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Spatial spread of dengue in a non-endemic tropical city in northern Argentina

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ABSTRACT

After more than eighty years dengue reemerged in Argentina in 1997. Since then, the largest epidemic in terms of geographical extent, magnitude and mortality, was recorded in 2009. In this report we analyzed the DEN-1 epidemic spread in Orán, a mid-size city in a non-endemic tropical area in Northern Argentina, and its correlation with demographic and socioeconomic factors. Cases were diagnosed by ELISA between January and June 2009. We applied a space-time and spatial scan statistic under a Poisson model. Possible association between dengue incidence and socio-economic variables was studied with the Spearman correlation test. The epidemic started from an imported case from Bolivia and space-time analysis detected two clusters: one on February and other in April (in the south and the northeast of the city respectively) with risk ratios of 25.24 and 4.07 ($p < 0.01$). Subsequent cases spread widely around the city without significant space-temporal clustering. Maximum values of the entomological indices were observed in January, at the beginning of the epidemic ($B = 21.96$; $LH = 8.39$). No statistically significant association between socioeconomic variables and dengue incidence was found but positive correlation between population size and the number of cases ($p < 0.05$) was detected. Two mechanisms may explain the observed pattern of epidemic spread in this non-endemic tropical city: a) Short range dispersal of mosquitoes and people generates clusters of cases and b) long-distance (within the city) human movement contributes to a quasi-random distribution of cases.

1. Introduction

Among arboviral diseases, dengue is the most important in terms of morbidity, mortality, economic burden as well as disability life-years lost (LaBeaud, 2008; Hotez et al., 2008; Guzman and Kouri, 2004; Meltzer et al., 1998). Dengue is transmitted mainly by *Aedes aegypti*, a mosquito species highly adapted to human habitats. In recent decades, an increase of severe forms of the disease has been reported with epidemic levels in some tropical and subtropical areas of Asia, Africa, America and Australia causing every year approximately 100 million new cases and 25,000 deaths (Lima et al., 1999; Hynes, 2012).

Since effective vaccines are not yet widely available and there is no specific antiviral chemotherapy, dengue control relies on vector control. Prevention measures include the elimination of oviposition habitats, health promotion and community participation (Sanchez et al., 2012; Gurtler et al., 2009). A common practice for the control of local outbreaks consists in the indoor spraying of the houses in the block of the house of residence of the index case and the houses in the surrounding eight blocks. In epidemiic situations spatial spraying, using heavy equipment vehicle-mounted is recommended (Esu et al., 2010; WHO, 2009).

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Dengue is endemic in many tropical areas around the world but dengue outbreaks also occur in other non-endemic regions where vectors are present. The likelihood of dengue epidemics in these areas, depends on many factors including vector abundance, living conditions as well as human population density and movement patterns, while virus introduction is due to long distance movement of infected persons from endemic areas (Shang et al., 2010; Rotela et al., 2007; Aviles et al., 1999, 2000; Vazquez-Prokopec et al., 2010; Stoddard et al., 2009; Wu et al., 2009; Khormi and Kumar, 2011, 2012; PAHO, 2009). Geographic expansion of *Ae. aegypti* has been observed during the last decades due to adaptation, global warming and urbanization among other factors increasing the area of risk of dengue transmission (Astrom et al., 2012).

North Argentina is an example of these non-endemic areas with recurrent dengue outbreaks. In fact, after 81 years without case notifications, dengue virus has reemerged in Argentina in 1997 (PAHO, 2009) and the four serotypes have been identified since then (Rotela et al., 2007; Aviles et al., 1999, 2000; PAHO, 2009; Ministerio de Salud de la Nación, 2010).

In 2009 Argentina experienced the largest dengue epidemic with 26.612 reported cases and five deaths. The northern provinces of Salta and Chaco reported the highest number of cases and the circulating serotype was DEN-1 (PAHO, 2009; Seijo, 2009).

In this report, we analyze the space-time dynamics of the 2009 dengue epidemic in San Ramón de la Nueva Orán, the most affected city in northwestern Argentina. At the beginning of the epidemics high larval indexes were observed across the city. Implications of our findings in the management and control of dengue epidemics in non endemic areas are discussed.

2. Materials and methods

2.1. Study area, patients and data collection

San Ramón de la Nueva Orán, located in Orán Department, in the Northeast of Salta Province (Fig. 1a) has an estimated population of approximately 82,000 inhabitants and it is predominantly an urban city surrounded by patches of pedemontana Yungas rainforest (ecological sub region of the subtropical rainforest in the north of Argentina) and agricultural/wood exploitation. Average rainfall is around 1000 mm per year, meanwhile the average maximum and minimum temperatures are is 32.4 °C (January) and 9.1 °C (July) respectively. The population size and the percentage of population with Unsatisfied Basic Needs (UBN) for each neighborhood (Fig. 1c) were provided by the General Direction of Statistics, Salta Province (INDEC, 2001). The UBN is a dichotomous variable used to identify poverty at a household or individual level. It considers four areas of basic needs: housing, sanitary services, education, and income. For example a household with overcrowding is considered a household with unsatisfied basic needs. We considered the *percentage of the population with Unsatisfied Basic Needs* for each neighborhood as a socio-economic variable. Suspected dengue patients were seen in the local tertiary care reference Hospital, San Vicente de Paul, between January and June 2009. Patient information was retrospectively obtained from the hospital medical records and loaded in a de-identified database.

Only laboratory positive cases were used in this study. Serological tests UM-ELISA (ultra-micro Enzyme Linked Immunosorbent Assay; Vázquez et al., 2007) and MAC-ELISA (IgM antibody capture; Martin et al., 2000) were performed at San Vicente de Paul Hospital of San Ramón de la Nueva Orán city. Approval for the study was obtained from the Bioethics Committee of San Vicente de Paul Hospital, San Ramón de la Nueva Orán, Salta.

2.2. Larval indexes

In the province of Salta a primary health care system provides various integrated health services. In particular, the city of San Ramón de la Nueva Orán is divided in eight Sectors of Primary Health Care which do not coincide with the city neighborhoods (Fig. 1b and c). Downtown Orán, a mostly commercial area, is not covered by this Primary Health Care System.

The primary health care system collected information about the presence of *Ae. aegypti* larvae in houses belonging to the eight Sectors covered by the Primary Health Care System. House index (HI, percentage of houses where larvae were detected) and Breteau index (BI, number of positive containers for *Ae. aegypti* over the total of houses evaluated, expressed in percentage; Sanchez et al., 2006, 2010) were obtained monthly between January and June 2009 with 3656, 4033, 1176, 713, 277 y 548 houses evaluated respectively. In the months of April and June, the survey of larval indices was not performed in health sectors 1, 4, 5 and 7 (neither in sector 3 during June; see Fig. 1b and Supplementary Table S1). The sections of the city without primary health care coverage (located in the center of the city) were not evaluated for larval presence (Fig. 1b).

2.3. Correlation and frequency analysis

Correlation between the incidence and the percentage of the population with Unsatisfied Basic Needs for each neighborhood was analyzed using the Spearman correlation test. This analysis was performed for each month as well as for the cumulative number of cases at the end of the epidemic. Spearman test was also used for the correlation analysis between the number of cases and population size by neighborhood. Chi-square test was used to compare the case frequencies by sex and by age for the sample of the population used in this study. The larval indices for each of the eight Sectors of Primary Health Care were calculated and compared in both, the whole period and monthly.

In all cases significant statistical differences were considered with p-values <0.05.

2.4. Mapping, spatial and space-time scan statistics

The digital cartography of San Ramón de la Nueva Orán was provided by the General Direction of Statistics of Salta Province. From this cartography we generated another cartographic slide in which we assigned a centroid point to each neighborhood. The different variables, like number of dengue cases, population size or socio-economic values, were attached to each centroid and used at this level of aggregation in our analysis.

Only 285 of the 541 reported cases have a more detailed data including home address and diagnosis date (Fig. 2). This subset was only used to display the space-time evolution of the epidemic using density point maps (Fig. 4).

The spatial analyses (cases by months and the accumulated number of cases for the total period) and space-time analyses were carried out using SaTScanTM v6.0 software (TM of Martin Kulldorff, available at http://www.satscan.org). Under the null hypothesis of random spatial (space-time) distribution, the clusters were then detected when the space-time distribution of cases was concentrated in a particular place and time (alternative hypothesis).

To detect such cluster, circles of varying area centered in each centroid (corresponding to the center of each neighborhood) were used (we set the maximum circle area as the 50% of the total area). The software compares the expected number of cases under the assumption of random distribution (which is proportional to the population in the circle, that is, the population of all the neighborhoods within the circle) with the observed number of cases, and therefore, the clustering detected is not due to a higher population

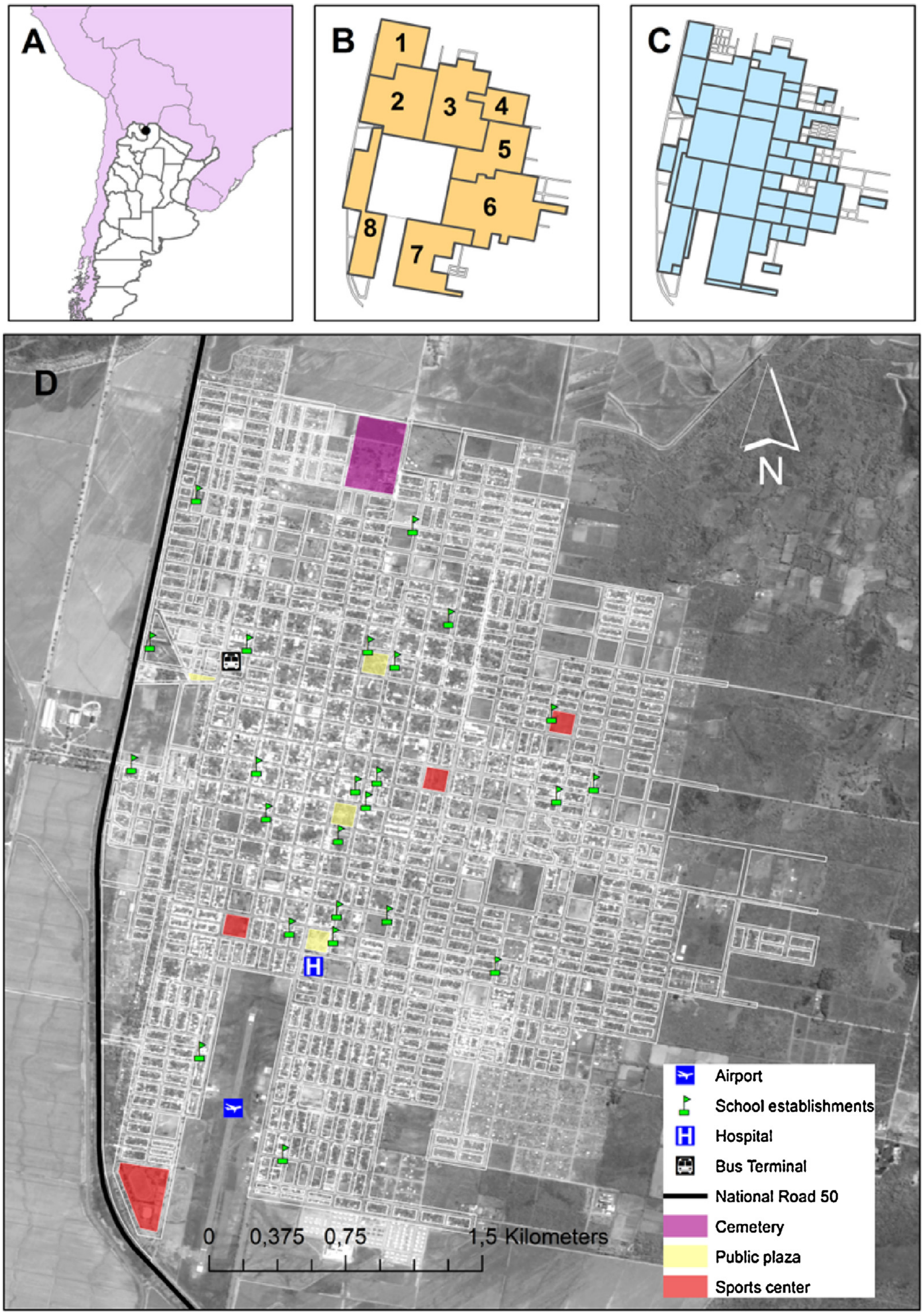

Fig. 1. Study area: (a) within America, Argentina is represented in white and the black point in the north of Argentina indicates de location of San Ramon de la Nueva Oran (SRNO), (b) eight sectors of Primary Health Care of SRNO. The center of the city has no coverage of primary health care (white zone), (c) Neighborhoods of SRNO, and (d) SRNO: mixed map using satellite image (CBERS 2B HRC 172A 126 2 L2-2009) and displaying some relevant sites.

size ratio (Kulldorff and Nagarwalla, 1995; Kulldorff, 1997). In the space-time analysis a cylindrical window is used where the height corresponds to time dimension.

For each cluster the software calculates a risk ratio (RR) and their p-values. Clusters with p-values <0.05 were considered statistically significant. In these analyses, only the cases which have spatial (neighborhood of residence) and temporal data (diagnosis date) were used (347 out of 541 cases, see Fig. 2). Since the health system records did not collect the date of onset of symptoms from the patient or the estimated vector contact dates, the temporal variation of the cases is calculated by the date of serological diagnosis.

3. Results

A total of 541 dengue cases were laboratory confirmed between January and June 2009 in the city of San Ramón de la Nueva Orán.

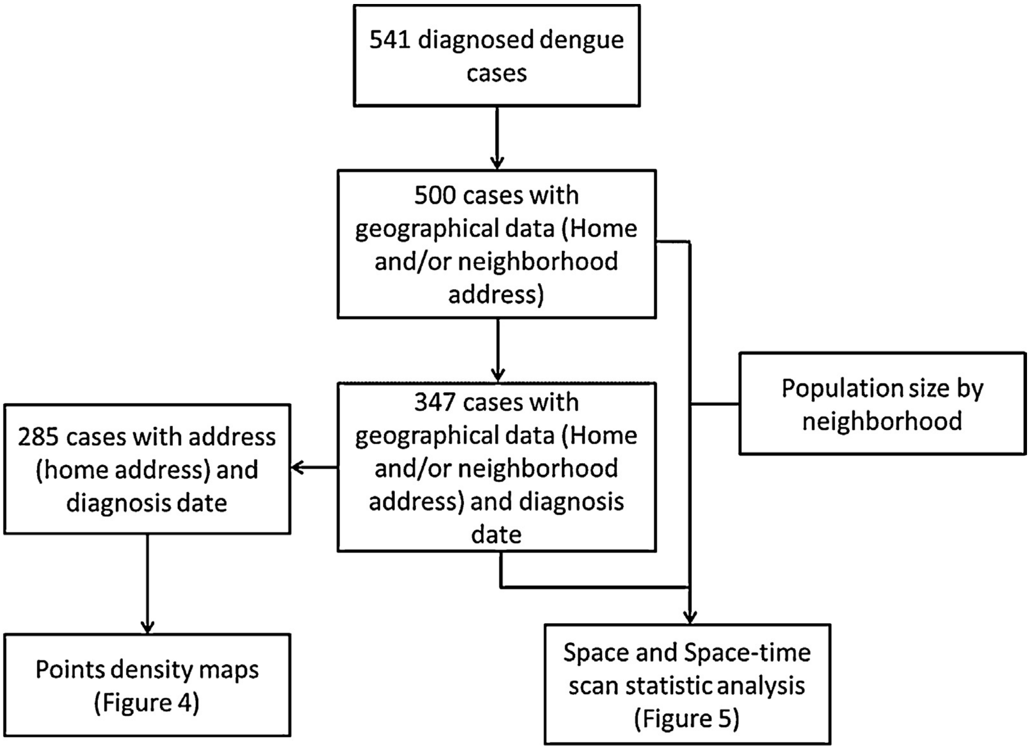

Fig. 2. Flow diagram for the Datasets selection used in the different analyses and figures.

The likely index case was an individual who acquired the infection in Santa Cruz de la Sierra, a major Bolivian city with a high burden of dengue at that time. This suspected first case was confirmed by January 8. The outbreak lasted 25 weeks ending up in June 18 and included the report of two confirmed cases of congenital transmission reported in April and May. Two well defined peaks were observed in February and April (Fig. 3).

From the 541 confirmed cases, neighborhood of residence and date of diagnosis were available for 347 (64%). This subset was used for the space-time analyses and correlation analyses. Finally, the set of cases for which home address was also available was used to produce Fig. 4 (see Fig. 2 for a summary).

The age groups most affected were 40–49, 50–59, 60–69, and 70–79 years old, followed for 10–19, 20–29, and 30–39 years old groups (see the supplementary Fig. S2 and Table S2). The lowest risk was observed in the groups of less than 9 years and more than 80 years. Also, statistically significant differences were detected between sexes for the whole population and age groups, 0–9 and 70–79 years old ($p < 0.05$, see Supplementary Fig. S2). Dengue incidence per neighborhood shows a high positive correlation with population size ($p < 0.0001$; $r = 0.805$; Supplementary Fig. S3) but not with the population density per neighborhood ($p > 0.05$; $r = -0.167$; Supplementary Fig. S4). However, no statistically significant differences were observed between dengue incidence and

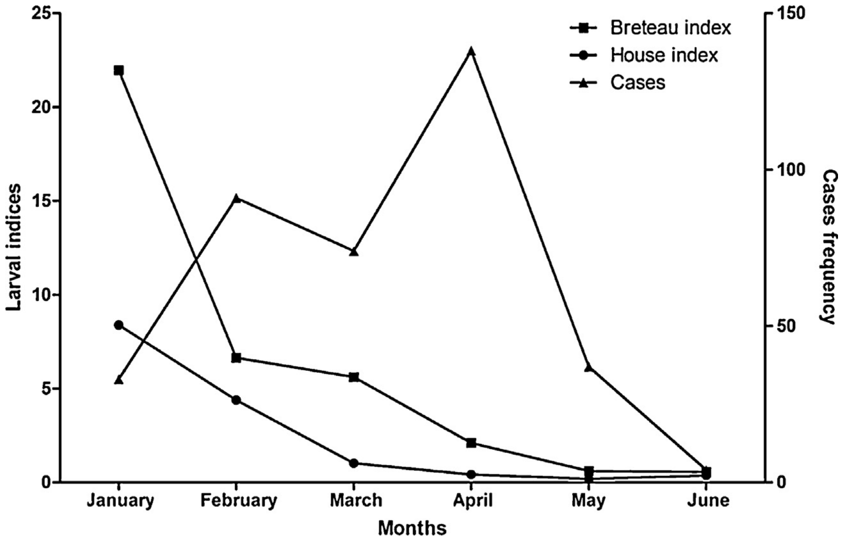

Fig. 3. Monthly variation of larval indexes and dengue cases. House index is defined as the percentage of houses where larvae were detected while Breteau index is the number of positive containers for *Ae. aegypti* over the total of houses evaluated (in percentage). Both larval indexes values were high at the beginning of the epidemic. Later control measures reduced them but could not stop the spread of the epidemic.

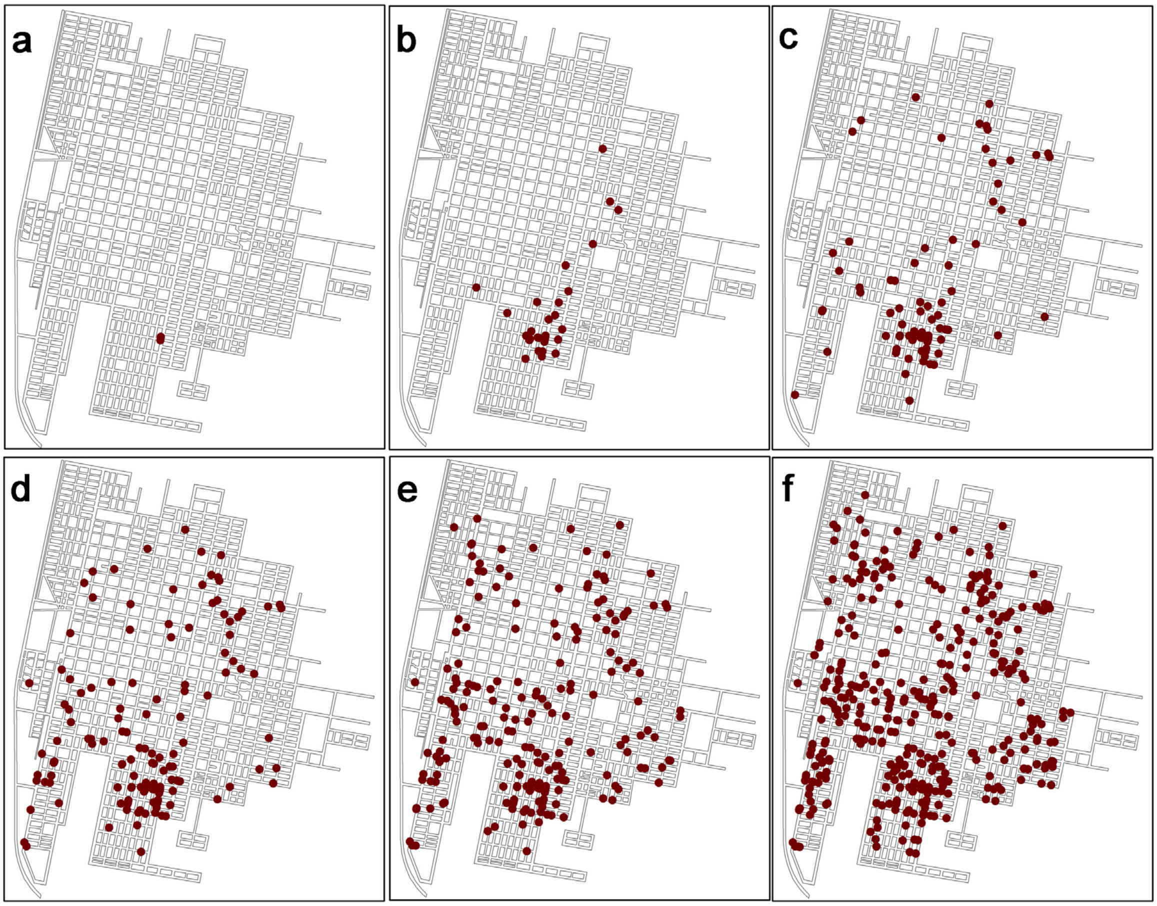

Fig. 4. Spatial distribution of the cumulated cases from January 8. (a) until January 11, (b) until January 31 (c) until February 28, (d) until March 28, (e) until April 25, and (f) until June 6.

Unsatisfied Basic Needs index. As a test for the robustness of this finding we generated an artificial series of incidence per neighborhood in which we introduced a bias due to potential under reporting. We assumed an increase of 50% for the incidence corresponding to the neighborhood with the higher percentage of Unsatisfied Basic Needs (80%) and no increase in incidence for neighborhoods with 0% of UBN, and a linear variation between the extremes. Neither in this case correlation between incidence and socioeconomic variables was detected.

House Index and Breteau Index were high during the first three months of the outbreak (Fig. 3), with an important spatial heterogeneity observed in January and February (Supplementary Table S1 and Fig. S5). The values of these larval indices decreased during the following months for all Sectors of Primary Health Care (Fig. 1b and Supplementary Table S1). Finally, on June only 3 out of the 8 sectors of the city were monitored and just one had a Breteau Index value greater than 1.5.

Space-time scan statistic analysis detected two clusters, one in February in the south of the city (cluster 1; 2009/2/26 – 2009/2/27) and the other in April to the northeast of the city (cluster 2; 2009/4/15 – 2009/4/30; Fig. 5). Cluster 1 exhibited a high risk ratio (RR) of 25.24 ($p < 0.01$; Log likelihood ratio = 71.13) when compared with cluster 2 (RR of 4.07, $p < 0.01$; Log likelihood ratio = 34.69) with 32 and 54 cases respectively. After April, a more random distribution is apparent which is confirmed by the absence of spatial clusters (Fig. 4f). The spatial scan statistic (for the whole data set) detected only one cluster to the south of the city (cluster red, Fig. 5) with a lower RR of 1.91 ($p < 0.05$; Log likelihood ratio = 25.91). Spatial analysis, for each month, detected the same two clusters (in February and April) as the space-time analysis.

4. Discussion

In 2009, Argentina experienced the largest dengue epidemic ever recorded for this country, with several Provinces affected, mainly in the northern regions but also extending into the Central region. It was estimated that only one out of 36 cases were confirmed by laboratory tests (OPS, 2009). In San Ramón de la Nueva Orán, one of the epicenters of this country-wide epidemic, 553 laboratory confirmed cases were reported between January and June 2009 (0.72% of the population).

The higher incidence observed in individuals between 10 and 69 years old could be explained by the higher mobility (and then, higher exposure) of adults compared to children and elderly people. This is consistent with what was observed in another study (Vazquez-Prokopec et al., 2010).

Dengue is not endemic in Argentina and therefore outbreaks are mostly produced by virus introduction from the neighboring countries of Bolivia, Brazil or Paraguay which in 2009 reported 60.526, 316.552 and 5.869 cases respectively (Aviles et al., 1999, 2000; Seijo, 2009).

In northwest Argentina, where San Ramón de la Nueva Orán is located, an intense transit to and from Bolivia is observed. It is also worth mentioning that Santa Cruz de la Sierra (neighboring Bolivian province) residents were also diagnosed in hospitals of Buenos Aires Province (located in central Argentina), a fact that could be responsible of the outbreak occurred in that Province (Seijo, 2009). These facts highlight the role of large scale human movement on dengue dynamics at regional level (Hynes, 2012; Aviles et al., 1999, 2000; Stoddard et al., 2009).

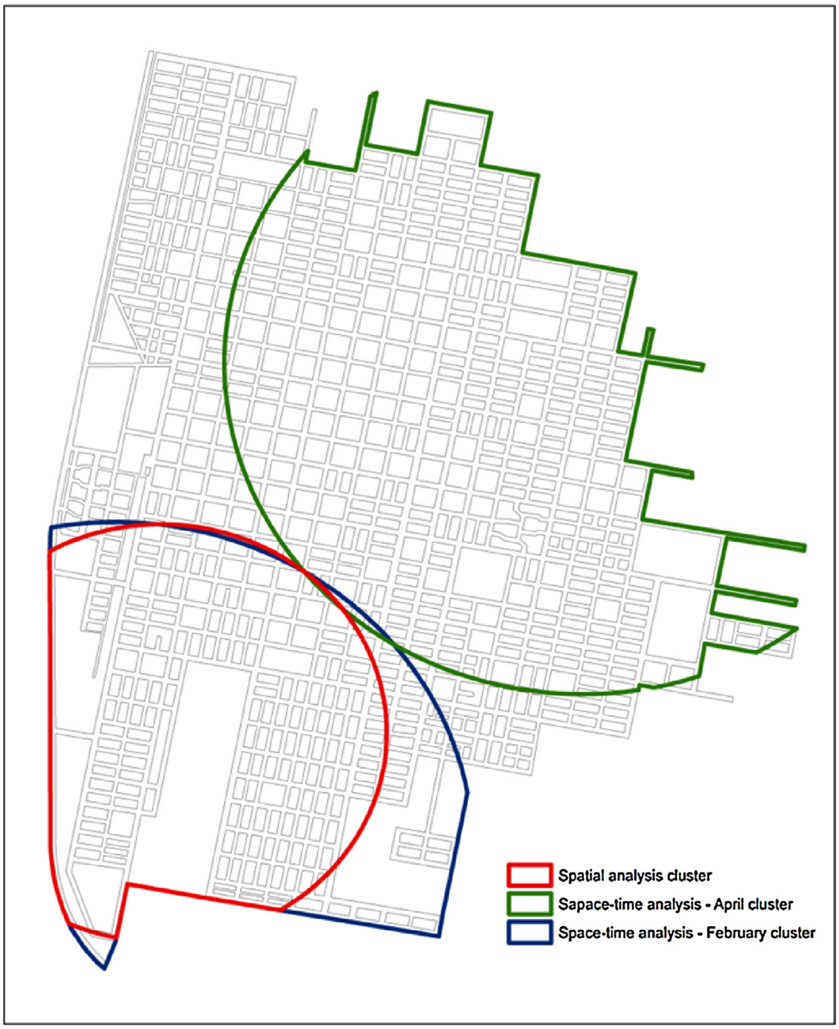

Fig. 5. Clusters for Scan Statistic. Between February 26 and 27 one cluster is detected in the south of the city (in blue) while between 12 and 15 of April another cluster is detected in the northern area (in green). Cluster for all cases (with spatial data) using a Poisson spatial scan statistic is shown in red. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

At the local level, two simultaneous mechanisms may explain the observed pattern of epidemic spread. Short range dispersal of mosquitoes and people generates clusters of cases while long-distance (within the city) human movement contributes to a quasi-random distribution of cases (see also Vazquez-Prokopec et al., 2010; De Benedictis et al., 2003; Stoddard et al., 2013). We could not statistically identify these clusters of cases attributed to local diffusion (e.g. at the block level) of mosquitoes and/or persons because cases were aggregated at neighborhood level (only for a fraction of the reported cases address was available, this subset is shown in Fig. 4 but was not used in the statistical analyses).

Within this level of aggregation, purely spatial analysis (for each month between January and June) and space-time analysis (for the whole epidemic period) detected only two clusters (one to the south and other to the northeast of the city, see Fig. 5). Spatial analysis using the total number of cases at the end of the epidemic found only one cluster at the south of the city similar to the clusters found by space-time or spatial analysis for February (Fig. 5); however, the relative risk is significantly lower in this last case. This reduction in risk is attributable to the progressive randomization of the distribution of the cases, however the fact that the initial cluster detected for February is still observed at the end of the epidemic shows the impact of local transmission. Furthermore, a previous study of the spatial distribution of oviposition in San Ramón de la Nueva Orán has shown that some areas are preferred for oviposition with a repetitive pattern in successive years. Those two main oviposition clusters are located close to the two clusters found in this work (Estallo et al., 2013).

The Breteau index and the House index values were markedly high at the beginning of the epidemic (above 10% in some areas; Supplementary Table S1). Dengue outbreaks may occur with low values of HI (less than 2% as described in Goh et al., 1987), and therefore the high levels observed in our study area at the beginning of the epidemic clearly indicating a high risk for an outbreak.

By April high incidence of dengue cases but low values of larval indices were observed (BI = 2.1%; HI = 0.42%). Subsequent interventions achieved a significant reduction of mosquito infestation but with no apparent impact on the course of the epidemic (Fig. 3). The interventions were of three types: (a) local indoor spraying, (b) spatial fumigation and (c) removal of potential breeding sites of immature forms. The epidemic lasted 25 weeks, from mid-summer to the beginning of winter, when *Ae. aegypti* populations reached its lower values. These two facts suggest that dengue may spread even without high mosquito densities.

The possible association between dengue incidence and socioeconomic factors (poverty, housing quality, use of air conditioning, etc.) has been addressed in several studies showing dissimilar results, as in some there was observes positive correlations and in some others not (Khormi and Kumar, 2011, 2012; Mondini and Chiaravalloti-Neto, 2008; da Costa and Natal, 1998; Reiter et al., 2003). A possible explanation may be that different urban epidemiological scenarios could define the importance of the socioeconomic factors as determinants of dengue transmission. In our study, no correlation was found between the percentage of the population with Unsatisfied Basic Needs and dengue incidence. This lack of correlation is a robust feature of our dataset (at neighborhood level of aggregation). Assuming that underreporting is higher for populations with higher UBN we created an artificial series in which we increased the incidence of neighborhoods proportionally to their values of UBN (a maximum value of 50% of increase for the neighborhood with the highest UBN was used). Even with this biased dataset no correlation was found between incidence and the percentage of the population with UBN.

Most previous studies, where heterogeneities in socioeconomic variables were associated with differential risks of infection, considered significantly larger spatial scales (including whole countries). However some studies have also shown association between dengue incidence and socioeconomic conditions at household level (Waterman et al., 1985; Reiter et al., 2003). We believe that the lack of correlation between cases and socioeconomic variables in our case is mostly due to the small size of the city, the widespread distribution of poverty (78% of neighborhoods have >20% of the population with UBN; Supplementary Fig. S1) and the observed high mobility of the inhabitants within the city which could render a homogenization of the risk. Our results show that at the neighborhood level of aggregation there is no correlation between dengue incidence and the percentage of the population with UBN but we cannot rule out correlation at household level.

We have not performed a statistical comparison between cases (aggregated into 45 neighborhoods) and larval indices (reported for eight Primary Care Sectors) because available data were aggregated at very different spatial scales. As expected, we found a high correlation between number of cases and population size, a fact that was noted in others works (Khormi and Kumar, 2011, 2012).

Our results are consistent with and support observations by others that epidemic spread is driven by high daily movement of city residents. Some facts that support this view are:

i) The wide spatial, almost random distribution, covering the entirety city (Fig. 4f);
ii) The significant heterogeneity in the spatial distribution of *Ae. aegypti* larvae (large variations in the larval index magnitudes between Sectors of Primary Health Care (Supplementary Table S1);
iii) the lack of correlation between the incidence and socioeconomic factors, and
iv) *Ae. aegypti* has short-range dispersion ($\leq$200 m) and multiples anthropic causes limit this dispersion (Hemme et al., 2010; Muir and Kay, 1998; Reiter et al., 1995).

The space-time and the spatial analyses were performed with 64% and 92% of the total cases respectively. All the data came from the same hospital and we did not observed any significant differences, in sex or age distributions, between the cases used in this study and those excluded due to insufficient data. Therefore, we have no reason to suspect a bias on the data set used and we assumed that the set of cases included in the analysis is close to a random sample. However, the use of the date of diagnosis (and not the date of infection onset) causes minor shifts in the temporal variation analysis.

In summary, in this work we showed as, in small subtropical cities, that dengue could disseminate from a few well defined foci and cover almost entirely a medium size urban area. Our results suggest that the elimination of vector larval forms is not sufficient, and that it is very important to strengthen the surveillance system of the suspected cases. This intensification of the surveillance may help preventing dengue outbreaks if suspected cases are treated as confirmed cases regarding to patient isolation, the respective intervention through the fumigation in the house of source cases and its surroundings and the active search of febrile cases.

Our results also suggest that the main driver of dengue spread was high human mobility. Therefore, usual strategy of focalized insecticide spraying in the surroundings of cases may be not enough to contain a dengue epidemic. For these reasons we believe that dengue control would be greatly improved with an active search and an early detection of new cases.

Finally, we generated a spatial data infrastructure which may be useful for a space-time follow-up of dengue spread as well as for identifying potentials risk factors, representing a powerful tool for the epidemiological and entomological surveillance and epidemic control.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.actatropica.2016.02.003.

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