Analytical report of the 2016 dengue outbreak in Córdoba city, Argentina

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Abstract

After elimination of the *Aedes aegypti* vector in South America in the 1960s, dengue outbreaks started to reoccur during the 1990s; strongly in Argentina since 1998. In 2016, Córdoba City had the largest dengue outbreak in its history. In this article we report this outbreak including spatio-temporal analysis of cases and vectors in the city. A total of 653 dengue cases were recorded by the laboratory-based dengue surveillance system and georeferenced by their residential addresses. Case maps were generated from the epidemiological week 1 (beginning of January) to week 19 (mid-May). Dengue outbreak temporal evolution was analysed globally and three specific, high-incidence zones were detected using Knox analysis to characterising its spatio-temporal attributes. Field and remotely sensed data were collected and analysed in real time and a vector presence map based on the MaxEnt approach was generated to define hotspots, towards which the pesticide-based strategy was then targeted. The recorded pattern of cases evolution within the community suggests that dengue control measures should be improved.

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Introduction

Dengue is one of the most widespread vector-borne diseases in the world (TDR/WHO, 2009). *Aedes aegypti*, the main vector of the dengue virus (consisting of four different strains, *i.e.* DEN1-4) in Latin America is a *day-biter* and peridomestic mosquito that breeds preferably in containers related to the house-hold (Gurber, 1997; Vezzani and Carbajo, 2008). The incidence of dengue has grown dramatically in recent decades, with a concomitant increasing trend in outbreaks in South America during the past few years (Brathwaite *et al*., 2012; WHO, 2015). After the successful vector eradication campaign, carried out at the national level in the 1960s, the first outbreak of dengue in Argentina was documented in 1998 (Aviles *et al*., 1999). The largest notified dengue outbreak in Argentina before 2016 occurred in 2009. It reached subtropical regions affecting more than 25,900 people from localities as far south as Córdoba and Buenos Aires (Seijo, 2009). Most infections (>90%) occurred in the northern provinces of Chaco, Catamarca and Salta (MSN, 2009).

Within the context of landscape epidemiology (Pavlovsky, 1996; Ostfeld *et al*., 2005), remotely sensed data and geospatial technologies are essential tools. Using these ideas and methodological tools for the case of dengue epidemics within Argentina, a number of interdisciplinary studies were produced and published as predictive risk models based on environmental conditions (Estallo *et al*., 2008; Espinosa *et al*., 2011, 2012, 2016; Vergara *et al*., 2013; Dantur *et al*., 2015) and operational tools (Porcasi *et al*., 2012). As the current approach for dengue control is mainly based on vector control (Guzmán and Kouri, 2002; Guzmán *et al*., 2004), models based on remotely sensed data integrated with urban demography and socioeconomic data would allow prediction of spatio-temporal variation of vector population abundance.

The strongest dengue outbreak in Argentina so far occurred in 2016. This outbreak started in early January 2015, coinciding with information from the International Research Institute for Climate and Society (IRI) (https://iri.columbia.edu/) that the Sea Surface Temperature (SST) exceeded the threshold indicating weak El Niño conditions. In August, the SST had increased to what is considered a strong El Niño level. The El Niño Southern Oscillation (ENSO) is the leading mode of year-to-year global climate variability (Cai *et al*., 2015) affecting global atmospheric circulation, thereby altering rainfall and weather patterns around the world and temporarily elevating global temperatures. In the last quarter of 2015, and the first quarter of 2016, extreme rainfall was recorded in several parts of South America, particularly in Paraguay, northern Argentina and southern Brazil. About 180,000 people were affected by flooding and more than 80,000

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were displaced. Córdoba Province was no exception. The World Meteorological Organization (WMO) (https://public.wmo.int/en) issued a statement regarding the status of the global climate (WMO, 2015) providing evidence that 2015 was the hottest year so far in many countries, and indeed also globally. The global average of temperatures over land areas in this year exceeded previous hot years, such as 2005, 2007 and 2010. The global average temperature over the sea surface in 2015 was equal to 2014 record. The combination of high temperatures, both over land and sea made 2015 a record year. In South America, the temperatures in 2015 were above normal for most of the continent, with anomalies of up to 2°C. The potential association of dengue epidemics and ENSO has been explored by several authors (Gagnon *et al*., 2001; Cazelles *et al*., 2005; Johansson *et al*., 2009). Taking the ENSO and the recent high temperatures into account, we present here an analytic report of the 2016 dengue outbreak in Córdoba, the second largest city in central Argentina. The objective was to describe the 2016 dengue outbreak including a spatio-temporal analysis of cases and vectors using similar concepts discussed by us previously (Rotela *et al*., 2007). We considered it particularly relevant to do this supporting the governmental surveillance system actions in real time with geospatial tools using a combination of case and vector field data mapping, complemented with climate observations, remote sensing and spatial statistics.

Córdoba City is located at the southernmost limit of dengue epidemics recorded so far (Estallo *et al*., 2014), and is showing an increasing number of cases since the first epidemics of 2009, with circulation of DEN-1 and DEN-4 strains. The analysis presented here is the first result of an integrated surveillance system including operational geospatial tools. The surveillance system records the coordinates and dates of each reported dengue case and periodical sampling of vector presence. Field data, together with ancillary climatic and remotely sensed variables, were used to produce continuous mapping of the epidemic, prediction maps of the vector distribution and space-time analysis of the epidemic. The presence probability of *A. aegypti* breeding sites was produced during March 2016 and used operationally to define insecticide application strategies during the outbreak.

Materials and Methods

Study area and climate context

Córdoba City is located at 31º24’30’’S, 64º11’02’’W, 450 m above mean sea level, in central Argentina (Figure 1A). It has a surface of 576 km^2 and, according to the census bureau in Argentina, *i.e*. El Instituto Nacional de Estadística y Censos de la República (INDEC), a population of about 1.33 million (INDEC, 2011); the urban area represents around 37.2% of the city surface, which is surrounded by agricultural fields. The city has a semi-dry climate, with a well-defined rainy season between October and March delivering an annual precipitation of about 750 mm. The mean annual temperature is 21ºC (range 12-38ºC). The winters are temperate, with several frosts days in June and July (range -3-28ºC) (Jarsún *et al*., 2003).

Data handling

The dengue cases were recorded as suspected, probable and confirmed according to the definition adopted by the Ministry of Health - Ministerio de Salud de la Nación Argentina (MSN, 1999) and the Centers for Disease Control and Prevention (CDC), Atlanta, GA, USA (CDC, 1990). The dengue cases considered in this study were the ones georeferenced by residential address and confirmed by blood analysis from suspected cases or cases identified by epidemiologic linkage. Autochthonous cases were defined as those originated within the region of Córdoba City during the outbreak, while those coming from a different region or country were termed imported cases. With confirmed virus circulation occurring during the outbreak, we assumed that a probable dengue case would have a high probability of being a confirmed case, even in the absence of laboratory confirmation. Based on this rationale, all suspected cases were included in the spatio-temporal analysis, together with the confirmed cases.

By the end of 2015, the national system for dengue risk stratification (Porcasi *et al*., 2012) predicted a high risk for the whole Centre-North area of Argentina (Figure 1B). The Córdoba outbreak (developed in the context of a large national dengue outbreak) counted about 76,734 notifications, 41,207 autochthonous confirmed cases, and a national disease rate of 96 cases per 100,000 inhabitants; the rate in Córdoba was about 19.1 per 100,000 inhabitants.

Density case maps were elaborated using the location of individual cases during all the period using the *heatmap* tool of Quantum Geographical Information Systems (QGIS) (http://www.qgis.org/en/site/) software used for this study. The *heatmap* indicates spatial clustering and is generated using the Kernel density algorithm that calculates the density of positive points for any given area. Using this methodology, all dengue hotspots could be shown for any time and place chosen.

Mapping the vector distribution

From December 2015 to May 2016, six monthly entomological samplings of *Ae. aegypti* larvae were carried out in Córdoba City through evaluation of all domestic containers belonging to 600 houses each time. The sampling scheme included 30 neighbourhoods covering all regions of the city. In all selected households (georeferenced using the coordinates of Google Earth), the water containers were classified into different categories (tires, tanks, drums, barrels vases, *etc*.) and the total number of containers recorded, including the presence of water and larvae in them. The larvae found were collected and transported to the laboratory for taxonomic identification using a specific morphological key (Rossi and Almiron, 2004). Houses found with at least one container with one or more *Ae. aegypti* larvae or pupae were considered positive. The QGIS software was used to build the point vector layers locating sampling points, sites with mosquito presence and larval abundance. The *Ae. aegypti* presence of February 2016, recorded by house surveillance sample that day, was chosen to develop a presence distribution map using MaxEnt (http://homepages.inf.ed.ac.uk/lzhang10/maxent.html), version 3.3.3a, according to the approach developed by Espinosa *et al*. (2016). For the model development, a SPOT 6 satellite multispectral image (4 bands) was processed through unsupervised classification with 20 classes. The fraction of each class surrounding each image pixel was used to build a raster per class (=20 rasters). The set of 20 landscape covers layers, together with distance to drinking water, Normalized Burn Ratio Thermal NBRT (Holden *et al*., 2005) were used as predictor variables (Peterson, 2001, 2003; Elith *et al*., 2006; Rotela *et al*., 2007). The

A

B

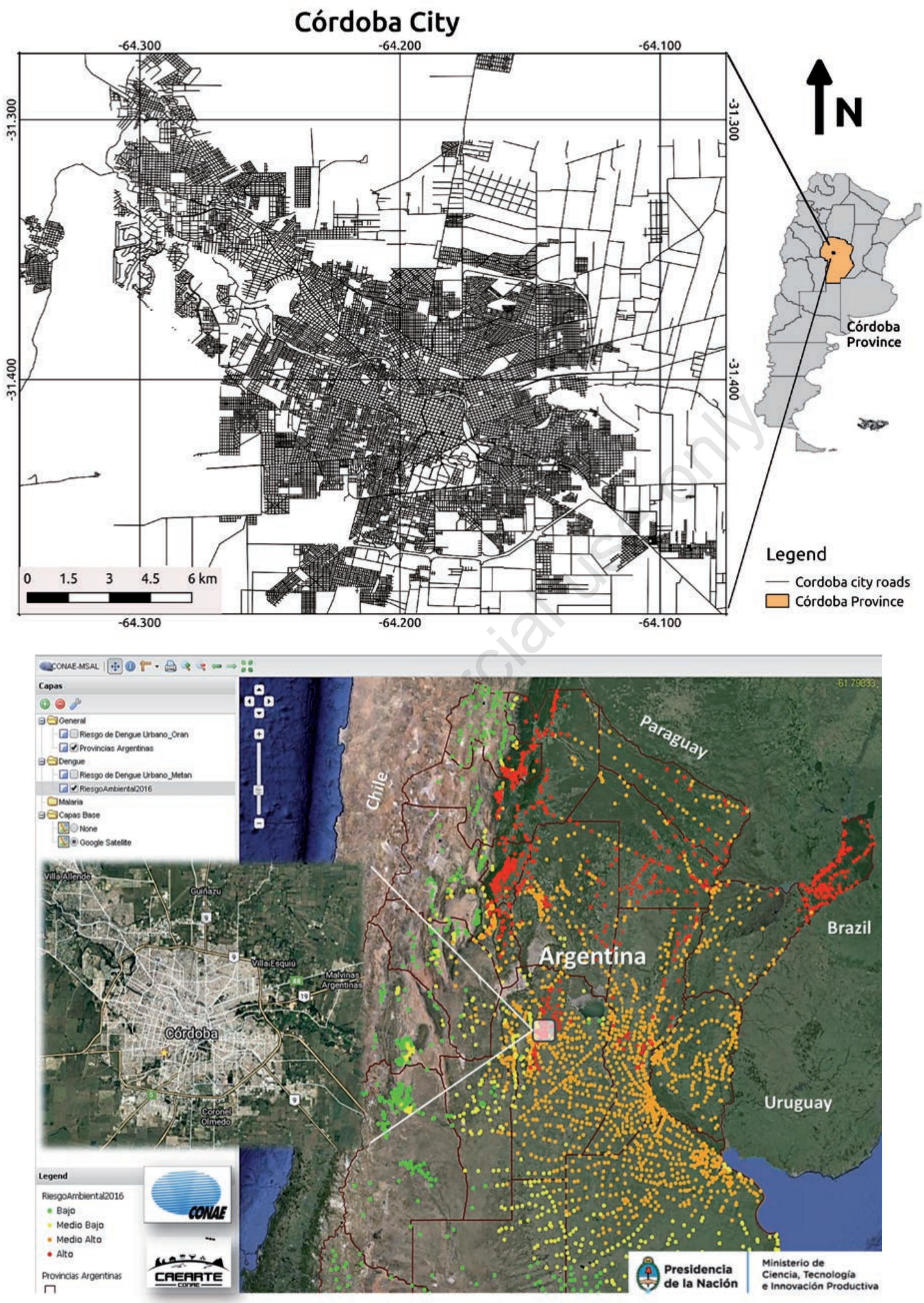

Figure 1. Location of Argentina and Córdoba City (A). Extract from the operative dengue risk stratification system web-GIS (Porcasi *et al.*, 2012), showing Argentina and Córdoba risk by the end of 2015 (B).

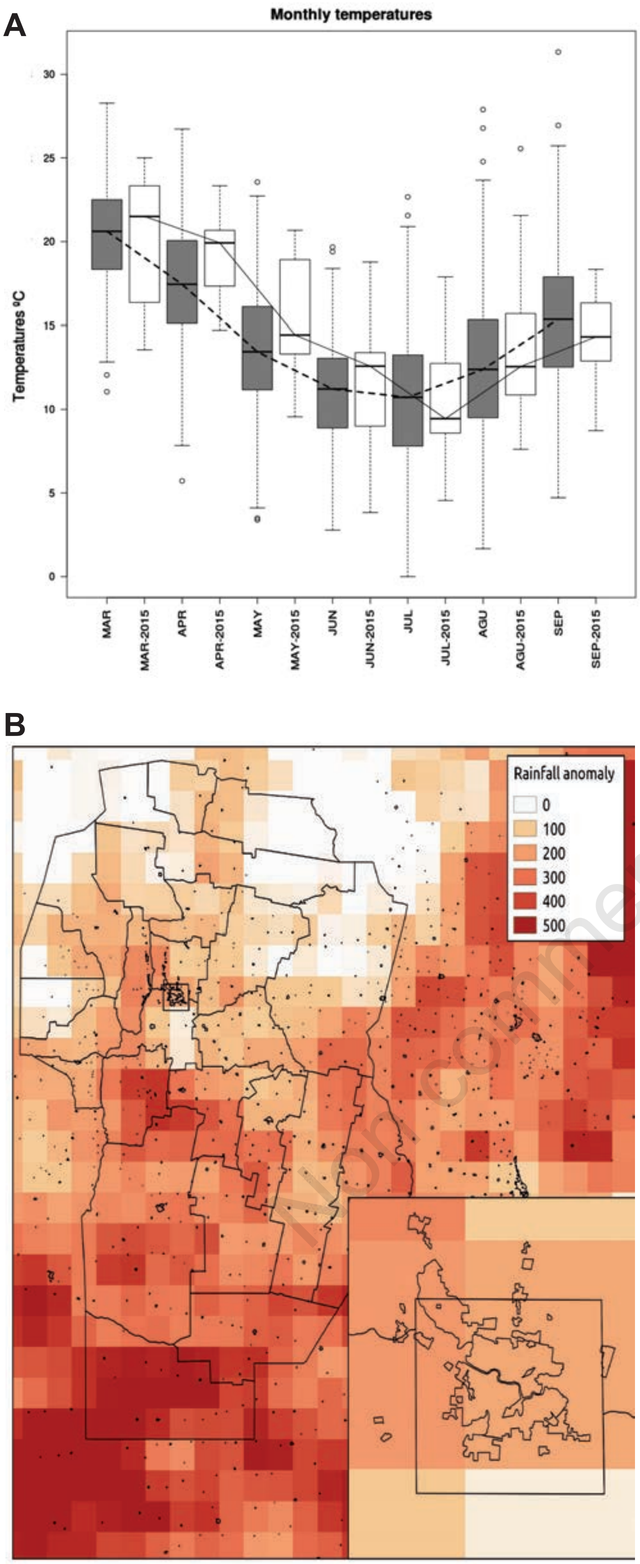

Figure 2. The 16-year average monthly temperatures *vs* the 2015 monthly temperatures in Córdoba City (A): dashed line represents 16-year average monthly temperatures, while solid line represents 2015 monthly temperatures. Anomaly of the accumulated rainfall in the region surrounding Córdoba City from December 2015 to April 2016 (B): expanded picture of Córdoba City shown in the lower, right corner.

MaxEnt algorithm was run with 1,000 repetitions using 75% of vector presence points for model training and 25% for validation. The MaxEnt algorithm detects non-random relationships between two datasets with the georeferenced records of the species presence and the set of raster land cover types representing the environmental and demographic variables considered relevant to determine the *Ae. aegypti* distribution (Philips *et al*., 2006). The environmental dataset used in the analysis included 23 raster format variables of 10-m spatial resolution (Espinosa *et al*., 2016). The predictive map produced by the model was assessed by measurement of the area under the curve (AUC), using the receiver operating characteristic (ROC) analysis, which indicates the global accuracy of the test (Deleo, 1993).

Spatio-temporal analysis

A spatio-temporal dengue case clustering analysis was carried out using the Knox test (Knox, 1964), as shown by (Kullfdorf and Hjalmars, 1999; Rotela *et al*., 2004; Phillips *et al*., 2006). The number of pairs of points found at a given space-distance (in meters) and time-distance (in days) were counted and compared with a random distribution of expected cases (basically a 3D histogram of cases for the space-time distance coordinates).

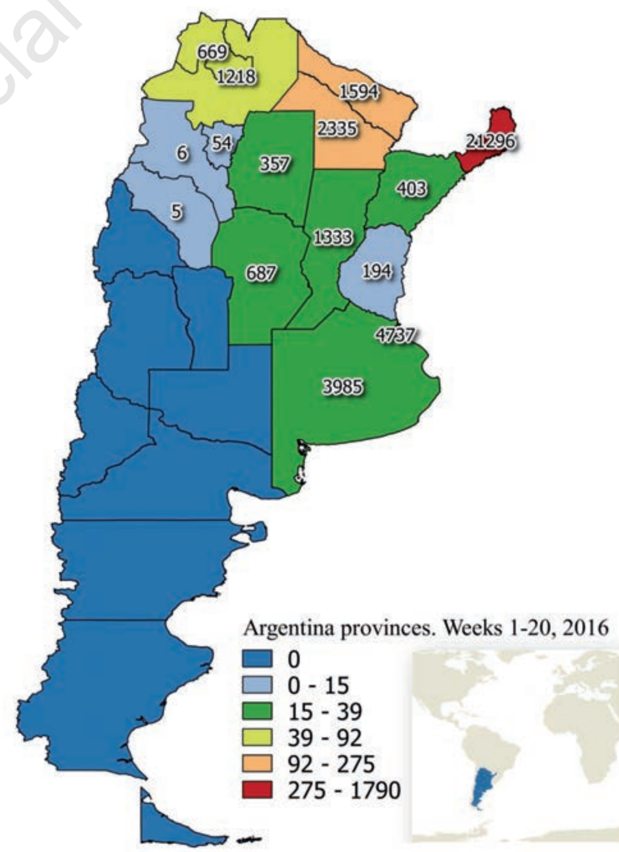

Figure 3. The rate of dengue in Argentina at the provincial level in 2016. Rate expressed per 100,000 inhabitants; all confirmed and probable cases up to the 20th week taken into account; the national disease rate at this point was 90.1/100,000 inhabitants.

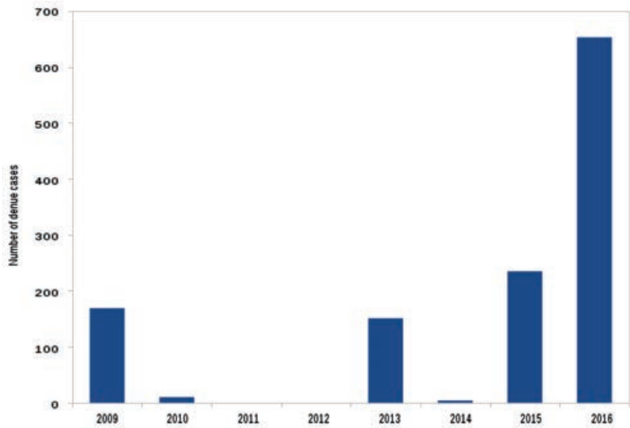

Figure 4. Annual dengue fever cases at provincial level in Cordoba (2009 to 2016).

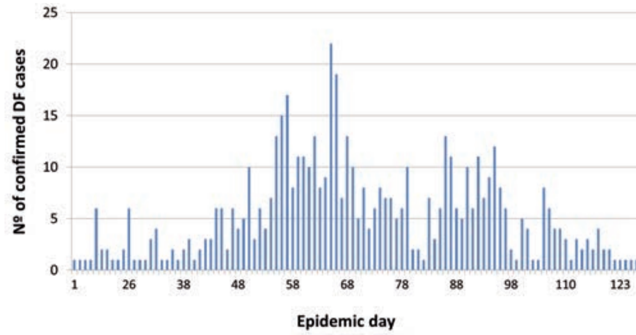

Figure 5. Number of daily, dengue confirmed cases in Córdoba City during the 2016 dengue outbreak. A total of 552 cases were recorded during the 129-day outbreak.

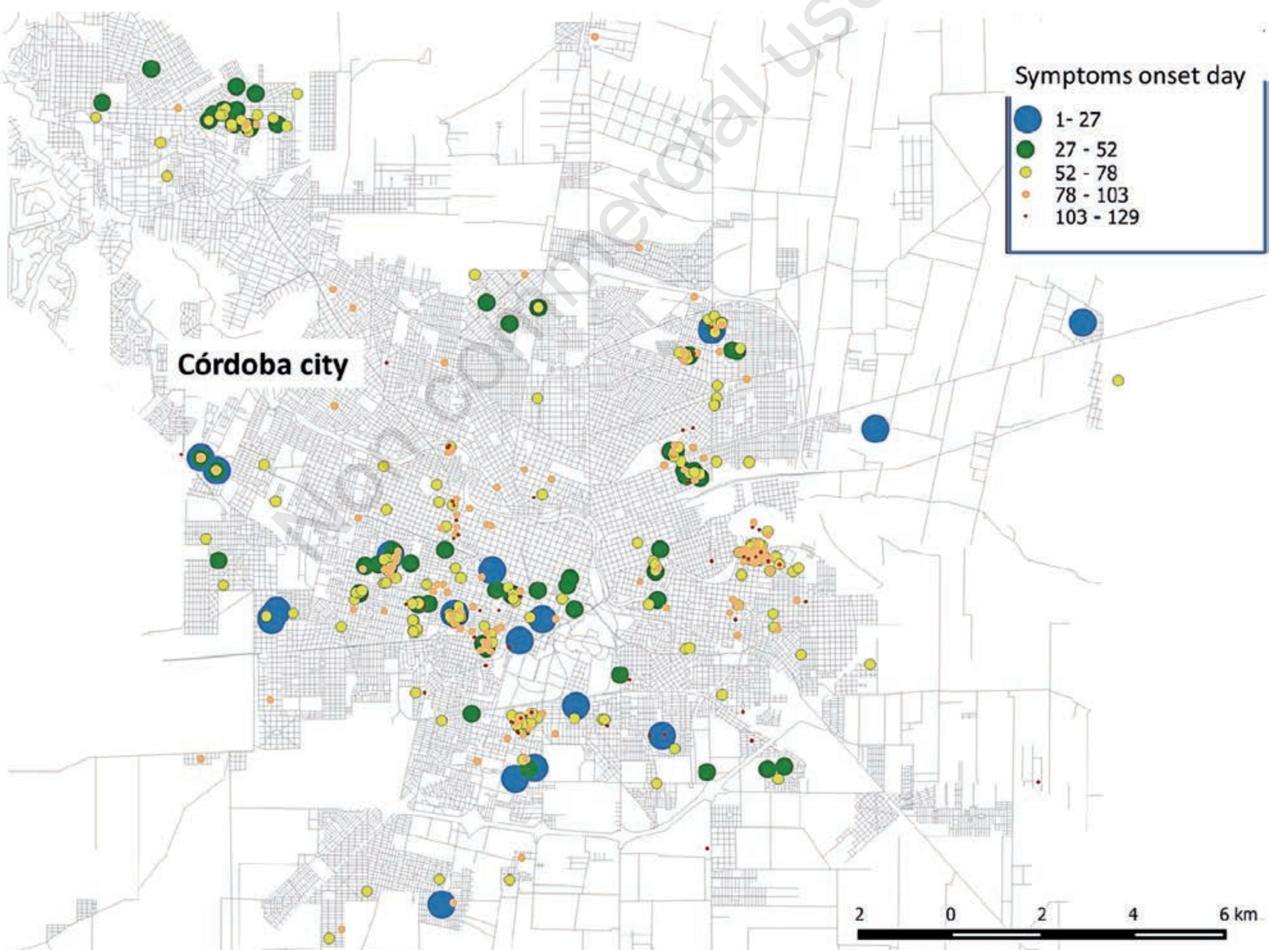

Figure 6. Space-time dynamics of the 2016 dengue outbreak in Córdoba City. Each circle represents a case; colour and size represent the days elapsed since the beginning of the outbreak; blue and larger circles represent the first cases; the yellow, small circles the latest cases reported.

Results

Temperature and rainfall

Climate anomalies occurred in Córdoba City during 2015. As shown by the temperature recorded at the Córdoba airport meteorological station, the near-surface temperature was remarkably superior to the average estimated with a 16-year time series (1998-2014 monthly data). During autumn 2015 (March-June) the temperature remained above the average, but from July to September the trend was the inverse (Figure 2A). The entire region had a positive anomaly of accumulated rainfall from December 2015 to April 2016, compared with the average of the period 1998-2014 (Figure 2B). The anomaly constituted a surplus rainfall varying between 200 and 300 mm. The raw data for rainfall anomaly were obtained from the Tropical Rainfall Measuring Mission (TRMM) (https://trmm.gsfc.nasa.gov/) with the specific Rainfall Estimate product TMPA/3B43, with a monthly frequency and a pixel size of 0.25 degree x 0.25 degree (25 km approximately).

Dengue cases

The national epidemiological scenario showed the highest number of cases in the period up to April 2016, particularly at the provincial level in northeastern and northern Argentina (MSN, 2016) (Figure 3). At the provincial level of Córdoba, the number of DF cases from the 2009 outbreak until the present 2016 outbreak shows an increasing trend, as reported by the Ministry of Health (Figure 4).

The provincial health agency recorded 2,197 suspected cases (with febrile illness), in the period from January 01 2016 to May 15 2016. During this period, 75% of the cases were reported by the public medical agencies with the rest by private medical care facilities (the latter probably providing strongly underreported data). The total number included 653 confirmed cases (572 autochthonous and 81 imported) constituting the highest number of cases reported ever for the province. The temporal variation of the total number of new cases during the 5 months of the epidemic showed a peak value in February-March 2016 (Figure 5) with the typical temporal wave-like pattern. Strain characterisation by routine protocol reported the virus associated with the autochthonous cases as apparently DEN-1 and as a mixture of the 4 serotypes in the imported ones. In this outbreak, 14% of the cases required hospital admission. The largest number of cases occurred in the age group of people between 20 and 29 years old (25% of the cases) followed by the group between 10 and 19 years (16% of the cases). The total age range varied between 6 months and 93 years of age.

At the city scale, the spatio-temporal variation of the number

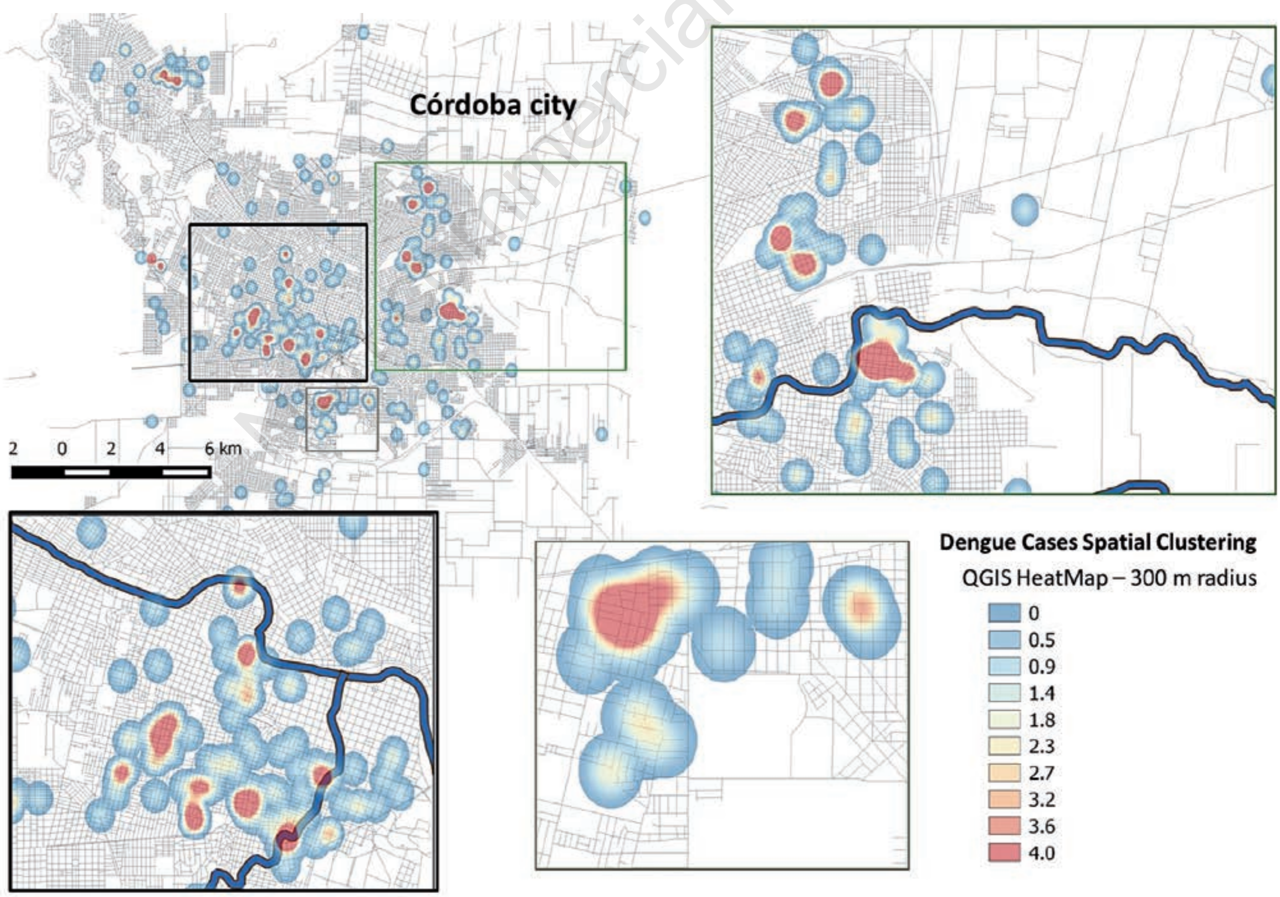

Figure 7. Distribution of the spatial clustering when accounting for confirmed cases during the 2016 dengue outbreak. The *heatmap* shown was obtained with a 300-m searching radius and a 10-m pixel output.

of cases is represented in Figure 6. Here it is interesting to see how, in the places where cases appear in a certain period, there are still cases in the later periods indicating that transmission in a certain place continues once it has started. The kernel density algorithm showed significant spatial aggregation of autochthonous cases, highlighted as inserted zoom windows in Figure 7. The temporal variation of the number of cases within each of these aggregations, are presented in Figure 8 showing the particular temporal pattern for each one.

Vector abundance and distribution

Between December 2015 and May 2016, the monthly sampling showed that 7.3% to 23.8% of the houses had containers with *Ae. aegypti* larvae; the maximum values were seen in February (an example of vector sampling data is shown in Figure 9A). Using the vector abundance data collected in February, the MaxEnt model showed that three environmental variables could correctly describe 83% of the breeding sites distribution: *urban coverage percentage*, *bare soil coverage percentage* and *distance to drinking water (public network)* here given in decreasing importance. The breeding site distribution map derived from the MaxEnt model showed an AUC of 0.942 with a standard deviation (SD) of 0.013, a very good performance according to Parolo *et al*. (2008). The probability map for *Ae. aegypti* breeding sites generated by this ecological niche model is shown in Figure 9B. This product was produced in March 2016 and operationally used to define the insecticide application strategy during the outbreak.

Spatio-temporal analysis

As seen in Figure 10, the distribution of the DF cases for each pair of distances showed the existence of three spatio-temporal clusters (red colour in the figure), with a strong spatial component and soft temporal oscillation. The first cluster (top left in Figure 10) occurred at a distance less than 500 m between pairs of cases, and within a period of 20 days. The second one (centre left in Figure 10) appeared between 2-3 km away and also within a period of 20 days. The third cluster occurred at a distance larger than 6 km and again within a period of 20 days. The spatial profile drawn as a vertical line (I) crossing the three clusters, shows the spatial variation in cases within 7-day periods. Lines II and III show temporal profiles at distances 2 and 6 km for 90 days. These temporal profiles suggest that cases are aggregated within periods of 40 or fewer days, as the case occurrence dropped strongly after that time.

Discussion

The 2016 dengue outbreak shows that a clear clustering of cases developed in Córdoba City showing specific neighbourhoods with hotspots of high virus transmission and others with almost no cases. Not all hotspots started simultaneously and it became clear that in regions with high-transmission rates, virus circulation remained active during the whole epidemic period. This indicates that the vector control activities carried out were not sufficient to interrupt transmission everywhere. On the other hand, it should admit that the occurrence of case clusters suggests that control activities carried out, together with the environment-driven vector distribution, curbed the outbreak from engulfing the whole city.

The number of dengue cases was highest in the 10-29 years age class, suggesting mainly *out of home* virus transmission. The mobility of young adults brings them into contact with hotspot neighbourhoods that may also account for the high number of cases in this age group. However, this finding contrast with several studies that report that dengue risk exposure is greater at home because of the endophilic habits of the *Ae. aegypti* vector (Rodhain, 1996; Diarrassouba and Dossou-Yovo, 1997; Chadee and Martinez, 2000).

The spatio-temporal pattern of dengue cases occurrence showed a heterogeneity similar to that seen in the 2009 outbreak, although with a stronger spatial clustering observable up to 6 km within temporal windows up to 20 days (Estallo *et al*., 2014). The first spatial cluster within 100 m may correspond to an intrinsic hotspot transmission, showing the typical scale of this phenomenon in each sector of the city. The other two spatial clusters could be more related to inter-cluster distance. In the case of temporal distance, two not well-defined peaks appeared, the first between 2 and 3 days might correspond to the extension of the disease due to several infected mosquitoes (with the 3-day duration possibly related to infected vectors surviving in the field). The second one of about 20 days could be related to an extrinsic incubation period (EIP) of about 15 to 18 days for dengue viruses, however, longer than the one recorded in northern Argentina reported by Rotela *et al*. (2007) plus approximately 3 days of infected life.

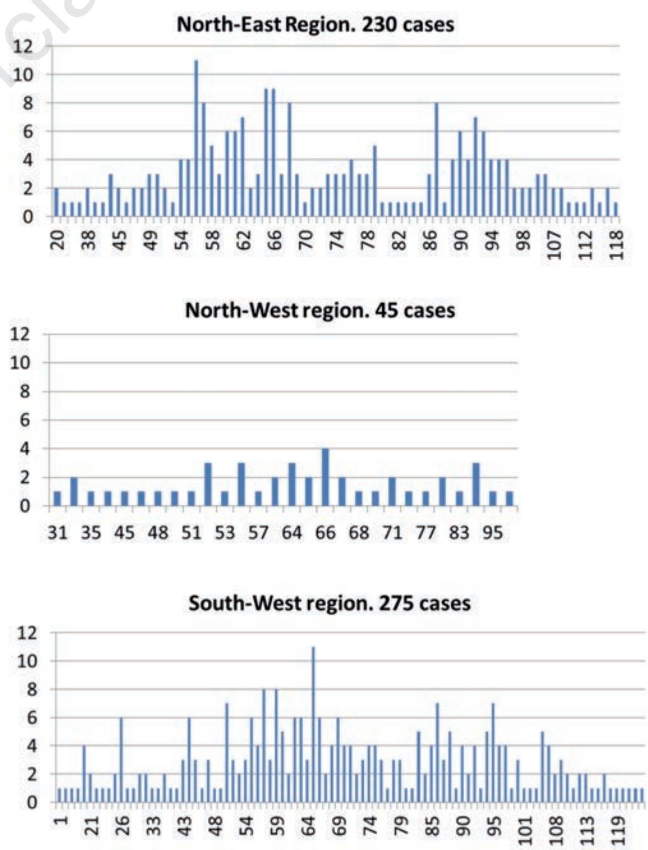

Figure 8. Number of daily, confirmed cases in three representative, clustered areas in Córdoba City during the 2016 dengue outbreak.

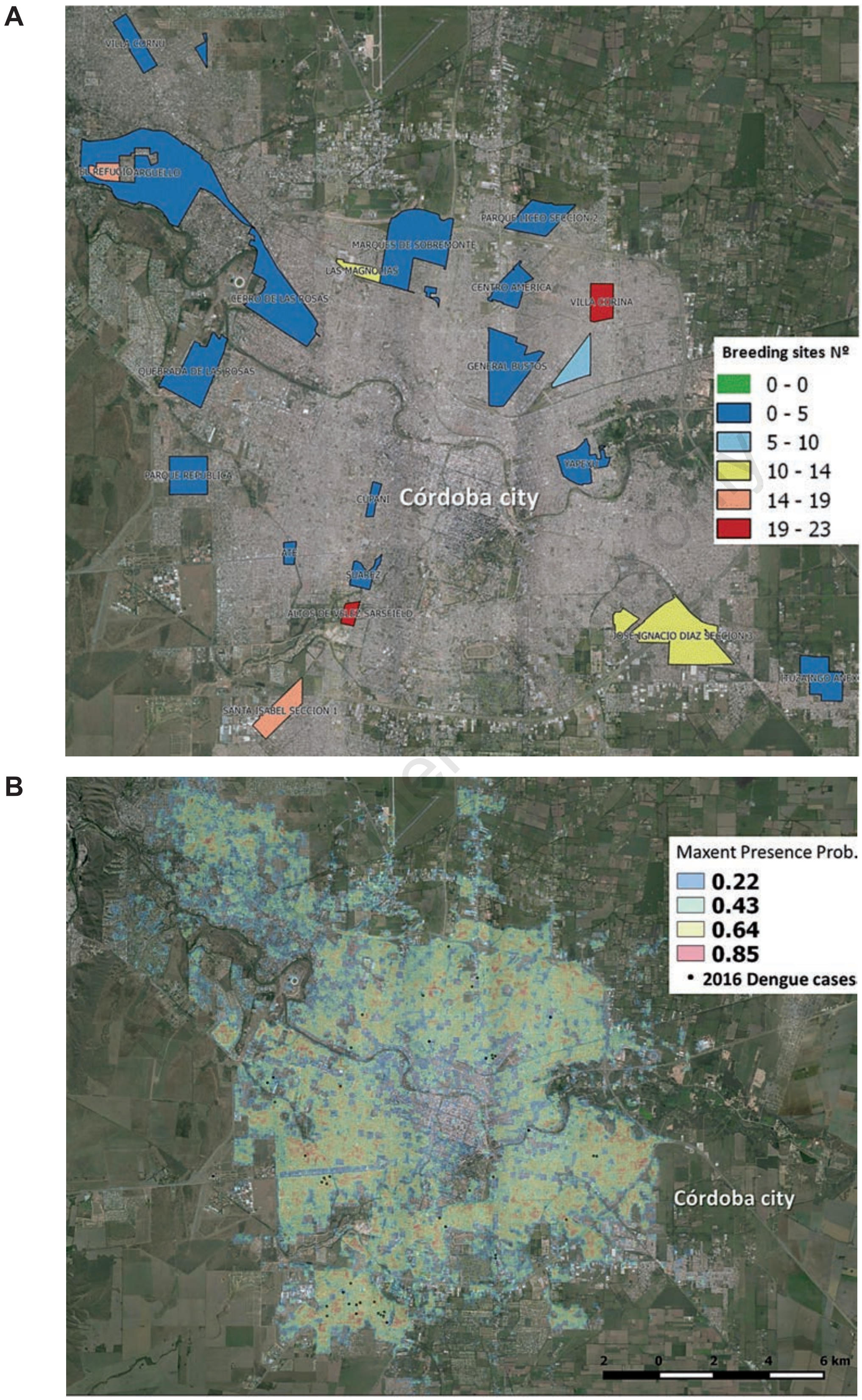

Figure 9. Entomological survey results for *Aedes aegypti* grouped by neighbourhood (A): coloured areas show places where mosquito breeding places were found; the colours indicate the numbers of breeding places in each area. Probability of *Aedes aegypti* presence (B): estimates were produced by the Maxent model based on 15 macro-environmental variables and trained using *Ae. aegytpi* breeding site survey results.

The mean survival of *Ae. aegypti* females under field conditions estimated by the Knox space-time analysis (Rotela *et al*., 2007) gives approximately 20 days, which is comparable with previous estimates (Muir and Kay, 1998; Harrington *et al*., 2001). However, this 20-day peak could also be related with the extrinsic dengue virus incubation period, usually found at mean summer temperatures like in Córdoba (Watts *et al*., 1987). The abundance of *Ae. aegypti*, as measured by the house index, was substantially higher than the values found in the 2009 outbreak (Estallo *et al*., 2014).

The non-simultaneous appearance of dengue cases throughout the city and in specific sites may have several explanations. First, in the context of a national outbreak, infected people from other cities could introduce the virus into the community at some specific places at the beginning of the outbreak and spread the virus in houses within neighbourhoods harbouring high vector populations. Second, the pattern may be due to a delayed response of the dengue surveillance system. The *Ae. aegypti* capacity to move over hundreds of meters (Reiter *et al*., 1995), and the environmental elements of each neighbourhood suggest that mosquito dispersal and its abundance could be the origin of the clustered distribution in the 2016 outbreak in Córdoba. This space-time pattern differs, however, with regard to the reported one in 2009 (Estallo *et al*., 2014) in that only very small clusters were detected.

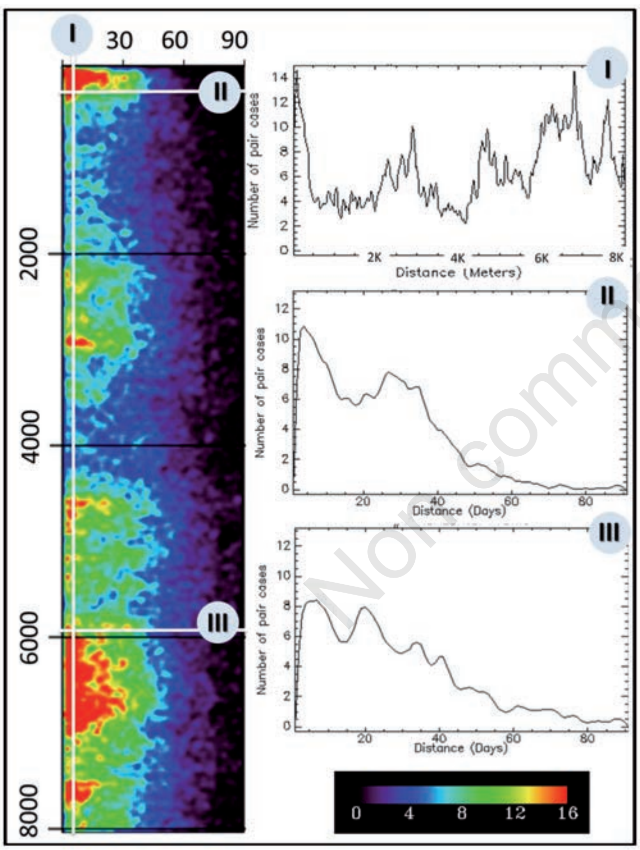

Figure 10. Knox space-time analysis of confirmed dengue cases for each pair of space-time distances. Distribution analysis based on pairs of cases occurring at different distances in time and space. To simplify interpretation, x and y profiles at certain places (white lines indicated by roman numbers) are shown on the right. The vertical axis in the coloured part of the figure represents spatial distances between case pairs (see I), and the horizontal axis represents the time (between case pairs, see II and III). The number of case pairs at each distance is represented by colour, from 0 (none) to 16 (high numbers) as indicated.

This and previous outbreaks in Córdoba, as reported by Radke *et al*. (2009), represent evidence for the emergence of dengue in subtropical regions where *Ae. aegypti* is present. This means that the awareness must be raised with regard to individual mosquito protection and the need for seeking medical assistance early. In addition, healthcare providers should implement rapid diagnosis and institute general mosquito control early on.

Even though the climatic context might be considered as one of the causes triggering the 2016 Córdoba dengue outbreak, we could not find a direct association between temperature or rainfall, which is in accordance with cases reported elsewhere (Thu, 2004). As Xu *et al*. (2007) have shown, these outbreaks have a number of associated limitations related to data access. Also our study had this kind of a limitation, especially linked with the under-reporting and with the localisation of individual infections at specific sites. In this connection, it is important to note that this study included only data at the city scale and in this sense it is not possible to include a spatial analysis of the climatic pattern, so we could not include the meteorological variables as potential explanations for the spatial pattern observed. This would be possible in a larger scale study including all dengue cases in Argentina, but this is beyond the objective of present contribution. In addition access to the georeferenced epidemiological data from the whole country would be problematic since they are reported at the provincial or departmental level, which means the polygons studied would need to be larger than 10,000 km^2

The present epidemiologic scenario and transmission of dengue, as well as of Chikungunya, Zika and other virus infections in Argentina and other Latin-American countries require a great effort to improve the response to these threats. In this context, the operational use of geospatial and remote sensing technologies would provide important contributions. However, as we noted in previous studies (Morrison *et al*., 1998; Rotela *et al*., 2007; Espinosa *et al*., 2016) and Earth observing satellite images for modelling vector distribution remains linked to large-scale factors related with the ecology of *Ae. aegypti*, that can explain some, but not all, elements of the outbreak (Ostfeld *et al*., 2005).

Conclusions

The results presented here enhance the landscape epidemiology perspective and the utility of geospatial tools for epidemic surveillance and control of dengue. This strategy emphasises the need to generalise this kind of approach over other outbreak events. Governmental agencies in Argentina are working to improve the efficiency of dengue surveillance in order to optimise the efforts of health stakeholders. This multi-institutional report shows another step in the operational implementation of this kind of approach.

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