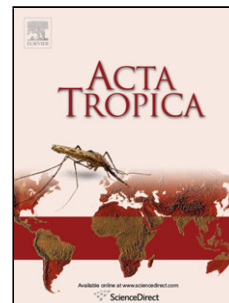


Accepted Manuscript

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

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PII: S0001-706X(14)00147-8
DOI: <http://dx.doi.org/doi:10.1016/j.actatropica.2014.04.024>
Reference: ACTROP 3361

To appear in: *Acta Tropica*

Received date: 8-1-2014
Revised date: 16-4-2014
Accepted date: 22-4-2014

Please cite this article as: Estallo, E.L., Carbajo, A.E., Grech, M.G., Frías-Céspedes, M., López, L., Lanfri, M.A., Ludueña-Almeida, F.F., Almirón, W.R., Spatio-temporal dynamics of dengue 2009 outbreak in Córdoba City, Argentina., *Acta Tropica* (2014), <http://dx.doi.org/10.1016/j.actatropica.2014.04.024>

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

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Abstract

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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).

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

1 like Bolivia, Brazil and Paraguay (Avilés et al. 2003; Vezanni and Carbajo 2008). The
2 objective of this paper was to study the spatio-temporal dynamics of DF 2009
3 outbreak in Córdoba city, Argentina.
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6 7 **2. Methods**

8 9 **2.1. Study site**

10 The study was done in Córdoba city (64°12' W, 31° 22' S), capital and main
11 city of the province of Córdoba (Argentina) (Figure 1), with a population of 1,330,023
12 inhabitants. The population is mainly composed for young individuals who
13 concentrate 66.2% of the population on the age class of 15-64 years old (INDEC
14 2010). Córdoba city is highly urbanized with a land area of 576 Km² that lies between
15 306 and 480 m above sea level (Jarsún et al. 2003). Young people move into the city
16 mainly from Northern provinces to study or work. The city climate is temperate with
17 mean annual precipitation of 694 mm mainly between October and March. The
18 warmest period is between November and March. The mean maximum, average, and
19 minimum temperatures are 24.03°, 17.28°, and 11.21° C, respectively (S.M.N. 2011).
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36 **2.2. Data**

37 Data on confirmed cases during the 2009 DF outbreak were given by the
38 Ministry of Health of Córdoba (Dirección de Epidemiología, Ministerio de Salud de
39 la Provincia de Córdoba, MHC herein). At the beginning of the outbreak, patients
40 serum samples of suspected cases were confirmed by isolation of DENV from serum,
41 or demonstration cDNA fragment by polymerase chain reaction (PCR) from a serum
42 sample, or IgM antibody by using an IgM capture enzyme-linked immunosorbent
43 assay (UM-ELISA®) by the National Reference Centre for Arbovirus, Instituto
44 Nacional de Enfermedades Virales Humanas "Dr. Julio I. Maiztegui" (INEVH). All
45 DF confirmed patients residences were georeferenced into a Geographic Information
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1 System (GIS) with city neighborhood division and demography (Arcview 3.2 [ESRI
2 200]). Ancillary information on each patient was also recorded: identification number,
3
4 date of onset of symptoms, age, sex and type of DF cases (imported or
5
6 autochthonous). Weekly maps of number of cases were built to visualize the
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8 beginning of the outbreak and the successive dispersion of cases.
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12 During February 2009 a monitoring of immature stages was performed in the
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14 city (MHC; Centro de Investigaciones Entomológicas de Córdoba- CIEC). Data
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16 consisted in a larval survey of 32 randomly selected neighborhoods with a total of 654
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18 houses inspected. Houses were inspected for artificial containers with *Ae. aegypti*
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20 larvae. The material collected was transferred to the laboratory of the CIEC in small
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22 plastic flasks. The 3rd and 4th instars larvae were killed and stored in 80% ethanol for
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24 taxonomic determination using keys (Darsie 1985). The younger instars were reared
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26 until the 4th in plastic trays containing water from natural larval habitat, and fed 0.25
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28 mg daily/larva of liver powder.
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34 To analyze the spatial relationship between *Ae. aegypti* infestation and
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36 confirmed DF cases, a regrouping of the premises was carried out as follows. First,
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38 the premises closer than 100 m were grouped together. Secondly, groups of premises
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40 which centroids were closer than 350 m were grouped. Remnant isolated premises
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42 were joined to groups closer than 400 m or if farther apart excluded from the analysis.
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44 This resulted in 31 groups with 7 to 39 premises each, and 7 premises excluded. The
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46 abundance of *Ae. aegypti* was estimated for each group as the ratio of premises with
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48 the mosquito to total premises (PI). From a total of 414 neighborhoods in the city, 44
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50 had infestation information. The spatial behavior of infestation was studied in order to
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52 find an adequate means to extrapolate infestation to all neighborhoods. PI spatial
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54 continuity was assessed with semivariograms and mean PI interpolated as a
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1 continuous surface through Córdoba city by kriging (Cressie 1993). This method
2 provides also interpolation error estimation (PI standard error). City neighborhoods
3 were classified as positive or negative for DF autochthonous and imported cases.
4 Differences in the mean PI value between positive and negative neighborhoods were
5 assessed with a Wilcoxon test. Neighborhoods with a PI standard error higher than
6 0.15 were excluded from the analysis.
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14 A map with the DF confirmed cases during the outbreak was done. The DF
15 cases distribution by age and sex was observed, and also the weekly frequency of DF
16 cases for each epidemiological week (EW). Differences in DF prevalence between
17 neighborhoods with autochthonous and imported cases was assessed with a t-test on
18 the transformed variable (arc sin of the square root of the prevalence).
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26 The human population density was compared between neighborhoods with
27 autochthonous, imported and no cases with an analyses of variance with Tukey
28 multiple comparisons (Zar 1999).
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34 A dengue risk index was calculated for each day during the epidemic (Carbajo
35 et al. 2012). The index estimates the theoretical number of days that would take the
36 virus to develop and be transmitted. The extrinsic incubation period (EIP) of the
37 dengue virus in the mosquito *Ae. aegypti* is the lapse from ingestion of infected blood
38 to the virus transmission in a subsequent feed. This period varies as a function of
39 temperature (McLean et al. 1974; Watts et al. 1984). If ambient temperature is low,
40 mosquitoes are unlikely to survive long enough to become infectious and transmit the
41 disease. Therefore, the duration of the EIP and the survival of vectors are key factors
42 in determining dengue transmission risk (Focks et al. 1993). The proportion of the
43 EIP completed was calculated as a function of air temperature. A mathematical model
44 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:

$$r(T_h) = (p_{(25^\circ\text{C})} (T_h/298) e^{x_1}) / (1 + e^{x_2}) \quad (1)$$

where

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

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

$r(T_h)$ represents the development rate (hr^{-1}) at temperature T ($^\circ\text{K}$) at hour h , $p_{(25^\circ\text{C})}$ 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 ($^\circ\text{K}$) where 50% of the enzyme is inactivated by high temperature, R is the universal gas constant ($1.987 \text{ cal/mol/}^\circ\text{C}$), 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°C as a limit for mosquito survival ($p_{(25^\circ)}=0.003$; $\Delta H^*_A=13000$; $\Delta H^*_H=110000$; $T_{0.5H}=313$). 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

1 more likely if the RND is lower than the vector's life expectancy. Therefore, the lower
2 the RND the higher is the risk.
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5 To identify the temporal and spatial clustering of cases we used the Knox test
6 (Knox 1964). The accumulative pairs of points found at a given space-distance
7 interval are counted and compared to the number of random expected cases for each
8 interval (Rotela et al. 2007, Tran et al. 2004). A p-value is obtained by Monte Carlo
9 simulation under the null hypothesis (Ho) that cases are distributed randomly in space
10 and time. IDL version 6.1 from RSI was used for this test.
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19 **3. Results**

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22 In Argentina the DF 2009 outbreak started in Northern provinces (in the last
23 months of 2008), and extended into central Argentina, affecting Córdoba city with
24 130 confirmed cases (imported and autochthonous). In Córdoba city, the outbreak
25 started because of imported cases from neighboring provinces. The first case
26 (imported) was reported on January 17th 2009 during EW 2 and it was located at the
27 central area of the city. The second case was reported during EW 4 in the Northeast
28 (NE) of Córdoba city (Figure 2). From there, the cases number started to increase with
29 2 confirmed cases (during EW 5), both in the Southwest (SW) of the city. The first
30 autochthonous cases reported occurred during EW 10, in the NE and Southeast (SE).
31 Three weeks later during EW 13 the number of cases reached 19, being 15
32 autochthonous and 4 imported cases. Cases were distributed all over the city, but
33 during the EW 13, 14 and 15 (between March 29th and April 18th 2009) the highest
34 number of confirmed cases were observed (Figures 2 and 3), which correspond to
35 53% of total confirmed cases during the outbreak (Figure 3). In EW 15 the number of
36 cases stabilizes in the maximum and therein begins to fall until the end of the
37 outbreak on EW 18 (Figure 3). Indeed, 33% of confirmed cases (42 cases) were
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1 imported and 67% (88 cases) were autochthonous. From EW 16 cases began to
2 decrease and no more imported cases were detected. The imported cases occurred
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4 mainly in the central region of the city, while the autochthonous cases occurred along
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6 the peripheral area (Figure1).
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10 No autochthonous case co-occurred in any neighborhood with imported cases. The
11 prevalence between neighborhoods with autochthonous and imported cases did not
12 differed significantly ($t = 0.9742$, $df = 48$, $p\text{-value} = 0.3349$). The population density
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14 comparison between neighborhoods with autochthonous, imported and no cases
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16 showed significant differences (7367, 9088 and 6991 inhabitants per square km
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18 respectively, $p=0.036$). According to the pair wise comparisons neighborhoods with
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20 imported cases presented significantly higher human population density than those
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22 without cases.
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29 The outbreak took 112 days between EW 2 and 18. The dengue risk index
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31 remained below 15.2 RND, since EW 2 to EW 14, when it reached 15.7. From that
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33 point it rose up to 29 in EW 19 (Figure 3). Considering that the index tells a potential
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35 number of days needed for transmission (e.g. 15), an equivalent time lag should be
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37 used to interpret the relation between the RND and the behavior of autochthonous
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39 cases (i.e. two weeks). Thus the signal for the cases decline in EW 17 would be 15.7
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41 RND of EW 14.
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46 The ratio of houses with *Ae. aegypti* larvae (PI) showed spatial continuity, thus a
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48 continuous surface through the city was interpolated. The highest infestation surface
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50 was observed in the east of the city, and decreased towards western areas (Figure 4).
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52 *Aedes aegypti* infestation did not differ significantly among the neighborhoods with
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54 and without autochthonous cases ($p=0.35$; $n=388$), or between neighborhoods with
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56 autochthonous vs. imported cases ($p=0.59$; $n=50$). According to *t*-test, the human
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1 population density was significantly higher in neighborhoods with imported cases
2 (t=2.26; p=0.03), than the rest of neighborhoods.
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5 The distribution of cases according to sex showed that 68 cases corresponded to
6 women, and 62 to man. DF cases reported all over the city were more likely to belong
7 into the age group of 25-44 years. Autochthonous cases were more frequent for ages
8 below 24 years old and imported cases from 25 and up ($X^2 = 5.778$, d.f. = 1, p =
9 0.162) (Figure 5). The distribution of imported cases by age class was symmetrical,
10 with 51% of the cases in the 25-44 years old age class. The autochthonous cases also
11 presented a peak at the 25-44 age class (37% of the cases), but the 0-24 ages summed
12 up 47%.
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24 Regarding the Knox test, Figure 6 shows the 2 dimensional histogram of both,
25 spatial and temporal distances between pairs of DF cases of 2009 dengue outbreak in
26 Córdoba city. Most frequent pairs are shown in red. Along the x axis, accumulations
27 of case's pairs can be observed at approximately 2.400 m intervals. All distance
28 clusters begin at the minimum, temporal separation (4 days). The highest temporal
29 spans, 24 days, coincides with distances between 8 km and 11 km. Clustering at more
30 than 12 km corresponds to up to 12 days of temporal clustering (Figure 6). It is noted
31 a main spatiotemporal cluster up to 20 days and 12 km with a probability close to 1 of
32 not being a random occurrence. For the 2009 dengue outbreak in the city of Córdoba,
33 the temporal correlation between cases decayed rapidly in contrast to the observed
34 recurrence in the spatial component. That is, as we increase the time separation
35 between cases it decreases the occurrence of pairs of cases having that temporal
36 separation.
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4. Discussion

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2 Including the spatio-temporal dimension of the DF 2009 outbreak in Córdoba city
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4 improved the understanding of the outbreak dynamics of one of the southernmost
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6 dengue epidemics recorded up to date. Our study provides an overview of an outbreak
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8 in a region which does not regularly suffer from DF and in a city that had an
9
10 independent vector sampling scheme shortly before the outbreak.
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14 In the present study *Ae. aegypti* infestation levels were not associated with either
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16 autochthonous or imported dengue cases. This may suggest effective mosquito control
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18 measures applied by the MHC in the most affected neighborhoods, but there is no
19
20 strong evidence since many other reasons may hold. In Brazil, dengue cases were not
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22 correlated with vector infestation levels (Honorio et al. 2009). Instead, the dengue
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24 cases pattern observed by these authors responded to displacements of viremic
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26 humans.
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32 Human movement is a key behavioral factor in many vector-borne disease systems
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34 because it influences exposure to vectors, and thus the transmission of pathogens
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36 (Stoddard et al. 2009). In a non endemic city like Cordoba, travel, migration and
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38 displacement within and outside the country becomes a significant risk factor for
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40 dengue emergence. The introduction of DENV in Córdoba city and the occurrence of
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42 DF outbreak during 2009, were associated with outbreaks in the neighboring countries
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44 of Bolivia, Brazil and Paraguay at the end of 2008, and also with the epidemiological
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46 situation in the Northern provinces of Argentina, where the 92% of DF cases occurred
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48 (M.S.N. 2009a). This may explain the high percentage of cases concentrated in the
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50 25-44 years old age class, which represents the active working individuals. At the
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52 beginning of the outbreak imported cases were registered mainly in the centre of
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54 Córdoba city. Also, neighborhoods with imported cases showed higher population
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1 densities. Both findings agree with a higher probability of viremic individuals arrival
2 in the most populated areas. Barrera et al. (2000) also observed in Venezuela a similar
3 association between incidence of dengue hemorrhagic fever and neighborhoods with
4 high population density.
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9 During the outbreak cases mainly comprised the working age group; working
10 facilities are located in the central area. The posterior spread to the surroundings,
11 evidenced by the autochthonous cases along the peripheral area, may also be
12 explained by this hypothesis. The typical behavior to work in the downtown and
13 reside in the periphery, matched with the diurnal biting habits of *Ae. aegypti*, suggest
14 focal transmission in the working area, while the report occurred at places of
15 residence in the periphery. But it still calls the attention the lack of coincidence of
16 autochthonous and imported cases in any neighborhood. These suggest that effective
17 control actions were taken immediately after detection of imported cases, thus
18 stopping autochthonous transmission. Nevertheless, there is no specific information
19 about the measures taken by the government.
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36 Based on a previous study, the survival of *Ae. aegypti* in Argentina was estimated
37 to be 15 days (Carbajo et al. 2001), then autochthonous dengue transmission might be
38 expect to be limited by RND values higher than fifteen. At higher values, virus
39 extrinsic incubation period could not be completed before mosquito death. In Córdoba
40 city the number of dengue cases decreased from EW 16, coinciding with an increase
41 of RND values above fifteen two weeks ago. Since the duration of the virus extrinsic
42 incubation period was modeled with an air temperature dependent function, the end of
43 the outbreak could be explained in terms of a decrease in temperature. The minimum
44 air temperature registered in this study since EW 16 fell below the oviposition activity
45 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.

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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.

5. Conclusions

1
2 A final thought on the epidemic might be done integrating all results. The low
3
4 total amount of confirmed cases suggests that the epidemic did not reach its potential
5
6 maximum. The spatio-temporal clustering strengths this hypothesis. A strong
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8 epidemic might be expected to show clustering at distances similar to the city radius
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10 (i.e. 15km), for extended periods of time (several transmission cycles). In our study
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12 the observed clusters were at most 10-12km and 2 to 3 weeks. The imported cases
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14 were absent after EW 16, ending the virus pressure. According to the temperature
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16 related model, conditions became limiting after EW 15. The spatial location of
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18 imported and autochthonous cases was disrupted. These elements suggest that the
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20 epidemic was a series of smaller outbreaks, triggered by imported cases. It did not
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22 reach full transmission status, and came to an end because of absence of virus
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24 pressure, seasonal temperature fall and maybe control intervention.
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31 The emergence of DF in Córdoba city, as well as others arboviral diseases
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33 circulating (e.g., Saint Louis Encephalitis or West Nile Virus) of public health
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35 concern, emphasize the need to develop innovative strategies of vector control and
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37 arboviral surveillance to prevent future outbreaks. The understanding of the dynamics
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39 of dengue outbreak during 2009 could help decision makers allowing them to improve
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41 the health system.
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Competing interest

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46
47 The authors declare that they have no competing interests.
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49

Acknowledgments

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51
52 Authors wish to acknowledge the assistance of the Consejo Nacional de
53
54 Investigaciones Científicas y Tecnológicas (CONICET) and the Universidad Nacional
55
56 de Córdoba, both of which support facilities used in this investigation. EEL, CAE and
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1 AWR are members of CONICET scientific carrier, GMG is a CONICET posdoc
2 fellow.
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4 The authors would like to thank all those from MHC who helped directly in field
5 work during larval surveys.
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Accepted Manuscript

Bibliography

- 1
2 Almirón, W.R., Ludueña-Almeida, F., 1998. *Aedes aegypti* (Diptera: Culicidae) en
3
4 Córdoba, Argentina. Rev. Soc. Entomol. Argent. 57, 27-28.
5
6
7 Avilés, G., Rangeón, G., Voendam, V., Briones, A., Baroni, P., Enria, D., Sabattini,
8
9 M., 1999. Dengue reemergence in Argentina. Emerg. Infect. Dis. 5, 575-578.
10
11
12 Avilés, G., Paz, M., Rangeon, G., Ranaivoarisoa, M., Verzeri, N., Roginski, S.,
13
14 Baroni, P., Enria, D., 2003. Laboratoy surveillance of Dengue in Argentina.
15
16 1995-2001. Emerg. Infect. Dis. 9, 738-742.
17
18
19 Barrera R., Delgado, N., Jiménez, M., Villalobos, I., Romero, I., 2000. Estratificación
20
21 de una ciudad hiperendémica en dengue hemorrágico. Pan. Am. J. Public
22
23 Health. 8, 225-233.
24
25
26 Carbajo, A.E., Schweigmann, N.J., Curto, S.I., de Garin, A., Bejarán, R.A., 2001.
27
28 Dengue transmission risk maps of Argentina. Trop. Med. Int. Health. 6, 170-
29
30 183.
31
32
33 Carbajo, A.E., Cardo, M.V., Vezzani, ., 2012. Is temperature the main cause of
34
35 dengue rise in non-endemic countries? The case of Argentina. Int. J. Health
36
37 Geogr. 11, 26. doi:10.1186/1476-072X-11-26
38
39
40
41 Cressie, N., 1993. Statistic for Spatial Data, John Wiley & Sons eds. New York.
42
43
44 Darsie Jr., R.F., 1985. The mosquitoes of Argentina: Part I. Keys for identification of
45
46 adult females and fourth stage larvae in English and Spanish (Diptera:
47
48 Culicidae). Mosq. Syst. 17, 153-253.
49
50
51 Díaz-Nieto L.M., Maciá, A., Perotti, M.A., Berón., C.M., 2013. Geographical limits
52
53 of the southeastern distribution of *Aedes aegypti* (Diptera, Culicidae) in
54
55 Argentina. PLoS. Negl. Trop. Dis. 7, 1-7.
56
57
58
59
60
61
62
63
64
65

- 1 Domínguez, M.C., Ludueña-Almeida, F. Almirón., W.R., 2000. Dinámica
2 poblacional de *Aedes aegypti* (Diptera: Culicidae) en Córdoba Capital. Rev.
3 Soc. Entomol. Argent. 59, 41-50.
4
5
6
7 Estallo, E., Grech, M., Ludueña-Almeida, F., Ainete, M., Frías Céspedes, M., Asís,
8 R., Almirón, W.R., 2009. Evolución de los índices de infestación por *Aedes*
9 *aegypti* (Diptera: Culicidae) en la ciudad de Córdoba, Argentina (1997-2009).
10 XII Simposio Internacional sobre Control Epidemiológico de Enfermedades
11 Transmitidas por Vectores. Buenos Aires: Mundo Sano. pp. 54.
12
13
14
15
16
17
18
19 Focks, D.A., Haile, D.G., Daniels, E., Mount, G.A., 1993. Dynamic Life Table Model
20 for *Ae aegypti* (Diptera:Culicidae): Analysis of the literature and model
21 development. J. Med. Entomol. 30, 1003-1017.
22
23
24
25
26
27 Focks, D., Alexander, N., Villegas, E., Romero-Vivas, C., Midega, J., Bisset, J.,
28 Morrison, A.C., Barrera, R., Barbaza, P., Nam, V.S., Arredondo-Jiménez, J.,
29 2006. Multicountry study of *Aedes aegypti* pupal productivity survey
30 methodology: findings and recommendations. Geneva: TDR/IRM. Available
31 at: http://www.who.int/tdr/publications/documents/aedes_aegypti.pdf
32
33
34
35
36
37
38
39 Gaudino, N.M., 1916. El dengue: Algunas consideraciones sobre la epidemia de Entre
40 Ríos de 1916. Rev. Sanidad Mil. 15, 617-627.
41
42
43
44 Grech, M., Visintin, A., Laurito, M., Estallo, E., Lorenzo, P., Rocchia, I., Korin, M.,
45 Goya, F., Ludueña-Almeida, F., Almirón, W., 2012. New records of mosquito
46 species (Diptera: Culicidae) from Neuquén and La Rioja provinces, Argentina.
47
48
49
50
51
52
53
54 Honório, N.A, Nogueira, R.M.R., Codeço, C.T, Carvalho, M.S, Cruz, O.G, de Avelar
55 Figueiredo Mafra Magalhães, M., Galvão de Araújo, J.M., Saraiva Machado
56 de Araújo, E., Quintela Gomes, M., Silva Pinheiro, L., da Silva Pinel, C.,
57
58
59
60
61
62
63
64
65

1 Lourenço-de-Oliveira, R., 2009. Spatial Evaluation and Modeling of Dengue
2 Seroprevalence and Vector Density in Rio de Janeiro, Brazil. PLoS Negl Trop
3 Dis 3(11), e545. doi:10.1371/journal.pntd.0000545
4
5
6

7 INDEC (Instituto Nacional de Estadística y Censo), 2010. Censo Nacional de
8 Población, Hogares y Viviendas 2010. Available from:
9
10 http://www.censo2010.indec.gov.ar/preliminares/cuadro_cordoba.asp
11
12
13

14 Jarsún, B., Gorgas, J.A., Zamora, E., Bosnero, E., Lovera, E., Ravelo, A., Tassile,
15 J.L., 2003. Caracterización general de la provincia. In: JA Gorjas, JL Tassile
16 (Eds), Recursos naturales de la Provincia de Córdoba. Los Suelos. Córdoba,
17 Argentina, Agencia Córdoba Ambiente e INTA, p. 23-60.
18
19
20
21
22
23

24 McLean, D., Clarke, A., Coleman, J., Montalbetti, C., Skidmore, A., Walters, T.,
25 Wise, R., 1974. Vector capability of *Aedes aegypti* mosquitoes for California
26 encephalitis and dengue viruses at various temperatures. Can. J. Microbiol. 20,
27 255-262.
28
29
30
31
32
33

34 M.S.N. (Ministerio de Salud de la Nación), 2006. Boletín Epidemiológico Anual
35 2004–2005. Buenos Aires. Available from:
36
37 http://msal.gov.ar/htm/Site/sala_situacion/PANELES/boletines/bepAnual/BEP
38 [anual2006_Zoonosis.pdf](http://msal.gov.ar/htm/Site/sala_situacion/PANELES/boletines/bepAnual/BEP)
39
40
41
42
43

44 M.S.N. (Ministerio de Salud de la Nación), 2009a. Informe de la situación
45 epidemiológica de las provincias. Available from:
46
47 http://www.msal.gov.ar/htm/site/Noticias_plantilla.asp?Id=1393.
48
49
50

51 M.S.N. (Ministerio de Salud de la Nación), 2009b. Plan Nacional para Prevención y
52 Control del Dengue y la Fiebre Amarilla. Available from:
53
54 [http://www.msal.gov.ar/dengue/descargas/plan_nacional%20prevencion_con](http://www.msal.gov.ar/dengue/descargas/plan_nacional%20prevencion_control_dengue_f_amarilla.pdf)
55 [trol_dengue_f_amarilla.pdf](http://www.msal.gov.ar/dengue/descargas/plan_nacional%20prevencion_control_dengue_f_amarilla.pdf) Ministerio de Salud de la Nación. 2009.
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57
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61
62
63
64
65
- Jetten, T.H., Focks, D.A., 1997. Potential changes in the distribution of dengue transmission under climate warming. *Am. J. Trop. Med. Hyg.* 57, 285-297.
- Knox, G., 1964. The detection of space-time interactions. *Applied Statistics* 13, 25-29.
- Lambrechts, L., Paaijmans, K., Fansiri, T., Carrington, L., Kramer, L., Thomas, M., Scott, T., 2011. Impact of daily temperature fluctuations on dengue virus transmission by *Aedes aegypti*. *P. Natl. Acad. Sci. USA.* 108, 7460-7465.
- Rossi, G.C., Lestani, E.A., D’Oria, J.M., 2006. Nuevos registros y distribución de mosquitos de la Argentina (Diptera: Culicidae). *Rev. Soc. Entomol. Argent.* 65, 51-56.
- Rotela, C., Fouque, F., Lamfri, M., Sabtier, P., Introini, V., Zaidenberg, M., Scavuzzo, M., 2007. Space–time analysis of the dengue spreading dynamics in the 2004 Tartagal outbreak, Northern Argentina. *Acta Trop.* 103, 1-13.
- Seijo, A., 2009. Dengue 2009: cronología de una epidemia. *Arch. Argent. Pediatr.* 107, 387-391.
- S.M.N. (Servicio Meteorológico Nacional), 2011. Ministerio de Defensa. Secretaría de Planeamiento. SMN. Climatología. Datos estadísticos-Turismo. Available from:
<http://www.smn.gov.ar/?mod=clima&id=30&provincia=C%F3rdoba&ciudad=C%F3rdoba>.
- Stoddard, S.T., Morrison, A.C., Vazquez-Prokopec, G.M., Soldan, V.P., Kochel, T.J., Kitron, U., Elder, J.P., Scott, T.W., 2009. The role of human movement in the transmission of vector-borne pathogens. *PLoS Negl. Trop. Dis.* 3, e481.

1 Tran, A.L., Deparis, X., Dussart, P. , Morvan, J., Rabarison, P., Remy, F., Polidori ,
2 L., Gardon, J., 2004. Dengue spatial and temporal patterns, French Guyana,
3
4 2001. *Emerg. Infect. Dis.* 10, 615-621.
5
6

7 Vezzani, D., Carbajo, A.E., 2008. *Aedes aegypti*, *Aedes albopictus*, and dengue in
8
9 Argentina: current knowledge and future directions. *Mem. Inst. Oswaldo*
10
11 Cruz. 103, 66-74.
12
13

14 Watts, D., Burke, D., Harrison, B., Whitmire, R., Nisalak, A., 1987. Effect of
15
16 temperature on the vector efficiency of *Aedes aegypti* for dengue 2 virus. *Am. J.*
17
18 *Trop. Med. Hyg.* 36,143-152.
19
20

21 Zar, J.H., 1999. *Biostatistical Analysis*. Prentice Hall, New Jersey.
22
23
24
25
26
27
28
29
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Figure legends

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

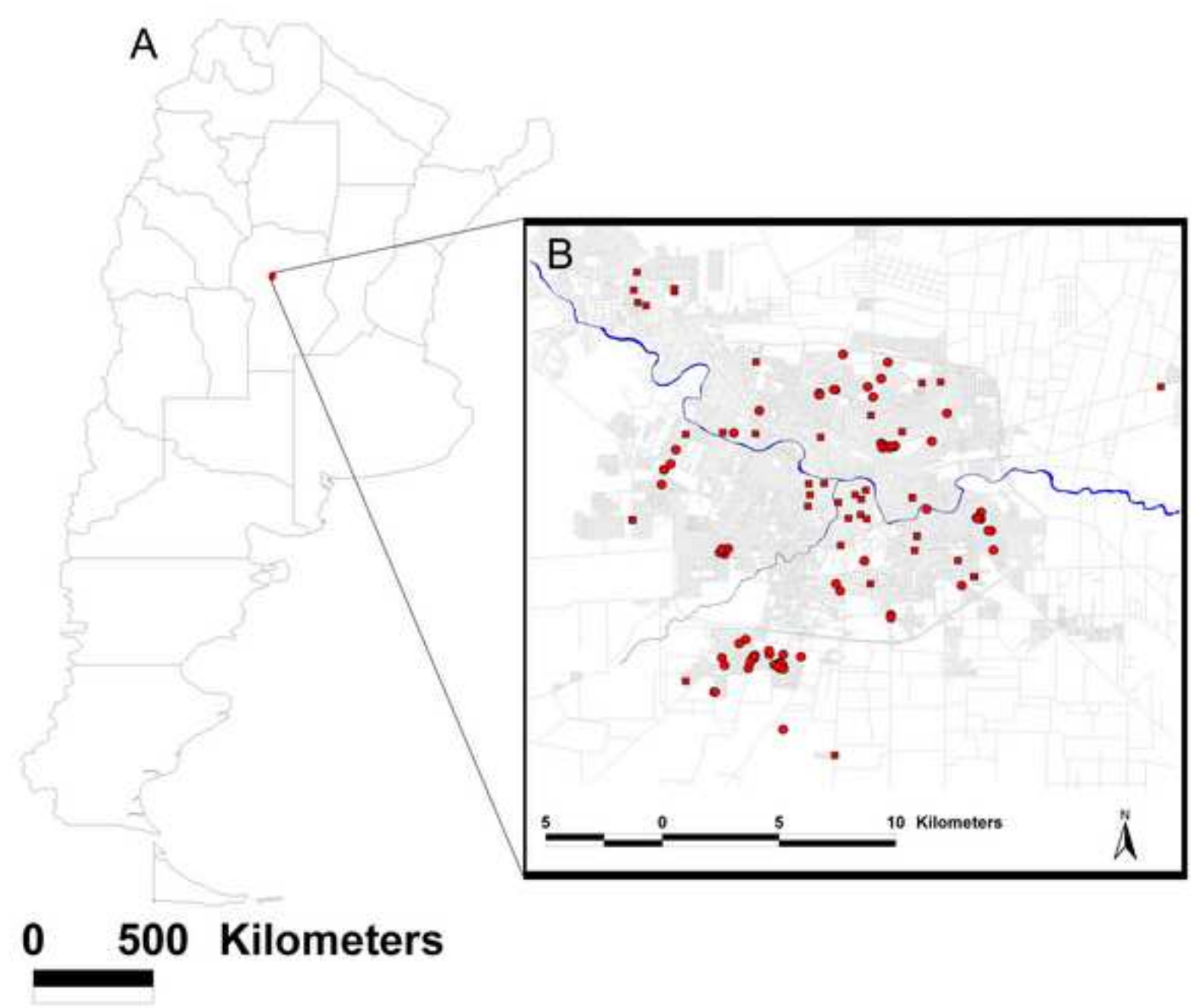
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Figure 2. Spatial distribution of dengue cases in Córdoba city. During the epidemiological week (EW) 13, 14 and 15 (between March 29th and April 18th 2009) the highest number of confirmed cases were observed. Imported cases, squares; autochthonous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

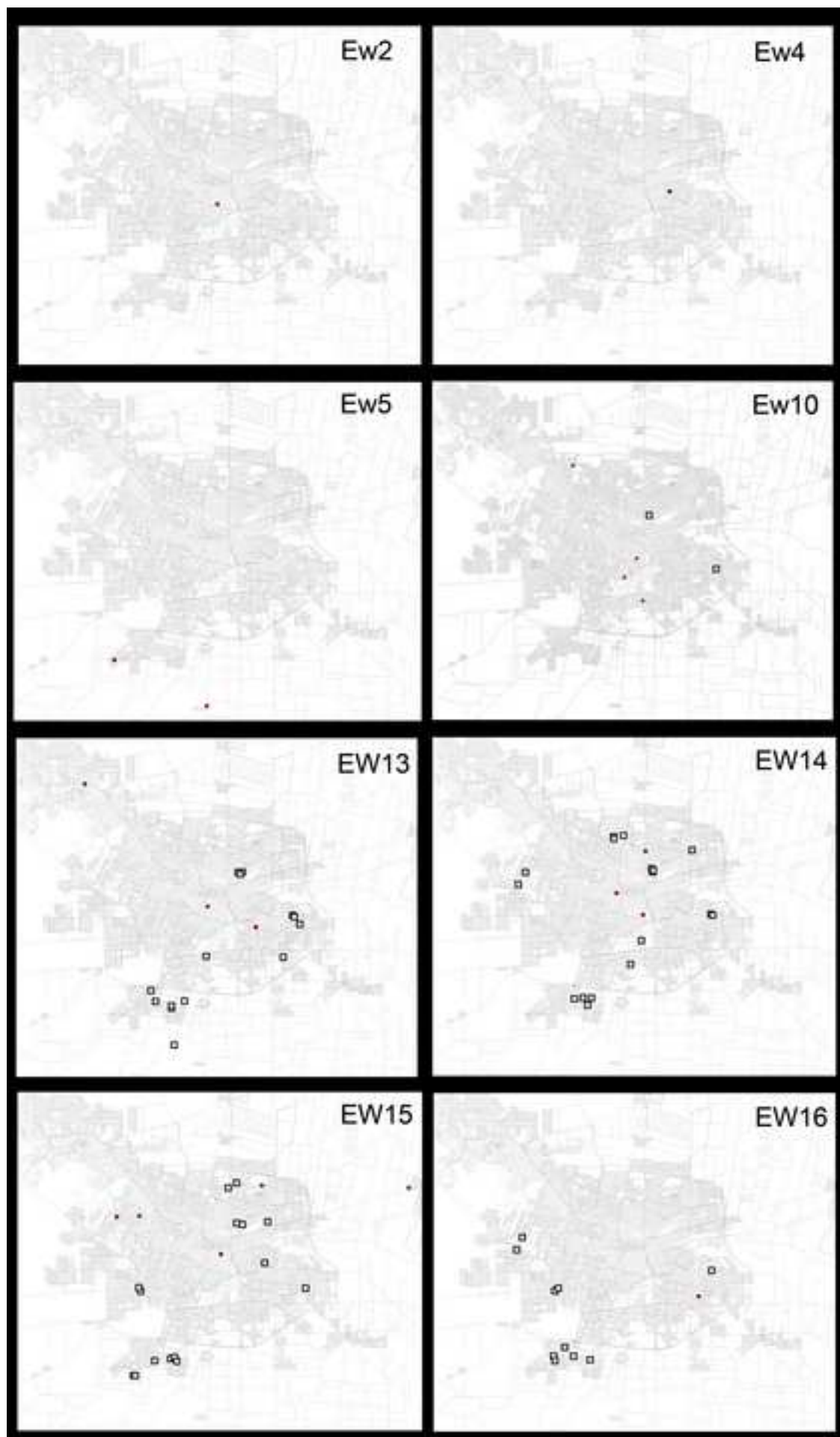
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Figure 3. Number of dengue cases (imported and autochthonous) registered in Córdoba city by epidemiological week (EW 2: January 17th-EW 18: May 10th 2009). The theoretical number of days required for virus transmission (RND) is shown for each week.

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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.

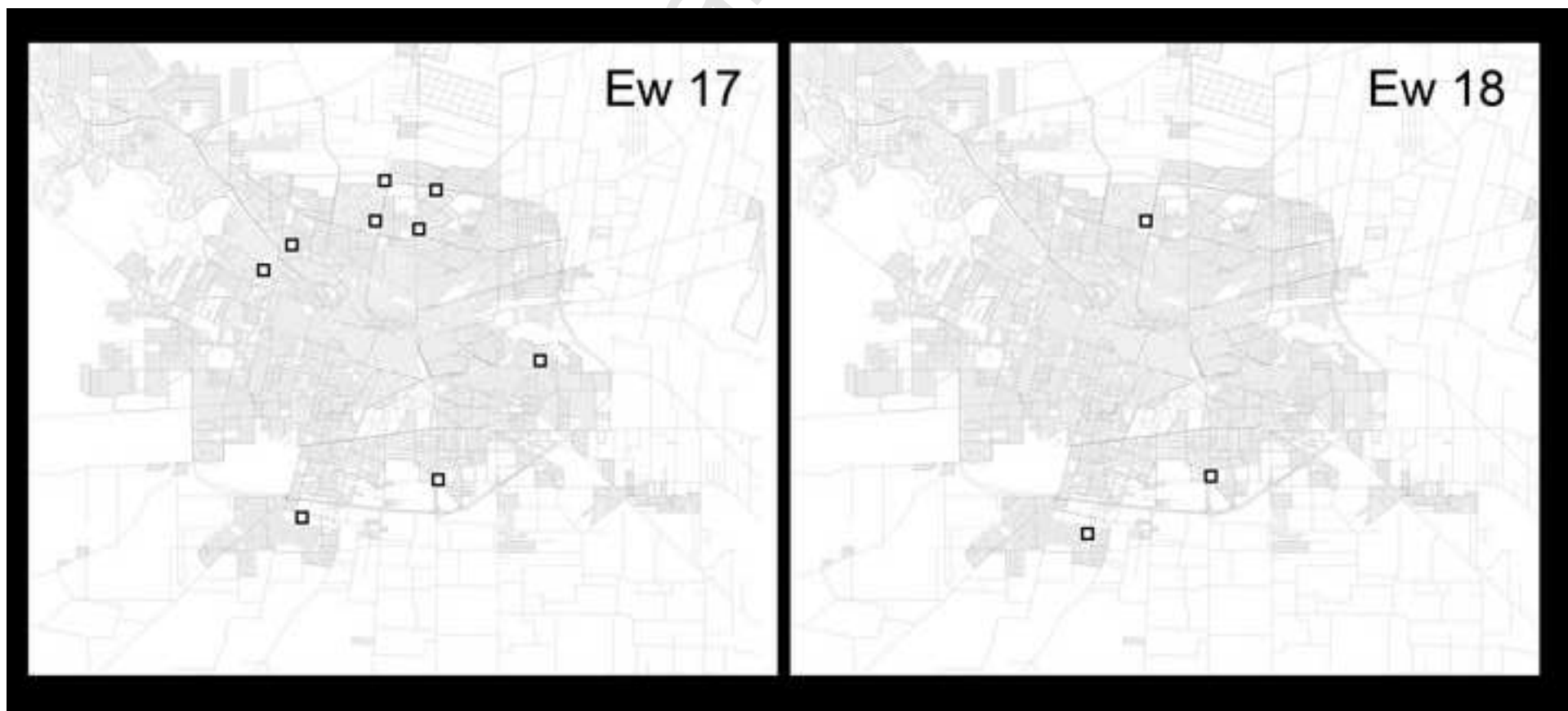
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Figure 5. Rate of cases by age class. Autochthonous (grey) and imported (white) DF cases by age class. Total population by age class, black squares.

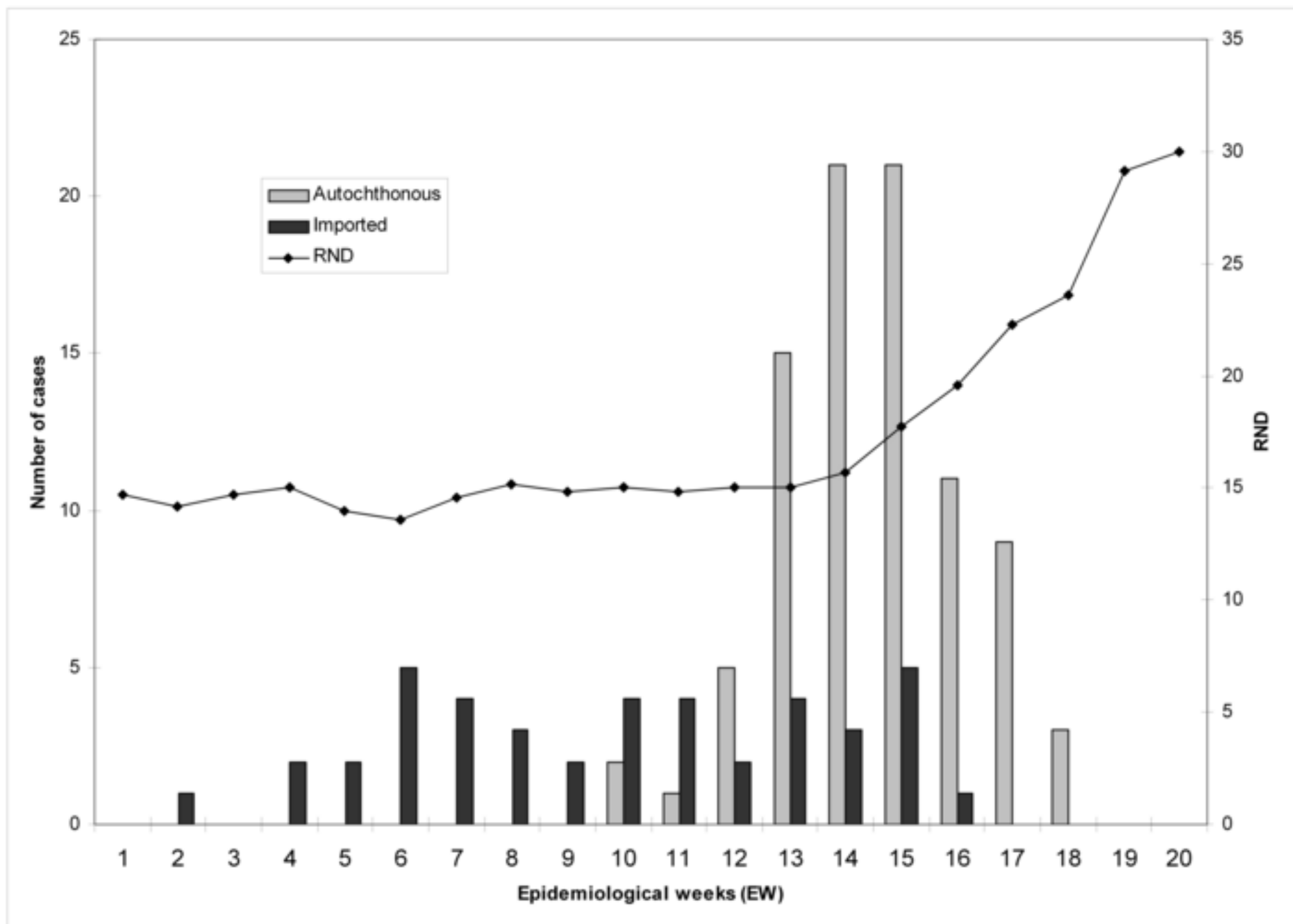
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Figure 6. Graphical representation of Knox analysis for the 130 confirmed dengue cases for each pair of cases according to spatial (meters) versus time (days) separation. The number of pairs of cases at each time and distance interval is represented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





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References

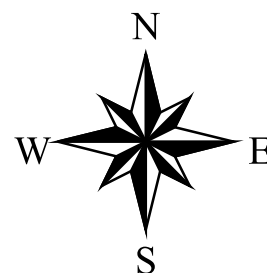
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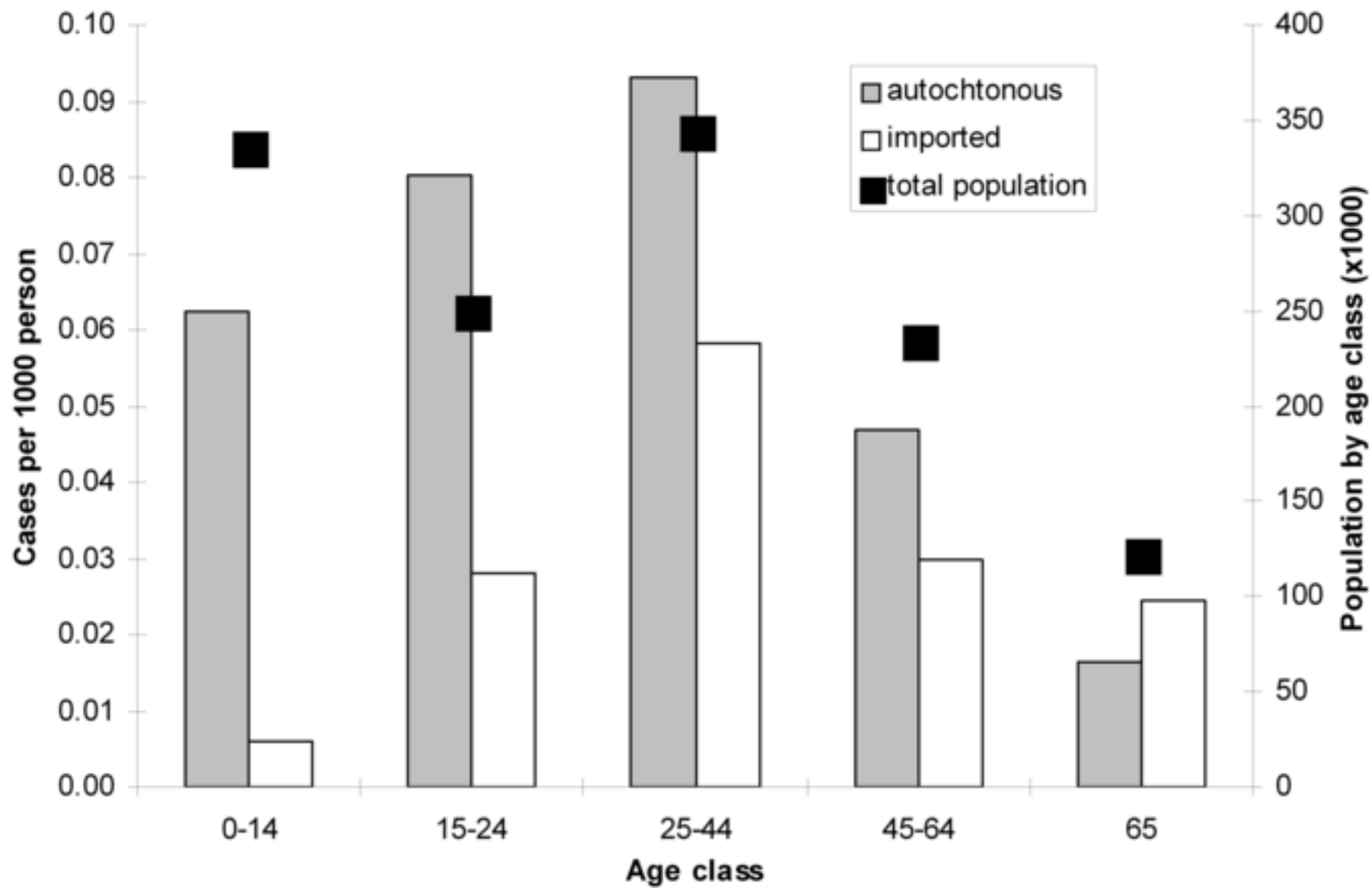
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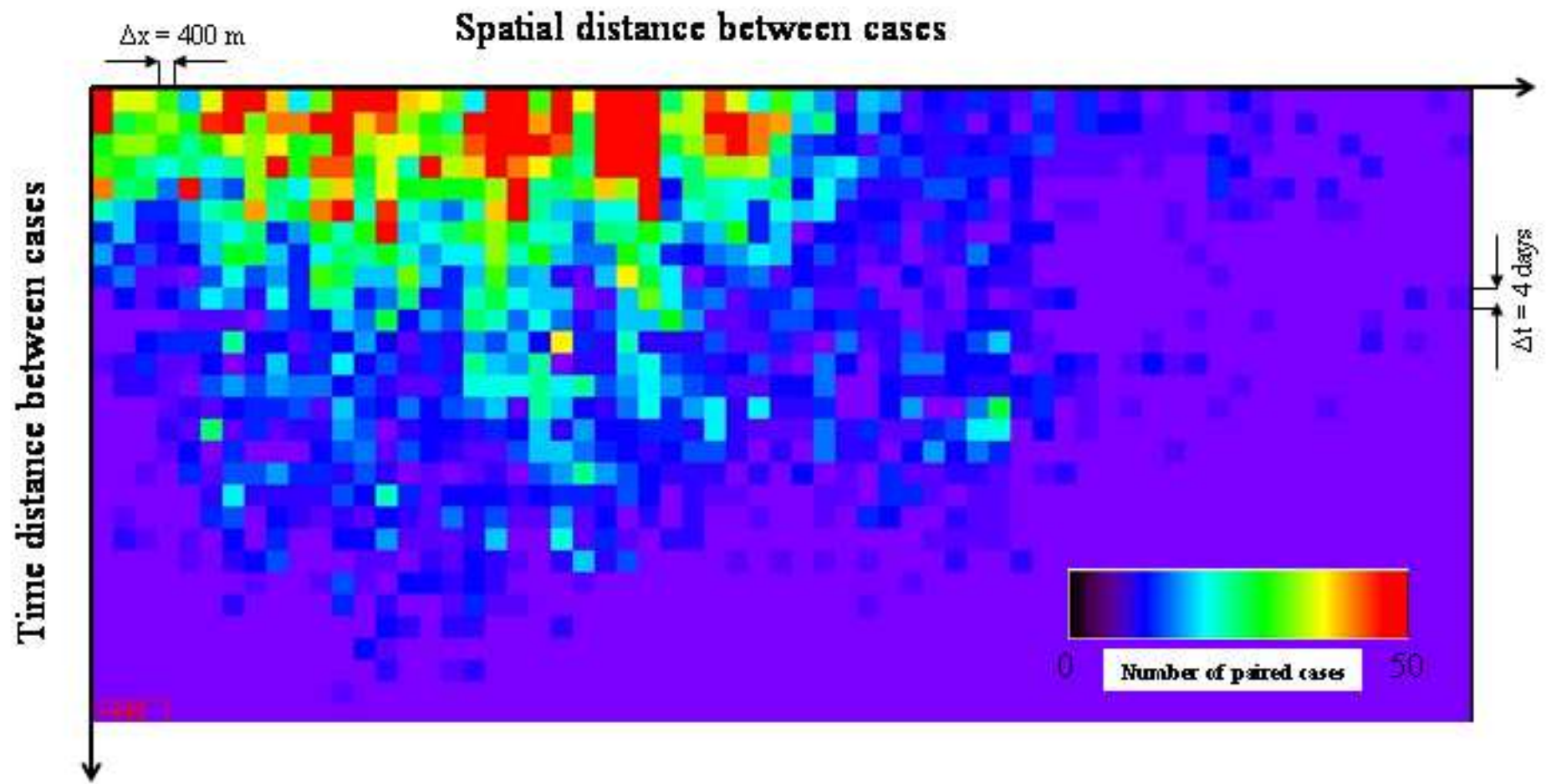
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HIGHLIGHTS

- 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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