Titles & Abstracts

Dengue arbovirus affecting temperate Argentina province for more than a decade 2009-2020.

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Dengue disease is found in tropical and subtropical climates and within the last decade it has extended to temperate regions. Santa Fe, a temperate province in Argentina, has experienced an increase in dengue cases and virus circulation in the last decade, with the recent 2020 outbreak being the largest since dengue transmission was first reported in the province in 2009. The aim of this work is to perform a description of spatio-temporal fluctuations of dengue (DENV) cases from 2009 to the present in Santa Fe province. The data presented in this work provide a detailed description of dengue virus transmission for Santa Fe province by department. This information is useful to assist in better understanding the impact of ongoing dengue emergence in temperate regions across the world. Indeed, this work provides data useful for future studies including those investigating socio-ecological, climate, and environmental factors associated with dengue transmission, as well as those investigating other variables related to the biology and the ecology of vector-borne diseases.

Background & Summary

Dengue virus (DENV serotypes 1-4) is considered one of the most important emerging and reemerging arboviruses today responsible for dengue fever, dengue hemorrhagic fever, and dengue shock syndrome. *Aedes aegypti* mosquitoes are the main vectors for DENV as well for yellow fever, Zika and chikungunya viruses. Dengue disease is found in tropical and subtropical climates, and in the past decade it has extended to temperate regions[1,2]. Vector-borne diseases are sensitive to environmental and climatic changes[3,4], which could bring on changes in vector distribution and abundance as well as changes in disease incidence rates[5]. In the last 10 years, DENV has undergone a rapid expansion into temperate regions, generating numerous epidemic events[1].

DENV was eradicated from Argentina in the middle of the past century due in part to successful *Ae. aegypti* control programs; however, during 1998 the first autochthonous transmission and subsequent outbreak was registered in subtropical northern Argentina[6]. After the reemergence, successive outbreaks appeared in the warmest months and were always closely related to outbreaks in neighboring countries[7]. Currently in Argentina most of its provinces (17 of 23) have reported autochthonous cases of dengue since its reemergence[8]. *Aedes aegypti* distribution has a wide range in the country, and therefore there is the risk of outbreaks if the virus circulates in those areas[9].

Santa Fe province is in central-northeastern Argentina, at the southern cone of South America (Fig. 1A) and according to the Köppen-Geiger climate classification[10] has a temperate climate with hot summers and no dry season. The province is one of the most populated and productive areas of the country. In fact, it features international road connections through the bi-oceanic corridor and the Parana-Paraguay waterway, which gives Santa Fe a privileged geo-strategic location. This central bi-oceanic corridor connects with Chile in the Pacific Ocean and Uruguay in the Atlantic Ocean. Santa Fe also connects the southern provinces of Argentina with those of the center and northeast (Fig. 1B). Indeed, Santa Fe is a place of passage for land cargo and passengers with Bolivia, Paraguay and Brazil which are neighboring countries with endemic DENV circulation[11].

According to the Argentina Ministry of Health (MoH), Santa Fe province is a central epidemiological region of the country together with Córdoba and Entre Ríos provinces and therefore we will be refereeing to the central region despite Santa Fe being climatically and geographically in central northeastern Argentina as we describe above. Argentina experienced for first time in the central region the report of dengue cases with the 2009 outbreak. Since them dengue cases have been reported each year with the largest number to date occurring in 2020 where more than 50% of the dengue cases of the whole country have been reported in this region. Moreover, Santa Fe province is facing the biggest dengue epidemic since dengue's re-introduction

in the country, despite control efforts of the Health Ministry of Santa Fe (MoS) and the MoH. Several protocols were implemented, that included entomological surveillance, environmental sanitation, focal control and emergency actions such as chemical spraying around dwellings with reported dengue cases[12].

The aim of the present work is to perform a detailed description of spatio-temporal fluctuations of dengue cases since 2009 to present in the temperate Santa Fe province of Argentina. Also, we present dengue case distribution and incidence by province jurisdiction. The data base included in this paper is important for future DENV cases studies in the central temperate region of the country, and it is an important source of information for researchers investigating dengue emergence worldwide. In the past few years, the MoS together with the Center for Climate Variability and Climate Change Studies (CEVARCAM, acronym in Spanish), have being working in collaboration to develop studies for a better understanding of the relationships between vector-borne diseases and climate[13]. Studies of the impacts of climate changes through meteorological and environmental variables, as well as socio-economic variables affecting the incidence and dengue transmission rates could be developed with the data sets presented here. Studies with mathematical models could utilize this data to investigate previous outbreaks and predict future outbreaks and dengue case occurrence. This study could be useful for stakeholders on making decisions related to dengue prevention, control, and management at local, national, or even international levels.

Methods

Dengue epidemics were documented between January 2009 and May 2020 in Santa Fe province (Fig. 1). The region is characterized by a homogeneous geomorphological conformation where the Chaco-Pampeana plain predominates. It consists in a mosaic of wet savannahs and grasslands, subtropical dry forests, gallery forests, shrublands, and a wide variety of wetlands (e.g., rivers, streams, marshes, swamps). The climate in the region is temperate with hot summers and no dry season, according to Köppen-Geiger's climate classification[10]. The study area presents a latitudinal gradient with maximum temperatures and rainfall in the north and minimums in the south. The average maximum temperatures in summer range between 32 and 30 °C, minimum temperatures in winter between 9 and 3 °C. In summer, the precipitation varies between 168 and 136 mm, in winter between 26 and 13 mm. There is more precipitation in the northeast and less in the southwest. These values were obtained from the National Weather Service of Argentina (SMN) based on average values of temperature and precipitation from the period 1981–2010[14]. The Paraná River is the main waterway and constitutes the eastern limit, along with a complex system of

islands, main channels, lagoons, and wetlands. The dynamics of the Paraná River floodplain are strongly shaped by cycles of rises and falls in water levels[15]. The Salado River is another important waterway that crosses the center of the province from west to east flowing into the Paraná River. Santa Fe province is divided into 19 departments and contains a total population of 3.2 million inhabitants[16].

Surveillance of arboviruses in Argentina is carried out in an integrated manner, within the surveillance framework for nonspecific acute febrile syndrome and cases that meet specific definitions for each arbovirus. Notifications of suspicious cases are made through the National Health Surveillance System. The MoH, through the National Directorate of Epidemiology and Analysis of the Health Situation, publishes monthly the Integrated Surveillance Bulletin in which the number of total dengue cases are detailed by province[17].

The reported data of cases, discriminated by department and locality of residence, were requested from the MoH by means of a facility known as the access to public information (National Law 27275), with the protection of personal data regulated by the National Law 25326. The National Health Surveillance System operated by the MoH reports dengue suspected infections at either private or public clinical sites. Samples from the central-northern region of the province were analyzed by the Central Reference Laboratory of the City of Santa Fe, while those from the southern region were analyzed by the Ambulatory Medical Center of Rosario city. The selection of the diagnostic methods is made on the basis of the days of evolution of the symptoms with respect to the date of sampling, using either direct methods of detection of NS1 antigen (nonstructural protein 1), viral genome or viral isolation, and / or indirect methods of detection of IgM and IgG antibodies by neutralization with flavivirus panel, according to the diagnostic algorithm and the level of complexity of each laboratory[18]. A subset of samples is sent to the National Reference Laboratory (INEVH-Maiztegui) in the city of Pergamino, Buenos Aires province, where the diagnostic methods are carried out by viral isolation and neutralization with a flavivirus panel.

We have compiled and reviewed all available data on dengue cases including confirmed and probable cases, autochthonous and imported cases, DENV serotypes, and provenance of imported cases (either from another country or another province of Argentina) between January 2009 and May 2020 period. This study does not include suspected and unconfirmed cases. The spatio-temporal fluctuation of DENV cases was analyzed and the areas and periods with the highest incidence of the disease were identified. A time series of monthly incidence (number of cases per 10,000 inhabitants), was created to determine the outbreaks progression during the whole study period January 2009-May 2020. Additionally, a time series was created with the number of cases per epidemiological week (EW) between January and May 2020, to describe the most recent and

most important outbreak in the province to date. A dengue incidence map (number of cases per 10,000 inhabitants) was prepared to facilitate determining the most affected departments.

Data Records

The database is publicly available online (via figshare[19]) as a set of four column separated files. The first contains the total number of cases and incidence per month and per year for the province of Santa Fe. The second contains the total number of cases and incidence discriminated by department. The third file contains the number of cases in the cities with a high number of DENV cases and incidence in Santa Fe province in 2020. The column headings of the files are as follows.

YEAR: The year of the date of the entry.

MONTH: The month of the date of the entry.

AUTO_CASES: Number of autochthonous cases

IMP_CASES: Number of imported cases

POP_SIZE: Population size

AUTO_INC: Incidence of autochthonous cases (per 10,000 people)

IMP_INC: Incidence of imported cases (per 10,000 people)

EPID_WEEK: The epidemiological week described by MoH bulletin of the given date.

AUTO_IMP_CASES: Number of autochthonous and imported cases.

DEPARTMENT: Santa Fe province department

INCIDENCE: Total incidence by Santa Fe province department (per 10,000 people)

A total of 6,454 DENV cases were reported between January 2009 and May 2020 (6,209 autochthonous, 245 imported). Figure 2 and Table 1 show the dengue emergence in the studied period. Four dengue outbreaks have been reported in Santa Fe province since 2009, with the most severe one reported in the 2020 season with 4521 dengue cases, 4457 of which were autochthonous and 64 of which were imported (total incidence of 14.16 per 10,000 people). As shown in Figure 2 during 2016 and 2019 the province experienced outbreaks, with 2016 being the more intense one of these two. The 2016 outbreak reported 1014 dengue cases with 929 autochthonous and 85 imported cases (total incidence of 3.05 per 10,000 people). During 2019, 484 dengue cases were reported with 467 autochthonous and 17 imported cases (total incidence of 1.51 per 10,000 people). During the first outbreak that reached central Argentina in 2009, 154 dengue cases were reported, where 120 were autochthonous and 34 imported cases (total incidence of 0.47 per 10,000 people) (Table 1). Imported dengue cases originated mainly from tropical countries where dengue fever is endemic, as well as the endemic northern region of Argentina, although there were also imported

cases from temperate countries such as Uruguay (Table 2). Although DENV circulation typically occurs between January and May each season, during August 2009 (N = 1), July 2011 (N = 1), October (N = 1) and December 2013 (N = 1), November 2016 (N = 2) and June 2018 (N = 4), ten autochthonous dengue cases were reported in Santa Fe between June and December.

Figure 3 shows the incidence of dengue by departments of the province of Santa Fe in the period January 2009 - May 2020. Dengue incidence in Santa Fe departments was clearly highest in the northeast area of the province that borders with Chaco and Corrientes provinces located northeast of the country. The predominant serotype that circulated among all outbreaks was DENV-1 although all four DENV serotypes were detected across outbreaks (Table 1). At present during the 2020 outbreak, 56.3% of the cases were detected as DENV-1 (488 cases), 42.98% as DENV-4 (371 cases) and 0.46% as DENV-2 (4 cases) (Table 1). DENV-4 was widely distributed in the province, although DENV-2 was reported in Rosario department and DENV-3 was not reported during this outbreak (Fig. 3). Between EW 9 and EW 17, five deaths were reported (0.11 % of total cases in the province). Table 2 shows the most affected cities during the 2020 outbreak, where almost 80 % of the cases were reported.

Technical Validation

All data presented within this work were requested to the MoH by means of a facility known as the access to public information (National Law 27275), with the protection of personal data regulated by the National Law 25326. These data requested from the MoH were tested with the reports sent by the MoS through the National Health Surveillance System.

Usage Notes

The data presented herein show the increases of DENV cases and DENV transmission in the last decade in the temperate Santa Fe province, highlighting the 2020 outbreak as it is most important outbreak to date. This data also highlights the importance of this area in dengue emergence because of its geographic location relative to other provinces and neighboring countries were DENV has endemic circulation.

In the last decade, the intensity of DENV circulation has increased with expansion to temperate regions of the globe and with the size of outbreaks in endemic and emerging regions increasing in magnitude[20]. This is evident in Santa Fe province, which experienced increases in dengue cases across the last decade with four dengue outbreaks. In fact, during August 2019 the World Health Organization (WHO) warned about the incoming dengue epidemic in the Americas for this last season. Reported dengue cases in the Americas have been at their highest, at 2,733,635

dengue cases reported through EW 42 of 2019[21], with neighboring countries of Argentina such as Brazil and Paraguay presenting the highest incidences[22,23,24].

Argentina experienced its most important season of dengue to date in 69.5% of the national territory (16 of 23 provinces were affected by the dengue outbreak). The dengue outbreak in Santa Fe province during 2020 was four times larger than the 2016 outbreak. The department of General Obligado, in the northeast region of the province, presented co-circulation of DENV 1 and 4. This area also connects with northern provinces of the country that border with the neighboring countries of Brazil and Paraguay were dengue has a high incidence, suggesting southern spread of dengue transmission resulting from importation via neighboring countries. In addition to increases in overall transmission, the presence of multiple serotypes co-circulating presents a risk for increased severity of dengue due to reactions among serotypes[25]. Areas of southern Brazil reported co-circulation of DENV 1, 2 and 4 until EW 23[23]. In Paraguay, cases of DENV 1, 2 and 4 were identified[24]. Rosario Department in the southeast of Santa Fe was the only one reporting DENV 2 circulation due to imported cases from travelers to Mexico and Brazil (Fig.3). The co-circulation with similar incidence of DENV 1 and 4 (Table 1) in Santa Fe province increases the possibility of severe dengue cases[25]. Co-circulation of more than 1 serotype and the increases in dengue severity caused by this is a high concern for Santa Fe province other temperate globe areas where dengue is actively emerging.

Several reasons could explain the advance of DENV and therefore dengue cases to the temperate areas, and those are related to the increased presence of the *Ae. aegypti* mosquito due to favorable environmental conditions for the mosquito's expansion[3], global travel, and environmental changes associated with increasing temperatures and changing precipitation patterns[26]. The favorable environmental conditions could be attributed to a combination of increased urbanization, human activities like forest devastation, expansion of agriculture areas, expansion of urban areas and the consequences of city areas without essential services such as garbage depots, sufficient health system, and comprehensive entomological surveillance[6]. Furthermore the 2020 outbreak is in unique context due to the COVID-19 pandemic where people in Argentina have a mandatory quarantine. It is possible that the epidemic has grown in part due to the increased time that people are spending in their homes, which potentially increases exposure to *Ae. aegypti* mosquitoes[27].

The Argentina dengue control plan is based on integrated strategies for diminishing the vector population. Therefore, it is necessary to focus researchers on spatio-temporal dynamics of DENV transmission to improve the entomological surveillance to facilitate the entomological monitoring situation. The data presented in this work provide a detailed description of DENV transmission for Santa Fe province by department to highlight the recent and ongoing emergence of

dengue in the province. This information together with other works in the temperate Argentina[2,27] will be useful in better understanding the impact of dengue emergence and reemergence in other areas of the world. Indeed, this work can be combined with other existing data sets to contribute to future studies including those aimed at investigating socio-ecological, climate, and environment factors associated with dengue emergence, as well as those aimed at understanding the influence of other variables related to the biology and the ecology of vector-borne diseases.

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Figure and Tables Legends

Fig. 1. Location of Santa Fe province in Argentina and the neighboring countries.

Fig. 2. Incidence of imported and autochthonous dengue cases each month between January 2009–May 2020. Incidence is calculated as the number of cases per 10,000 inhabitants of Santa Fe province.

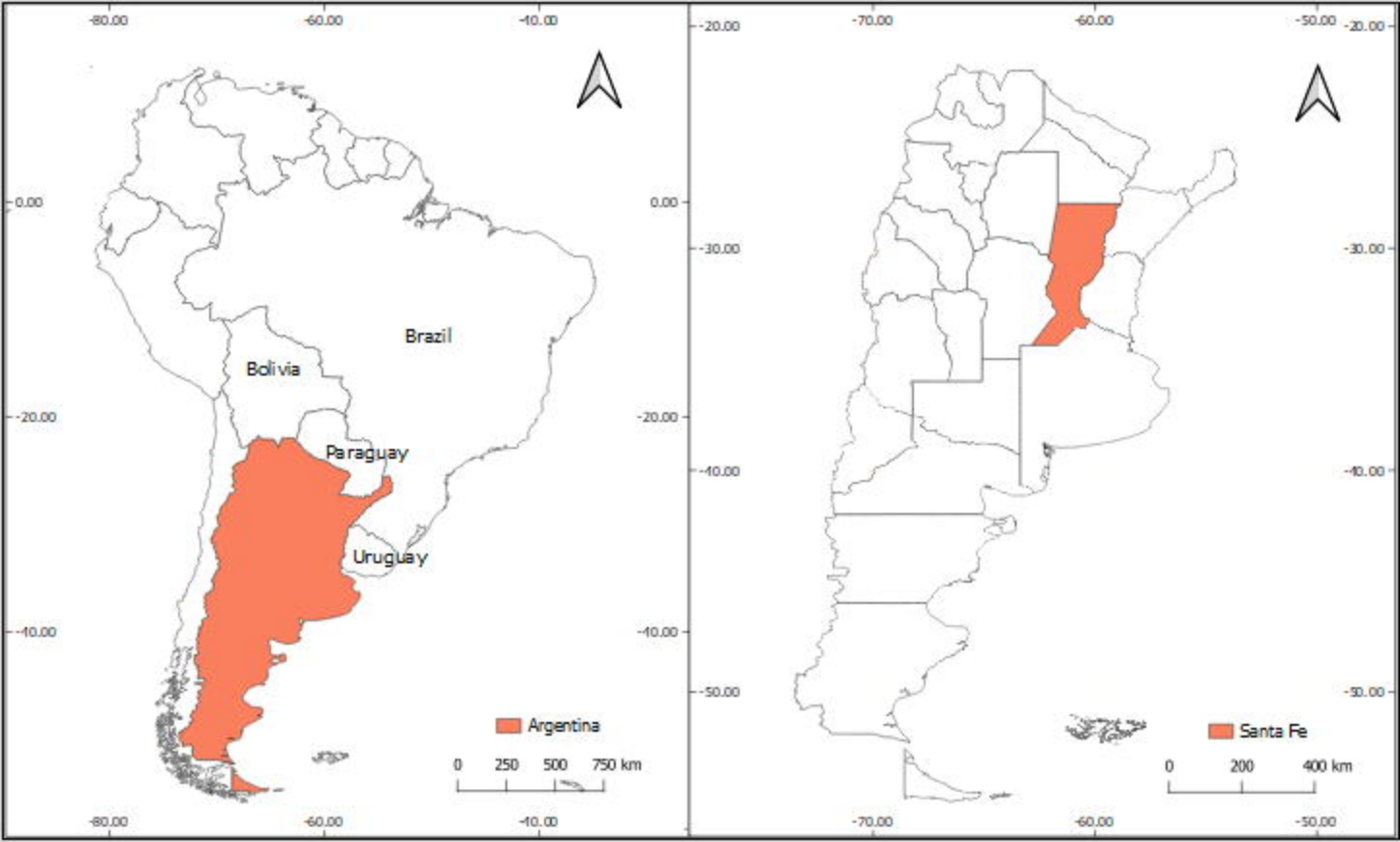
Fig. 3. Total incidence of imported and autochthonous dengue cases between January 2009–May 2020 by department. Incidence is calculated as the number of cases per 10,000 inhabitants by department of Santa Fe province.

Table 1. Total incidence of confirmed and probable cases, number of cases confirmed by serotypes, confirmed DENV serotypes and origin of imported cases. Incidence is calculated as the number of cases per 10,000 inhabitants of Santa Fe province.

Table 2. Cities with the highest number of dengue cases in the 2020 outbreak in the province of Santa Fe. Incidence is calculated as the number of cases per 10,000 inhabitants.

YEAR	Total incidence of confirmed and probable cases	N° cases identified by serotypes	DENV Serotypes Detected	Origins of imported cases
2009	0.472682	88	DENV-1 (N = 88)	Argentina provinces: Chaco, Córdoba, Santiago del Estero
2010	0.062606	6	DENV-1 (N = 4), DENV-2 (N =1), DENV-4 (N = 1)	Brazil
2011	0.303644	32	DENV-1 (N = 30), DENV-2 (n = 2)	No information
2012	0.009391	2	DENV-1 (N = 1), DENV-4 (N = 1)	Brazil
2013	0.046955	14	DENV-1 (N = 3), DENV-2 (N =5), DENV-4 (N = 6)	Brazil, Paraguay
2014	0.015651	3	DENV-1 (N = 3)	Brazil, Republica Dominicana
2015	0.053215	15	DENV-1 (N = 15)	Brazil, Ecuador. Argentina provinces: Formosa and Misiones
2016	3.05208	277	DENV-1 (N = 267), DENV-4 (N = 10)	Brazil, Paraguay, Tailandia, Uruguay. Argentina provinces: Buenos Aires, Chaco, Cordoba, Corrientes, Entre Ríos , Formosa, Mendoza, Misiones
2017	0.328686	76	DENV-1 (N = 76)	Brazil, Chile. Argentina provinces: Buenos Aires, Cordoba, Jujuy
2018	0.062606	8	DENV-1 (N = 7), DENV-3 (N = 1)	Argentina provinces: Formosa
2019	1.51508	75	DENV-1 (N = 71), DENV-2 (N =3), DENV-4 (N = 1)	Brazil, Indonesia, México. Argentina provinces: Misiones, Salta
2020	14.1648	863	DENV-1 (N = 488), DENV-2 (N = 4), DENV-4 (N = 371)	Brazil, Mexico, Paraguay. Argentina provinces: Chaco, Córdoba, Corrientes, Formosa, La Rioja, Misiones, Salta.

Cities	Total of confirmed and probable cases	Total incidence of confirmed and probable cases
Rosario	1212	12.78
Reconquista	1096	149.53
Rafaela	629	67.67
Avellaneda	280	107.71
Santa Fe	239	6.10
San Jorge	147	81.41
Fray Luis Beltran	102	66.28


Brazil
Bolivia
Paraguay
Uruguay
Argentina
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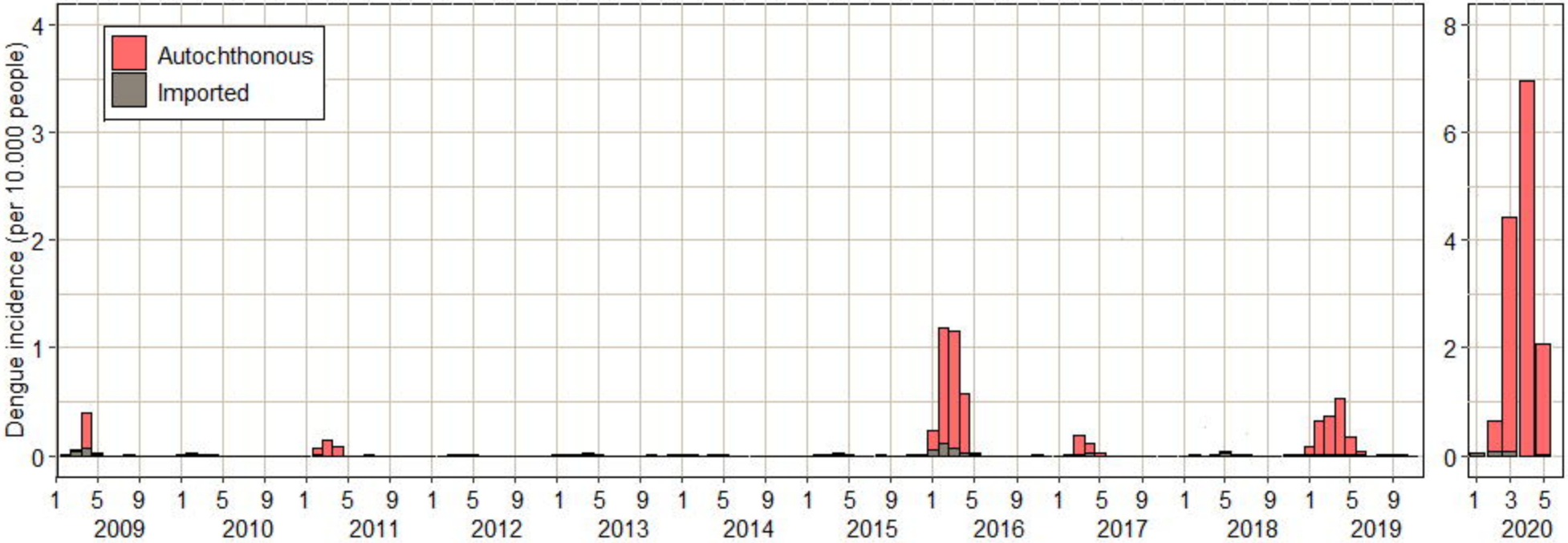
Santa Fe
0 200 400 km


Autochthonous
Imported
Dengue incidence (per 10.000 people)
0
1
2
3
4
0
2
4
6
8
1 5 9 1 5 9 1 5 9 1 5 9 1 5 9 1 5 9 1 5 9 1 5 9 1 5 9 1 5 9 1 5 9 1 3 5
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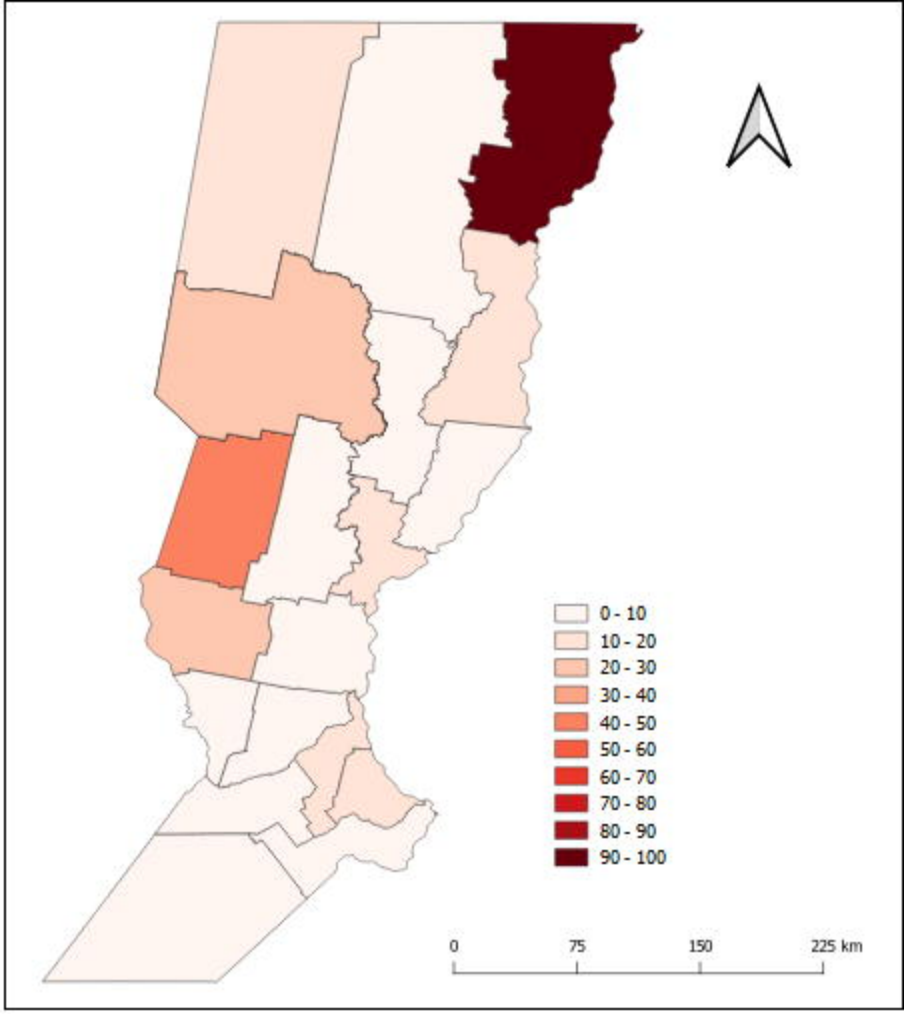
0 - 10
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75
150
225 km