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The role of inter-regional flows in the spread of epidemics in a city of regional influence with a tropical climate

El papel de los flujos interregionales en la diseminación de epidemias de dengue en una ciudad de clima tropical

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ABSTRACT The aim of this research was to investigate the origin of imported cases of dengue in the city of Araraquara, Brazil and to describe the disease's main epidemiological characteristics. The study encompassed all confirmed cases of dengue recorded in the Information System for Notifiable Diseases (SINAN) [*Sistema de Informação de Agravos de Notificação*] from 1998 to 2013. Cases whose origin of infection was likely located outside Araraquara were considered imported. The epidemiological study entailed a descriptive analysis of the data, regarding the distribution of cases by sex, age, and classification of imported and autochthonous cases. A geographic information system was used to map flows and estimate distances. There were 6,913 confirmed cases, 419 of which were imported. In most cases, the origin of infection was located in the state of São Paulo as well as other Brazilian regions. The results indicate the relevance of imported cases and differences in the epidemiological profile with respect to age and sex. Conclusions indicate the need to increase epidemiological and environmental health surveillance at ports, airports, truck stops, and bus and train terminals.
KEY WORDS Dengue; Spatial Analysis; Geographic Information Systems; Epidemiological Surveillance; Brazil.

RESUMEN El objetivo de este trabajo fue investigar el origen de los casos importados de dengue en la ciudad de Araraquara, Brasil y describir las principales características epidemiológicas. El estudio abarcó todos los casos confirmados de dengue registrados en el Sistema de Información de Enfermedades de Notificación (SINAN) [*Sistema de Informação de Agravos de Notificação*] de 1998-2013. Se consideraron como casos importados aquellos cuyo lugar de origen de infección se ubicara fuera de Araraquara. Se realizó un análisis descriptivo de la distribución de los casos por género, edad y clasificación de casos importados y autóctonos. Se utilizó un sistema de información geográfica para mapear los flujos y estimar las distancias de los puntos de contagio. Se incluyeron 6.913 casos confirmados, de los cuales 419 fueron importados. En la mayoría de estos casos, el origen de infección se ubicó en el estado de San Pablo, además de otras regiones brasileñas. Los resultados indican la relevancia de los casos importados y diferencias en el perfil epidemiológico por edad y sexo. Las conclusiones indican la necesidad de aumentar la vigilancia epidemiológica y de salud ambiental en los puertos, aeropuertos, paradas de camiones y terminales de buses y trenes.
PALABRAS CLAVES Dengue; Análisis Espacial; Sistemas de Información Geográfica; Vigilancia Epidemiológica; Brasil.

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INTRODUCTION

Among the infectious diseases affecting urban populations, dengue is of particular concern, posing a serious global public health problem because its risks affect a large contingent of the world population. The Americas were a virtually dengue-free zone because of the eradication of *Aedes aegypti* in a continent-wide vector control campaign,[1] which was then followed by a period of re-emergence and subsequent failure to control dengue in Latin America.[2]

In many Latin American countries, the rapid expansion of urban sprawl with poor water supply, associated waste management problems, increased circulation of people within and among countries, as well as the resistance of mosquitoes to insecticides, are all factors contributing to the return of dengue virus circulation, and the rise in dengue transmission in recent years[3,4,5,6] with the occurrence of millions of dengue infections annually in the region.[2] Epidemic dengue occurs cyclically every three to five years, with evidence of an increase in the magnitude and severity of cases with each new epidemic.[1] In the 1980s the highest concentrations were reported in the Spanish Caribbean, however in the 1990s and 2000s there was a shift to the Southern Cone with over 60% of the cases.[1]

In Brazil, dengue is currently one of the most common infectious diseases present nationwide. The models for controlling diseases such as dengue are centered essentially on the use of insecticides and lack the inter-sectoral integration required, proving insufficient for controlling the disease.[7] Barreto *et al.*[8] list dengue among the group of diseases for which control has been largely unsuccessful in Brazil.

Travel plays an important role in the acquisition and dissemination of infections. Increased speed and flows of both people and goods on a national, regional and global level have a major impact on the process of spreading infectious diseases – particularly those that are vector-based, such as dengue – in urban areas, settings that are favorable for proliferation.[9,10]

Imported cases are a prerequisite for the onset of an epidemic, but the number of such cases hinges on the capacity for detection, notification and response of health systems.[11] According to Al Abri *et al.*,[12] there is a need for studies investigating the possible associations between infectious diseases and travelers. In Latin America, human migration and travelers have shown to be important elements in the dispersion of dengue's four different serotypes, as was observed in Mexico and Uruguay.[2,13,14] However, most investigations regarding imported cases focus on international borders.

The adoption of measures to detect imported cases in a rapid and effective manner can help prevent the emergence of dengue epidemics and reduce harm to population health. Shu *et al.*[15] described some countries that have adopted strategies for screening potentially infected travelers returning from areas endemic for dengue.

Knowledge on the role of imported and autochthonous dengue cases in the city of Araraquara, Brazil can further understanding on the dynamic of transmission of the disease at a local and national level, and inform actions of epidemiological surveillance involving the adoption of adequate and timely measures for epidemic prevention and control.

The municipality of Araraquara is located in the central region of the state of São Paulo, Brazil. Its latitude is 21°74′38′′S and its average altitude is 646 meters above sea level. It has a high-altitude tropical climate, with dry winters and rainy summers. The average annual temperature is 20.4°C, the average minimum temperature is 10°C, and the average maximum temperature is 28°C. Annual rainfall is around 1,352 mm. According to the Brazilian National Census,[16] in 2010 Araraquara had 208,725 inhabitants, making it a medium-size city. The municipality is made up of 1,005 km^2 and the majority of population (97.16%) lives in the urban area. It is in one of the major sugar cane production regions of the state and of Brazil. Oranges

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represent the second most important crop in rural area. The fruits are largely processed into juice for export. Therefore industrial activity in the municipality is mainly related to agriculture. The Human Development Index (HDI) of the municipality was 0.815 (very high) in 2010.

Imported cases of dengue in Araraquara have been recorded in all years since surveillance began in 2008. However, studies investigating the nature of imported cases of dengue remain scarce. Investigating the origin of imported cases can help elucidate the possible impact of flows of local, regional and global travelers in the process of spreading dengue. The objective of the present study was to perform a descriptive analysis to determine the origin of imported cases of dengue in the city of Araraquara and to describe the main epidemiological characteristics of the disease.

Understanding the epidemiologic characteristics of imported cases of dengue can help identify the important elements influencing the processes involved in the dengue epidemic, allowing the adoption of measures for preventing and attenuating the impact of the disease.

METHODS

An ecological study with a time-trend design involving notified and confirmed dengue cases between 1998 and 2013 was carried out in the city of Araraquara, in the center of the state of São Paulo, Brazil.

All data analyzed were extracted from the Information System for Notifiable Diseases (SINAN) [*Sistema de Informação de Agravos de Notificação*] managed by the Ministry of Health and run by the cities. The time series analyzed cover the period from 1998 to 2013. The cartographic bases georeferenced from the network of Brazil's cities, municipal centers and states were downloaded directly from the Brazilian Institute of Geography and Statistics (IBGE) [*Instituto Brasileiro de Geografia e Estatística*] website. Population estimates were carried out by the IBGE and provided by the Ministry of Health on the DATASUS information system.

The city of Araraquara was selected as a case study because it is a regional capital, has epidemiological dengue data at a local level, and constitutes an emblematic area in the tropical world for its rising incidence of the disease, like other Latin American cities.[1,2] Despite carrying out control actions, the city has registered successive epidemics over the past decade.

The present study involved imported and autochthonous cases of dengue. As discussed by Degallier *et al.*,[17] the inclusion of autochthonous and imported cases is essential to model the dynamic of the epidemic and investigate the nature of the flows that may have contributed to the worsening of dengue epidemics. The analyses of imported cases were performed separately in order to ascertain their contribution in each year analyzed, together with the city and state of origin.

Imported cases were defined according to the information on the probable site of infection noted in the SINAN. This information is reported by patients at the moment notification forms are completed.

The epidemiological study entailed a descriptive analysis of the data, regarding the distribution of cases by sex, age, and classification of imported and autochthonous cases. The Chi-squared test was applied to perform comparisons and assess the statistical significance of differences according to sex and age group of imported and autochthonous cases.

The flow map was produced to graphically determine the probable place of origin of imported cases and calculate mean distances between these places and Araraquara. To this end, dengue cases were georeferenced and combined with latitudes and longitudes of the centers of all cities obtained from the IBGE. These procedures were carried out using the *Terraview* 4.2 software program. The thematic maps and geocoding of dengue cases were done using the ArcMap 10.1 software program. Graphs and statistical analyses were performed using the SPSS 11.0 statistics package.

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RESULTS

A total of 6,913 cases of dengue were notified and confirmed between 1998 and 2013. Annual incidence ranged from 7.53 cases per 100,000 inhabitants/year in 1998 to 1209.4 per 100,000 inhabitants/year in 2011. Imported cases were observed for all years analyzed, albeit at different intensities and magnitudes, particularly for epidemic and inter-epidemic years.

As shown in Figure 1, most imported cases in the series contracted the disease between epidemiologic weeks 1 and 21 (May), peaking at weeks 13-16 (March to April). A declining curve until week 21 can be noted after the peak.

Figure 2 depicts the percentage of imported and autochthonous dengue cases in the city of Araraquara between 1998 and 2013. Up to 2006, imported cases accounted for over 50% of all occurrences. From 2008 onwards, imported cases represented approximately 10% of all occurrences.

Differences in the sex of infected patients can be observed in the series analyzed. Of the 419 imported cases of dengue, 54.5% were in males and 45.5% in females. Among autochthonous cases, 53.8% were in females and 46.2% in males ($X^2 = 11.091$. $p = 0.001$). Considering the totality of cases, incidence by sex varied annually. Overall totals for each year of the series analyzed are given in Table 1.

Distribution of cases by age group

Differences in age group were evident between imported and autochthonous cases (Figure 3). Regarding imported cases of dengue, 86.6% involved individuals aged more than 19 years and 13.4% aged 19 years or less ($X^2 = 5.002$; $p = 0.02$).

The highest incidence occurred in the age group over 19 years. From 2001 onwards, there was a slight rise in the number of cases (in absolute terms) among individuals aged 19 years or less. A total of 11 cases were

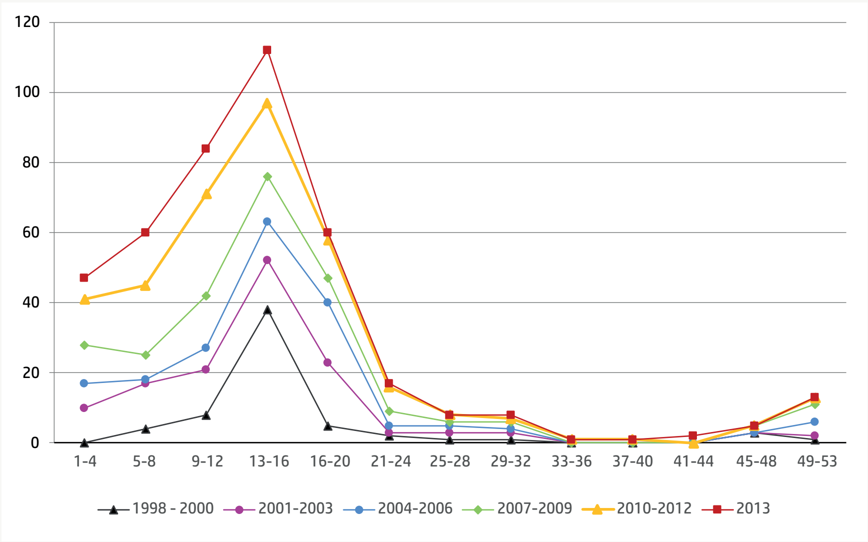

Figure 1. Number of imported dengue cases by epidemiologic week. Araraquara, Brazil, 1998-2013.

Source: Own elaboration using data from SINAN [*Sistema de Informação de Agravos de Notificação*] of the Brazilian Health Ministry and SESA [*Serviço Especial de Saúde de Araraquara*], Faculdade de Saúde Pública, Universidade de São Paulo, Brazil.

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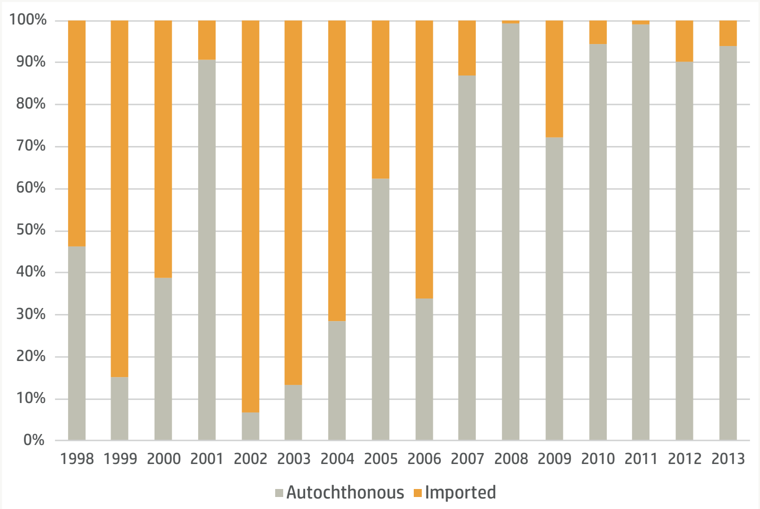

Figure 2. Percentage of imported and autochthonous dengue cases. Araraquara, Brazil, 1998-2013.

Source: Own elaboration using data from SINAN [*Sistema de Informação de Agravos de Notificação*] of the Brazilian Health Ministry and SESA [*Serviço Especial de Saúde de Araraquara*], Faculdade de Saúde Pública, Universidade de São Paulo, Brazil.

Table 1. Notified and confirmed dengue cases by gender. Araraquara. Brazil. 1998-2013.

Year	Female		Male		Total
	n	%	n	%	N
1998	0	0.00	8	100.00	8
1999*	28	52.83	25	47.17	53
2000	12	66.67	6	33.33	18
2001*	116	54.72	96	45.28	212
2002	20	45.45	24	54.55	44
2003	8	53.33	7	46.67	15
2004	3	42.86	4	57.14	7
2005	3	37.50	5	62.50	8
2006	27	41.54	38	58.46	65
2007*	177	50.43	174	49.57	351
2008*	642	54.04	546	45.96	1,188
2009	19	44.19	24	55.81	43
2010*	705	53.21	620	46.79	1,325
2011*	1,365	53.57	1,183	46.43	2,548
2012	77	62.60	46	37.40	123
2013*	481	53.39	420	46.61	901
Total	3,688	53.35	3,225	46.65	6,913

Source: Own elaboration using data from SINAN [*Sistema de Informação de Agravos de Notificação*] of the Brazilian Health Ministry and SESA [*Serviço Especial de Saúde de Araraquara*], Faculdade de Saúde Pública, Universidade de São Paulo, Brazil.

*Epidemic years.

recorded in this age group in 1999, versus 60 cases in 2007, and 221 cases in 2008, representing 20% of all cases recorded throughout the period. A slight rise in the number of dengue cases was observed among individuals aged 11-19 years in 2009.

Figure 4 graphically depicts the origin of imported cases of dengue during the period analyzed. Line thickness indicates flow intensity. Greater intensity flows are evident in the state of São Paulo and are derived from cities with high population density. The distribution of imported cases by Brazilian state showed that 51% of notified and confirmed cases during the period had as probable infection sites the coastal cities Guarujá, Santos, and Praia Grande and the inland city Ribeirão Preto, all in the in the state of São Paulo. Fewer cases were contracted in other cities in the state of São Paulo, followed by the states of Minas Gerais with 7% of cases, Bahia with 3.6%, Rio de Janeiro with 3.83%, Goiás with 3.11%, and Mato Grosso do Sul with 2.39%. Mean distance observed between probable place of infection and Araraquara center was 400 kilometers, whereas minimum and maximum distances were 17 and 2,435 kilometers, respectively.

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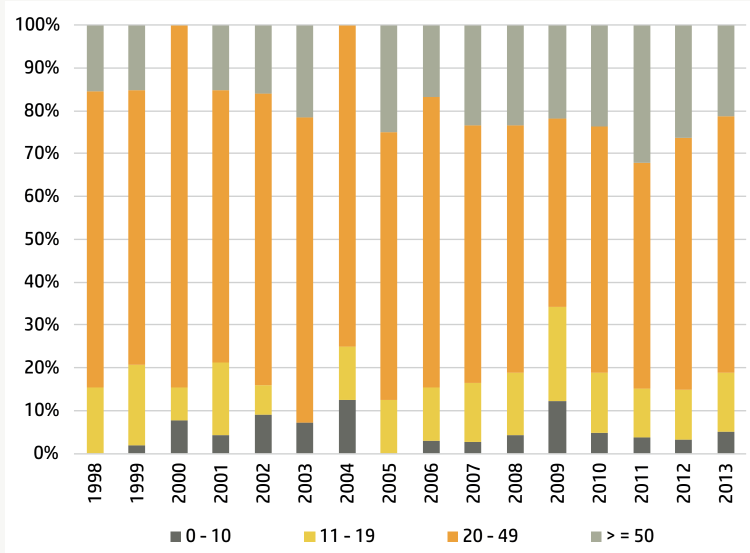

Figure 3. Percentage of dengue cases by age group. Araraquara, Brazil, 1998-2013.

Source: Own elaboration using data from SINAN [*Sistema de Informação de Agravos de Notificação*] of the Brazilian Health Ministry and SESA [*Serviço Especial de Saúde de Araraquara*], Faculdade de Saúde Pública, Universidade de São Paulo, Brazil.

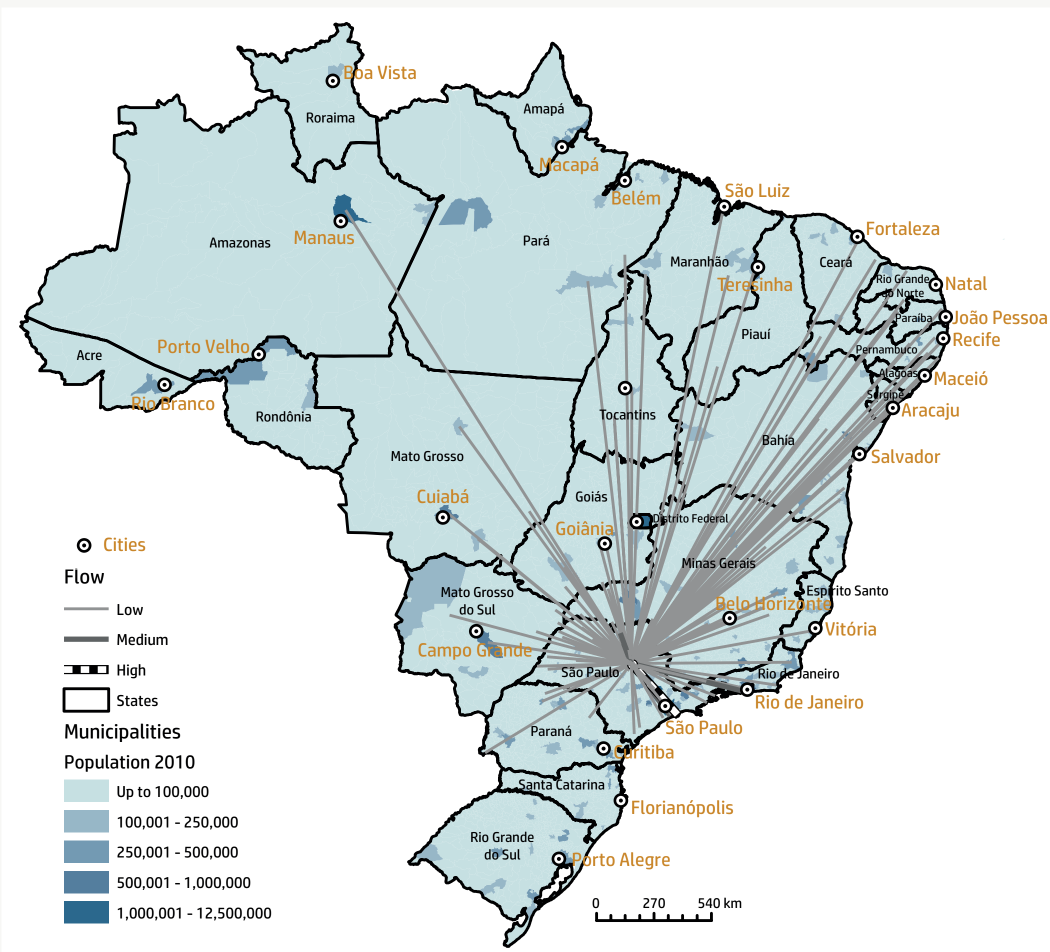

Figure 4. Flow of probable places of infection of imported dengue cases. Araraquara, Brazil, 1998-2013.

Source: Own elaboration using data from SINAN [*Sistema de Informação de Agravos de Notificação*] of the Brazilian Health Ministry; SESA [*Serviço Especial de Saúde de Araraquara*], Faculdade de Saúde Pública, Universidade de São Paulo.; IGBE [*Instituto Brasileiro de Geografia e Estatística*]; and DATASUS.

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DISCUSSION

The study results reveal a worsening of dengue in the city, the same trend observed throughout the Americas in recent decades, where dengue morbidity and mortality has been increasing.[1] Six epidemics were seen in the period analyzed, in the years 1999, 2001, 2007 and 2008, 2010 and 2013; the first four were described by Oliveira.[18] For the other years, the disease appears to have had an endemic pattern with occurrence of cases mainly between summer and fall. However, the contribution of imported cases is clear, not only in introducing the disease into the city, but also in promoting its persistence, particularly during inter-endemic years. According to SINAN records, with the exception of 2008, all index cases recorded were imported cases.

The factors responsible for periodic epidemics in the same area remain unclear. However, these factors likely include a combination of increased virus circulation in people between countries and regions, group immunity level, specific serotypes of the virus in human populations, and genetic changes in the circulating or introduced virus conferring greater epidemic potential.[19]

In Brazil, dengue occurs endemically in the states of the Northeast, Southeast, North and Mid-west regions. However, the findings of the present study show that most imported dengue cases in Araraquara originated from the state of São Paulo, especially port cities and tourism centers, as well as coastal cities in the Baixada Santista region. There was also a substantial contribution from the states of Rio de Janeiro, Minas Gerais and Bahia, possibly associated with the flow of farm laborers, particularly sugar-cane cutters and orange pickers, the main crops in the region.

Distant subpopulations of mosquitoes may be connected by this movement. The population of travelers often acts as a major disseminator of the dengue virus, because it can introduce more virulent strains (subtypes) of the virus into areas until that time subject only to mild forms of the disease.[9,20]

These results are similar to those of Shang *et al.*,[21] who also observed variation in the impact of imported dengue cases at different phases of epidemics in Taiwan. In the present study, a decline in the number of imported cases was seen during the series over time, falling from 85% in 1999 to 0.67% in 2008, and rising again in 2009. However, further studies focusing on the relationship between imported and autochthonous cases should investigate whether, akin to the findings of Shang *et al.*,[21] imported cases of dengue are responsible for the emergence of local cases in Araraquara. It is important to emphasize that cases were not imported from other countries.

A recent study in Bogotá, Colombia, revealed that inhabitants acquired dengue infection in diverse localities throughout the country but the largest proportion of cases were contracted at popular tourist destinations in dengue-endemic areas near Bogotá (at less than a 200-km radius from city limits) and the number of imported dengue cases increased after major holidays.[13]

Over the period analyzed, notifications of dengue cases occurred in all age groups, with the 20-29 year age group most affected. This age group is predominantly made up of adult laborers and/or students who are more likely to move throughout the city, or of other individuals that, on account of their activities, are more exposed to the vector in different environments. During inter-epidemic years, there was a higher number of imported cases, which might be associated with movement of males for work or leisure. In Latin America as a whole, the highest incidence is among adolescents and young adults.[1] In Southeast Asia, dengue is a predominantly pediatric disease,[15] as in Venezuela, where dengue and dengue hemorrhagic fever incidences are highest among children and infants respectively.[1,22] In Mexico, dengue incidence is higher in the age group of 10-19 years,[22] whereas in Brazil until 2006, the incidences of dengue fever and hemorrhagic dengue fever were much higher in adults.[8] However, there is an increasing trend of severe cases in younger ages over the last 10 years in Latin America,

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compared to previous period when it was most frequent in young adults.[22]

The higher percentage of males in imported cases, and of females in autochthonous cases, in Araraquara, was in partial agreement with the findings of Vasconcelos *et al*.[11]

The dynamic of dengue transmission in Araraquara cannot be overcome through local actions alone. Some macro-determinant factors contribute to the increase in dengue cases: population growth, population density, uncontrolled urbanization, poverty, population movement (migration, tourism), rainfall and climatic change.[22,23,24] Concerted efforts involving all cities nationwide in which dengue is endemic are needed. Studies at other sites are crucial to provide a more comprehensive map of global transmission patterns in cities within tropical settings. Studies in the area of Geography of Health can make an important contribution in these investigations and help gain a better understanding of the transmission dynamic.[25,26,27,28,29]

The study highlights the role of imported dengue cases in introducing the disease in the city and possibly in triggering epidemics. It also reveals cities systematically identified as likely locations of infection of imported cases.

According to Tauil,[28] it is practically impossible to bar entry of infected individuals at the transmissible stage of the disease into areas where the vector is present. Modern means of transport are fast and frequent and can bring in individuals carrying the virus from distal locations extremely rapidly.

Measures for preventing dengue should be incorporated into health inspection and education practices in areas associated with high movement of laborers and tourists such as ports, bus terminals, truck stops, and train stations. Some professions potentially involved in disease transmission should also be investigated: a) laborers on sugar-cane and citric fruit plantations, the most prevalent crops in the region, with an influx of seasonal harvesters from the Northeast; b) truck drivers hauling harvests to the coastal port of Santos for export; and c) representatives of multinationals who sell products to the agriculture industry and traverse states. More in-depth studies should also be carried out on tourist flows between the region and the highly infested coast as well as the hinterland rodeo centers. Internal migration, inter-regional movement and occurrence of the disease during the period were connected with the course of the dengue epidemic in the area studied. The heavy traffic of private vehicles, passenger transport, and truck transportation may therefore become important in the dissemination of dengue virus to non-endemic areas of Brazil and bordering countries.

The weekly flows of bus passengers for distances of over 400 km were common and this appear to be a worldwide trend. The high HDI of Araraquara is also an indication that epidemics are not necessarily related to poverty. In this respect, it is important that systems of epidemiologic surveillance and environmental health incorporate strategies that reach the population circulating within cities endemic for dengue in an effort to reduce the chances of spreading. Several basic practices such as fish farming to reduce larvae and the vector, use of repellants, or rapid notification of symptoms associated with dengue to health services, can all help reduce epidemics, in conjunction with traditional actions implemented by health officers: policing of trash piles, untended swimming pools, water tanks without lids, flower vases, watering troughs, among other sites favorable for the proliferation of mosquitoes.[30]

Moreover, it is vital that exams screening for the virus and its serotypes are carried out and managed by the epidemiologic surveillance units of the city, as a priority action, thereby allowing the dynamic of dengue transmission to be established. In this sense, a limitation of the study was the absence of information on the serotypes responsible for the epidemics in the city of Araraquara, as well as the fact that the study only included cases of dengue that had been notified and confirmed at the SINAN. The results reported may have been underestimated since the symptoms of dengue are not always correctly identified by health services and by the population.

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CONCLUSIONS

The explanations for the emergence of the epidemics in Araraquara are complex, largely because they involve the influx of many imported cases that can introduce types of virus different to those in circulation, and against which most of the population have not acquired immunity. In addition, gaining an understanding of this dynamic can help prevent the entry – and epidemics –of other diseases more serious than dengue similarly transmitted in by the mosquito *Aedes aegypti*, such as chikungunya fever, the Zika virus and yellow fever.

The great relevance of imported cases of dengue in the city of Araraquara, particularly during inter-epidemic periods, underscores the need for reformulating epidemiologic surveillance actions, which should incorporate guidance for the population on recognizing the symptoms associated with dengue, especially when their citizens travel to other regions of the country endemic for the disease. Actions combating dengue are also needed in schools, workplaces and at gateways to the city, such as bus stations and terminals, airports and freight shipping terminals in general.

All movements of people and goods provide the opportunity for transmission of dengue from one region to another. Strategies to combat the disease require inter-sector health planning actions that embrace the complex nature of the process of disease spread, which appears to involve a network of cities. This factor calls for government agencies to be coordinated and provide a rapid response to the risk of the spread of dengue and other infectious diseases, deploying containment and blocking mechanisms ranging from basic to more complex measures such as the production of vaccines. The Pan American Health Organization's Integrated Management Strategy for Dengue Prevention and Control is designed to bolster national strategies and has six axis of action: 1) the strengthening of surveillance systems; 2) environmental policies for vector control; 3) integrated vector management; 4) patient care; 5) regional networks of laboratories; 6) social communication for behavioral impact.[22]

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