduction of dengue follows transportation infrastructure changes in the state of Acre, Brazil: A network-based analysis. *PLoS Negl Trop Dis, 11*(11), e0006070. doi:10.1371/journal.pntd.0006070

Lippi, C. A., Stewart-Ibarra, A. M., Muñoz Á, G., Borbor-Cordova, M. J., Mejía, R., Rivero, K., . . . Ryan, S. J. (2018). The Social and Spatial Ecology of Dengue Presence and Burden during an Outbreak in Guayaquil, Ecuador, 2012. *Int J Environ Res Public Health, 15*(4). doi:10.3390/ijerph15040827

Messina, J. P., Brady, O. J., Pigott, D. M., Golding, N., Kraemer, M. U. G., Scott, T. W., . . . Hay, S. I. (2015). The many projected futures of dengue. *Nature Reviews Microbiology, 13*(4), 230-239. doi:10.1038/nrmicro3430

Mulligan, K., Dixon, J., Joanna Sinn, C.-L., & Elliott, S. J. (2015). Is dengue a disease of poverty? A systematic review. *Pathogens and Global Health, 109*(1), 10-18. doi:10.1179/2047773214Y.0000000168

Padmanabha, H., Durham, D., Correa, F., Diuk-Wasser, M., & Galvani, A. (2012). The interactive roles of Aedes aegypti super-production and human density in dengue transmission. *PLoS Negl Trop Dis, 6*(8), e1799. doi:10.1371/journal.pntd.0001799

Ramos-Castañeda, J., Barreto Dos Santos, F., Martínez-Vega, R., Galvão de Araujo, J. M., Joint, G., & Sarti, E. (2017). Dengue in Latin America: Systematic Review of Molecular Epidemiological Trends. *PLoS Negl Trop Dis, 11*(1), e0005224. doi:10.1371/journal.pntd.0005224

Reiter, P. (2001). Climate change and mosquito-borne disease. *Environmental health perspectives, 109 Suppl 1*(Suppl 1), 141-161. doi:10.1289/ehp.01109s1141

Resendes, A. P., Silveira, N. A., Sabroza, P. C., & Souza-Santos, R. (2010). Determination of priority areas for dengue control actions. *Rev Saude Publica, 44*(2), 274-282. doi:10.1590/s0034-89102010000200007

Rodrigues, N. C. P., Daumas, R. P., de Almeida, A. S., Dos Santos, R. S., Koster, I., Rodrigues, P. P., . . . Leite, I. D. C. (2018). Risk factors for arbovirus infections in a low-income community of Rio de Janeiro, Brazil, 2015-2016. *PLoS One, 13*(6), e0198357. doi:10.1371/journal.pone.0198357

Sacramento, R. H. M., de Carvalho Araújo, F. M., Lima, D. M., Alencar, C. C. H., Martins, V. E. P., Araújo, L. V., . . . de Góes Cavalcanti, L. P. (2018). Dengue Fever and Aedes aegypti in indigenous Brazilians: seroprevalence, risk factors, knowledge and practices. *Tropical Medicine & International Health, 23*(6), 596-604. doi:10.1111/tmi.13061

Salmón-Mulanovich, G., Blazes, D. L., Guezala, V. M., Rios, Z., Espinoza, A., Guevara, C., . . . Pan, W. K. (2018). Individual and Spatial Risk of Dengue Virus Infection in Puerto Maldonado, Peru. *Am J Trop Med Hyg, 99*(6), 1440-1450. doi:10.4269/ajtmh.17-1015

Santos, J. P. C. d., Honório, N. A., & Nobre, A. A. (2019). Definition of persistent areas with increased dengue risk by detecting clusters in populations with differing mobility and immunity in Rio de Janeiro, Brazil. *Cadernos de Saúde Pública, 35*. Retrieved from http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0102-311X2019001405006&nrm=iso

Schafrick, N. H., Milbrath, M. O., Berrocal, V. J., Wilson, M. L., & Eisenberg, J. N. (2013). Spatial clustering of Aedes aegypti related to breeding container characteristics in Coastal Ecuador: implications for dengue control. *Am J Trop Med Hyg, 89*(4), 758-765. doi:10.4269/ajtmh.12-0485

Tapia-Conyer, R., Betancourt-Cravioto, M., & Méndez-Galván, J. (2012). Dengue: an escalating public health problem in Latin America. *Paediatrics and international child health, 32 Suppl 1*(s1), 14-17. doi:10.1179/2046904712Z.00000000046

Velasco-Salas, Z. I., Sierra, G. M., Guzmán, D. M., Zambrano, J., Vivas, D., Comach, G., . . . Tami, A. (2014). Dengue seroprevalence and risk factors for past and recent viral transmission in Venezuela: a comprehensive community-based study. *Am J Trop Med Hyg, 91*(5), 1039-1048. doi:10.4269/ajtmh.14-0127

Vincenti-Gonzalez, M. F., Grillet, M.-E., Velasco-Salas, Z. I., Lizarazo, E. F., Amarista, M. A., Sierra, G. M., . . . Tami, A. (2017). Spatial Analysis of Dengue Seroprevalence and Modeling of Transmission Risk Factors in a Dengue Hyperendemic City of Venezuela. *PLoS Neglected Tropical Diseases, 11*(1), e0005317. doi:10.1371/journal.pntd.0005317

World Health Organization. (2018). Immunization, Vaccines and Biologicals. Retrieved from https://www.who.int/immunization/research/development/dengue_q_and_a/en/#:~:text=One%20dengue%20vaccine%20has%20been,now%20in%20Phase%20III%20trials.

World Health Organization. (2020a). Dengue and severe dengue. Retrieved from https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue

World Health Organization. (2020b). Mosquito-borne diseases. Retrieved from https://www.who.int/neglected_diseases/vector_ecology/mosquito-borne-diseases/en/