APPROVAL SHEET

Title of Thesis: Chikungunya in Brazil and Venezuela 2014-2017: An Exploratory Analysis of the Influence of Environmental, Social, and Economic Factors

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ABSTRACT

Title of Document: CHIKUNGUNYA IN BRAZIL AND VENEZUELA 2014-2017: AN EXPLORATORY ANALYSIS OF THE INFLUENCE OF ENVIRONMENTAL, SOCIAL, AND ECONOMIC FACTORS

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Objective: The purpose of this study was to observe trends in chikungunya incidence in Brazil and Venezuela during 2014-2017 and describe potential factors contributing to these findings.

Background: Strikingly high numbers of reported and suspected chikungunya were reported in Brazil and Venezuela during 2013-2017 (Pan American Health Organization, 2017a). Data collected from Pan American Health Organization (PAHO) described nearly 384,000 suspected cases of chikungunya, with almost 272,000 confirmed through laboratory testing (2017). Disparate patterns were noted for the two countries, whereby the Venezuelan incidence rate peaked early and then stabilized, the Brazilian cases took longer to rise in number and spiked later.

Research Question: What factors are associated with the observed chikungunya incidence rates in Brazil and Venezuela?

Methods: Incidence data were gathered from reports released by PAHO from 2014-2017 (2017a) and a systematic review of literature was used to identify typical patterns of mosquito reproduction and disease transmission to determine which independent variables to include. We identified three primary categories: climate, economy, and “disease awareness,” (i.e., the number of Google searches using the search term “chikungunya” from wireless access points throughout Brazil and Venezuela).

Findings: We found a correlation between economy and the chikungunya incidence rate. In addition, the findings suggest that an influx of migrants could potentiate disease spread through lack of preparedness and available resources in the destination location. These factors are likely due to a combination of diminished public health initiatives, a decrease in available resources, and a population increase in areas unprepared to provide care for a great influx of individuals.

CHIKUNGUNYA IN BRAZIL AND VENEZUELA 2014-2017: AN EXPLORATORY ANALYSIS OF THE INFLUENCE OF ENVIRONMENTAL, SOCIAL, AND ECONOMIC FACTORS

By

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Chapter 1: Introduction

Problem Statement

Chikungunya, which is transmitted through the bites of *Aedes aegypti* and *Ae. albopictus* mosquitoes, has threatened the people of Latin America with its rapid spread and risk of infection (The World Bank, 2014). Within Latin America, Columbia, Venezuela and Brazil have reported strikingly high numbers for suspected and confirmed cases in the data collected between 2013 and 2017 (Pan American Health Organization, 2017a). Overall, the data collected from the Pan American Health Organization (PAHO) describes nearly 384,000 suspected cases of chikungunya, with almost 272,000 cases being confirmed through laboratory testing (2017). A disparate pattern of disease incidence between Brazil and Venezuela is observed, posing the question of whether this discrepancy in findings is due to measurement error, availability or cessation of testing methods, level of media involvement, or other factors. The underlying environmental, social and economic influences on the incidence of chikungunya in Brazil and Venezuela were explored.

Background and Significance

Chikungunya is spread to humans through the bite of an infected *Aedes aegypti* or *Ae. albopictus* mosquito and typically presents with high onset fever, severe joint pain, headache, back pain, nausea, vomiting, rash, and conjunctivitis (Pan American Health Organization, 2011). With an incubation period of three to seven days, the acute symptom phase of this disease typically lasts three to ten days (Pan American Health Organization, 2011). Chronic symptoms may continue, including various arthritis and vascular disorders, which can last for years after initial diagnosis. Due to the nonspecific nature of these symptoms, chikungunya is commonly confused with a similar set of symptoms caused by other mosquito-borne illnesses, such as dengue fever or Zika virus (Pan American Health Organization, 2011). Therefore, confirmation through either virus isolation, reverse transcriptase-polymerase chain reaction (RT-PCR) or serology should be obtained to determine expected clinical manifestations, treatment, and prevention within the population. The type of test to administer is based on time from onset of symptoms to specimen collection. If a sample is collected during the first week after symptom onset, both serological (immunoglobulin M (IgM) and G) and virological (RT-PCR and isolation) methods are to be performed (Pan American Health Organization, 2011). Unfortunately, serology may inaccurately test negative during the first week after onset. Therefore, to definitively rule out chikungunya, convalescent samples should be obtained to definitively rule out disease in patients whose acute samples tested negative (Pan American Health Organization, 2011). During the initial introduction of chikungunya to a region, it is suggested that comprehensive testing be performed to confirm the presence of chikungunya within that area. After area-specific confirmation, limited testing is appropriate dependent on clinical presentation (Pan American Health Organization, 2011).

Since 2004, the spread of chikungunya has increased, leaving countries with tropical or subtropical areas at high risk for disease acquisition (Pan American Health Organization, 2011). First described in the 1770s, chikungunya typically follows a cyclical outbreak pattern, ranging from 4 to 30 years of impact (Pan American Health Organization, 2011). After years of quiescence, an outbreak in Kenya during 2004 resulted in an estimated 500,000 cases from spring 2004 to the summer of 2006 (Pan American Health Organization, 2011). As of 2016, almost every country in Latin America had reported cases of chikungunya, creating acute and chronic threat within this region and amongst neighboring areas (Rodriguez-Morales, Sardona-

Ospina, & Villamil-Gomez, 2016). A 2014 outbreak in Latin American and Caribbean regions was reported to have 6,000 cases and 21 fatalities. The heightened threat to Latin America is magnified due to its anticipated spread through frequent travel and migrations (The World Bank, 2014).

On December 9, 2013, PAHO devoted its attention to addressing the increasing prevalence of chikungunya throughout Brazil, Canada, French Guinea, Guadeloupe, Martinique, and the United States (Pan American Health Organization, 2015). The exact causes for this increase are unknown, but it is predicted that social factors, economy, climate change, and local/global ecosystems are all factors that play a role in this sudden increase (Pan American Health Organization, 2015). In addition to these ideas, increased travel to and from the Caribbean has been a suggested route of transmission, leaving countries whose residents have little to no prior antibodies to chikungunya at extreme risk for infection (The World Bank, 2014). As PAHO continues its efforts to decrease mosquito-borne illness throughout the Americas, its primary recommendation is to perform timely detection of cases in humans to provide proper response and identification of the virus (Pan American Health Organization, 2011). From adequate surveillance efforts, data can be collected, which may help epidemiologists determine the sources of infection and appropriate measures for implementation that would prevent the spread of disease, regardless of the country's prior known exposure and immunity to the disease.

Aims and Objectives

Objective #1: Observe trends in chikungunya incidence throughout Brazil and Venezuela from 2014 to 2017 and describe potential factors contributing to these findings.

- Aim #1a: Provide analysis of social, economic and environmental factors contributing to the rise and fall of vector-borne illness within an area.
- Aim #1b: Compare the patterns of disease incidence throughout Brazil and Venezuela between 2014 and 2017.

Chapter 2: Literature Review and Conceptual Models

Literature Review

Historically, chikungunya has followed a cyclical pattern of disease, where its inter-epidemic stages range from 4 to 30 years (Pan American Health Organization, 2011). Nearly undetected for 32 years, chikungunya re-emerged in October 2005 during an outbreak in India that persists within the area (Mohan, Kiran, Manohar, & Kumar, 2010). This arboviral disease, which presents with a rapid onset and spread, gained heightened attention within the medical community after the spread of disease extended to countries where chikungunya had not previously been described (Mohan, Kiran, Manohar, & Kumar, 2010). Prior to 2013, chikungunya had been identified in Africa, Asia, Europe and along the Indian and Pacific Oceans. By late 2013, the first local transmission of the disease was recorded in the Americas, which began in Caribbean areas and spread throughout the region (Centers for Disease Control and Prevention, 2019). By 2014, more than 440,000 cases of disease were recorded in over 50 countries, which left many dengue-endemic countries at risk for chikungunya through increased travel and an uncontrolled abundance of *Ae. aegypti* and *Ae. albopictus* mosquitoes (Morrison, 2014) (Fernandez-Salas, et al., 2015) .

Chikungunya occurs in three phases: acute, subacute, and chronic (Rodriguez-Morales, Sardona-Ospina, & Villamil-Gomez, 2016). With an incubation period broadly ranging from 1-12 days, the acute phase begins at the first sign of symptoms and continues 10 days from first onset. Symptoms such as arthralgia, fever and rash are likely present within this period, and can be accompanied by other symptoms such as headache, dizziness, and myalgia (Rodriguez-Morales, Sardona-Ospina, & Villamil-Gomez, 2016). In this phase, these clinical manifestations involve a variety of systems, which could result in mortality due to severity of illness. After day

10, individuals will either experience a cessation of symptoms, or will enter the subacute phase, where symptoms persist but are likely improved. If symptoms continue for at least two or three months, individuals are referred to as “chronic” (Rodriguez-Morales, Sardona-Ospina, & Villamil-Gomez, 2016). Although many symptoms of patients with chikungunya will resolve over-time, approximately 42% of infected people will develop chronic inflammatory rheumatism (Rodriguez-Morales, Sardona-Ospina, & Villamil-Gomez, 2016). While inflammatory diseases are common amongst those with chikungunya, instances of new-onset Guillain-Barre syndrome, neuropsychiatric disorders, congestive heart failure, and vision defects have been reported as debilitating chronic effects after initial infection of chikungunya (Rodriguez-Morales, Sardona-Ospina, & Villamil-Gomez, 2016).

While there are no vaccinations for chikungunya, it is believed that exposure to chikungunya triggers individual immunity to reinfection (Pan American Health Organization, 2011). The first-line of defense to prevent chikungunya infection includes the use of insect repellants, individual coverage (sleeved clothing, screened homes, mosquito netting, etc.) and eliminating areas of standing water. Unfortunately, once infected with chikungunya, treatment focuses on the treatment of symptoms rather than curing the disease (Centers for Disease Control and Prevention, 2019).

Chikungunya is socially and financially disruptive due to its intense combination of symptoms and tendency to overwhelm healthcare systems during severe outbreaks (Kaye & Yuill, 2015). While efforts to eradicate *Ae. aegypti* have been attempted, deterioration of mosquito control program support, as seen during the *Ae. aegypti* eradication program in the Americas during the 1960’s, resulted in subsequent outbreaks of disease, loss of institutional knowledge, and critical infrastructure, leading to increased outbreak occurrence and a loss of hope for disease cessation (Kaye & Yuill, 2015). In areas where chikungunya did not previously exist, populations are at increased risk due to their absence of antibodies, resulting in an inability to resist disease transmission (The World Bank, 2014). In Latin America, chikungunya has evolved from a simple threat to an established disease, with nearly every country throughout the continent having reports of transmission (Rodriguez-Morales, Sardona-Ospina, & Villamil-Gomez, 2016).

Latin America, which has historically been a dengue-endemic region, has experienced an increase of chikungunya transmission due to increased travel and a lack of properly implemented vector-control programs (Fernandez-Salas, et al., 2015). Like chikungunya, dengue is transmitted by the same vector and creates the same social and financial consequences, which overwhelm healthcare systems. Situations which cause a lack of trash collection, weak vector control methodologies, poorly piped water supply lines, uncontrolled urban development, and more, are at the forefront of re-infestations and leave populations with increased vulnerability for disease (Fernandez-Salas, et al., 2015). In some Venezuelan locations, such as the states of Bolivar and Amazonas, illegal mining activities have resulted in increased areas of standing water, which serve as vector breeding grounds (Page, et al., 2019). In addition, mosquito resistance to insecticides and the inability to appropriately surveil disease due to financial instability results in a lack of protection against the vector (Fernandez-Salas, et al., 2015). Studies show that individuals with severe disease symptoms are more likely to receive laboratory testing due to urgency of symptoms (Fernandez-Salas, et al., 2015). Therefore, there are a great number of cases of mild disease not being reported, leading to potentially unreliable data and the failure to recognize the need for vector control programs within specific areas (Fernandez-Salas, et al., 2015). The under-diagnosis of disease leaves individuals at risk due to under-reporting within vector-infested areas. Therefore, surveillance programs must not rely solely on confirmed laboratory cases but must adjust to appropriately identify high-risk areas through suspected cases based on symptomatology (Fernandez-Salas, et al., 2015). The World Health Organization (WHO) and PAHO have worked with countries across the region to strengthen preparedness and response to chikungunya through early recognition and prevention (Pan American Health Organization, n.d.).

Shortly after PAHO published an epidemiological alert on the magnitude of chikungunya in the Americas in December 2013, Brazil implemented a national chikungunya surveillance and prevention system to obtain reliable and accurate data on outbreak occurrence throughout the country (Messias da Silva, et al., 2018). In September 2014 the first cases within Brazil were identified in the states of Bahia (eastern) and Amapa (northern), but spread rapidly throughout the Federation, resulting in a large number of suspected cases between 2014 to 2016 (Messias da Silva, et al., 2018). When analysis of the mosquito origin and progression were studied, it was found that more than 4,000 municipalities were infested with the *Ae. aegypti* mosquito, while 3,285 had the *Ae. albopictus* mosquito (Messias da Silva, et al., 2018). With four main genotypes of mosquitoes, it was found that the East-Central-South-African (ECSA) genotype was first introduced to Roraima, Brazil in July 2016, which was six months prior to a massive outbreak (Naveca, et al., 2019). Since the first detection of disease within Brazil was reported in August 2014, it is hypothesized that the Asian lineage originally existed, but was replaced with the ECSA genotype, which could be due to a variety of ecological factors (Naveca, et al., 2019).

With such a wide-spread pre-existing mosquito population and the human population's overall susceptibility to infection, a coexistence of various arboviruses resulted in severe cases and deaths, which placed large demands on Brazil's healthcare system (Messias da Silva, et al., 2018). In 2016, an estimated 200 deaths were attributed to chikungunya infection, while more than 50 were reported in 2017 with exact parameters unknown (Moraes Figueiredo, 2017). As of September 2018, 697,564 cases had been reported since 2014, which included 94,672 laboratory-confirmed cases. The circulation of these two distinct mosquito species (*Ae. aegypti* and *Ae. albopictus*) can be attributed to various factors, such as a lack of population immunity, poor housing conditions, and increased mobility of vectors and humans between regions (Naveca, et al., 2019). Overall, it is critical that surveillance for the disease is conducted in order to prevent and control the spread of illness within Brazil. Through the combination of traditional surveillance and digital technologies, such as electronic medical records and news releases, origin of disease can be identified and early notification of threat toward the population can be made (Naveca, et al., 2019).

Surveillance, which is necessary to prevent and eradicate disease, is impacted by the crises of governance in Venezuela, which has limited financial funding and public health services, leading to inadequate data collection within the healthcare sector. Since 2016, the Venezuelan Ministry of Health (MOH) had stopped collecting critical public health data, which has prevented the ability to appropriately assess the magnitude of disease and its consequences (Page, et al., 2019). Throughout Venezuela, services such as laboratory testing and pharmacies were unavailable to residents and approximately one-third of registered physicians had fled the country (Page, et al., 2019). In addition to the absence of resources country-wide, 72% of surveyed individuals interviewed by the Encuesta Nacional de Médicos Unidos de Venezuela had agreed that the working conditions throughout public hospitals were unethical and violated human rights, leading to emigration amongst medical professionals and a decrease in medical specialty capabilities (Page, et al., 2019).

Although the political and economic crisis has largely contributed to the inability to carry out surveillance and prevention programs due to financial instability, government officials have refused to release epidemiological reports and have threatened those who attempt to gather evidence, which complicates the ability for public health officials to fully understand the extend of disease transmission throughout the nation (Page, et al., 2019). As of 2019, force has been used to stop protests, doctors have been arrested, and armed groups have been placed at hospitals to prevent the media from obtaining information regarding the public health crisis (Page, et al., 2019). Therefore, humanitarian needs are not being met due to the government's unwillingness to acknowledge the ongoing humanitarian crisis (Doocy, Page, Hoz, Spiegel, & Beyrer, 2019). As disease rises within Venezuela, individuals have migrated to border areas, specifically Brazil and Columbia, in search for healthcare, food security, and economic opportunity (Doocy, Page, Hoz, Spiegel, & Beyrer, 2019).

As of 2019, more than three to four million individuals have fled the country, placing the surrounding border areas at increased risk for disease through migration of infection, as well as through placing increased stress on host country resources (Page, et al., 2019). As of 2018, 114,974 Venezuelans crossed the Pacaraima border of Brazil, which is the primary location of settlement for Venezuelan refugees due to monetary restriction regarding the use of private or public transportation, which impacts the overall healthcare need within that area (Doocy, Page, Hoz, Spiegel, & Beyrer, 2019). While the Brazilian constitution declares universal healthcare for all residents of Brazil, including foreign-born individuals, Venezuelan immigrants must obtain a national health card to access services (Doocy, Page, Hoz, Spiegel, & Beyrer, 2019). With such a highly-populated migrant area on the Brazilian side of the border, civilian and military physicians were deployed to the border town of Pacaraima to provide screening and vaccination services. Screening and testing was conducted for common mosquito-borne illnesses, such as malaria, dengue, chikungunya, and Zika (Doocy, Page, Hoz, Spiegel, & Beyrer, 2019). As of March 2018, a total of 4,455 Venezuelans had received services at that site (Doocy, Page, Hoz, Spiegel, & Beyrer, 2019). Within one year, the number of patients seen at the largest hospital in Roraima had doubled, resulting in severe medication and supply shortages (Doocy, Page, Hoz, Spiegel, & Beyrer, 2019). This has resulted in increased disease transmission, personnel shortages, and an increased need for monetary support from the Brazilian federal government (Doocy, Page, Hoz, Spiegel, & Beyrer, 2019).

Appropriately identifying suspected and confirmed cases within Latin America is crucial to gaining control of the disease outbreak. Unfortunately, infections caused by arboviruses typically have similar disease presentations, which can lead to misdiagnosis based on symptomatology alone. Therefore, testing for coinfection through laboratory testing is crucial for gathering adequate data and reporting appropriate statistics (Suwanmanee, et al., 2018). Due to financial restraints, syndromic surveillance is typically used throughout developing countries, which helps with early detection where there are shortages of doctors and minimal technology available (Unite For Sight, 2000-2015). Syndromic surveillance, which uses a variety of health indicators such as drug purchases and school absences to rapidly identify an outbreak, can provide early identification and warning of disease (Unite For Sight, 2000-2015). When syndromic surveillance is paired with traditional surveillance methods, it has shown to be extremely functional (Unite For Sight, 2000-2015). As of November 16, 2019, 166,664 cases of chikungunya were reported as “suspect” in Brazil and 93,000 were reported as “confirmed” cases (European Centre for Disease Prevention and Control, 2019). As of November 30, 2019, 180 cases had been reported as “suspect” cases in Venezuela, with nine “confirmed” cases (European

Centre for Disease Prevention and Control, 2019). While these numbers show a significant difference between the two countries, a lack of surveillance efforts may be the reason for these vastly different incidence rates, resulting in the inability to truly understand the situation throughout Latin America (Page, et al., 2019).

Conceptual Models

Chikungunya has a multitude of variables that affect its prevalence within a population. Social construct, economy, climate, and vegetation, which may all impact the reproduction of mosquitoes, are several factors that impact the spread of disease within an area (Pan American Health Organization, 2015). Therefore, it is vital to understand the natural factors contributing to chikungunya incidence, as well as the human behavioral factors that play into illness and how these categories interact with one another. Figure 1 pictured below demonstrates natural variables, while Figure 2 demonstrates human-based interactions that may impact incidence rates. Figure 3 shows the relationships between natural and human factors, with the assumption that all sub-categories remain relevant.

Figure 1. Natural Factors of Chikungunya

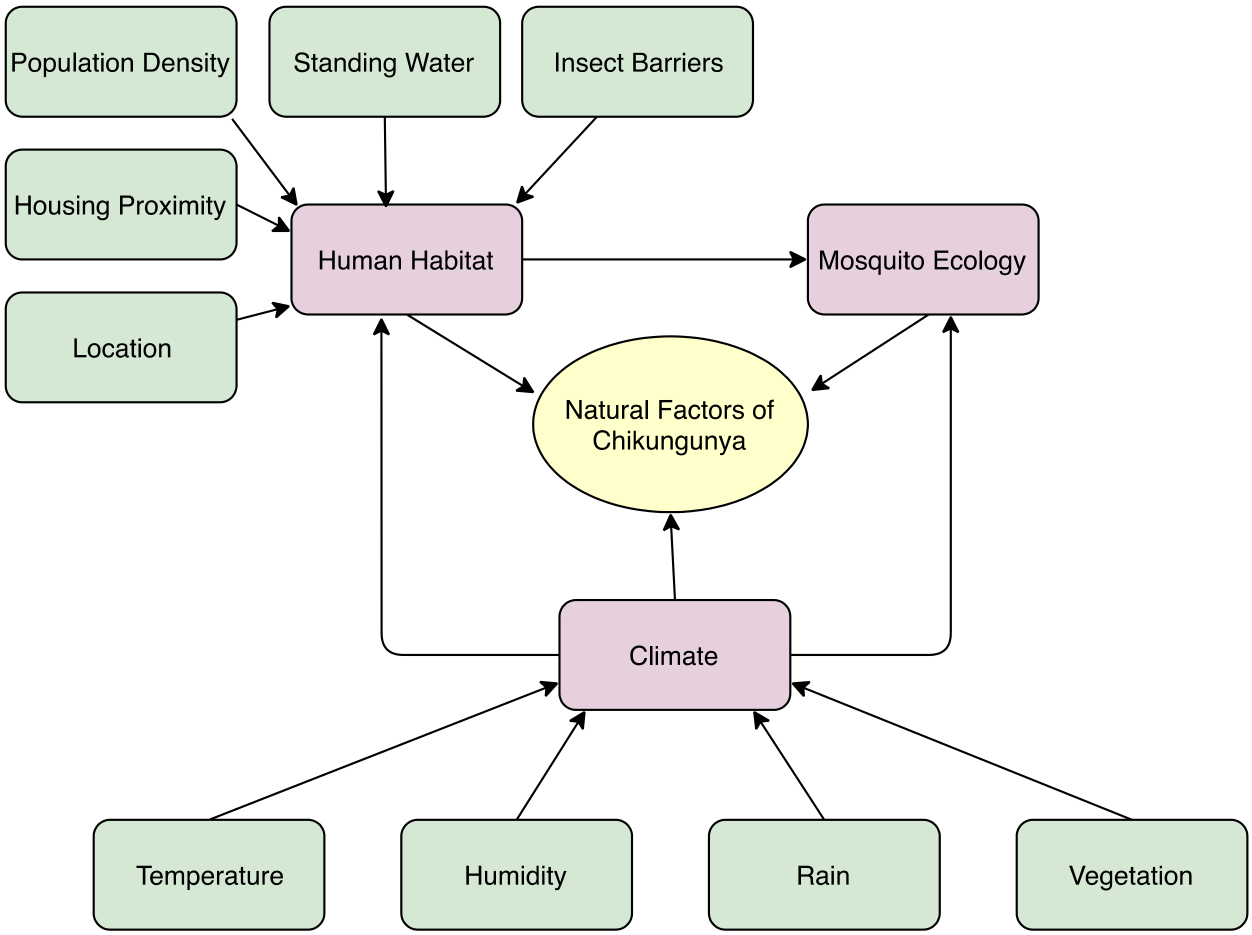


Figure 1a. Key

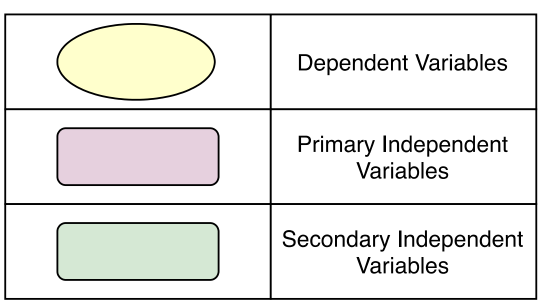


Figure 2. Human Behavior and Chikungunya

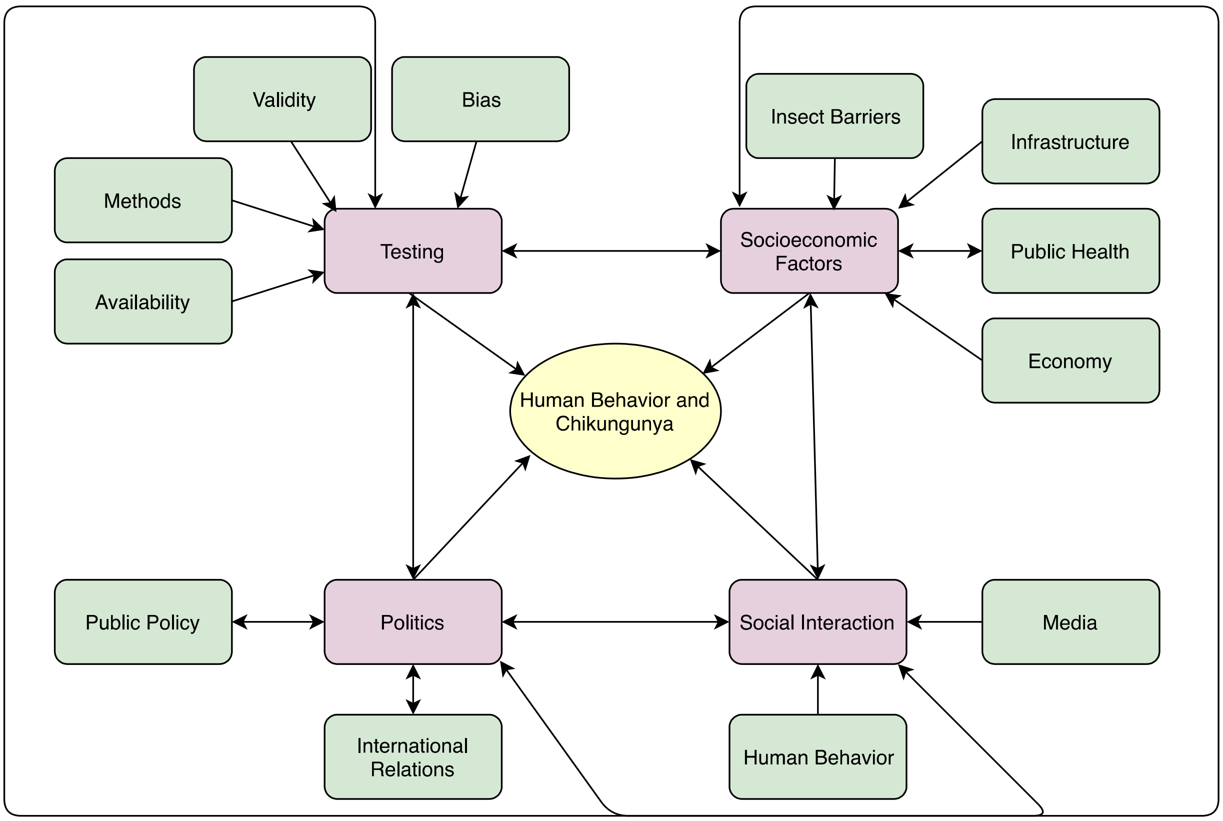


Figure 2a. Key

	Dependent Variables
	Primary Independent Variables
	Secondary Independent Variables

Figure 3. Chikungunya Incidence Rates

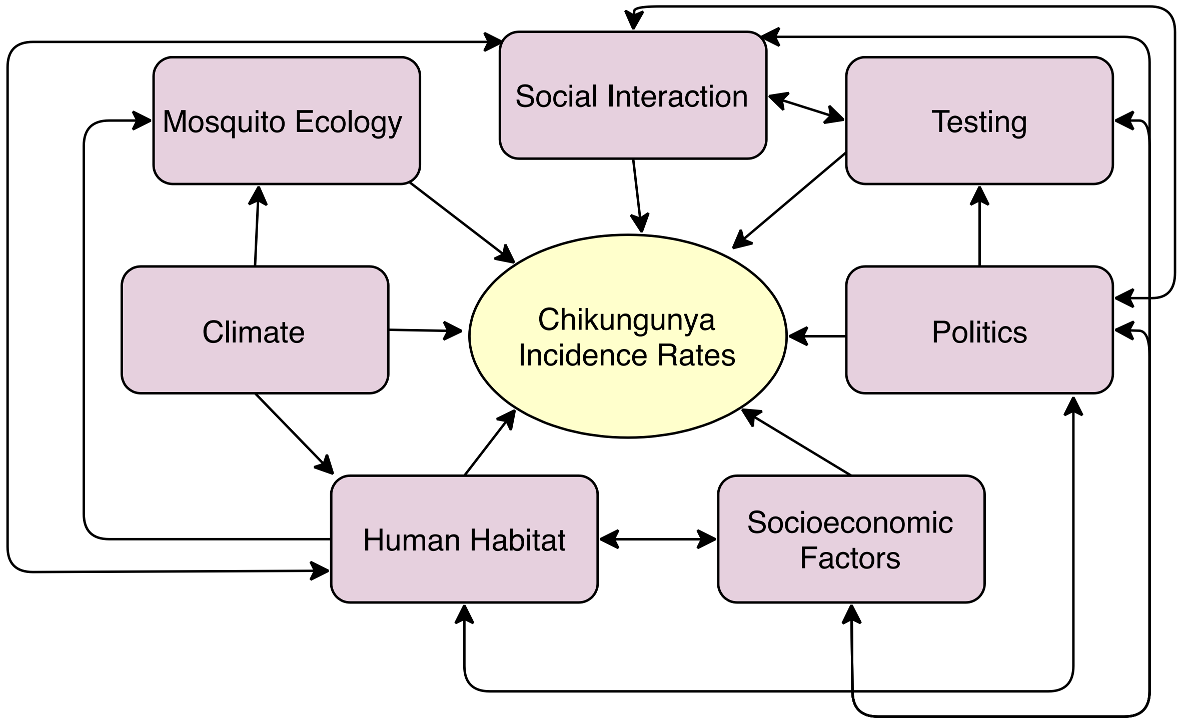
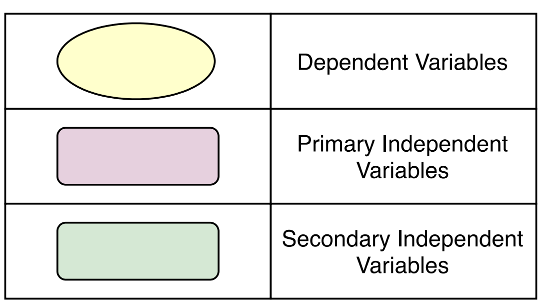


Figure 3a. Key



Definitions

- **Natural Factors of Chikungunya** – Natural factors such as climate, mosquito ecology and human habitat may impact how quickly a group of mosquitoes can reproduce (Hosangadi, 2019). These factors must be taken into account when considering a population's risk for disease contraction. While some may assume that surveillance begins with identifying and recording disease incidence within a population, surveillance measures must begin with appropriately identifying and maintaining a record of these risk factors (Morabia, 1996).
- Mosquito Ecology- The transmission of chikungunya begins with its two main vectors; the *Aedes aegypti* and *Aedes albopictus* mosquitoes (Pan American Health Organization, 2011). Therefore, understanding the way these vectors reproduce and spread throughout a population is vital to decreasing rates of disease within a region. The *Aedes aegypti* mosquito favors conditions within people's homes and prefers its larval habitats to be on indoor containers, while the *Aedes albopictus* typically resides near human habitats or within natural habitats (Pan American Health Organization, 2011). As the *Aedes aegypti* typically rests indoors, its most common larval habitat consists of containers of water on household premises (Pan American Health Organization, 2011). On the other hand, the *Aedes albopictus* primarily reproduces within the natural habitat (Pan American Health Organization, 2011). Both mosquito types prefer high temperatures, ample vegetation and standing water in containers for their breeding sites (Pan American Health Organization, 2015).
- Climate- Environmental conditions such as hurricanes, floods and extreme temperatures give rise to mosquito-borne illness due to increased vector reproduction and spread

(Meason & Paterson, 2014). Therefore, the overall state of global climate change can allow mosquitoes to thrive where they once were largely absent and to spread rapidly to unprepared areas (Meason & Paterson, 2014). In addition, climate can impact human habitat due to the desire to live in specific areas based on the average temperature and rainfall throughout the year.

- Temperature- The overall behavior, ecology and physiology of mosquitoes depend on the surrounding temperature and their ability to thermoregulate within that environment (Reinhold, Lazzari, & Lahondere, 2018). The lower survivable temperature threshold for the *Aedes aegypti* is 16 degrees Celsius, with the upper threshold being 34 degrees Celsius. On the other hand, the *Aedes albopictus* can survive and develop in a somewhat wider range of temperatures, which range from 15 degrees Celsius to 35 degrees Celsius (Reinhold, Lazzari, & Lahondere, 2018). At lower temperatures these mosquitoes are unable to move, and therefore die within a couple days. At higher temperatures, full development is unable to occur (Reinhold, Lazzari, & Lahondere, 2018).
- Humidity- Mosquitoes have a limited range of humidity they can tolerate due to their high surface area to volume ratio. This makes mosquitoes extremely sensitive to environments with low humidity (Yamana & Eltahir, 2013). At low humidity levels, mosquitoes have a decrease in overall water loss, which ends up being fatal to these organisms after several hours (Yamana & Eltahir, 2013).
- Rain- The production of larvae and pupae depends on the existence of a saturated breeding ground. Specifically, in the *Aedes aegypti* mosquito, eggs are laid above the water line and hatch when there is enough water present to wet them after

rainfall. Although the *Aedes aegypti* prefers to breed indoors, an increase in rainfall and the lack of accessibility to indoor habitats may precedent these insects to breed outdoors within open containers. The *Aedes albopictus*, which prefers natural habitats, would be directly affected by an increase in rainfall, which would increase the reproduction of these mosquitoes (Valdez, Sibona, & Condat, 2018). In addition, the increase in rainfall will directly relate to vegetation, which affects the mortality of mosquitoes (Pan American Health Organization, 2015).

   - Vegetation- The *Aedes aegypti* mosquito tends to live predominantly in natural locations and feed on the nectar of plants (Centers for Disease Control and Prevention, 2012). Plants, which are typically grown in flower pots, potted plants, and containers may provide an adequate water source for mosquito reproduction (Centers for Disease Control and Prevention, 2012). Therefore, it is vital to consider plant cavities and tree holes as a place for breeding, while the existence of numerous plant nectar sources may help the mosquitoes to thrive within a population.

- Human Habitat- Land use factors such as agriculture, urbanization and deforestation can impact the rise of mosquito-borne illness within a population (Meyer-Steiger, Ritchier, & Laurance, 2016). These changes may increase the number of favorable environments for mosquitoes, which would increase survival rates, growth rates and available food sources. With stronger insects, the overall vector-host relationship would become altered, putting humans at an increased risk for disease (Meyer-Steiger, Ritchier, & Laurance, 2016).
   - Location- Geographical location determines many factors such as vegetation, the existence of water sources, temperature, elevation, and much more. While

mosquito-borne viruses once were limited by the restraints of tropical areas, diseases are now emerging from the "Old World" areas into the Americas (Rezza, 2014). Recently spreading into India, Europe, and the Caribbean, chikungunya is predicted to extend further into North, Central and South America (Gonzalez-Sanchez & Ramirez-Arryoyo, 2018). While the spread of chikungunya is expanding to various areas, tropical locations with high humidity, extensive rainfall and high temperatures are more likely to attract a high mosquito population (Pan American Health Organization, 2015).

- Housing Proximity- Having limited space between houses within an area can create similar standing water sources, similar sewer sources, similar infrastructure and an increase in density of humans susceptible to mosquito contact. An increase in human contact may promote transmission   Therefore, one must observe the overall relationship between housing proximity and disease to determine if close living quarters impact transmission rates in the same environment.
- Population Density- The initial transmission of chikungunya to a mosquito begins with the bite of an infected person. Then, when the mosquito feeds on another human it spreads the virus through its bite (Centers for Disease Control and Prevention, 2019). Due to the need for an infected source for the vector to become infected, the disease may transmit quicker throughout a highly populated area.
- Standing Water- Female mosquitoes lay several hundred eggs along the walls of water-filled containers. When water rises above these eggs, they hatch and become adults in close to a week (Centers for Disease Control and Prevention, 2015). The number of containers present directly relates to the number of

mosquitoes hatched, and therefore, should be considered as a factor for disease prevalence.

  - Insect Barriers- Without the use of insect barriers, such as mosquito nets or screened windows within commonly visited areas and/or areas of residence, mosquitoes are easily able to access populations which, in turn, transmits infection throughout the area. Therefore, the existence or absence of this device is necessary when considering the source of illness and the likely point of human contact with the infected mosquito.

- **Human Behavior and Chikungunya-** Human behavior can play a large role in the spread and prevention of disease within a population. First, socioeconomic factors, such as the ability to perform appropriate community-based surveillance and to report those findings, can play a large role in prevention (Osterholm & Hedberg, 2015). In addition, social interaction, such as the influence of media on a population, can increase the amount of preventative actious taken by a population, which may be accompanied by fewer hospital visits (Elsevier, 2016). Finally, the availability of testing and having the appropriate people to perform those tests can affect the validity and reliability of the data collected.
- Socioeconomic Factors- Socioeconomic factors, which can be broken down into employment status, education, and income can impact the overall state of a population's health system (PDHPE, 2015). A system's available infrastructure (buildings, roads, bridges, etc.), public health measures, and overall economy will directly impact prevention, surveillance and treatment methods within an area. Socioeconomic factors can also impact social interaction through the affordability of direct communication (i.e.

media) and can directly impact testing measures due to the ability for public health measures to appropriately relay the importance of diagnosis through testing.

- Infrastructure- The ability for public health to respond to disease outbreak depends on physical accessibility to that area. Then, the ability to treat and carry out surveillance/treatment methods depends on the existence of buildings and resources capable of carrying out those activities. Infrastructure, such as bridges, roads, buildings and all other facilities needed to perform these tasks must be available to plan, deliver, and evaluate public health measures (Association of State and Territorial Health Officials, 2019). The absence of infrastructure can lead to an increase of water-filled uncovered containers, which serve as mosquito breeding sites.
- Public Health- Public health, which aims to promote and protect the health of those within a community, does so through the conduction of various surveillance, research, and public education programs (American Public Health Association, 2019). While these efforts often serve to better a community, such initiatives require adequate funding and resources to carry out the mission. Therefore, it is vital to consider the population's overall public health assets to understand their advantages and disadvantages in preventing illness and injury.
- Economy- In 2016, the United States requested approximately $1.9 billion during the Zika outbreak for supplemental funding. In addition, $526 million was requested for international relief efforts (Seelke, Salaam-Blyther, & Beittel, 2016). Without this funding, the attempted efforts to control disease would be unobtainable and the population would continue to suffer without relief.

Therefore, the overall economy and willingness for the government to allocate those funds to public health initiatives will impact the disease rates of chikungunya.

    - Insect Barriers- As previously stated within the “Natural Factors” description, the existence or absence of mosquito barriers is a crucial consideration when observing disease risk and infection. The economic ability to purchase these devices and/or the resident’s willingness to obtain these resources, whether in the form of mosquito nets, screened windows, doors, etc., will determine a considerable amount of one’s risk of exposure to infected insects. In addition, the existence or absence of air conditioning is a crucial component, as this has shown to decrease one’s exposure to insects (Centers for Disease Control and Prevention, 2019).

- Social Interaction- Components of social interaction can affect a population’s awareness and response to disease. If a community is highly involved in communications with one another, it is likely that news and information of disease would be spread throughout that region. In addition, the circulating knowledge of disease can help a community prevent disease through community clean-up or the elimination of man-made breeding sites. Therefore, social interaction can be used as a free and natural public education initiative that can provide useful information for protection and response to those within that area. In addition, the presence of media and overall international relief efforts can serve to provide information to a community that one would have not had access to without these resources. The presence of media and international relations may serve to provide an increase in funding, public health measures and overall infrastructure to improve quality of life.

  - Human Behavior- The way a community interacts with one another impacts the way disease spreads throughout a population, as well as how information is spread throughout that area. It is important to consider the difference between information spreading through person to person, versus information spreading through media or other global sources. In addition, it is vital to consider individual sanitation efforts, career paths, and overall living circumstances to identify possible sources of outbreak and commonalities among those infected through cleaning habits and one's attention to the elimination of potential breeding sites within their homes.
  - Media- The existence of media reporting for disease can serve to both benefit and hinder the process of disease prevention. While mass media coverage can provide tips for isolation and vaccination procedures, it can also decrease population concern when reported to be a non-urgent measure. This may affect healthy behavioral procedures, and therefore, hinder the performance of specific public health measures (Collinson, Khan, & Heffernan, 2015).

- Testing- The ability to appropriately detect disease within a population is crucial for determining disease prevalence within an area. In addition, the ability for those tests to specify which disease is being spread is vital to providing appropriate treatment measures within that population. Testing efforts can impact both socioeconomic factors and social interaction through the need for extra resources, as well as through the ability to provide useful information to surrounding areas.

- Availability- In order for an area to detect disease, the appropriate testing must be available. While preliminary diagnosis of chikungunya consists of a clinical assessment, laboratory testing is needed for a confirmed diagnosis (Centers for Disease Control and Prevention, 2019).
- Methods- Multiple ways of testing exist to diagnose chikungunya. While all methods consist of serum or plasma collection, these collections can either be tested to detect virus, viral nucleic acid or virus-specific IgM and neutralizing bodies (Centers for Disease Control and Prevention, 2019). The diagnostic methods that are utilized have varying validity, reliability, sensitivity, specificity and time constraints.
- Validity- The various testing methods used to detect chikungunya have different validity which depend on the time frame in which detection can be measured. The method used to detect active disease within six days of onset is an RT-PCR, while testing for acute illness after six days of illness onset is achieved using IgM capture enzyme-linked immunosorbent assay (MAC-ELISA) (Johnson, Russell, & Goodman, 2017). Due to the differences in these tests and the timing of their utility, it is important for the patient to know when their symptoms truly began. If one of these tests is performed outside of their accepted windows, their utility in identifying disease may decrease.
- Bias- As with all surveillance efforts, bias must be considered and avoided to ensure accuracy in results. Bias, which can be defined as any systematic error resulting in an incorrect estimate of effect, is a result of errors within the methodology (Barratt, Kirwan, & Shantikumar, 2018). Specific types of bias,

such as information bias and selection bias, must be considered when interpreting results. Specific instances, such as an observer expecting to find a specific result or the ability for patients to recall events leading to illness may result in skewed data.

- Politics- The political state of a nation can determine available resources, governmental dependence on other nations, government involvement in the public's overall wellbeing, and more. Within the subject of politics, public policy and international relations may determine the existence or absence of appropriate public health measures. When considering country-specific characteristics, it is important to consider if that area is developed, or developing, to examine current efforts and resources appropriate to that country's model.
    - Public Policy- The existence or absence of strong public policy regarding public health measures is critical in the success of that initiative. If public officials do not support surveillance, prevention, and treatment efforts, it is likely that all strategies will fail, regardless of the effort put in from external nations. It is important to understand current policies, as well as a country's willingness to improve those regulations. As public policy is impacted by the political state of that area, the strength of these policies serves to strengthen or weaken the overall political efforts.
    - International Relations- The existence of positive international relations among neighboring countries can impact the amount of international relief provided (Margesson, 2015). Therefore, one must consider the overall state of these relationships to determine where the aid will come from, as well as how much

relief should be expected. As politics impacts international relations through trade, agreements, etc., these relationships affect the overall political state of the nation.

Research Question

Research Question: What factors are associated with the observed chikungunya incidence rates in Brazil and Venezuela?

Chapter 3: Research Design and Methods

Methods of Data Collection

Incidence data were gathered from pre-existing reports released by PAHO from 2014-2017 (Pan American Health Organization, 2017a). Suspected and confirmed cases were reported to PAHO/WHO from either the International Health Regulations Focal Points, member states, official news publications, or a combination of these. Suspected cases were defined as a patient with acute onset of fever greater than 38 degrees Celsius accompanied by severe arthralgia or arthritis not explained by other medical conditions. In addition, a history of visitation and/or residence within an epidemic/endemic area within two weeks prior to symptom onset must be present (Pan American Health Organization, 2017a). Unfortunately, the symptomatology associated with chikungunya can imitate diseases such as Zika, malaria, and dengue, which may result in the number of suspected cases being higher or lower than the true number. To clarify these suspected cases, differential diagnosis is performed, which may include information such as place of residence, travel history, and potential exposure (Pan American Health Organization, 2011). A confirmed case consisted of any suspected individual with a positive specific chikungunya test. Appropriate tests consist of the following: viral isolation, RT-PCR, detectable IgM antibodies, or four-fold increase of chikungunya-specific IgG antibody titers. Incidence was calculated from (autochthonous suspected + autochthonous confirmed) /100,000 population (Pan American Health Organization, 2017a). We performed a systematic review of literature to observe typical patterns of mosquito reproduction and disease transmission to determine the variables analyzed within this study. The three primary categories analyzed are climate, economy, and “disease awareness” amongst the local population.

Temperature and rainfall, which were used to describe climate within Brazil and Venezuela, were obtained from the National Oceanic and Atmospheric Administration (NOAA), which coordinated with the World Meteorological Organization to prepare monthly global climate reports. These climate indicators were measured in stations placed within Brasilia, Brazil and Caracas, Venezuela. Temperature units are listed in Celsius and rainfall is measured in mm (NOAA, 2018). Economy is measured on the basis of gross domestic product (GDP) change and unemployment rates, which were gathered from Country Economy and was cross-referenced using Macrotrends, which are both data-gathering websites (Country Economy, n.d.) (Macrotrends, 2018). These data were collected from a combination of sources, such as the Ministry of Finance, Central Bank, National Statistics Offices, World Bank, and the International Monetary Fund (Country Economy, n.d.). GDP change was reported on a yearly basis, while unemployment was reported on a monthly basis. GDP change was used in analysis, rather than overall GDP due to the cessation of publications of economic indices from Venezuela as of 2015 (CNBC, 2019). Therefore, GDP change was determined by The World Bank through estimations of the country's annual inputs and outputs (The World Bank, 2019). Media attention was estimated by the frequency of Google searches from a Wireless Access Point within either Brazil or Venezuela. Frequency is measured on a 0-100 scale, which is based on the topic's proportion of searches compared to all other topics with zero being none and 100 representing a peak popularity search term (Google, 2019). Throughout this paper, Google Trends and its relation to media attention will be referred to as "disease awareness."

Methods of Analysis

To test the strength of the relationship between incidence and the chosen external factors, statistical analysis was performed using Crunch IT and incidence data were entered per month.

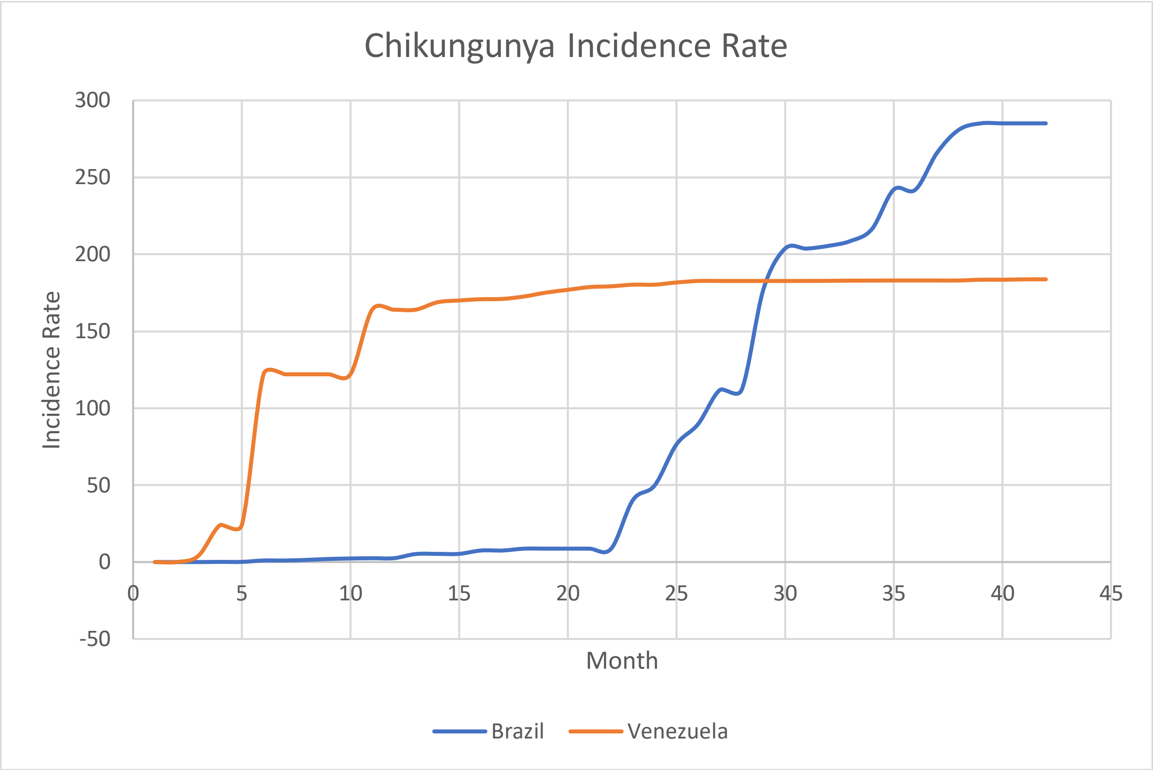
The data were compiled into a statistics summary table and correlations between possible predictor variables and incidence were measured using the Pearson's r test of correlation, where r= 0.10 to 0.29 shows a weak correlation, r= 0.30 to 0.49 shows a moderate correlation, and r= 0.50 to 1.0 shows a strong correlation. These variables were graphed using a scatterplot to confirm the assumption of linearity prior to performing this test. All data showing a correlation with an r value greater than 0.10 or less than -0.10 were analyzed using a bivariate linear regression model to determine strength of evidence against the null hypothesis, which states there is no relationship between incidence of chikungunya and the numerical value of the possible predictor variable. This model was built with a 95% confidence interval, with statistical significance determined by a p-value less than 0.05.

Chapter 4: Results

The study compared chikungunya incidence data gathered in Brazil and Venezuela by PAHO from 2014-2017, using incidence rates per month. External factors, such as temperature, rainfall, and GDP change were analyzed using linear regression and statistical summary tables to determine if correlations exist between incidence and various external factors. Overall, the analysis shows that unemployment in both countries has a moderate correlation with incidence of disease, while GDP change shows a strong correlation with chikungunya disease only in Venezuela. For these values, a significant p-value (<0.05) is shown across both country's unemployment categories, with a positive relationship in Brazil ($r=0.397$) and a negative relationship in Venezuela ($r=-0.450$). All values in the following tables are rounded to the third decimal place, when necessary. Within the tables, NaN indicates a value that is not a real number, indicating no correlation. All areas where no number exists are based on a non-significant r value. Only factors with an r value greater than 0.10 were considered for linear regression.

After comparing the cumulative incidence rate of chikungunya over three years within Brazil and Venezuela, we found disparate surges of disease incidence over time between these two countries (Figure 4). Brazil initially had a slow incidence increase but showed a steep incline around month 22, which continued to rise. Venezuela had a high number of initial cases, which tapered off near month 11, showing a slow increase until the end of 2017. While incidence was calculated using the equation (autochthonous suspected + autochthonous confirmed) /100,000 population, separate analysis was also performed for the cumulative suspected and the confirmed data sets. These illustrations are shown in Figure 5 and Figure 6 of the Appendix, which present with similar patterns on a larger graphing scale. While data were statistically analyzed on an incidence per month basis, graphs were used to show cumulative data over the timespan of collection.

Figure 4. Chikungunya Incidence Diagram



Brazil's data summary was reported in Table 1a and reports the sample number (n), sample mean, standard deviation, minimum value, median, and maximum value. These values are based on the incidence of chikungunya per month and the recorded external factors, as described within the "methods" section.

Table 1a. Brazil Data Summary

	n	Sample Mean	Standard Deviation	Min	Median	Max
Incidence	41	6.953	13.24	0	0.300	65.23
Temperature	41	22.18	1.568	17.70	22	25.70
Rainfall	40	112.3	116.2	0	73	398
GDP Change	4	-1.300	2.439	-3.500	-1.400	1.100
Unemployment	41	0.103	0.023	0.065	0.112	0.137
Google Trends	41	16.95	18.70	2	10.40	86

**Incidence per 100,000 persons *Temperature in Celsius *Rainfall per mm *GDP change per percentage *Unemployment per percentage *Google Trends on a 0-100 scale*

In Brazil, data suggests that the mean chikungunya incidence during 41 months of sampling from 2014-2017 is 6.953/100,000 persons. This estimate describes incidence measured at monthly intervals, with a minimum increase of zero cases per month, and a maximum increase of 65.23/100,000 cases per month. The standard deviation for the mean incidence per month is 13.24/100,000 persons. The average rainfall is 112.3 mm per month and the average temperature is 22.18 degrees Celsius. An overall decrease in chikungunya incidence is seen with respect to the GDP, while an increase in chikungunya incidence is concurrent with an increase of unemployment. An increase in "disease awareness" for chikungunya is seen concomitant with the progression of disease from 2014-2017. While the majority of variable markers for each researched category collected ranged between 40 and 41, GDP change is only represented by 4 samples due to incomplete availability of data. This made the data unreadable by statistical software, as shown in Table 1b.

Table 1b. Pearson's R and Linear Regression- Brazil

	R Value	Estimate	Std. Error	t value	Pr(>|t|)	CI
Temp	**-0.176**	**-1.481**	**1.331**	**-1.113**	**0.273**	**(-4.172, 1.210)**
Rainfall	**-0.122**	**-0.014**	**0.019**	**-0.759**	**0.453**	**(-0.051, 0.023)**
GDP Change	**NaN**					
Unemployment	**0.397**	**227.1**	**84.03**	**2.703**	**0.010**	**(57.17, 397.1)**
Google Trends	**-0.075**					

**Incidence per 100,000 persons *Temperature in Celsius *Rainfall per mm *GDP change per percentage *Unemployment per percentage *Google Trends on a 0-100 scale*

A weak correlation is seen between chikungunya monthly incidence and temperature and rainfall, respectively, with both correlations having a p-value greater than 0.05. A moderate correlation is shown between chikungunya incidence and unemployment, with an r value of 0.397. This dataset has a point estimate of 227.1, a p-value of 0.010 and a confidence interval of (57.17, 397.1). Google Trends, which is used to represent "disease awareness," is not significantly correlated with chikungunya incidence and was therefore, not considered for linear regression.

Although data collected from Brazil and Venezuela were both gathered from PAHO, reporting within Venezuela was not consistent, which resulted in lower sample sizes available for analysis within various research categories. Chikungunya incidence, reported by PAHO, still had 41 months of data, but factors such as temperature and rainfall were not uniformly reported by the country. Venezuela's data summary is outlined in Table 2a.

Table 2a. Venezuela Data Summary

	n	Sample Mean	Standard Deviation	Min	Median	Max
Incidence	41	4.481	16.59	0	0.060	98
Temperature	29	27.08	1.537	21.50	27.30	30
Rainfall	26	24.69	41.29	0	11	192
GDP Change	4	-10.70	6.613	-17	-10.95	-3.900
Unemployment	41	0.070	0.006	0.055	0.070	0.083
Google Trends	41	8.521	19.64	1	1.250	89

**Incidence per 100,000 persons *Temperature in Celsius *Rainfall per mm *GDP change per percentage *Unemployment per percentage *Google Trends on a 0-100 scale*

Overall, Venezuela shows an incidence mean of 4.481/100,000 cases per month, which differs from Brazil's 6.953/100,000 sample mean. While Venezuela has an estimated monthly rainfall average of 24.69 mm between 2014-2017, these numbers may be unreliable due to the inability to obtain continuous data. As shown in Table 1a, Brazil experienced an average monthly rainfall of 112.3 mm, which differs dramatically from the numbers found within Venezuela's data. Although both Brazil and Venezuela present with an average decrease of GDP in both fields, Venezuela's change shows a larger decline, with an overall GDP change of -10.70 per year and an increasing unemployment rate. "Disease awareness," on average, increased each month, but the progression of searches was approximately half of those in Brazil. A moderate correlation exists between incidence and unemployment, while a strong correlation is seen between incidence and GDP change. These values are shown in Table 2b.

Table 2b. Pearson's r and Linear Regression- Venezuela

	r Value	Estimate	Std. Error	t value	Pr(>|t|)	CI
Temp	-0.112	-1.419	2.431	-0.583	0.564	(-6.408, 3.569)
Rainfall	-0.139	-0.069	0.101	-0.689	0.497	(-0.278, 0.139)
GDP Change	-0.644	-0.121	0.102	-1.190	0.356	(-0.560, 0.317)
Unemployment	-0.450	-1263	401.1	-3.148	0.003	(-2074, -451.3)
Google Trends	0.285	0.241	0.130	1.860	0.070	(-0.021, 0.503)

**Incidence per 100,000 persons *Temperature in Celsius *Rainfall per mm *GDP change per percentage *Unemployment per percentage *Google Trends on a 0-100 scale*

Weak correlations are seen between incidence and temperature, rainfall, and "disease awareness." While all of these values had p-values greater than 0.05, the r value shown in Google Trends suggests moderate strength of association, with a p-value of 0.070. Moderate correlation is seen between chikungunya incidence and unemployment, with an r value of -0.450 and a p-value of 0.003 (CI (-2074, -451.3)). These values show statistical significance in favor of rejecting the null. Therefore, there is 95% confidence that as unemployment increases, incidence decreases. This finding may explain the relationship between Venezuela's economic stability and the government's willingness to report disease (Page, et al., 2019). These issues will be addressed in the "Discussion" section. GDP change shows a strong effect, indicating that as GDP increases, incidence decreases, and presents with a p-value of 0.356 and a confidence interval of (-0.560, 0.317). While the r value shows correlation, the linear regression does not show strong evidence against the null, which is likely due to the small sample size.

Overall, the only variable from the Venezuela data that shows a strong correlation with chikungunya incidence is GDP change, although this finding is not statistically significant in the linear regression analysis. Moderate correlations exist in both countries between incidence and unemployment (p-values <0.05). While Google searches show only weak evidence of correlation with disease incidence, data indicates that there is some evidence against the null, with a p-value of 0.070 and a point estimate of 0.241. While this analysis suggests important relationships between chikungunya disease burden and environmental, economic, and social factors, there may be external influences affecting diagnosis and reporting of chikungunya in Brazil and Venezuela, such as the unwillingness to report, the inconsistency of data collection, and the potential for falsified data being released due to sociopolitical factors (Page, et al., 2019).

Brazil is disproportionately larger than Venezuela, creating greater challenges in the generalizability of results. Therefore, additional research was performed to determine the overall spread of chikungunya throughout Brazil. In December 2014, Brazil's MOH reported 792 cumulative cases of chikungunya to PAHO (Pan American Health Organization, 2017a). These cases were reported primarily within the south-eastern coast of Brazil, with additional autochthonous transmission reported in the State of Amapa, with lies in the north between the border of Brazil and French Guiana (Pan American Health Organization, 2017b). During the last epidemiological month of 2015, as reported by PAHO, the majority of cases were reported along the north-western border and southern Brazil, with minimal incidence throughout central Brazil (Pan American Health Organization, 2017b). In 2016, it was reported that chikungunya was seen "nationwide," which is confirmed through mapping technologies (Pan American Health Organization/ World Health Organization, 2016). In 2017, large numbers of increasing cases from 2016 to 2017 were seen in Ceara, Roraima, and Tocantins, which are located in the north-east, north, and south-western regions of Brazil (Pan American Health Organization/ World Health Organization, 2017). Reported cases throughout Venezuela did not appear isolated to a single location, which could be due to the relative size of the country (Pan American Health Organization, 2017b).

Chapter 5: Discussion

Summary of Findings

The results of this study, analyzing factors influencing chikungunya incidence in Venezuela and Brazil, show a correlation between the economy and disease incidence. In addition, findings from this study suggest that an influx of migrants could potentiate the spread of disease through a lack of preparedness and available resources in their new location. As shown in Appendix B, chikungunya was seen nationwide in Venezuela throughout 2014 (Pan American Health Organization, 2017b). The majority of cases in Brazil during this time period were isolated to the south-eastern and south-western borders, settling primarily in Bahia, Minas Gerais, and Meto Grosso do Sul (Pan American Health Organization, 2017b). In 2015, disease began to spread throughout the southern border area, as well as in the north over the border of Columbia and Venezuela near the Amazonas (Pan American Health Organization, 2017b). By 2016 and throughout 2017, chikungunya was seen country-wide in both Venezuela and Brazil. Unfortunately, the data gathered on disease incidence were unable to identify in what geographic region the cases were exposed. Therefore, we were unable to confirm the relationship between migration and disease spread. Although this conclusion cannot be supported by the available data, it is highly suspected that the influx of migrants potentiated an outbreak of disease within the northern region of Brazil, as the map indicates disease increase along the Venezuelan-Brazilian border in 2015, which is the same year that mass numbers of Venezuelans began to migrate into Brazil (CNN World, 2019).

Although the relationship between movement of migrants into an area and incidence of disease might be expected, numerous other environmental and socioeconomic variables likely contributed to the findings of this study. As explained in the conceptual model, natural factors such as mosquito ecology, human habitat and climate play a role in the ability for mosquitoes to reproduce and survive in a given environment. In poorer countries, the lack of mosquito protection devices, such as netting, repellant, and screened doors is likely to increase one's exposure to insects. During civil strife, migrants who are attempting to flee the country may be exposed to mosquitoes due to homelessness or displacement. These factors, which are potentiated by a decline in economy, can severely stress the public health system, contributing to an even worsened economy due to the inability to successfully treat patients. When patients cannot obtain medical treatment, they may be unable to work due to disability or death. During civil strife, international relations may be affected, decreasing the ability to rely on imports and exports as well as international relief assistance. This can further decrease the economy and leave the population with little to no resources. Finally, the fall of one's public health system can limit testing and reporting, which can severely compromise data gathering, leaving the population vulnerable to disease through a lack of knowledge. Although this paper analyzes the effects of climate, economy, and "disease awareness" on chikungunya incidence, we recognize that the spread of disease is not limited to these measurable factors.

As of September 17, 2019, chikungunya continues to have a global impact through local and country-wide transmission (Centers for Disease Control and Prevention, 2019). This study, which aimed to examine potential relationships between external variables and the relationship of chikungunya incidence within Brazil and Venezuela examined its spread and impact within these regions. We viewed incidence rates and compared them to variables categorized into climate, economy, and "disease awareness." "Disease awareness" was estimated by the frequency of Google searches under the search term "chikungunya" from a Wireless Access Point within either Brazil or Venezuela. Of these three factors potentially influencing chikungunya incidence rates, economic indicators had the greatest strength of association, based on analysis of GDP and unemployment rates. Economy can have a large impact on the overall state of a population's health system due to the region's ability to fund prevention, surveillance, and treatment efforts within a population (PDHPE, 2015). While the economic variables analyzed do not explain the specific relationship between Brazil and Venezuela's differing patterns of association with chikungunya disease incidence, the observed correlations suggest the importance of continuous prevention and surveillance mechanisms when combatting the effects of chikungunya disease in a population.

The relationship between the incidence of chikungunya in Brazil and Venezuela presented with disparate surges in disease incidence over time (2014-2017). As disease incidence in Venezuela began to stabilize, Brazil's incidence began to rise. These disparate findings raise questions about each region's prevention and treatment efforts, specifically regarding healthcare infrastructure, available resources, and surveillance efforts throughout each region. In this analysis of chikungunya incidence, Brazil displayed a steep incline of chikungunya cases around month 22 (representing May 2016) of the analysis period, while Venezuela had an early initial spike in cases that then tapered off around month 11 (representing June 2015). For both counties, external influences played a role in decreasing the effectiveness of public health efforts and valid public health data reporting.

For Brazil, the observation of an increasing incidence of chikungunya over time may be related to a struggling expansion of its healthcare system resulting in a strain on quality of care. Brazil's healthcare system aims to provide Universal Health Coverage (UHC) and had great expansion of this process between 2003-2017 (Massuda, Hone, Gomes Leles, Castro, & Atun, 2018). Unfortunately, this expansion was limited by structural problems within the United Health

System that inhibited continued growth within the UHC due to low public funding, a lack of organization and governance, and inappropriate resource allocation (Massuda, Hone, Gomes Leles, Castro, & Atun, 2018). Brazil experienced its worst recession in 2014, resulting in major cuts to the healthcare budget in 2015. Between 2003 and 2016, the government's contribution to health financing dropped from 50.0% to 40.8% (Massuda, Hone, Gomes Leles, Castro, & Atun, 2018). These problems have contributed to a loss of private health plan coverage and may have negatively impacted concurrent outbreaks of infectious diseases, posing threats to the most vulnerable populations throughout Brazil (Massuda, Hone, Gomes Leles, Castro, & Atun, 2018). With chikungunya disease first presenting in 2014, Brazil quickly acted to identify cases and prevent the disease through the implementation of the Health Surveillance system, which had previously monitored dengue (Messias da Silva, et al., 2018). While the initial surveillance response was timely, many reports indicated that notifications were not made immediately after recorded onset of symptoms, which hindered surveillance activities (Messias da Silva, et al., 2018).

Unlike Brazil, whose chikungunya incidence reflects increasing disease rising with decreasing healthcare infrastructure, Venezuela's disease incidence measurements likely reflect a complete collapse of disease surveillance infrastructure and a dearth of data reporting. Throughout Venezuela, healthcare efforts have massively decreased since the economic crisis, which began around 2013 after the election of President Nicolas Maduro (Page, et al., 2019). Once one of the most prosperous countries in South America, Venezuela followed a free healthcare system model in the late 20th century, which aimed to decrease social inequalities. Unfortunately, an increase in government spending from 2000-2013 paired with a decrease in export production (e.g., of oil) resulted in significant budget deficits, leading to healthcare collapse due to an increase in public debt (Page, et al., 2019). The lack of export product was a result of several variables, with the apparent most powerful being an embargo of Venezuelan oil exports and a simultaneous ban on selling spare parts for Venezuela's drilling and oil extraction machinery (Eaton & Cohen, 2019) (Parraga, 2017). In an attempt to pressure the Maduro regime toward changing policies or stepping down from leadership, the United States and numerous other countries enacted this embargo toward Venezuelan oil products, which led to budget deficits and a collapse of the Venezuelan economy (Eaton & Cohen, 2019). The result of this economic collapse led to extensive out-migration of Venezuela, leaving the United States and Spain as the top recipients of talented and well-financed Venezuelan citizens (Faiola, 2018). This severely depleted available resources throughout Venezuela.

Due to unsatisfactory data, officials have inhibited the release of epidemiological reports, which has led to the inability to appropriately monitor disease throughout the country (Page, et al., 2019). In regard to external data collected for the means of this report, data containing total yearly GDP was unobtainable per The World Bank after 2014 and climate data were released to NOAA only until the beginning of 2017 (The World Bank, 2019) (NOAA, 2018). All incidence reports released by PAHO represent reported data from the applicable countries, which may reflect potential inconsistencies in available information due to non-uniform surveillance and reporting efforts (Pan American Health Organization, 2017a). Therefore, as incidence of chikungunya disease was shown to taper off in Venezuela around June 2015, it is likely that these data underreported actual case numbers, due to the government's threats of potential physical harm toward those releasing epidemiologic reports (Page, et al., 2019).

As of 2019, 4 million Venezuelans had left their country and fled to surrounding areas with approximately 168,000 refuges settling in Brazil (UNHCR, 2019). While Brazil supplies primary healthcare to these Venezuelans, the Brazilian healthcare system has experienced great strain as a result of these migrations due to the increased need for provision of care as well as the inability to obtain substantial quantities of needed medications and supplies (Doocy S. , Page, Hoz, Spiegel, & C., 2019). The mass migration of Venezuelans to Brazil, which began in 2015, preceded a steep incidence increase of chikungunya cases, occurring around May 2016. On the other hand, Venezuelan-reported cases were shown to have leveled-off around June 2015, which was six months prior to President Maduro declaring a state of economic emergency (CNN World, 2019). With the occurrence of these specific events, it is likely that incidence of chikungunya within Venezuela did not truly stabilize, but that incomplete reporting has led to a decrease in awareness of disease and surveillance. In addition, Brazil's spike in disease, which was preceded by an influx of migrants, may be linked to viremia amongst Venezuelan refugees, resulting from disease spread across borders. While the specific correlation between refugee migration and incidence is unmeasurable with currently available data, economic markers serve to represent the overall state of country resources in relation to reported incidence.

Climate

Climate is an essential factor in mosquito borne disease epidemiology, as specific environmental circumstances can either promote or diminish mosquito reproduction and survival. Variables such as temperature, vegetation, rain, and humidity can lead to an increase in breeding sites and survivability, resulting in an increase of potential chikungunya vectors. Global climate change can allow mosquitoes to thrive in areas where they once were unable to survive, leading to rapid spread of disease amongst unprepared populations (Meason & Paterson, 2014) The *Aedes aegypti* and *Aedes albopictus* mosquitoes thrive in warm, humid, and rainy environments (Pan American Health Organization, 2015). With these factors in mind, climate change has been predicted to increase the prevalence of mosquito-borne illness based on studies that "empirically parameterize models of viral transmission by the vectors *Aedes aegypti* and *Aedes albopictus"* (Ryan, Carlson, Mordecai, & Johnson, 2019). This model shows the increased risk of viruses, such as chikungunya and Zika, due to an increase in more favorable conditions; specifically, in areas where mosquitoes did not previously thrive (Ryan, Carlson, Mordecai, & Johnson, 2019). This has threatened global health security and lends support to the need for continuous surveillance worldwide (Ryan, Carlson, Mordecai, & Johnson, 2019).

This study examined the effects of potential climate change from 2014-2017, focusing specifically on temperature and rainfall. These factors were compared to the incidence of chikungunya to determine if one potentiated the other. Analysis of the variables that were used in this analysis were not able to detect a measurable relationship between climate and disease incidence, but it is reasonable to assume that a relationship may exist, given the biological plausibility of the existence of a relationship between mosquito ecology and climate factors. Due to a limited data collection period and the lack of observation across all of Latin America, which would include a variety of locations experiencing various environmental pressures, it is likely that limitations within the data itself contributed to an inconclusive relationship. In addition, the inability to obtain Venezuela climate data after January 2017, due to a lack of published data, serves as a significant limitation to these findings. Global data suggests that on average, the global temperature increases around 0.15-0.20 degrees Celsius per decade (Earth Observatory, 2020). Although this marginal change in global temperature likely does not impact findings observed over a few years, climate observation was crucial to analyze in this study, as it is a major factor of mosquito-borne disease globally. It is also understood that the effects of climate change do not hit all of the earth's locations with the same speed or severity. Therefore, future epidemiologic studies might consider the interaction between human outcome and local measures of climate change throughout a specific time frame.

Media

Historically, the use of media, specifically the release of public information, has been shown to raise citizen awareness on present or potential hazards, leading to an increase in performance of prevention and protection strategies (Coppola, 2015). Many studies have been performed to describe the specific effect that media has on a population regarding disaster preparedness, which has historically been linked to a positive correlation, leading to an increase in resource utilization such as medical services and prevention strategies (Coppola, 2015). Unfortunately, some countries in Latin America have limited access to the internet, making this an unreliable outlet for broad communication with the public (Coppola, 2015). Although there may be some sections of the population in Brazil and Venezuela who have periodic and/or limited access to electronic media technologies, there is substantial evidence suggesting the impact of media on public health initiatives, making this a crucial area of study.

We did not hypothesize the direction of the effect of disease awareness on incidence due to the possibility that an increase in awareness could have a positive or negative correlation with incidence. On one hand, the knowledge of threat could lead to increased prevention strategies, resulting in a successful decrease of disease incidence through implemented mosquito-prevention measures. On the other hand, the knowledge of the circulation of this disease and its potential effects could lead to an influx of reported disease cases, due to an increase in population testing, health-seeking behavior, or presumptive diagnoses. One study which observed mass media coverage during the H1N1 influenza pandemic, suggests that the number of media reports and hospital visits had a negative correlation with disease incidence, which was hypothesized to be due to preventative actions then taken by the population (Elsevier, 2016). On the other hand, a study done to examine the association of mass media coverage regarding invasive group A streptococcal disease in the pediatric emergency department found that a surge of media coverage for a specific disease was associated with an increase in testing for that disease (Sharma, Dowd, & Swanson, 2003). While each study has specific limitations, it is important to acknowledge the potential for both a positive and negative effect of media attention on disease incidence.

Overall, media coverage was measured through the analysis of Google Trends. Google Trends data has been frequently used for predictive modeling, indicating the potential for future outbreaks based on specific search terms, such as with the use of Google Flu Trends (Calster, Lemahieu, & Baesens, 2015). While it is not certain that measuring these terms adds a large benefit to prediction of outbreak, it has been shown that media attention has a positive correlation with Google searches (Calster, Lemahieu, & Baesens, 2015). This event, known as the "celebrity effect," causes an increase in search terms based on media coverage and campaign events (Calster, Lemahieu, & Baesens, 2015). Although this does not guarantee a predictive effect, Google Trends was used as a factor to estimate overall media coverage based on the "celebrity effect" theory.

Analysis of Google Trends data for the search term "chikungunya" indicates a clear, but weak positive correlation with disease incidence in Venezuela, but no correlation with chikungunya incidence is seen in Brazil. It was predicted that as "disease awareness" increased, incidence would increase as the population became more aware of the importance of obtaining medical assistance and disease testing. Since Google Trends was the sole source of data used to measure "disease awareness" within this study, it is noted that availability of technology within the areas of study served may differ, therefore having a variable effect on the findings of this study. While economy and the availability of technology would limit the ability to obtain recorded interest of the subject via Internet media searches, it may also inhibit the distribution of knowledge via social media across the interest area, limiting the population's ability to gain information necessary to take precautionary measures against the disease.

Economy

Globally, economic strain throughout a region increases social vulnerability, which results in extensive social inequities within the population (Bissell, 2013). This inequity further inhibits the ability to provide healthcare to areas where prevention methods are ineffective, and resources are scarce, resulting in heightened morbidity and mortality. In Brazil, the time period from 2003 to 2014 showed great economic advancement, but was followed by a period of recession, leaving the country with a slow country growth rate, which contracted in 2015 and 2016 (The World Bank, 2019). Although the beginning of economic recovery was marked in 2017, subsequent progress has been slow due to the need to restore fiscal sustainability throughout the country (The World Bank, 2019). On the other hand, Venezuela experienced a large economic collapse in 2014, which led to a decrease in GDP, leaving the nation in ruin (Kiger, 2019). As a result, the country's public health system has been threatened due to an inadequate and unstable health-care infrastructure (Page, et al., 2019). Unfortunately, a lack of reported data from the Venezuelan government has resulted in the inability to quantify the effects of economy on healthcare, but it is suspected that infectious diseases are increasing as public health services are decreasing (Page, et al., 2019).

In this study, GDP and unemployment were evaluated and measured with respect to the incidence of chikungunya. In tandem with the overall lack of disease reporting throughout

Venezuela, the inability to confirm GDP and unemployment estimates due to a country-wide ban on data release from governmental authorities raises concerns regarding the strength of correlation between analyzed variables. In Venezuela, a strong negative correlation is seen between GDP and incidence, but it is not statistically significant. This finding indicates that as GDP change values increased, disease decreased. This finding was to be expected, as an increase in economy allows for improved prevention and surveillance efforts. Pertaining to unemployment, strong, moderate correlations are shown within Brazil (p-value= 0.010) and Venezuela (p-value = 0.003), but in opposite directions. While in Brazil, a positive correlation between incidence and unemployment is seen, a negative correlation is observed in Venezuela. Since it would be expected that increasing unemployment would indicate a suffering economy, it is predicted that incidence and unemployment would have a positive correlation. The findings in Venezuela indicate that as unemployment decreased, disease increased. As of 2019, 4 million Venezuelans had left their country and fled to surrounding areas with approximately 168,000 refugees settling in Brazil (UNHCR, 2019). Therefore, while disease is shown to increase in Venezuela as unemployment decreased, it is hypothesized that this result may be due to the change in the denominator of total population, skewing the data regarding unemployment.

As stated previously, Brazil is disproportionately larger than Venezuela, creating extreme difficulty in the generalizability of results. With this disproportionate geographic distribution, the richest five percent of the Brazilian population accounted for 50 percent of the country's national income (Pasquali, 2019). Therefore, the ability to generalize results across the whole population of Brazil is hindered due to the likelihood of social inequity throughout the country. In addition, on-the-border testing has the ability to severely skew data points for incidence throughout the country due to migrants receiving medical treatment for diseases which were acquired in other bordering countries.

Limitations

The findings presented herein suggest that a relationship between economy and chikungunya incidence exists and demonstrate the potential for a relationship between migration and incidence. Unfortunately, we were unable to quantify the relationship between migration and incidence, but it is clear that as migration from Venezuela to Brazil grew, incidence of chikungunya in Brazil increased. Much of the data from Venezuela were either not reported or had evidence to suggest falsified information. This may be due to the governmental ban on epidemiologic reports, as well as the overall collapse of the health-care infrastructure, which has resulted in the inability to quantify public health issues (Page, et al., 2019). While literature suggests that disease reporting throughout Venezuela diminished during the collapse of the health-care infrastructure, reporting of climate and GDP data also reduced, which resulted in years of unreported data and necessitated the use of estimated benchmarks from outside sources used as proxies to estimate the potential impact of those factors, such as seen with GDP change. While analysis was performed with available data from Brazil and Venezuela, data collection and reporting methods varied considerably, therefore making it difficult to directly compare the two countries. Further recommendations would include the performance of uniform methods of diagnostic testing across both countries to decrease potential confounding factors within the analysis. Although this study aimed to evaluate the incidence of chikungunya from 2014-2017, this brief period of time had limited available data, hampering the analysis. We believe that an increase in measurable data might have resulted in demonstrating a stronger relationship between variables.

Venezuelans typically cross the Pacaraima border of Brazil, which is the primary location of settlement for Venezuelan refugees due to transportation costs, impacting the overall healthcare efforts needed within that area (Doocy, Page, Hoz, Spiegel, & Beyrer, 2019). This heavily-populated migrant area resulted in an increase of healthcare workers to the area, who were responsible for providing screening and vaccination services (Doocy, Page, Hoz, Spiegel, & Beyrer, 2019). The increase in screening efforts and available healthcare potentially within Brazil contributed to an increase in reporting and hence an increased incidence detection, despite the likelihood the disease was previously contracted in Venezuela. To control for these factors, we suggest that further surveillance efforts throughout the country capture information on place of likely exposure and recent travel to or from other countries. This type of information would help researchers determine the impact of migration on disease, leading to a better understanding of future public health efforts needed to prepare for an influx of neighboring populations.

Chapter 6: Conclusion

This study analyzing country-specific influences on chikungunya incidence showed relationships with economy, climate, and "disease awareness" in Brazil and Venezuela that can be attributed to the interface between the surrounding natural and manmade environments in each country. Although our study shows evidence in favor of a relationship between economy and disease incidence, variables such as political strife, human habitat, testing availability, and public health initiatives were not measured, but likely contribute to the relationship found between economy and disease. Climate, economy, and "disease awareness" were chosen as representative variables given that they were data points available from both countries, were well defined, and allowed comparison, but it is important to consider additional external variables that could influence chikungunya epidemiology when interpreting the findings of this study. Overall, our findings indicate a relationship between economy and disease incidence, and given the political situation during the study period, suggests that an unanticipated large influx of migrants could potentiate the spread of disease through a lack of preparedness and available resources. Despite notable data-gathering and reporting limitations, especially in Venezuela, available data suggested our hypothesized findings, which is that as economy indicators worsened, chikungunya incidence increased. This is likely due to a combination of diminished public health initiatives, a decrease in available resources, and an increase in population toward areas that were unprepared to provide care for such a great influx of individuals. This drop in economic performance was largely due to political turmoil as well as external economic barriers imposed by other countries (Eaton & Cohen, 2019).

The findings presented within this study represent the importance of global health security and the need for public health preparedness when accepting migrants from bordering areas. The spread of chikungunya across Brazil, which began shortly after the recorded influx of Venezuelans, shows a lack of preparedness within Brazil's healthcare system, leading to a decrease in medical resources and contributing to a recorded increase of disease. This analysis highlights the importance of pre-determined plans for the surveillance and control of communicable diseases that may arise after the influx of neighboring populations. In addition, this paper demonstrates the importance of public health surveillance to ensure public awareness, regardless of the political or economic situation. Unfortunately, a population may be unprepared to mitigate the effects of communicable disease if they are unaware of the disease's presence and potential for rapid spread throughout that environment. Therefore, it is crucial that the public and its public health infrastructure are made aware of disease circulation through population-appropriate means and that government officials distribute information, even under conditions of political crisis.

Overall, further research is needed to determine the origin and dissemination of disease in both Brazil and Venezuela in order to further correlate the influx of migrants from Venezuela with disease occurrence in Brazil. The utilization of a uniform data collection system, containing records of country of origin and recent travel, may better expose the etiology of disease transmission and identify high-risk populations throughout Venezuela and Brazil. Globally, countries should be aware of the consequences faced when the healthcare system is unprepared for an influx of migrants, which could lead to severe health effects. The spread of non-endemic communicable diseases paired with the strain on healthcare services places the accepting country at risk, which can lead to the host population having increased exposure to non-endemic diseases. Mass migration from one country to another is a hallmark of human history, which is unlikely to change based on public health effects or other potential consequences. Therefore, it is crucial that national and international organizations prepare for the occurrence of migration and create a public health model that can withstand the forces of rapid population increase. Through the coordination of pre-planned response outlines, dedicated infrastructure, trained healthcare staff, and a surplus of medical supplies, a strong international response can be made on short notice to provide medical care to receiving countries. This may serve to mitigate the impact of disease influx from neighboring countries, further strengthening global health security and allowing mass migration across borders without experiencing economic strain or public health collapse.

Appendix

Appendix A

Figure 5. Suspected Cases of Chikungunya

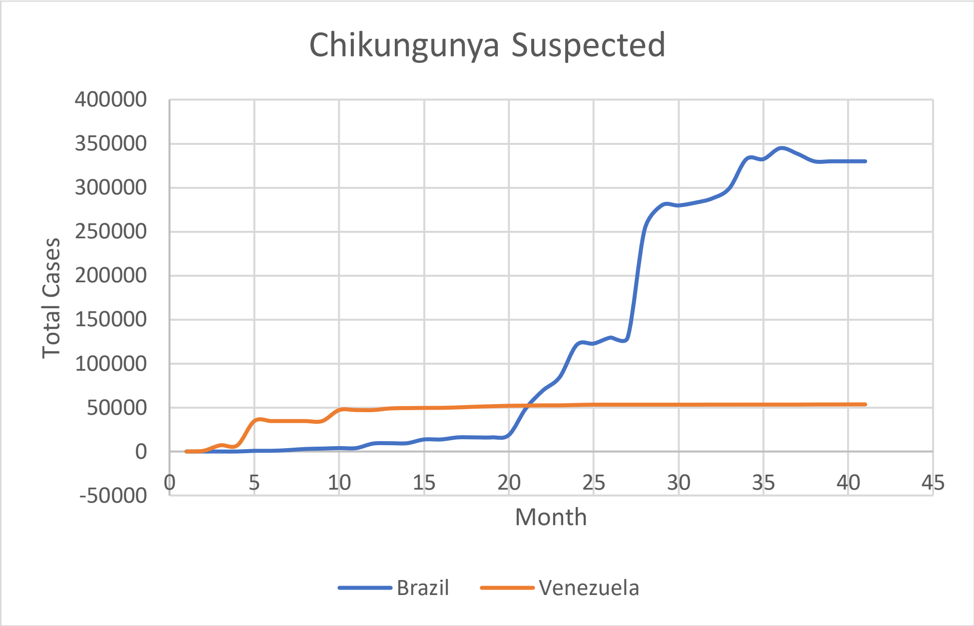
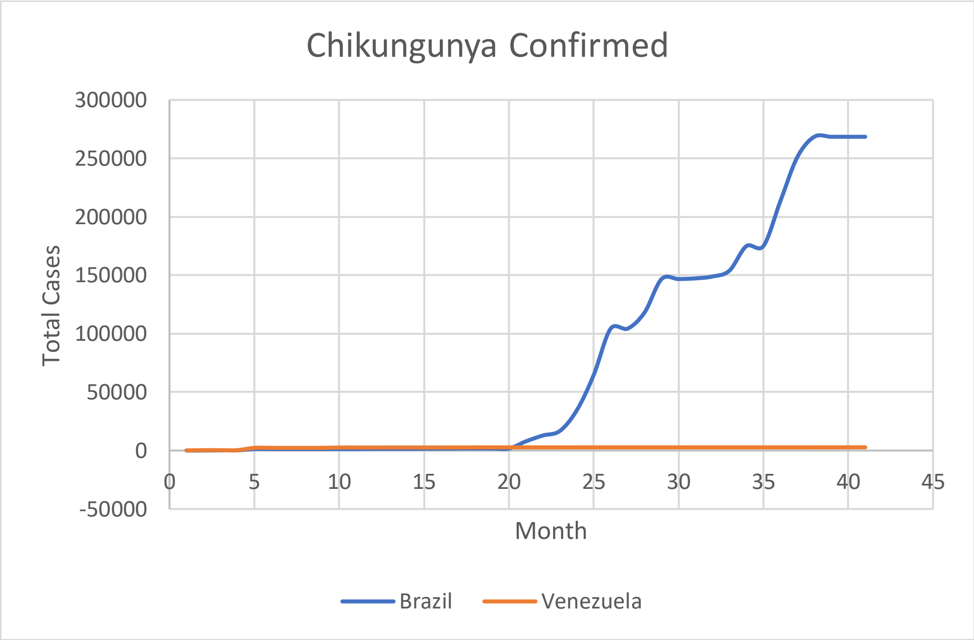
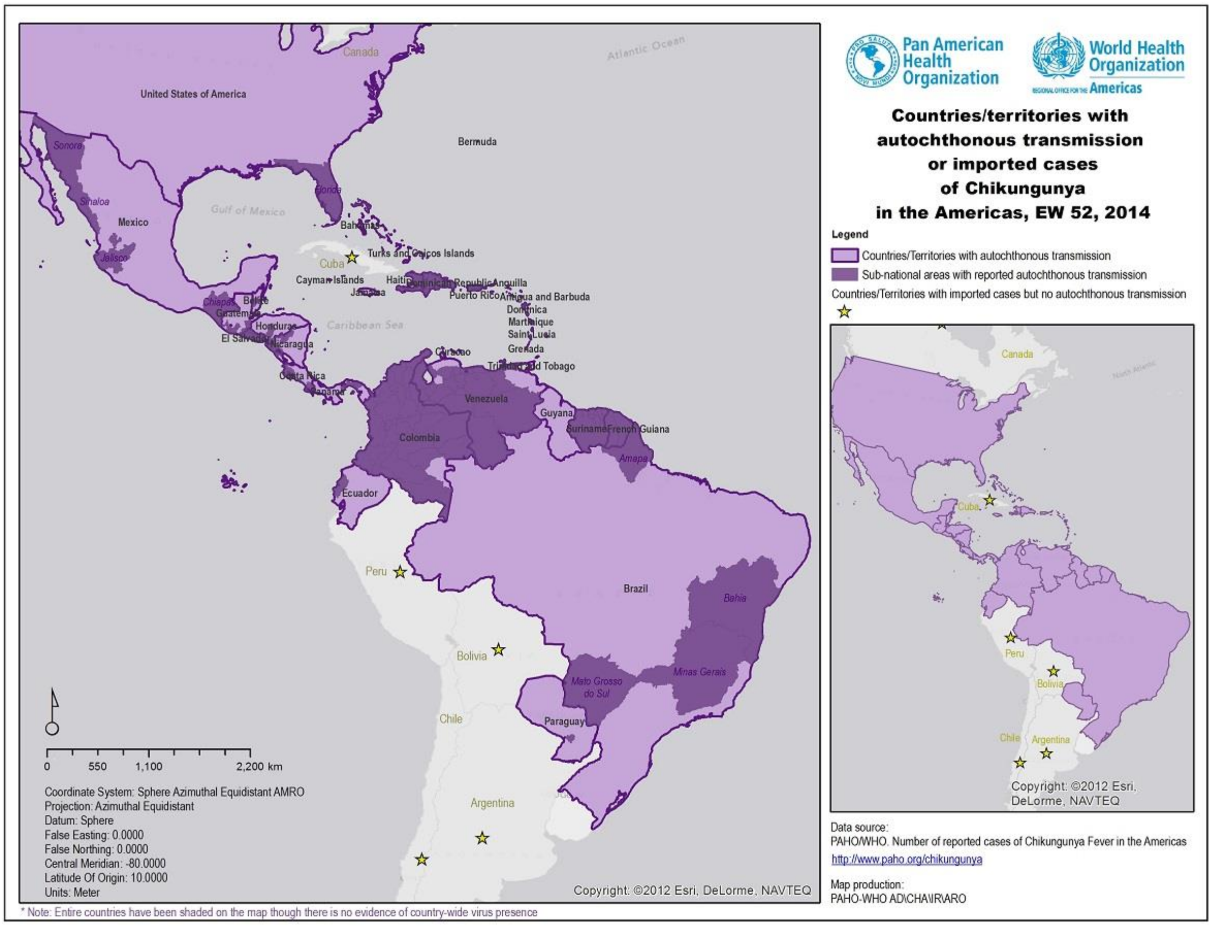


Figure 6. Confirmed Cases of Chikungunya



Appendix B

Figure 7. Countries/territories with autochthonous transmission or imported cases of Chikungunya in the Americas, EW 52, 2014



(Pan American Health Organization, 2017b)

Figure 8. Countries/territories with autochthonous transmission or imported cases of Chikungunya in the Americas, EW 49, 2013 – EW 50, 2015

(Pan American Health Organization, 2017b)

Figure 9. Countries/territories with autochthonous transmission or imported cases of Chikungunya in the Americas, EW 49, 2013 – EW 52, 2016

(Pan American Health Organization, 2017b)

Figure 10. Countries/territories with autochthonous transmission or imported cases of Chikungunya in the Americas, EW 49, 2013 – EW 51, 2017

(Pan American Health Organization, 2017b)

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