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Spatio-temporal dynamics of dengue 2009 outbreak in Córdoba City, Argentina.

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Abstract

During 2009 the biggest dengue epidemic to date occurred in Argentina, affecting almost half the country. We studied the spatio-temporal dynamics of the outbreak in the second most populated city of the country, Córdoba city. Confirmed cases and the results of an *Aedes aegypti* monitoring during the outbreak were geolocated. The imported cases began in January, and the autochthonous in March. Thirty-three percent of the 130 confirmed cases were imported, and occurred mainly in the center of the city. The autochthonous cases were more frequent in the outskirts, specially in the NE and SE. *Aedes aegypti* infestation showed no difference between neighborhoods with or without autochthonous cases, neither between neighborhoods with autochthonous vs. imported cases. The neighborhoods with imported cases presented higher population densities. The majority of autochthonous cases occurred at ages between 25 and 44 years old. Cases formed a spatio-temporal cluster of up to 20 days and 12 km. According to a mathematical model that estimates the required number of days needed for transmission according to daily temperature, the number of cases begun to fall when more than 15.5 days were needed. This may be a coarse estimation of mean mosquito survival in the area, provided that the study area is close to the global distribution limit of the vector, and that cases prevalence was very low.

Keywords. Dengue outbreak; *Aedes aegypti;* Córdoba; Argentina; Geographic Information System (GIS).

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1. Introduction

Dengue fever (DF) is a mosquito-borne viral disease of humans that has become a major international public health concern in recent years. *Aedes* (*Stegomyia*) *aegypti* (L.) (Diptera: Culicidae) is the main vector of dengue virus (DENV) in Argentina and neighboring countries. Recently, the geographical distribution of *Ae. aegypti* has expanded southwards (Díaz-Nieto et al. 2013), including the provinces of La Pampa (Rossi et al. 2006), and Neuquén (Grech et al. 2012).

After the *Ae. aegypti* eradication campaign in the Americas during the 1960s, the vector was reported in 1995 in Córdoba (Almirón and Ludueña-Almeida 1998). During 2009 the infestations levels of *Ae. aegypti* in Córdoba city, detected by traditional indexes (House, containers and Breteau index) were 25%, 7% and 34, respectively (Estallo et al. 2009).

The first DF epidemic record in Argentina was in the beginning of XX century in the province of Entre Ríos, with 15,000 DF cases reported (Gaudino 1916). After the re-infestation of the country with *Ae. aegypti*, DF re-emergence begun with a few DENV- 2 serotype cases reported in 1997 (Avilés et al. 1999), and the first epidemic by the same serotype during 1998. Outbreaks followed in the northern provinces during the warm season by DENV-3, DENV-2 and DENV-1 serotypes (M.S.N. 2006). During the last months of 2008, and outbreak by DENV-1 serotype was recorded in several departments of Bolivia, and shortly after in several Argentinean provinces. This resulted in the major DF epidemic recorded in Argentina affecting 13 provinces with more than 26,000 confirmed cases, 3 dengue hemorrhagic cases and 5 deaths (M.S.N. 2009 a,b). Ten provinces, including Córdoba, reported autochthonous cases for the first time. The occurrence of DF in Argentina is mainly during the warm season, from November to May, and is related to outbreaks in neighboring countries

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like Bolivia, Brazil and Paraguay (Avilés et al. 2003; Vezanni and Carbajo 2008). The objective of this paper was to study the spatio-temporal dynamics of DF 2009 outbreak in Córdoba city, Argentina.

2. Methods

2.1. Study site

The study was done in Córdoba city (64°12' W, 31° 22' S), capital and main city of the province of Córdoba (Argentina) (Figure 1), with a population of 1,330,023 inhabitants. The population is mainly composed for young individuals who concentrate 66.2% of the population on the age class of 15-64 years old (INDEC 2010). Córdoba city is highly urbanized with a land area of 576 Km^2 that lies between 306 and 480 m above sea level (Jarsún et al. 2003). Young people move into the city mainly from Northern provinces to study or work. The city climate is temperate with mean annual precipitation of 694 mm mainly between October and March. The warmest period is between November and March. The mean maximum, average, and minimum temperatures are 24.03°, 17.28°, and 11.21° C, respectively (S.M.N. 2011).

2.2. Data

Data on confirmed cases during the 2009 DF outbreak were given by the Ministry of Health of Córdoba (Dirección de Epidemiología, Ministerio de Salud de la Provincia de Córdoba, MHC herein). At the beginning of the outbreak, patients serum samples of suspected cases were confirmed by isolation of DENV from serum, or demonstration cDNA fragment by polymerase chain reaction (PCR) from a serum sample, or IgM antibody by using an IgM capture enzyme-linked immunosorbent assay (UM-ELISA®) by the National Reference Centre for Arbovirus, Instituto Nacional de Enfermedades Virales Humanas "Dr. Julio I. Maiztegui" (INEVH). All DF confirmed patients residences were georeferenced into a Geographic Information

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System (GIS) with city neighborhood division and demography (Arcview 3.2 [ESRI 200]). Ancillary information on each patient was also recorded: identification number, date of onset of symptoms, age, sex and type of DF cases (imported or autochthonous). Weekly maps of number of cases were built to visualize the beginning of the outbreak and the successive dispersion of cases.

During February 2009 a monitoring of immature stages was performed in the city (MHC; Centro de Investigaciones Entomológicas de Córdoba- CIEC). Data consisted in a larval survey of 32 randomly selected neighborhoods with a total of 654 houses inspected. Houses were inspected for artificial containers with *Ae. aegypti* larvae. The material collected was transferred to the laboratory of the CIEC in small plastic flasks. The 3rd and 4th instars larvae were killed and stored in 80% ethanol for taxonomic determination using keys (Darsie 1985). The younger instars were reared until the 4th in plastic trays containing water from natural larval habitat, and fed 0.25 mg daily/larva of liver powder.

To analyze the spatial relationship between *Ae. aegypti* infestation and confirmed DF cases, a regrouping of the premises was carried out as follows. First, the premises closer than 100 m were grouped together. Secondly, groups of premises which centroids were closer than 350 m were grouped. Remnant isolated premises were joined to groups closer than 400 m or if farther apart excluded from the analysis. This resulted in 31 groups with 7 to 39 premises each, and 7 premises excluded. The abundance of *Ae. aegypti* was estimated for each group as the ratio of premises with the mosquito to total premises (PI). From a total of 414 neighborhoods in the city, 44 had infestation information. The spatial behavior of infestation was studied in order to find an adequate means to extrapolate infestation to all neighborhoods. PI spatial continuity was assessed with semivariograms and mean PI interpolated as a

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continuous surface through Córdoba city by kriging (Cressie 1993). This method provides also interpolation error estimation (PI standard error). City neighborhoods were classified as positive or negative for DF autochthonous and imported cases. Differences in the mean PI value between positive and negative neighborhoods were assessed with a Wilcoxon test. Neighborhoods with a PI standard error higher than 0.15 were excluded from the analysis.

A map with the DF confirmed cases during the outbreak was done. The DF cases distribution by age and sex was observed, and also the weekly frequency of DF cases for each epidemiological week (EW). Differences in DF prevalence between neighborhoods with autochthonous and imported cases was assessed with a t-test on the transformed variable (arc sin of the square root of the prevalence).

The human population density was compared between neighborhoods with autochthonous, imported and no cases with an analyses of variance with Tukey multiple comparisons (Zar 1999).

A dengue risk index was calculated for each day during the epidemic (Carbajo et al. 2012). The index estimates the theoretical number of days that would take the virus to develop and be transmitted. The extrinsic incubation period (EIP) of the dengue virus in the mosquito *Ae. aegypti* is the lapse from ingestion of infected blood to the virus transmission in a subsequent feed. This period varies as a function of temperature (McLean et al. 1974; Watts et al. 1984). If ambient temperature is low, mosquitoes are unlikely to survive long enough to become infectious and transmit the disease. Therefore, the duration of the EIP and the survival of vectors are key factors in determining dengue transmission risk (Focks et al. 1993). The proportion of the EIP completed was calculated as a function of air temperature. A mathematical model based on enzyme kinetics that relates the virus development to air temperature

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developed by Jetten and Focks (1997) was modified to estimate the completion of EIP hourly:

$$r(T_h) = (p_{(25°C)}\,(T_h/298)\,e^{x1}\,)\,/\,(1+ e^{x2}) \qquad (1)$$

where

$$x_1 = \Delta H^*_A\,/R\,(\,(1/298)-(1/T_h)\,)\text{ and}$$

$$x_2 = \Delta H^*_H\,/R\,(\,(1/\,T_{0.5H}\,)-(1/T_h)\,)$$

$r(T_h)$ represents the development rate (hr^{-1}) at temperature T (°K) at hour h, $p_{(25°C)}$ is the development rate (hr^{-1}) at 25°C assuming no temperature inactivation of the critical enzyme, ΔH^*_A is the enthalpy of activation of the reaction that is catalyzed by the enzyme (cal/mol), ΔH^*_H is the enthalpy change associated with high temperature inactivation of the enzyme (cal/mol), $T_{0.5H}$ is the temperature (°K) where 50% of the enzyme is inactivated by high temperature, R is the universal gas constant (1.987 cal/mol/°C), and CD, represents cumulative development. The parameters were modified to match the EIP given in Focks et al. (2006), and to include a temperature of 40 ºC as a limit for mosquito survival ($p_{(25°)}$=0.003; ΔH^*_A=13000; ΔH^*_H=110000; $T_{0.5H}$=313). Considering that daily temperature behavior affects virus development (Lambrechts et al. 2011), calculations were made for each day on a two-hour basis through the asymmetric interpolation of minimum and maximum daily temperatures. A linear rise between 6 am and 2 pm (i.e. the time of minimum and maximum temperature, respectively) and a linear fall from 2 pm to 6 am of the following day was used. The proportion of the EIP completed each day, was added up beginning on each day to find the required number of days needed to sum unity. This index was considered as the required number of days needed for transmission (RND). The mean of the RND for each epidemiological week was recorded. Transmission would be

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more likely if the RND is lower than the vector's life expectancy. Therefore, the lower the RND the higher is the risk.

To identify the temporal and spatial clustering of cases we used the Knox test (Knox 1964). The accumulative pairs of points found at a given space-distance interval are counted and compared to the number of random expected cases for each interval (Rotela et al. 2007, Tran et al. 2004). A p-value is obtained by Monte Carlo simulation under the null hypothesis (Ho) that cases are distributed randomly in space and time. IDL version 6.1 from RSI was used for this test.

3. Results

In Argentina the DF 2009 outbreak started in Northern provinces (in the last months of 2008), and extended into central Argentina, affecting Córdoba city with 130 confirmed cases (imported and autochthonous). In Córdoba city, the outbreak started because of imported cases from neighboring provinces. The first case (imported) was reported on January 17th 2009 during EW 2 and it was located at the central area of the city. The second case was reported during EW 4 in the Northeast (NE) of Córdoba city (Figure 2). From there, the cases number started to increase with 2 confirmed cases (during EW 5), both in the Southwest (SW) of the city. The first autochthonous cases reported occurred during EW 10, in the NE and Southeast (SE). Three weeks later during EW 13 the number of cases reached 19, being 15 autochthonous and 4 imported cases. Cases were distributed all over the city, but during the EW 13, 14 and 15 (between March 29th and April 18th 2009) the highest number of confirmed cases were observed (Figures 2 and 3), which correspond to 53% of total confirmed cases during the outbreak (Figure 3). In EW 15 the number of cases stabilizes in the maximum and therein begins to fall until the end of the outbreak on EW 18 (Figure 3). Indeed, 33% of confirmed cases (42 cases) were

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imported and 67% (88 cases) were autochthonous. From EW 16 cases began to decrease and no more imported cases were detected. The imported cases occurred mainly in the central region of the city, while the autochthonous cases occurred along the peripheral area (Figure1).

No autochthonous case co-occurred in any neighborhood with imported cases. The prevalence between neighborhoods with autochthonous and imported cases did not differed significantly (t = 0.9742, df = 48, p-value = 0.3349). The population density comparison between neighborhoods with autochthonous, imported and no cases showed significant differences (7367, 9088 and 6991 inhabitants per square km respectively, p=0.036). According to the pair wise comparisons neighborhoods with imported cases presented significantly higher human population density than those without cases.

The outbreak took 112 days between EW 2 and 18. The dengue risk index remained below 15.2 RND, since EW 2 to EW 14, when it reached 15.7. From that point it rose up to 29 in EW 19 (Figure 3). Considering that the index tells a potential number of days needed for transmission (e.g. 15), an equivalent time lag should be used to interpret the relation between the RND and the behavior of autochthonous cases (i.e. two weeks). Thus the signal for the cases decline in EW 17 would be 15.7 RND of EW 14.

The ratio of houses with *Ae. aegypti* larvae (PI) showed spatial continuity, thus a continuous surface through the city was interpolated. The highest infestation surface was observed in the east of the city, and decreased towards western areas (Figure 4). *Aedes aegypti* infestation did not differ significantly among the neighborhoods with and without autochthonous cases (p=0.35; n=388), or between neighborhoods with autochthonous vs. imported cases (p=0.59; n=50). According to *t*-test, the human

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population density was significantly higher in neighborhoods with imported cases (t=2.26; p=0.03), than the rest of neighborhoods.

The distribution of cases according to sex showed that 68 cases corresponded to women, and 62 to man. DF cases reported all over the city were more likely to belong into the age group of 25-44 years. Autochthonous cases were more frequent for ages below 24 years old and imported cases from 25 and up (X^2 = 5.778, d.f. = 1, p = 0.162) (Figure 5). The distribution of imported cases by age class was symmetrical, with 51% of the cases in the 25-44 years old age class. The autochthonous cases also presented a peak at the 25-44 age class (37% of the cases), but the 0-24 ages summed up 47%.

Regarding the Knox test, Figure 6 shows the 2 dimensional histogram of both, spatial and temporal distances between pairs of DF cases of 2009 dengue outbreak in Córdoba city. Most frequent pairs are shown in red. Along the *x* axis, accumulations of case's pairs can be observed at approximately 2.400 m intervals. All distance clusters begin at the minimum, temporal separation (4 days). The highest temporal spans, 24 days, coincides with distances between 8 km and 11 km. Clustering at more than 12 km corresponds to up to 12 days of temporal clustering (Figure 6). It is noted a main spatiotemporal cluster up to 20 days and 12 km with a probability close to 1 of not being a random occurrence. For the 2009 dengue outbreak in the city of Córdoba, the temporal correlation between cases decayed rapidly in contrast to the observed recurrence in the spatial component. That is, as we increase the time separation between cases it decreases the occurrence of pairs of cases having that temporal separation.

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4. Discussion

Including the spatio-temporal dimension of the DF 2009 outbreak in Córdoba city improved the understanding of the outbreak dynamics of one of the southernmost dengue epidemics recorded up to date. Our study provides an overview of an outbreak in a region which does not regularly suffer from DF and in a city that had an independent vector sampling scheme shortly before the outbreak.

In the present study *Ae. aegypti* infestation levels were not associated with either autochthonous or imported dengue cases. This may suggest effective mosquito control measures applied by the MHC in the most affected neighborhoods, but there is no strong evidence since many other reasons may hold. In Brazil, dengue cases were not correlated with vector infestation levels (Honorio et al. 2009). Instead, the dengue cases pattern observed by these authors responded to displacements of viremic humans.

Human movement is a key behavioral factor in many vector-borne disease systems because it influences exposure to vectors, and thus the transmission of pathogens (Stoddard et al. 2009). In a non endemic city like Cordoba, travel, migration and displacement within and outside the country becomes a significant risk factor for dengue emergence. The introduction of DENV in Córdoba city and the occurrence of DF outbreak during 2009, were associated with outbreaks in the neighboring countries of Bolivia, Brazil and Paraguay at the end of 2008, and also with the epidemiological situation in the Northern provinces of Argentina, where the 92% of DF cases occurred (M.S.N. 2009a). This may explain the high percentage of cases concentrated in the 25-44 years old age class, which represents the active working individuals. At the beginning of the outbreak imported cases were registered mainly in the centre of Córdoba city. Also, neighborhoods with imported cases showed higher population

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densities. Both findings agree with a higher probability of viremic individuals arrival in the most populated areas. Barrera et al. (2000) also observed in Venezuela a similar association between incidence of dengue hemorrhagic fever and neighborhoods with high population density.

During the outbreak cases mainly comprised the working age group; working facilities are located in the central area. The posterior spread to the surroundings, evidenced by the autochthonous cases along the peripheral area, may also be explained by this hypothesis. The typical behavior to work in the downtown and reside in the periphery, matched with the diurnal biting habits of *Ae. aegypti*, suggest focal transmission in the working area, while the report occurred at places of residence in the periphery. But it still calls the attention the lack of coincidence of autochthonous and imported cases in any neighborhood. These suggest that effective control actions were taken immediately after detection of imported cases, thus stopping autochthonous transmission. Nevertheless, there is no specific information about the measures taken by the government.

Based on a previous study, the survival of *Ae. aegypti* in Argentina was estimated to be 15 days (Carbajo et al. 2001), then autochthonous dengue transmission might be expect to be limited by RND values higher than fifteen. At higher values, virus extrinsic incubation period could not be completed before mosquito death. In Córdoba city the number of dengue cases decreased from EW 16, coinciding with an increase of RND values above fifteen two weeks ago. Since the duration of the virus extrinsic incubation period was modeled with an air temperature dependent function, the end of the outbreak could be explained in terms of a decrease in temperature. The minimum air temperature registered in this study since EW 16 fell below the oviposition activity thermal threshold of 17°C observed for *Ae. aegypti* in Córdoba city (Domínguez et al.

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2000). Thus, from this week onwards, vector activity could have decreased and DENV transmission ended. In Buenos Aires city Seijo et al. (2009) observed during the DF outbreak, that low autumn temperatures were an important factor limiting the spread of dengue cases.

Another possible explanation for the end of the outbreak since EW 16 in Córdoba city could be that human population acquired immunity. However, the low levels of immunization in Argentina (Carbajo et al. 2001), and the low number of autochthonous dengue cases registered in a highly populated area like Córdoba city, certainly did not explain the interruption of the outbreak. On the other hand, the applications of vector control measures by local authorities may have interrupted DENV transmission. The MHC, in an attempt to reduce adult mosquito population and suppress dengue transmission during the outbreak, applied focal treatments at dengue positive houses. Besides, it carried out awareness campaigns to reduce mosquito breeding sites, and performed entomological surveys to estimate traditional larval indices.

Our results suggest cases accumulation (clusters) at approximately 2400 m, showing 6 clusters at different distances with peaks around 3, 5, 8, 10 and 12 km, from 4 up to 24 days. Tran et al. (2004) studied the dynamics of dengue outbreak during 2001 in Iracoubo (French Guiana) using Knox test, and identified temporal periodicity with peaks of risk every 3 days. They also found spatial breaks at the approximate distances 20-25 m, 45-50 m, and 80-85 m, showing three different risk levels. Rotela et al. (2007) for the 2004 DF outbreak in Tartagal, northwestern of Argentina, found using Knox test three spatio-temporal clusters for 1 day-100 m, 1-3 day between 500 and 2800 m, and the last cluster at 12-15 days between 700 and 2800 m.

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5. Conclusions

A final thought on the epidemic might be done integrating all results. The low total amount of confirmed cases suggests that the epidemic did not reach its potential maximum. The spatio-temporal clustering strengths this hypothesis. A strong epidemic might be expected to show clustering at distances similar to the city radius (i.e. 15km), for extended periods of time (several transmission cycles). In our study the observed clusters were at most 10-12km and 2 to 3 weeks. The imported cases were absent after EW 16, ending the virus pressure. According to the temperature related model, conditions became limiting after EW 15. The spatial location of imported and autochthonous cases was disrupt. These elements suggest that the epidemic was a series of smaller outbreaks, triggered by imported cases. It did not reach full transmission status, and came to an end because of absence of virus pressure, seasonal temperature fall and maybe control intervention.

The emergence of DF in Córdoba city, as well as others arboviral diseases circulating (e.g., Saint Louis Encephalitis or West Nile Virus) of public health concern, emphasize the need to develop innovative strategies of vector control and arboviral surveillance to prevent future outbreaks. The understanding of the dynamics of dengue outbreak during 2009 could help decision makers allowing them to improve the health system.

Competing interest

The authors declare that they have no competing interests.

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Figure legends

Figure 1. Location of Córdoba city in Argentina (A). Dengue cases reported during 2009 outbreak. Imported cases, squares; autochthonous cases, circles (B).

Figure 2. Spatial distribution of dengue cases in Córdoba city. During the epidemiological week (EW) 13, 14 and 15 (between March 29th and April 18th 2009) the highest number of confirmed cases were observed. Imported cases, squares; autochthonous cases, circles (B).

Figure 3. Number of dengue cases (imported and autochthonous) registered in Córdoba city by epidemiological week (EW 2: January 17th-EW 18: May 10th 2009). The theoretical number of days required for virus transmission (RND) is shown for each week.

Figure 4. *Aedes aegypti* infestation in Cordoba city, Argentina. Black circles show the central location of the houses groups and the measured infestation. Interpolated infestation is represented by shading.

Figure 5. Rate of cases by age class. Autochthonous (grey) and imported (white) DF cases by age class. Total population by age class, black squares.

Figure 6. Graphical representation of Knox analysis for the 130 confirmed dengue cases for each pair of cases according to spatial (meters) versus time (days) separation. The number of pairs of cases at each time and distance interval is represented by the color gradient of the cells.

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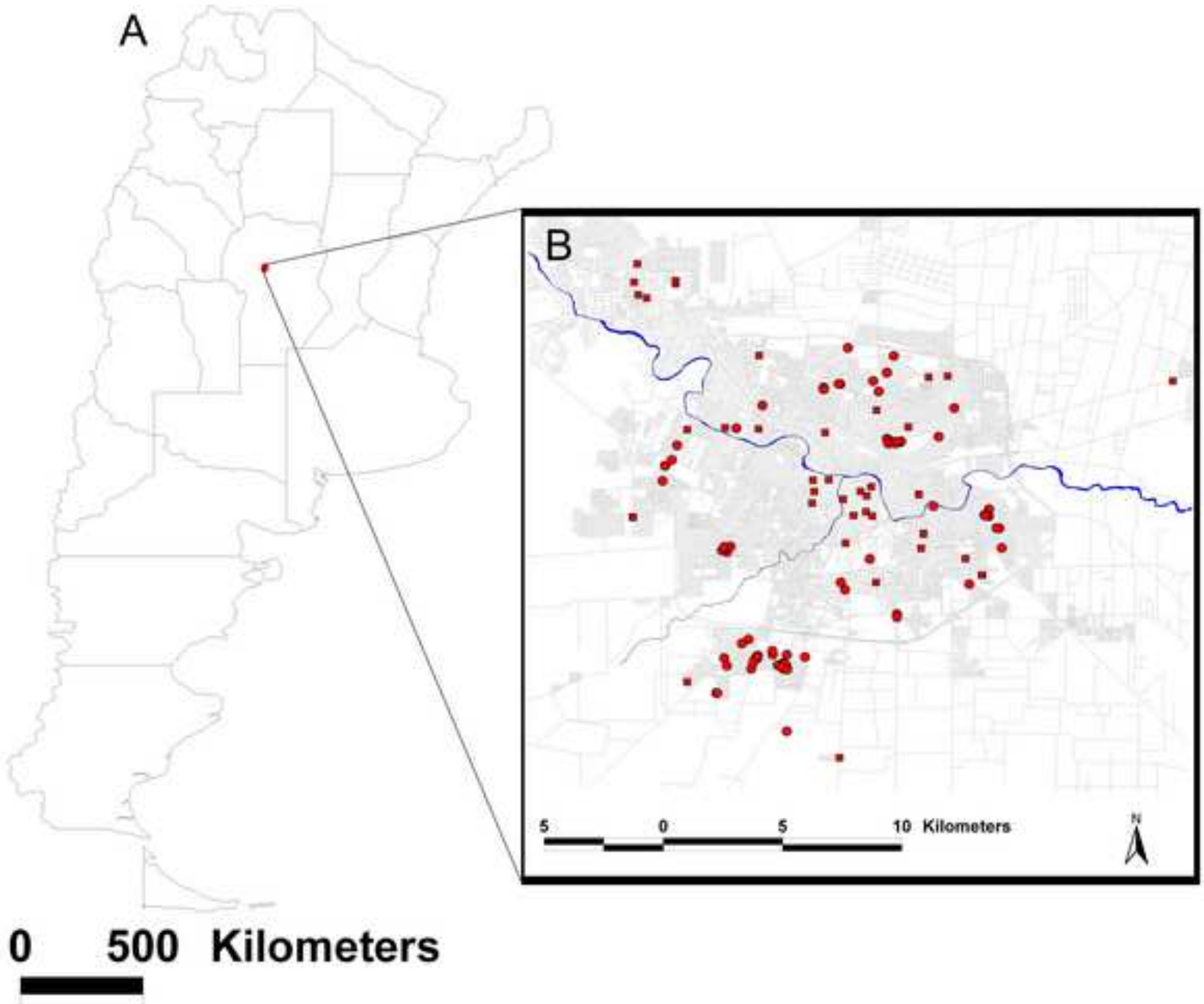
Figure



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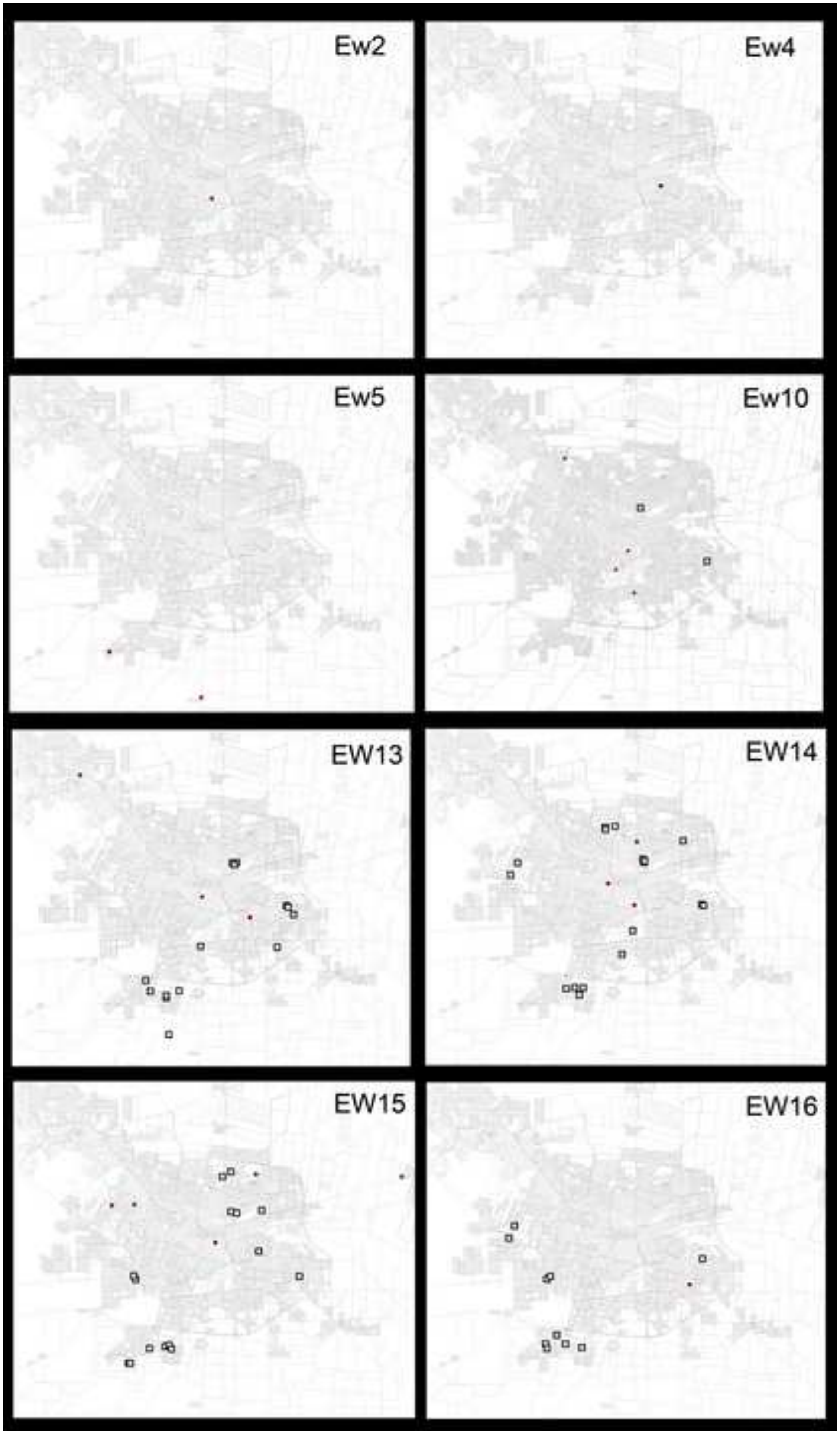

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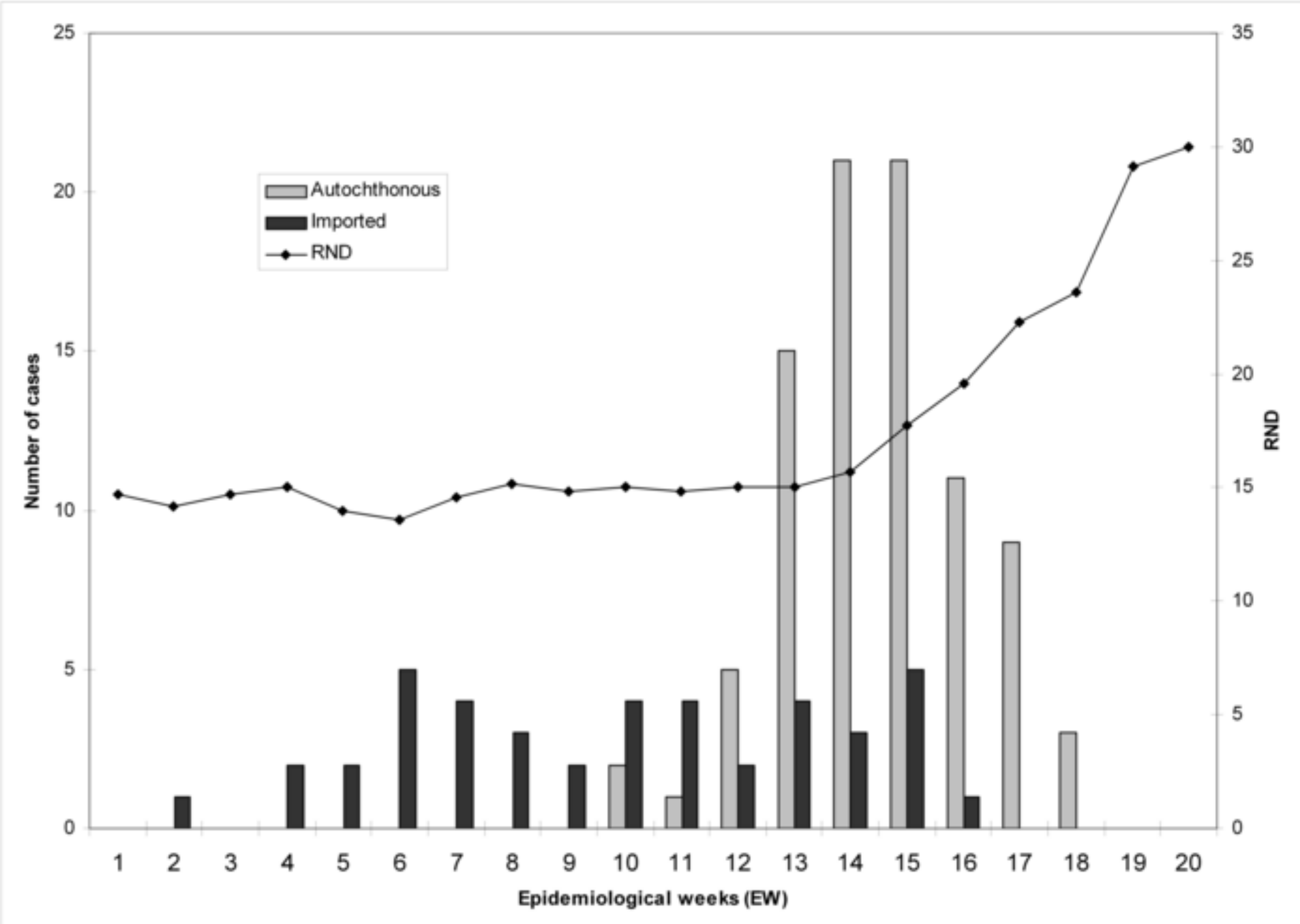
Figure



Autochthonous
Imported
RND
Number of cases
RND
Epidemiological weeks (EW)
25
20
15
10
5
0
35
30
25
20
15
10
5
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20

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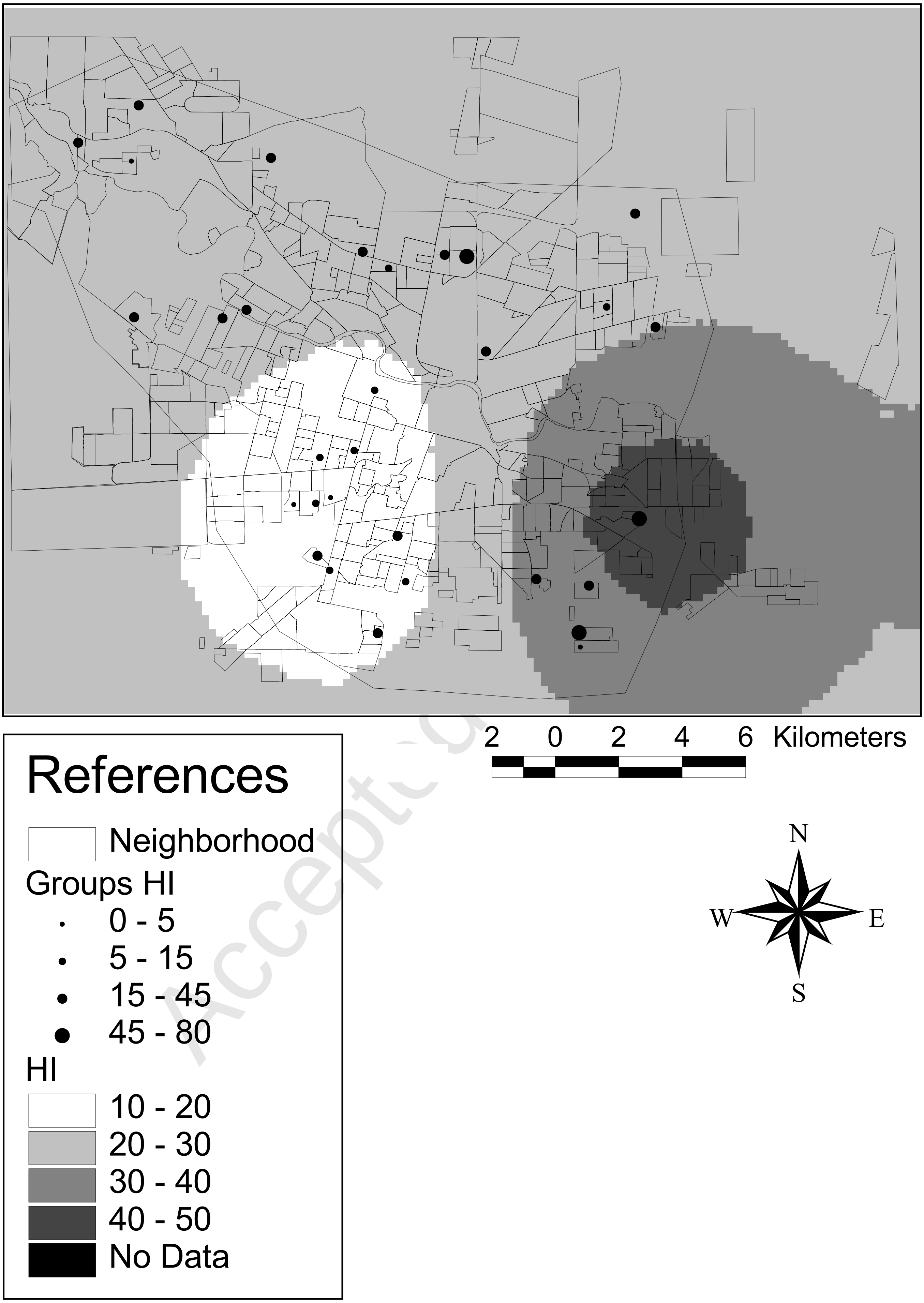

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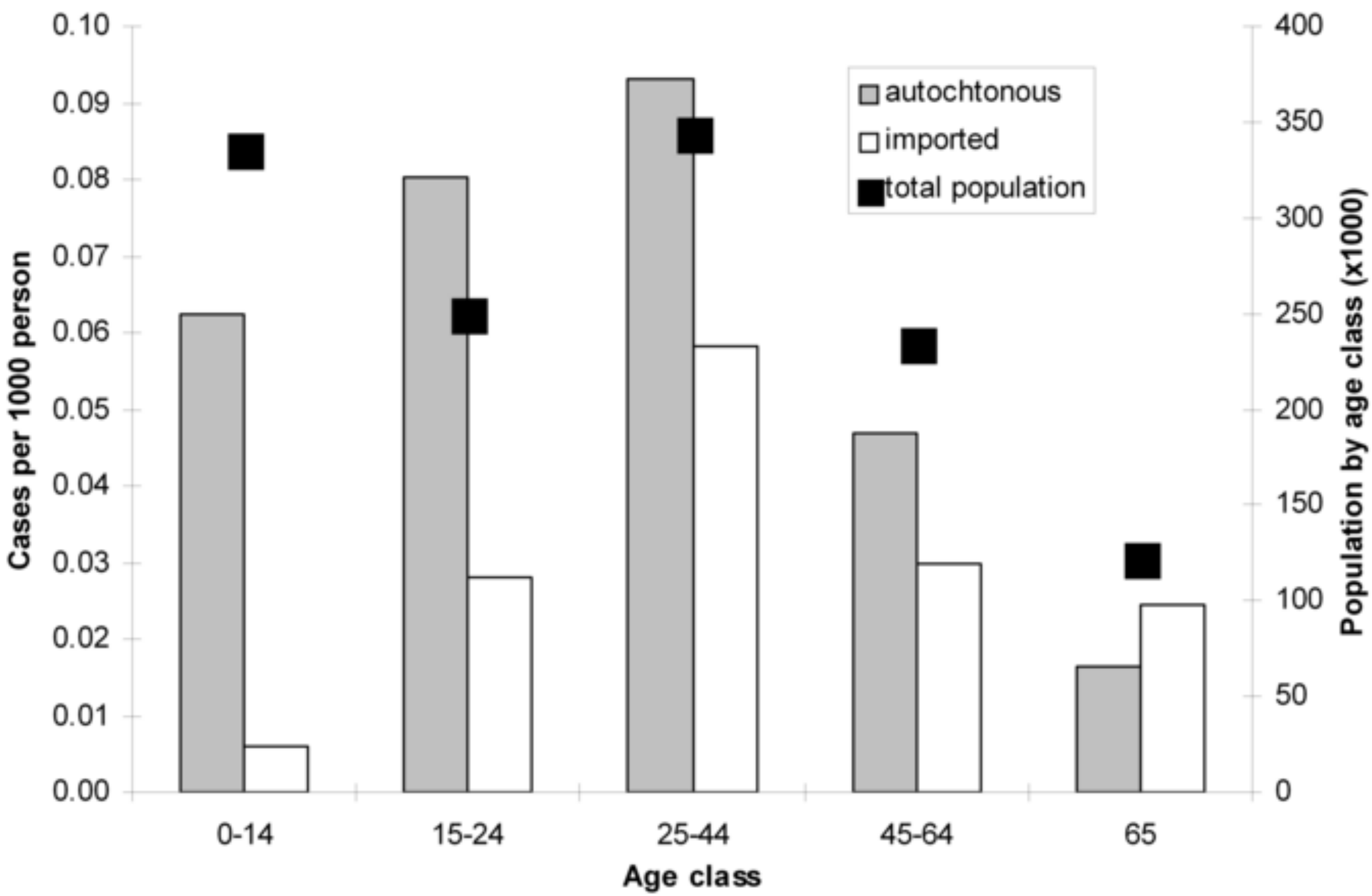
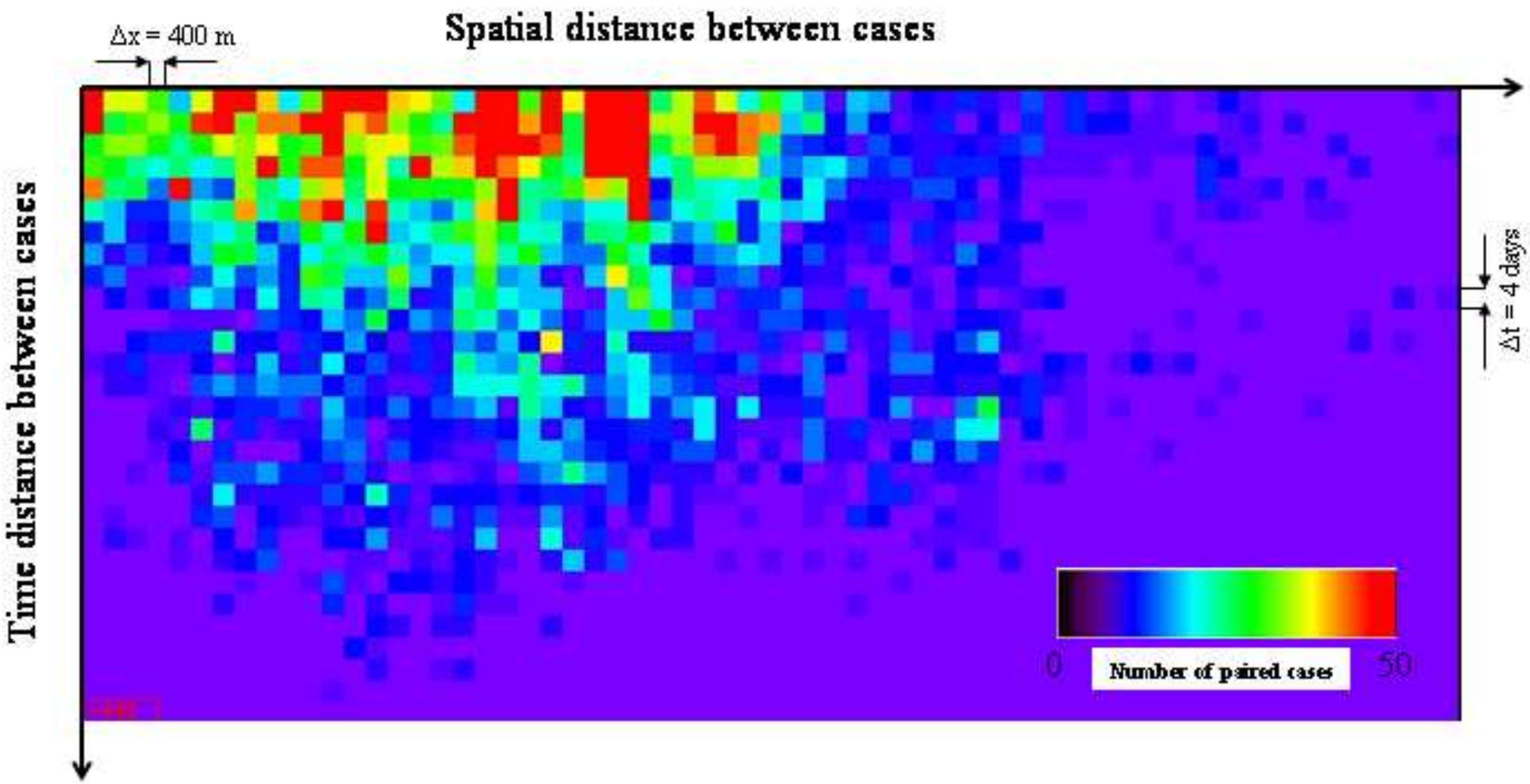


0.10
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0.00
Cases per 1000 person
400
350
300
250
200
150
100
50
0
Population by age class (x1000)
autochtonous
imported
total population
0-14
15-24
25-44
45-64
65
Age class

Figure


Spatial distance between cases
Δx = 400 m
Time distance between cases
Δt = 4 days
0
Number of paired cases
50

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HIGHLIGHTS

- Córdoba city reported autochthonous Dengue Fever cases for the first time.
- No autochthonous cases co-occurred in any neighborhood with imported cases.
- In epidemiological week 15 the number of cases stabilized in the maximum
- Cases dropped for theoretical required number of days for transmission above 15.5

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***Graphical Abstract (for review)**