Maternal and congenital syphilis epidemic in Sao Paulo, Brazil: an ecological study assessing time trends and associated socio-demographics and maternal & child health indicators

Epidemia de sífilis congênita em São Paulo, Brasil:

um estudo ecológico avaliando tendências temporais e a associação com fatores sociodemográficos e indicadores de saúde materno-fetal

Dr. Samuel Soares-Filho, MD

Supervisors: Dr. Yves Bergevin and Dr. Tibor Schuster

Committee members: Dr. Alex Cassenote and Dr. Julie Martins

“A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Master’s of Science.”

Abstract

Background:

Congenital syphilis (CS) is an easily preventable and treatable infectious disease acquired by the fetus in the uterus before birth. Despite a noted global decline in CS rates during the early 2000s, recent data suggest alarming worldwide incidence rates, especially in developing countries. In Brazil, Latin America's most populous country, the incidence of CS has more than tripled since 2010. CS is related to abortion, stillbirths, premature delivery, neurologic sequelae of newborns, and other impairing conditions.

A better understanding of these current trends and potentially underlying proliferating factors are critical to inform urgently needed public policies to revert this concerning development.

Objective:

This research aims to understand the current trends in maternal and congenital syphilis rates in one of Latin America's highest density populations, the city of Sao Paulo, Brazil. Employing an ecological research approach, this study explores the association between maternal syphilis (MS) & CS incidence rates and population-level socio-demographic factors, and mother & child health indicators.

Methods:

Epidemiological surveillance data collected at Sao Paulo's administrative district and technical health supervision (STS) level were extracted for the years 2007 to 2018. The data was linked with mother & child health indicator variables available from 'Data SUS', the Brazilian national health information system. In addition, socio-demographic data was obtained from 'Rede Nossa Sao Paulo,' a research network that aims at increasing inclusiveness, equity, and transparency in public policy. Descriptive analysis and linear mixed effects regression models were used to characterize time trends in MS and CS incidence rates. In addition, graphical modeling using smooth spline functions was applied to assess direction, magnitude, and consistency of ecological associations between MS / CS incidence rates and socio-demographic and mother & child health variables.

Results:

Both maternal and congenital syphilis rates have increased since 2007 with a stronger incline in MS rates (increase of 2.1 vs 0.5 / 1000 livebirths per year). The respective increases for both MS and CS were below the Brazilian national average. However, there was large heterogeneity in incidence rates across districts and STS levels. Profound inverse associations were detected between MS / CS incidence rates and infant mortality rates as well as the rate of adolescent pregnancies in the respective district / STS, suggesting that effective prenatal care helping lowering infant mortality is currently not sufficient for effective prevention of congenital syphilis.

Conclusion:

The study findings indicate large variation in MS and CS rates across districts and STS within the city of Sao Paulo. Therefore, within the local context of the city, there are opportunities to further investigate why certain territories perform better (or much worse) in terms of disease control and prevention than others. Factors contributing to the aggravating MS and CS syphilis epidemic may not only be sought at the population level but also at the local health care provision level.

Résumé

Contexte:

La syphilis congénitale (SC) est une maladie infectieuse facilement évitable et traitable, acquise par le fœtus dans l'utérus avant la naissance. Malgré une baisse mondiale notable des taux de SC au début des années 2000, des données récentes suggèrent une augmentation alarmante des taux d'incidence dans le monde entier, en particulier dans les pays en développement. Au Brésil, les pays les plus peuplés d'Amérique latine, l'incidence de la SC a plus que triplé depuis 2010. La SC est liée à l'avortement, aux mortinaissances, aux accouchements prématurés, aux séquelles neurologiques des nouveau-nés et à d'autres affections invalidantes.

Une meilleure compréhension de ces tendances actuelles et des facteurs de prolifération potentiellement sous-jacents est essentielle pour informer les politiques publiques nécessaires et urgentes afin d'inverser cette tendance en matière de développement.

Objectif:

Cette recherche vise à comprendre les tendances actuelles des taux de syphilis maternelle et congénitale dans l'une des populations les plus denses d'Amérique latine, la ville de Sao Paulo, au Brésil. En utilisant une approche de recherche écologique, cette étude explore l'association entre l'incidence de la syphilis maternelle (SM) et de la SC et les facteurs sociodémographiques au niveau de la population et les indicateurs de santé maternelle et infantile.

Méthodes:

Les données de surveillance épidémiologique recueillies au niveau du district administratif et de la supervision technique sanitaire (STS) de Sao Paulo ont été extraites pour les années 2007 à 2018. Les données ont été mises en relation avec les variables des indicateurs de santé de la mère et de l'enfant disponibles auprès de "Data SUS", le système national d'information sanitaire brésilien. De plus, des données sociodémographiques ont été obtenues auprès de "Rede Nossa Sao Paulo", un réseau de recherche qui vise à accroître l'inclusion, l'équité et la transparence des politiques publiques. Une analyse descriptive et des modèles de régression linéaire à effets mixtes ont été utilisés pour caractériser les tendances temporelles des taux d'incidence de la SM et SC. En outre, une modélisation graphique utilisant des fonctions spline lisses a été appliquée pour évaluer la direction, l'ampleur et la cohérence des associations écologiques entre les taux d'incidence des SM et SC et les variables sociodémographiques et de santé maternelle et infantile.

Résultats:

Les taux de syphilis maternelle et congénitale ont augmenté depuis 2007 avec une plus forte inclinaison des taux de SM (augmentation de 2,1 contre 0,5 / 1000 naissances vivantes par an). Les augmentations respectives de la SM et de la SC ont été inférieures à la moyenne nationale brésilienne. Toutefois, on a constaté une grande hétérogénéité des taux d'incidence entre les districts et les niveaux de STS. Des associations inverses profondes ont été détectées entre les taux d'incidence des SM et SC les taux de mortalité infantile ainsi que le taux de grossesses d'adolescentes dans les districts respectifs, ce qui suggère que des soins prénataux efficaces contribuant à réduire la mortalité infantile ne sont actuellement pas suffisants pour prévenir efficacement la syphilis congénitale.

Conclusion:

Les résultats de l'étude indiquent une grande variation des taux de SM et de SC entre les districts et les STS au sein de la ville de Sao Paulo. Par conséquent, dans le contexte local de la

ville, il est possible d'étudier plus en détail les raisons pour lesquelles certains territoires obtiennent de meilleurs (ou de bien moins bons) résultats que d'autres en termes de contrôle et de prévention des maladies. Les facteurs contribuant à l'aggravation de l'épidémie de syphilis maternelle et congénitale peuvent être recherchés non seulement au niveau de la population mais aussi au niveau de la prestation de soins de santé locaux.

Table of contents

List of abbreviations

AIDS	Acquired Immunodeficiency Syndrome
APS	*Atenção Primária à Saúde Santa Marcelina* or Santa Marcelina Primary Health Care Network
BHU	Basic Health Unit or *Unidade Básica de Saúde*
CAAE	*Certificado de Apresentação para Apreciação Ética* or Certificate of Presentation for Ethical Appreciation
CHWs	Community Health Workers
CSV	Comma-Separated Values
DALYs	Disability-Adjusted Life Years
ESF or FHS	*Estratégia Saúde da Família* or Family Health Strategy
FHTs	Family Health Teams
HIV	Human Immunodeficiency Virus
INCA	*Instituto Nacional de Câncer* or Brazilian National Cancer Institute
IQR	Interquartile Range
LMICs	Low- and Middle-Income Countries
MS	Maternal Syphilis
NASF	*Núcleo de Apoio à Saúde da Família* or Family Health Support Units
NCDs	Noncommunicable Diseases
PHC	Primary Health Care
STS	*Supervisão Técnica de Saúde* or Technical Health Supervision
SUS	*Sistema Único de Saúde* or Unified Health System
Tp	*Treponema pallidum*
UN	United Nations
WHO	World Health Organization

List of Figures

List of Tables

Acknowledgments

The last two years have been the most illuminating journey I have been on. The successful conclusion of this thesis would not have been possible without the encouragement of many people that I would like to recognize here.

First, I would like to thank my supervisor Dr. Yves Bergevin, who was fundamental in tailoring the idea of a global health-oriented thesis project, with all his expertise in global health. Furthermore, his connection with Sister Monique, his former student, and the now-former director of Santa Marcelina Primary Healthcare Network Sao Paulo made this plan feasible. Dr. Bergevin gave me the chance to pursue this degree with trust, encouragement, and feedback. Dr. Bergevin has also helped me adapt to a totally different country, to which I am very thankful.

I would also like to disclose my entire gratefulness and admiration to my co-supervisor, Dr. Tibor Schuster, who has excelled his role in providing me every kind of support throughout the elaboration and completion of this project and in endorsing me in other research projects as well. Dr. Tibor Schuster is a role model in terms of scientific excellence, and without his proficiency this project would not have been concluded. I would like to thank all his organization and consistency throughout this fabulous journey. Dr. Tibor Schuster had demonstrated a strong leadership and discipline to guide me through this important step on my career.

I am also very thankful to my thesis committee members, Dr. Julie Silvia Martins and Dr. Alex Cassenote. Both are experienced scholars in Brazil and had led me through the research paths in our country. Julie has been very generous through the long process of organizing my research within Santa Marcelina Network in Sao Paulo and has been a key contributor to the successful data collection and overall study. I would also like to thank Dr. Alex Cassenote, whose delight and hard-working behavior are gladly noticeable.

None of this project could have been possible without the dedication and ambition of Sister Monique Bourget. Her career and endeavours in Brazil are an inspiration to thousands of people. Her visionary leadership, hard work and compassion have fostered the strong partnership between McGill University's Department of Family Medicine and the *Atenção Primária à Saúde Santa Marcelina*, which in turn has allowed the realization of this project.

This project has also counted on tremendous support from Dr. Catherine Ji, Dr. Sara Turcotte, Dr. Dawid Karczewski, Dr. Roland Grad, Dr. Josué Yang, Amanda Marcinowska, and Dr. Wagner Nicola, whose inputs and sensitive support were essential.

I must explicit as well my entire gratefulness to prodigious leaders that guided me within this program, remarkably Vilma Venâncio, Santa Marcelina PHC Network director, Dr. José Carlos Junior, medical manager at Santa Marcelina PHC Network, Dr. Martim Elviro, medical supervisor at Santa Marcelina PHC Network, Dr. Paulo Fontao, medical supervisor at Santa Marcelina PHC Network, Dr. Morris Pimenta, medical supervisor at Santa Marcelina PHC

Network, Dr. Henrique Francé, medical supervisor at Santa Marcelina PHC Network, Dr. Humberto Alonso, medical supervisor at Santa Marcelina PHC Network, Dr. Patricia Guanabara, medical supervisor at Santa Marcelina PHC Network, Dr. Daniele Bargas, medical supervisor at Santa Marcelina PHC Network, Soeur Rosane Ghedin, President of Santa Marcelina Hospital, Dr. Bruno Pinto, former medical manager at Santa Marcelina PHC network, Dr. Howard Bergman, former Chair of the Department of Family Medicine, Dr. Gillian Bartlett, former research and graduate programs director at the Department of Family Medicine, Sherrie Child, the graduate programs coordinator, Rachel Simmons, and Tamara Carver, without whom this thesis would have never been finalized.

I am grateful for funding support I received through the Graduate Programs in Family Medicine Excellence Awards.

Finally, I must release that the support of my family, especially Samuel Soares, my father, Regina Brandão, my mother, Caroline Brandão, my sister, Felipe Brandão, and Raquel Soares, my cousins was fundamental to me. Without their support and encouragement this achievement would have never been possible. I would like to say as well that my grandmothers Lea and Eunice, as well as my grandfathers Brandão and Antenor would be proud to accompany this accomplishment. However, unfortunately they have passed away during the process and could not observe the final results. I am certain that they are very proud of this wherever they are now.

Preface

This master's thesis is presented in the traditional format (i.e., not by manuscript). It is an original work by Dr. Samuel Soares-Filho. No part of this thesis has been published yet.
This thesis follows McGill requirements for thesis preparation of traditional (non-manuscript-based) theses.

Contributions

As the M.Sc. candidate and author of this thesis, I was responsible for designing and planning most of the effort and data acquisition, interpreting the results and writing. The overall concept for the research was determined by myself, and my supervisors, Drs. Yves Bergevin and Dr. Tibor Schuster. Drs. Yves Bergevin, Tibor Schuster, Alex Cassenote, and Julie Martins provided their guidance and feedback on the content of the thesis and assisted with analysis and interpretation of the findings.

Both supervisors and the thesis committee members have approved the final version of the thesis.

1. Introduction

Despite the availability of inexpensive, easily administered, and effective antibiotic treatment programs against the *Treponema pallidum* bacterium, venereal and congenital syphilis (CS) continues to be a significant global health problem. It afflicts at least 11 million people and as many as two million pregnant women annually (1, 2). In 2016, the global prevalence of maternal syphilis was estimated to be 0.69% and the accompanying reported global rate of congenital syphilis 473 per 100,000 live births and an estimation of 661,000 prevalent congenital syphilis cases at that time. These international rates contributed to an estimated total of about 355,0000 adverse birth outcomes, such as miscarriages, stillbirths, and hospitalizations (3).

In the United States, the CS rate increased from 9.2 to 23.3 cases per 100,000 live births from 2010 to 2016 (3, 4). These increased rates are gradually more reported among women of reproductive age (6), and in low-income contexts as well (7). This adds to the generally lower health status of vulnerable populations experiencing poverty, violence, and social inequity (8).

Developing countries not only have more vulnerable populations but also superior birth rates compared to developed countries. The comparative excess in susceptible individuals both in absolute and relative numbers may be accompanied by structural deficiencies in the primary healthcare clinics and communities, which can contribute to unfavorable deficits in preventive measures or limited response to ongoing epidemic situations (9–12). Furthermore, lack of proper training of health care professionals may imply risks not only to an adequate quality of antenatal care, as well as to a chance of missing timely interventions both at prevention and therapy levels.

The World Health Organization (WHO) estimates that more than 90% of the 11 million new cases emerging every year occur in developing countries, such as Brazil (7,13,14).

The city of Sao Paulo is the largest metropolis of Brazil and is experiencing a substantial rise in congenital syphilis over the last decade. Growth rates are estimated to be as high as 55%, supported by recent data from 2014 to 2017 that reported an increase from 440 to 680 cases per 100,000 live births (15). There is a lack of studies in the literature that investigate the ongoing epidemics in the Brazilian context. Such research is urgently needed to understand barriers to limiting the continuing increase of the health burden due to these preventable, treatable, and curable conditions in women of childbearing age and their offspring.

To better understand possible root causes of these alarming recent developments and to identify potential strategies to improve the situation, systematic research is needed that leverages on existing knowledge and available data sources. With this master's thesis, current trends in maternal and congenital syphilis in the city of Sao Paulo will be investigated using municipal surveillance data. Through linkage to administrative district and technical health supervision data on socio-demographics and maternal & child health indicators, ecological associations of population-level variables and incidence rates will be explored. The specific aim is to investigate how urban-regional differences in both epidemics are potentially coupled to established population and public health indicators, enabling effective investigations of the matter by detecting relevant signals in the sizeable administrative district database. Similarly, the gathered evidence from this research will contribute to eliminating or demoting first-level explanations for the apparent trends that are not supported or contradicted by the data.

2. Background and review of the literature

Etiology of syphilis

Treponema pallidum is the etiologic agent of equally venereal and congenital syphilis. It is known that previously infected women or those that acquired syphilis during pregnancy have a high risk – between 50 to 90% – of spreading bacteria through the vertical transmission to their fetuses. The bacterial transmission may occur at any time from conception to delivery (3, 16–22).

Worldwide it is estimated that nearly 2 million pregnant women are affected by maternal syphilis each year (1, 2). If untreated, approximately 50% of these women will present with adverse outcomes in their offspring (21). According to a 2013 systematic review and meta-analysis on untreated maternal syphilis and adverse effects of pregnancy, about 25% of T. pallidum infected pregnant women experienced abortions or stillbirth. About 12% of the newborns died, and the proportion of children born preterm or with low birth weight was approximately 12% as (22).

In 2018, the incidence of *T. pallidum* infections in pregnant women in Brazil was estimated to 21.4 cases per 1,000 live births, with about nine reported congenital syphilis cases per 1,000 live births (23). These figures represent an increase of nearly threefold (factor 2.97 – for maternal syphilis) and almost twofold (factor 1.87 – for congenital syphilis) when compared to the official epidemiological reported in 2013.

The infant mortality attributed to congenital syphilis was 8.2 / 100,000 livebirths in 2018, depicting a substantial increase when compared to the mortality rates reported in 2011 (3.8/100,000) and 2006 (2.3/100,000).

There are considerable regional variations in the magnitude of both epidemics in Brazil. Sao Paulo, as one of Brazil's most densely populated areas experienced (and continues to experience) a steep increase in congenital syphilis rates. Between 2012 and 2018, the reported CS rates in Sao Paulo increased by about 60% (8, 23, 24).

Route of mother-child transmission of T. pallidum

Transmission of T. pallidum from the mother to the fetus during pregnancy occurs through the transplacental route (vertical transmission) at any time during pregnancy or at birth. The clinical-symptomatic manifestation of the infection is generally divided into early (symptom development within 2 years from birth) and late manifestations (more than 2 years from birth).

Studies of fetuses of infected mothers have provided insight on the extent to which the infection affects multiple organs and tissues. Among clinical pathologies associated with congenital syphilis, manifestations include lymphadenopathy, hepatitis, osteitis, pneumonitis, anemia, hemorrhage and mucocutaneous lesions (1,25). In settings where congenital syphilis manifests at a relative late stage, pathologies of the central nervous system, teeth, skin, eyes, bones, or cartilage are possible (1,26).

Prevention strategies and susceptible populations

The primary strategy to prevention of congenital syphilis is primary prevention through education on STI prevention. The second most important strategy is effective prenatal care as studies have shown associations between late start or absence of prenatal care and an increased risk of congenital syphilis (3, 4). Countries worldwide have implemented policies to improve prenatal care quality and delivery. For example, the United Kingdom National Health System adopts as an indicator of good practice in prenatal care the percentage of pregnant women attending the booking appointment with a family doctor or a midwife before 12 weeks of pregnancy (27). More specific measures to target reduction of congenital syphilis cases are implemented by the United States through utilizing electronic medical records that enable a time-bound and effective diagnosis and treatment of maternal syphilis (5,28). Still, in the United States the use of rigorous laboratory data checking have shown significant importance in averting CS cases (29). In Latin America, the Brazilian *Unified Health System* ("Sistema Único de Saúde", SUS) has developed context-based clinical guidelines with electronic surveillance over new cases and their treatment (9,30–32). Furthermore, the family health strategy model, first implemented on 1994, added the roles of the family physician, the primary care nurse, and the community health worker as important team members towards an improved prenatal care (9).

A number of personal, structural and service-related factors delay or prevent access to antenatal care (27,33). These missed opportunities result from the confluence of socioeconomic, demographic, and behavioral factors that promote mother-to-child transmission. Most congenital syphilis cases occur among black and minority ethnic groups, including refugees and asylum seeker mothers (26,34). Several studies have already investigated the predictors to congenital syphilis incidence. There are two Brazilian studies that compared the clinics under the family health strategy and the traditional clinical model (12,35). There are two Brazilian studies that compared the management of private organizations (such as Santa Marcelina network, and the municipal administration)(36,37). No study, however, has compared those indicators in Sao Paulo city.

In sum, a vast body of knowledge exists focusing on pregnancy follow-up impediments and their relation to congenital syphilis outcomes. However, the vast majority of those studies were conducted in high-income countries. And those piloted in low and middle-income countries are concentrated on rural and small-town primary healthcare settings (3,11,12,24,26,34). Before this thesis, no study has thus far contributed findings related to syphilis transmission in urban settings in Brazil.

The role of the Brazilian Unified Health System

Improvement of primary health care is one of the best ways of achieving better health outcomes in every country, especially developing ones. The World Health Organization (WHO) and United Nations (UN) have stablished as the third development goal to “Ensure healthy lives and promote well-being for all at all ages.” (38). Therefore, countries worldwide organize their healthcare system management to achieve this goal and its 13 targets. However, to improve healthcare management and surveillance over infectious diseases, health systems worldwide adopt different approaches.

With a new constitution in 1988, Brazil adopted the recognition of health as a fundamental right of citizen and duty of the state. This central commitment led to the creation of the *Unified Health System* (“Sistema Único de Saúde”, SUS) in 1990 (18).

Through the SUS, universal comprehensive, preventive, and curative care is provided to all Brazilian citizens. The respective public and private (both not-for-profit and for-profit) health care institutions provide health services in a decentralized way, enabling continuity of care at the community (primary and secondary care) and hospital (secondary and tertiary care) levels (18, 19).

For all citizens, health services as well as most common mediations are free and accessible through the various points of service (19).

One of the central pillars of the SUS is the *Family Health Strategy* ("Estratégia de Saúde da Família", ESF). This component was established in 1994 to restructure primary health care (PHC) as to integrate health promotion and prevention of diseases with medical care as well as to orient care more towards families and communities (18, 20).

The nationwide deployment of multidisciplinary *family health teams* ("Equipes de Saúde da Família", eSF) was one major step in implementing the Family Health Strategy. These teams are typically composed of at least four to six *community health workers* ("Agentes Comunitários de Saúde", ACS), one physician, one nurse and one nurse assistant (19). Family health teams are grouped together in so called *basic health units* ("Unidade Básica de Saúde", UBS) where one UBS comprises up to ten teams. The UBS are strategically located in the centers of the communities they provide health services to. The geographical area surrounding the respective UBS is divided between the family health teams and each eSF is responsible for up to one thousand households. All residents of the households are meant to receive longitudinal, comprehensive, and coordinated care through monthly ACS home visits. This way, the ACS take a key role in implementing and delivering public health programs (39,40). This infrastructure and continuing proactive outreach to the community offers opportunities to also engage in health promotion and preventive strategies related to both non-communicable and communicable diseases (41,42). From an epidemiological standpoint, the ties between ACS and households further enable an advantageous environment for disease surveillance. In terms of prevention of sexually transmitted infections, in the developed countries such as the USA, ACS have a longstanding history specifically in regards to human immunodeficiency virus (HIV) prevention and populations susceptible of or experiencing acquired immunodeficiency syndrome (AIDS) (40).

In 2008, so called Family *Health Support Teams* (“Núcleo de Apoio à Saúde da Família”, NASF) were created to scale up primary health care by including services provided by psychologists, physiotherapists, social workers but also specialists such as gynecologists, psychiatrists, and pediatricians. These health professionals are based within the UBSes to enable integrated patient care (43–45).

The support demands of the family health teams as well as the health needs of the served area are the determining factors for the composition of the NASFs (9,44,46).

The implementation of the Family Health Strategy has reached remarkable levels over the past two decades: starting with about 2,000 family health teams and 60,000 ACS in 1998 that covered just about 4% of the Brazilian population, the number of health teams has now reached nearly 40,000 with about 270,000 ACS providing health services to more than 60% of the population in 2014 (9,41,46). The success of this significant primary care approach is reflected by increased patient satisfaction when compared to conventional models of primary health care, largely attributed the superior integrated and comprehensive care and outreach services (47–51).

Among other achievements in improving the health of the people and safeguarding Brazil's communities, ACS and the Family Health Strategy have been attributed to have instigated significant reductions in neonatal, infant, and infant mortality caused by diarrheal disease and infections of the lower respiratory tract. These achievements together with the proven success in general prenatal care and implementing and promoting universal preventive methods, predestinate ACS to take on a leading role maybe also in the prevention of maternal and congenital syphilis (16-19, 22).

The promising journey of Brazil's public health system is not underway without encountering major challenges at political, financial, and organizational levels that impose barriers to the full potential and effectiveness of the health system and the Family Health Strategy. In 2016, severe budgetary restrictions have been put in place that are expected to largely affect the health and education sectors for the next 20 years (9,47).

Due to the decentralized and municipality-governed management of the Family Health Strategy and its components, capacities and quality of family health teams vary largely across health jurisdictions. These variations can imply significant differences in supply of basic equipment, institutional support for health teams including the availability and integration of the various types of health professionals.

To what extend such differences in the local health system organization may play a role in the worsening epidemic situation with regard to maternal and congenital syphilis, requires in-depth scientific investigation. The description and characterisation of heterogeneities in the respective incidence rates and trends across health administrative districts and technical health supervisions is a first step that will help to identify patterns and allow for hypothesis generation that is informed by objective data.

2.1. Research questions

This thesis research is aiming to address three primary questions:

- First, in the municipality of Sao Paulo, Brazil, how have the rates of maternal and congenital syphilis cases evolved over the last ten years?

- Second, what are the variations in the incidence rates with respect to the different health management regions i.e., the administrative districts and technical health supervisions of the city?

- Third, what are population-level factors that are associated with the course of maternal and congenital syphilis rates in the target populations?

3. Methods

3.1. Study setting and partnership

This thesis has been written to fulfil the requirements for completing a Master of Science degree in Family Medicine at the Department of Family Medicine, McGill University. The research project has emerged through the author's involvement as primary care management member at the *Santa Marcelina Primary Healthcare Network* ("Atenção Primária à Saúde Santa Marcelina", APS Santa Marcelina) in Sao Paulo, Brazil. The APS Santa Marcelina manages over 220 family health teams distributed in more than 50 Basic Health Units that cover a population of almost 2 million people. This management network delivers care to five vulnerable urban and rural *Health Technical Supervisions* ("Supervisões Técnicas de Saúde", STS) in the outer limits of the eastern city of São Paulo (59, 60). The five STSes are: "Cidade Tiradentes", "Guaianases", "Itaim Paulista", "Itaquera" and "São Miguel Paulista", where population vary from 212,000 to 524,000 (61). However, the focus of this study comprises the entire city of Sao Paulo with 26 STSes. The research conducted and summarized within this thesis is focused on the population of childbearing women and their offspring residing in the city of Sao Paulo.

The city of Sao Paulo counts a total population of approximately 12 million people with about 3.1 million women in childbearing age (52,53).

3.2. Study design

The study data is comprised of maternal and congenital syphilis surveillance statistics reported at the official health system websites, allowing for portraying the course of these epidemics over time and across regions within the larger health jurisdiction of the city of Sao Paulo, Brazil.

The study design can therefore be described as repeated cross-sectional epidemiological study. The study methodology will be built on descriptive as well as exploratory cross-sectional (repeated) analyses. The descriptive component aims at characterization of time trends and regional (district or STS level) differences in the primary endpoint variable “annual incident [reported] cases of maternal or congenital syphilis”. The exploratory part of the study refers to bivariate comparison of time trends related to the primary outcome variable and secondary, potentially explanatory variables.

3.3. Target population and spatial coverage of the research

The target population of this study were women in childbearing age and their offspring residing in the city of Sao Paulo between 2007 and 2018 (available data at time of data extraction for this thesis research, July 2020).

The map in Figure 2 displays spatial coverage of the epidemiological research study, i.e., Sao Paulo's municipal health network by regional health coordination, technical health supervision (STS) and administrative district.

3.4. Primary study outcome and indicator variables

3.4.1. Primary *outcome* variable

The primary variable of interest is the number of reported maternal and/or congenital syphilis cases in a given time interval (year) and regional division, i.e., the administrative district (short: district) or technical health supervision (short: STS), relative to the number of livebirths in that region and time interval i.e., the annual incident [reported] cases of maternal and/or congenital syphilis. Note that, although the primary outcome indices of this study relate to the annual incident [reported] cases, the term *incidence* (of maternal and/or congenital syphilis) will be used interchangeably. This is justified by the statistical property that case incidence takes the same value in settings where the population under risk is followed for a fixed time (e.g., one year) so that the number of livebirths per year approximates closely the actual total of person times.

3.4.2. Socio-demographic and maternal & child health indicator variables

The following socio-demographic and maternal- & child health indicator variables were considered in within the ecological study embedded in this thesis research:

- Adolescent pregnancies [Number of Pregnant women of the of 19 years or less per 100 livebirths]
- Child mortality [Number of deaths in younger than 1yo / total newborns x 1,000]
- Low birth weight [Number of live births underweighted / number of newborns x 100]
- Suboptimal prenatal care [Number of newborns with <7 prenatal visits / total newborns x 100]
- Reported violence against women* [Number of notified violence / Women 20 - 59yo x 10,000]

3.5. Data sources and data collection

3.5.1. Data sources

In Brazil, the public health system is governed by federal, state, and municipal health authorities, following a decentralized governance approach. In their role, the respective authorities are mandated to report, on a regular and transparent base, all relevant health data to the public (54). As a result, with increasing advancement and availability of information technology, a large repository of information and data related to the health care system (e.g., health care utilisation, population indicators of health and epidemiological data) are routinely collected and reported on different official web platforms. The monitoring and control of infectious diseases is one of the main frontlines of the Brazilian health system and is informed by the national health surveillance secretariat (55). At the municipal level, epidemiological data is systematically collected through mandatory notifications by the different health service providers at all three levels of care i.e., primary, secondary, and tertiary care. The cases identified through the notification system are centrally collected and administered in a national information system ("Sistema Nacional de Agravos de Notificação ", SINAN) (56).

This system serves as central information and data access point for researchers, policy makers and health care workers. In particular, the system provides access to epidemiological case data for a selected number of conditions including infectious diseases. The data can be extracted at various measurement levels i.e., stratified by year, sex, gender, type of health facility reporting the respective cases (e.g., clinic, hospital) and health jurisdiction i.e., district, *technical health supervision* ("Supervisão Técnica de Saúde", STS).

The population of livebirths studied was extracted from the official database *livebirths national information system* ("Sistema Nacional de Informação sobre Nascidos Vivos", SINASC) extracted by year and regional level of birth. The SINASC aims to gather information related to births that occurred throughout the national territory. It was developed by the Ministry of Health / DATASUS to gather epidemiological information on informed births. The source of the data is the Live Birth Declaration, standardized by the Ministry of Health, with 52 fields, among which can be highlighted: duration of pregnancy, newborn weight, mother's age, location of birth stratified by levels, and type of delivery.

From the SINASC database it is possible to:

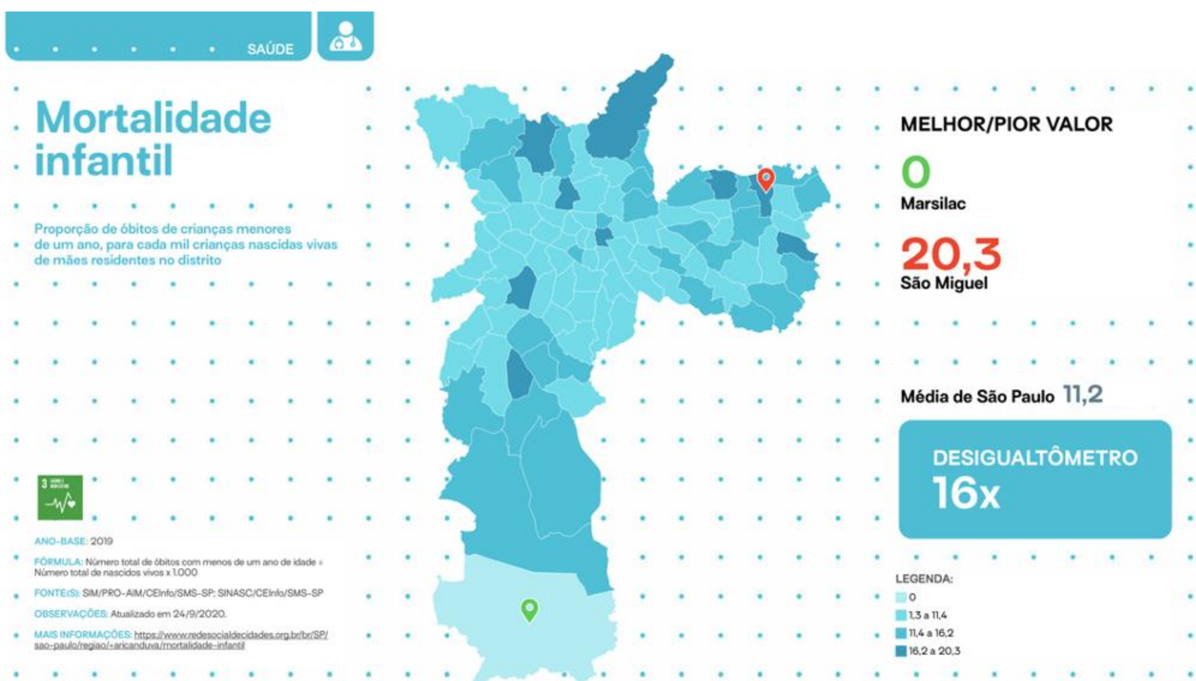
- Know the profile of livebirths, identifying their different aspects: birth weight, vitality conditions, mother's age, prematurity, spatial and temporal distribution, among others.
- Subsidize for the development of actions to improve care for pregnant women and newborns, identifying risk situations.
- Calculate indicators such as the percentage of cesarean deliveries, live births with low birth weight and the mother's age group. The number of livebirths is also used as a denominator for calculating vaccination coverage, infant and maternal mortality coefficient.

The implementation of SINASC took place slowly and gradually, starting in 1990, in all States of the Federation. In the municipality of São Paulo, SINASC was implemented in 1999, with the goal of registering all live births that occurred in the municipality. The system is managed by the Coordination of Epidemiology and Information of the Municipal Health Secretariat, together with the 26 Technical Health Supervisions, which consolidate the databases entered by the health establishments where births take place in the city of São Paulo and by notaries (home births). In 2004, SINASC data collection and flow were regulated by Ordinance SMS.G nº 325.

Throughout this period, it was observed that the number of registrations at SINASC is greater than the number obtained by the Civil Registry Offices, which demonstrates high coverage of SINASC and a delay in the official registration of children. In 2003, in order to facilitate access to the Civil Registry, the daily displacement of Civil Registry Officers to public or private maternity wards was regulated in order to proceed with the registration of birth on the premises of these health establishments (Provision nº 3/2003).

In addition, the civil society organization "Rede Nossa São Paulo" (RNSP) (57), is taking a role in various segments of society to establish an agenda that articulates actions which adhere to fair, democratic and sustainable public health goals to be achieved city of São Paulo. One concrete example of RNSPs contributions is an inequality map of Sao Paulo that was established in 2016 for helping to identify disparities in populations' housing, environment, traffic, security, human rights, health, education, and income for the city of Sao Paulo (Figure 1.).

***Figure 1** Municipal administrative districts with a heat map presenting the differences in infant mortality throughout Sao Paulo. Sao Miguel, a district in eastern Sao Paulo, presents with 20,3 children younger than one year old per 1,000 livebirths*



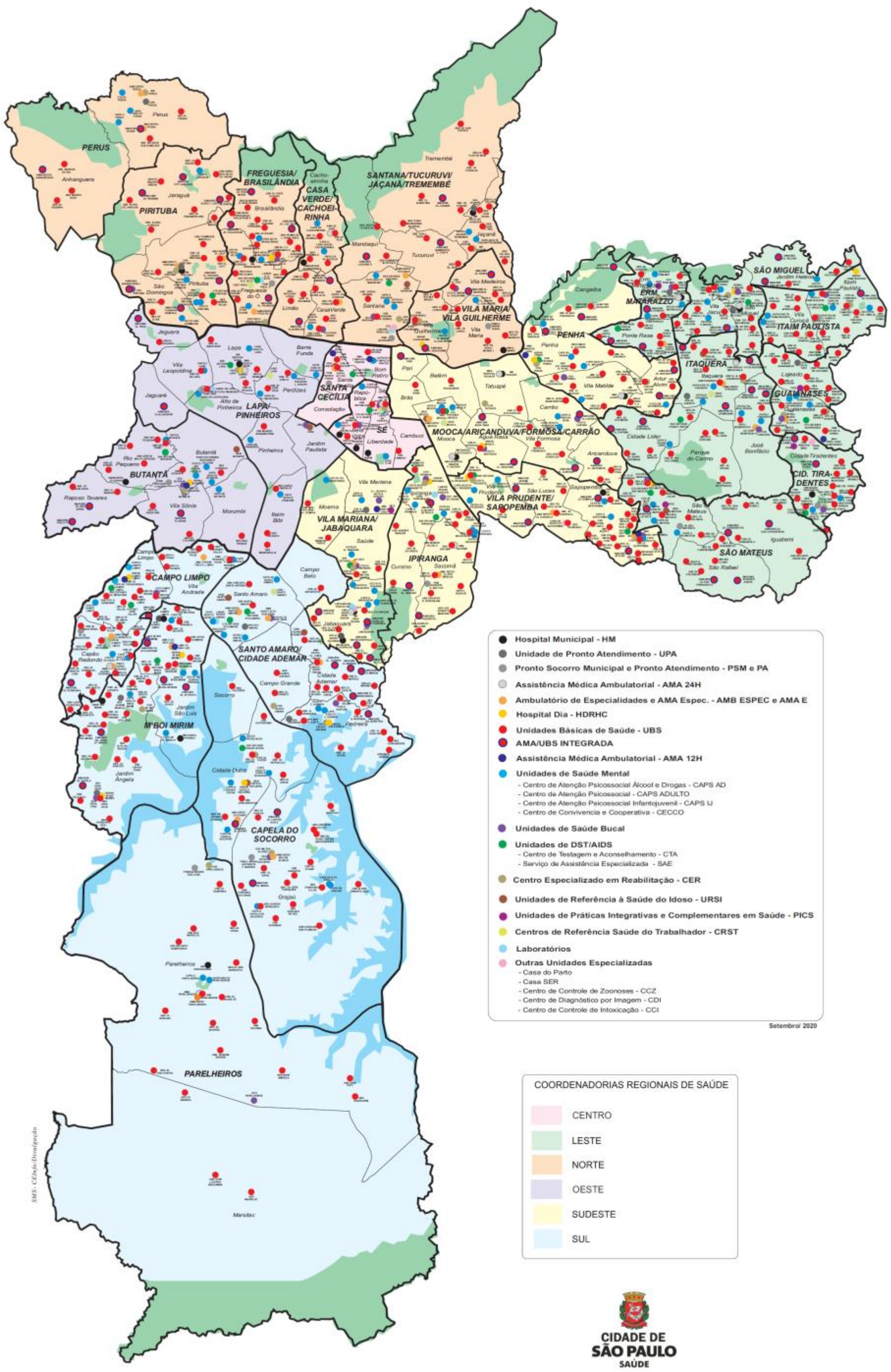
Therefore, to address the objectives of this thesis, the primary data sources being used were SINAN, SINASC and Rede Nossa Sao Paulo. The respective data can be accessed at the central data platform of the Brazilian Health system ("Data Sistema Único de Saúde", Data SUS) (58).

3.5.2. Data extraction

Data sources Through the Data SUS web portal, case data on maternal and congenital syphilis were extracted via download of the respectively available data files in comma-separated-value (csv) format.

These files were then merged with data on relevant population size i.e., number of live births in the same administrative districts and technical health supervisions (i.e., the smallest available common aggregation level) and year. Finally, data on socio-demographic variables were obtained in the same format and at the respective aggregation level, allowing to generate a master database combining case statistics, appropriate denominators (live births) as well as socio demographic variables.

Figure 2 Municipal health network sites by regional health coordination, technical health supervision (STS) and administrative district for the municipality of Sao Paulo.
(source:
https://www.prefeitura.sp.gov.br/cidade/secretarias/upload/saude/arquivos/ceinfo/mapoteca/crs_sp_sts_munic.pdf)



3.6. Data analysis

3.6.1. Statistical Software

All statistical analyses were performed using the statistical software R, version 4.02 (59).

3.6.2. Descriptive Statistics

Frequency distributions of continuous variables were characterized using means, standard deviations and quartiles at district or STS levels and year.

To illustrate differences in the annual incident [reported] cases of maternal and/or congenital syphilis over time and across different regions, scatterplots with smooth spline line functions, displaying moving averages, as well as box plots (displaying distribution quartiles) were used.

3.6.3. Statistical Modeling of time trends and regional heterogeneity

To estimate time-trends in maternal and/or congenital syphilis rates, linear mixed effect models were used (60,61).

This model class allows for the estimation of so fixed and random effects that explain variation in the outcome variable. Fixed effects represent variables with a finite set of categories (i.e., the levels of a factor) that are measured within the study. Random effects describe outcome variation due to factor variables that are naturally clustered such as geographical areas or health units.

The factor variables administrative district (97 levels) and technical health supervision (26 levels) were used as random effect variables to account for variations in baseline incidence rates as well as variations in time trends across age categories.

To assess if changes of incidence rates over time were inconsistent with the null-hypothesis of "no increase or decrease in the incidence of maternal and/or congenital syphilis over the study period", a likelihood ratio test was applied comparing a linear mixed effect model with the main factors "district" or "STS" versus a mixed effect model with the same factors plus the fixed effect variable "year". For the associated statistical tests for time trend, a two-sided type I error probability of 5% was pre-specified. Accordingly, the estimated average increase or decrease in incidence rates over time were reported with 95% confidence intervals. No correction of type I error was performed within this study. However, all statistical tests being conducted were pre-specified and reported so that an informal adjustment for multiplicity of type I error rates can be performed by the reader (62).

3.6.4. Ecological assessment of factors associated with maternal and/or congenital syphilis rates

To explore region- and population-level factors that are associated with time trends in maternal and/or congenital syphilis, smooth spline functions of syphilis incidence rates were mapped onto the time course of respective socio-economic variable distributions. While this is a marginal associational approach that does not take interdependencies of background variables (i.e. unmeasured confounding variables) into account, the approach enables identification of signals in the data that may either support (i.e., be consistent with) or oppose (i.e., be in contradiction with) pre-existing expert knowledge or evidence, which in turn, will inform investigations on possible underlying structural dependencies that explain the observed associations and hence helping "to expand the terrain for the location of causes for disease [spread] and [possible] interventions to improve the public's health."(63).

3.7. Ethics approval

This is an ecological study using data from official municipal government and health authority resources that are publicly available. All data used were anonymous and aggregated at the administrative district or technical health supervision level. Due to the public and observational nature of the data, no approval was seeked from an ethics commission.

4. Results

4.1. Characterisation of population sizes (number of livebirths) by STS and district

The Figures 3 and 4 display the number of livebirths for the years 2007 to 2018 by *technical health supervision* ("STS") and *administrative district* ("Distrito") respectively.

The STS with the lowest number of livebirths was Santa Cecilia counting between 2000 and 1800 livebirths in the years 2007 to 2018. The largest STS was 'MBoi Mirim'/'Campo Limpo' with nearly 10 times higher numbers in terms of livebirths, i.e., counting approximately 20,000 livebirths in the same time period. Figure 4 illustrates the frequency distribution of relative changes in number of livebirths by STS between 2007 and 2018. According to this graph, the majority of STS showed a decrease in livebirths over the 12 years study period with relative reductions in livebirths of up to 15%. On the other hand, some STS increased their number of livebirths by up to 15% to 20%.

The administrative district with the lowest number of livebirths was ‘Marsilac’ counting between 110 and 122 livebirths in the years 2007 to 2018. The largest district was ‘Grajaú’ counting approximately 7,000 livebirths in the same time period with a decreasing tendency (Figure 5). Figure 6 illustrates the frequency distribution of relative changes in number of livebirths by district between 2007 and 2018. The majority of changes in livebirths fell in between +/- 20%, with a few extremer changes (both in negative as well positive direction), observed for smaller districts. Overall, the distribution of changes in livebirths over time and across districts was balanced, i.e., not indicating an extreme shift in either demographic direction.

Figure 3 Number of livebirths by technical health supervision ("STS") for the years 2007 to 2018 – color coding indicates magnitudes of figures on a green-red continuum i.e., lower numbers green, medium numbers yellow and higher numbers orange / red.

Technical Health Supervision (STS)	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Santa Cecília	2016	1948	2073	1965	1988	1897	1812	1877	1782	1716	1748	1798
Perus	2379	2471	2412	2530	2592	2484	2597	2624	2678	2391	2597	2391
Parelheiros	2397	2403	2443	2605	2657	2587	2642	2638	2799	2731	2868	2779
Ermelino Matarazzo	3102	3171	3101	3259	3094	3282	3146	3230	3176	2974	2907	2903
Sé	3444	3573	3596	3547	3516	3540	3303	3349	3371	3123	3061	3085
Cidade Tiradentes	3530	3632	3743	3830	3818	4006	3806	3956	4006	3798	3711	3696
Vila Maria/Vila Guilherme	4624	4790	4831	4842	4832	4883	4734	4637	4839	4524	4652	4597
Casa Verde/Cachoeirinha	5310	5266	5350	5224	5291	5268	5216	5312	5245	5203	4910	4914
Guaianases	4655	4673	4913	4854	4975	5022	5051	5207	5050	5012	5139	4921
Itaim Paulista	6090	6240	6210	6214	6337	6390	6272	6449	6511	6092	6102	5883
São Miguel	6337	6108	6486	6100	6284	6056	6179	6335	6251	5849	6125	5940
Butantã	7099	7219	7326	7076	7209	7158	7214	7104	7000	6640	6546	6116
Vila Mariana/Jabaquara	6790	6953	6831	7029	6983	6908	6677	6563	6401	6271	6409	6210
Pirituba	6854	6923	6796	6796	7085	6944	6765	6915	6929	6479	6557	6336
Penha	6543	6773	6608	6766	6694	6773	6575	6721	6767	6356	6541	6383
Ipiranga	6381	6203	6390	6335	6584	6542	6536	6642	6724	6417	6329	6413
Freguesia/Brasilândia	7240	7341	7255	7161	7255	7181	6967	7044	7205	6817	6770	6620
Lapa/Pinheiros	6467	6534	6678	6829	6993	7020	7001	7274	7162	6701	7202	6893
Vila Prudente/Sapopemba	7681	7611	7692	7600	7774	7701	7452	7516	7600	7110	7356	6897
São Mateus	6852	7156	7065	7042	7205	7174	7112	7084	7204	7000	7079	7087
Moóca/Aricanduva	7886	7912	8117	8217	8125	8264	7938	8097	8207	7765	7744	7749
Santana/Tucuruvi/Jaçanã/Tremembé	8537	8873	8458	8621	8357	8329	8087	8192	8090	7938	7953	7891
Itaquera	8249	8426	8113	8140	8453	8516	8181	8570	8532	8162	8234	8107
Santo Amaro/Cidade Ademar	9682	9725	9918	9984	10088	10182	10229	10164	10118	9679	9763	9407
Capela do Socorro	10648	10756	10672	10673	10670	10418	10411	10508	10680	10007	10085	9955
MBoi Mirim/Campo Limpo	19910	20260	20601	20875	21403	21154	20815	21284	21462	20248	20758	20258

Figure 4 Relative change in number of livebirths across technical health supervisions between 2007 and 2008

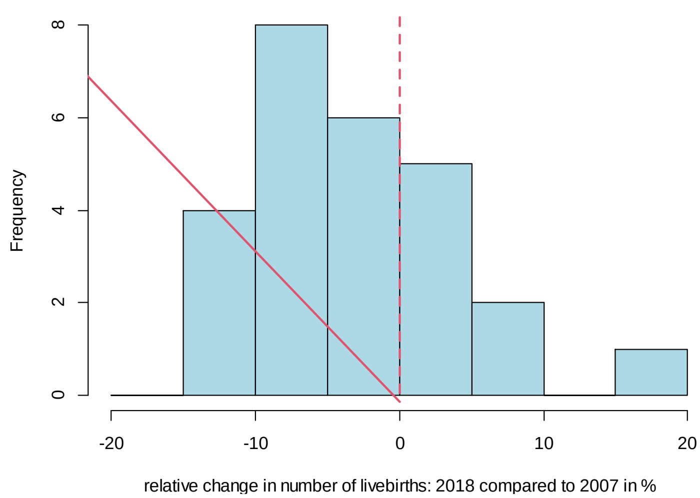


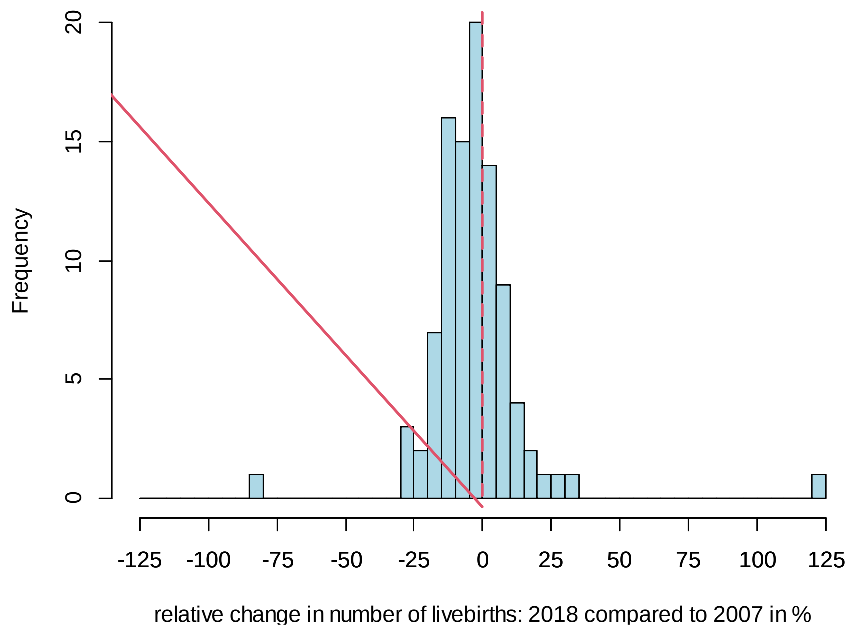
Figure 5 Number of livebirths by administrative district ("Distrito") for the years 2007 to 2018

Distrito	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Marsilac	110	83	101	113	114	106	128	124	129	118	102	122
Ignorado	873	562	177	161	188	212	230	523	492	275	143	157
Alto de Pinheiros	371	341	385	382	360	341	351	316	303	285	290	261
Jaguara	354	311	350	335	312	293	312	295	295	285	336	309
Pari	297	276	302	281	324	315	308	335	296	286	316	324
Socorro	462	453	448	452	452	447	395	412	395	378	393	377
Consolação	483	487	478	423	466	421	414	448	417	399	376	394
Barra Funda	197	199	198	220	235	260	334	375	406	389	425	435
Sé	492	530	544	522	489	537	500	514	520	504	476	435
Butantã	632	641	619	585	587	578	549	568	579	512	512	448
República	592	700	679	646	646	731	630	673	624	579	573	495
Cambuci	583	549	614	574	572	505	525	536	571	507	501	529
Bom Retiro	587	539	587	567	545	568	537	532	516	560	563	564
Brás	613	585	554	575	614	595	559	568	547	512	543	577
Vila Leopoldina	544	522	521	529	607	644	648	697	698	592	604	587
Morumbi	808	799	825	777	774	742	797	754	747	692	643	624
Pinheiros	718	671	688	683	680	659	656	656	628	641	678	655
Liberdade	847	816	841	847	874	901	759	797	763	749	703	759
Lapa	724	737	733	798	720	778	780	836	813	759	809	765
Campo Belo	776	750	821	841	827	805	796	817	849	783	762	805
Jardim Paulista	780	834	868	834	895	862	874	871	858	804	880	818
Vila Guilherme	733	857	864	823	891	915	884	854	870	764	831	826
Santa Cecília	946	922	1008	975	977	908	861	897	849	757	809	840
Santo Amaro	755	789	767	840	854	853	913	917	868	845	892	845
Moema	854	876	891	941	917	873	914	854	877	789	868	853
Jaguaré	692	706	734	746	830	836	810	862	851	804	885	861
Bela Vista	930	978	918	958	935	866	889	829	893	784	808	866
Carrão	922	936	932	914	930	972	994	971	1009	884	876	875
Moóca	847	790	875	948	973	986	982	947	1018	888	933	917
Tatuapé	954	975	1009	1072	945	999	908	934	937	918	919	920
Perdizes	1099	1136	1085	1180	1175	1123	1089	1128	1087	961	996	936
Água Rasa	1027	995	1038	1118	995	1039	1032	1080	1090	1099	1014	965
Vila Formosa	1039	1109	1144	1010	1036	1035	962	1018	1003	959	980	967

Distrito	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Tucuruvi	1158	1215	1109	1193	1159	1092	1013	1061	1080	968	1046	1002
Belém	978	1003	1015	1082	1115	1045	1003	1052	1061	1031	1030	1014
Casa Verde	1244	1146	1189	1183	1191	1125	1148	1141	1117	1085	995	1032
Anhanguera	949	967	1005	1042	1085	1082	1121	1120	1189	1037	1119	1093
São Domingos	1262	1200	1208	1146	1170	1222	1168	1231	1225	1131	1116	1093
Mandaqui	1413	1497	1355	1348	1340	1298	1251	1243	1257	1232	1161	1115
Limão	1372	1339	1340	1321	1350	1394	1393	1404	1362	1396	1229	1163
Ponte Rasa	1264	1262	1226	1290	1240	1339	1286	1270	1268	1134	1121	1164
Parque do Carmo	1211	1204	1168	1186	1225	1259	1243	1265	1250	1195	1197	1175
Santana	1612	1687	1502	1486	1287	1302	1307	1232	1159	1186	1176	1176
Aricanduva	1209	1243	1248	1217	1193	1278	1190	1192	1246	1188	1133	1181
Campo Grande	1225	1245	1214	1248	1190	1301	1335	1351	1415	1227	1235	1191
Saúde	1366	1388	1433	1386	1407	1410	1249	1302	1257	1208	1269	1218
Vila Mariana	1193	1269	1307	1351	1300	1376	1324	1339	1273	1200	1291	1222
Vila Prudente	1253	1312	1404	1374	1316	1329	1272	1324	1317	1252	1303	1232
Jaçanã	1211	1273	1249	1290	1218	1277	1182	1243	1192	1187	1197	1240
Vila Matilde	1348	1381	1375	1372	1344	1343	1330	1351	1397	1304	1303	1251
Arthur Alvim	1430	1479	1450	1414	1399	1416	1367	1373	1376	1328	1267	1261
Itaim Bibi	988	1077	1116	1122	1179	1224	1147	1238	1223	1181	1299	1279
Cursino	1325	1308	1407	1438	1403	1416	1393	1376	1365	1307	1368	1280
Perus	1430	1504	1407	1488	1507	1402	1476	1504	1489	1354	1478	1302
Vila Sônia	1456	1543	1569	1635	1587	1640	1670	1624	1693	1506	1506	1421
Ipiranga	1348	1428	1426	1393	1485	1479	1481	1556	1550	1511	1395	1426
São Miguel	1860	1702	1768	1634	1713	1633	1669	1689	1655	1556	1602	1554
Penha	1714	1689	1677	1726	1691	1757	1641	1692	1645	1617	1711	1659
São Lucas	1903	1754	1760	1709	1795	1795	1771	1813	1807	1703	1826	1666
José Bonifácio	1600	1823	1653	1700	1794	1840	1731	1754	1752	1713	1673	1691
Raposo Tavares	1947	1890	2004	1789	1948	1878	1856	1902	1802	1801	1756	1736
Ermelino Matarazzo	1838	1909	1875	1969	1854	1943	1860	1960	1908	1840	1786	1748
Vila Medeiros	1987	1962	1964	1975	1924	1962	1896	1812	1950	1825	1753	1823
Freguesia do Ó	2115	2182	2136	2161	2115	2046	1938	2074	2039	1872	1881	1857
Guaianases	1872	1864	2025	1973	1938	1976	2039	2043	1912	1911	2000	1861
Vila Jacuí	1957	1965	2085	1996	1991	1975	1960	2027	1978	1849	1949	1894

Distrito	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Rio Pequeno	2256	2346	2309	2290	2313	2320	2342	2256	2179	2129	2129	1924
Vila Maria	1904	1971	2003	2044	2017	2006	1954	1971	2019	1935	2068	1936
Cidade Líder	2049	2061	2114	1990	2105	2117	1961	2245	2104	2046	2102	2057
Pirituba	2506	2509	2495	2487	2537	2409	2395	2462	2361	2235	2192	2110
Cangaíba	2051	2224	2106	2254	2260	2257	2237	2305	2349	2107	2260	2167
Pedreira	2290	2183	2336	2318	2469	2468	2519	2474	2410	2332	2344	2245
São Rafael	2219	2284	2226	2264	2290	2250	2312	2187	2266	2265	2219	2262
Vila Curuçá	2283	2345	2354	2409	2415	2402	2459	2502	2624	2383	2442	2351
São Mateus	2459	2452	2501	2504	2489	2451	2427	2464	2416	2361	2432	2363
Iguatemi	2174	2420	2338	2274	2426	2473	2373	2433	2522	2374	2428	2468
Jardim Helena	2520	2441	2633	2470	2580	2448	2550	2619	2618	2444	2574	2477
Vila Andrade	1983	2063	2140	2192	2294	2430	2443	2551	2512	2433	2448	2591
Parelheiros	2287	2320	2342	2492	2543	2481	2514	2514	2670	2613	2766	2653
Cachoeirinha	2694	2781	2821	2720	2750	2749	2675	2767	2766	2722	2686	2749
Cidade Dutra	3137	3193	3141	3184	3093	2994	2968	3101	3027	2804	2857	2771
Jabaquara	3377	3420	3200	3351	3359	3249	3190	3068	2994	3074	2981	2899
Lajeado	2783	2809	2888	2881	3037	3046	3012	3164	3138	3101	3139	3038
Jaraguá	3086	3214	3093	3163	3378	3313	3202	3222	3343	3113	3249	3079
Itaquera	3389	3338	3178	3264	3329	3300	3246	3306	3426	3208	3262	3232
Tremembé	3143	3201	3243	3304	3353	3360	3334	3413	3402	3365	3373	3344
Campo Limpo	3460	3558	3689	3764	3760	3725	3632	3691	3820	3557	3768	3519
Itaim Paulista	3807	3895	3856	3805	3922	3988	3813	3947	3887	3709	3660	3592
Cidade Tiradentes	3530	3632	3743	3830	3818	4006	3806	3956	4006	3798	3711	3657
Sacomã	3708	3467	3557	3504	3696	3647	3662	3710	3809	3599	3566	3723
Sapopemba	4525	4545	4528	4517	4663	4577	4409	4379	4476	4155	4227	4014
Jardim São Luis	4396	4515	4502	4584	4573	4539	4268	4339	4434	4076	4251	4134
Cidade Ademar	4636	4758	4780	4737	4748	4755	4666	4605	4576	4492	4530	4295
Capão Redondo	4594	4583	4633	4608	4693	4617	4617	4656	4635	4519	4422	4371
Brasilândia	5125	5159	5119	5000	5140	5135	5029	4970	5166	4945	4889	4791
Jardim Ângela	5477	5541	5637	5727	6083	5843	5855	6047	6061	5663	5869	5599
Grajaú	7049	7110	7083	7037	7125	6977	7048	6995	7258	6825	6835	6823

Figure 6 Relative change in number of livebirths across administrative districts between 2007 and 2008



4.2. Socio-demographic and maternal- & child health indicator variables

In Table 1, the distribution of the socio-demographic and maternal- & child health indicator variables of the study are displayed. Note that measurements of these indicators are based on the administrative districts as this was the only available aggregation level for both, maternal and infant data.

Overall, apart from the indicator “reported violence against women”, there was a consistent tendency in decreased indicator levels over time.

Adolescent pregnancies per 100 livebirths, decreased from 13 points in 2007 to about 9 points in 2018.

Table 1 Distribution of the socio-demographic and maternal- & child health indicator study variables at administrative district level for the years 2007 and 2018

socio-demographic and maternal- & child health indicator variables**	**Year:** 2007	2018	Overall
Adolescent pregnancies [per 100 livebirths]			
Mean [SD]	13.3 [4.95]	9.26 [4.21]	10.6 [4.86]
Median [Q25, Q75]	13.7 [9.93, 16.8]	10.4 [6.56, 12.4]	10.8 [7.38, 13.5]
Min, Max	1.89, 19.9	0.353, 18.9	0.353, 19.9
Infant mortality [Number of deaths in younger than 1yo / total newborns x 1,000]			
Mean [SD]	12.4 [3.65]	10.2 [3.14]	10.9 [3.49]
Median [Q25, Q75]	13.1 [8.98, 15.2]	10.8 [8.43, 12.8]	11.3 [8.43, 13.5]
Min, Max	2.59, 35.4	1.07, 24.6	1.07, 35.4
Low birth weight [Number of live births underweighted / number of newborns x 100]			
Mean [SD]	9.51 [0.871]	9.50 [0.924]	9.50 [0.906]
Median [Q25, Q75]	9.76 [9.05, 10.0]	9.55 [8.89, 10.1]	9.61 [8.95, 10.1]
Min, Max	5.05, 13.7	6.50, 12.8	5.05, 13.7
Suboptimal prenatal care [number of newborns with <7 prenatal visits / total newborns x 100]			
Mean [SD]	22.4 [8.37]	18.5 [5.04]	19.8 [6.63]
Median [Q25, Q75]	22.1 [18.5, 26.2]	19.0 [16.5, 21.6]	19.3 [16.8, 23.5]
Min, Max	3.54, 46.0	5.40, 31.9	3.54, 46.0
Reported violence against women* [Number of notified violence / Women 20 - 59yo x 10,000]			
Mean [SD]	2.89 [4.48]	21.9 [17.0]	15.5 [16.7]
Median [Q25, Q75]	1.13 [0.0690, 4.01]	19.1 [6.18, 28.9]	8.44 [2.64, 23.0]
Min, Max	0, 22.6	0.554, 100	0, 100

* Data for 2008 and 2017 as no data was available for 2007 and 2018.
** Measured at the technical health supervision (STS) level

4.3. Time trends in maternal syphilis across administrative districts

In this section, different graphical illustrations as well as linear mixed effects regression analyses are used to describe the time dynamics of the maternal syphilis epidemic across the 97 administrative districts.

In Figure 7, boxplots, and smooth spline curves with 95% confidence band display an overall increase in maternal syphilis incidence over time. The global likelihood ratio test for time trend was statistically significant ($p<0.0001$) with an estimated average increase of 2.11 maternal syphilis cases per 1000 livebirths each year (95% confidence interval: 1.98/1000 to 2.23/1,000). The random effect (i.e., standard deviation in maternal syphilis rates across districts) was estimated to be 7.23 cases / 1,000, 95% confidence interval 6.52 cases / 1,000 to 8.83 cases / 1,000 (Table 1).

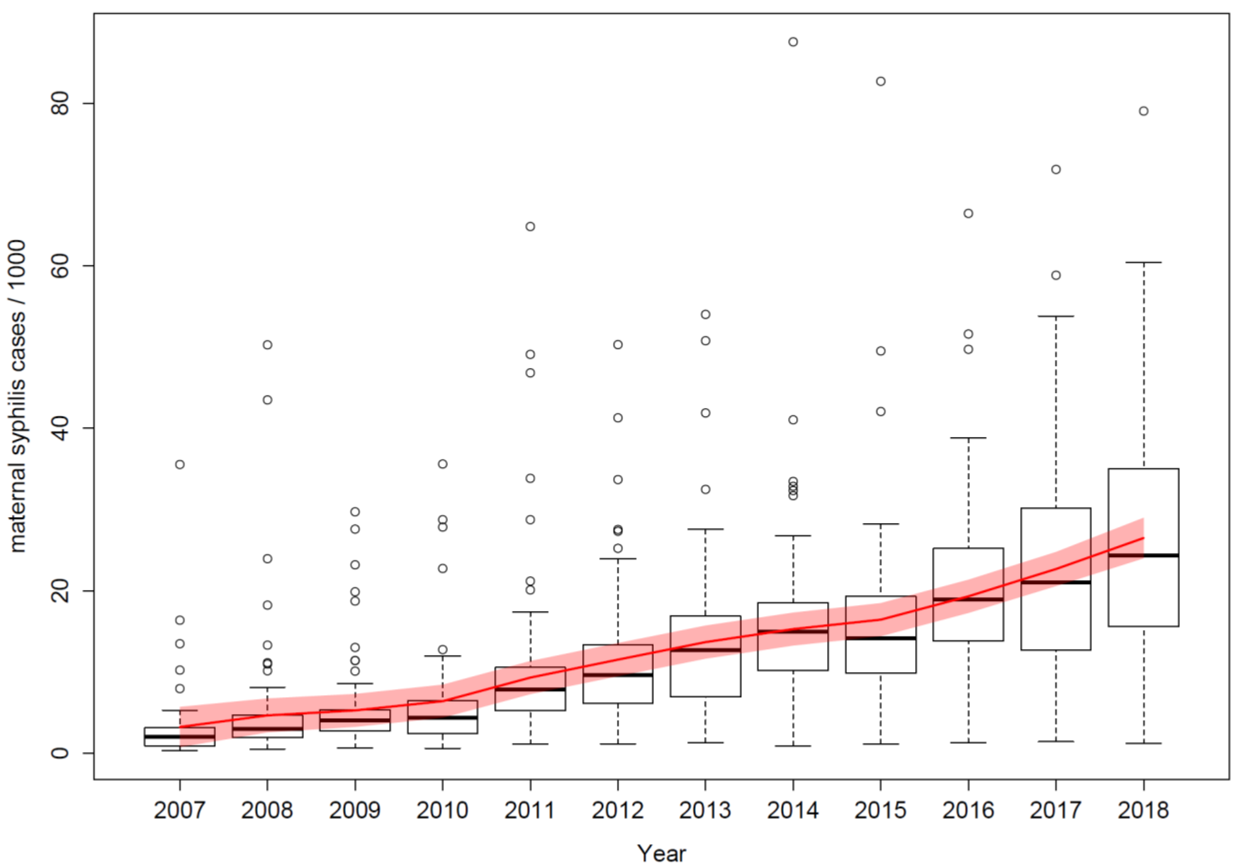
The time trend reveals three major episodes associated with different growing rates in maternal syphilis: 2007 to 2010, 2011 to 2015 and 2016 to 2018. The descriptive statistics of the maternal syphilis rates in these periods are displayed in Table 2. The expected value (mean) of maternal syphilis prevalence increased form 4.8 cases / 1000 in 2007-2010 to 13.3 cases / 1000 in 2011-2015, up to 23 cases / 1000 in 2016-2018. This increasing tendency is also reflected in the quartiles and range of prevalence values across administrative districts.

Table 2 Annual incident [reported] cases of maternal syphilis across all 97 administrative districts of the city of Sao Paulo for the time intervals 2007 to 2010, 2011 to 2015 and 2016 to 2018.

	Year: 2007-2010	2011-2015	2016-2018	Overall
Maternal syphilis cases / 1,000				
Mean [SD]	4.81 [6.11]	13.3 [10.2]	23.0 [13.1]	13.1 [12.2]
Median [Q25, Q75]	3.33 [1.78, 5.10]	11.4 [6.71, 16.8]	21.1 [14.7, 30.3]	9.94 [3.99, 18.3]
Min, Max	0.283, 50.3	0.887, 87.5	1.17, 79.0	0.283, 87.5

SD= Standard Deviation, Q25= 0.25 quantile, Q75= 0.75 quantile

Figure 7 Annual incident [reported] cases of maternal syphilis across all 97 administrative districts of the city of Sao Paulo over time (year 2007 to 2018) – quartiles (boxplots) and mean trends (smooth spline with 95% confidence band)



4.4. Annual seasonal trends in maternal syphilis across administrative districts

The risk for acquiring sexually transmissible infections such as syphilis may vary by season due to dynamics in opportunities to engage with others, especially with respect to major socio-cultural events such as carnival. To further investigate possible common seasonal variations in maternal syphilis rates across districts, the data was analyzed for seasonal time trends. The linear mixed effects model with additional random effect “month” revealed a statistically significant improvement of goodness of fit (p-value likelihood ratio test <0.0001). The district-level standard deviation (i.e., the random intercept) of maternal syphilis incidence over the months was estimated to be 1.15 cases / 1,000 with 95% confidence interval 0.72 cases / 1,000 to 1.93 cases / 1,000. Hence, the variation of maternal syphilis rates within districts over the season was much lower than the variation of maternal syphilis rates across districts (ratio in variances $7.23^2/1.14^2=6.34$).

In Figure 8 the seasonal time variations in maternal syphilis incidence rates are shown for six selected administrative districts (seasonal data for all districts are summarized in Appendix A). The area plots in that figure illustrate similar tendencies in the dynamics of maternal syphilis cases. First, the increase in annual incident [reported] cases over the years is clearly noticeable through the increasing area surfaces with time i.e., the lighter colored areas (towards the bottom of each graph) are taking proportionally larger space than darker shaded areas (towards the top of each graph). Second, higher incidence rates appear to be more prevalent in the second half of the year. Third, there is a noticeable consistency of peaks in reported cases in the months of January, February and March followed by a rate decline towards the month of April.

Figure 8 Annual seasonal trends in reported incident cases of maternal syphilis within administrative districts of the city of Sao Paulo over time (year 2007 to 2018).

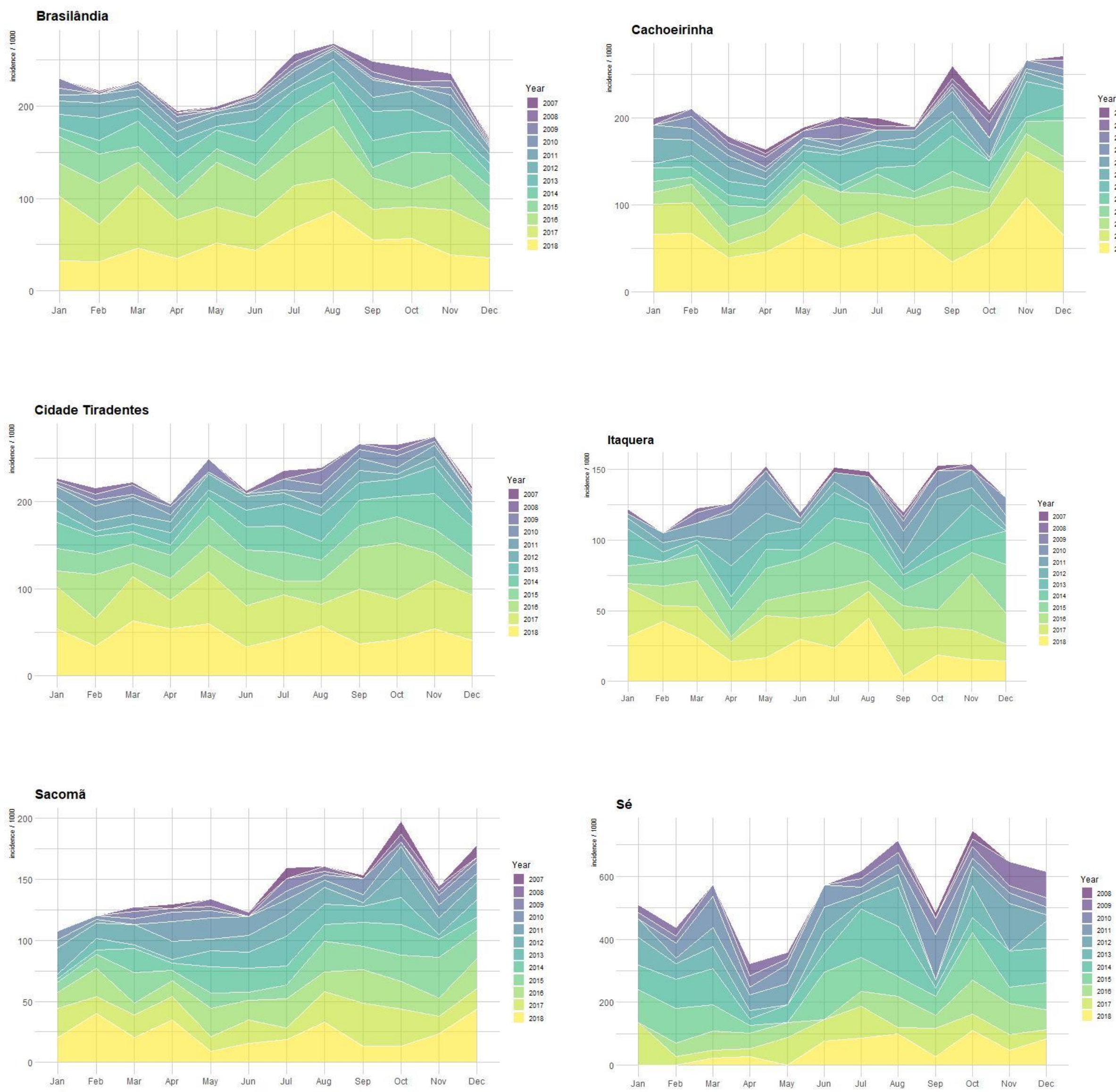
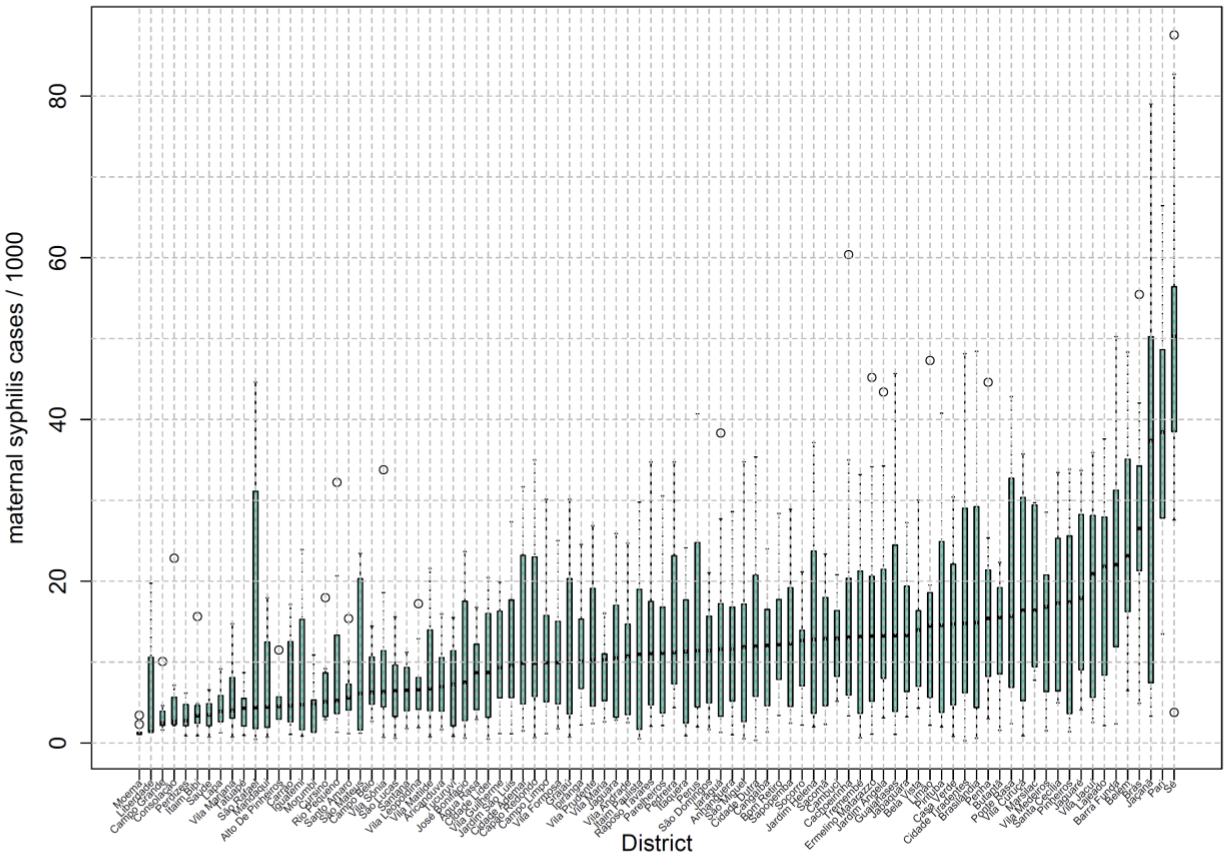


Figure 9 Annual incident [reported] cases of maternal syphilis within administrative districts of the city of Sao Paulo over time (year 2007 to 2018).



4.5. Time trends in congenital syphilis across administrative districts

In this section, different graphical illustrations as well as linear mixed effects regression analyses are used to describe the time dynamics of the congenital syphilis epidemic across the 26 technical health supervisions (STS).

In Figure 10, boxplots, and smooth spline curves with 95% confidence band display an overall increase in congenital syphilis incidence over time. The global likelihood ratio test for time trend was statistically significant ($p<0.0001$) with an estimated average increase of 0.49 congenital syphilis cases per 1,000 livebirths each year (95% confidence interval: 0.40/1,000 to

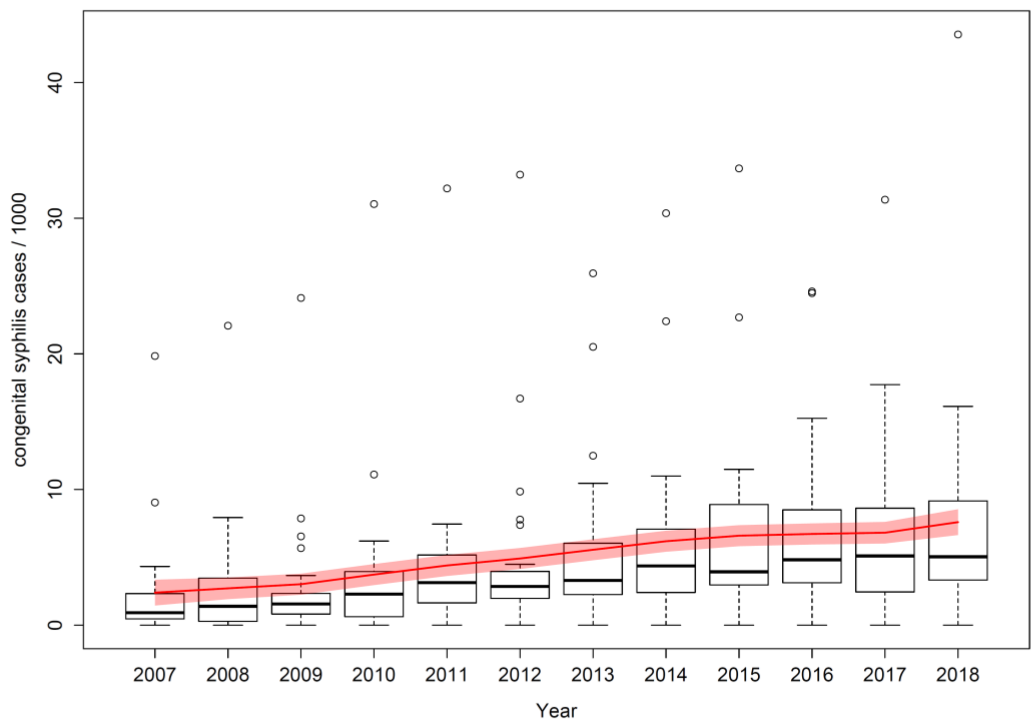
0.58/1,000). The random effect (i.e., standard deviation in congenital syphilis rates across STS) was estimated to be 5.58 cases / 1,000 with 95% confidence interval 4.22/1,000 to 7.41/1,000. The descriptive statistics of the congenital syphilis rates in the intervals 2007-2010, 2011-2015 and 2016-2018 are displayed in Table 3. The expected value (mean) of congenital syphilis prevalence increased from 3 cases / 1,000 in 2007-2010 to 5.5 cases / 1,000 in 2011-2015, up to 7 cases / 1,000 in 2016 -2018. This increasing tendency is also reflected in the quartiles and range of prevalence values across administrative districts.

Table 3 Annual incident [reported] cases of congenital syphilis across the 26 technical health supervisions (STS) of the city of Sao Paulo for the time intervals 2007 to 2010, 2011 to 2015 and 2016 to 2018.

	Year: **2007-2010**	**2011-2015**	**2016-2018**	**Overall**
Congenital syphilis cases / 1,000				
Mean [SD]	2.96 [4.88]	5.53 [6.56]	7.04 [7.20]	5.05 [6.42]
Median [Q25, Q75]	1.57 [0.537, 3.31]	3.41 [2.05, 6.38]	5.00 [3.00, 8.80]	3.12 [1.44, 6.09]
Min, Max	0, 31.0	0, 33.7	0, 43.5	0, 43.5

SD= Standard Deviation, Q25= 0.25 quantile, Q75= 0.75 quantile

Figure 10 Annual incident [reported] cases of congenital syphilis across the 26 technical health supervisions (STS) of the city of Sao Paulo over time (year 2007 to 2018) – quartiles (boxplots) and mean trends (smooth spline with 95% confidence band)



4.6. Annual seasonal trends in congenital syphilis across STS

To investigate possible common seasonal variations in congenital syphilis rates across STS, the data was analyzed for seasonal time trends. The linear mixed effects model with additional random effect “month” revealed no statistically significant improvement of goodness of fit (p-value likelihood ratio test: 0.67). The corresponding standard deviation of congenital syphilis incidence rates across months) was estimated to be 0.12 cases / 1,000 with 95% confidence interval >0 cases / 1,000 to 0.40 cases / 1,000.

In Figure 11 the seasonal time variations in congenital syphilis incidence rates are shown for the 26 STS that correspond to the selected administrative districts on maternal syphilis rates presented in the previous section of this thesis (seasonal data for all STS are summarized in Appendix B). The area plots show, like for the maternal syphilis cases, an increase in annual incident [reported] cases over the years. It is noticeable that the seasonal variation of congenital syphilis cases varies largely across STS, with some STS showing quite consistent and distinct annual trend patterns. For example, the STS ‘Cidade Tiradentes’ shows repeatedly throughout the years rather extremely low (in comparison to neighbor months) congenital syphilis cases for the months August and October, whereas the month of September consistently shows the relative maximum of reported cases throughout the year. Note that the statistical assessment for seasonal trends pre-specified a “common seasonal trend” across STS, hence, was not sensitive to large variations in seasonal trends across STS.

Figure 11 Annual seasonal trends in reported incident* cases *of congenital syphilis within administrative districts of the city of Sao Paulo over time (year 2007 to 2018).

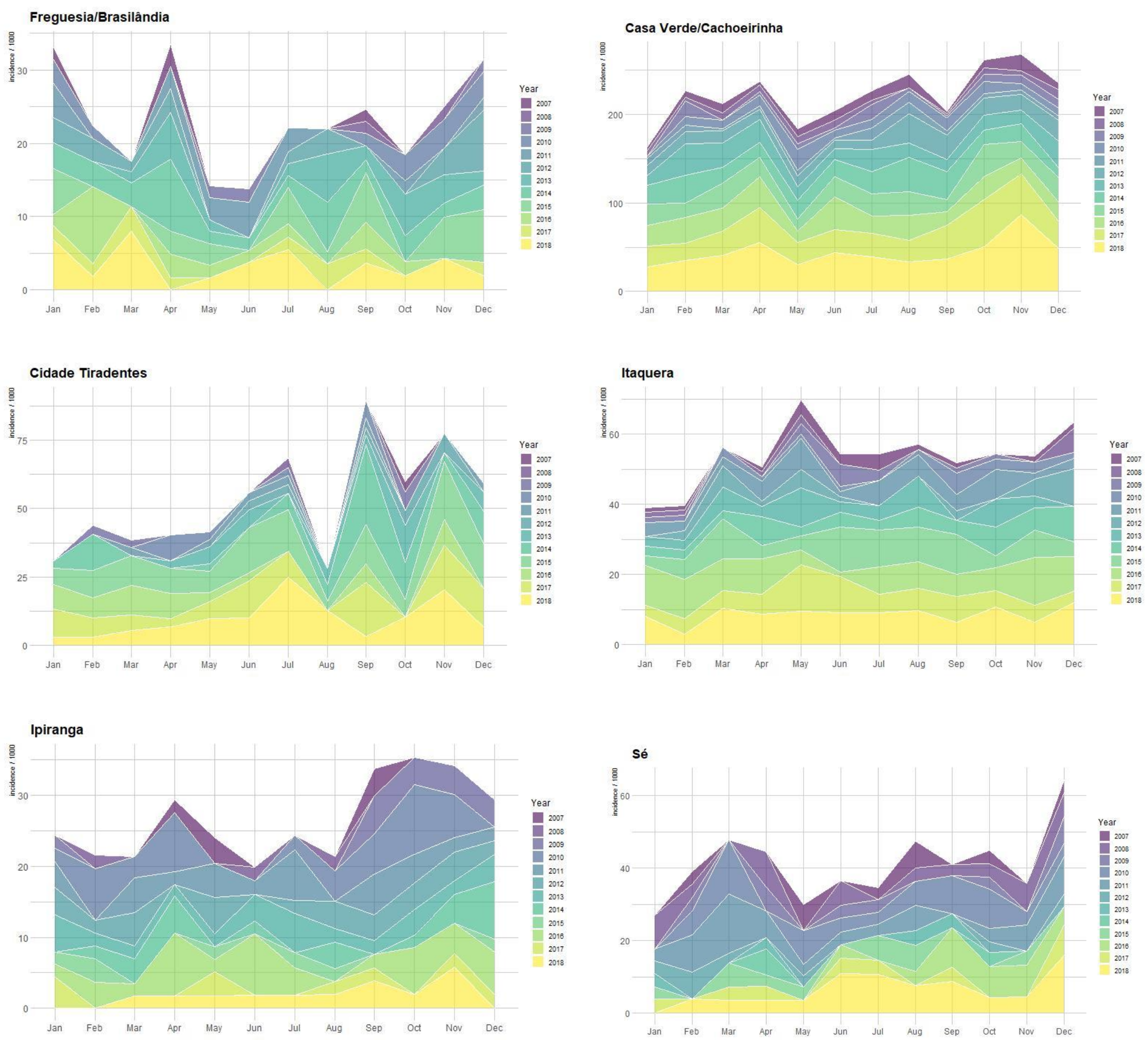
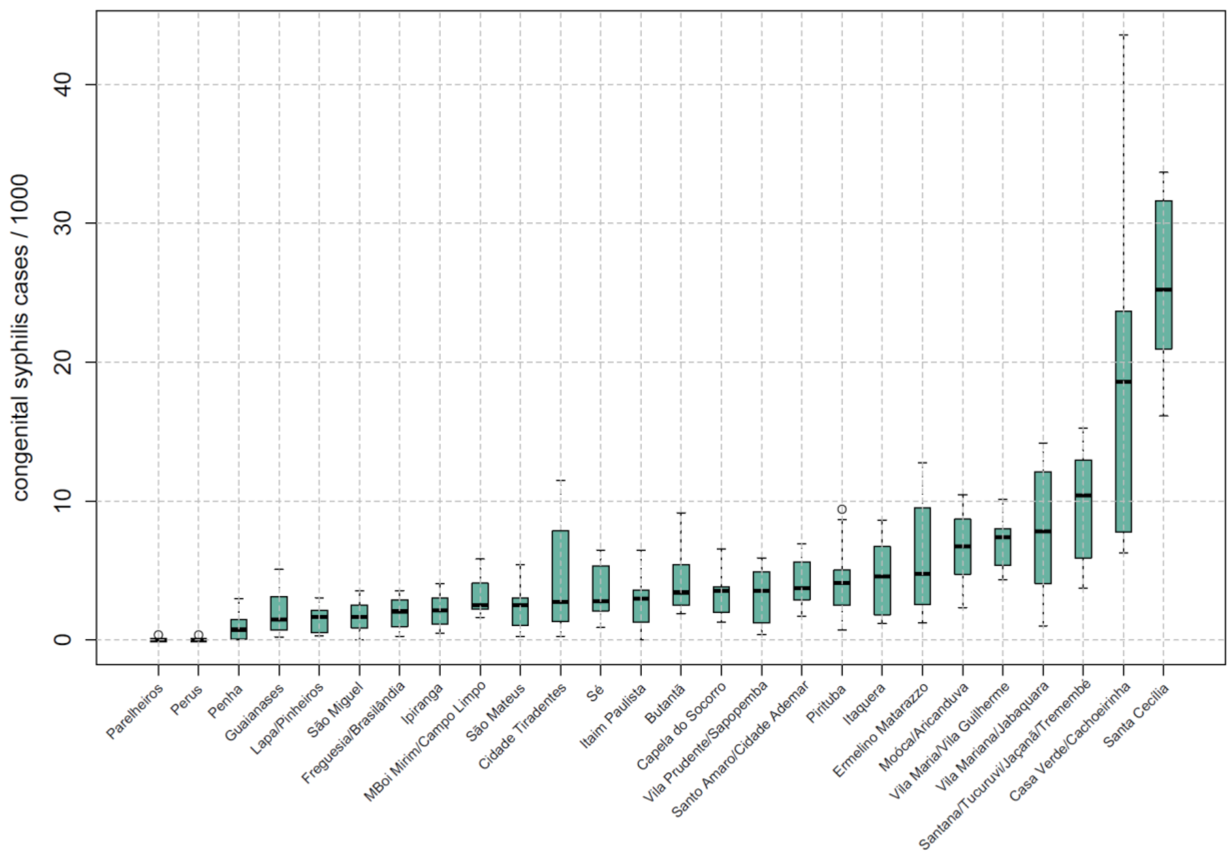


Figure 12 Annual incident [reported] cases of congenital syphilis within STS of the city of Sao Paulo over time (year 2007 to 2018).



4.7. Ecological factors associated with the incidence of maternal and congenital syphilis

The Figures 13 to 17. the distribution of the six socio-demographic and maternal- & child health indicators adolescent pregnancies per 100 livebirths, infant mortality, suboptimal prenatal care, low birth weight and reported violence against women are displayed over time. The distributions are summarized as boxplots depicting the quartiles of the respective distribution allowing for an assessment of the general time trends in the population variables. On top of each graph, two smooth spline functions illustrating the respective course of maternal and congenital syphilis incidence rates are added with a separate ordinate (2nd y-axis). This graphical representation allows for an indirect comparison of time trends at the indicator variable and incidence of disease level. Below each graph, using a panel of two scatter plots, a direct projection of STS or district-level syphilis incidence rates and indicator variable levels is provided. These scatter plots and fitted regression curves help to distill the direction and magnitude of the underlying associations. The graphical results are interpreted in a wholistic fashion, i.e., taking into consideration the overall bivariate data distribution including the apparent trends with uncertainty intervals but also the role of outliers and extreme values. As these analyses are exploratory in nature, a qualitive rather strict quantitative interpretation[1] is provided and elaborated on in the discussion section of this thesis.

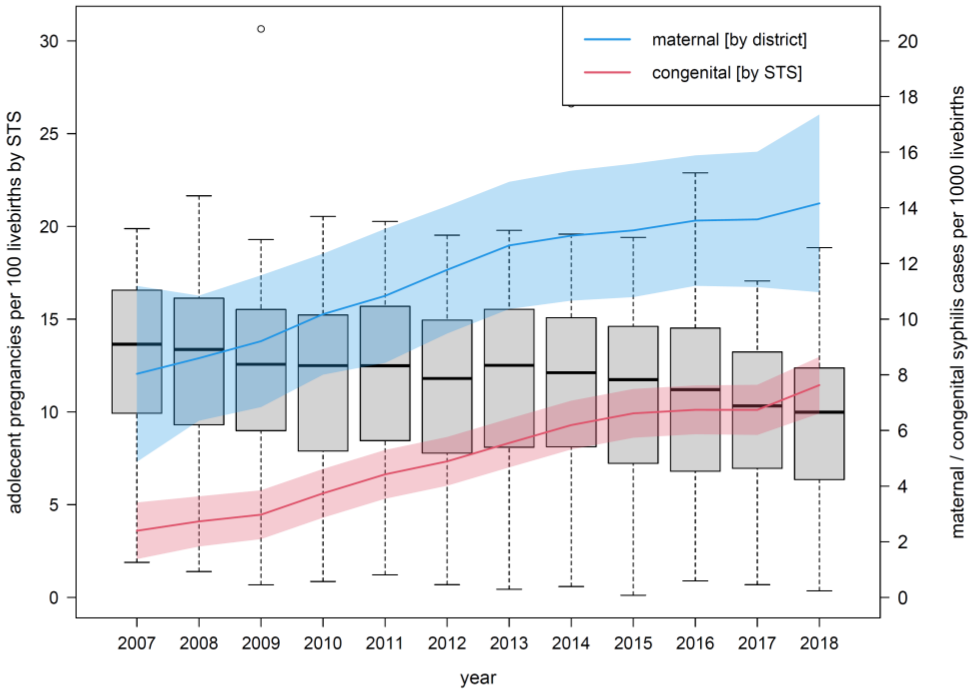
Adolescent pregnancies

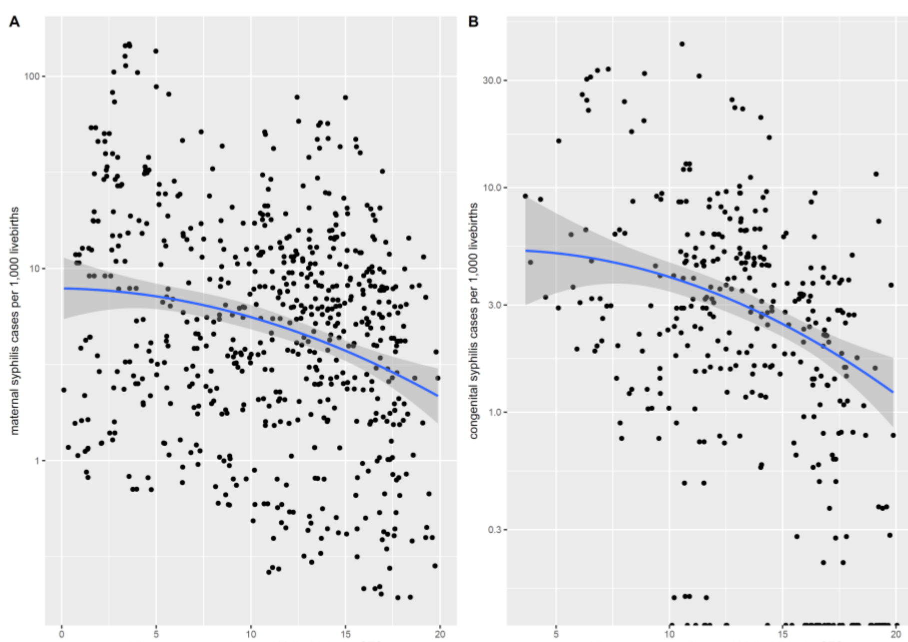
The proportion of adolescent pregnancies per 100 livebirths steadily decreased over time and therefore indicates an inverse ecological association with the increasing incidence rates of maternal and congenital syphilis (Figure 13 - upper panel). Beyond this contrast, the figure illustrates distinctly the similarity of the time course in both maternal and congenital syphilis incidence rates. The direct association between incidence rates and indicator variable levels (Figure 13 – lower panel) suggests a relative profound inverse correlation between the rate of adolescent pregnancies and incidence rates of maternal and congenital syphilis. Note that for illustrative purposes, the ordinates of the panel graphs A and B are log-scaled so that the

[1] Except for graphical assessment, no regression models were fitted to the data and no respective estimates of model (correlation) coefficients were provided to prevent over interpretation of these exploratory findings out of the context.

apparent linear associations are in fact log-linear correlations on the original scale of syphilis incidence.

Figure 13 Time course of STS-level indicator variable "adolescent pregnancies per 100 livebirths" and the incidence of maternal and congenital syphilis between 2007 and 2018 for the city of Sao Paulo, Brazil. Solid lines and shaded areas represent smooth spline functions for incidence rates with 95% confidence bands.





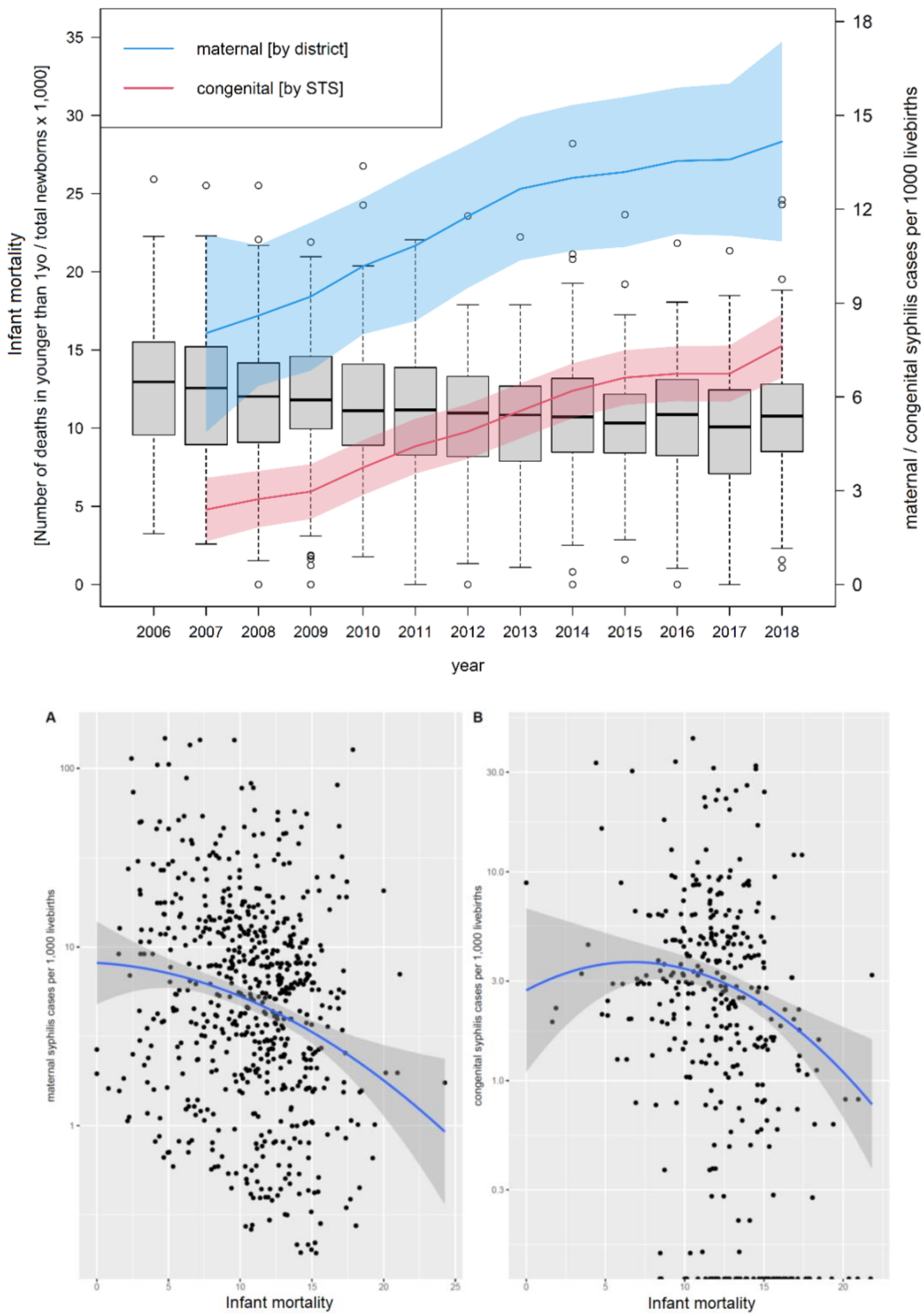
Infant mortality

Similar to the course of adolescent pregnancies, infant mortality rates decreased over time, indicating an inverse ecological association with the increasing incidence rates of maternal and congenital syphilis (Figure 14 - upper panel). The direct association between incidence rates and indicator variable levels (Figure 14 – lower panel) suggests a profound inverse correlation between infant mortality and incidence rates of maternal syphilis.

The apparent association between infant mortality at the STS level and congenital syphilis incidence is less pronounced in supervisions with relatively low infant mortality rates i.e., STS with less than 10 deaths per 1000 newborns of age below one year.

Despite the apparent log-linear inverse association between infant mortality and incidence of maternal syphilis, the overall residual variance i.e., individual data points deviating from the regression fit line, is large. This indicates a relatively low explanatory contribution of the factor infant mortality to the phenomenon of rapidly increasing maternal and subsequent congenital syphilis cases in the city of Sao Paulo.

Figure 14 Time course of STS-level indicator variable "infant mortality" and the incidence of maternal and congenital syphilis between 2007 and 2018 for the city of Sao Paulo, Brazil. Solid lines and shaded areas represent smooth spline functions for incidence rates with 95% confidence bands.



Suboptimal prenatal care

The indicator variable suboptimal prenatal care showed a monotonous decrease over time and hence, overall, an inverse ecological association with the increasing incidence rates of maternal and congenital syphilis (Figure 15 - upper panel).

Assessing the direct association between incidence rates and indicator variable levels (Figure 15 – lower panel) confirms this inverse association only in STS with relatively low to moderate frequencies of maternal syphilis cases (less than 30 per 1000 livebirths). Furthermore, despite a more homogenous log-linear association with regard to congenital syphilis, the overall magnitude of correlation was rather weak. This qualitative assessment is prompted by the relative mellow slope of the fitted regression curve and the rather wide 95% confidence bands at the tails of the indicator variable distribution.

Low birth weight

The rates of children born at relative low birth weight only slightly improved over the 12-year study period (Figure 16 - upper panel). The direct correlation between low-birth-weight rates and syphilis incidence rates indicated a distinct non-linear association at the maternal syphilis level. The fitted regression curves suggest a moderate inverse correlation among STS with relatively low to moderate rates of birth with low weight (less than 9 per 100 live births, Figure 16 – lower panel A).

In contrast, the association between low birth weight and congenital syphilis was, although similar in its general pattern, statistically not robust as indicated by the relatively wide confidence band surrounding the respective regression fit curve (Figure 16 – lower panel B).

Figure 15 Time course of STS-level indicator variable "suboptimal prenatal care" and the incidence of maternal and congenital syphilis between 2007 and 2018 for the city of Sao Paulo, Brazil. Solid lines and shaded areas represent smooth spline functions for incidence rates with 95% confidence bands.

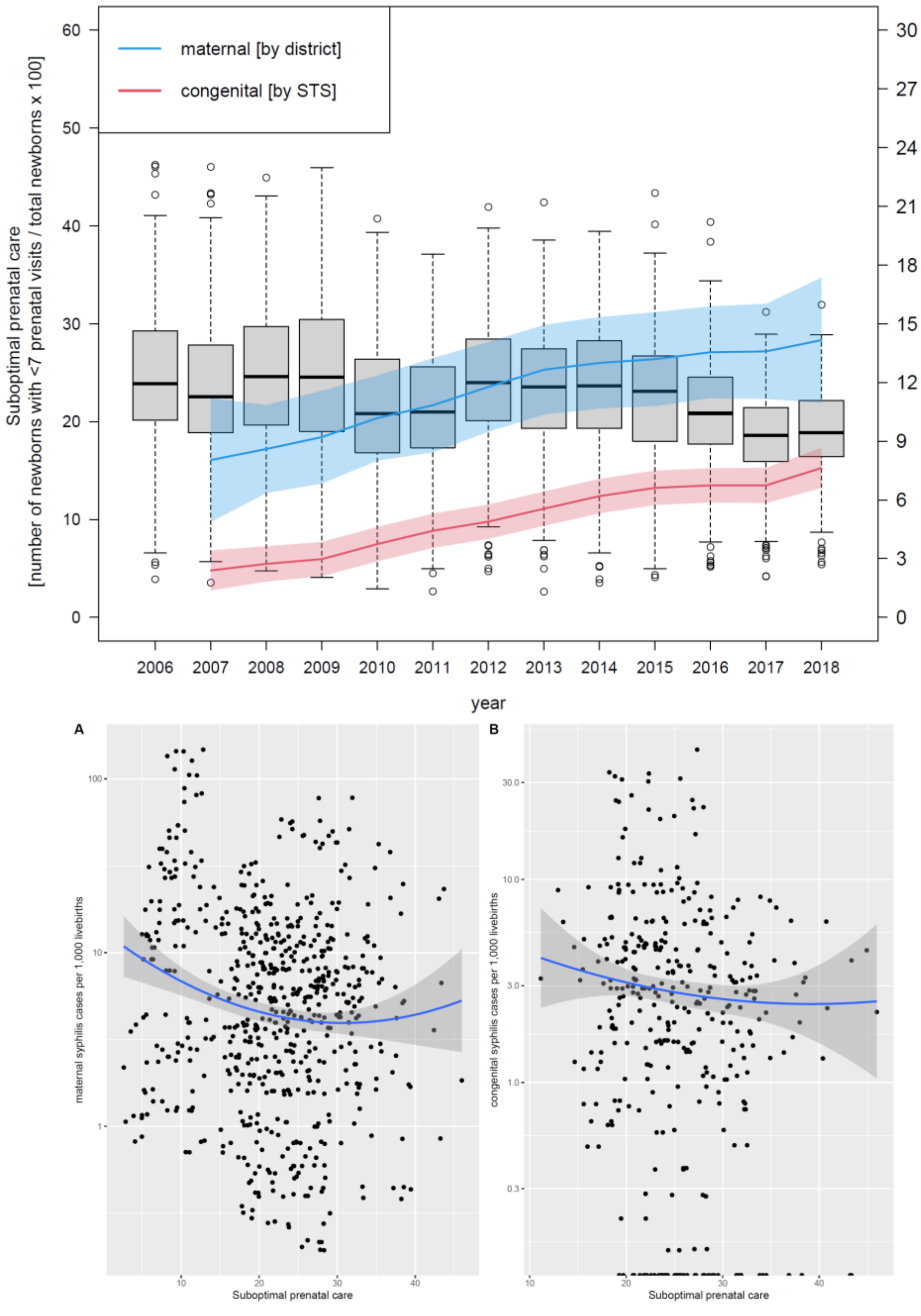
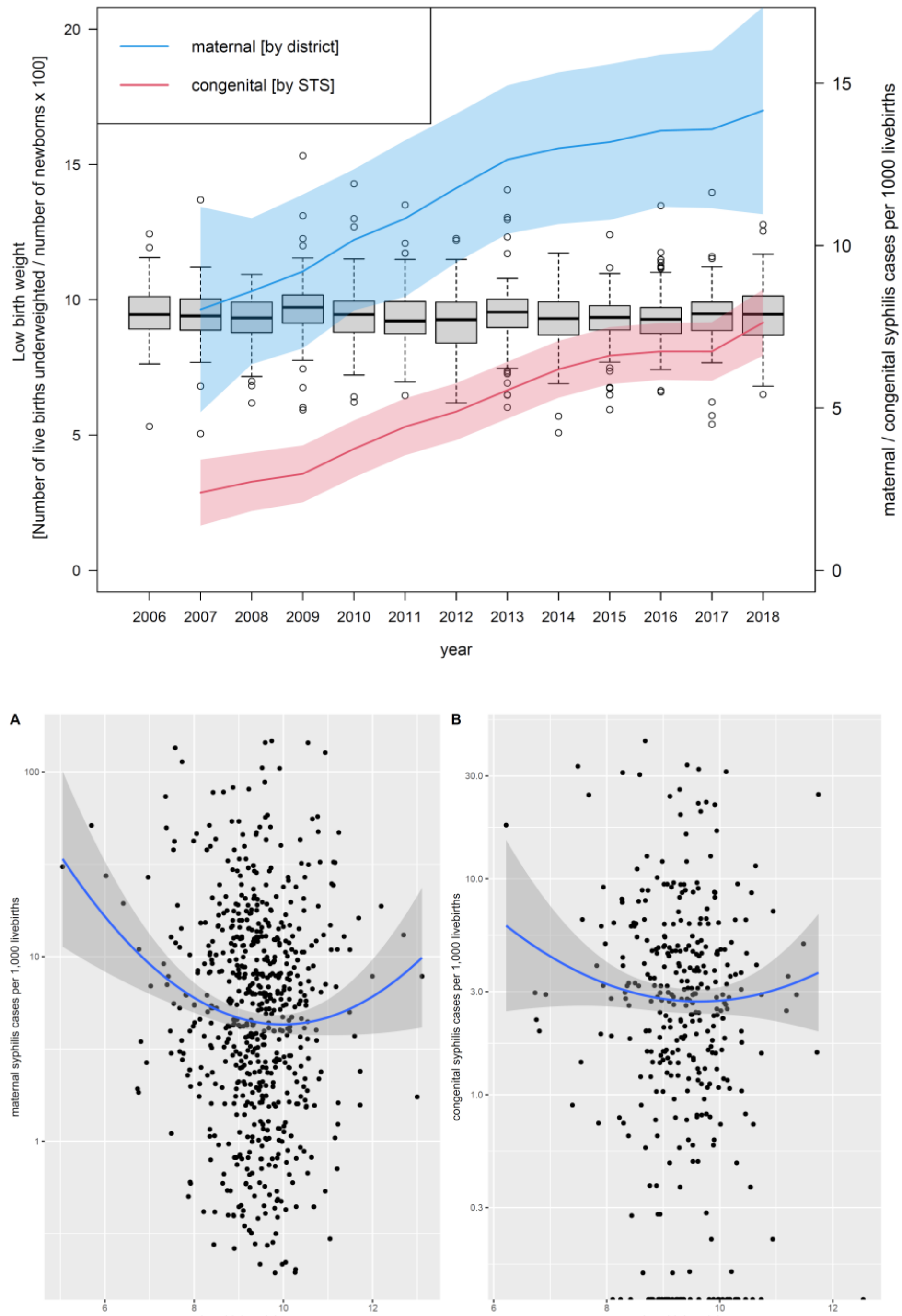


Figure 16 Time course of STS-level indicator variable "low birth weight" and the incidence of maternal and congenital syphilis between 2007 and 2018 for the city of Sao Paulo, Brazil. Solid lines and shaded areas represent smooth spline functions for incidence rates with 95% confidence bands.



Reported violence against women

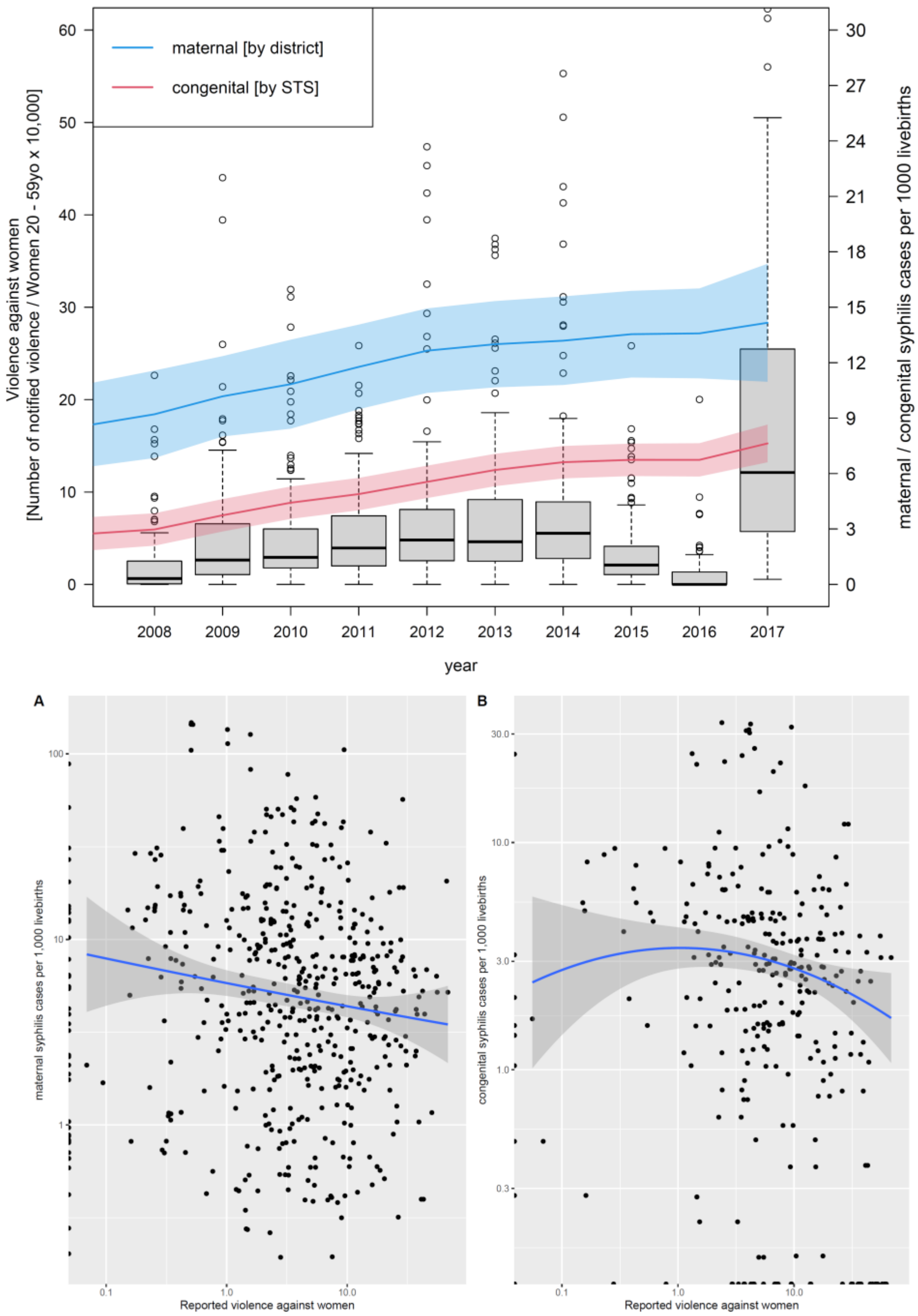
The time course of the indicator variable "reported violence against women" showed large irregularities over time (Figure 17 – upper panel). While there was a notable monotonous increase of reported violence against women between the years 2008 and 2014, rates strongly declined in the years 2015 and 2016, followed by an abrupt steep rise between 2016 and 2017. It is also noticeable that overall, the variance, i.e., heterogeneity in reporting levels across STS, drastically increased in that final[2] year of observation. This increase in reporting variance indicates large disparities in either report documentation, actual cases or reporting across the STS.

Despite the irregular time trends in this indicator, the direct association of indicator data and incidence rates in syphilis revealed a consistent, log-linear inverse correlation of reported violence against women with maternal syphilis rates (Figure 17 – lower panel A).

A similar association is apparent with regard to congenital syphilis rates, however, only in STS with relatively high reported numbers of cases of violence against women (Figure 17 – lower panel B).

[2] Note that, at the time of data extraction (June 2020), no data on this indicator variable was available for the year 2018.

Figure 17 Time course of STS-level indicator variable "reported violence against women" and the incidence of maternal and congenital syphilis between 2007 and 2018 for the city of Sao Paulo, Brazil. Solid lines and shaded areas represent smooth spline functions for incidence rates with 95% confidence bands.



5. Discussion

The purpose of this thesis research was to study current trends in, and factors associated with, the maternal and congenital syphilis epidemic in the city of Sao Paulo, Brazil. The primary data source for this study was Data SUS, the Brazilian public health database. This ministerial database contains regular health data reports, population statistics and epidemiological surveillance data for all regions in Brazil, including the municipality of Sao Paulo.

The study findings suggest a consistent increase of both maternal and congenital syphilis incidence rates over the past twelve years. The average increase in the rate of maternal syphilis was estimated 2.11 maternal syphilis cases per 1000 livebirths each year (95% confidence interval: 1.98/1000 to 2.23/1,000. The average increase in the rate of congenital syphilis was estimated 0.49 congenital syphilis cases per 1,000 livebirths each year (95% confidence interval: 0.40/1,000 to 0.58/1,000).

These trends are below the growing rates at the Brazilian national level (2.25 / 1,000 livebirths for maternal syphilis and 0.83/1,000 livebirths for congenital syphilis; reference period 2010 to 2018) (64).

There was considerable variation in the incidence rates and time trends across administrative districts and technical health supervisions. The standard deviation of maternal syphilis rates across districts was estimated 7.23 cases / 1,000 (95% confidence interval 6.52 cases / 1,000 to 8.83 cases / 1,000) and the standard deviation of congenital syphilis cases across STS was estimated 5.58 cases / 1,000 (95% confidence interval 4.22/1,000 to 7.41/1,000).

Accordingly, while current time trends suggest significant worsening of the epidemic situation over time, there profound existing disparities in incidence rates across districts and/or technical health supervisions. For instance, while an average growing incidence rate of 2.25 per year suggests an increase of about 7 cases per 1,000 livebirths over three years, differences of such magnitude are already expected when comparing different administrative districts, as indicate by the district level standard deviation of 7.3 / 1,000 livebirths.

Regarding maternal syphilis, there were also seasonal trends apparent from the data, suggesting higher incidence rates towards the end of the year and comparatively low incidence rates in the fall. In contrast, while there was large heterogeneity in congenital syphilis rates over the year within the different technical health supervisions, no consistent patterns of low or high incidence seasons were identifiable from the data. In a recent report by de Souza et al. researchers found that no evidence for an annual endemic period for syphilis, but February was identified as the most susceptible to an endemic event of both gestational syphilis and mother to infant transmission was February (65).

Using an ecological study approach, part of this thesis research investigated the association of socio-demographic and mother & child health indicator variables and the incidence rates in maternal and congenital syphilis. The motivation for this investigative approach was to better explain the large observed heterogeneity in incidence rates across administrative districts and STS. As indicator variables were available both at district and STS level, direct ecological correlation analyses were possible.

The correlation analyses revealed profound inverse associations between MS and CS incidence and infant mortality. This finding suggests that inappropriate prenatal care may not be exclusively held responsible for the ongoing worsening in congenital syphilis rates as such underperformance would likely have resulted in an increase of infant mortality as well.

The observed inverse correlation between adolescent pregnancies and MS/CS incidence rates can be explained by the confounding factor age: according to the recent epidemiological data on syphilis infections in Brazil, women in the age category <19 years have, compared to their older peers, lower risk of acquiring venereal syphilis (64). Hence, if a district or STS shows higher percentage of adolescent pregnancies among all pregnancies (and livebirths), the relative case count of maternal and congenital syphilis is expected to be lower in this location. The association between suboptimal prenatal care and MS / CS rates were less pronounced compared to the infant mortality and adolescent pregnancies. In fact, only among districts / STS with relatively low suboptimal prenatal care, an inverse association with the incidence rates was apparent from the data. Selection bias due to the increased likelihood of mothers from richer areas seeking private instead of public prenatal care services may explain the observed paradox, i.e., an inverse and not a positive association. This is because not all private administrative health data is also captured by the public health data system, potentially leading to an unfavorable selection that may explain, in part, the inverse correlation apparent from the data.

Another possible explanation relates to a possibly higher risk of underdiagnosis in districts or STS that have higher rates of suboptimal pre- and postnatal care. This would explain why with increasing deficits in maternal and infant health care settings, detections rates and hence reported incidence of maternal and congenital syphilis are relatively lower.

Selection bias due to a third latent variable may also explain the apparent inverse correlation between rates of low birth weights in an administrative district and the rate of maternal syphilis. As pregnant women who contracted Treponema pallidum are at higher risk of abortion and/or still birth which in turn, may reduce the likelihood of observing low weight births in these women due to the well-known depletion of susceptibles phenomenon due to “collider stratification” that has explained other long-standing birth-weight paradoxes in the history of epidemiology (66).

Limitations

The presented study has some important limitations that must be taken into consideration. First, the disease surveillance data used in this research was only available at administrative district and technical health supervision levels. It was not possible to analyse data based on reporting health units such as hospitals or clinics as there were no data sources that allowed for matching of socio-demographic and mother & child health indicators.

Second, some of the prenatal care data being used in this study are likely to only reflect statistics of procedures and indicators covered through the public and not the private health system.

This selection based on the status of private care coverage may have led to an over representation of populations with relative lower social economic status as private health services are not free as compared to public services.

Third, the ecological associations investigated in this study are to be considered “crude” i.e., do not take third level, i.e., latent variables into account. It is therefore critical to understand the findings as associational and explorative (i.e., hypothesis generating) in nature. In future studies, potential confounding issues must be addressed to enable more robust conclusions about possibly underlying structural phenomena that may explain the marginal data distributions and associations.

Furthermore, the data used in this study was repeated cross-sectional by nature, i.e. it was not possible to follow a prospectively defined cohort of (future) mothers who have (or would acquire) syphilis infection at some point in the study period.

Strengths

Despite the limitations of the study and the data it employed, there are also strengths of the presented research findings. One strength is the relative long observation period and the quality standards of the data due the official governmental and private data sources. These sources adhere to reporting standards and established procedures in collecting data for official dissemination. Furthermore, data collection and aggregation are done in an auto-generated manner by the respective data systems in place, i.e., relying on administrative electronic data records rather than human data entries.

Conclusions and future directions

Overall, the study findings indicate large variation in maternal and congenital syphilis rates across districts and technical health administrations within the city of Sao Paulo. Therefore, within the local urban context, there are opportunities to further investigate why certain territories perform better (or much worse) in terms of disease control and prevention than others. Factors contributing to the aggravating maternal and congenital syphilis epidemic may not only be sought at the population level but also at the local health care provision level. While the analysis of routinely collected disease surveillance and health administrative data may provide important directions to identifying possible explanations for the current epidemic trends, involvement of key stakeholders, in particular patients and health care providers in future studies is paramount to better understand and effectively tackle this ongoing health crisis.

6. References

1. Read JS, Schleiss MR. Congenital and Perinatal Infections [Internet]. Oxford University Press; 2018 [cited 2019 Jan 28]. 329 p. Available from: http://oxfordmedicine.com/view/10.1093/med/9780190604813.001.0001/med-9780190604813

2. AAP Committee on Fetus and Newborn AAPC, ACOG Committee on Obstetric Practice, Kilpatrick SJ, Papile L, Macones GA, Watterberg KL. Guidelines for Perinatal Care [Internet]. Elk Grove Village, UNITED STATES: American Academy of Pediatrics; 2017 [cited 2019 Jan 28]. Available from: http://ebookcentral.proquest.com/lib/mcgill/detail.action?docID=5061177

3. Korenromp EL, Rowley J, Alonso M, Mello MB, Wijesooriya NS, Mahiané SG, et al. Global burden of maternal and congenital syphilis and associated adverse birth outcomes—Estimates for 2016 and progress since 2012. PLOS ONE. 2019 Feb 27;14(2):e0211720.

4. Lancet T. Congenital syphilis in the USA. The Lancet. 2018 Oct 6;392(10154):1168.

5. Slutsker JS. Factors Contributing to Congenital Syphilis Cases — New York City, 2010–2016. MMWR Morb Mortal Wkly Rep [Internet]. 2018 [cited 2019 Feb 3];67. Available from: https://www.cdc.gov/mmwr/volumes/67/wr/mm6739a3.htm

6. Workowski KA. Centers for Disease Control and Prevention Sexually Transmitted Diseases Treatment Guidelines. Clin Infect Dis. 2015 Dec 15;61(suppl 8):S759–62.

7. World Health Organization. WHO guideline on syphilis screening and treatment for pregnant women. [Internet]. 2017 [cited 2019 Mar 24]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK499742/

8. Kupek E, Petrou S, Vause S, Maresh M. Clinical, provider and socio-demographic predictors of late initiation of antenatal care in England and Wales. BJOG Int J Obstet Gynaecol. 2002 Mar 1;109(3):265–73.

9. Paim J, Travassos C, Almeida C, Bahia L, Macinko J. The Brazilian health system: history, advances, and challenges. The Lancet. 2011 May;377(9779):1778–97.

10. Massuda A, Hone T, Leles FAG, de Castro MC, Atun R. The Brazilian health system at crossroads: progress, crisis and resilience. BMJ Glob Health. 2018 Jul;3(4):e000829.

11. Qin J-B, Feng T-J, Yang T-B, Hong F-C, Lan L-N, Zhang C-L. Maternal and paternal factors associated with congenital syphilis in Shenzhen, China: a prospective cohort study. Eur J Clin Microbiol Infect Dis. 2014 Feb;33(2):221–32.

12. Araújo CL de, Shimizu HE, Sousa AIA de, Hamann EM. Incidence of congenital syphilis in Brazil and its relationship with the Family Health Strategy. Rev Saúde Pública. 2012 Jun;46(3):479–86.

13. Avelleira JCR, Bottino G. Sífilis: diagnóstico, tratamento e controle. An Bras Dermatol. 2006 Mar;81(2):111–26.

14. Global incidence and prevalence of selected curable sexually transmitted infections: 2008: World Health Organization, Department of Reproductive Health and Research, 2012 ISBN 978 92 4 150383 9. Reprod Health Matters. 2012 Mar;20(40):207–8.

15. Boletim CEInfo - Saúde em Dados | Secretaria Municipal da Saúde | Prefeitura da Cidade de São Paulo [Internet]. [cited 2019 Jan 28]. Available from: https://www.prefeitura.sp.gov.br/cidade/secretarias/saude/epidemiologia_e_informacao/index.php?p=258529

16. CDC Call to Action: Let's Work Together to Stem the Tide of Rising Syphilis in the United States. :11.

17. Congenital syphilis- ClinicalKey [Internet]. [cited 2019 Apr 20]. Available from: https://www-clinicalkey-com.proxy3.library.mcgill.ca/#!/content/playContent/1-s2.0-S0146000518300119

18. Karmody CS, Schuknecht HF. Deafness in Congenital Syphilis. Arch Otolaryngol. 1966 Jan 1;83(1):18–27.

19. Murphy EA, Hahn RD, Haskins HL. NERVE DEAFNESS ASSOCIATED WITH CONGENITAL SYPHILIS: REPORT OF A CASE TREATED WITH PREDNISONE AND PENICILLIN. J Am Med Assoc. 1958 Aug 16;167(16):1925–8.

20. Kahn RH. Recommendations for Public Health Surveillance of Syphilis in the United States. :58.

21. Gomez G. Investment case for eliminating mother-to-child transmission of syphilis: promoting better maternal and infant health and stronger health systems. WHO; 2012.

22. Gomez GB, Kamb ML, Newman LM, Mark J, Broutet N, Hawkes SJ. Untreated maternal syphilis and adverse outcomes of pregnancy: a systematic review and meta-analysis. Bull World Health Organ. 2013 Mar 1;91(3):217–26.

23. Boletim Epidemiológico Sífilis 2019 [Internet]. Departamento de Doenças de Condições Crônicas e Infecções Sexualmente Transmissíveis. [cited 2020 Dec 13]. Available from: http://www.aids.gov.br/pt-br/pub/2019/boletim-epidemiologico-sifilis-2019

24. Pelegrina IML. P3.354 Vertical Transmission of Syphilis: Current Reality in the City of Bauru. Sex Transm Infect Lond. 2013 Jul;89:A260.

25. Wendel GD, Sheffield JS, Hollier LM, Hill JB, Ramsey PS, Sánchez PJ. Treatment of syphilis in pregnancy and prevention of congenital syphilis. Clin Infect Dis Off Publ Infect Dis Soc Am. 2002 Oct 15;35(Suppl 2):S200-209.

26. Serruya SJ, Duran P, Martinez G, Romero M, Caffe S, Alonso M, et al. Maternal and congenital syphilis in selected Latin America and Caribbean countries: a multi-country analysis using data from the Perinatal Information System. Sex Health. 2015 Mar 2;12(2):164–9.

27. Hatherall B, Morris J, Jamal F, Sweeney L, Wiggins M, Kaur I, et al. Timing of the initiation of antenatal care: An exploratory qualitative study of women and service providers in East London. Midwifery. 2016 May;36:1–7.

28. Developing public health clinical decision support systems (CDSS) for the outpatient community in New York City: our experience | BMC Public Health | Full Text [Internet]. [cited 2019 Apr 23]. Available from: https://bmcpublichealth.biomedcentral.com/articles/10.1186/1471-2458-11-753

29. Kidd S, Bowen VB, Torrone EA, Bolan G. Use of National Syphilis Surveillance Data to Develop a Congenital Syphilis Prevention Cascade and Estimate the Number of Potential Congenital Syphilis Cases Averted. Sex Transm Dis. 2018 Sep;45(9):S23–8.

30. BE-2017-038-Boletim-Sifilis-11-2017-publicacao-.pdf [Internet]. [cited 2019 Apr 7]. Available from: http://portalarquivos.saude.gov.br/images/pdf/2017/novembro/13/BE-2017-038-Boletim-Sifilis-11-2017-publicacao-.pdf

31. Gonçalves DA, Matida LH. GUIA DE REFERÊNCIAS TÉCNICAS E PROGRAMÁTICAS PARA AS AÇÕES DO PLANO DE ELIMINAÇÃO DA SÍFILIS CONGÊNITA. :197.

32. guiadebolsodasifilis_2edicao2016.pdf [Internet]. [cited 2019 Feb 14]. Available from: http://www.saude.campinas.sp.gov.br/doencas/sifilis/guiadebolsodasifilis_2edicao2016.pdf

33. Haddrill R, Jones GL, Anumba D, Mitchell C. A tale of two pregnancies: A Critical Interpretive Synthesis of women's perceptions about delayed initiation of antenatal care. Women Birth. 2018 Jun 1;31(3):220–31.

34. Social Vulnerability in Congenital Syphilis Case Mothers: Qualitative Assessment of Cases in Indiana, 2014 to 2016 | Ovid [Internet]. [cited 2019 Feb 9]. Available from: https://oce-ovid-com.proxy3.library.mcgill.ca/article/00007435-201807000-00003/HTML

35. Mororó RM, Lima VC, Frota MV de V, Linhares MSC, Ribeiro SM, Martins MA. THE PERCEPTION OF NURSES HEALTH STRATEGY FAMILY ABOUT THE FOLLOWING OF CONGENITAL SYPHILIS. Rev Saúdecom. 2015 Nov 1;11(3):291–302.

36. Ramos ALP, Seta MHD. Atenção primária à saúde e Organizações Sociais nas capitais da Região Sudeste do Brasil: 2009 e 2014. Cad Saúde Pública [Internet]. 2019 Apr 8 [cited 2019 Apr 18];35(4). Available from: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0102-311X2019000405003&lng=pt&tlng=pt

37. Silva SB de M e, Silva B-CN, Silva MP. Organização social e indicadores socioeconômicos no Brasil: um estudo exploratório. Cad CRH. 2009;22(57):617–33.

38. Sustainable Development Goals [Internet]. [cited 2020 Dec 15]. Available from: https://www.who.int/westernpacific/health-topics/sustainable-development-goals

39. Rosenthal EL, Brownstein JN, Rush CH, Hirsch GR, Willaert AM, Scott JR, et al. Community Health Workers: Part Of The Solution. Health Aff (Millwood). 2010 Jul;29(7):1338–42.

40. Love MB, Gardner K, Legion V. Community Health Workers: Who they are and What they do. Health Educ Behav. 1997 Aug 1;24(4):510–22.

41. Sharma N, Harris E, Lloyd J, Mistry SK, Harris M. Community health workers involvement in preventative care in primary healthcare: a systematic scoping review. BMJ Open. 2019 Dec 1;9(12):e031666.

42. Maciel ELN, Vieira R da CA, Milani EC, Brasil M, Fregona G, Dietze R. O agente comunitário de saúde no controle da tuberculose: conhecimentos e percepções. Cad Saúde Pública. 2008 Jun;24(6):1377–86.

43. Silva ATC da, Aguiar ME de, Winck K, Rodrigues KGW, Sato ME, Grisi SJFE, et al. Núcleos de Apoio à Saúde da Família: desafios e potencialidades na visão dos profissionais da Atenção Primária do Município de São Paulo, Brasil. Cad Saúde Pública. 2012 Nov;28(11):2076–84.

44. Campos GW de S, Figueiredo MD, Pereira Júnior N, Castro CP de. A aplicação da metodologia Paideia no apoio institucional, no apoio matricial e na clínica ampliada. Interface - Comun Saúde Educ. 2014 Dec;18(suppl 1):983–95.

45. Ruschi GEC, Antônio FF, Zandonade E, Miranda AE. Qualidade dos dados de assistência pré-natal na Atenção Básica em prontuário eletrônico e relação com apoio matricial, Vitória, Espírito Santo, 2013-2014: corte transversal. Rev Bras Med Fam E Comunidade. 2017;12(39):1–13.

46. Macinko J, Harris M. Brazil’s Family Health Strategy. N Engl J Med. 2015 Sep 24;373:1278.

47. Castro MC, Massuda A, Almeida G, Menezes-Filho NA, Andrade MV, de Souza Noronha KVM, et al. Brazil’s unified health system: the first 30 years and prospects for the future. The Lancet. 2019 Jul 27;394(10195):345–56.

48. Fertonani HP, Pires DEP de, Biff D, Scherer MD dos A. The health care model: concepts and challenges for primary health care in Brazil. Ciênc Amp Saúde Coletiva. 2015 Jun;20(6):1869–78.

49. Harris M, Haines A. Brazil's Family Health Programme. BMJ. 2010 Nov 29;341(nov29 1):c4945–c4945.

50. Macinko J, Guanais FC. Evaluation of the impact of the Family Health Program on infant mortality in Brazil, 1990–2002. J Epidemiol Community Health. 2006 Jan;60(1):13–9.

51. Guanais FC, Macinko J. The health effects of decentralizing primary care in Brazil. Health Aff Proj Hope. 2009 Aug;28(4):1127–35.

52. IBGE | Brasil em Síntese | São Paulo | Pesquisa | Censo | Sinopse [Internet]. 2019 [cited 2019 Mar 22]. Available from: https://cidades.ibge.gov.br/brasil/sp/pesquisa/23/27652?indicador=27690

53. IBGE Censo 2010 [Internet]. [cited 2020 Dec 13]. Available from: https://censo2010.ibge.gov.br/sinopse/index.php?uf=35&dados=26#topo_piramide

54. Conselho Nacional de Saúde - Conselho Nacional de Saúde [Internet]. [cited 2020 Dec 13]. Available from: http://conselho.saude.gov.br/web_sus20anos/20anossus/legislacao/constituicaofedera

55. Biblioteca Virtual em Saúde MS [Internet]. [cited 2020 Dec 13]. Available from: http://bvsms.saude.gov.br/bvs/publicacoes/diretrizes_nacionais_vigilancia_saude

56. SINANWEB - Página inicial [Internet]. [cited 2020 Dec 13]. Available from: http://portalsinan.saude.gov.br/

57. Mapa da Desigualdade 2020 apresenta diferenças entre distritos de SP [Internet]. Rede Nossa São Paulo. 2020 [cited 2020 Dec 13]. Available from: https://www.nossasaopaulo.org.br/2020/10/29/mapa-da-desigualdade-2020-revela-diferencas-entre-os-distritos-da-capital-paulista/

58. Informações de Saúde (TABNET) – DATASUS [Internet]. [cited 2020 Dec 13]. Available from: https://datasus.saude.gov.br/informacoes-de-saude-tabnet/

59. Bunn A, Korpela M. An Introduction to dplR. :16.

60. Pinheiro JC, Bates DM, editors. Nonlinear Mixed-effects Models: Basic Concepts and Motivating Examples. In: Mixed-Effects Models in S and S-PLUS [Internet]. New York, NY: Springer; 2000 [cited 2020 Dec 13]. p. 273–304. (Statistics and Computing). Available from: https://doi.org/10.1007/0-387-22747-4_6

61. Pinheiro JC, Bates DM, editors. Theory and Computational Methods for Nonlinear Mixed-Effects Models. In: Mixed-Effects Models in S and S-PLUS [Internet]. New York, NY: Springer; 2000 [cited 2020 Dec 13]. p. 305–36. (Statistics and Computing). Available from: https://doi.org/10.1007/0-387-22747-4_7

62. Saville DJ. Multiple Comparison Procedures: The Practical Solution. Am Stat. 1990 May 1;44(2):174–80.

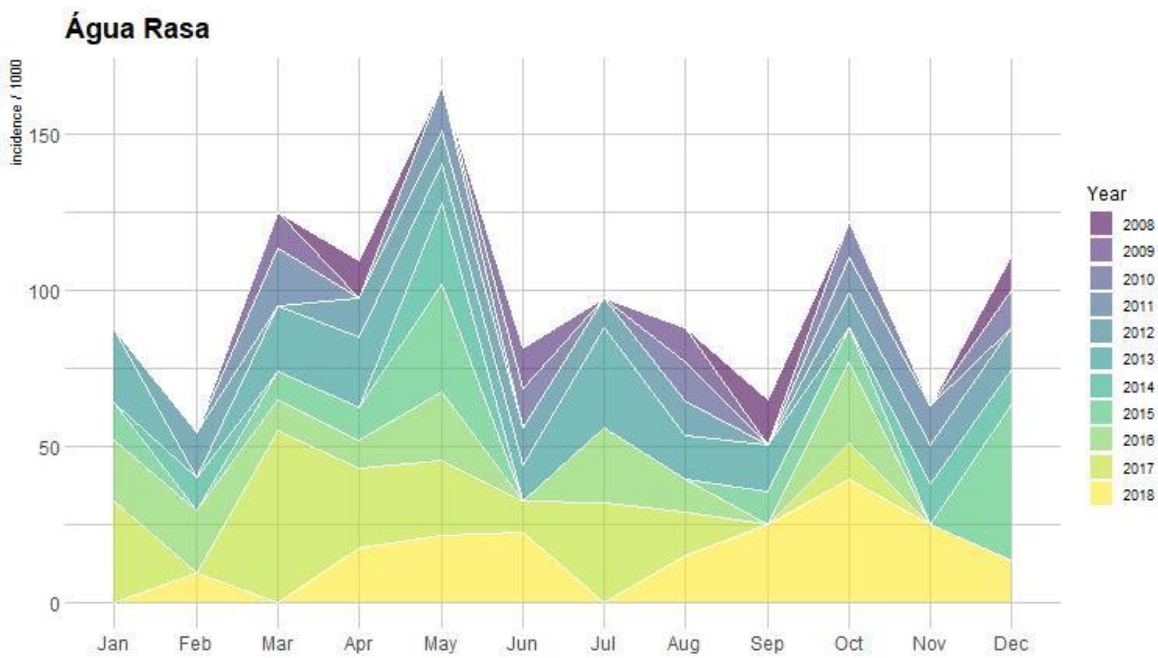
63. Schwartz S. The fallacy of the ecological fallacy: the potential misuse of a concept and the consequences. Am J Public Health. 1994 May;84(5):819–24.

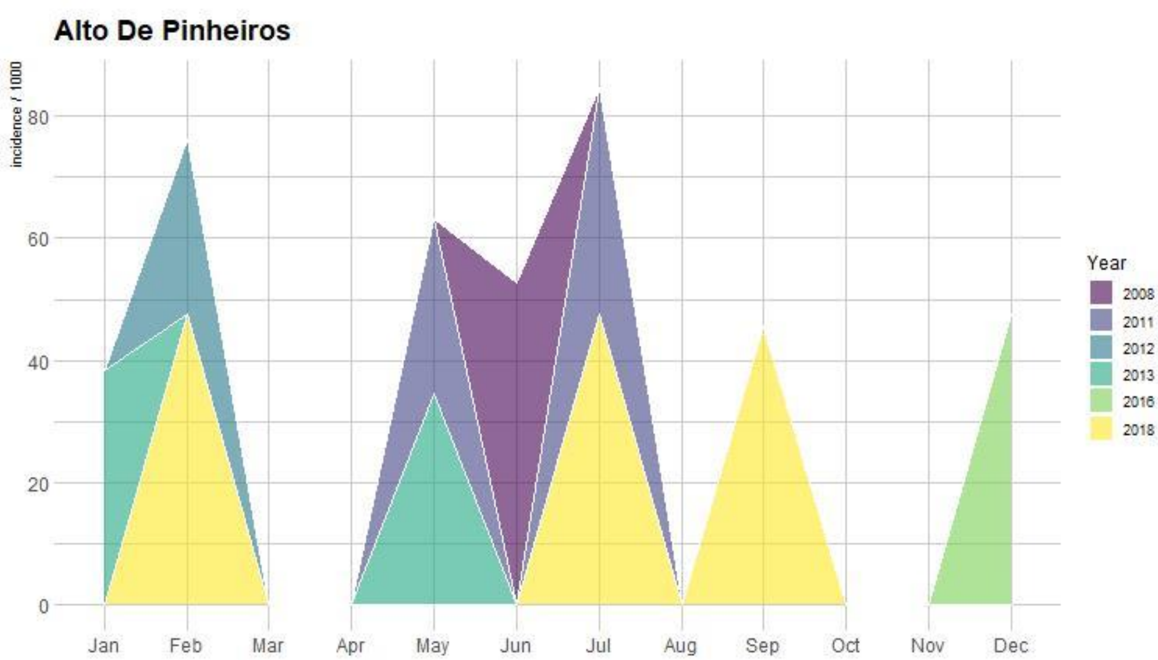
64. Boletim Sífilis 2020 [Internet]. Departamento de Doenças de Condições Crônicas e Infecções Sexualmente Transmissíveis. [cited 2020 Dec 13]. Available from: http://www.aids.gov.br/pt-br/pub/2020/boletim-sifilis-2020

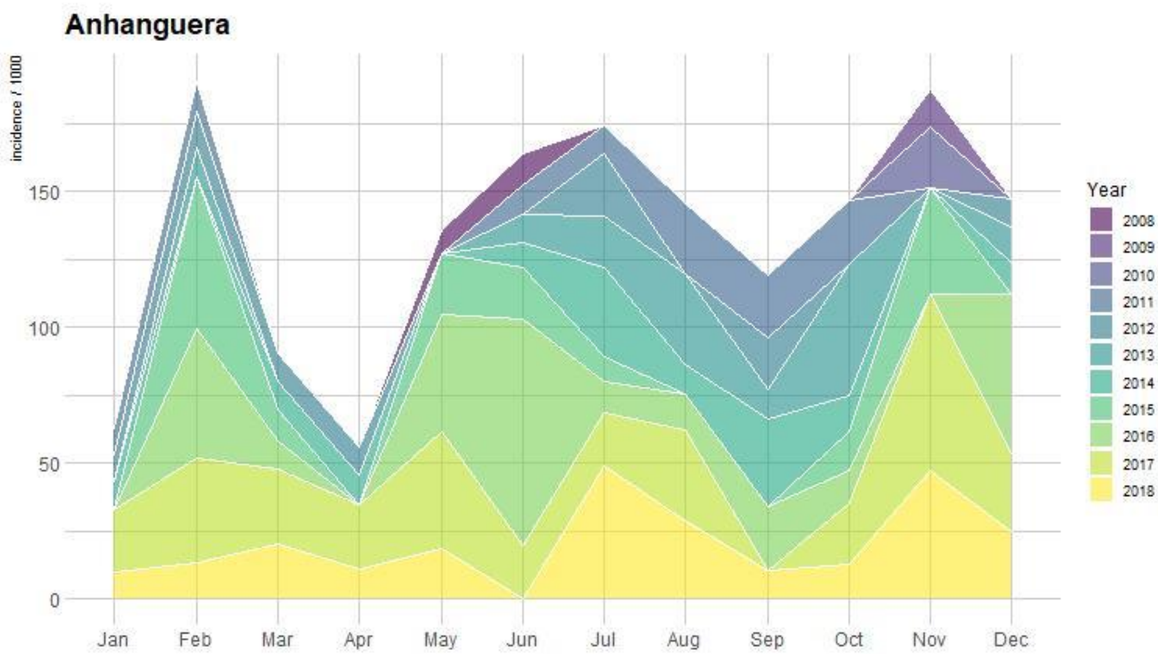
65. Mother-to-child transmission and gestational syphilis: Spatial-temporal epidemiology and demographics in a Brazilian region [Internet]. [cited 2020 Dec 15]. Available from: https://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0007122

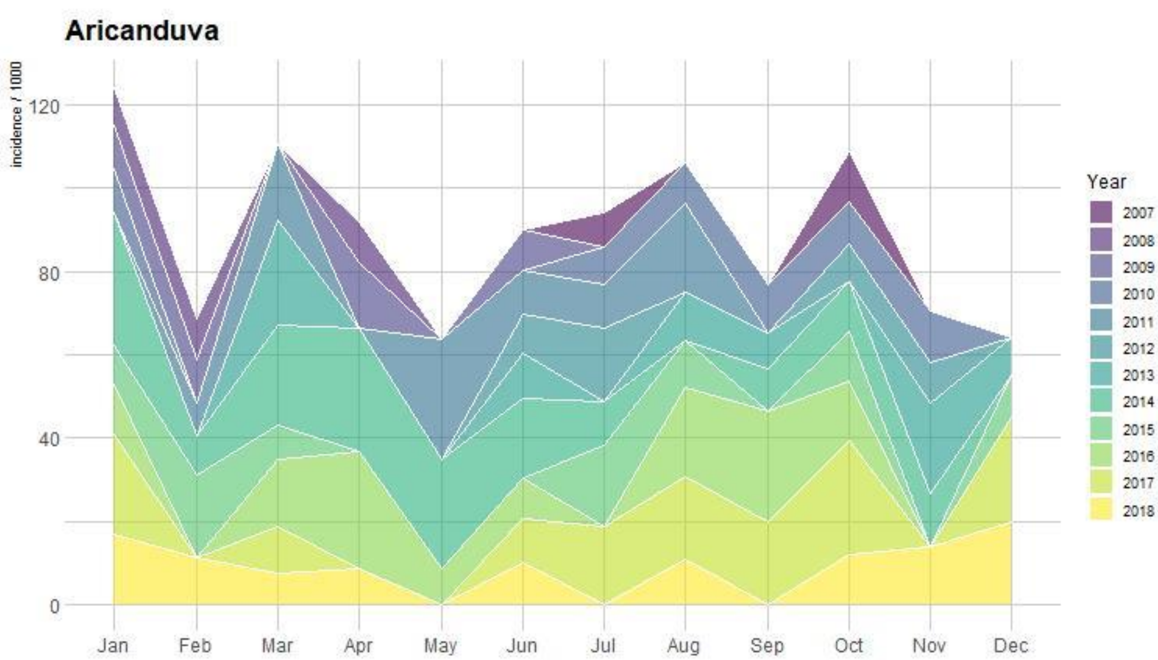
66. VanderWeele TJ. Commentary: Resolutions of the birthweight paradox: competing explanations and analytical insights. Int J Epidemiol. 2014 Oct;43(5):1368–73.

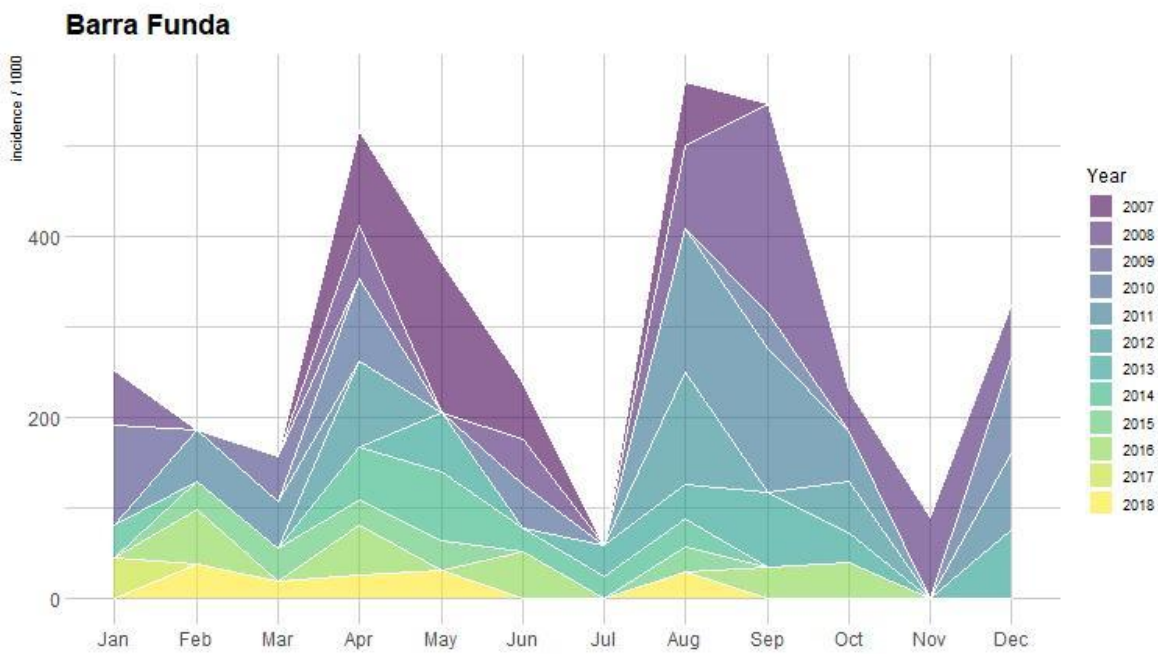
7. Appendix A – Maternal syphilis Incidence over time & district

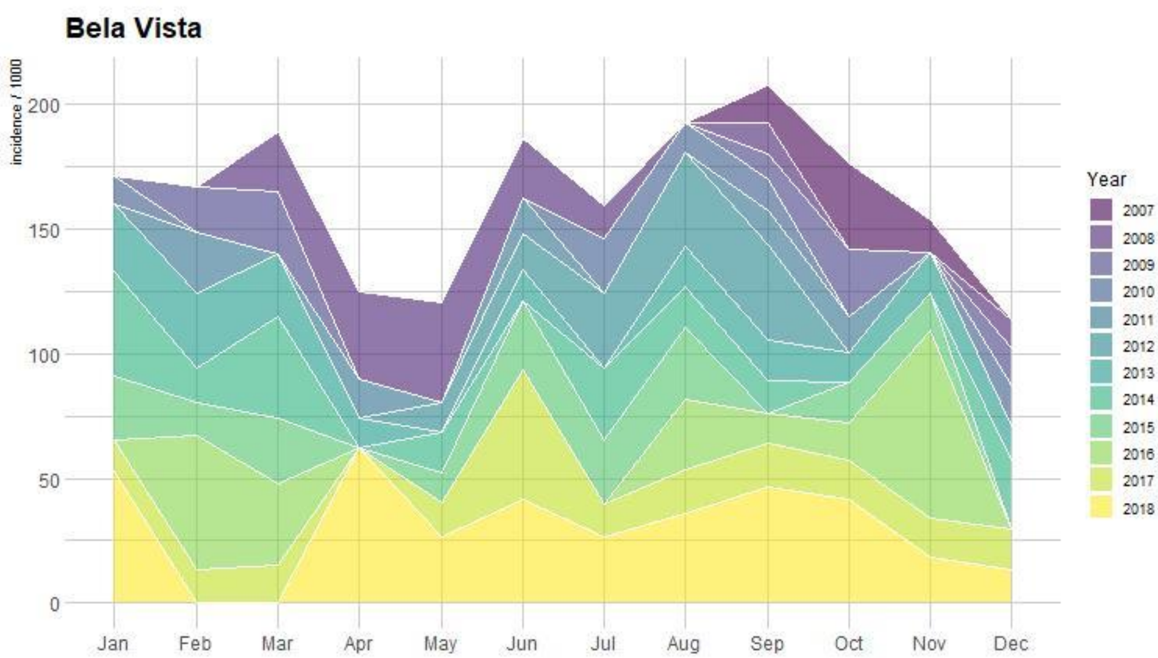


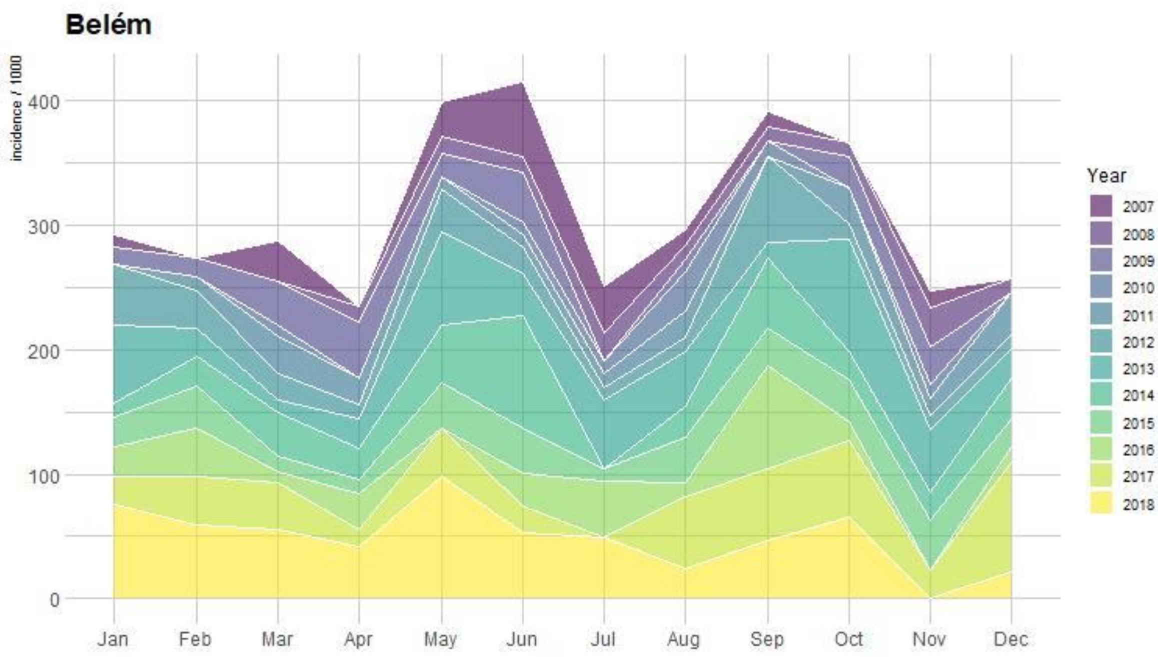


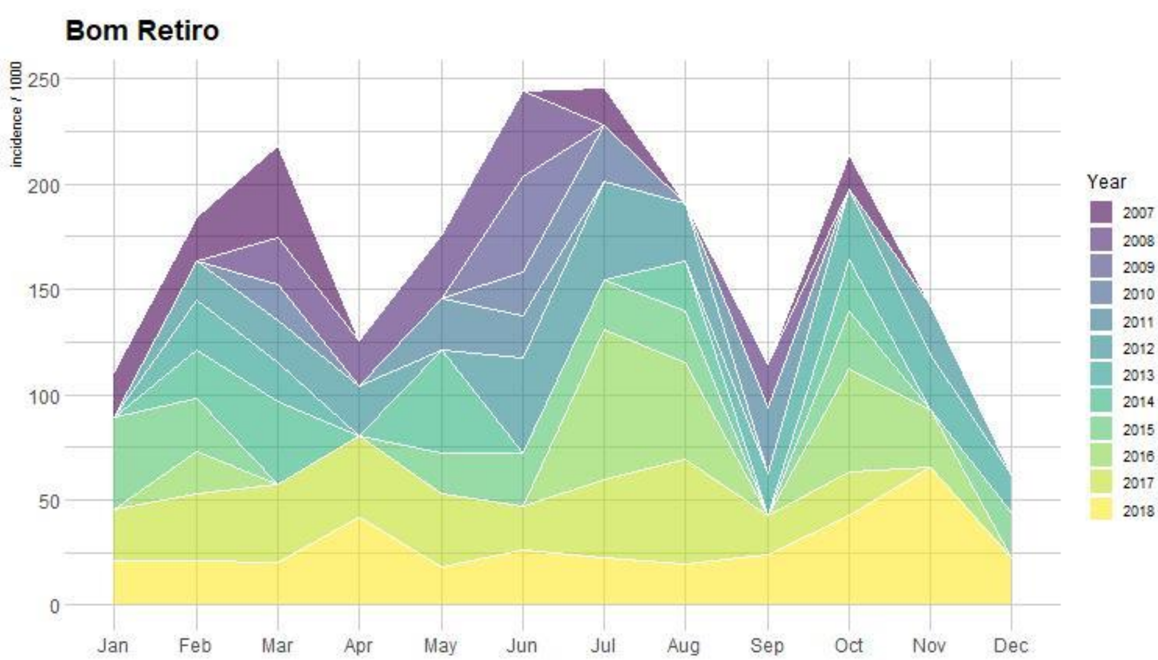

Anhanguera
incidence / 1000
0
50
100
150
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

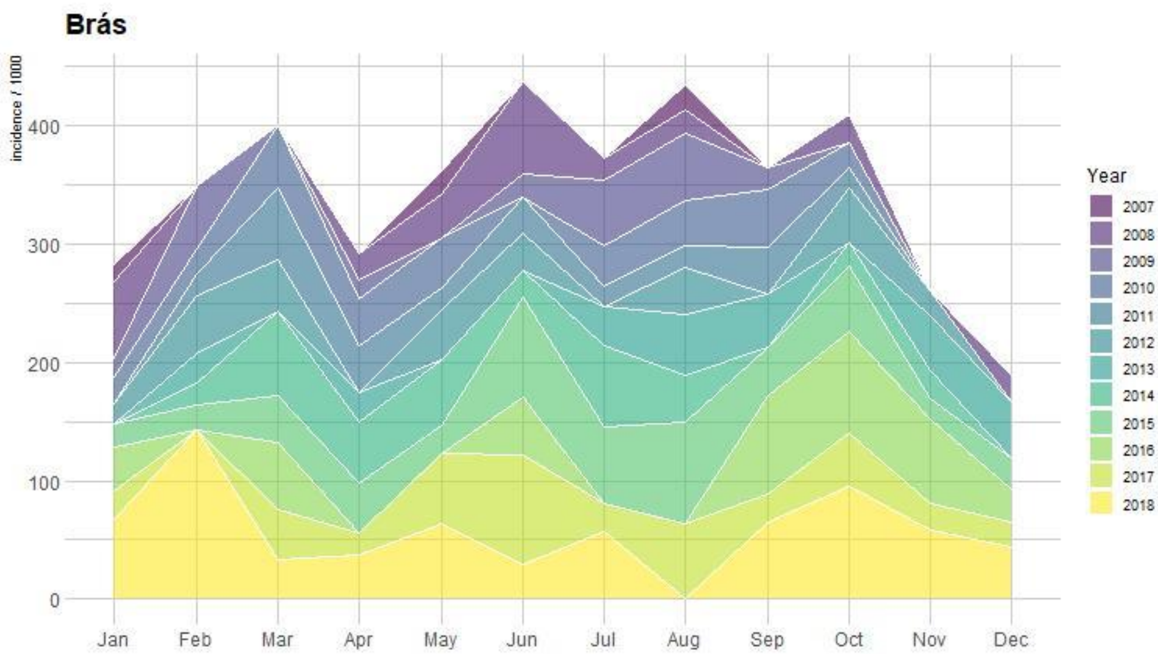

Aricanduva
incidence / 1000
0
40
80
120
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

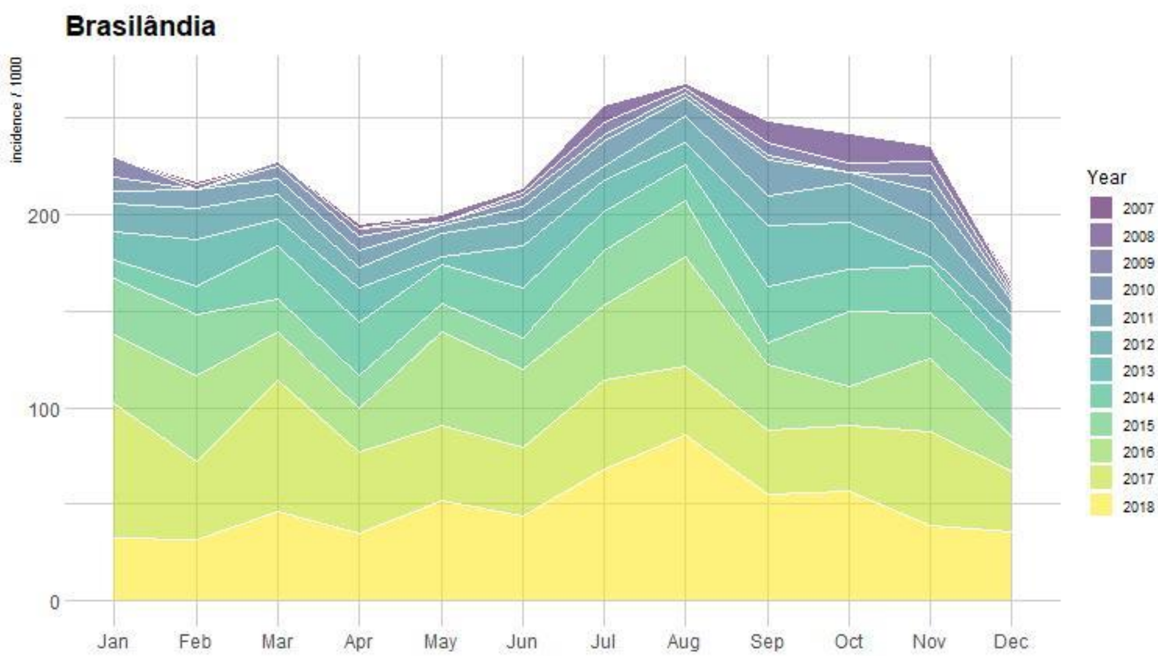

Barra Funda
incidence / 1000
0
200
400
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

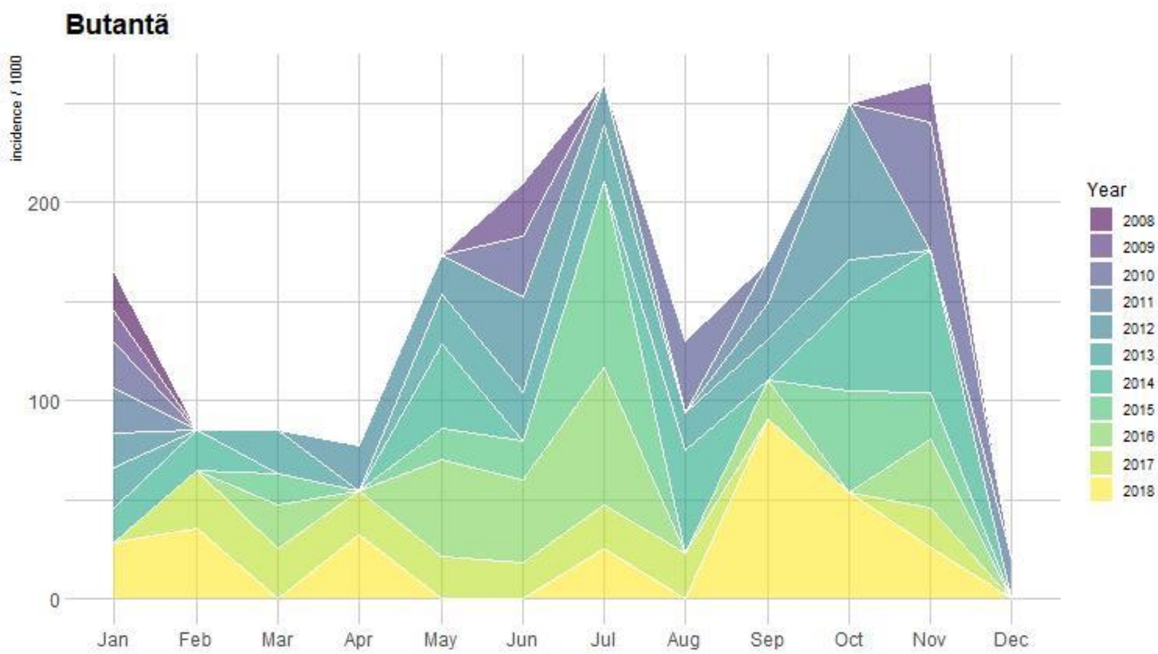

Bela Vista
incidence / 1000
0
50
100
150
200
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

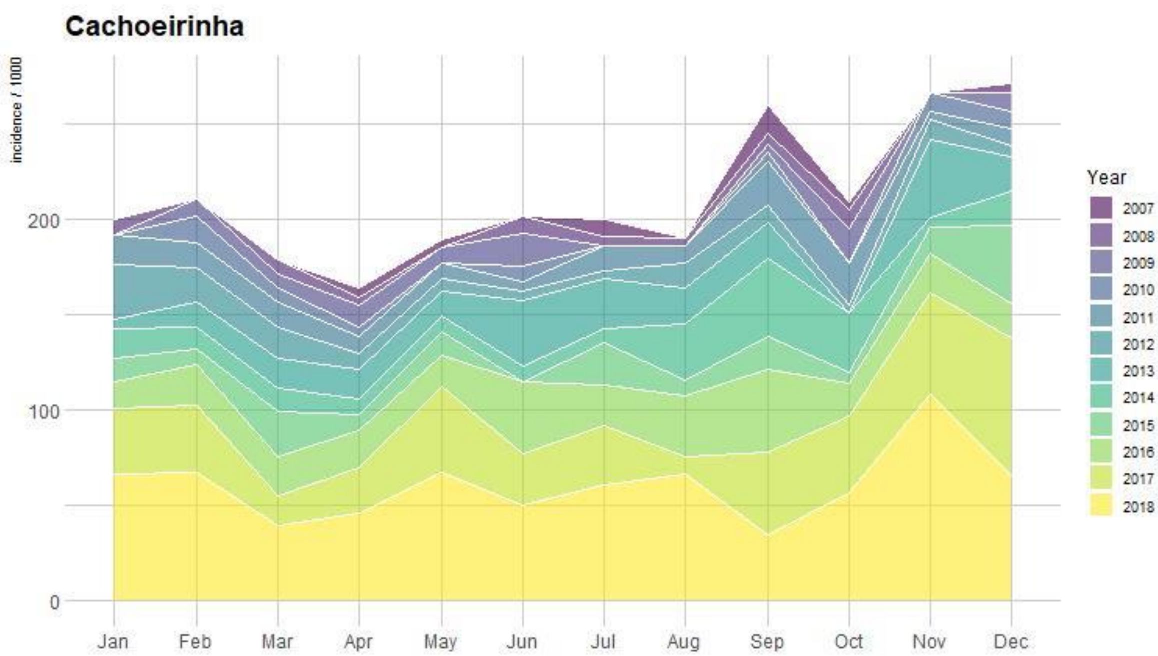

Belém
incidence / 1000
0
100
200
300
400
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

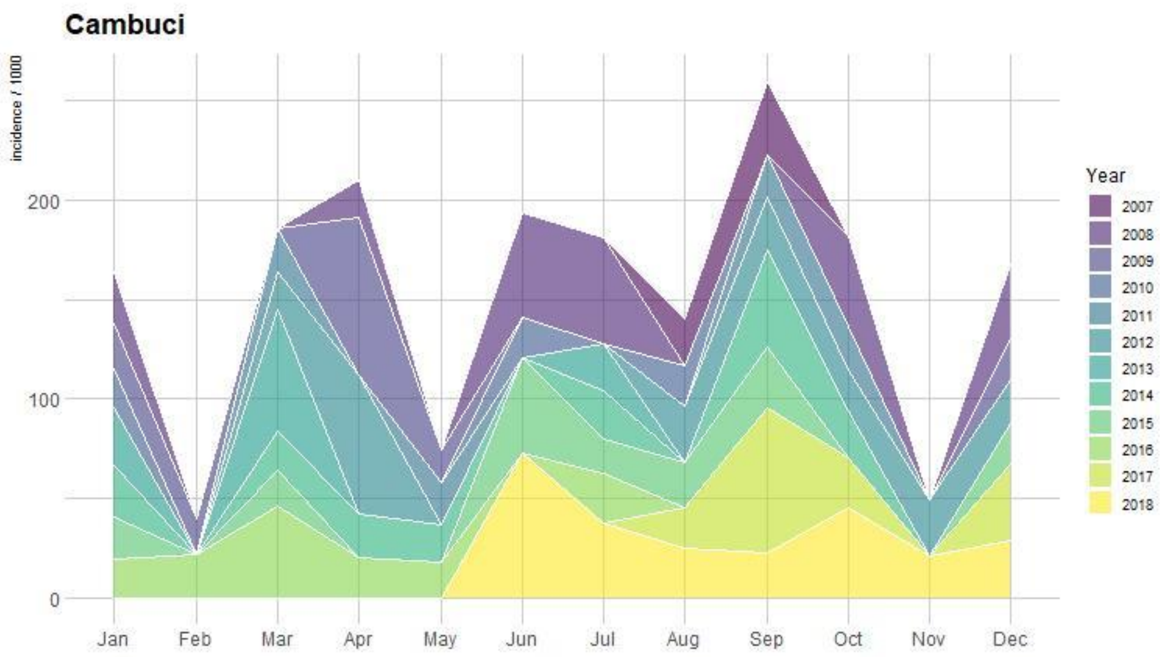

Bom Retiro
incidence / 1000
0
50
100
150
200
250
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

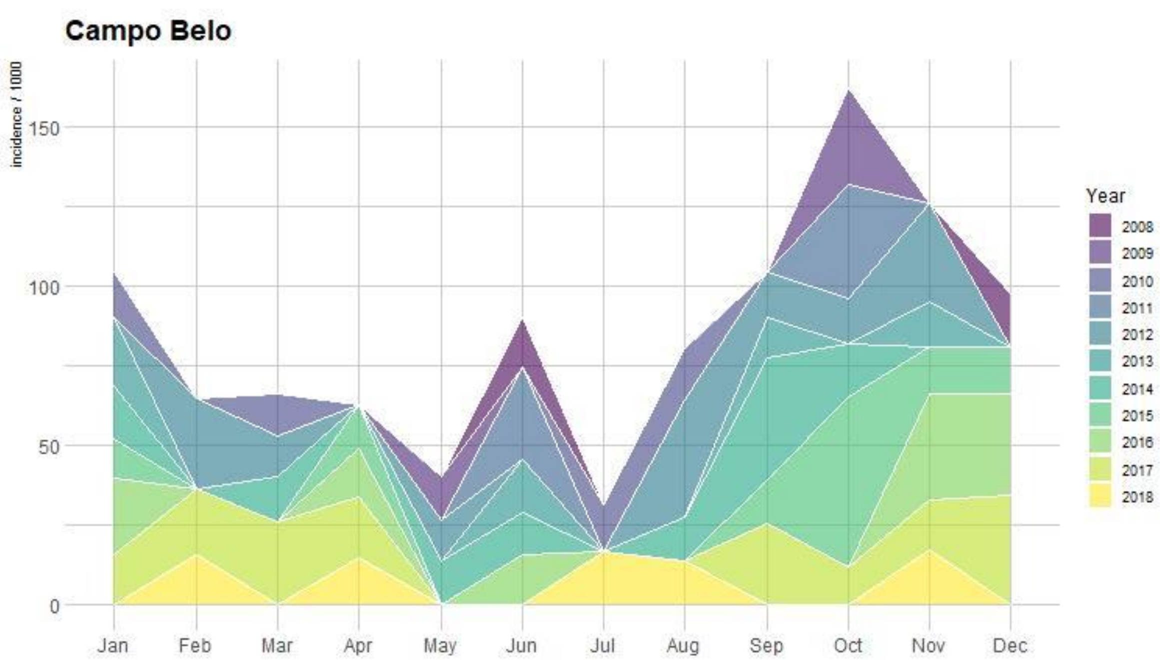

Brás
incidence / 1000
0
100
200
300
400
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

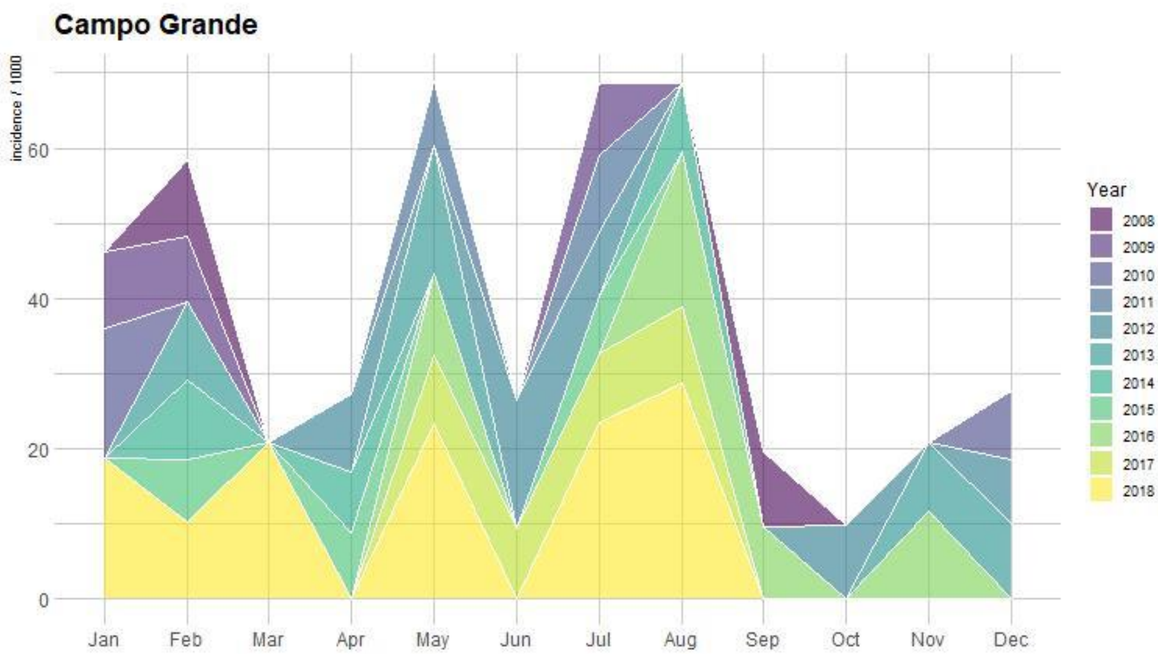

Brasilândia
incidence / 1000
0
100
200
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

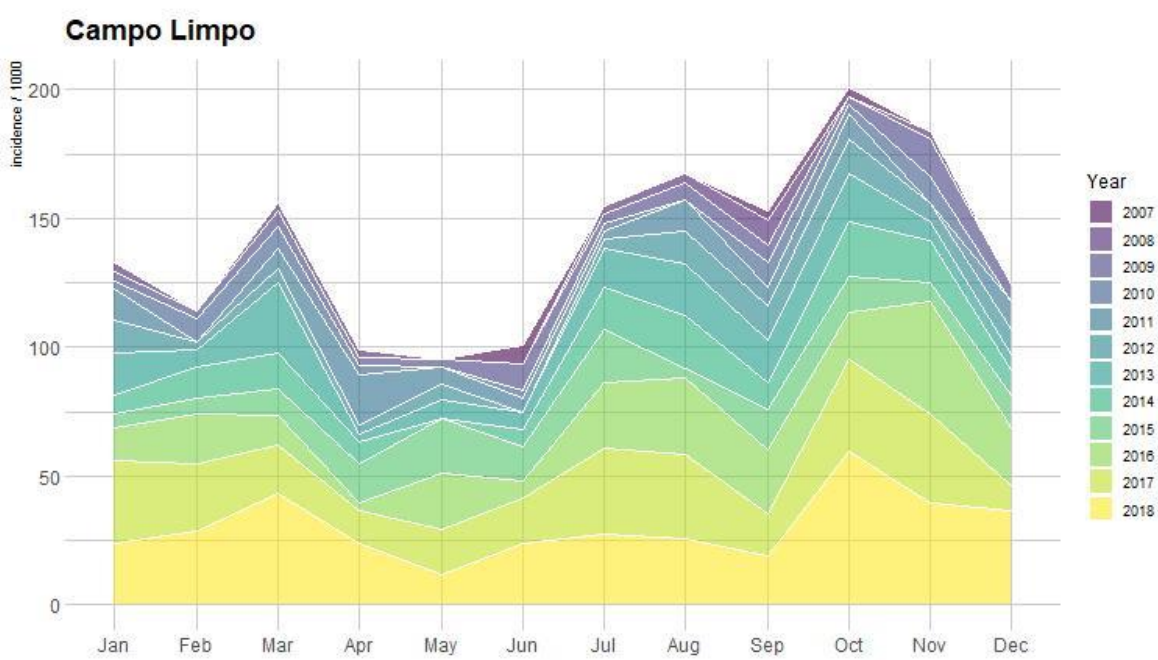

Butantã
incidence / 1000
0
100
200
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

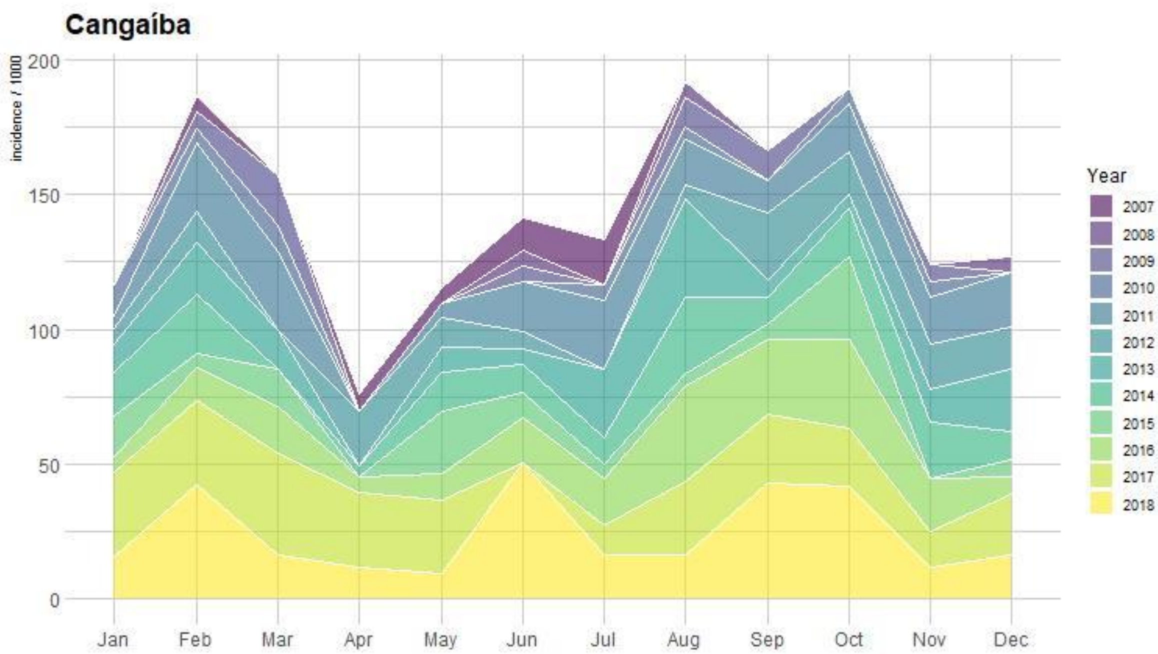

Cachoeirinha
incidence / 1000
0
100
200
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

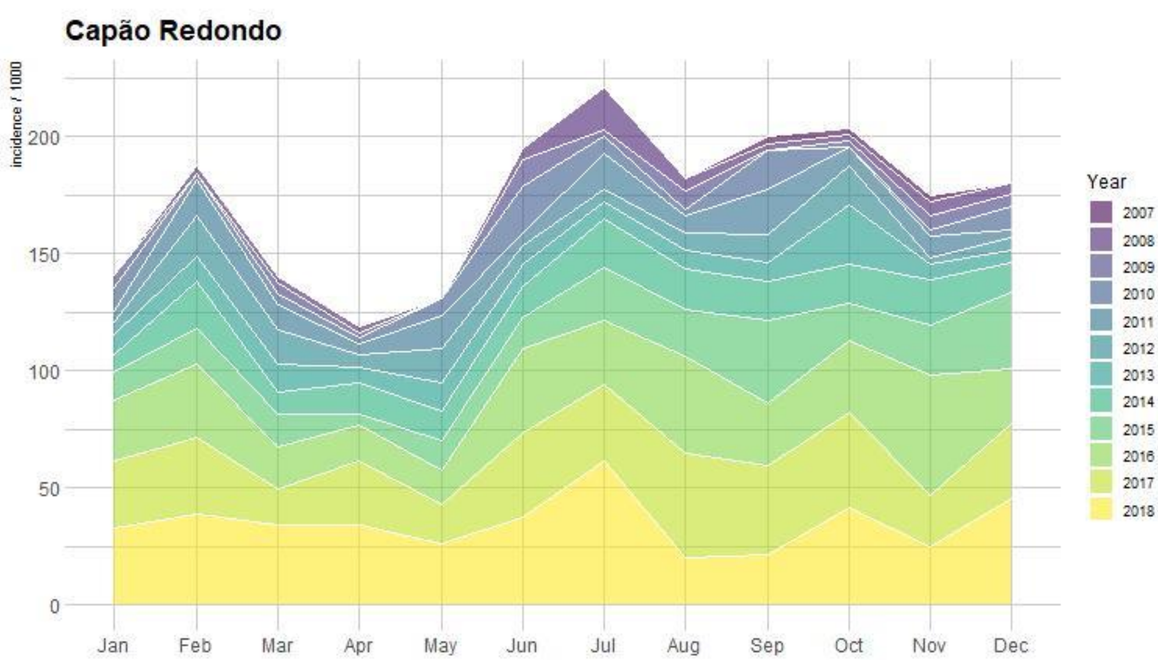

Cambuci
incidence / 1000
0
100
200
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

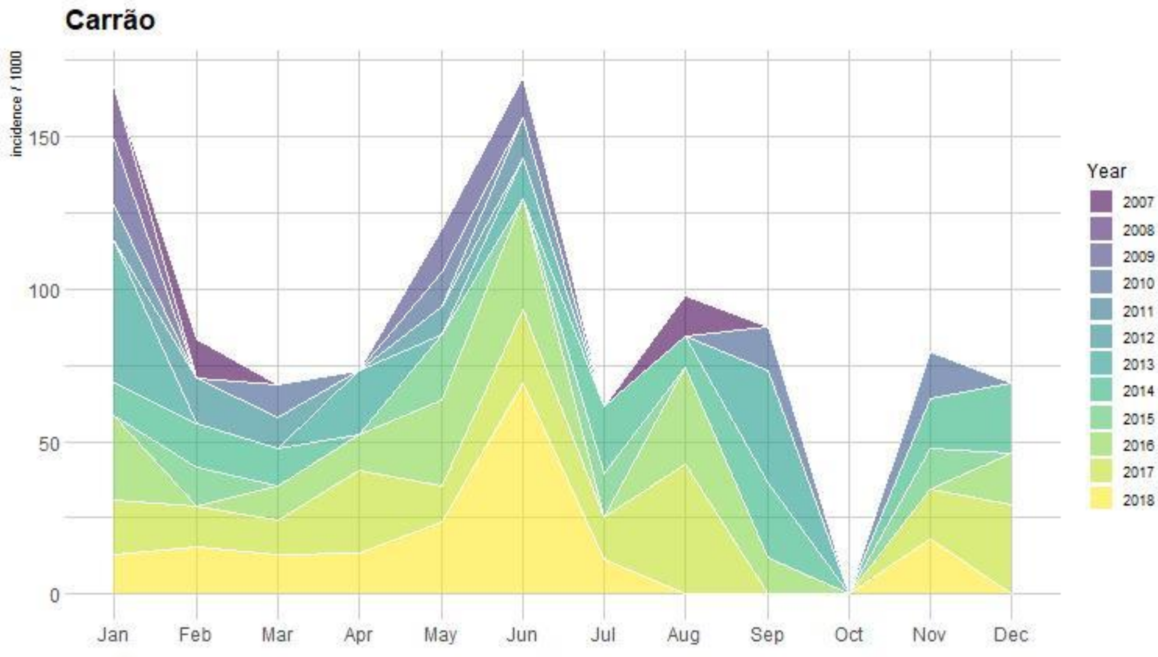

Campo Belo
incidence / 1000
0
50
100
150
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

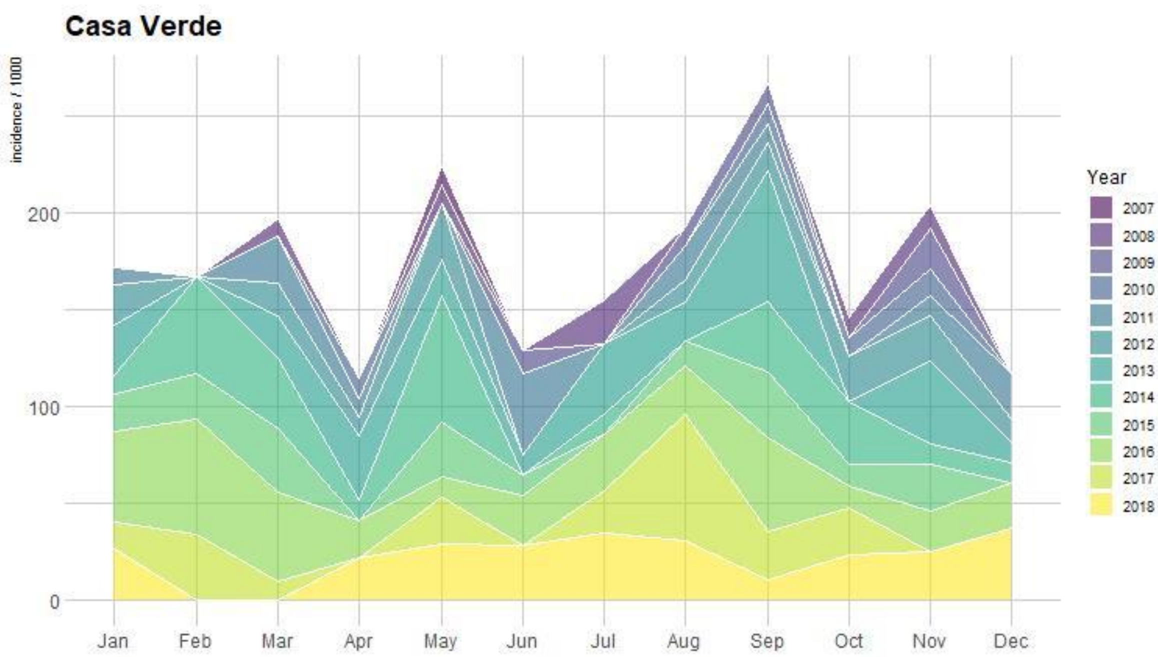

Campo Grande
incidence / 1000
0
20
40
60
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

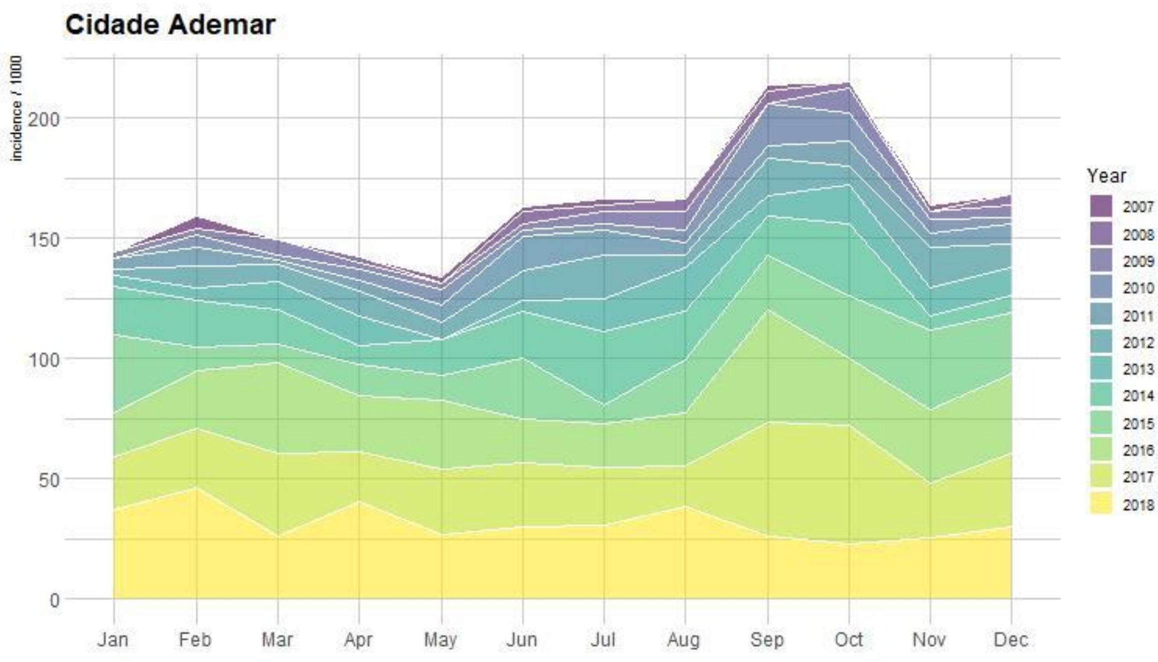

Campo Limpo
incidence / 1000
0
50
100
150
200
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

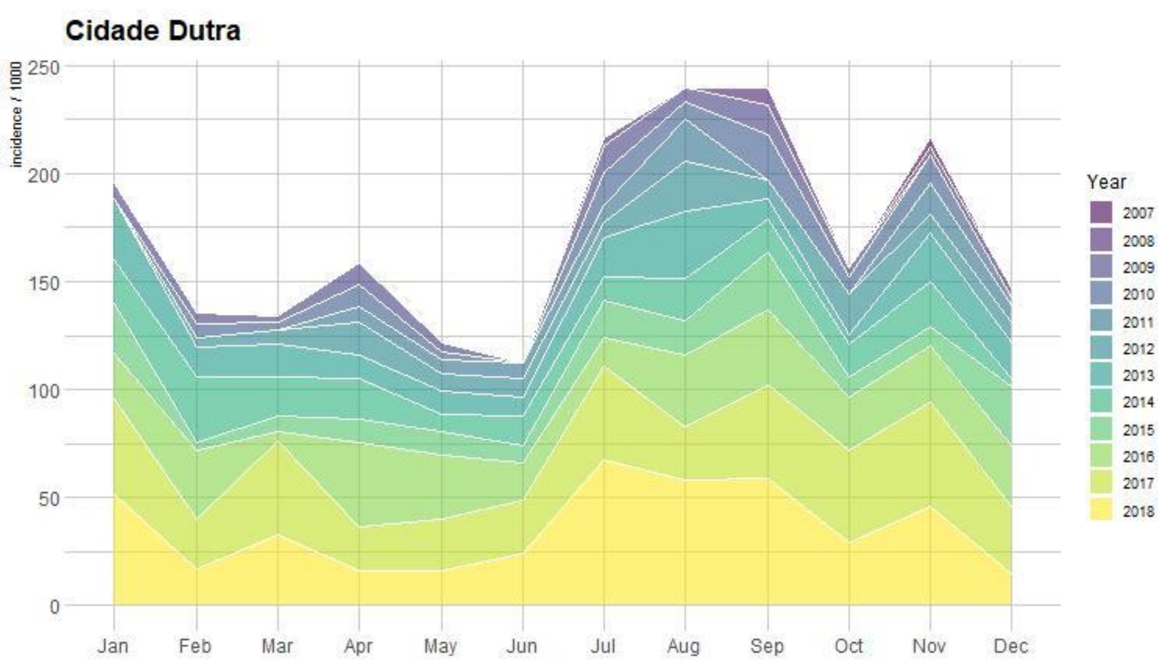

Cangaíba
incidence / 1000
200
150
100
50
0
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

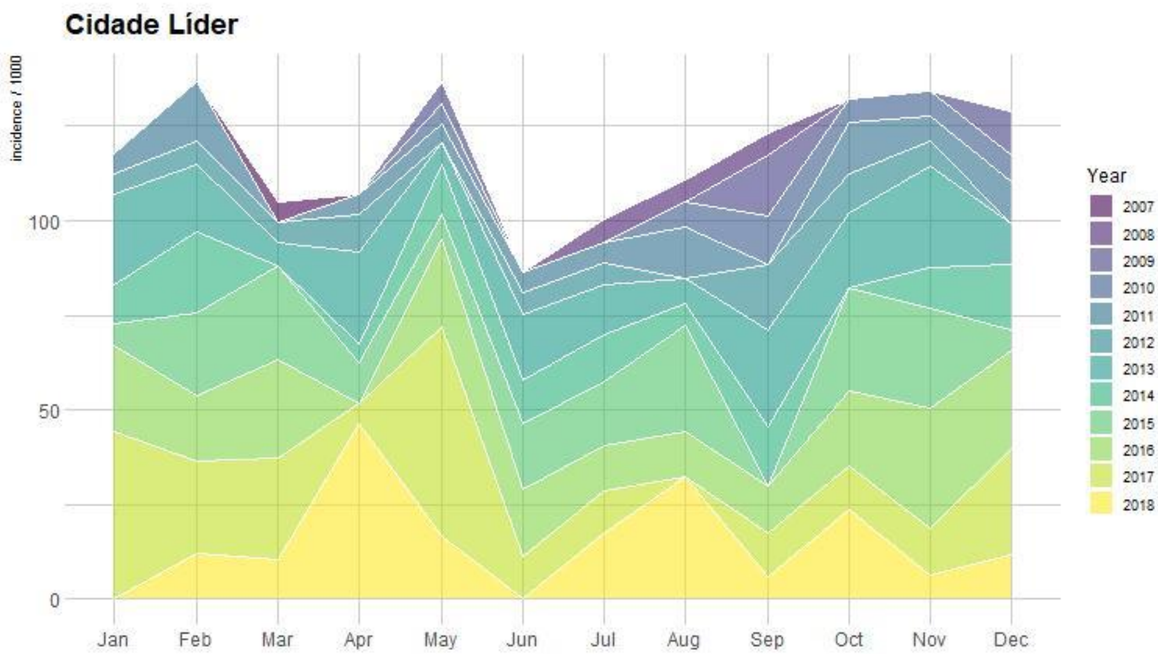

Capão Redondo
incidence / 1000
200
150
100
50
0
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

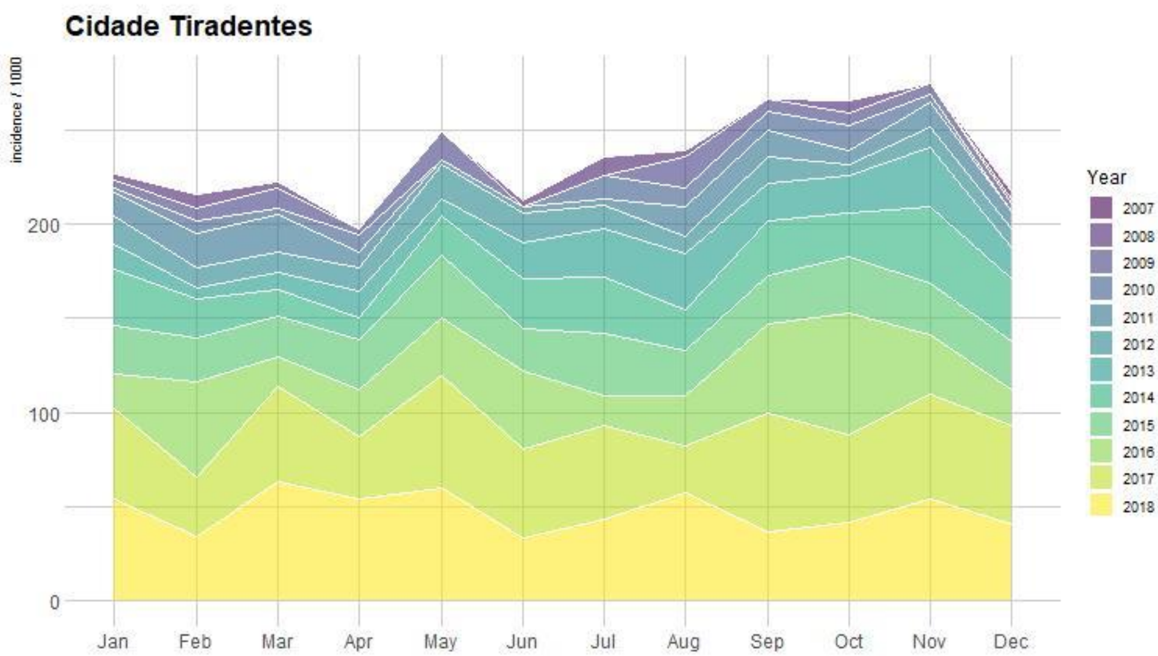

Carrão
incidence / 1000
0
50
100
150
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

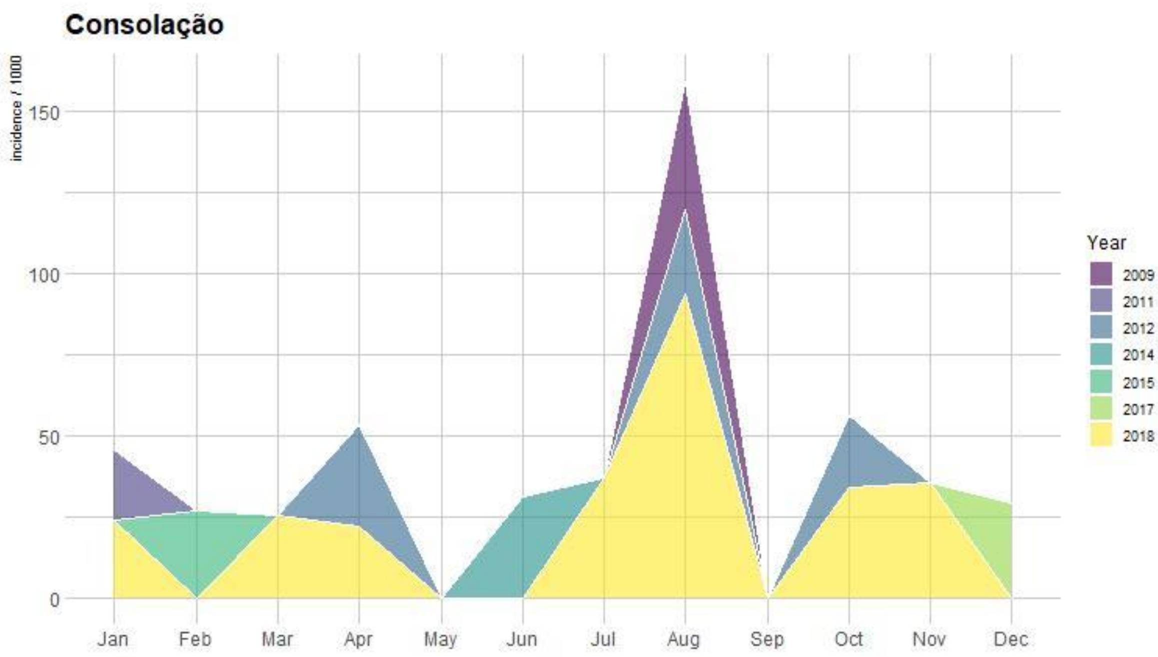

Casa Verde
incidence / 1000
0
100
200
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

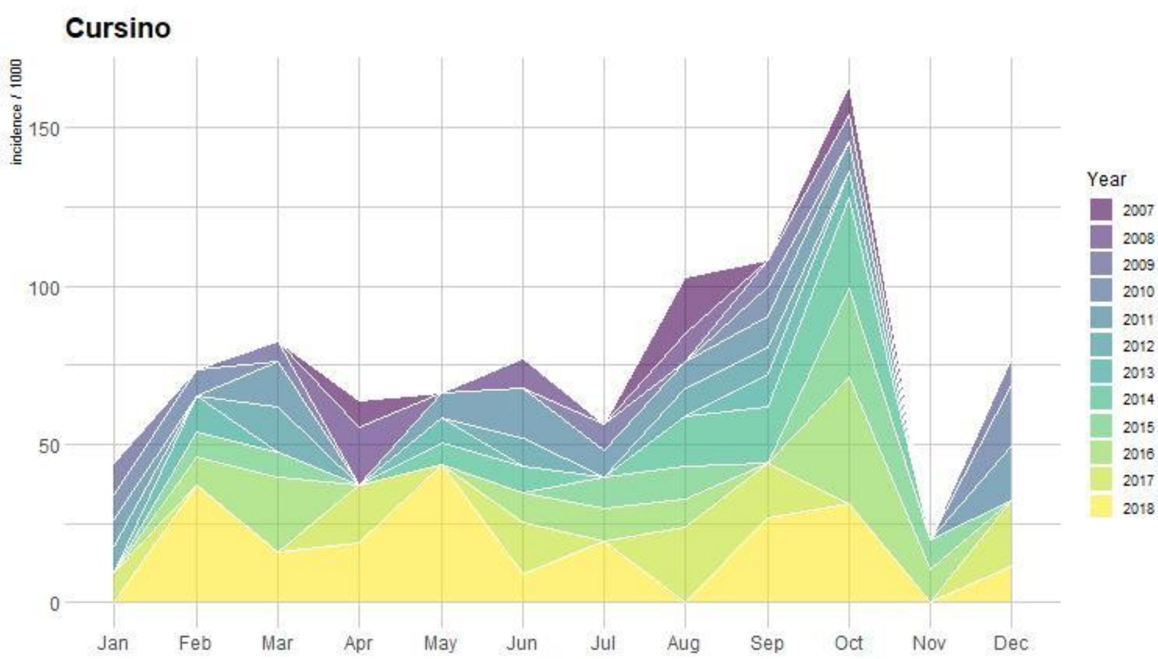

Cidade Ademar
incidence / 1000
0
50
100
150
200
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

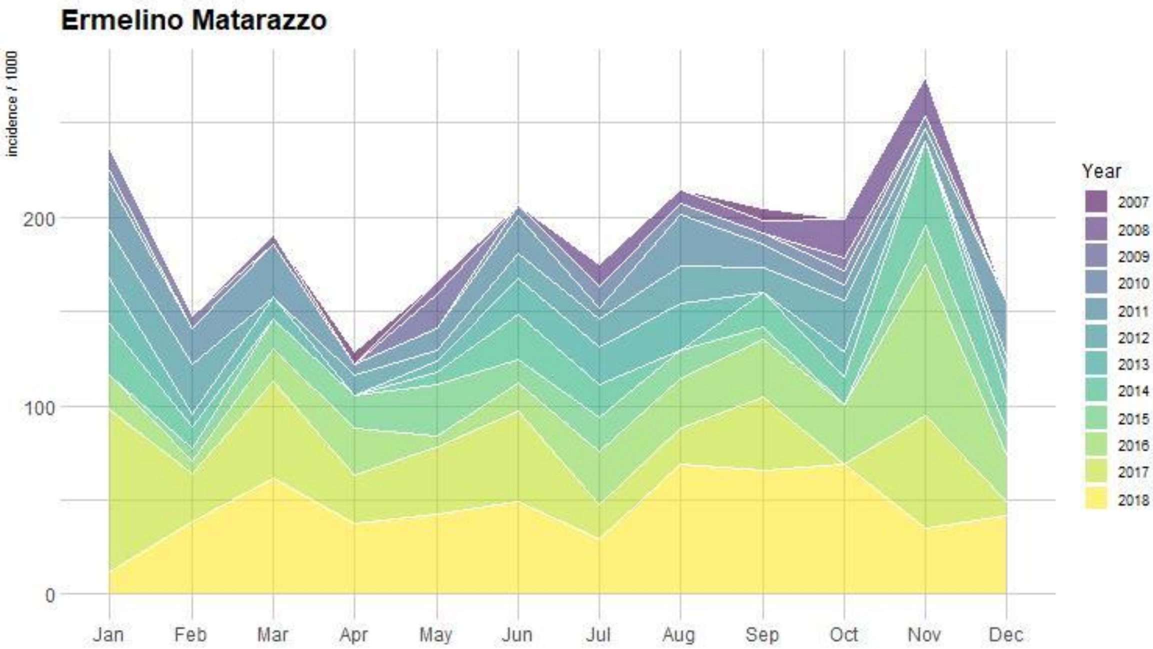

Cidade Dutra
incidence / 1000
0
50
100
150
200
250
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

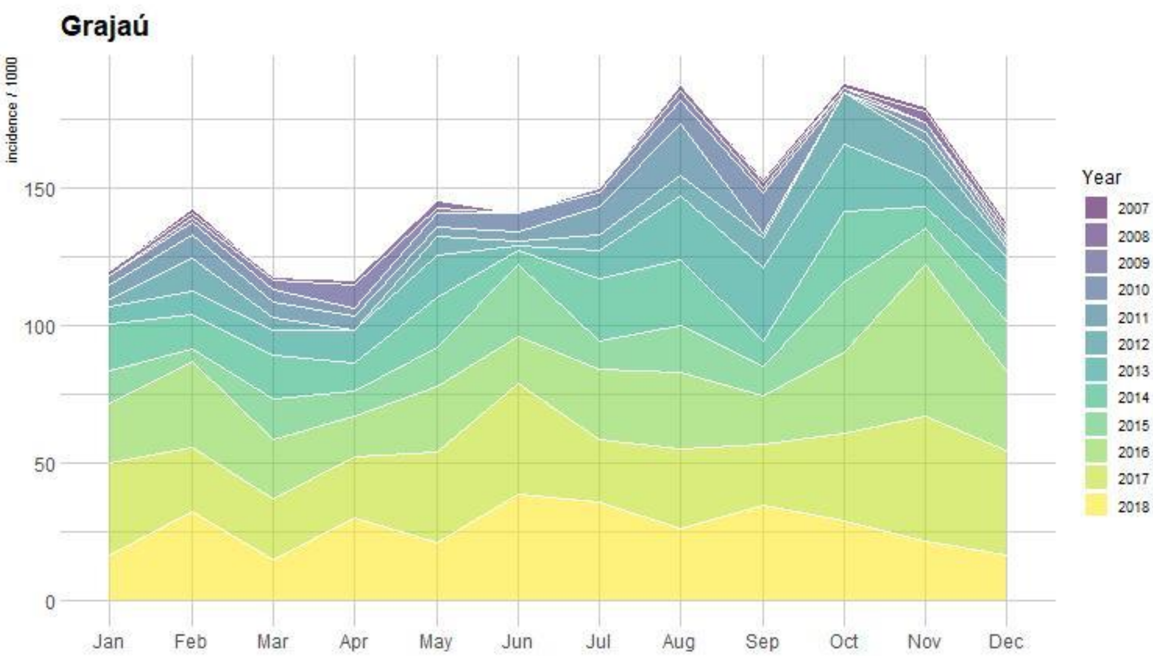

Cidade Líder
incidence / 1000
0
50
100
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

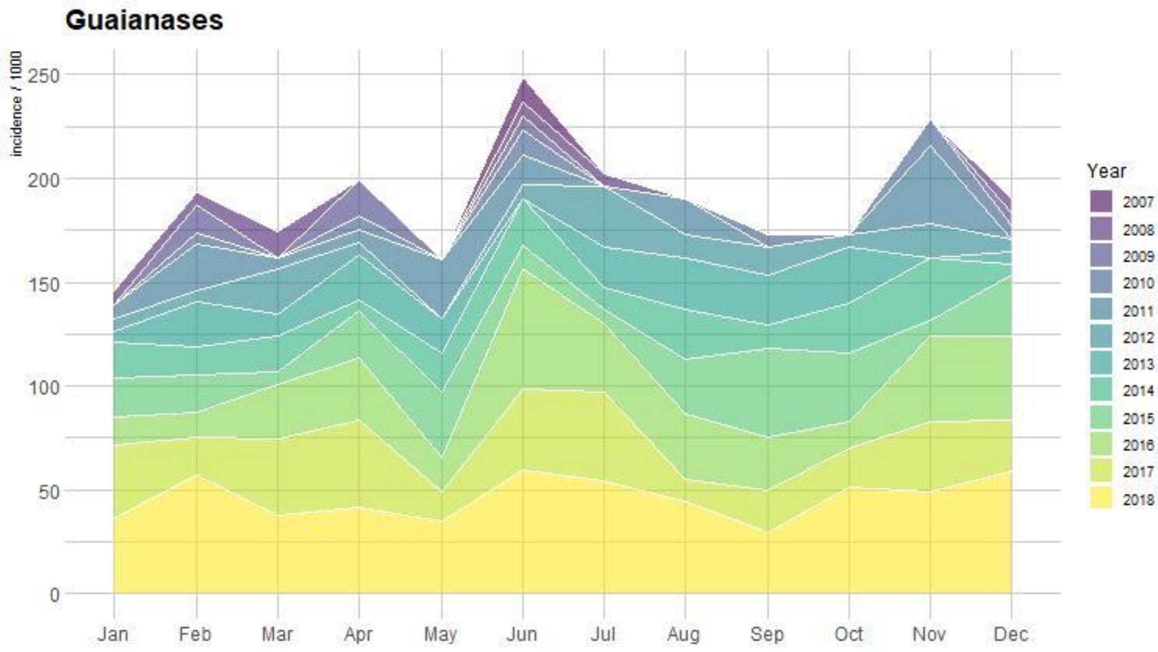

Cidade Tiradentes
incidence / 1000
0
100
200
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

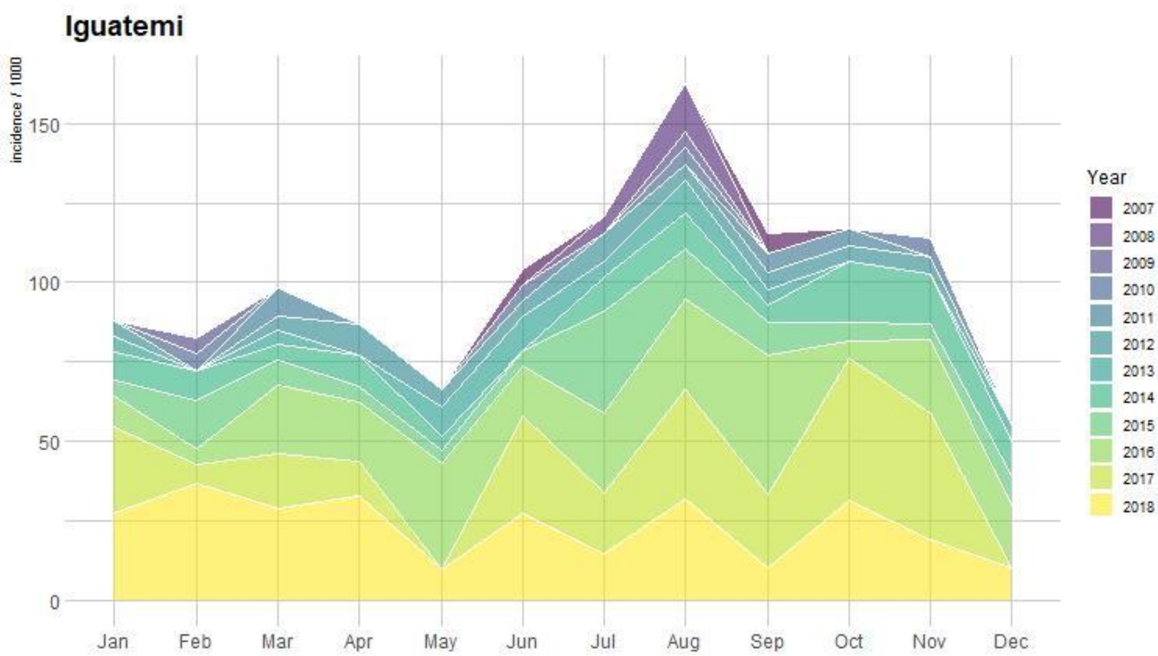

Consolação
incidence / 1000
0
50
100
150
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2009
2011
2012
2014
2015
2017
2018

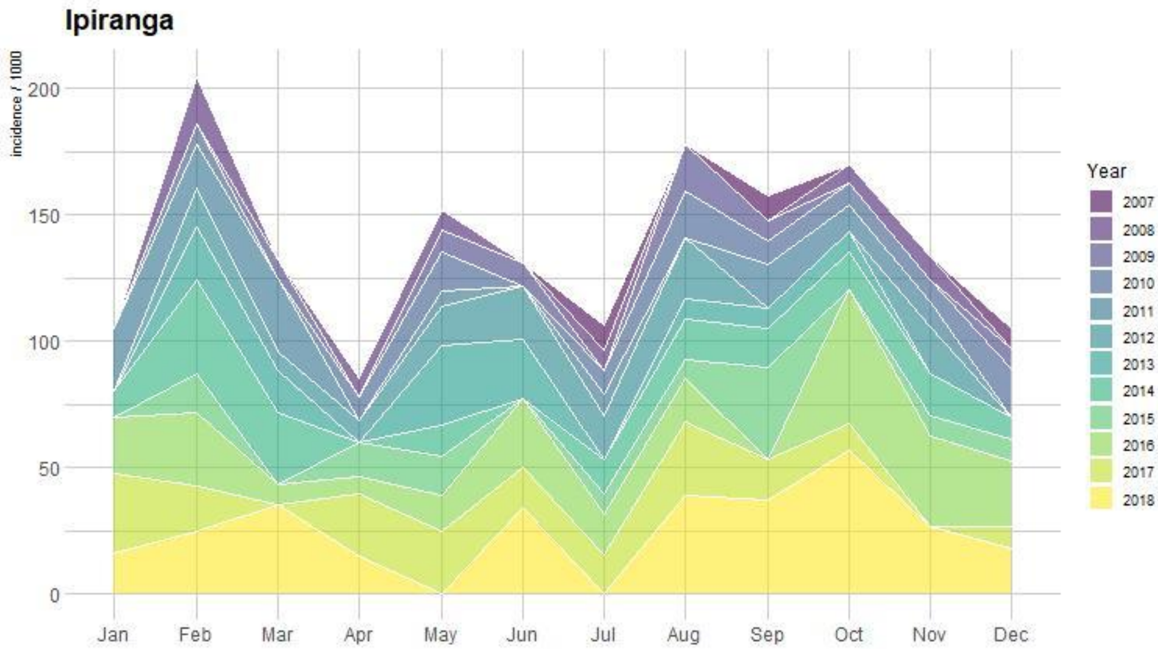

Cursino
incidence / 1000
0
50
100
150
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

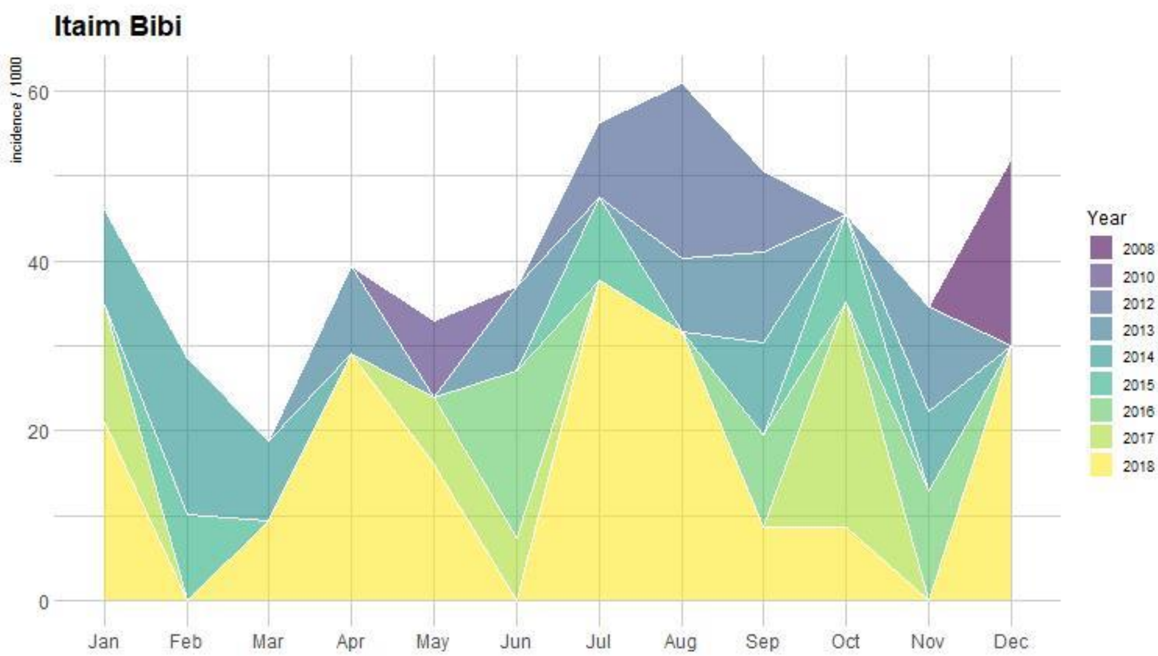

Ermelino Matarazzo
incidence / 1000
0
100
200
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

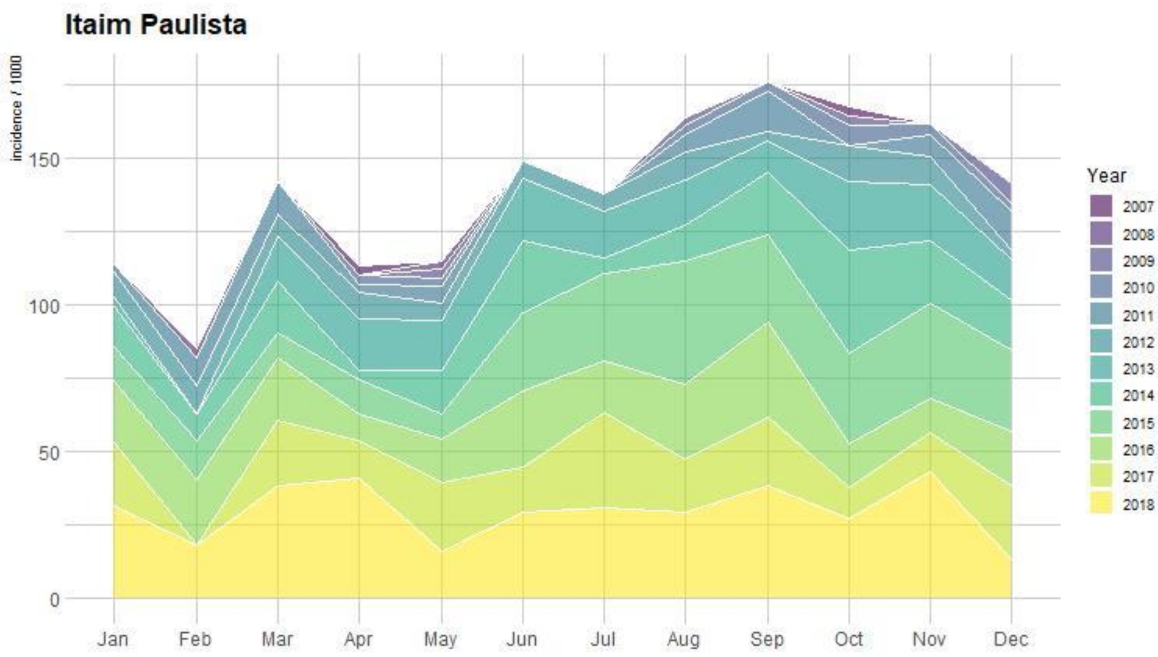

Grajaú
incidence / 1000
0
50
100
150
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

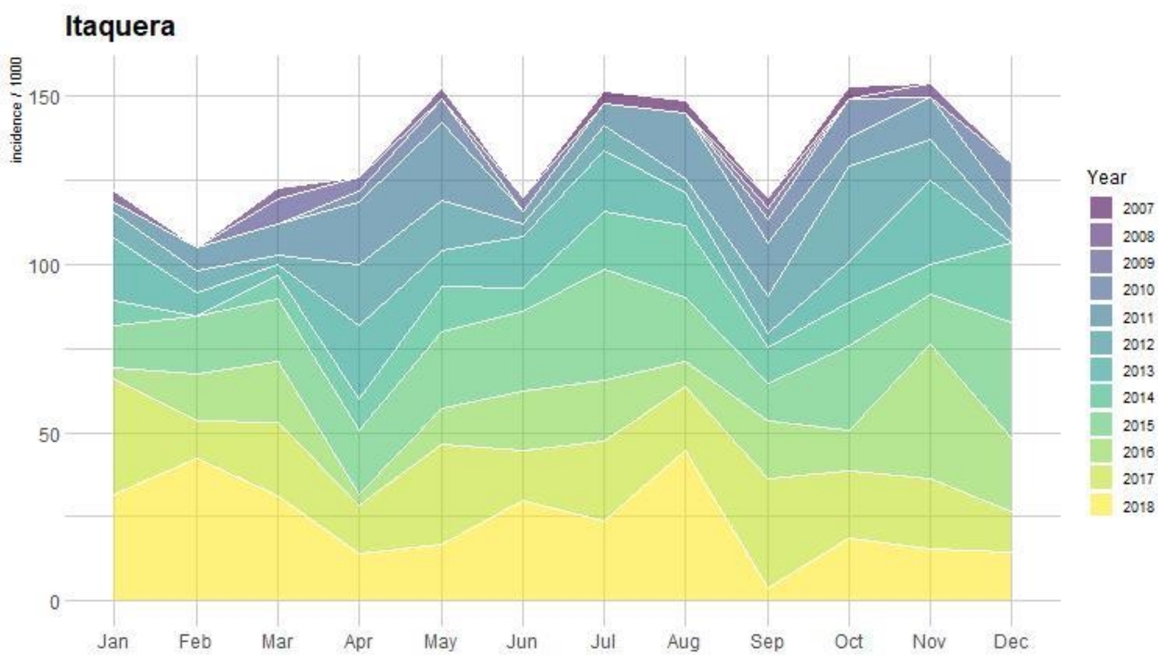

Guaianases
incidence / 1000
250
200
150
100
50
0
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

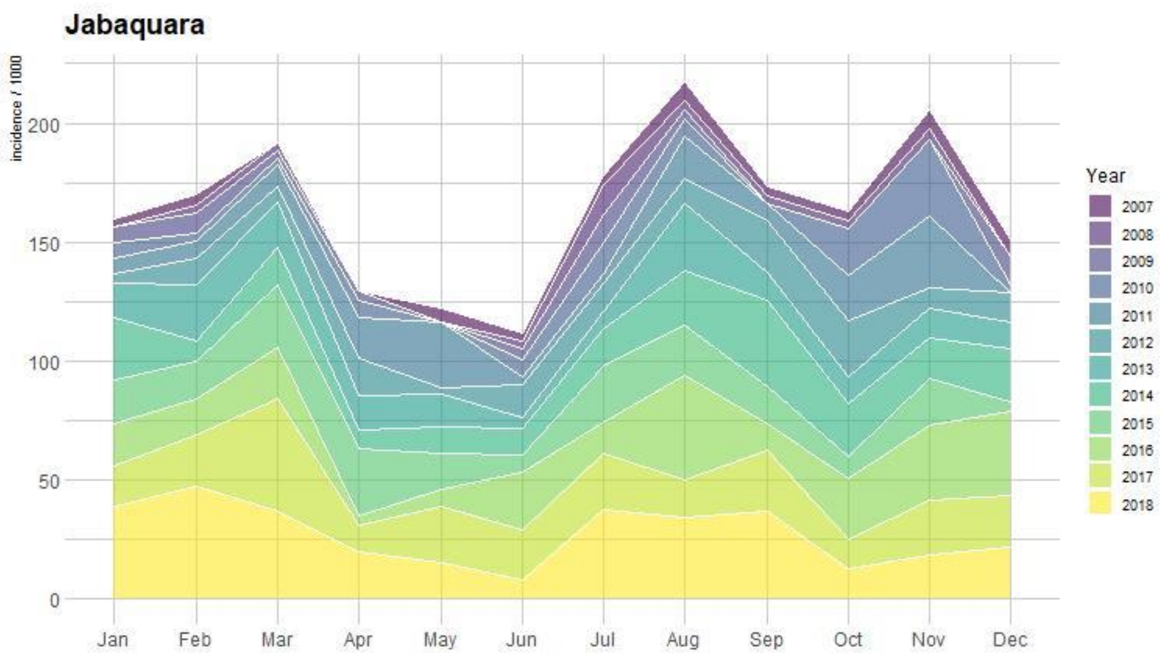

Iguatemi
incidence / 1000
150
100
50
0
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

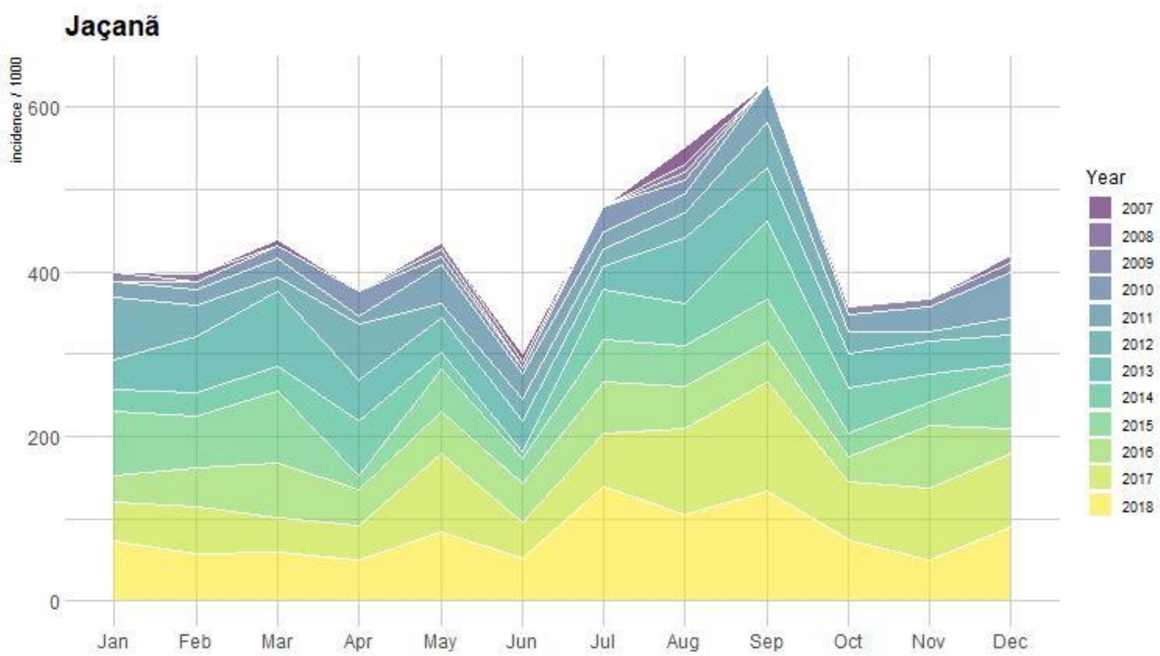

Ipiranga
incidence / 1000
200
150
100
50
0
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

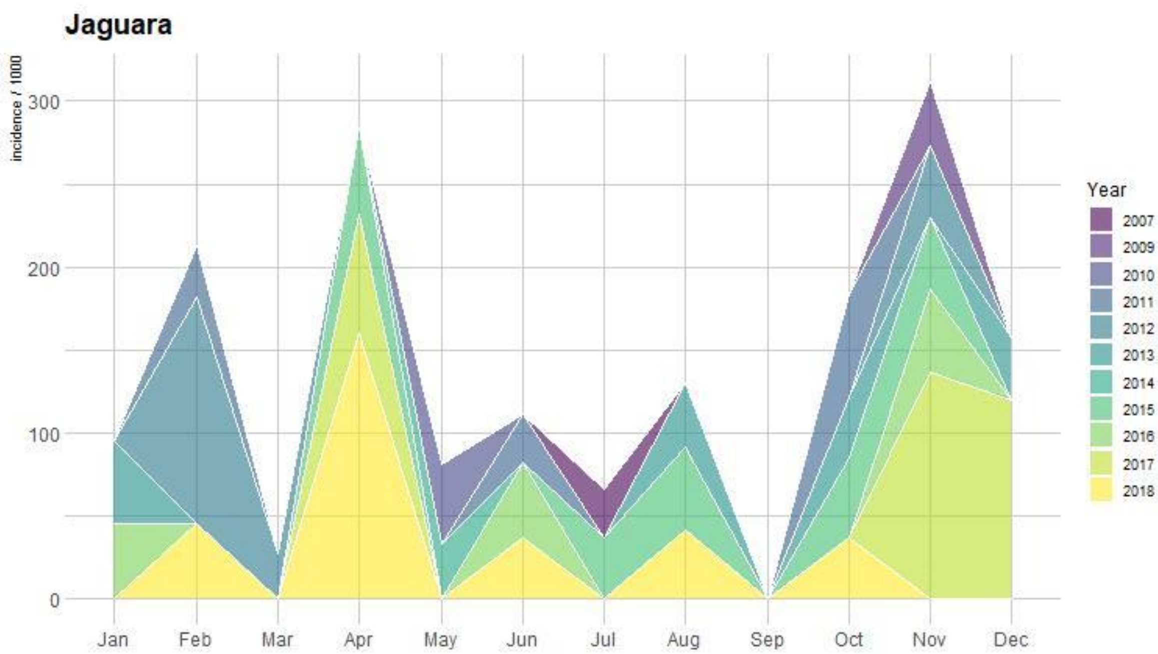

Itaim Bibi
incidence / 1000
60
40
20
0
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2008
2010
2012
2013
2014
2015
2016
2017
2018

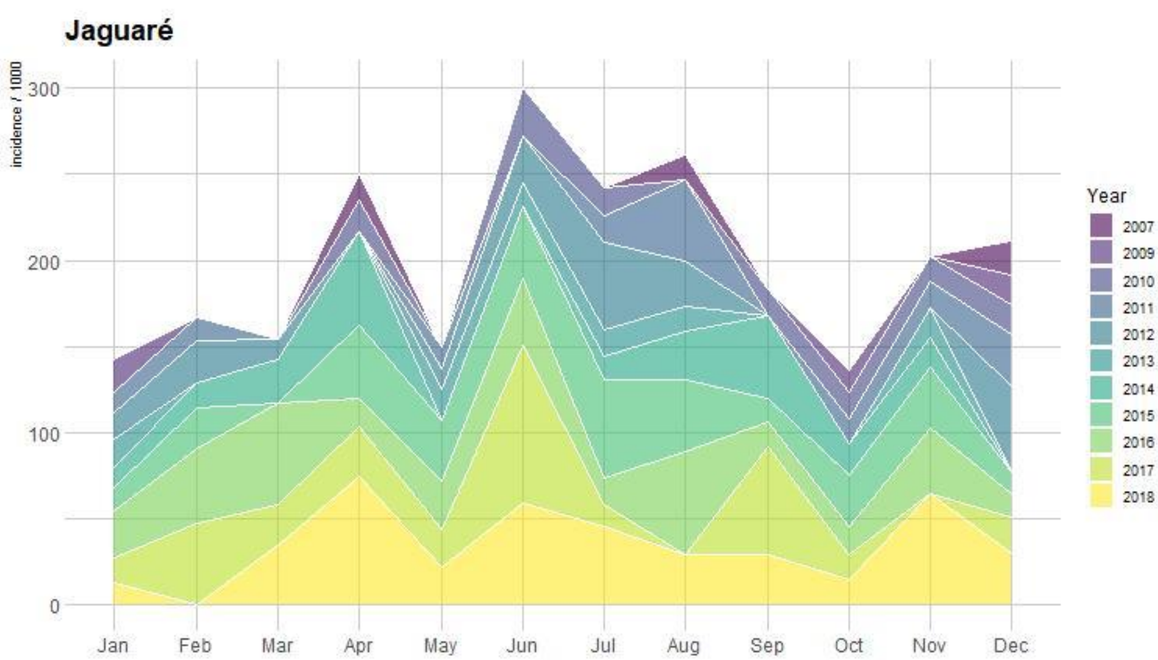

Itaim Paulista
incidence / 1000
0
50
100
150
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

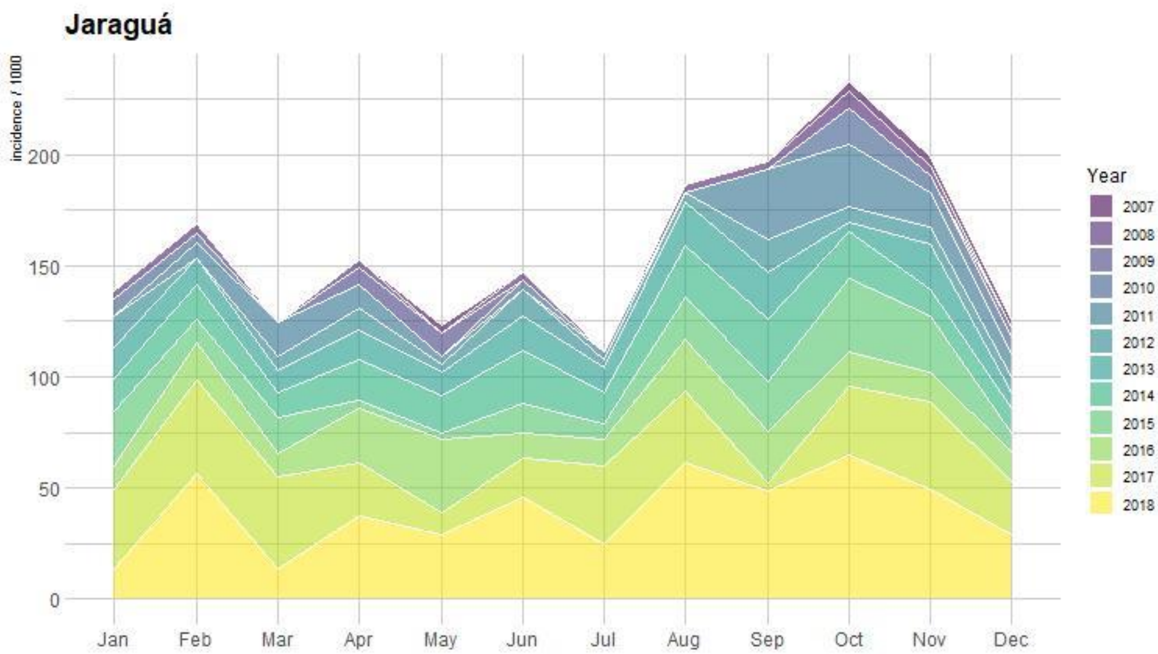

Itaquera
incidence / 1000
0
50
100
150
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

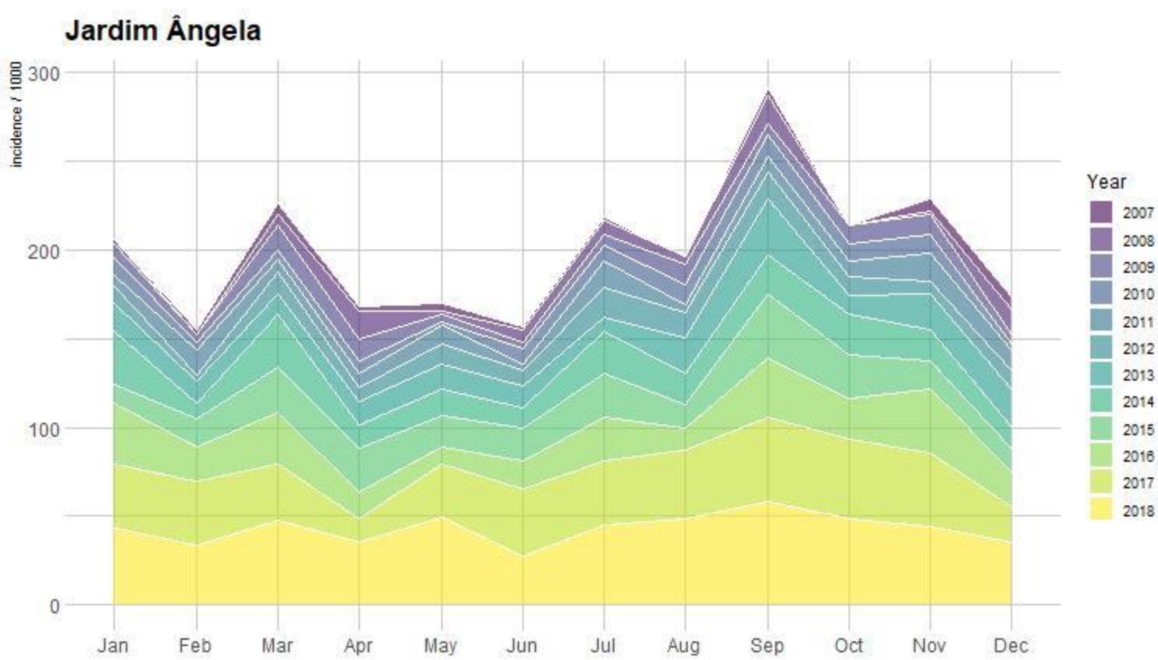

Jabaquara
incidence / 1000
0
50
100
150
200
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

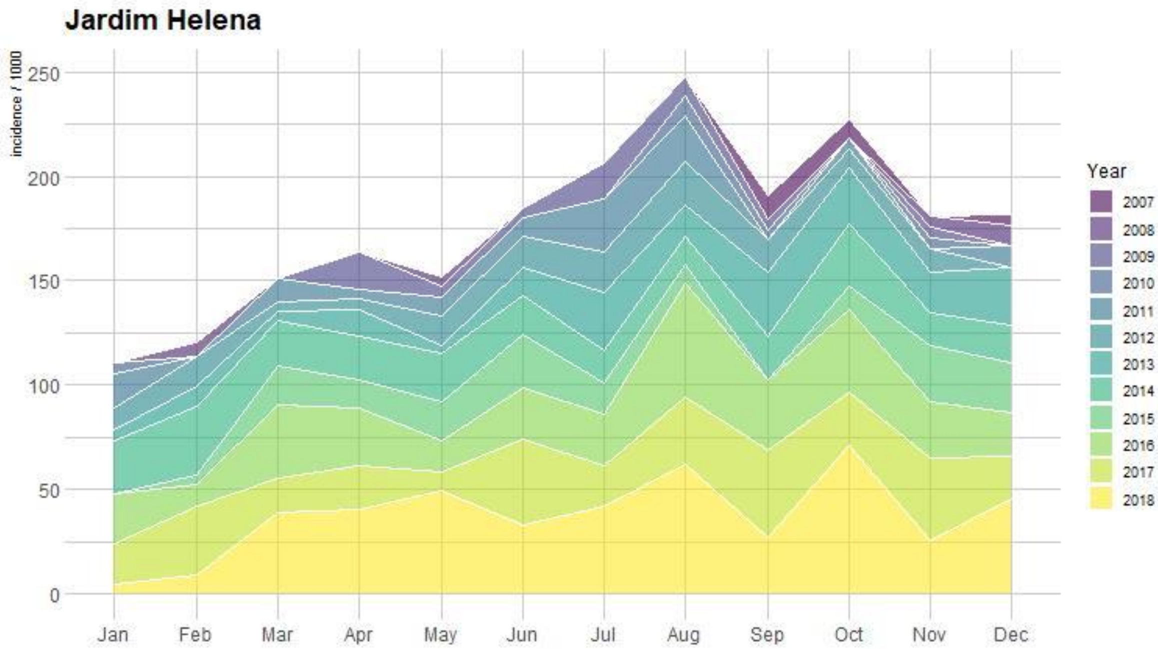

Jaçanã
incidence / 1000
0
200
400
600
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

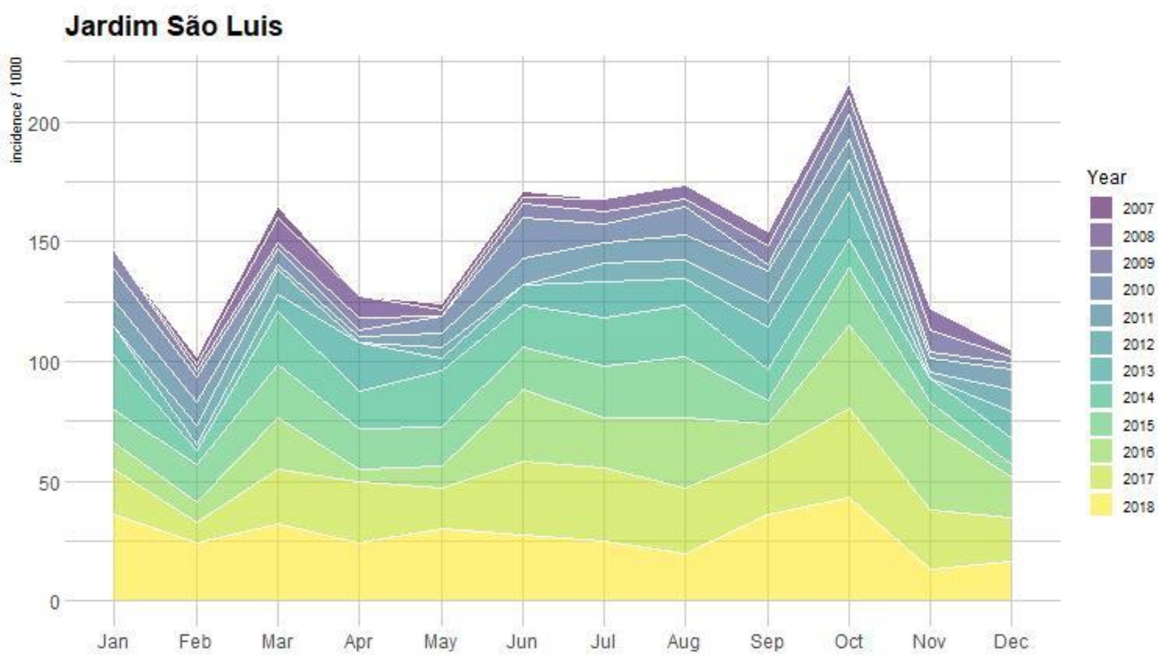

Jaguara
incidence / 1000
0
100
200
300
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

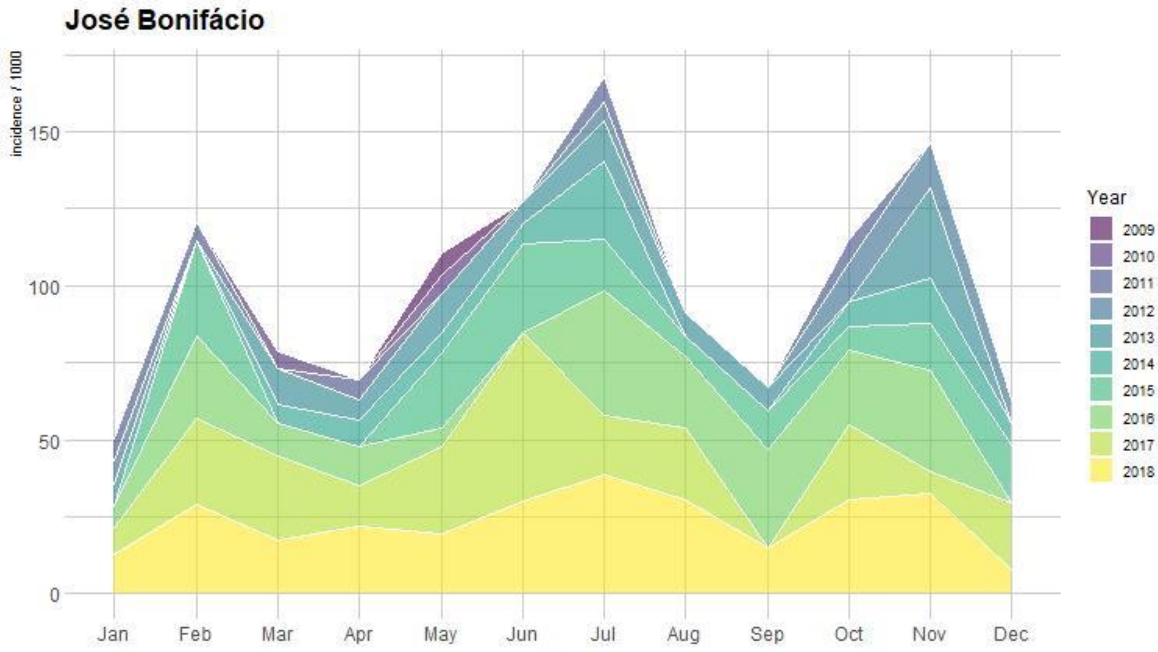

Jaguaré
incidence / 1000
0
100
200
300
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

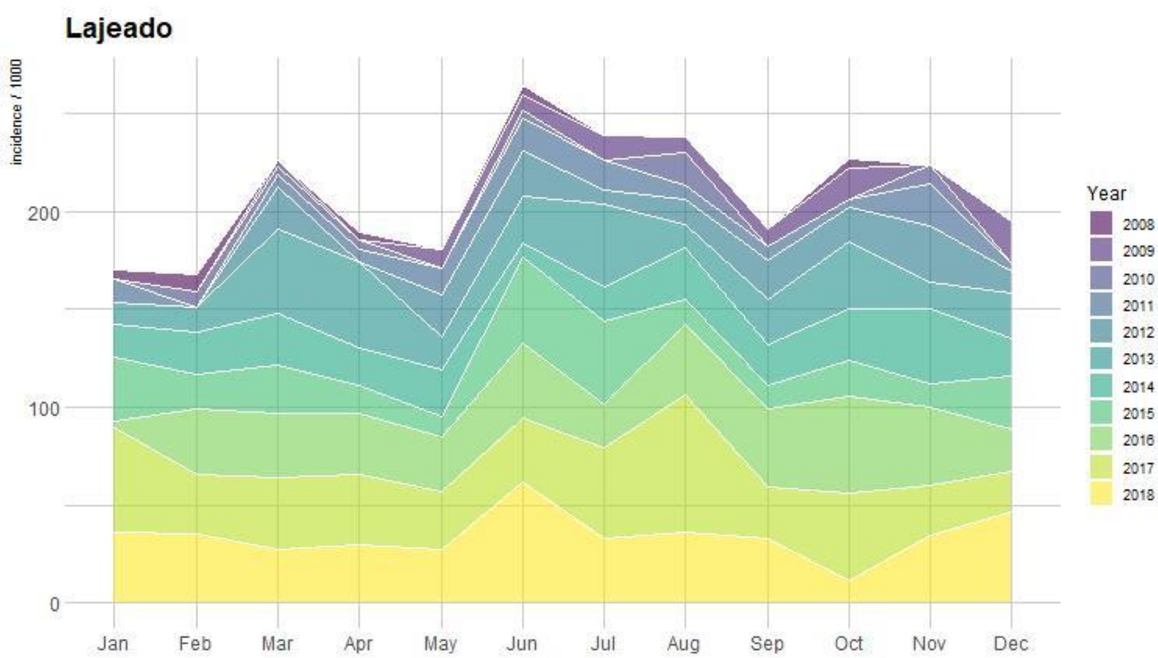

Jaraguá
incidence / 1000
0
50
100
150
200
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

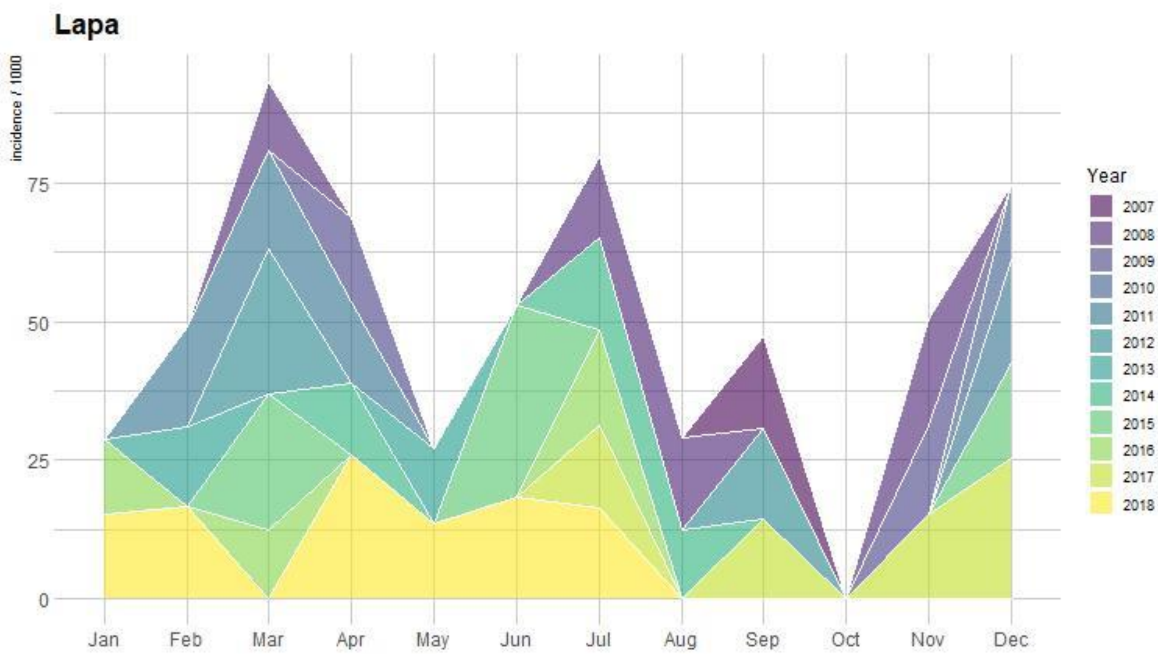

Jardim Ângela
incidence / 1000
0
100
200
300
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

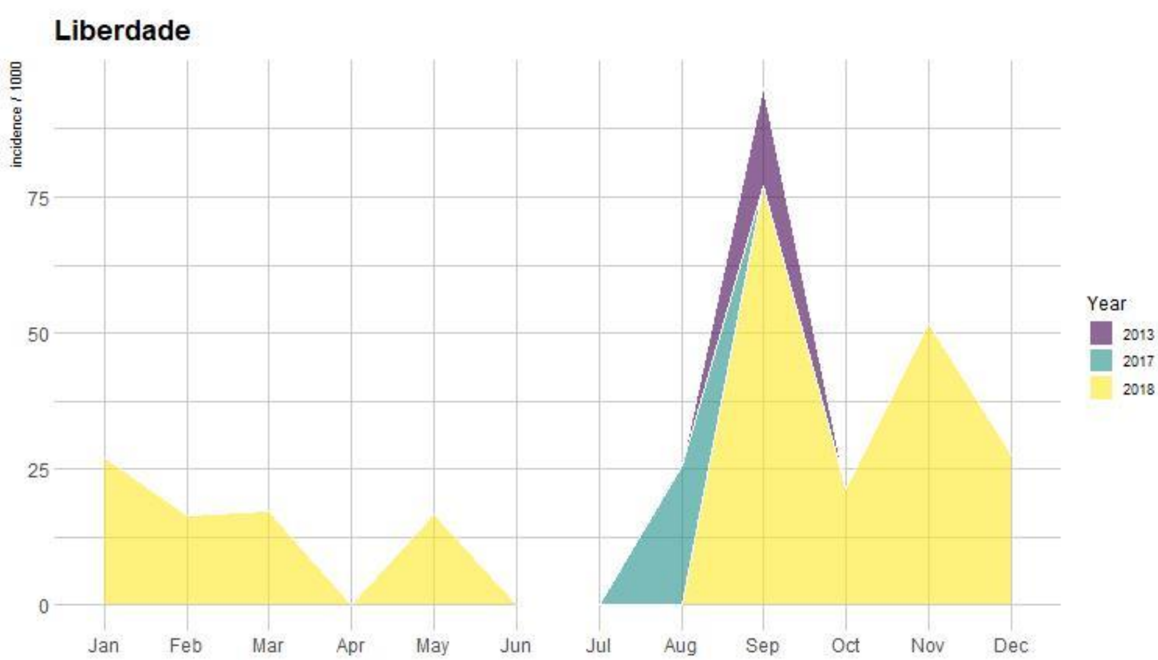

Jardim Helena
incidence / 1000
250
200
150
100
50
0
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

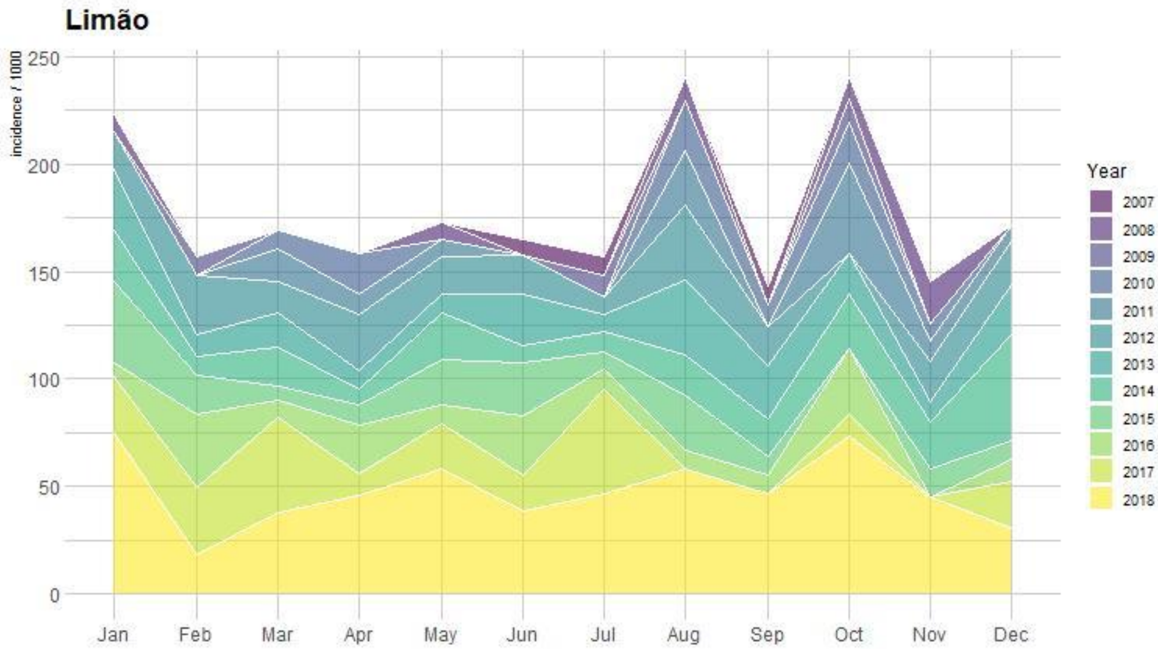

Jardim São Luis
incidence / 1000
200
150
100
50
0
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

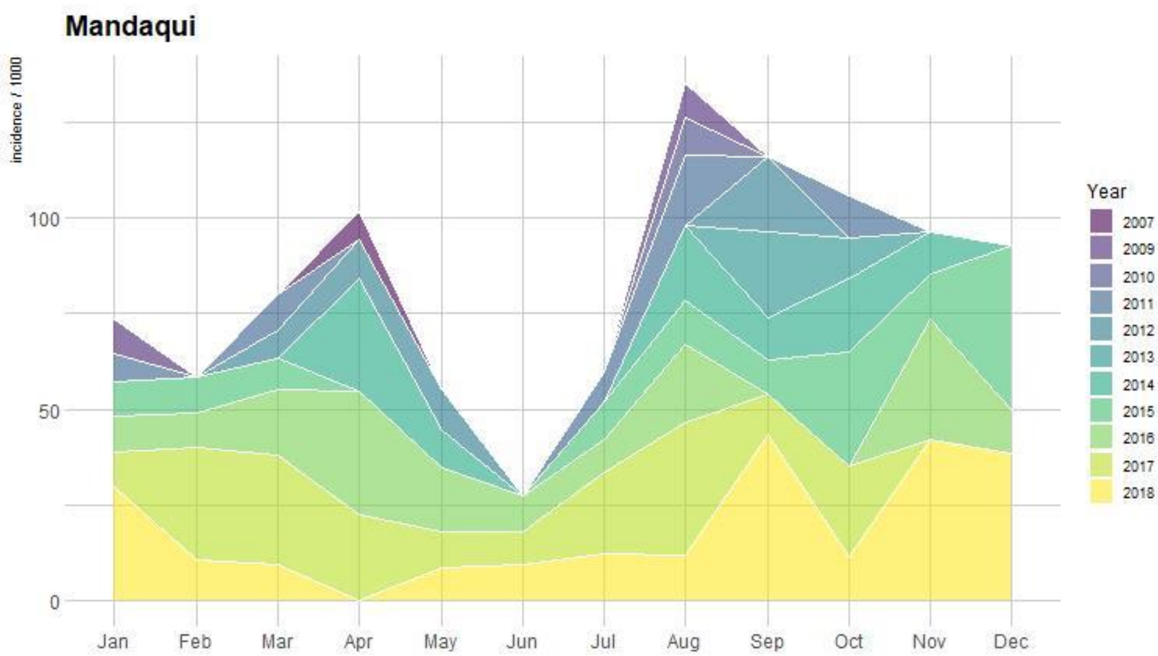

José Bonifácio
incidence / 1000
0
50
100
150
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

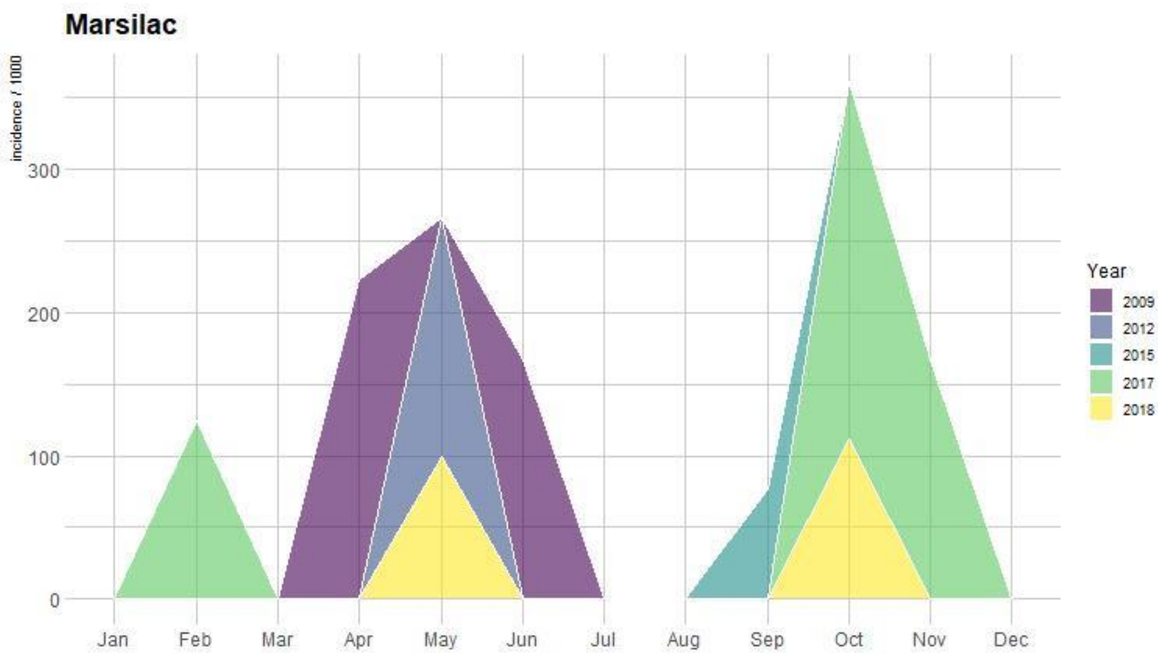

Lajeado
incidence / 1000
0
100
200
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

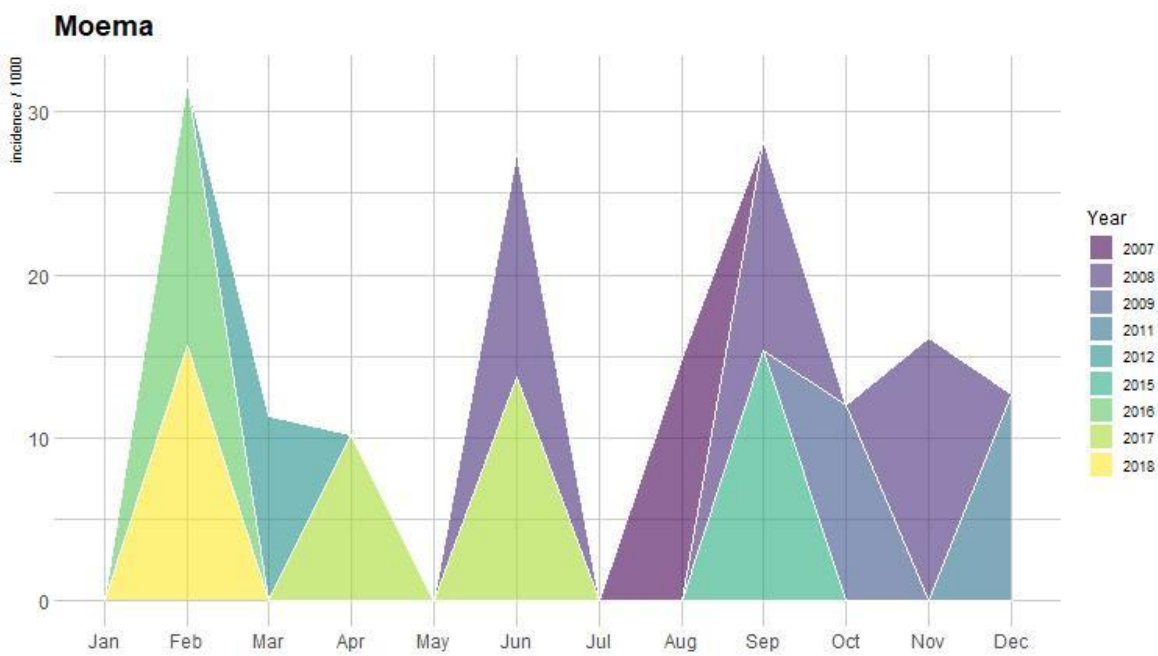

Lapa
incidence / 1000
0
25
50
75
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

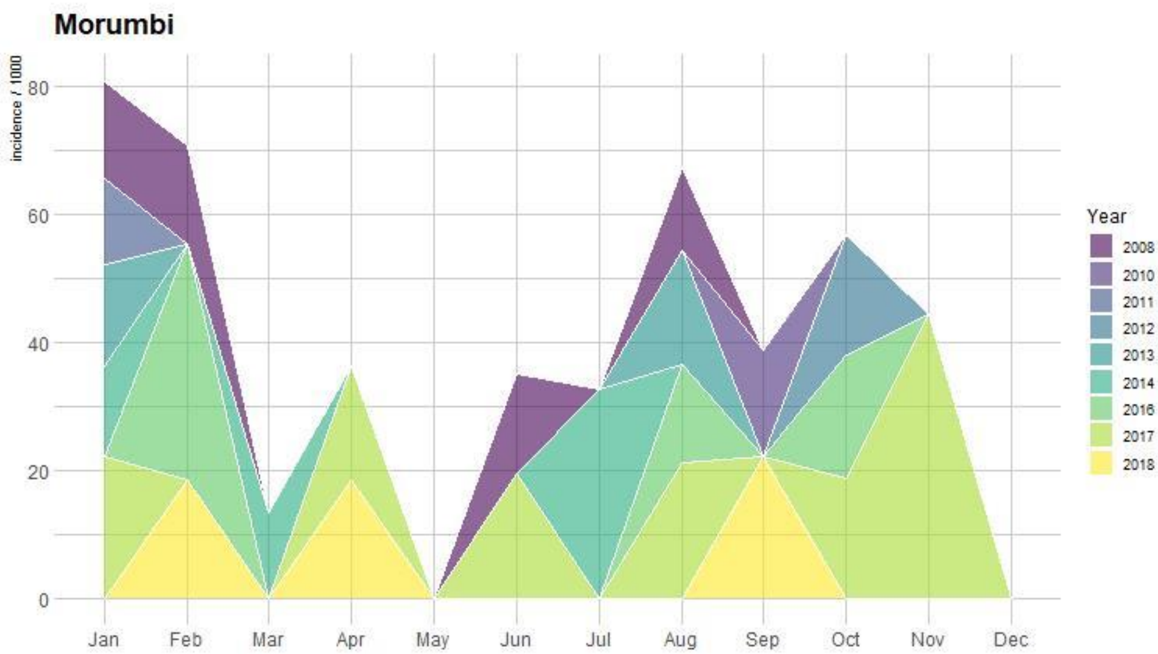

Liberdade
incidence / 1000
0
25
50
75
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2013
2017
2018

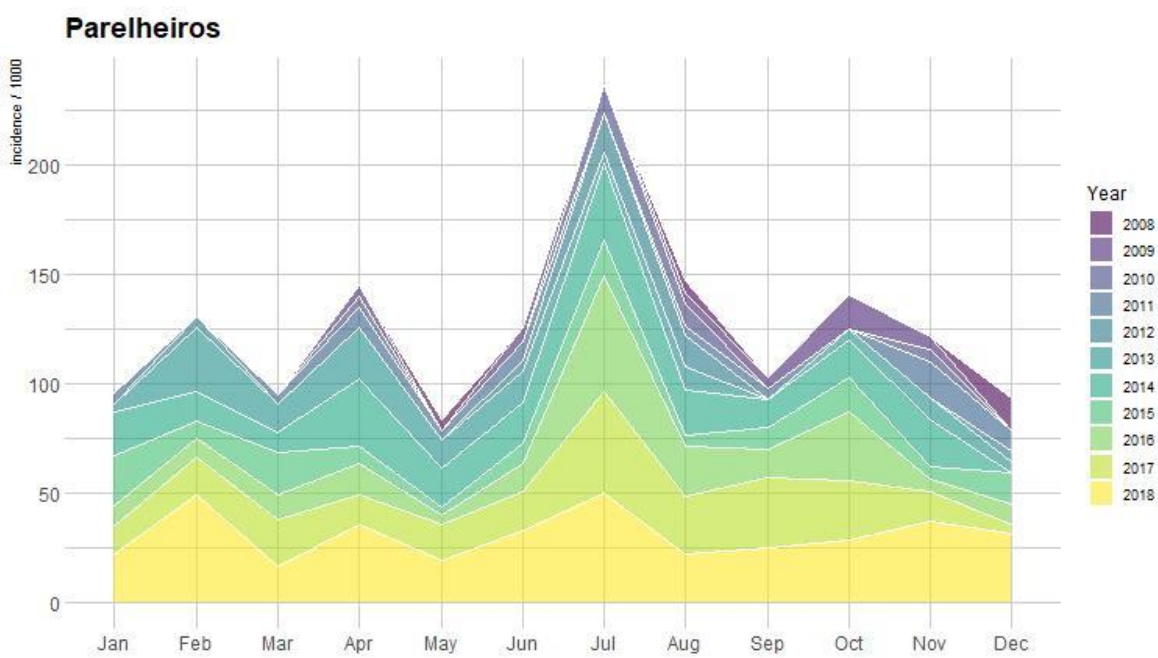

Limão
incidence / 1000
250
200
150
100
50
0
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

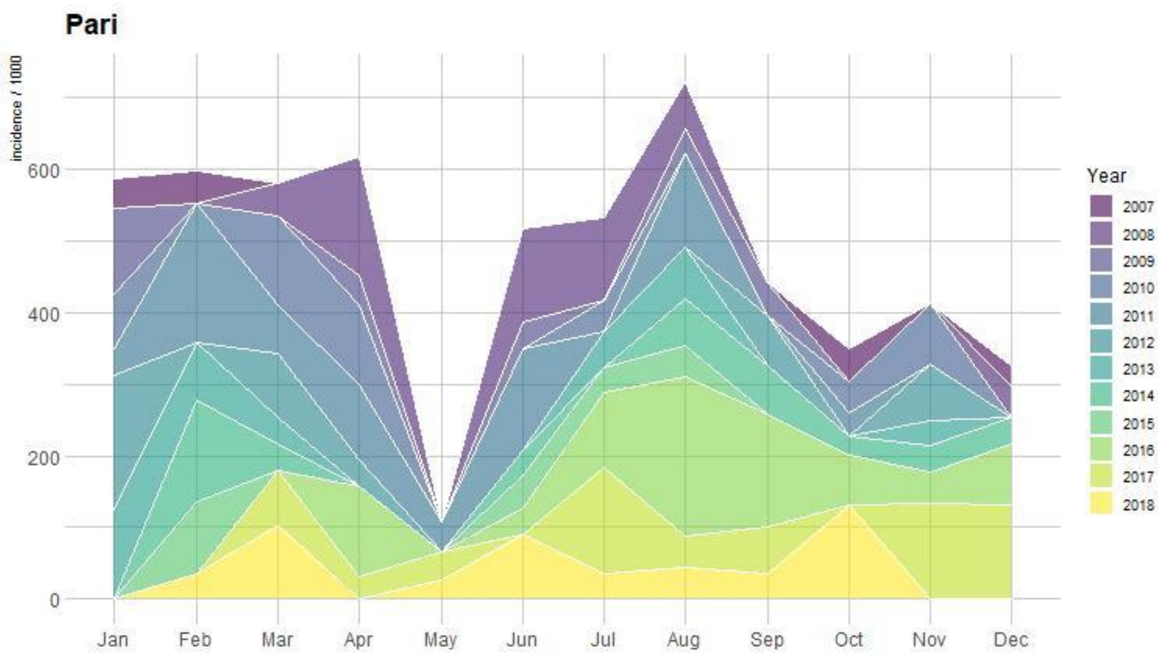

Mandaqui
incidence / 1000
100
50
0
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

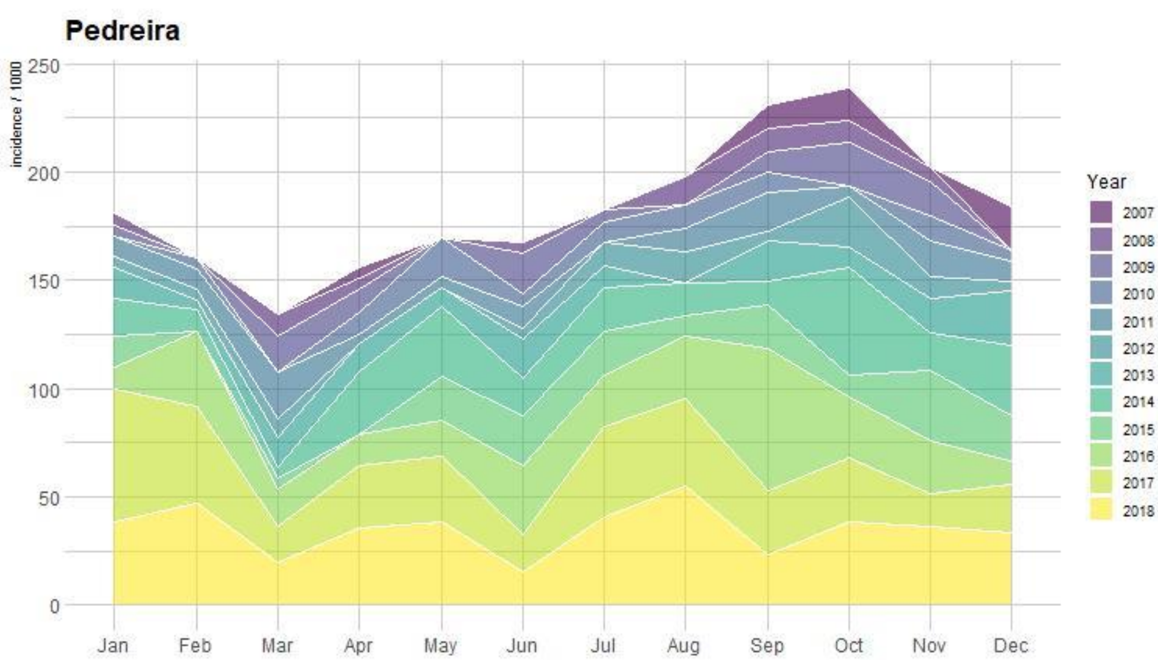

Marsilac
incidence / 1000
0
100
200
300
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2009
2012
2015
2017
2018

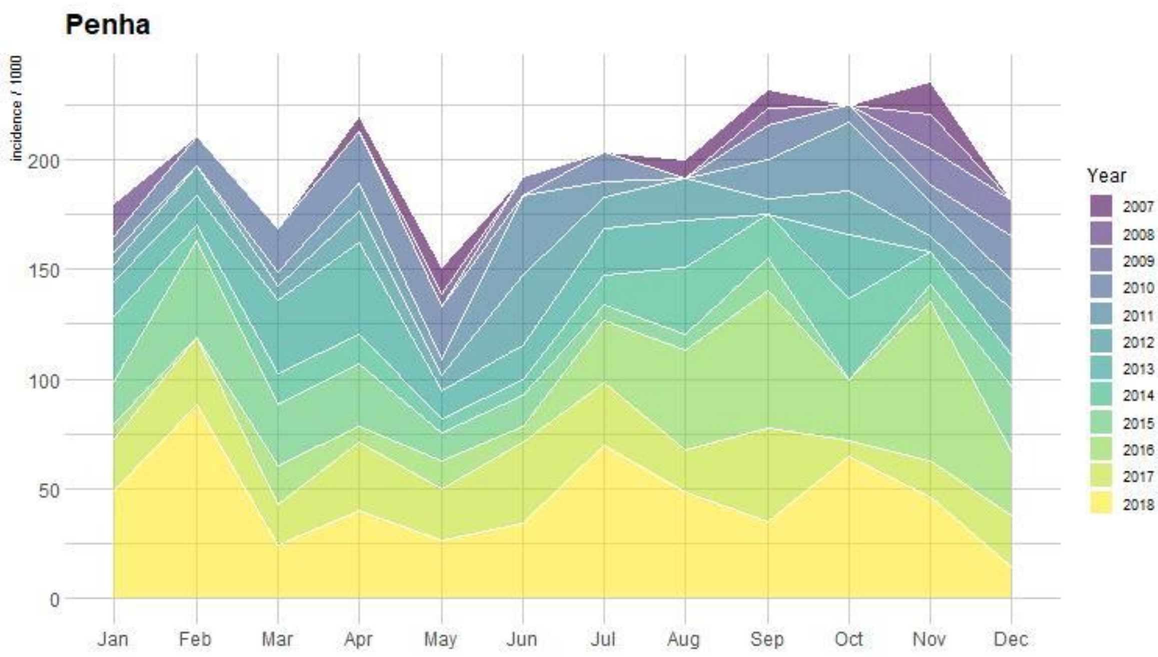

Moema
incidence / 1000
0
10
20
30
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2011
2012
2015
2016
2017
2018

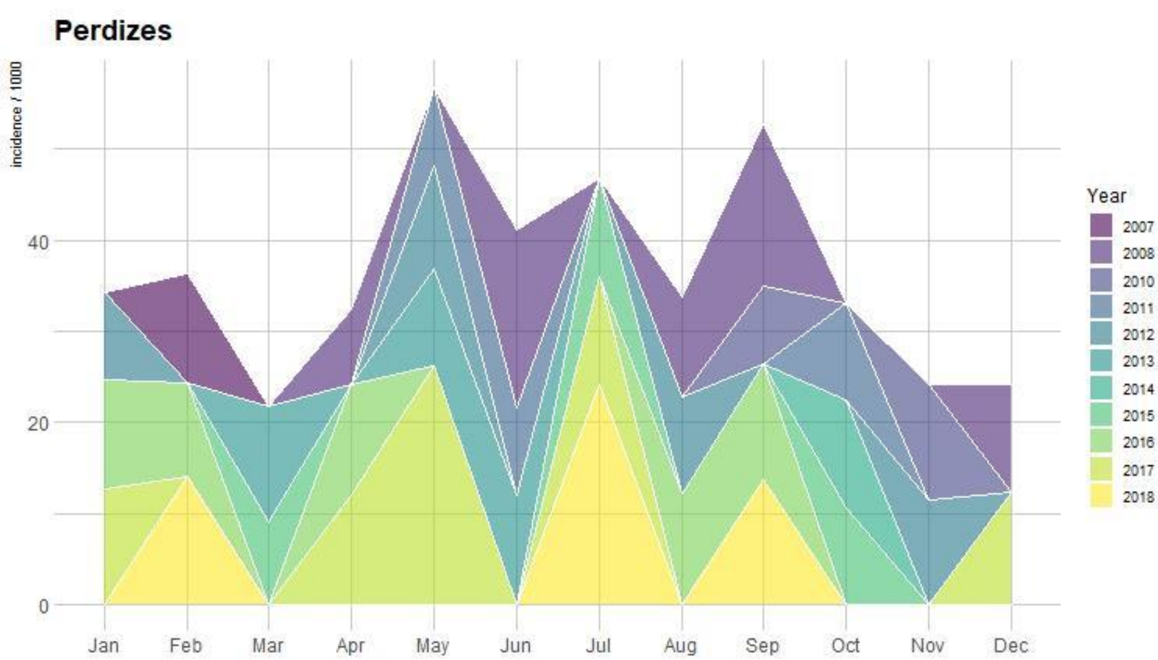

Morumbi
incidence / 1000
0
20
40
60
80
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2008
2010
2011
2012
2013
2014
2016
2017
2018

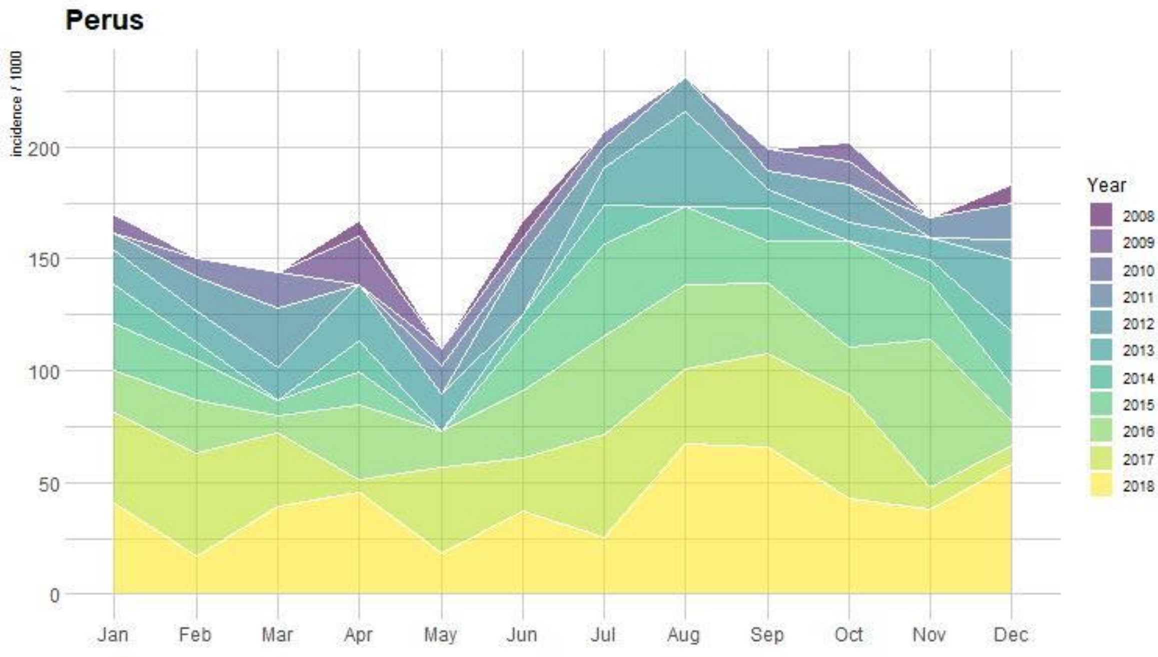

Parelheiros
incidence / 1000
0
50
100
150
200
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

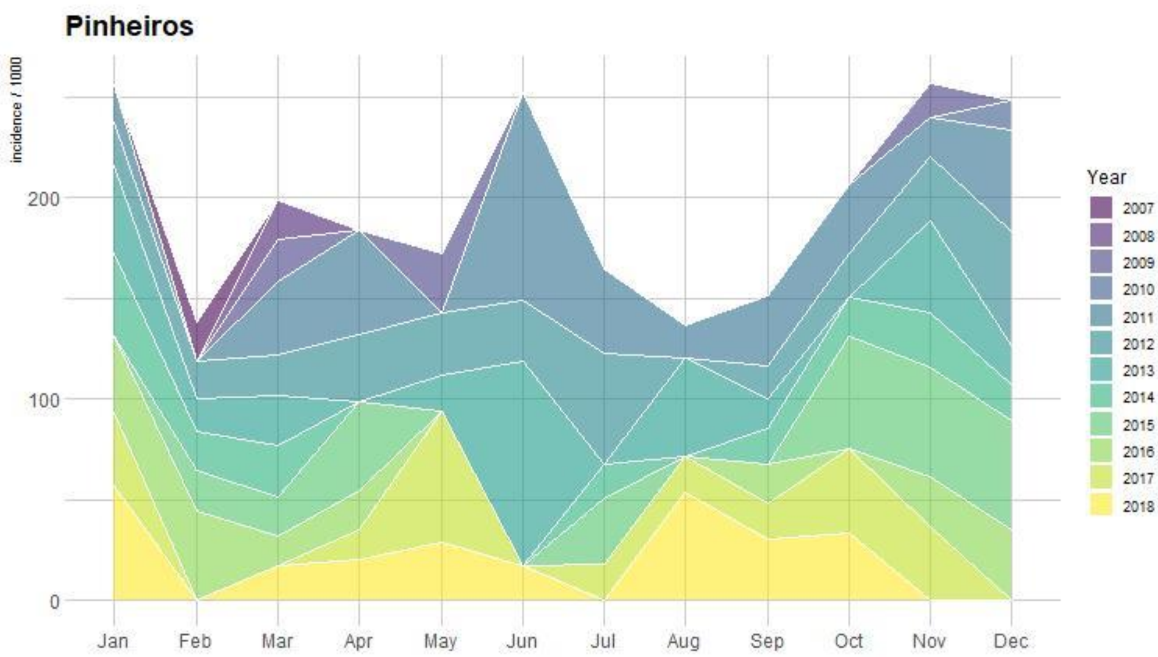

Pari
incidence / 1000
0
200
400
600
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

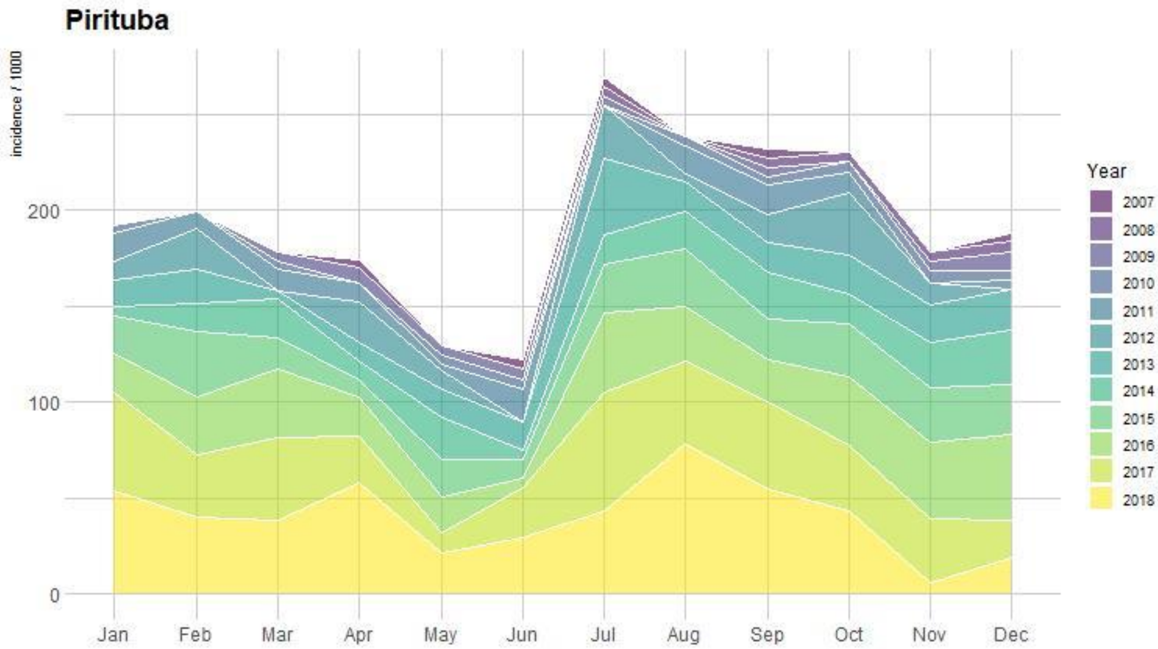

Pedreira
incidence / 1000
0
50
100
150
200
250
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

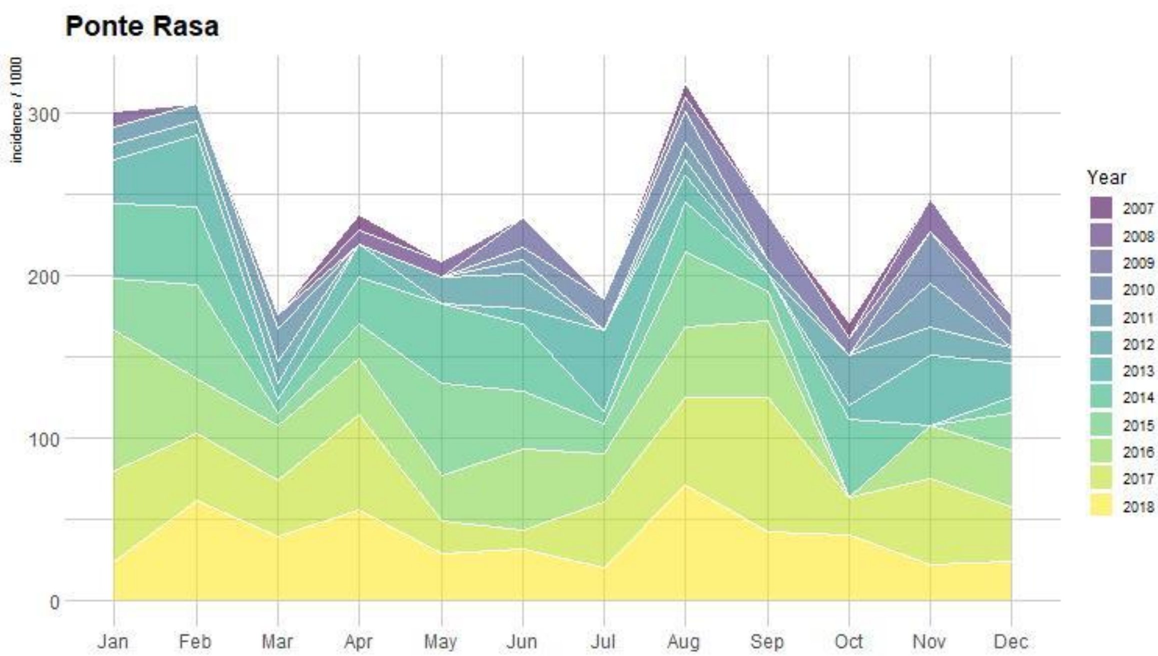

Penha
incidence / 1000
0
50
100
150
200
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

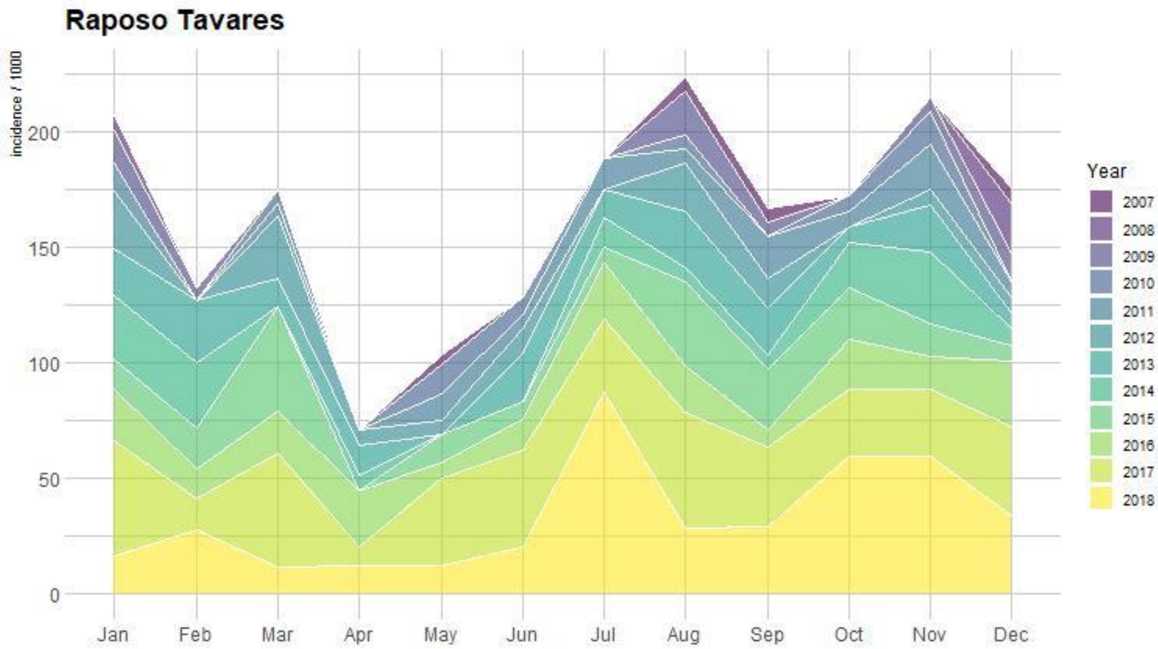

Perdizes
incidence / 1000
0
20
40
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2010
2011
2012
2013
2014
2015
2016
2017
2018

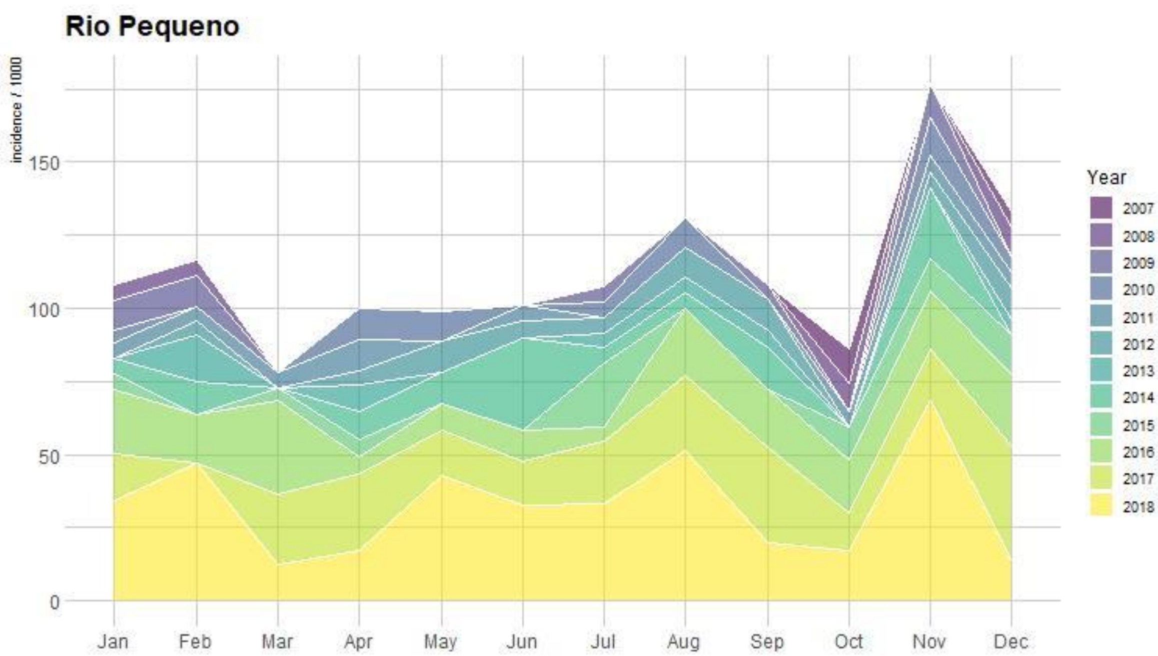

Perus
incidence / 1000
0
50
100
150
200
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

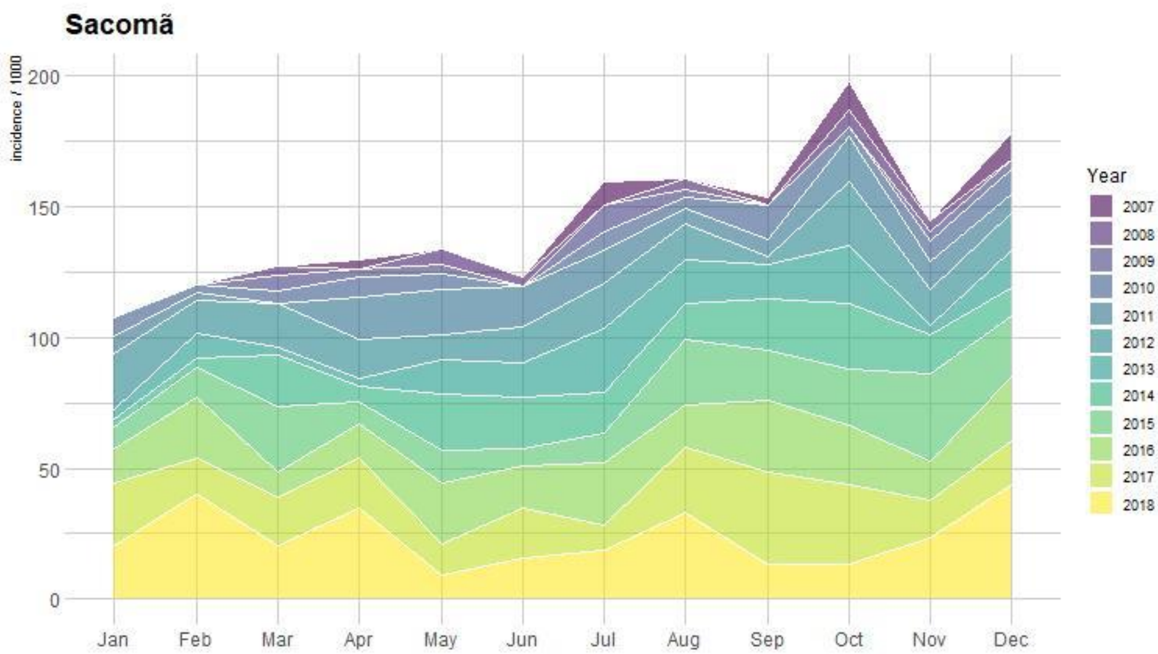

Pinheiros
incidence / 1000
0
100
200
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

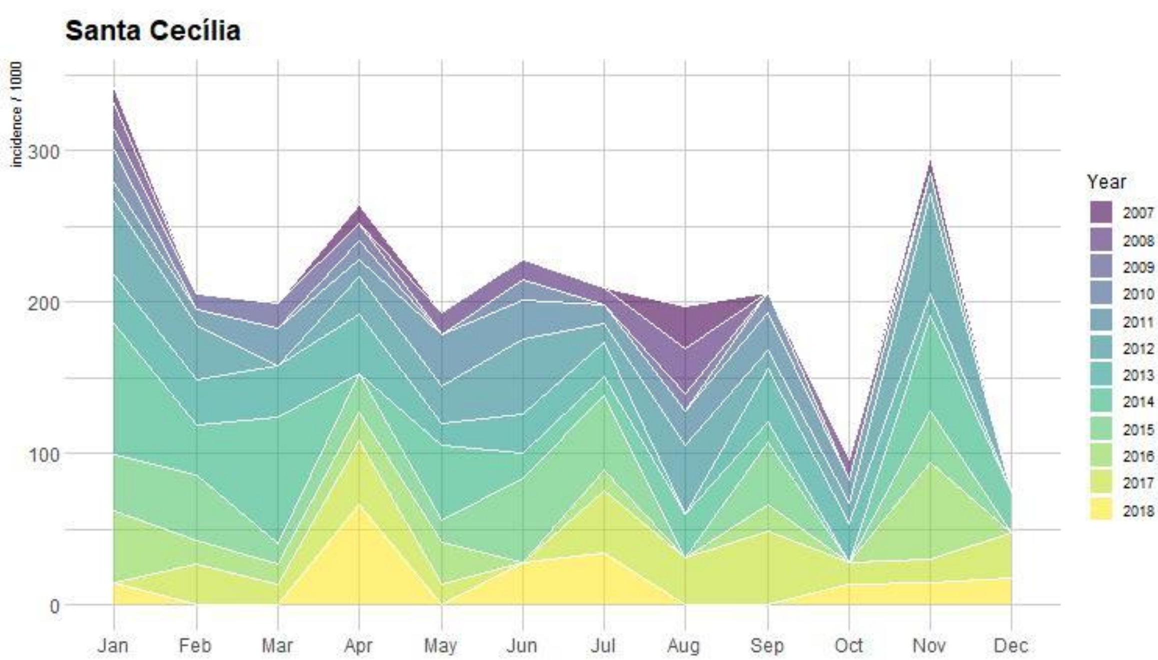

Pirituba
incidence / 1000
0
100
200
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

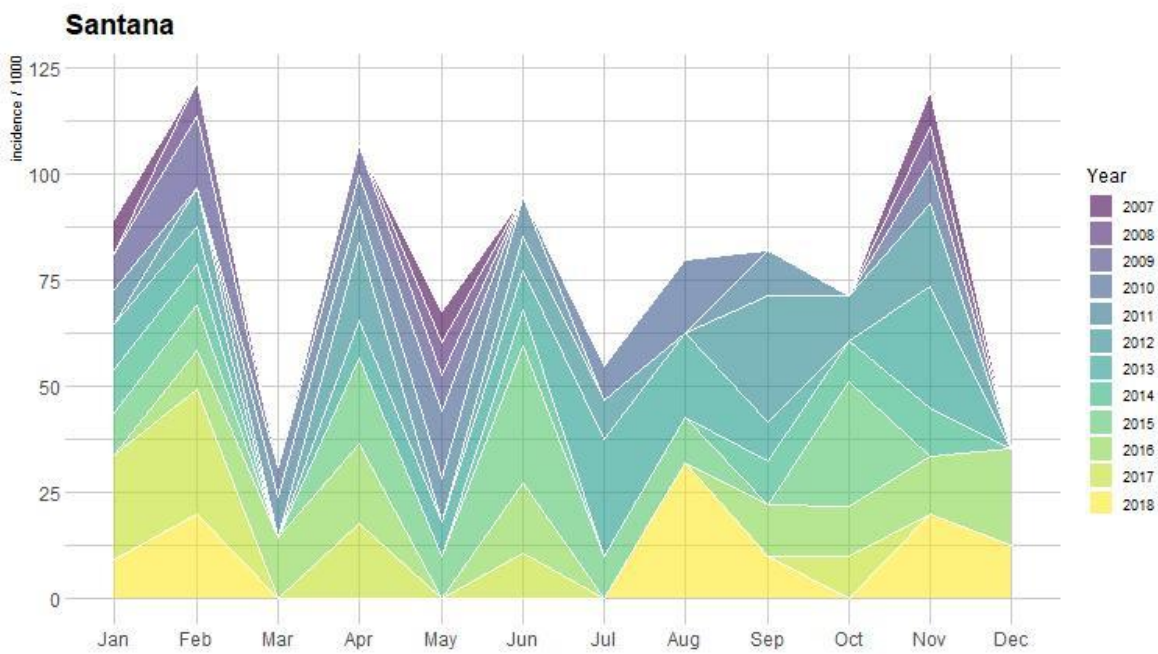

Ponte Rasa
incidence / 1000
0
100
200
300
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

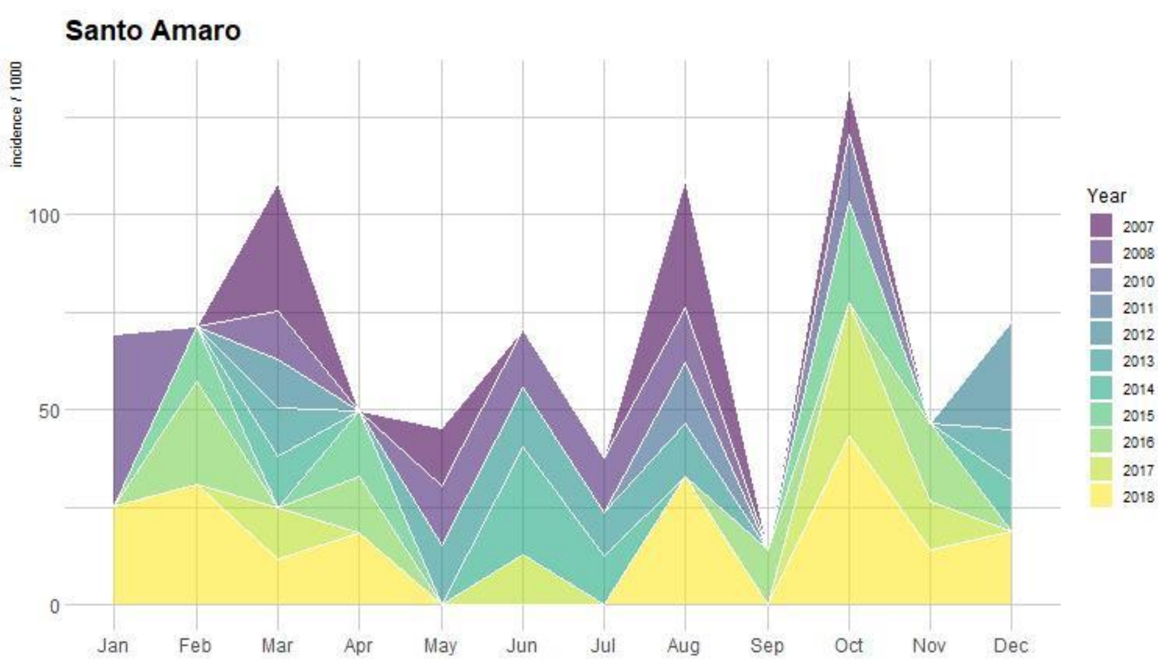

Raposo Tavares
incidence / 1000
0
50
100
150
200
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

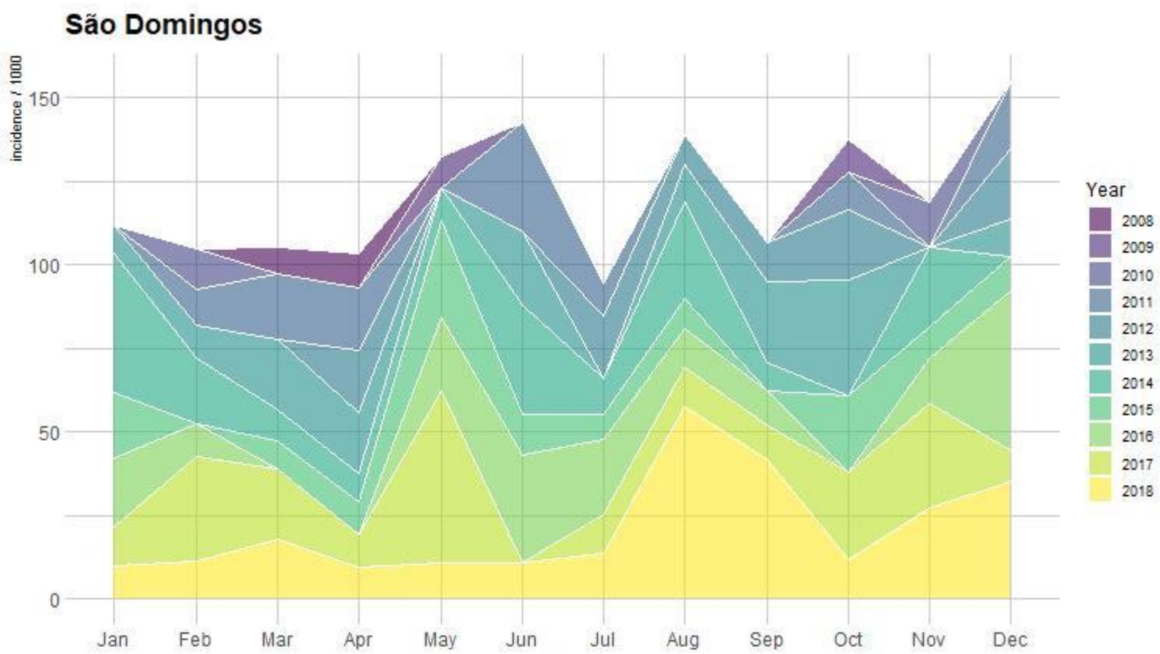

Rio Pequeno
incidence / 1000
0
50
100
150
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

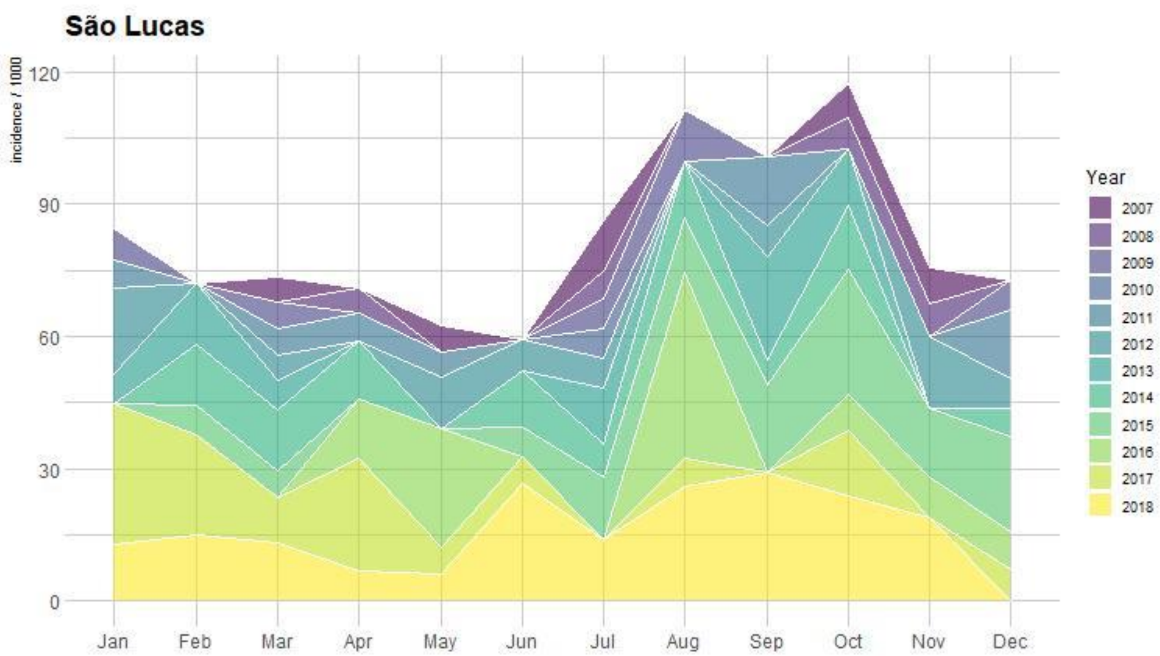

Sacomã
incidence / 1000
0
50
100
150
200
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

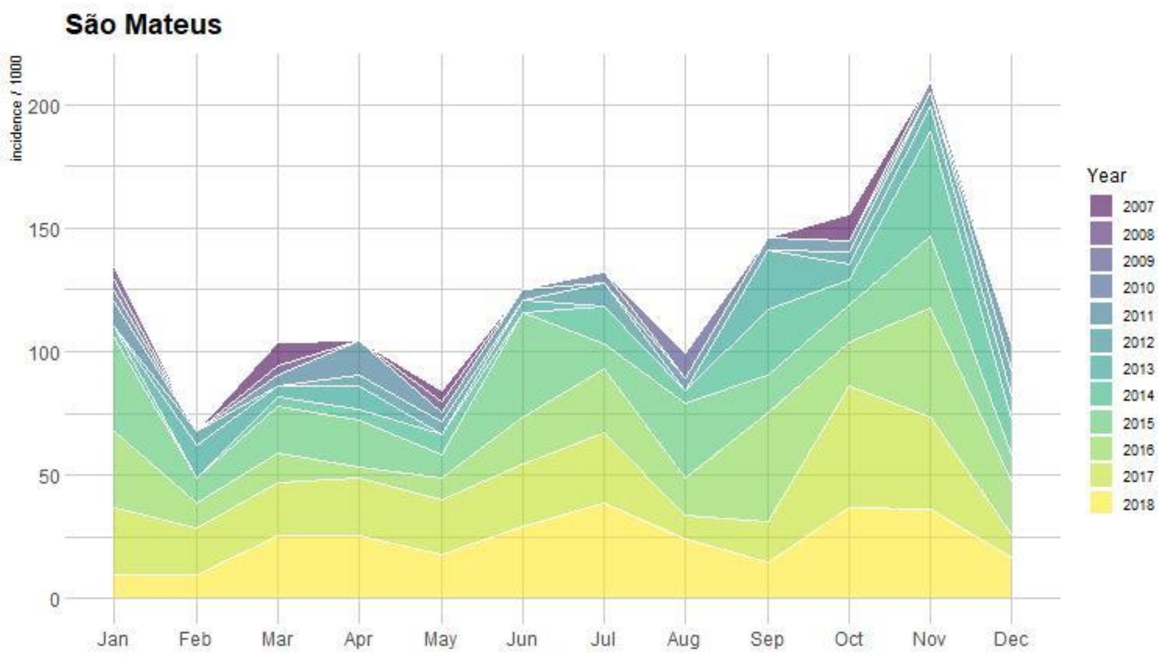

Santa Cecília
incidence / 1000
0
100
200
300
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

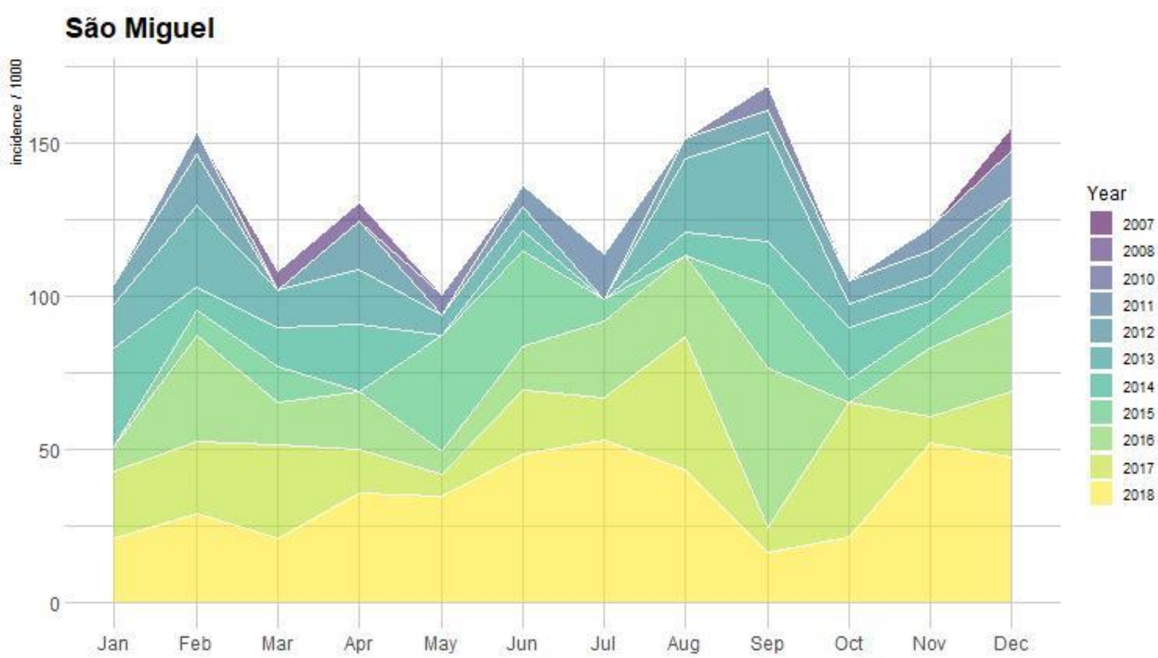

Santana
incidence / 1000
0
25
50
75
100
125
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

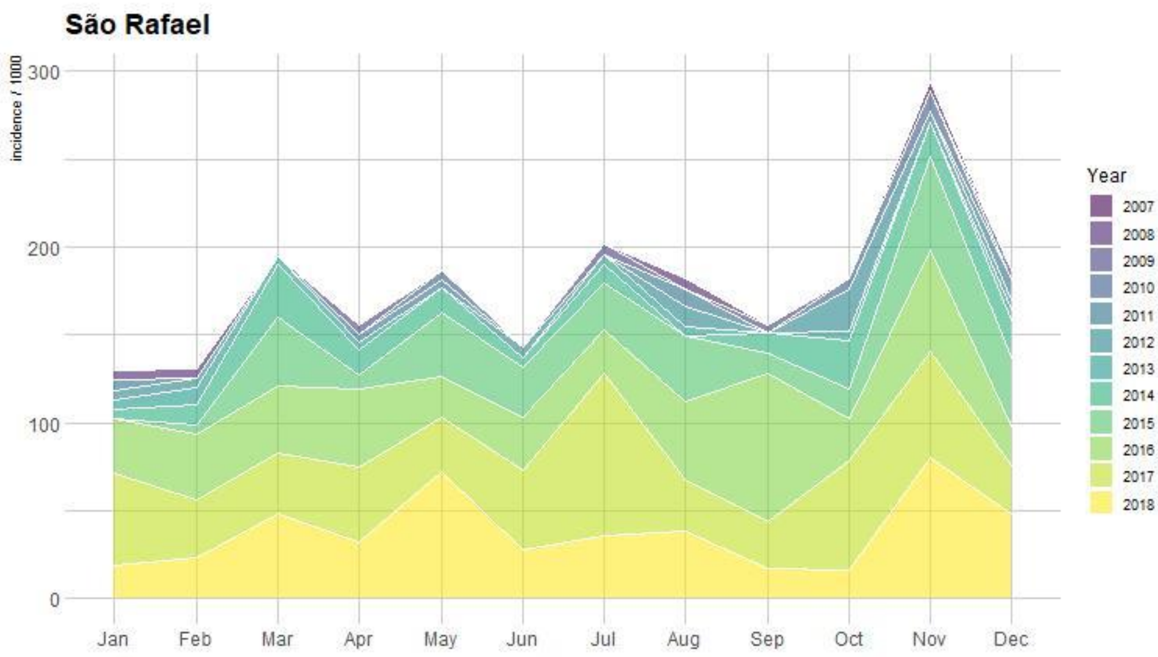

Santo Amaro
incidence / 1000
0
50
100
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2010
2011
2012
2013
2014
2015
2016
2017
2018

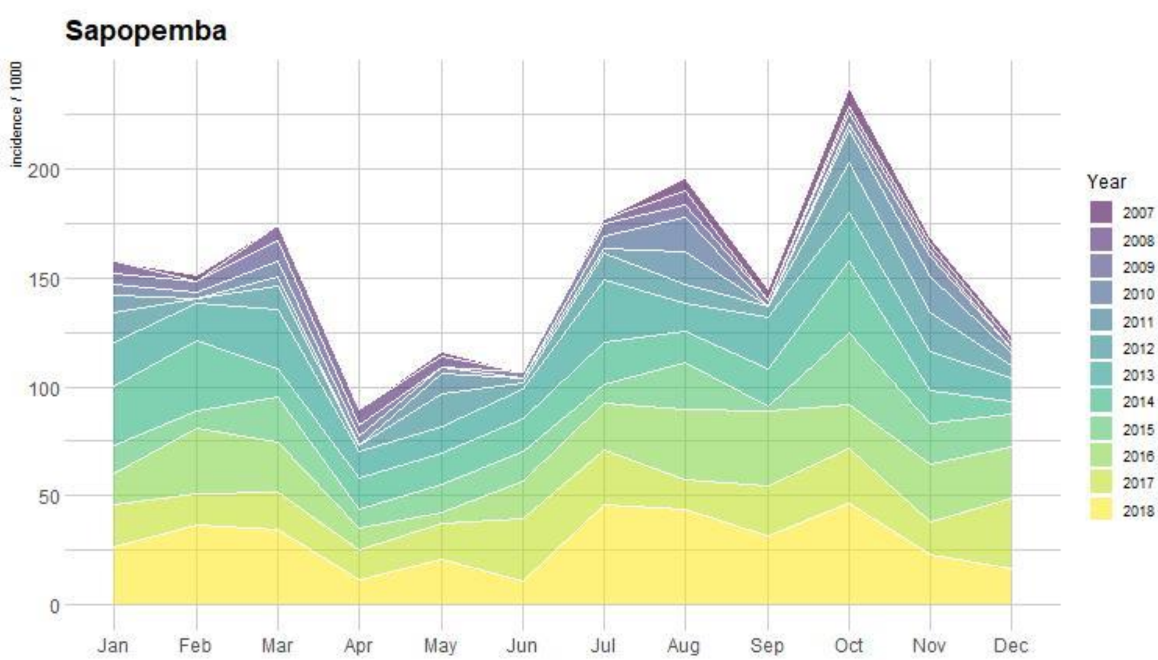

São Domingos
incidence / 1000
0
50
100
150
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

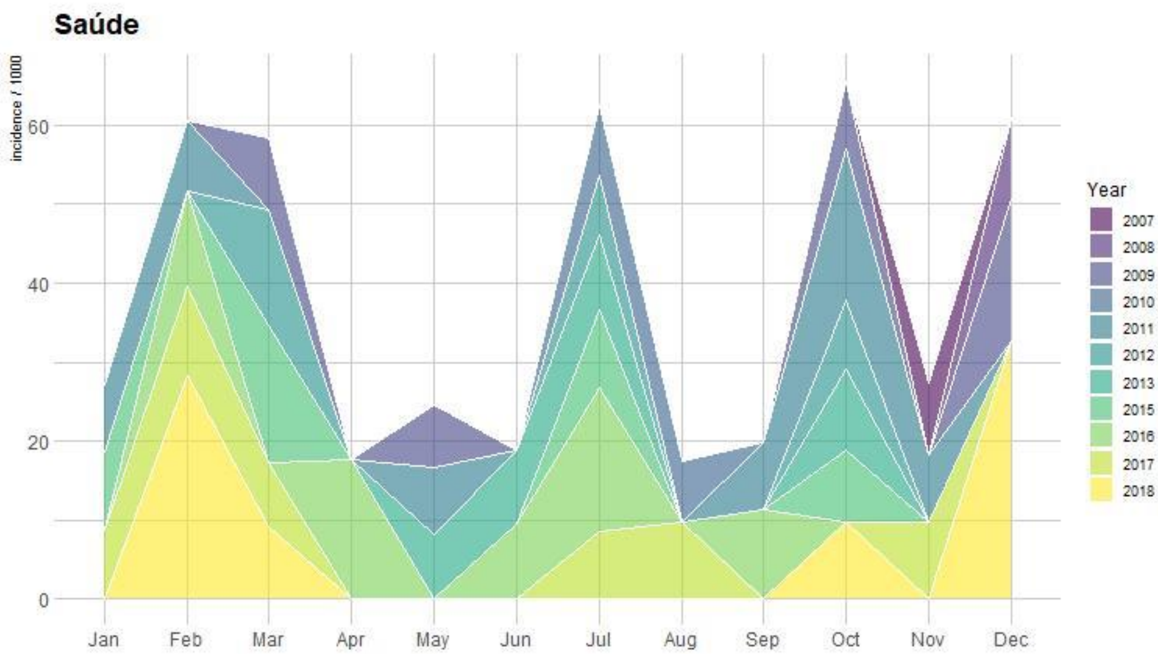

São Lucas
incidence / 1000
0
30
60
90
120
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

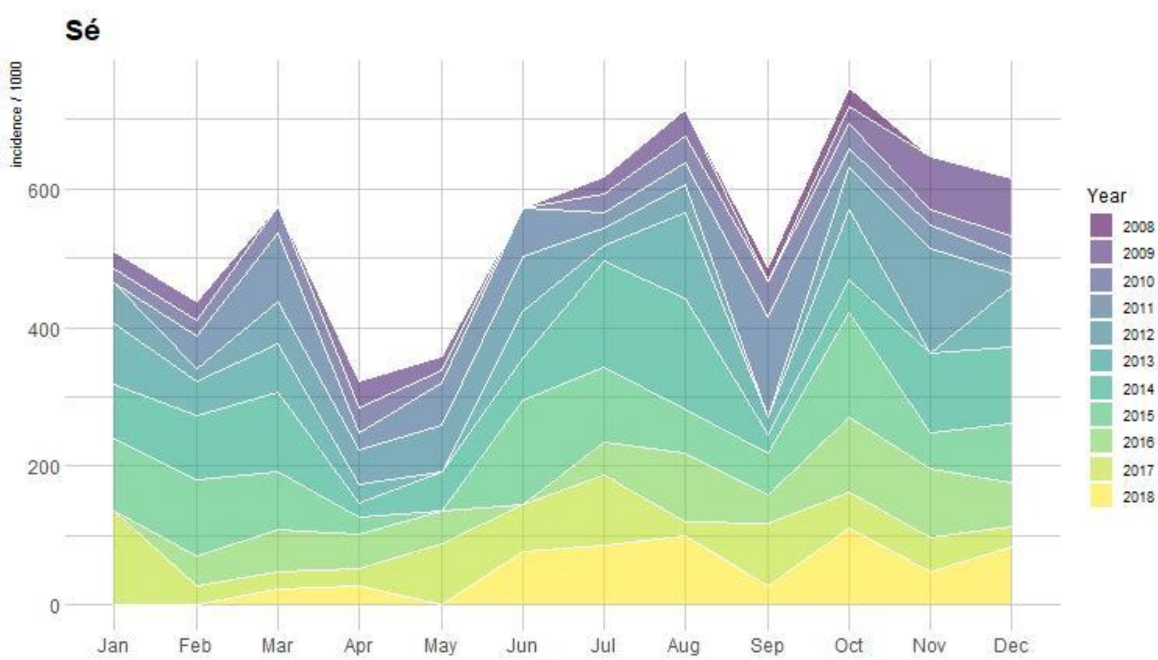

São Mateus
incidence / 1000
0
50
100
150
200
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

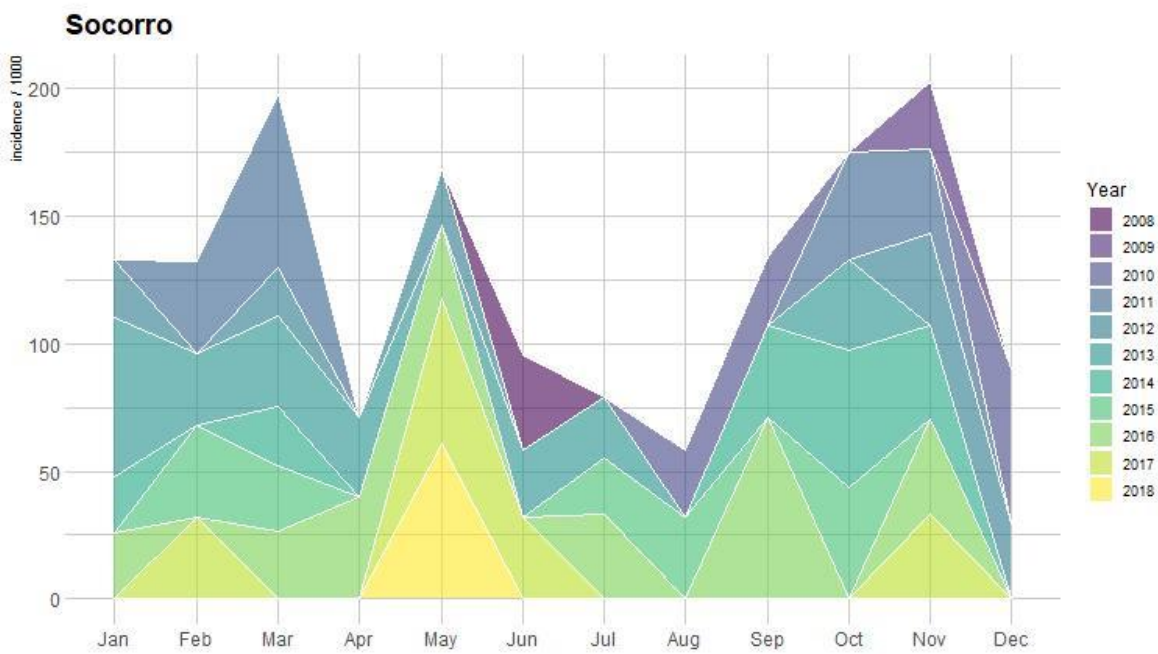

São Miguel
incidence / 1000
0
50
100
150
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2010
2011
2012
2013
2014
2015
2016
2017
2018

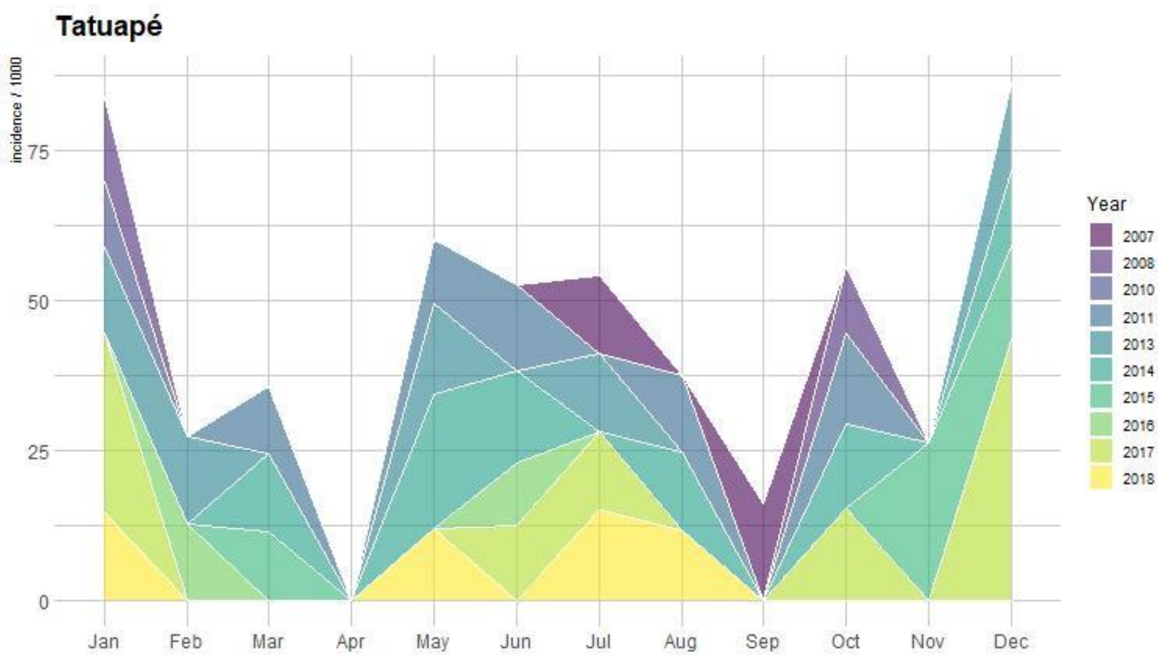

São Rafael
incidence / 1000
0
100
200
300
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018


Sapopemba
incidence / 1000
0
50
100
150
200
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

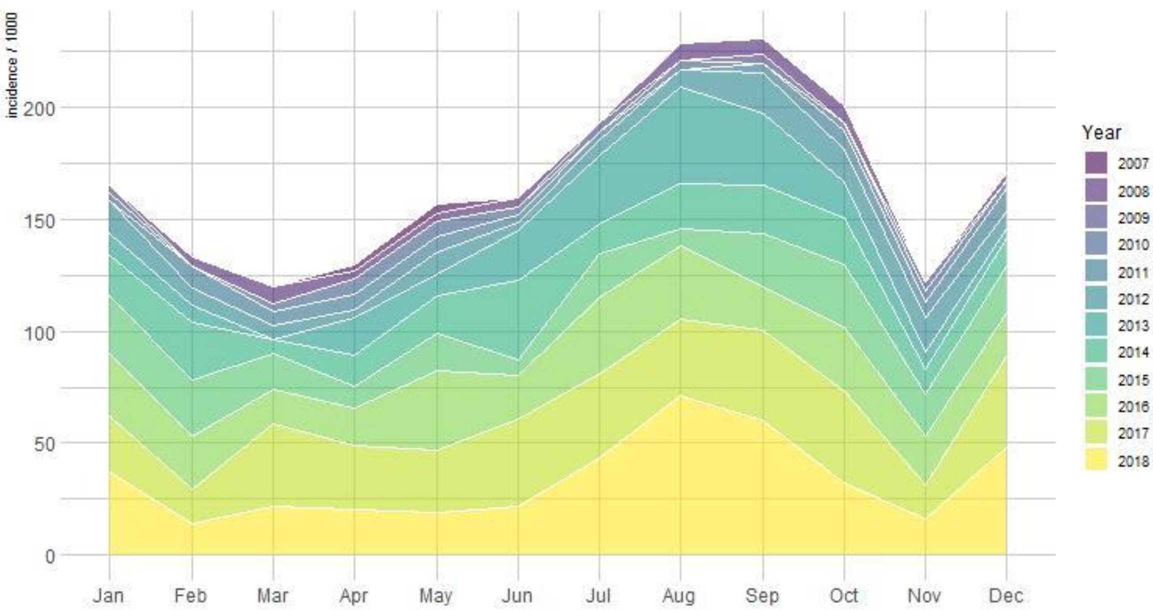

Saúde
incidence / 1000
0
20
40
60
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2015
2016
2017
2018


Sé
incidence / 1000
0
200
400
600
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

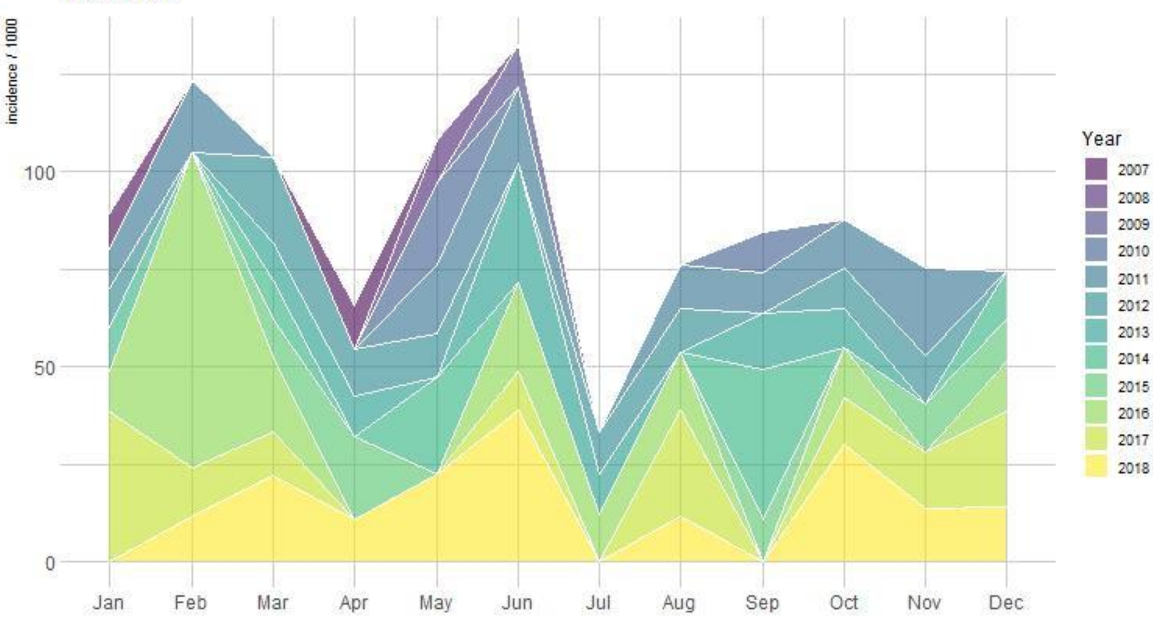

Socorro
incidence / 1000
0
50
100
150
200
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

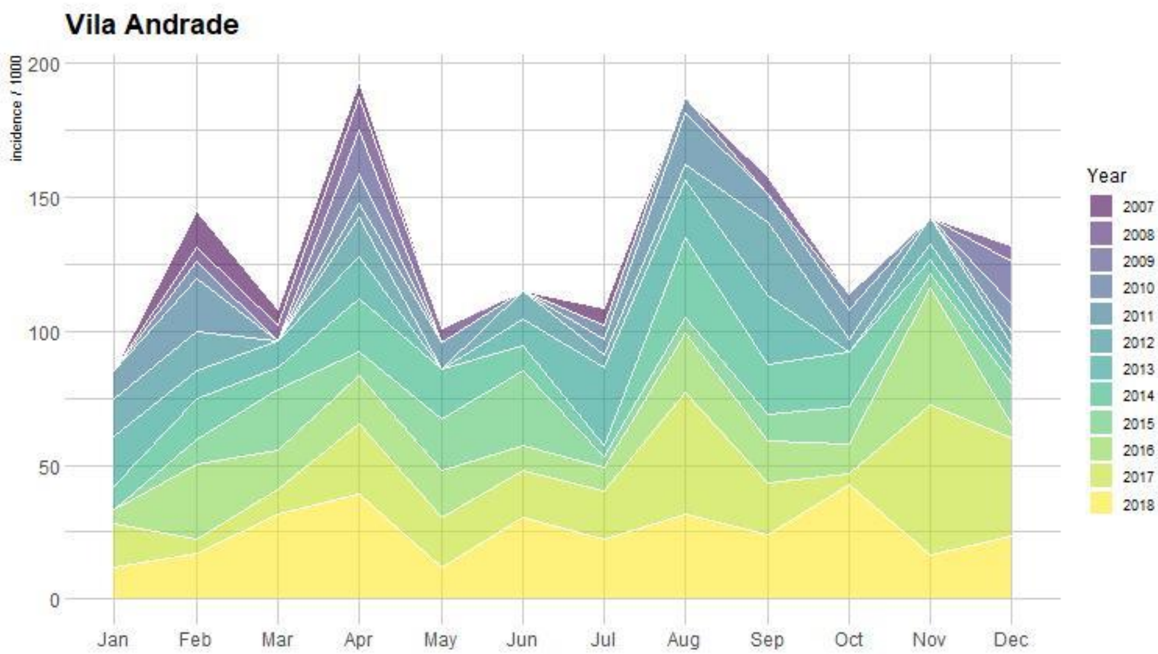

Tatuapé
incidence / 1000
0
25
50
75
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2010
2011
2013
2014
2015
2016
2017
2018

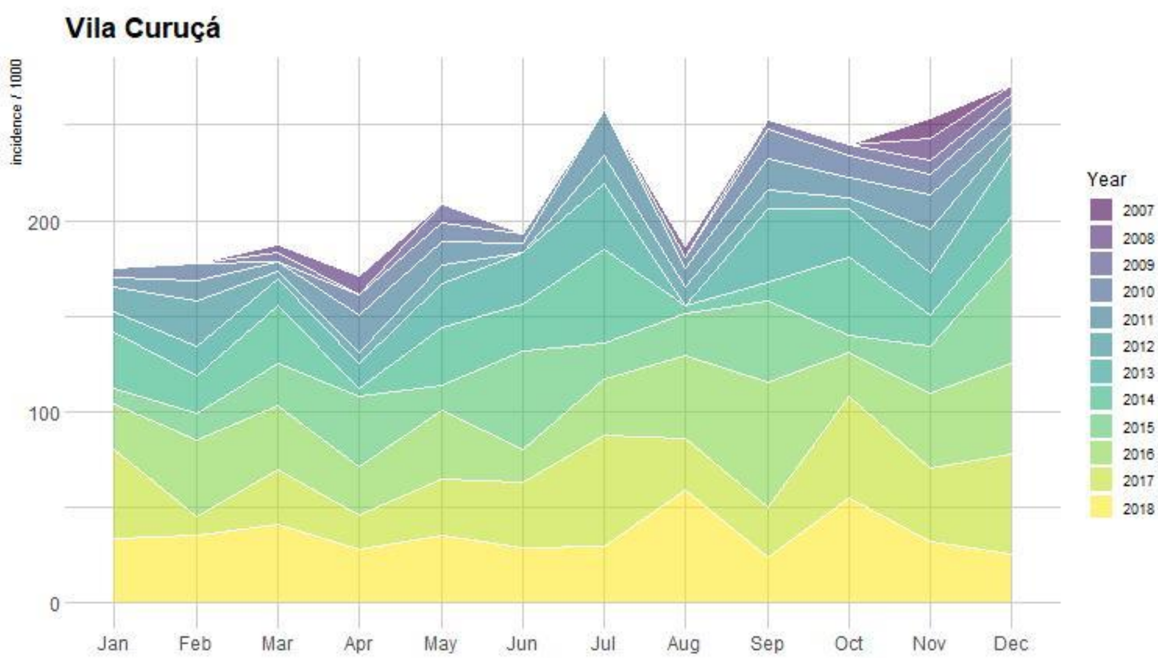
Tremembé

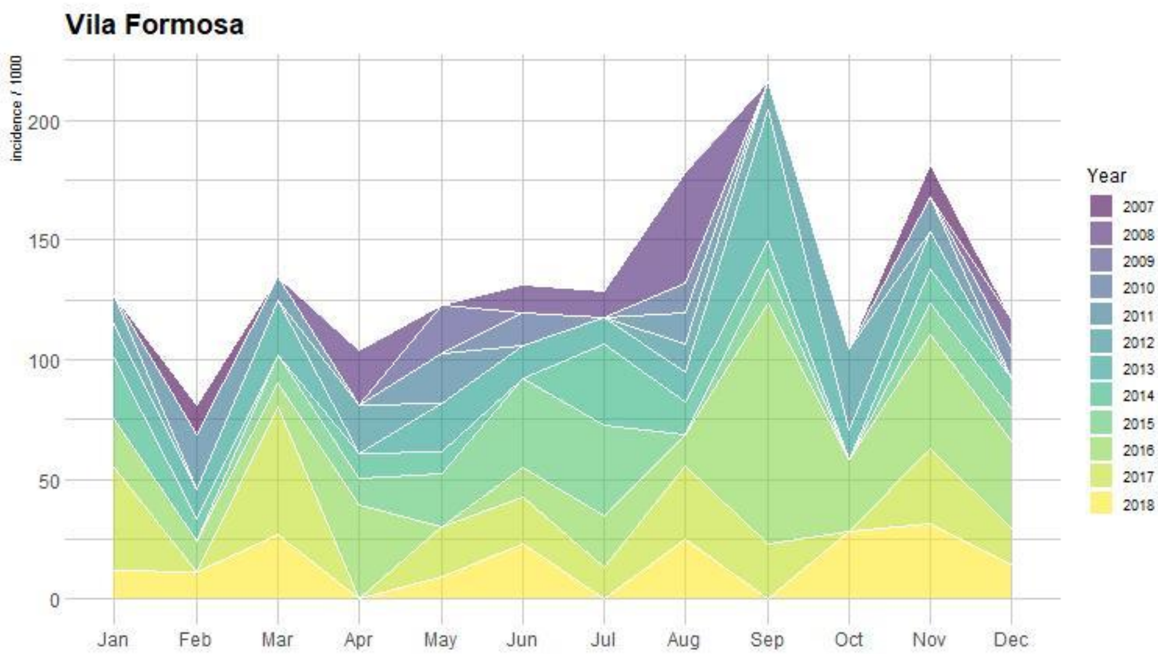


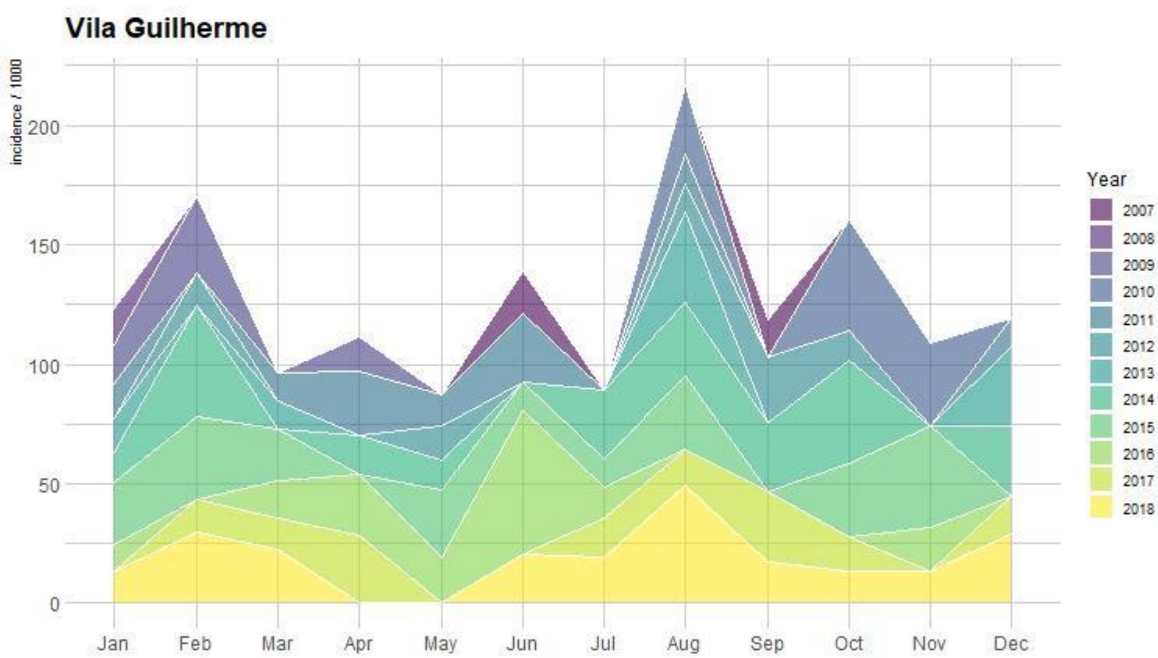
Tucuruvi

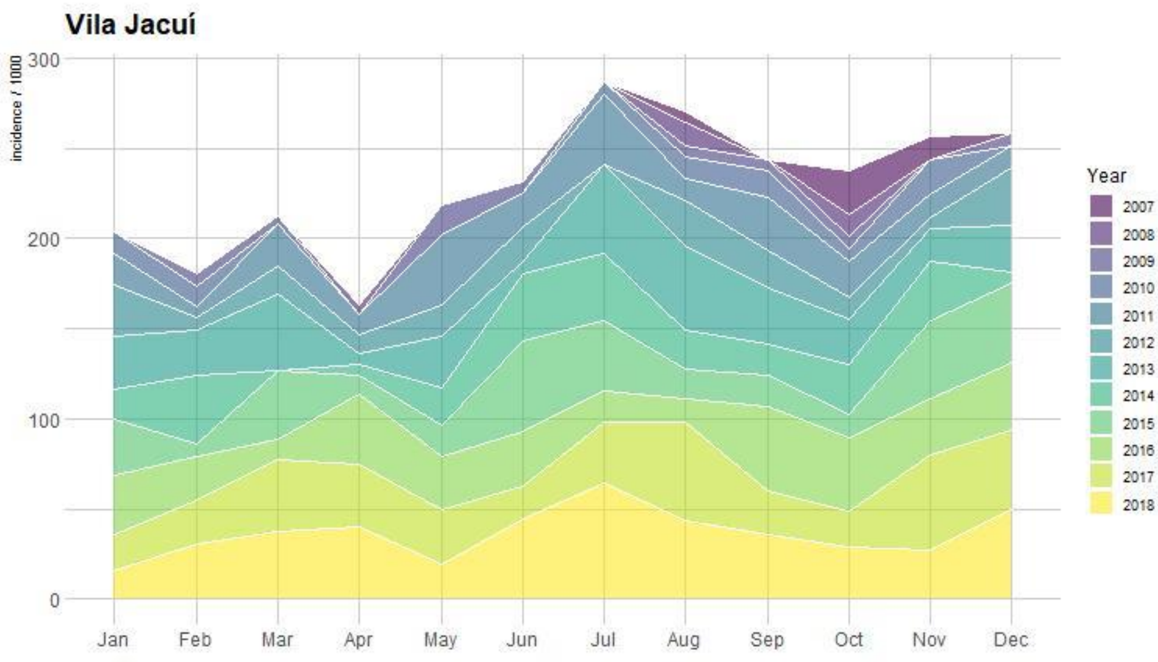


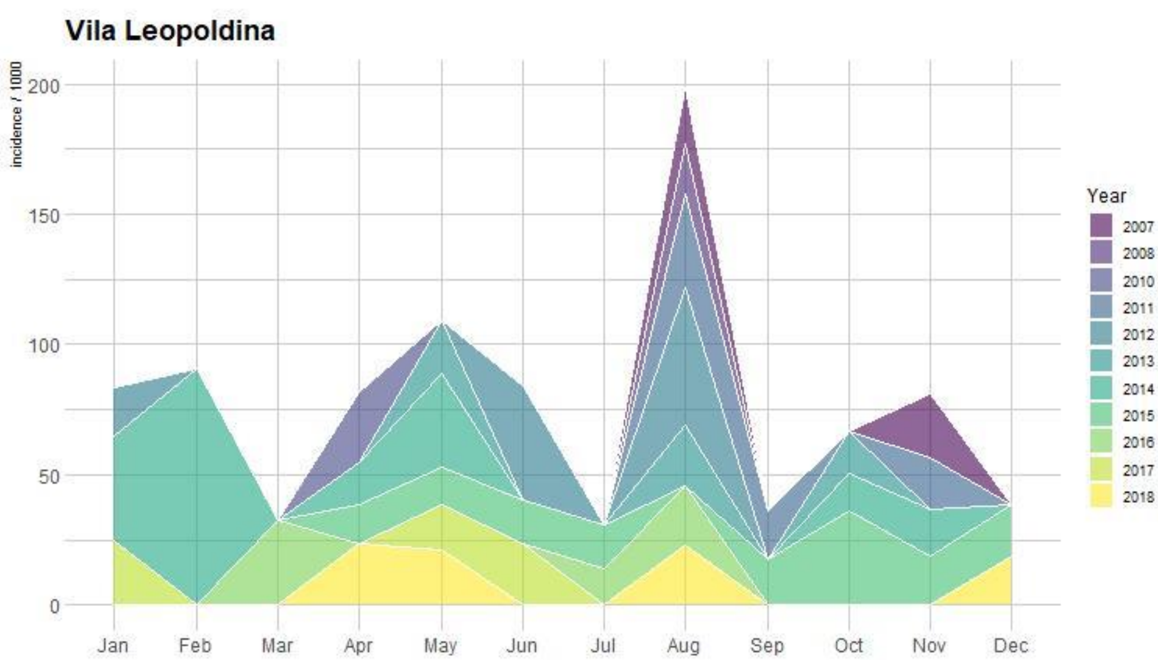

Vila Andrade
incidence / 1000
200
150
100
50
0
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

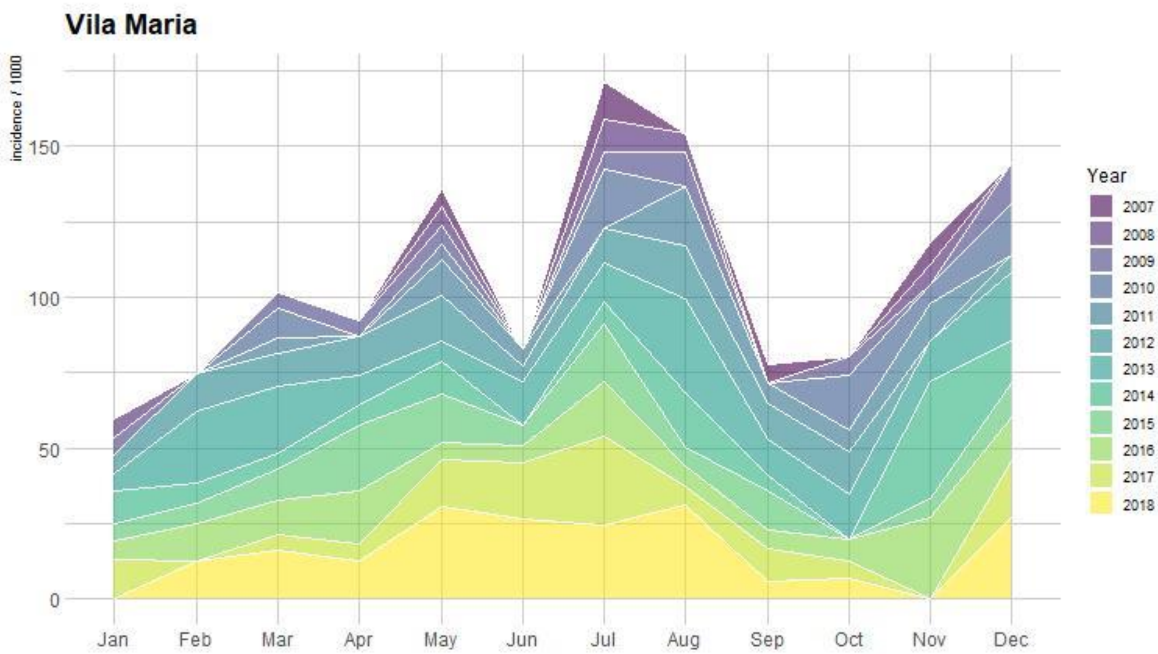

Vila Curuçá
incidence / 1000
200
100
0
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

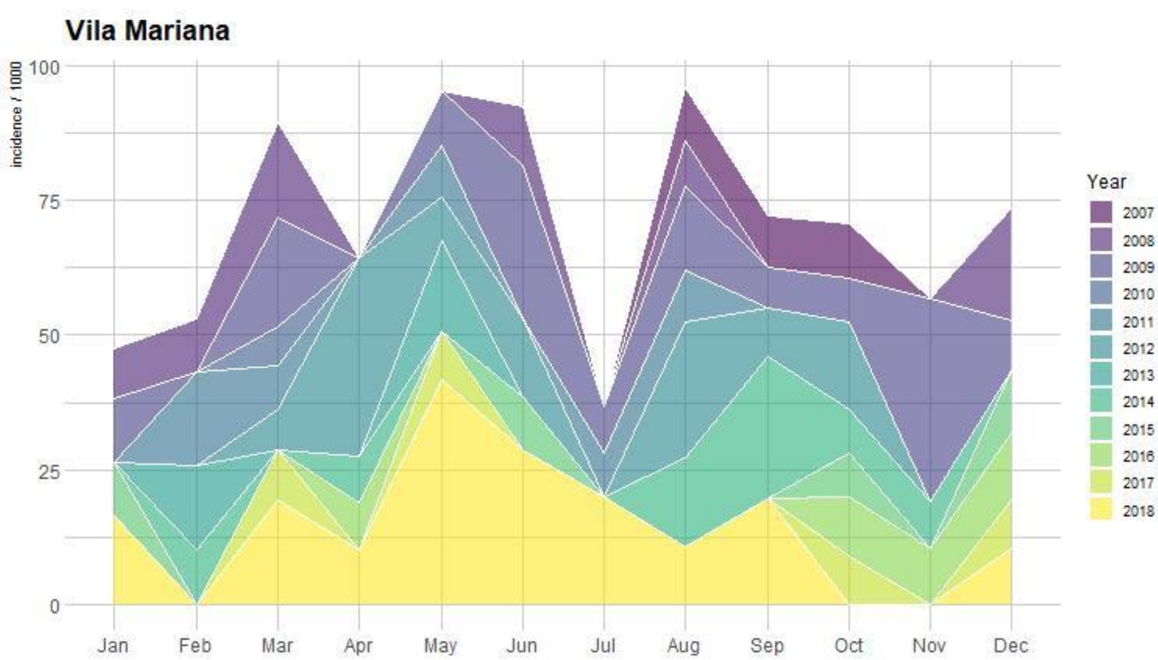

Vila Formosa
incidence / 1000
0
50
100
150
200
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018


Vila Guilherme
incidence / 1000
0
50
100
150
200
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

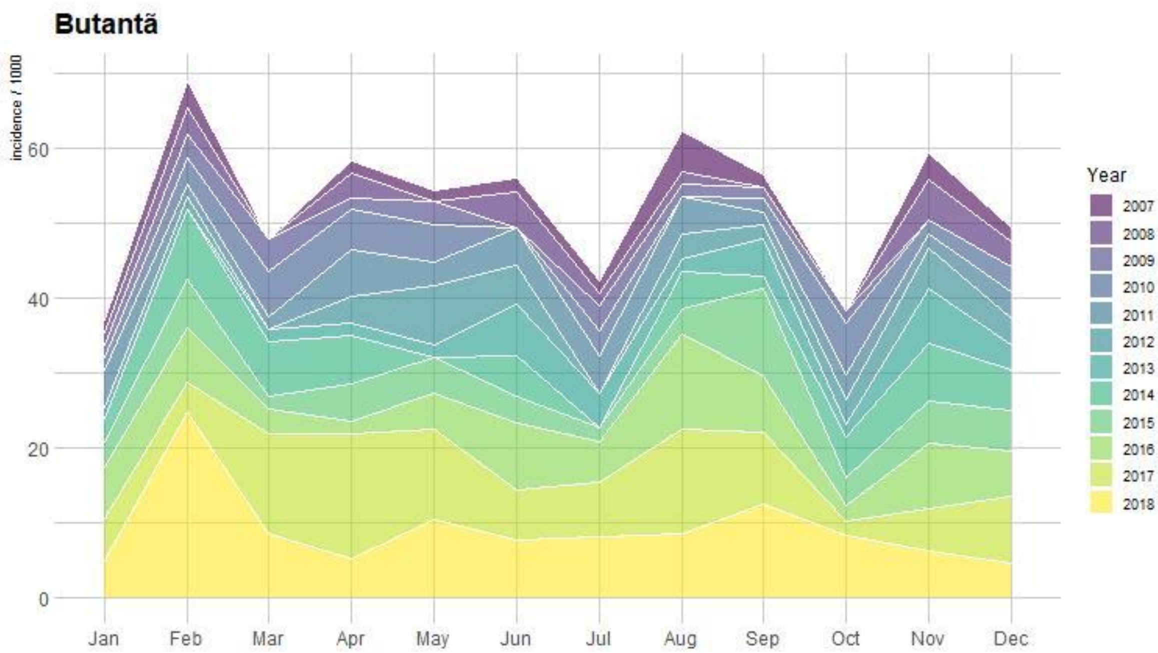

Vila Jacuí
incidence / 1000
300
200
100
0
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

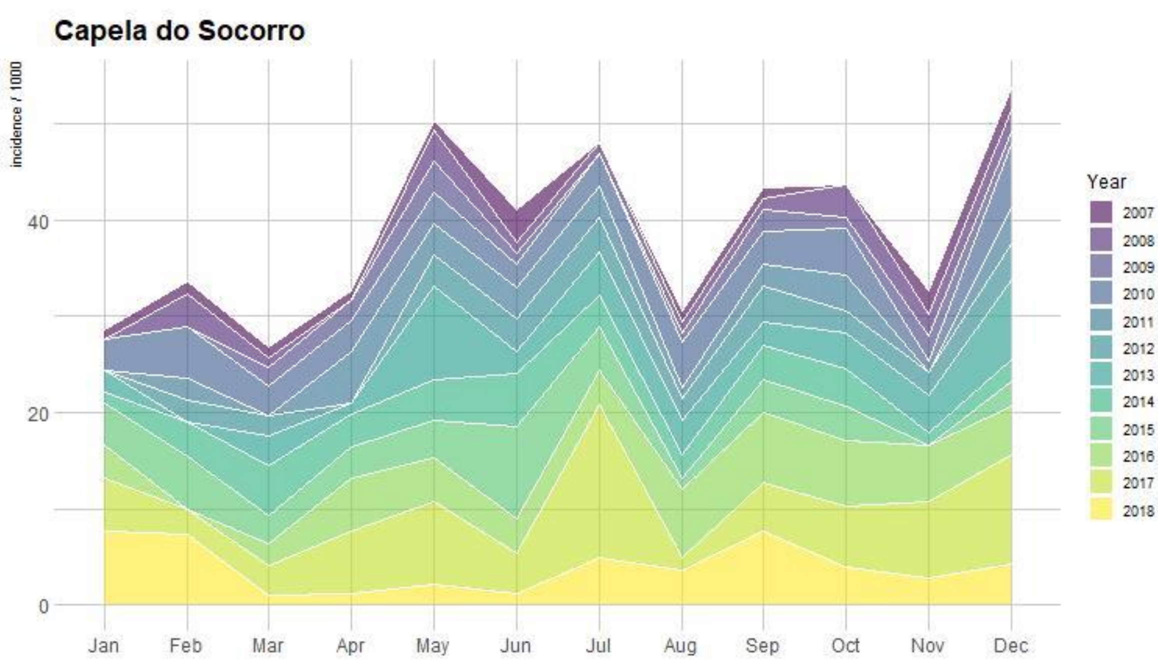

Vila Leopoldina
incidence / 1000
200
150
100
50
0
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2010
2011
2012
2013
2014
2015
2016
2017
2018

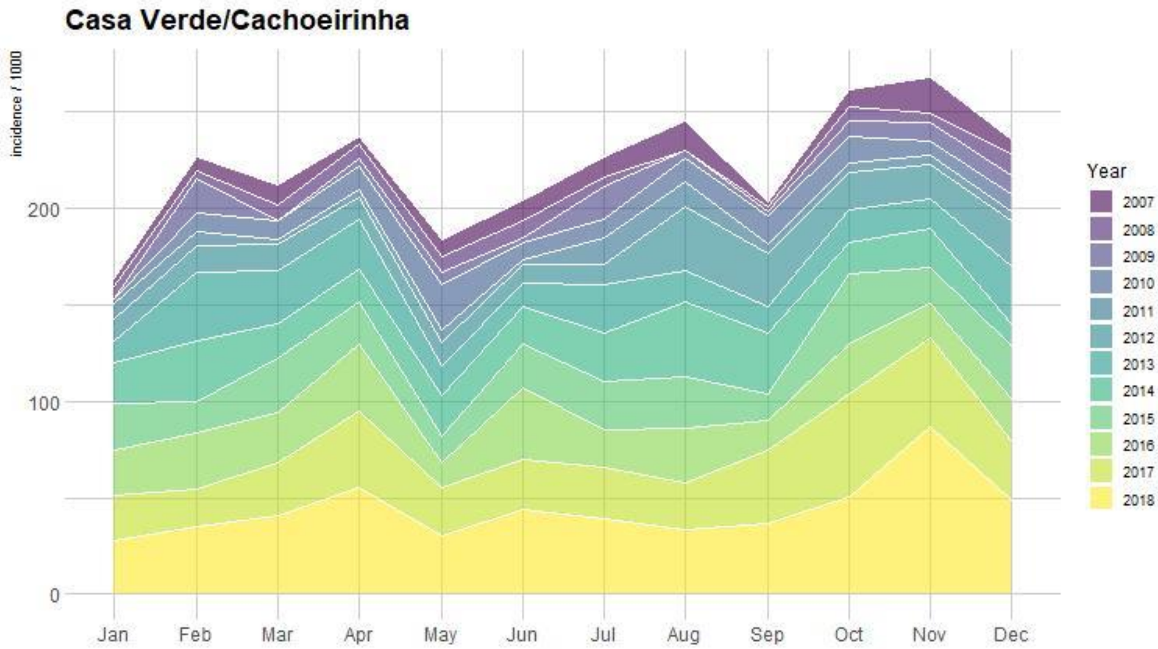

Vila Maria
incidence / 1000
0
50
100
150
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

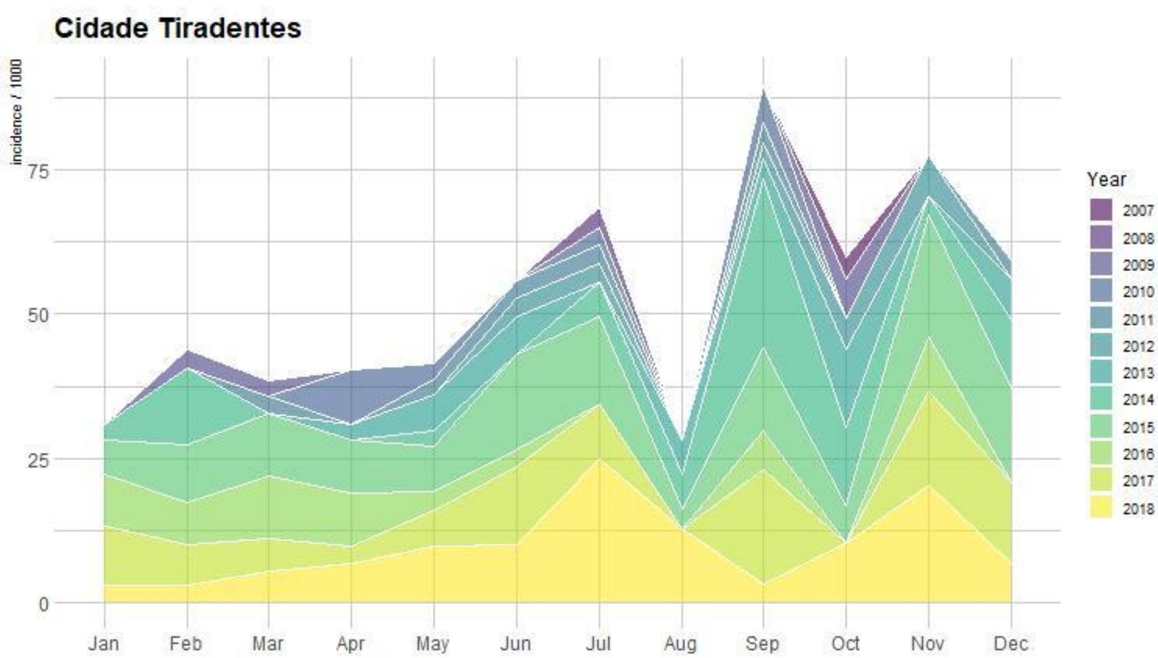

Vila Mariana
incidence / 1000
0
25
50
75
100
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

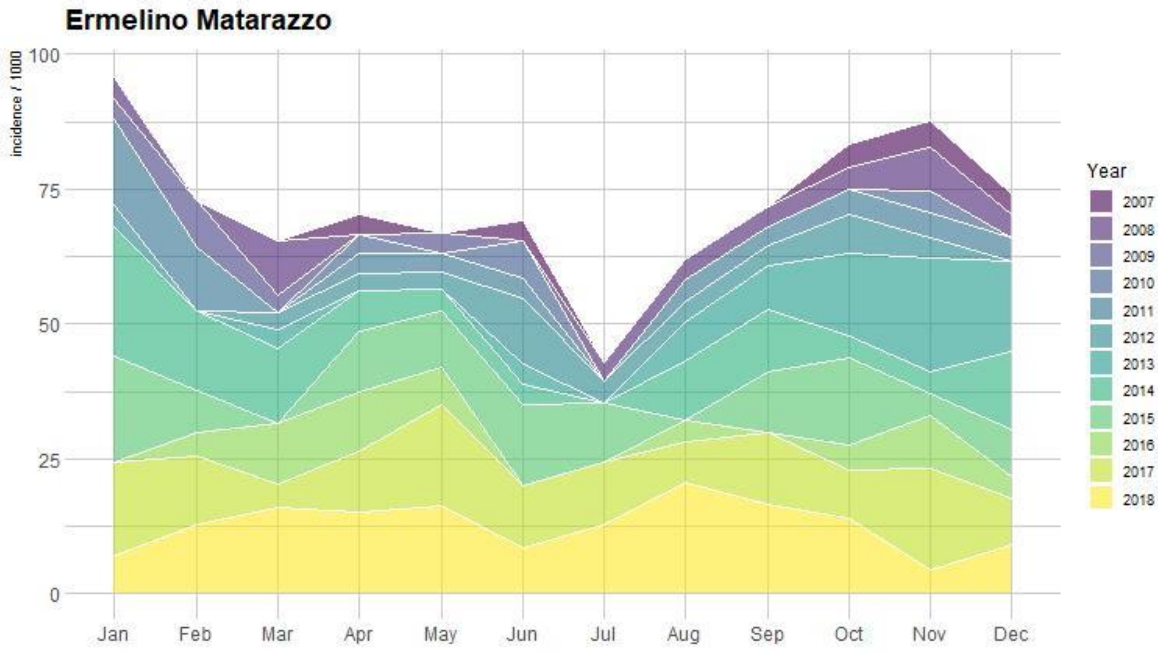
8. Appendix B – Congenital syphilis Incidence over time & STS

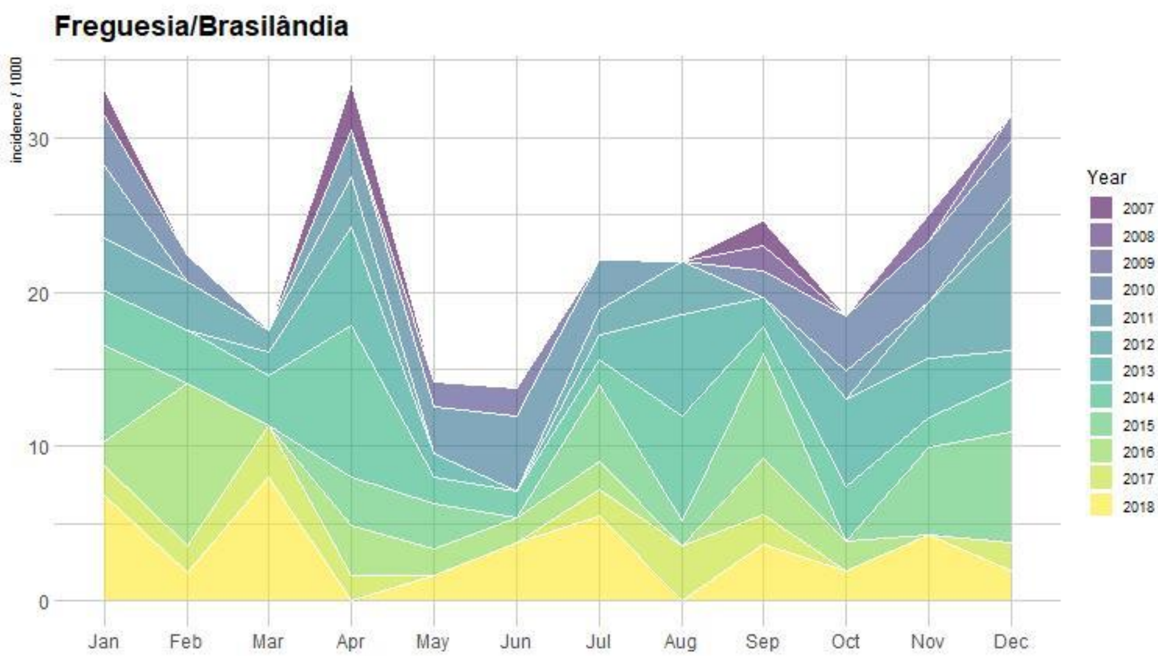


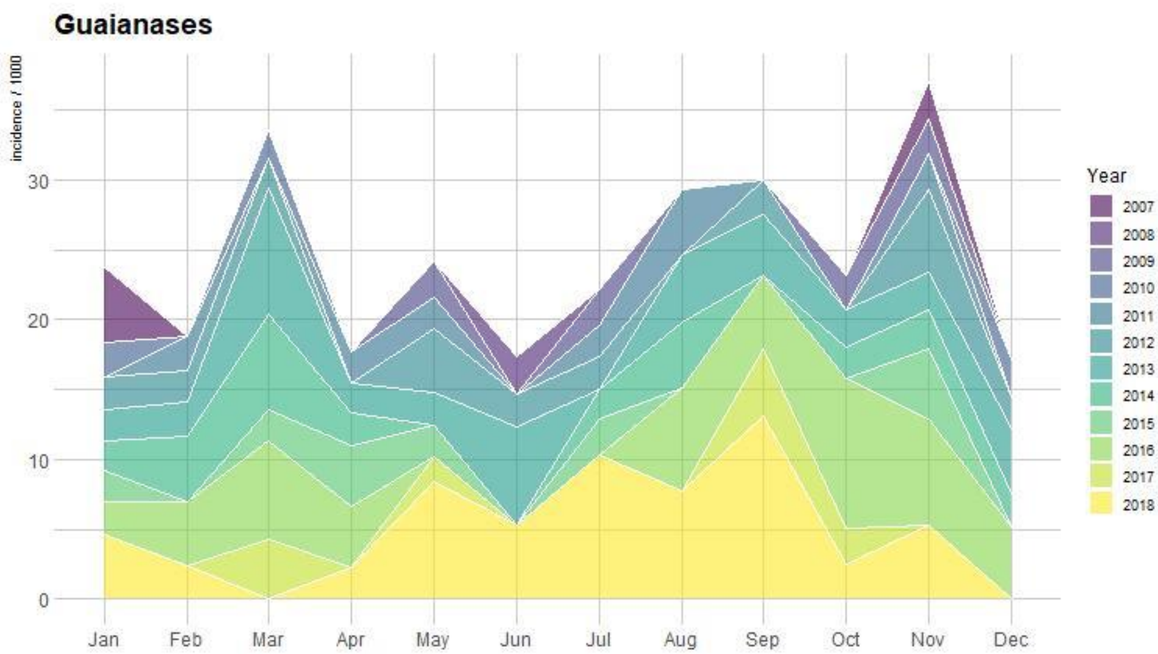


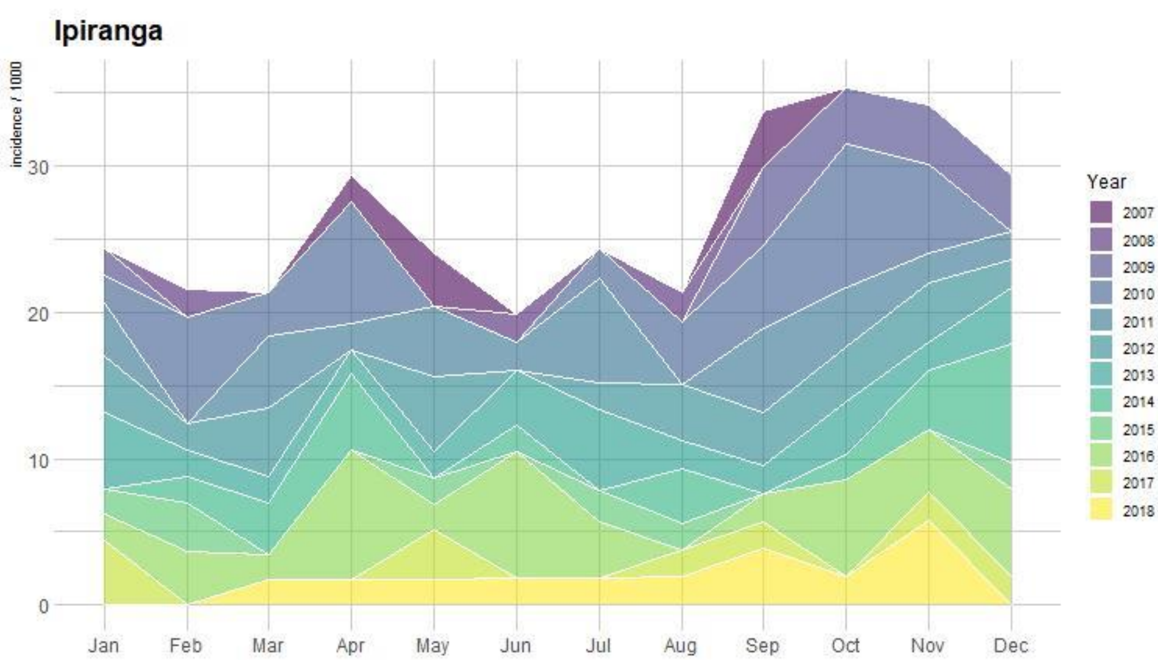

Casa Verde/Cachoeirinha
incidence / 1000
0
100
200
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

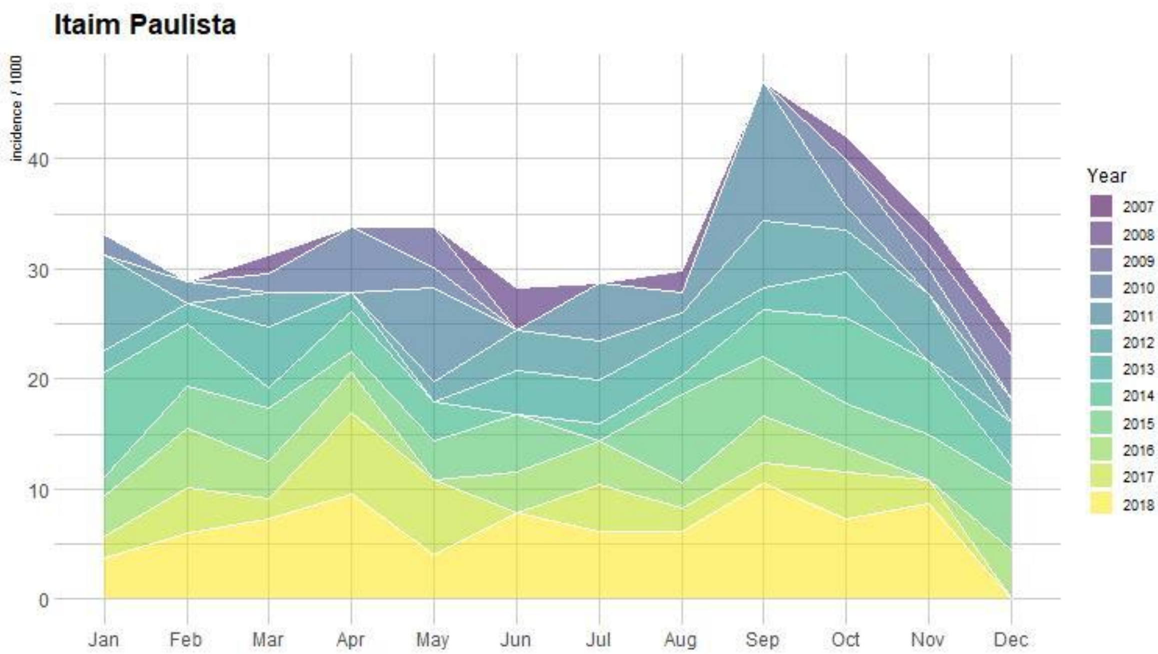

Cidade Tiradentes
incidence / 1000
0
25
50
75
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

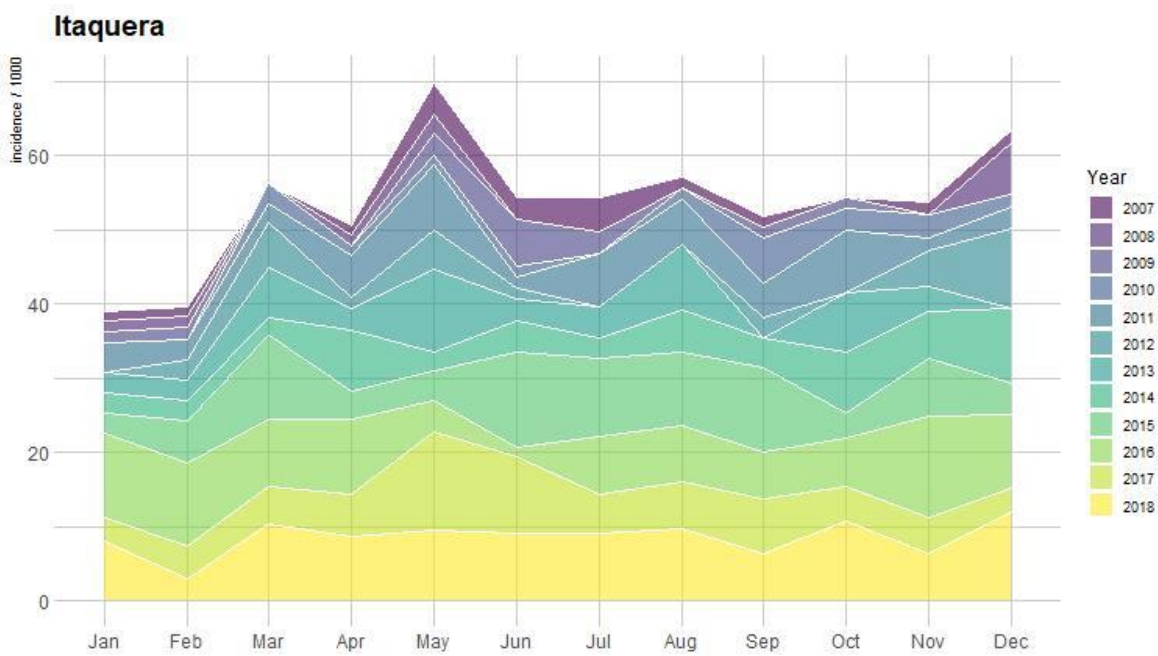

Ermelino Matarazzo
incidence / 1000
100
75
50
25
0
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

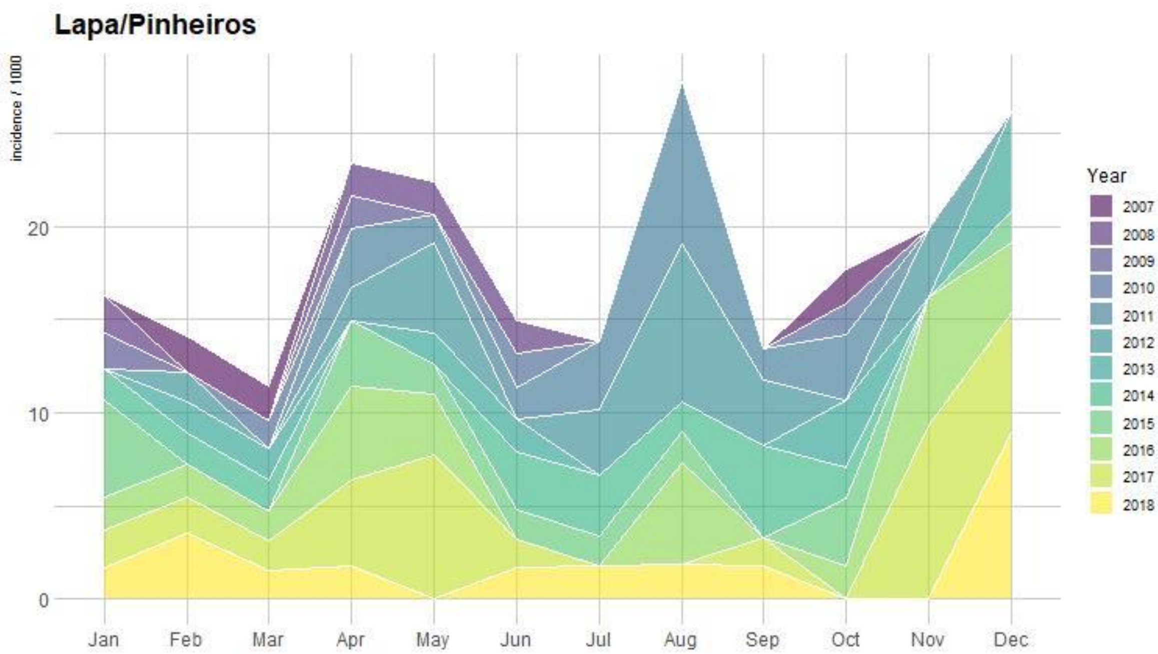

Freguesia/Brasilândia
incidence / 1000
30
20
10
0
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

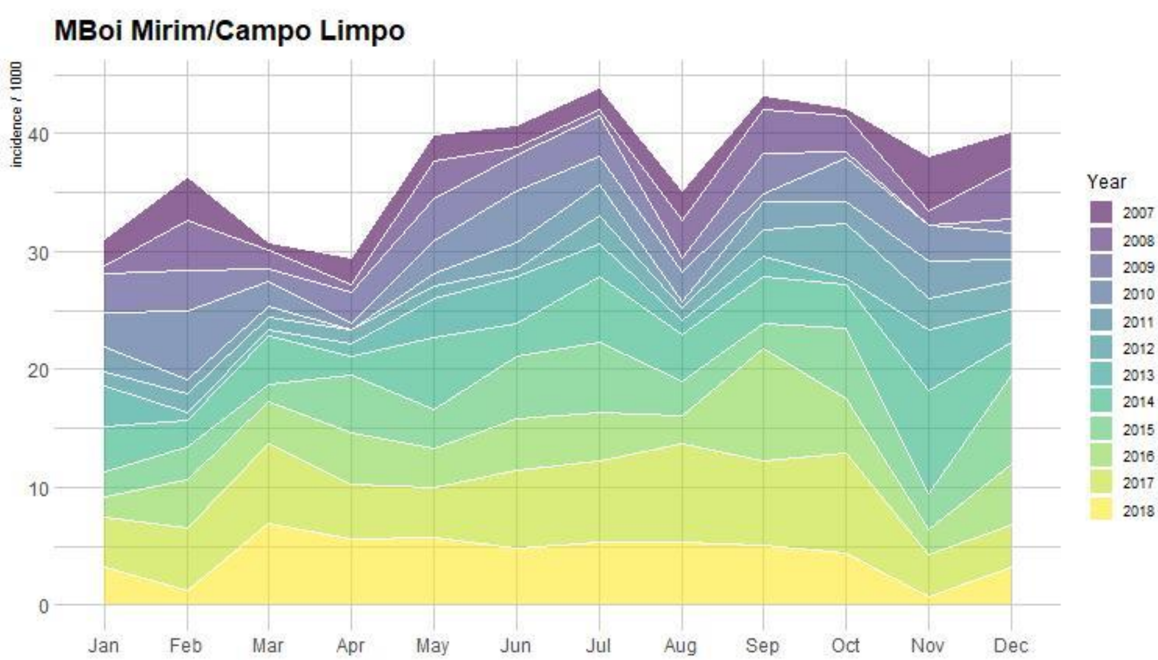

Guaianases
incidence / 1000
0
10
20
30
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

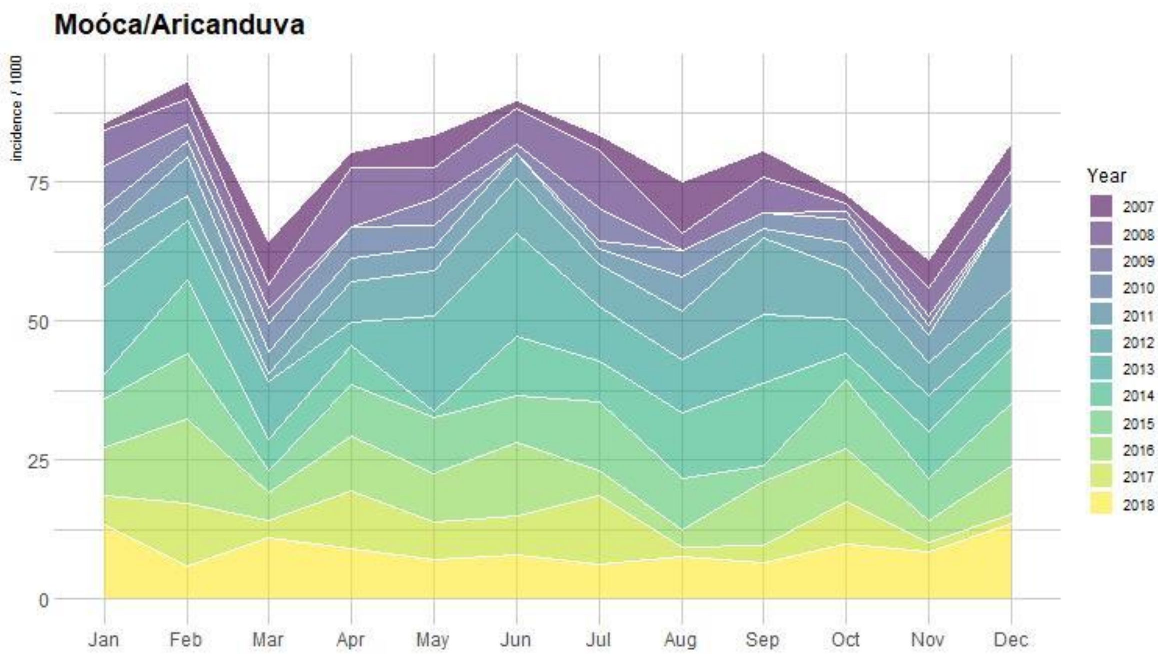

Ipiranga
incidence / 1000
0
10
20
30
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

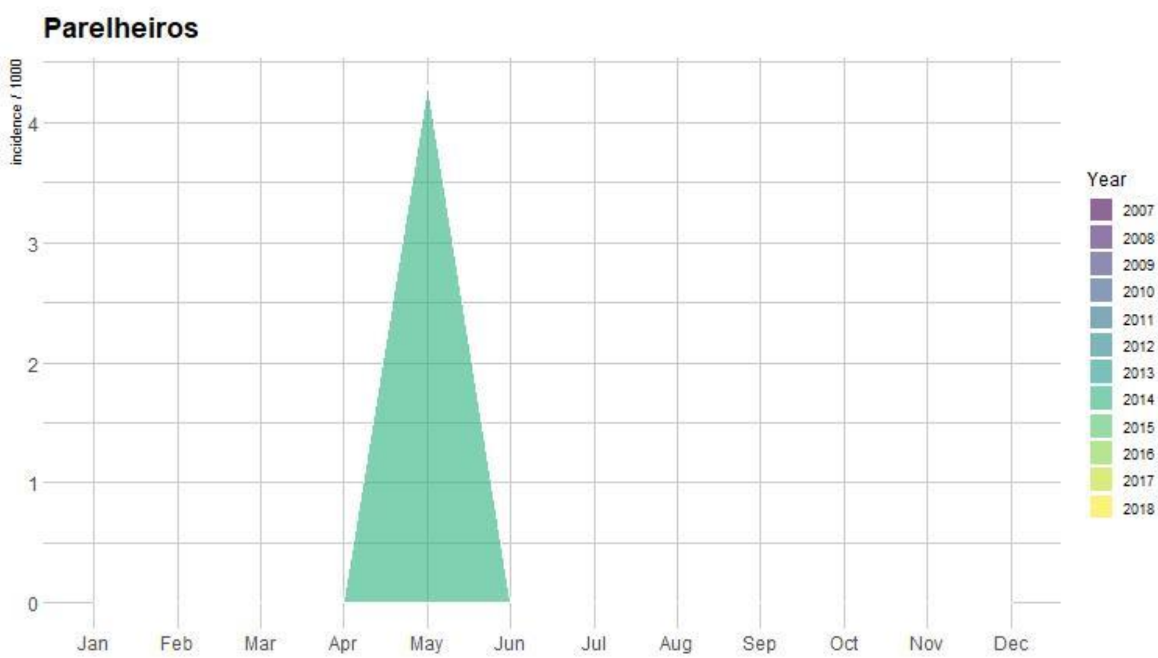

Itaim Paulista
incidence / 1000
0
10
20
30
40
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

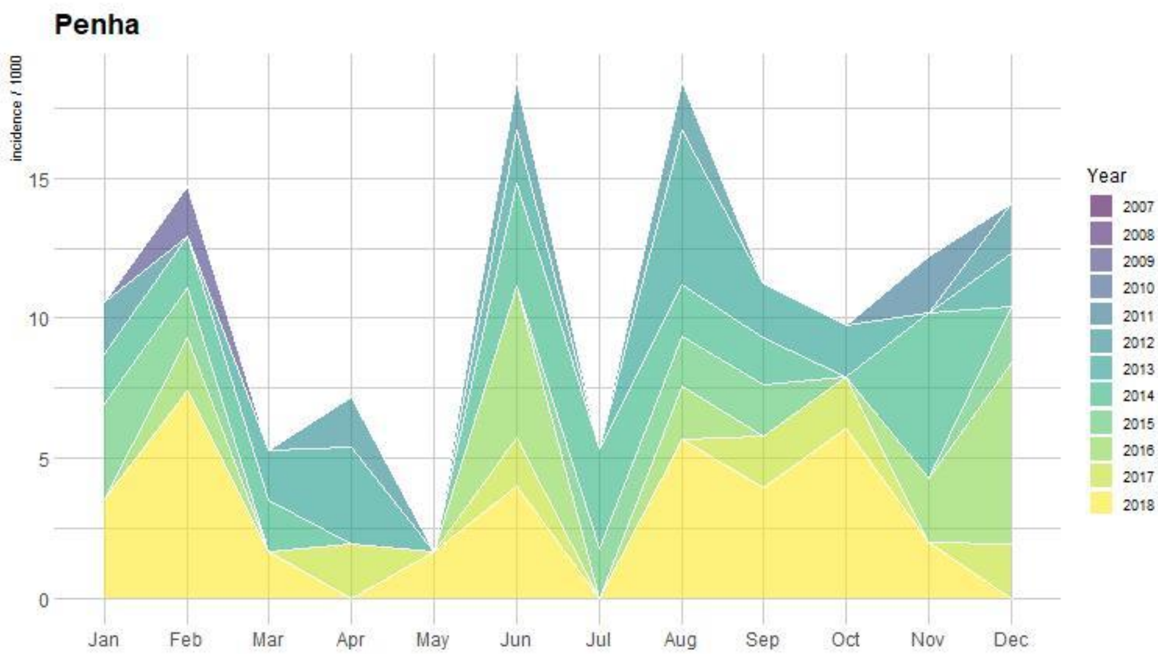

Itaquera
incidence / 1000
0
20
40
60
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

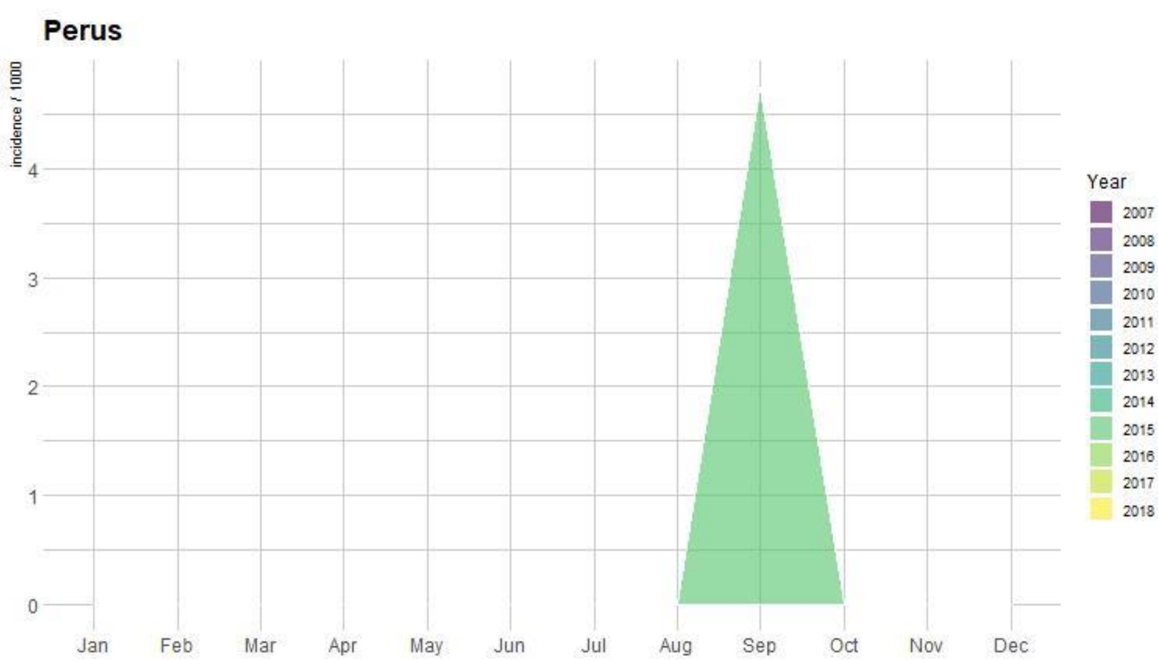

Lapa/Pinheiros
incidence / 1000
0
10
20
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

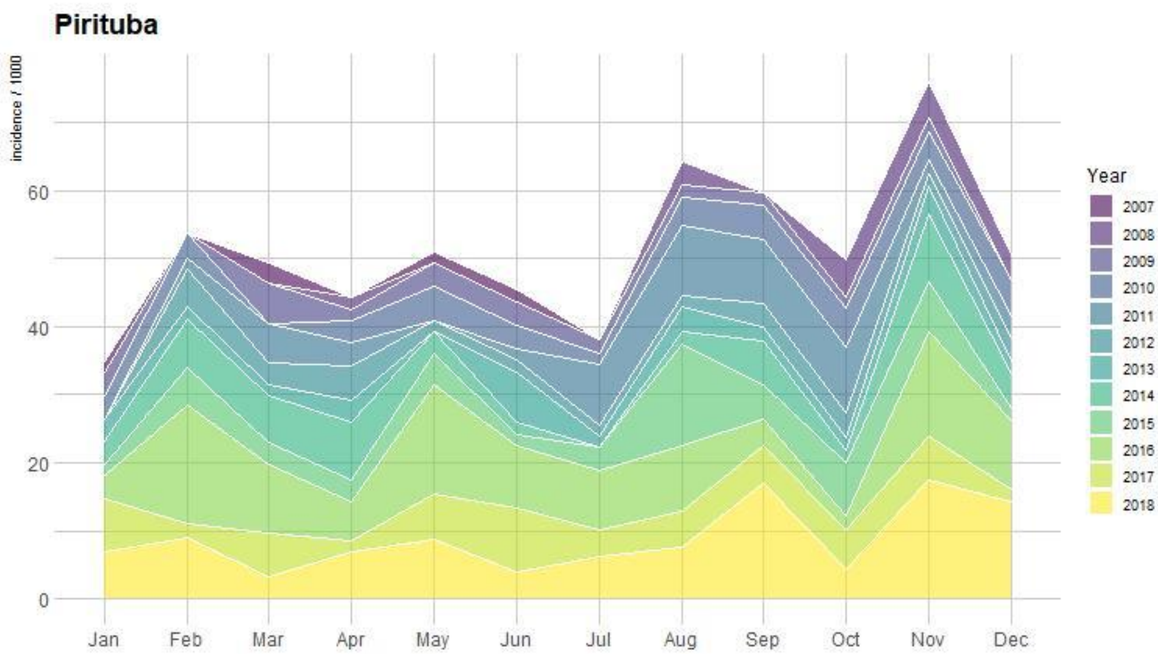

MBoi Mirim/Campo Limpo
incidence / 1000
0
10
20
30
40
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

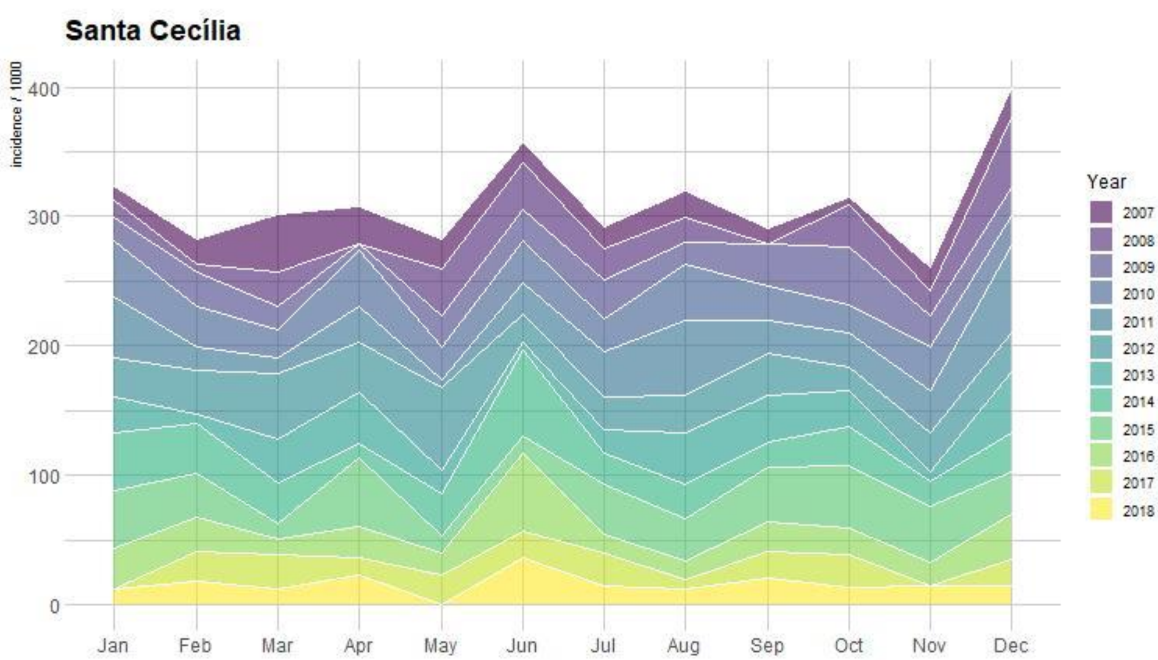

Moóca/Aricanduva
incidence / 1000
0
25
50
75
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

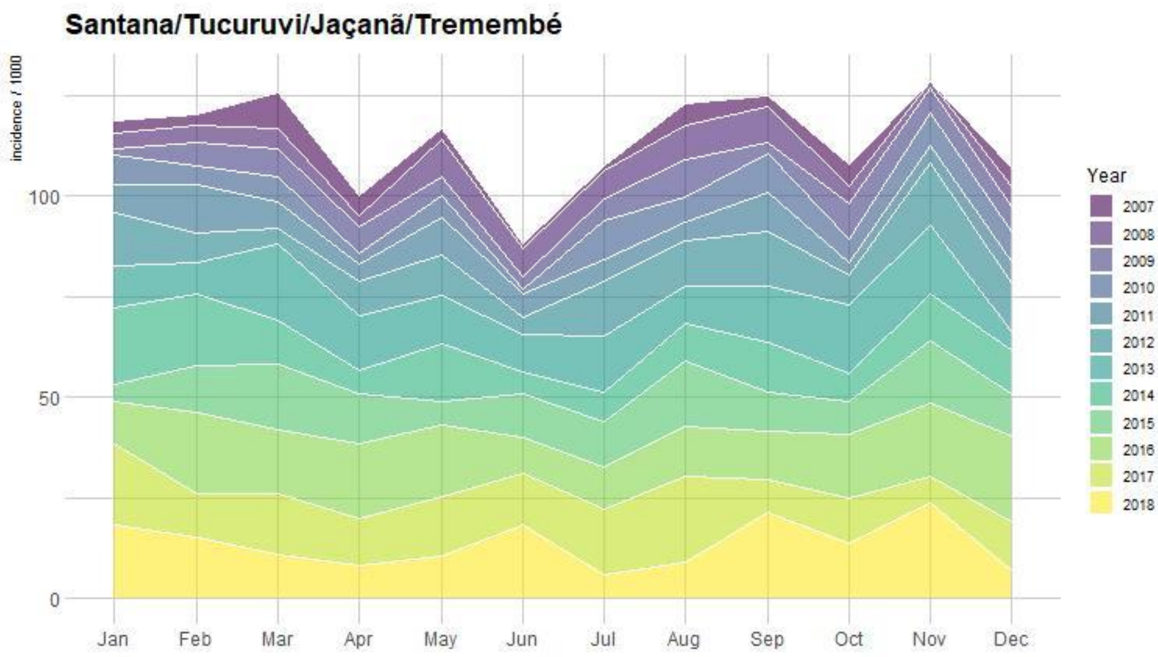

Parelheiros
incidence / 1000
0
1
2
3
4
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

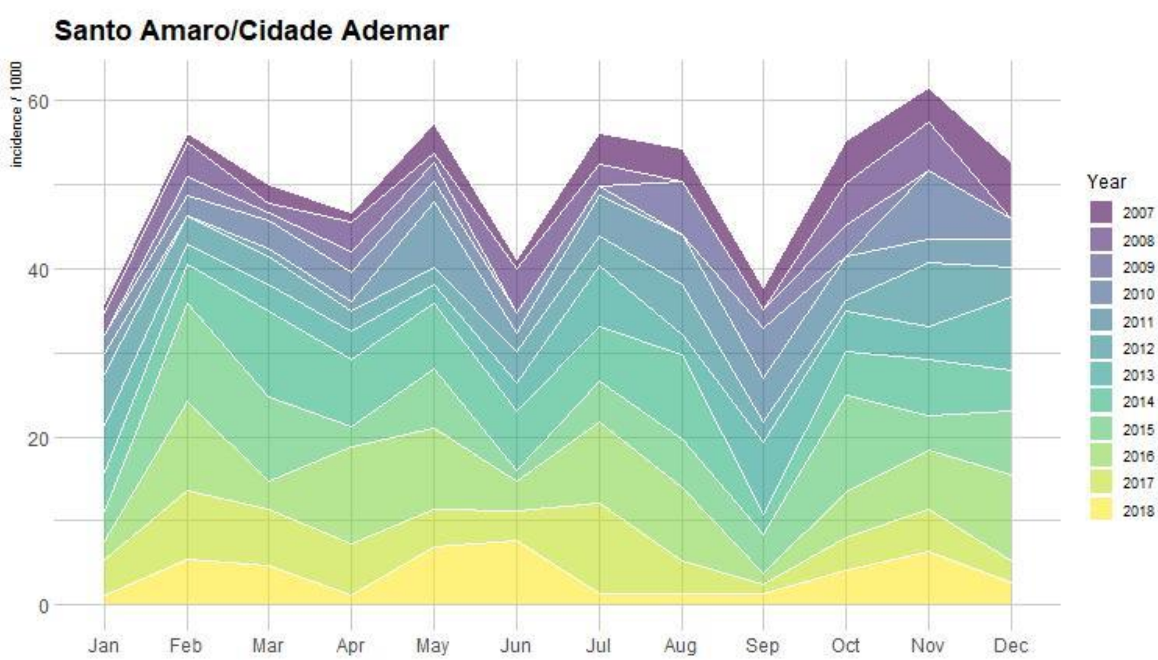

Penha
incidence / 1000
0
5
10
15
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

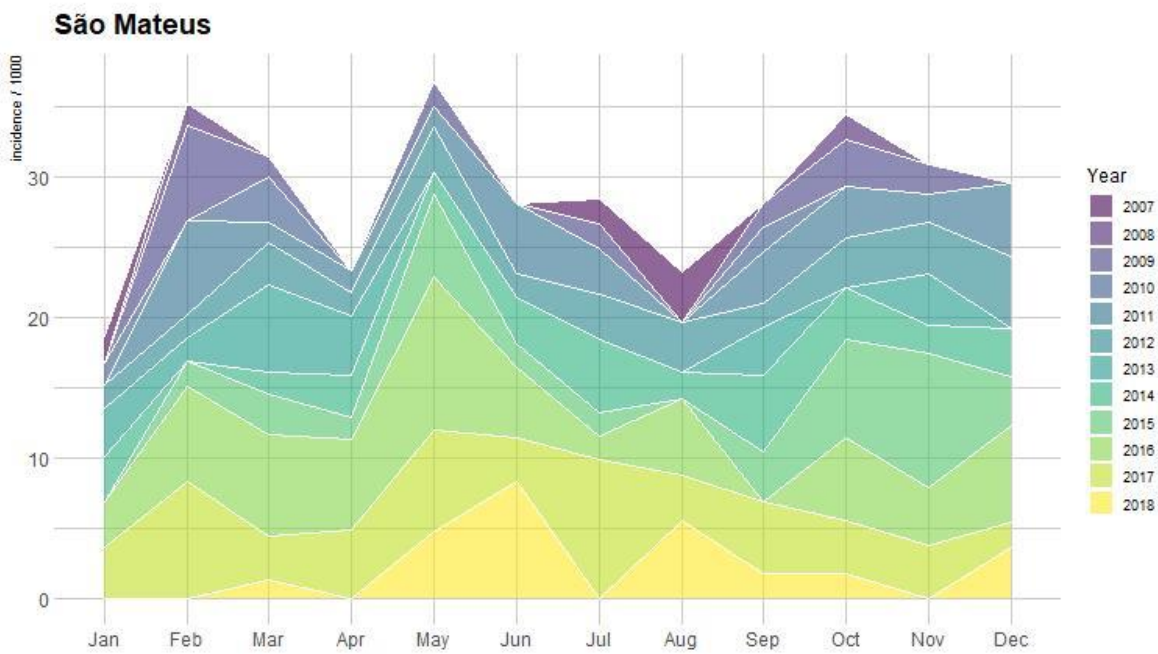

Perus
incidence / 1000
0
1
2
3
4
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

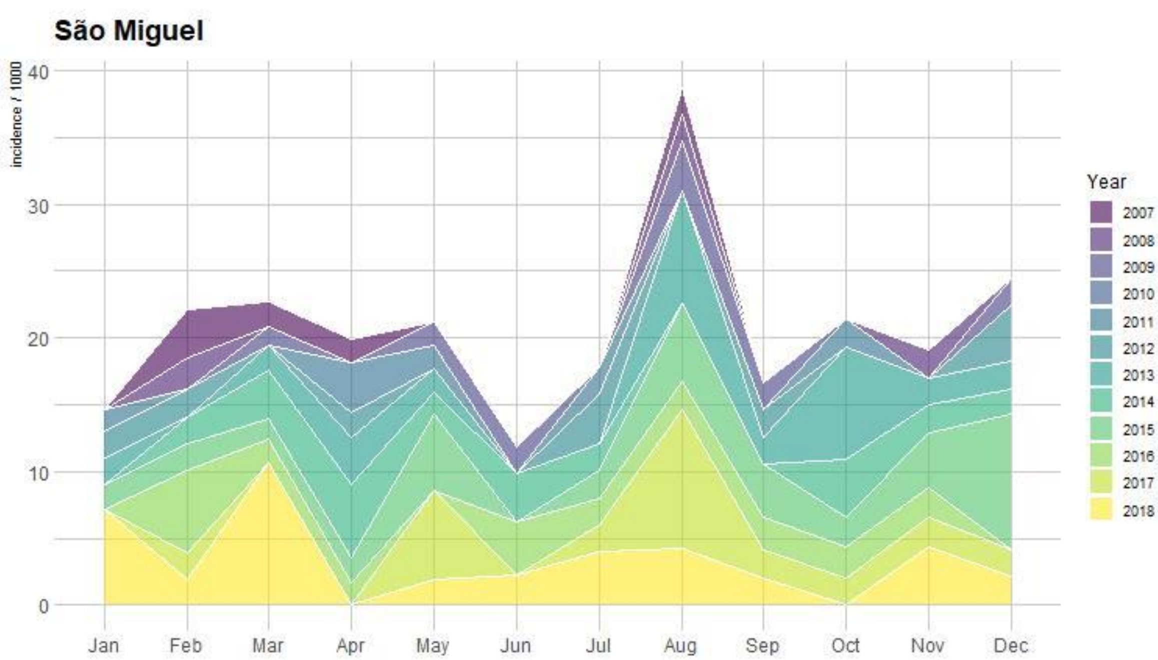

Pirituba
incidence / 1000
0
20
40
60
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

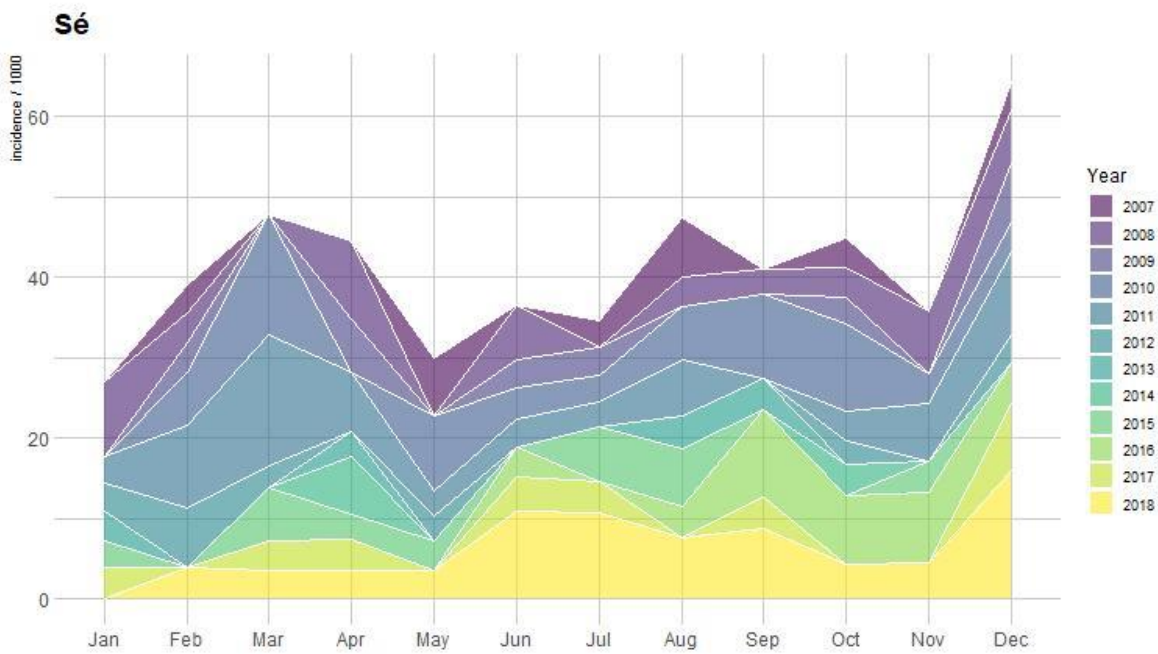

Santa Cecília
incidence / 1000
0
100
200
300
400
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

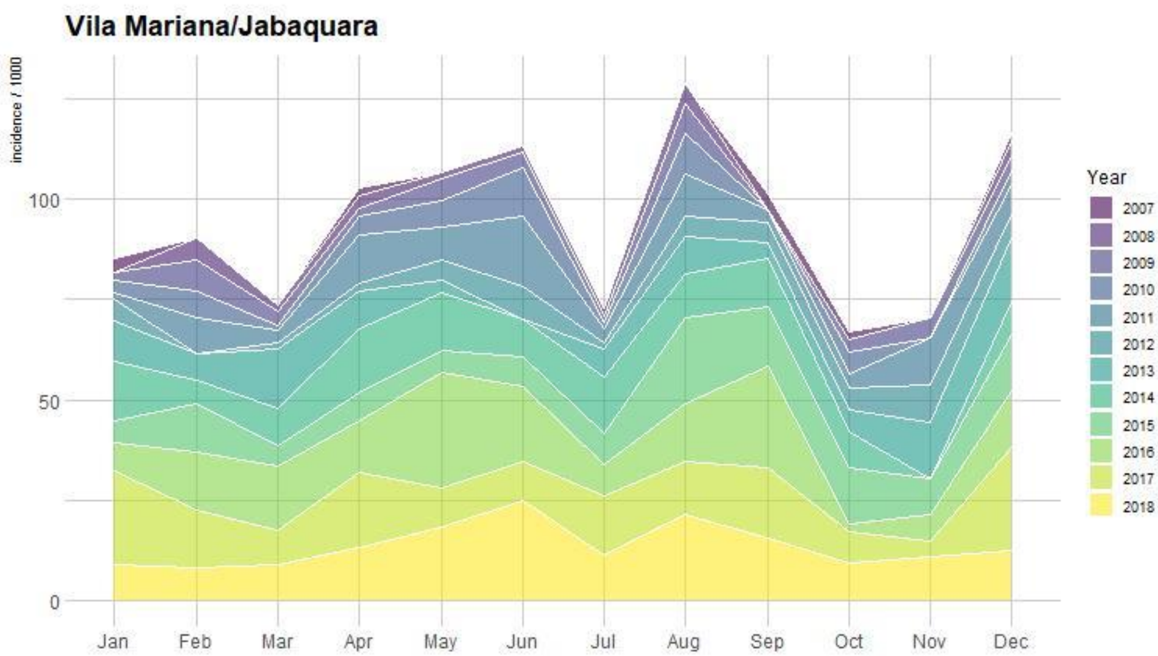

Santana/Tucuruvi/Jaçanã/Tremembé
incidence / 1000
100
50
0
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

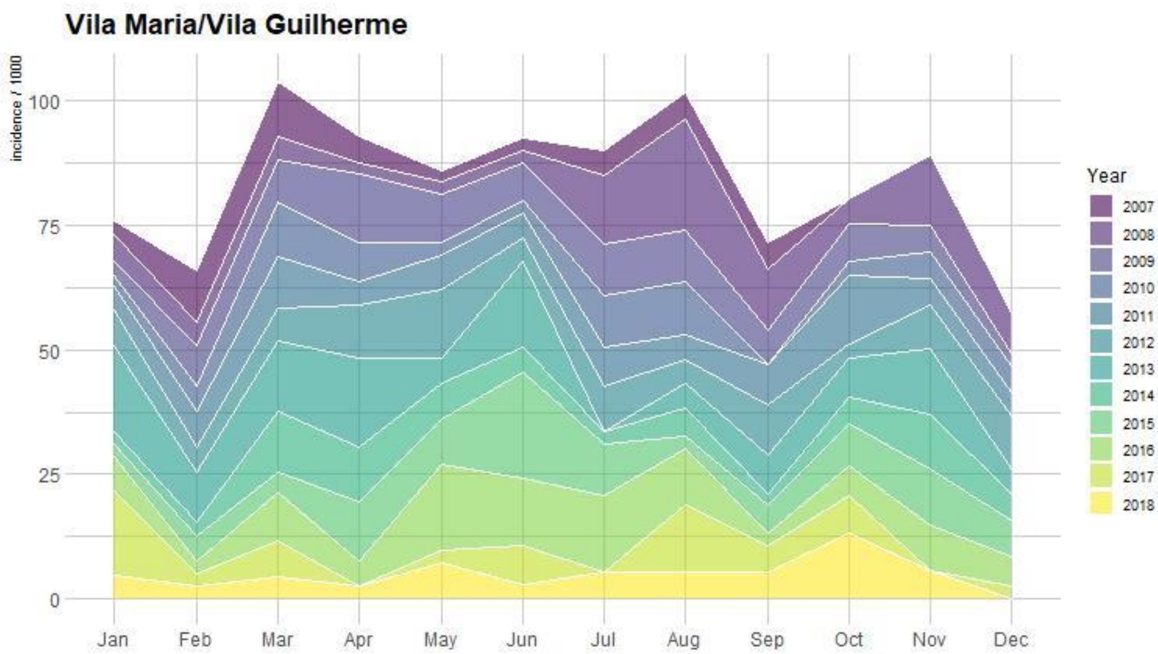

Santo Amaro/Cidade Ademar
incidence / 1000
60
40
20
0
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

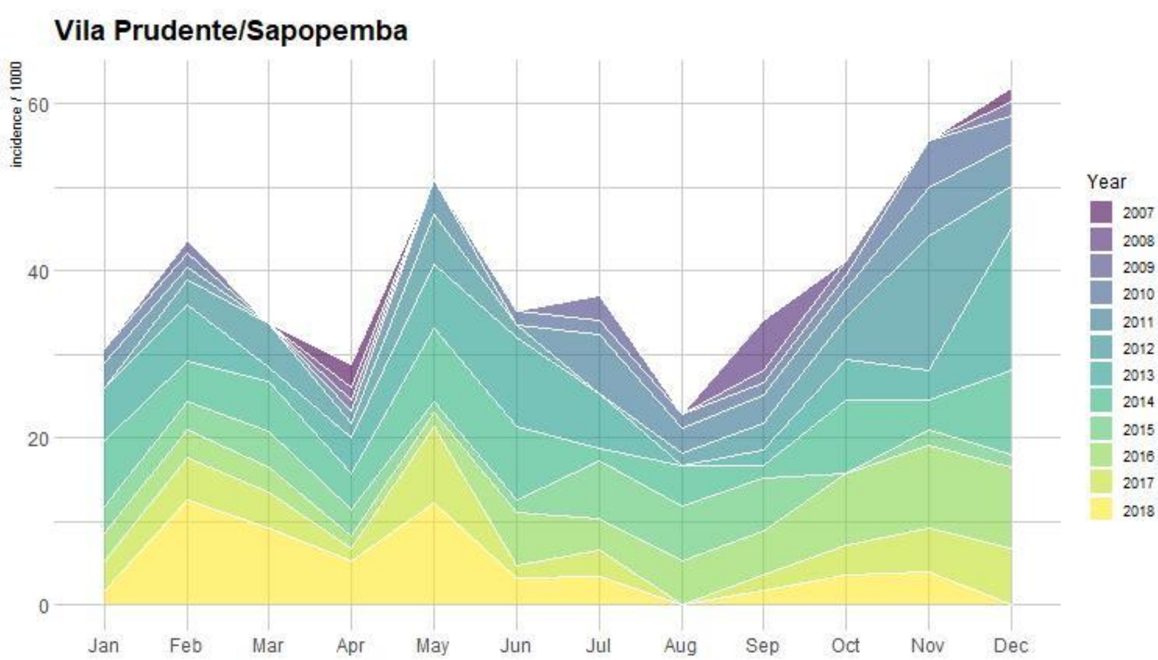

São Mateus
incidence / 1000
0
10
20
30
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018


São Miguel
incidence / 1000
0
10
20
30
40
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018


Sé
incidence / 1000
0
20
40
60
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018


Vila Mariana/Jabaquara
incidence / 1000
0
50
100
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018


Vila Maria/Vila Guilherme
incidence / 1000
100
75
50
25
0
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018


Vila Prudente/Sapopemba
incidence / 1000
60
40
20
0
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Year
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018