#### Investigating Spatio- Temporal trends of dengue infections on Curaçao from 1995-2016.

Bart Roelofs Master's Thesis research paper

# Abstract

The dengue virus is a major cause of disease around the world, with over 390 million infections annually and over 40% of the world population being at risk at this moment. Curaçao has seen different pandemics over the last 25 years, which are investigated in this study. This study aims to contribute knowledge on the effect of geographical and temporal processes on the number of dengue cases, which may contribute to preventing dengue cases in the future. Data on 6572 cases of dengue infections on Curaçao from the period of 1995 until 2016 were used. Statistical analysis of the distribution of cases using Moran's I identified the presence of spatial autocorrelation, with the Moran's statistic of 0,06 (p<0,01) for the total study period. The majority of cases was recorded in highly populated areas and there was a relationship found between population density and dengue cases. Temporal analysis discovered that cases mostly occurred from October to January, which is the rainy season. Additionally, lower average temperatures, more precipitation and a lower sea surface temperature appeared to be related with more dengue cases. This effect has a direct relationship to La Niña, which is the cooling phase of El Niño Southern Oscillation.

### 1. Background

Vector borne diseases (VBD), such as dengue, Zika or Chikungunya, are diseases which are transmitted through mosquitos (Bisanzio et al. 2018). The presence of disease carrying mosquitos results in threats towards public health, which is a phenomenon that needs to be addressed. Dengue has been spreading to formerly unaffected areas since the 1970's. Fifty years ago, there were only 9 countries with reported dengue virus transmission (Elsinga, 2018), but as of today, over 100 countries, ranging from Asia to America, Africa, the Caribbean and more recently Europe, face the challenges related to dengue transmissions (Vincenti Gonzalez, 2018). Currently, almost half of the world population is at risk for dengue fever (Kraemer, 2019; Vincenti Gonzalez, 2018), with over 390 million infections annually (WHO, 2019). Dengue virus is a large threat towards public health, as an infection with the virus results in an abrupt fever lasting two to seven days. It is possible that a dengue infection transforms into severe dengue, which can have major effects on a person's health (Elsinga, 2018) and in the worst-case scenario result in death (Vincenti Gonzalez, 2018). The dengue virus is transmitted by the females of the Aedes Aegypti and the Aedes Albopictus mosquito, which are both day-biting mosquito's (Vincenti-Gonzalez, 2018).

Vector Borne Diseases (VBD's) are related to spatial heterogeneity (Vincenti Gonzalez, 2018). Spatial heterogeneity in a point pattern setting is explained by Dutilleul et al. (1993) as the distribution of individuals or objects through space and their corresponding variation in density as opposed to a randomly distributed variation in density. The density variation in insect populations is affected by the dispersive ability of the vector, according to Vinatier et al. (2011). They also state that the investigation of spatial heterogeneity in combination with ecological processes is key for understanding insect populations.

A large and growing body of literature has investigated the circumstances in which the mosquitos are able to thrive. For example, Cheong, Leitão and Lakes (2014) identified a relationship between the type of land use and dengue cases, with bodies of water and settlements increasing the probability of dengue infections. The dengue virus appears to have a strong heterogeneity within cities, as there are large differences between neighbourhoods in cities (Bisanzio et al. 2018). There is also a perceived relationship between the socioeconomic status of a neighbourhood and the number of infections (i.e. Bavia et al., 2020; Bisanzio et al., 2018; Yue et al., 2018). A low socioeconomic status of a neighbourhood is related to more dengue transmissions, while a high socioeconomic status is related to less infections (Elsinga, 2018). On a smaller scale, there are multiple factors which contribute to mosquito presence, such as containers, pet food bowls and car tires (Vincenti-Gonzalez, 2018). Li et al. (2018) found a relationship between the

presence of flowerpots, which can have standing water in them, and a higher mosquito presence. These breeding sites are often found around the house, making the immediate environment places where infection is more likely to happen (Elsinga, 2018).

The climate has an effect on dengue incidence as well. There are however, different results found, depending on the study area. Studies conducted in Venezuela (Vincenti-Gonzalez et al., 2018), China (Xiao, 2017) and Brazil (Bavia et al., 2020) studies showed an increase in mean temperature result in more dengue cases. This is in sharp contrast to the results by Limper et al., the only research on the influence of climatic variables on Curaçao. Limper et al. (2014) found an increase in average temperature to be related to less dengue cases, while a decrease in average temperature resulted in more dengue cases. There are multiple studies which discovered a link between dengue and El Niño Southern Oscillation (ENSO) and specifically the warming phase which is a climatic event which happens every two to seven years and results in an increase in sea surface temperature and warmer temperatures (Vincenti-Gonzalez et al., 2018 & Xiao, 2017).

The aim of this study is to shine new light on the spread and distribution of dengue cases throughout Curaçao from 1995 until 2016. This may provide insights in the way dengue has evolved throughout the 21-year study period, which in turn can increase the understanding of future dengue behaviour. The combination of the investigation of spatial heterogeneity and geographical clusters, as well as the changes over time and weather will provide a concise overview of the patterns in dengue infections on Curaçao.

# 2. Methods

#### Study Area and data

This study focused on analysing spatial and temporal trends in dengue cases on the island of Curaçao, which is an island in the southern Caribbean Sea. There are around 160.000 inhabitants and it covers an area of 444km2, the climate is semiarid and there is a rainy season from September until January (Meteo Curaçao, 2020). The data covers 6572 registered dengue infections on Curaçao over the period of 1995-2016 and originates from the Ministry of Health (MoH) of Curaçao. When working with patient data on the individual level, it is important to make ethical decisions regarding the storing, handling and presentation of the data. The data was stored securely throughout the whole research process and anonymized on a personal level. Since the data is represented on a household level, no maps which display individual data points were included in this research to prevent patients being identifiable based on their home address. The population data originated from the Curaçao Office for Statistics, as well as the data on income, which originated from the 2011 Census which is conducted by the Curaçao Office for Statistics (CBS, 2011). The data on temperature, humidity and precipitation was obtained from the Hato Airport Meteorological weather station. The Sea Surface Temperature (SST) time-series were obtained from the Climate Prediction Centre of the National Oceanic and Atmospheric Administration (CPC, 2016).

The dengue case data was obtained in tabular format, containing patient ID and home address, and thus had to be geocoded in order to perform spatial analysis. Geocoding is the process of transforming a description of a location into actual geographical coordinates. There are no postal codes on Curaçao, which increased the difficulty for accurate geocoding. The LocalFocus geocoder (Localfocus, 2020) was used, which makes use of OpenStreetmap data and the Pelias geocoder.

#### Spatial analysis of dengue cases

A multitude of geographical analyses were conducted to identify the spread and patterns of dengue virus infections on Curaçao. Preliminary empirical analysis was conducted to gain insight in the spread and distribution of dengue cases and population. Mean and median centres were calculated for every year using ArcGIS Pro 2.5.1 (Esri, 2020), to gain insights into the change of the geographical centre over the study period. The total dataset was tested for spatial autocorrelation in order to test whether the observed patterns were statistically significant. Optimized Hot spot analysis was conducted using the Getis-Ord Gi\* statistic to identify hot and cold spots of dengue infection occurrence using ArcGIS Pro 2.5.1. In this analysis, the cell size was set to 150 meters, representing the lifespan range of the mosquito's (Vincenti-Gonzalez, 2018). Additionally, the Kulldorff's Scan was conducted, which can detect clusters based on space and time. This analysis is performed using ClusterSeer 2.5 (Biomedware, 2020).

#### Temporal analysis of dengue cases

The temporal analysis consisted of multiple parts, with the first being empirical analysis. The total number of cases were plotted per month of occurrence, which presented an overview of the distribution of cases per month. A time series analysis was conducted on dengue cases using the statistical software R (R Core Team, 2020). The decomposition of these time series allowed for the comparison of trends and seasonality. Finally, epidemiological events and climatic time-series, are strongly non-stationary, meaning they vary over time. We used a specialized time series analysis method known as wavelet analyses (WA) to detect the periodic cycles and dominant components (i.e. the most frequently repeated signal) of the time series and how they change over time. By representing the power of the time series as a function of the time and the duration period, the data got decomposed which allowed for insights in patterns over short as well as long periods (Schulte, 2016). All Wavelet analyses were conducted using MATLAB (MATLAB, 2019).

#### Explanatory analysis

To bring insights into the patterns that will result from the spatial and temporal analysis of dengue cases, multiple analyses which combine different variables were conducted. Ordinary Least Squares (OLS) regression tests were conducted to test for relationships between socio-economic variables and dengue cases. Additionally, time series analysis was conducted on climatic variables such as average temperature, precipitation, humidity and sea surface temperature. These time series were further investigated using cross correlation functions, which calculated correlation effects between the time series of climatic variables and dengue cases. This analysis shed a retrospective vision on the effects of climatic variables on dengue cases. Furthermore, the standardized anomalies of dengue incidence and Sea Surface Temperature (SST) were calculated by subtracting from each monthly observation the long-term (21 years) mean value of each particular month and dividing this by the long-term standard deviation. These data were plotted against each other to display the different trends of these variables over the study period as compared to their baseline. Anomalies of more than +0,5 and -0,5 are considered El Niño Southern Oscillation (ENSO) events (Anyamba et al. (2019). La Niña can be classified in the SST anomaly index as a weak (0.5 to 0.9 SST anomaly), moderate (1.0 to 1.4 SST anomaly) or strong (>1.5 SST anomaly) (Vincenti-Gonzalez et al., 2019).

Finally, a wavelet coherence spectrum analysis of dengue Cases and the climatic variables was conducted, to compare the frequency components of dengue and climate time-series in order to quantify the statistical association between the variables.

# 3. Results

# 3.1 Spatial analysis

To investigate the spatial and temporal trends, preliminary data exploration was conducted. On figure 1 the population distribution on Curaçao is presented. The majority of the people live in the south eastern part of the island, or in villages near the north west. The distribution of cases, displayed in density for anonymization purposes, is visible in Figure 2 with most cases clustered around Willemstad, the capital of Curaçao. In figure 3, the case density is displayed over the population maps.



Figure 1: Population distribution per Geozone



Figure 2: Density of dengue cases

Figure 3: Population distribution and density of dengue cases

By creating the median and mean centre for every year (Figure 4), the change of the centre of the epidemic is be displayed. The mean centre is the mean location of all cases in the dataset, the median centre is the median centre of all cases in the dataset. These centres appear to move over the northwest, south-eastern axis of the island, but no continuous direction could be identified.



Figure 4: Mean (red) and Median (blue) centres, the number and intensity of the color corresponds with the year

## Spatial autocorrelation

The total set of acquired cases were tested for spatial autocorrelation using Moran's I. This resulted in a Moran's Index of 0,06 and a p-value <0,0001, which resulted in a rejection of the null hypothesis, that there is no spatial autocorrelation. The same analysis was conducted on the individual years and displayed similar significant spatial autocorrelation results.

# Cluster / Hot Spot analysis

Hot spot analysis was conducted for all study years where n>100 cases. The analyses resulted in statistically significant hot spots for every tested year, which is displayed in figure 5. There appeared to be variation in the intensity and locations of the hot spots. The locations of the hot spots seemed to be clustered around Schottegat, the bay in the centre of the island. As is visible in Figure 1, this is a densely populated area, which may be a major cause for the identification of hot spots in this area. Additionally, there were some consistent hot spots in the northern part of the island, mainly around the densely populated villages.



Figure 5: Hot Spots of dengue infections for n>100 cases

# Kuldorff's scan statistic

The Kulldorff's scan statistic was conducted on all years with cases present in every month. Statistically significant clusters were detected in every year that was analysed. This method provided a most likely cluster (MLC), a second most likely cluster and a third most likely cluster. The location of the MLC shifts throughout the different years studied, indicating that there is not a single location with the highest intensity of dengue cases on a yearly basis. Figure 6 displays the clusters discovered by the Kulldorff's scan for 2002, the scan results for the other years are displayed in appendix 1.



# Figure 6: Kulldorff's scan 2002

## 3.2 Temporal analysis

# Cases

The preliminary temporal analysis displayed a temporal distribution in the infections, as the majority of the cases occurred during the rain season, which lasts from October until February. This data is presented in figure 7.



Figure 7: Distribution of dengue cases by month

#### Time series analysis

A time series analysis was conducted for dengue cases which is presented in figure 8. There is a clear seasonality in dengue cases, which is visible through the repeating pattern in a 1-year cycle in the 'seasonal' graph. There appears to be no clear increasing or decreasing trend throughout the study period.



Figure 8: Decomposition of time series of dengue cases

#### Wavelet analysis

The wavelet power spectrum (WPS) of dengue cases is displayed in figure 9. The main panel is the WPS, in which the y-axis describes the period in year cycles. This means that period 1 indicates a 1-year cycle, period 2 indicates a 2-year cycle and so on. The x-axis shows the actual year of study. The colour intensity indicates the power, with the spectrum ranging from dark blue for no power, towards green to yellow and ultimately red for maximum power. The dashed lines indicate significant periods and the curved line near the sides of the figure indicate the part of the data that is not affected by edge effects. The top panel displays the original time series of precipitation. The right panel displays the Global Spectrum (GS), with the x-axis being the power at a certain period-time range and the dashed line indicates the significant interval. This figure indicates that dengue is significant on a 1-year cycle between 2007 and 2013, which is in direct relationship with the seasonality. Additionally, there is a significant trend on the three-year cycle.



Figure 9: dengue Cases WPS

#### 3.3 Explanatory analysis

### Linear regression

An OLS regression analysis was conducted to test whether socio economic variables are related to dengue cases. The number of dengue cases per Geozone for 2011 was selected as the dependent variable; population, inactivity ratio, average gross income and population density were used as independent variables. This data originated from the Curaçao census of 2011. As the Koenker BP statistic was significant, the Robust\_Pr were the probabilities used to assess the significance. Only the population related variables displayed significant results, with both the total population per Geozone and the population density being significant on the p <0,05 level. Economic variables were not related to higher dengue infections. The results are displayed in table 1.

#### Summary of OLS Results - Model Variables

Variable	Coefficient [a]	StdError	t-Statistic	Probability [b]	Robust_SE	Robust_t	Robust_Pr [b]	VIF [c]
Intercept	-2,773075	7,687355	-0,360732	0,719764	8,535280	-0,324896	0,746566	
Total population	0,005436	0,000584	9,311745	0,000000*	0,000676	8,041130	0,000000*	1,555347
Inactive ratio	0,170839	0,167749	1,018422	0,313190	0,186653	0,915273	0,364271	1,356648
Avg gross incom	e 0,000745	0,000528	1,412303	0,163820	0,000616	1,209408	0,231976	1,089290
Population densi	ity -0,002069	0,001097	-1,886236	0,064855	0,000895	-2,311931	0,024775*	1,277880

Input Features:	Dengue cases	Dependent Variable: RE	GRESSION ANALYSISCSV_
Number of Observations:	57	Akaike's Information Criterion (AICc) [d]:	376,146982
Multiple R-Squared [d]:	0,686786	Adjusted R-Squared [d]:	0,662693
Joint F-Statistic [e]:	28,505228	Prob(>F), (4,52) degrees of freedom:	0,000000*
Joint Wald Statistic [e]:	107,503917	Prob(>chi-squared), (4) degrees of freedom	0,000000*
Koenker (BP) Statistic [f]:	11,975658	Prob(>chi-squared), (4) degrees of freedom	0,017533*
Jarque-Bera Statistic [g]:	1,036772	Prob(>chi-squared), (2) degrees of freedom	. 0,595481

#### Notes on Interpretation

\* An asterisk next to a number indicates a statistically significant p-value (p < 0,01).

[a] Coefficient: Represents the strength and type of relationship between each explanatory variable and the dependent variable

[b] Probability and Robust Probability (Robust\_Pr): Asterisk (\*) indicates a coefficient is statistically significant (p < 0,01); if the Koenker

(BP) Statistic [f] is statistically significant, use the Robust Probability column (Robust\_Pr) to determine coefficient significance.

[c] Variance Inflation Factor (VIF): Large Variance Inflation Factor (VIF) values (> 7,5) indicate redundancy among explanatory variables.

[d] R-Squared and Akaike's Information Criterion (AICc): Measures of model fit/performance.

[e] Joint F and Wald Statistics: Asterisk (\*) indicates overall model significance (p < 0,01); if the Koenker (BP) Statistic [f] is

statistically significant, use the Wald Statistic to determine overall model significance.

[f] Koenker (BP) Statistic: When this test is statistically significant (p < 0,01), the relationships modeled are not consistent (either due to

non-stationarity or heteroskedasticity). You should rely on the Robust Probabilities (Robust\_Pr) to determine coefficient significance and on the

Wald Statistic to determine overall model significance.

[g]]arque-Bera Statistic: When this test is statistically significant (p < 0,01) model predictions are blased (the residuals are not normally distributed).

Table 1: Results of OLS

#### Anomaly comparison

An anomaly comparison of the dengue cases and the sea surface temperature (SST) was conducted, to explore whether there was a potential relationship between the two. SST is a proxy for El Niño Southern Oscillation (ENSO), which consists of El Niño, the warming phase and La Niña, the cooling phase. A sudden drop in SST with an anomaly below 0.5 is expected to be caused by La Niña (Vincenti-Gonzalez et al. 2018). The results are displayed in figure 10. There seemed to be a clear pattern, as an increase in SST happens alongside a decrease in dengue cases, while a decrease in SST happened simultaneously with an increase in dengue cases.



Figure 10: Anomalies of SST and dengue cases

#### Time series analysis

A time series analysis was conducted for climatic variables to investigate whether there was a relationship between climate and dengue cases. The variables tested were humidity, average temperature, precipitation and SST. The time series decomposition for SST is presented in figure 11, the time series decomposition for the other variables are presented in appendix 2.



# **Cross correlation functions**

The time series were further analysed using cross correlation functions. The correlation between SST and dengue cases is presented in figure 12. There is a statistically significant negative correlation between these variables, with a lag of up to four months being significant. This implies that a lower SST results in more dengue cases in the following month and up to four months, albeit with a declining effect. The variables "precipitation" and "dengue cases" are correlated as well, although positively, which can be seen in figure 13. This indicates that an increase in dengue cases can be explained by an increase in precipitation the previous month and up to three months prior.



Figure 12: Cross correlation function SST & dengue cases

Figure 13: Cross correlation function precipitation & dengue cases

The WPS of Sea Surface Temperature (SST) is displayed in figure 14. As the GS in the right panel shows, there is a large significance in the 4/5-year cycles. SST can be interpreted as a proxy for La Niña (Vincenti Gonzalez, 2018), and the large cycles correspond with the cycle of ENSO. Figure 15 displays the WPS of the average temperature, which is clearly only affected by seasonality as there is a continuous significance on the 1-year cycle. The WPS of the average temperature is displayed in figure 16, and it indicates a 1-year cycle as well as a 4-6-year cycle.





Figure 15: Precipitation WPS

The Wavelet Coherence Spectrum of dengue Cases and SST is displayed in figure 17. There seems to be a repeating significant relationship on the 1-year annual cycle. The significance on the 3-5-year cycles indicate that there is coherence between the sea surface temperature and the number of dengue cases on a 3 to 5-year period. Figure 18 displays the coherence between dengue cases and Precipitation. The significantly coherent areas, which are outlined with the dashed line, appear to be on a 1-year cycle as well as larger 3 to 4-year cycles.



Figure 17: Wavelet Coherence Spectrum dengue cases & SST



Figure 18: Wavelet Coherence Spectrum dengue cases & Precipitation

## 4. Discussion

This study has emphasized the importance of both geographical and temporal analysis in understanding the spread and distribution of dengue on Curaçao.

Geographical variables such as population density have a profound effect on dengue infections, which has been proven by authors such as Bisanzio (2018), Elsinga (2018) & Vincenti-Gonzalez (2018). The findings observed in this study mirror those of the previous studies that have examined the effect of population density on dengue infections. Spatial autocorrelation was discovered throughout the total study period and cluster analysis resulted in the identification of multiple significant hot spots of dengue infections. When comparing the results of the two different methods of cluster analysis, it is interesting to see that the Optimized Hot Spot analysis indicates hot spots without making a distinction in power level. A hot spot is a significant cluster of values, but there is no difference between hot spots. The Kuldorff's Scan statistics however, creates an ordering in clusters, which indicates that some clusters are more intense than others. The majority of the hot spots in the Optimized Hot Spot analysis are located in the central part of the island, but the Kuldorff's scan clearly indicates that the most likely cluster changes location per year, which indicates that there is not one continuous largest cluster in a specific location.

Next to the geographical variables, temporal variables such as climatic effects are found to be determinants of dengue infections as well. The direction of the effect of these climatic variables however, appear to differ between locations, as an increase in temperature results in more dengue cases in Venezuela (Vincenti-Gonzalez, 2018) but in fewer cases in Curaçao (Limper et al. 2014). The findings of this study on the effect of climatic variables are consistent with those of Limper et al (2014), who discovered a relationship between a decrease in mean temperature and an increase in dengue cases. This relationship has been further investigated in this study using cross correlation functions, which resulted in a negatively correlated lag effect between sea surface temperature and dengue infections as well as a positively correlated lag effect between precipitation and dengue infections. The various wavelet analyses displayed a relationship between dengue, sea surface temperature and precipitation. The effect however, appears to be more profound than just a yearly seasonality, as larger cycles which correspond to the cycles of ENSO and specifically La Niña have been discovered to be significant. The combination of these findings has resulted in the previously unreported hypothesis that there is a positive relationship between La Niña and dengue infections on Curaçao. The relationship between ENSO and dengue have been studied profoundly in the past, but contrastingly enough these studies reported a positive relationship between dengue and El Niño, which is the opposite of La Niña, being the

warming phase of ENSO. The identification of the relationship between La Niña and dengue infections suggest that there may be a variety of circumstances, geographical as well as temporal, which influence the effect of ENSO on dengue infections.

Socio-economic variables such as gross average household income or the inactivity ratio have, contrastingly to other studies, not been proven to have a relationship with the number of dengue cases. This may be due to data limitations, as only aggregated data from 2011 was available for the socio-economic variables.

## 5. Conclusion

This study aimed to identify geographical as well as temporal trends in dengue virus infections on Curaçao between 1995 and 2016. Clusters of dengue infections were found throughout the different years and a significant link to population density was identified. Trends on the temporal spectrum were found to be related to a combination of climatic variables which appear to be present on a four-year cycle, clearly indicating a relationship with La Niña, the cooling phase of ENSO.

The findings in this report are subject to at least three limitations. Firstly, the geographical data has been through many stages of editing, which may have decreased the accuracy of the dengue cases. Second, the cases are analysed on the household level, not the location of infection. Finally, only recorded cases are included in this study, while non-registered cases are most likely present but not included.

Future studies can build upon this research in two different ways. First, within Curaçao, by further investigating the identified dengue clusters and further researching the effect of socio-economic variables which have been found in other studies. Second, outside of Curaçao, the relationship between La Niña and dengue cases may be investigated. While the link between La Niña and dengue on Curaçao has been established, it remains yet unclear which geographical or climatic circumstances are responsible for this effect. As there is a discrepancy between the effect of ENSO on dengue cases between this study and other studies, it becomes evident that it is important to be wary of knowledge transfer on dengue between different locations. There are specific geographical and climate related variables which create the circumstances in which the mosquitos carrying the dengue virus appear to thrive. It is necessary to study the trends and patterns of dengue infections on every region which experience problems regarding dengue, as drawing conclusions based upon research elsewhere might yield wrong outcomes.

This study has given insight in the distribution and trends of dengue on Curaçao between 1995 and 2016, which can contribute to the knowledge and awareness of actors involved.

# 6. References

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# 7. Appendices

Appendix 1. Kulldorff's Scan results





Appendix 1: 2007



Appendix 1: 2008



Appendix 1: 2009



Appendix 1: 2010



Appendix 1: 2011



Appendix 1: 2012



Appendix 1: 2013



Appendix 1: 2016

Appendix 2. Decomposition of time series of humidity, precipitation and average temperature



Decomposition of additive time series

Appendix 2: Decomposition Humidity





Decomposition of additive time series

