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# Spatial analysis of *Aedes aegypti* immatures in Northern Argentina: Clusters and temporal instability

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ABSTRACT

The objective of this study was to analyze the spatio-temporal patterns of *Aedes aegypti* immatures based on four entomological surveys that inspected over 6000 households in a large neighborhood of the city of Clorinda between 2007 and 2008. Global and local spatial point pattern analyses of immature presence or absence, habitat quality (estimated using a previously obtained statistical model) and pupal production were performed. Global analyses showed aggregation of both infestation and habitat quality up to 10 times bigger than previously described, ranging from 150 to 400 m between surveys. Pupal production was also clustered but at smaller scales than infestation presence/absence. The location of the clusters was temporally unstable between surveys. There was no spatial structure related to the control strategy; lots treated with temephos and lots uninspected (i.e., closed or refusing) were randomly distributed. These results suggest a combination of exogenous (the aggregation of better quality habitats) and endogenous (dispersal) processes explaining the observed patterns of larger-scale infestation. A spatial targeting strategy at the neighborhood scale would not be as cost-effective in Clorinda as in other sites where stable smaller-scale clusters permit the identification of key premises.

## 1. Introduction

Dengue is currently the most important arboviral disease of humans, with an estimated 50–100 million annual cases of dengue fever and 250,000–500,000 annual cases of its most severe forms, dengue hemorrhagic fever and dengue shock syndrome (Kroeger and Nathan, 2006; Kourí et al., 2007). Almost four billion people are at risk in 128 countries worldwide (Brady et al., 2012). *Aedes aegypti* (Diptera: Culicidae) (L.) is the main vector of dengue and other diseases such as chikungunya and yellow fever. It is a highly anthropophilic, domestic vector that breeds mainly in artificial water-holding containers (Kyle and Harris, 2008). In the absence of a vaccine, dengue prevention has most frequently relied on vector control. However, current control interventions are not sufficiently effective or sustainable and more cost-effective strategies are needed (Morrison et al., 2008).

Spatial analysis has gained an important role in epidemiology over the past two decades (Auchincloss et al., 2012). The analysis of spatial patterns of disease incidence and/or vector occurrence and abundance can provide insight into processes that determine disease risk and identify areas where control actions are more needed (Kitron, 1998; Reisen, 2010). Identifying hot spots, suitable for targeting control actions, can be one way to make control programs more efficient (Barrera, 2012; Bousema et al., 2012). The drivers of spatial patterns can be either exogenous, generated by factors or processes not directly related to the variable under study (e.g., landscape heterogeneity), or endogenous, generated by factors or processes inherent to the variable or event under study (e.g., vector dispersal), or a combination of both (Fortin and Dale, 2005).

Spatial analysis of *Ae. aegypti* adults and immatures was first performed in Iquitos, Peru using point pattern analysis (Getis et al., 2003). Clustering was found at small scales ($\leq$30 m) and this was attributed to the restricted flight range of *Ae. aegypti*. Other studies have reported similar or smaller-scale aggregation tendencies (Chansang and Kittayapong, 2007; Barrera, 2012). Clusters were found to be temporally unstable (i.e., their location varied over time) in Iquitos (Getis et al., 2003), whereas temporal stability was reported in Puerto Rico (Barrera, 2012).

The city of Clorinda is one of the high-risk zones of potential dengue transmission in Argentina (Carbajo et al., 2001). A temephos-based citywide larval control program conducted between 2003 and 2008 successfully limited dengue transmission and significantly reduced larval indices but failed to maintain them below target levels (Gürtler et al., 2009). The duration of residual effects of temephos were substantially reduced by local water use practices (Garelli et al., 2011). This problem, coupled with untreated

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foci caused by incomplete coverage of breeding sites in lots closed or whose dwellers refused inspection, limited the effectiveness of the temephos-based control strategy. Large tanks were the most productive type of water-holding container, despite being the main target for control (Garelli et al., 2009), as in several studies around the world. Statistical modeling showed that container infestation was strongly associated with water use practices and factors related to the spatial and temporal infestation context of containers (Garelli et al., 2012).

The search for improved control of *Ae. aegypti* motivated this study which aims at analyzing the spatio-temporal patterns of infestation in the context of the control strategy executed in Clorinda. Surprisingly, the analyses revealed significant aggregation at scales larger than previously reported (Getis et al., 2003; Chansang and Kittayapong, 2007; Barrera, 2012). In order to describe and explain these patterns and identify putative 'hot spots', global and local spatial point pattern analyses were performed for presence/absence of infestation, pupal production, habitat quality and treated and untreated lots along four successive entomological surveys.

## 2. Materials and methods

### 2.1. Study area

The city of Clorinda (latitude 25°17′S, longitude 57°43′W) is located in the Province of Formosa in northern Argentina on the border with Paraguay. Clorinda had 38 identified neighborhoods with 10,752 houses and 47,240 inhabitants in 2001 (Indec, 2001). This study was carried out in Primero de Mayo, a large neighborhood with over 10,000 inhabitants in approximately 2500 houses (20% of the city) and relatively high infestation levels (house and Breteau indices averaged 10.7% and 13.7% between 2003 and 2008, respectively). The piped (tap) water service in the neighborhood was intermittent and insufficient, especially during summer. During 2007–2008, mean temperature was 23.1 °C, with mean monthly maxima (32.4–34.6 °C) in January-February and minima (8.7–12.1 °C) in May–August (Cooperativa de Provisión de Obras y Servicios Públicos Clorinda Limitada). Annual cumulative rainfall was 1560–1159 mm/year.

### 2.2. Entomological surveys

Surveys were carried out in the fall of 2007 (between 26 March and 17 May), spring of 2007 (between 8 October and 29 November), fall of 2008 (15 April–16 May) and spring of 2008 (5 November–17 December). During the 2008 spring survey the location of the entrance to each lot in the neighborhood was georeferenced with a GPS receiver (Trimble GeoXM or Garmin Legend). All 2488 lots in the neighborhood were visited in each survey. During the second and third surveys, if a lot was closed or its residents refused inspection, it was revisited within the next 2 weeks at a different time of the day. The surveys were carried out by experienced personnel of Fundación Mundo Sano (FMS).

The household head was asked for oral consent to examine the premises. The yard and the interior of each house were thoroughly inspected and all water-holding containers found were examined for mosquito immature stages. Samples of larvae and every pupa detected were collected with large-mouth pipettes and small sieves, when needed, in order to strain the containers. Collected immatures were placed in test tubes, labeled and transported to the laboratory for processing and counting. Larvae were identified to species using an entomological magnifying glass and an illustrated key (Rossi and Almirón, 2004). Pupae were kept in small water-filled plastic vials until emergence for accurate species identification.

The variables selected in the best model constructed in a previous study (Garelli et al., 2012) were registered in every container examined, except in the 2007 Spring survey which preceded the model. Containers were classified as tires; large tanks or barrels; trays; drums; buckets; bottles; ceramic jugs ("cántaros"); sailcloth; pots, and other types (in a frequency lower than 1%, including construction materials, discarded vehicle parts, discarded home appliances, toilettes, boots, toys, etc.). The material of large tanks also was registered (fibrocement, metal or plastic). Other variables recorded included location within the lot (inside or outside the house), sun exposure (considered low if any structure such as a ceiling or a tree overshadowed the container, or high otherwise), lid status (only for large tanks, classified as fully lidded or not) and water type (rain; piped; pump, or rain and piped water). Householders were also asked for the main purpose of the water held in each container (water use) and the frequency of water addition (coded as a factor with 4 levels: every 1 or 2 days; every 3–5 days; every 5 days or more; or rain filled). Water use categories included animal drinking, bathing, human drinking, all-purpose, flower pot, nothing, other (breeding fish, construction purposes, cooking, ice-making), storage, watering, and washing. Water addition frequency was only registered for large tanks because householders were generally uncertain for other container types.

After inspection, every container found was turned upside down, destroyed or treated with 1% temephos (Abate, BASF, Ludwigshafen, Germany) at 1 mg per liter applied as sand granules using spoons. Animal drinking pots and natural containers were not treated with temephos because it is toxic to some of the local domestic animals. These were the only vector control campaigns conducted in the area and no further vector control actions were applied between surveys.

### 2.3. Data analysis

Spatial point pattern analyses were performed using the position of each lot as the minimum unit of spatial resolution. Global and local analyses were performed for three types of entomological data for each lot: infestation status (presence or absence of immatures), number of pupae and habitat quality. All data types were analyzed in all four surveys except for habitat quality which was unavailable for the initial survey conducted in Spring 2007.

Spatial patterns of variables directly related to the control strategy were also analyzed because vector control actions may modify the spatial distribution of *Ae. aegypti* (Barrera, 2012). Global analyses of lots treated with temephos and of uninspected lots (i.e., closed or whose dwellers refused inspections) were performed.

Global analyses were performed to describe the general properties of the patterns for all data types in all available surveys. For infestation status, the *O*-ring statistic $O_{11}(r)$ was used to evaluate if the number of points within a ring of radius *r* and a given width, centered at each point of the pattern, corresponds on average to a random process (i.e., a homogeneous Poisson process; $O_{11}(r) = 1$); aggregation ($O_{11}(r) > 1$), or regularity ($O_{11}(r) < 1$) (Stoyan and Stoyan, 1994). Ring width was set at 24 m; maximum radius, 560 m (approximately one-third of the shortest dimension of the study site); 999 simulations were performed, and the upper and lower 25th simulations were used as a 95% confidence envelope. For number of pupae and probability of infestation (i.e., marked processes), the mark-correlation function (Illian et al., 2008) was used as statistic in an analogous manner.

Local analyses were performed to detect the areas were hot spots for each data type occurred. The Getis Gi*(*r*) statistic was used to identify whether each lot was a member of a cluster with a significance level of 0.05 (Ord and Getis, 1995).

**Table 1**
Average house index, container index, Breteau index, *Ae. aegypti* pupae per container and percentage of revisited lots between successive surveys. Clorinda 2007–2008.

| Survey | House index | Container index | Breteau index | Pupae per inspected container | % revisited lots |
|---|---|---|---|---|---|
| Spring 2008 | 9.7 | 21.9 | 11.3 | 3.94 | 78 |
| Fall 2008 | 14.3 | 25.1 | 20.9 | 2.81 | 91 |
| Spring 2007 | 6.3 | 8.2 | 7.8 | 0.96 | 89 |
| Fall 2007 | 19.4 | 30.2 | 27.0 | 6.66 | |

Spatio-temporal dependence was studied via independent labeling (de la Cruz et al., 2008) which considered the spatial distribution of lots infested at a given survey with respect to the lots at the immediately subsequent survey. Null models were built maintaining the pattern of infestation for each of the first three surveys fixed and randomizing the status of infestation of the lots at the respective subsequent surveys. The *O*-ring statistic was used for this analysis as previously described.

Global analyses were performed using Programita (Wiegand and Moloney, 2004) and local analyses using Clusterseer 2.3 (BioMedware Inc., Ann Arbor, MI). Maps were constructed using ArcGIS 9.1 (Environmental Systems Research Institute [ESRI], Inc., Redlands, CA).

### 2.4. Statistical model for habitat quality

Habitat quality was estimated using probability of infestation of each lot as proxy. Probabilities of infestation of water-holding containers were obtained according to a multiple logistic regression model (Garelli et al., 2012) and were scaled up to lot level as the complement of the product of the complements of the probability of infestation of every water-holding container per lot (i.e., 1 – the probability that the lot is not infested).

The model was previously constructed using model selection techniques based on Akaike's Information Criterion. Different a priori selected variable types were used in the process, including physical characteristics of containers (type, material, lid status, location and sun exposure), water use practices (water addition frequency and water use), factors related to the spatial and temporal infestation context of containers (number of pupae in the block and survey period), history of chemical control (amount of temephos used in the preceding control round at different scales) and weather (mean, minimum and maximum temperature tested at several lags).

Variables reflecting every putative process considered, except history of chemical control, were selected in the best models obtained for infestation and productivity. Overall model quality was good; the area under the receiver operating characteristic (ROC) curve was 0.81; sensitivity, 73%, and specificity 75%, with 75% of observations correctly classified. Further descriptions and maps of the model can be found in Garelli et al. (2012). For the purpose of the current study, the model was re-fitted excluding pupae per block as an explanatory variable because it was considered a spatial context factor (i.e., not a variable directly linked to habitat quality). No qualitative differences in parameter estimates were found (Table S1).

## 3. Results

In total, 7214 water-holding containers were inspected during the three surveys, and 18,567 *Ae. aegypti* pupae collected in 1645 infested houses (Table 1). Surveys were heterogeneous with respect to infestation and pupal production, climate patterns and water use profiles in containers, without clear trends found between surveys or season (Table 2).

Global analyses showed spatial aggregation at varying scales between surveys and type of data (Fig. 1). The occurrence of infestation (infestation status) was found aggregated up to radii of 385, 350, 400 and 150 m for each successive survey (Fig. 1). In each of these patterns, an oscillatory curve is observed, which is particularly important in the last survey where clustering is intermittently significant, showing evidence of an aggregated distribution of the clusters. Habitat quality was also aggregated and the scale of aggregation was smaller (up to 240 m), similar (up to 420 m) and bigger (up to 400 m) than for infestation status in the last three surveys, respectively. The number of pupae was also aggregated, although the intensity and scales were smaller, with small peaks of significant aggregation up to scales of 280, 40, 320 and 30 m. In this case, the first survey showed three scales of aggregation, with peaks up to 150 m, 220 m and 320 m. The third survey showed two scales of aggregation, a stronger peak up to 150 m and a second weaker peak at 320 m, evidencing aggregation of clusters.

Clustering was also found using local spatial statistics at scales similar to those reported by global analyses for infestation status, habitat quality and number of pupae (Fig. 2). Clusters of observed infestation, number of pupae and habitat quality partially

**Table 2**
Percentage of lots, pupae per lot, house index, average values of climatic variables of habitat model and container index by main water use categories (not registered in Spring 2007 survey) of habitat model. All values are shown for lots inside and outside of infestation clusters and all the study area for every survey. Clorinda 2007–2008.

| Survey | Spring 2007 | | | Fall 2007 | | | Spring 2008 | | | Fall 2008 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Area | Non-cluster | Cluster | All | Non-cluster | Cluster | All | Non-cluster | Cluster | All | Non-cluster | Cluster | All |
| % Lots | 75 | 25 | 100 | 73 | 27 | 100 | 77 | 23 | 100 | 85 | 15 | 100 |
| Pupae per lot | 3.9 | 4.4 | 4.1 | 0.8 | 1.3 | 1 | 3.9 | 4.4 | 4.1 | 3.1 | 2.9 | 3.1 |
| House index | 17 | 36 | 22 | 7 | 18 | 10 | 17 | 36 | 22 | 24 | 32 | 25 |
| Mean temperature (lag 3 days) | 24 | 26 | 25 | 25 | 24 | 24 | 28 | 25 | 27 | 19 | 21 | 19 |
| Total Rain in mm per lot visited lLag 3 days) | 17 | 15 | 16 | 17 | 4 | 15 | 12 | 36 | 18 | 11 | 9 | 11 |
| Total Rain in mm per lot visited (lag 6 days) | 9 | 8 | 9 | 5 | 4 | 5 | 6 | 3 | 5 | 8 | 10 | 8 |
| Mean high temperature (lag 1 day) | 27 | 22 | 26 | 25 | 22 | 24 | 27 | 22 | 26 | 20 | 18 | 20 |
| Container index by water use category | | | | | | | | | | | | |
| Animal or human drinking | | | | 30 | 22 | 28 | 21 | 20 | 20 | 25 | 26 | 25 |
| Washing | | | | 39 | 35 | 38 | 35 | 38 | 35 | 29 | 36 | 30 |
| Nothing, storage | | | | 23 | 35 | 26 | 17 | 27 | 19 | 32 | 28 | 32 |
| All purpose | | | | 8 | 8 | 8 | 28 | 16 | 25 | 14 | 11 | 13 |

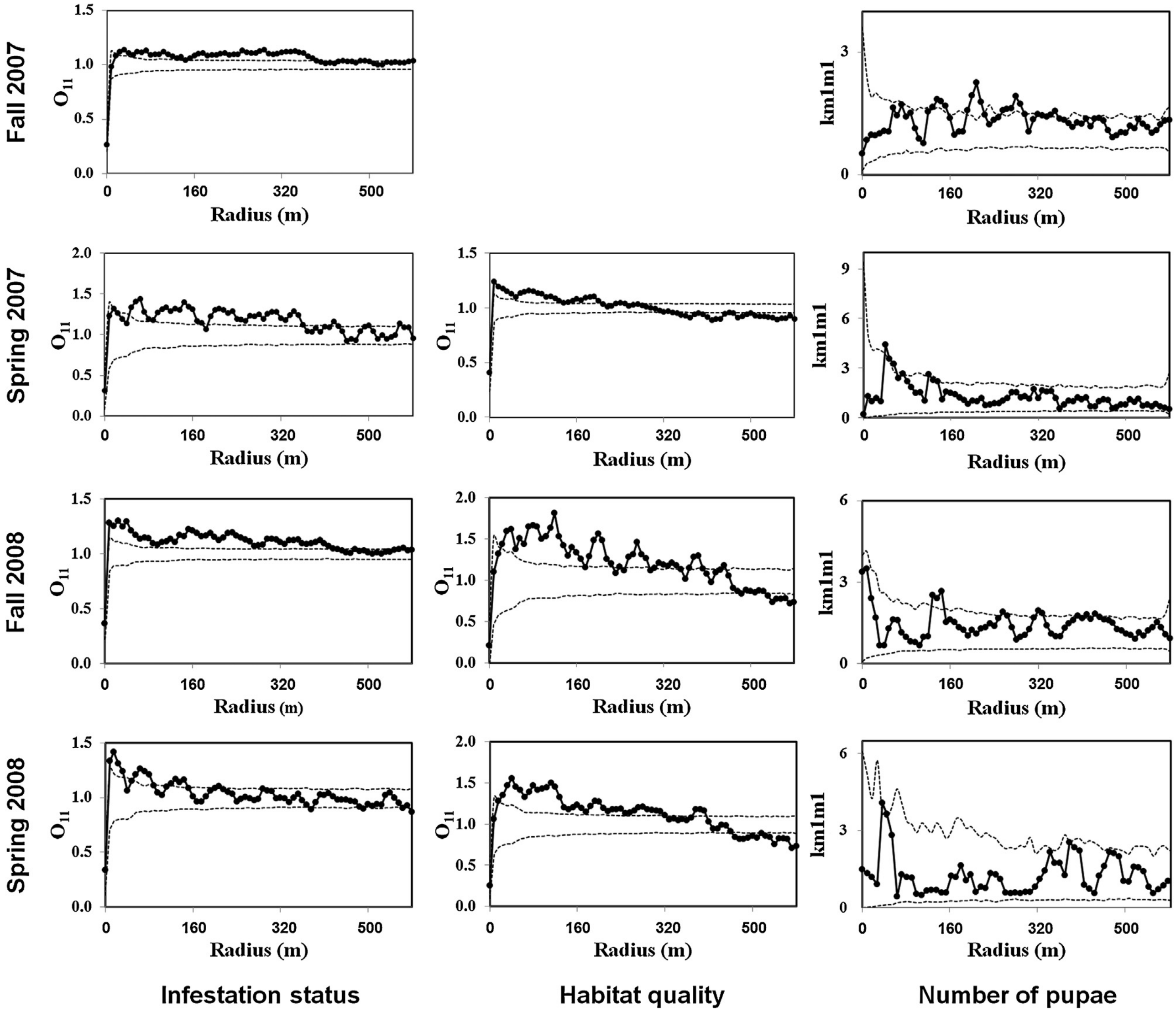

**Fig. 1.** Global spatial point pattern analyses. Univariate o-ring statistics (o11) were used with a random labeling null model for infestation status and habitat quality in every survey available. A univariate mark correlation function (Km1m1) with a random labeling null model was used for number of pupae. Clorinda, 2007–2008.

overlapped in every survey. However, there was high temporal instability between surveys in the location of the clusters.

Considering the lots that were examined in more than one survey (i.e., were not closed or whose dwellers refused inspections more than twice), only 4% were infested in every survey; 2% in 3 of 4 surveys; 40% were infested once or twice, and 50% were never found infested. The lots infested in 75% or more of the surveys were spatially aggregated up to a radius of 350 m globally. These lots were located throughout the neighborhood, yet more intensely in the center (Supplementary Figure 1).

Highly productive lots were not temporally stable (Supplementary Figure 2); roughly 75% of the lots with 100 or more pupae at a given survey did not have more than 10 pupae in the rest of the surveys and 92% of those lots were not productive in the subsequent survey.

The spatio-temporal global analysis showed significant aggregation at 0 m (i.e., household level) and weak clustering at larger scales, showing evidence of a weak relation between the patterns of infestation in subsequent surveys, which occurred approximately 6 months apart (Fig. 3).

No spatial structure was found with regards to the control strategy; only very few, small peaks of aggregation were revealed in two of the surveys. Both treated and uninspected (closed or refusing) lots were randomly distributed throughout the study area (Supplementary Figure 3).

## 4. Discussion

The patterns found showed spatial aggregation of *Ae. aegypti* immatures at scales one order of magnitude larger than previously reported. These patterns were temporally unstable, showing heterogeneity between surveys in both the scale of aggregation and the location of hot spots for all data types considered (infestation status, habitat quality and number of pupae).

The scales of aggregation found were rather surprising because previous studies involving spatial point pattern analyses had reported smaller scales likely related to the limited dispersal tendencies of the vector (Getis et al., 2003). The results found are more in concordance with studies of adult dispersal distances which in some cases have reached up to 800 m (Honório et al., 2003).

According to the spatial analysis of habitat quality, the best sites were clustered in every survey and ‘hot spots’ partially overlapped to those of infested sites. Therefore, our results suggest a combination of both exogenous (the aggregation of better quality habitats)

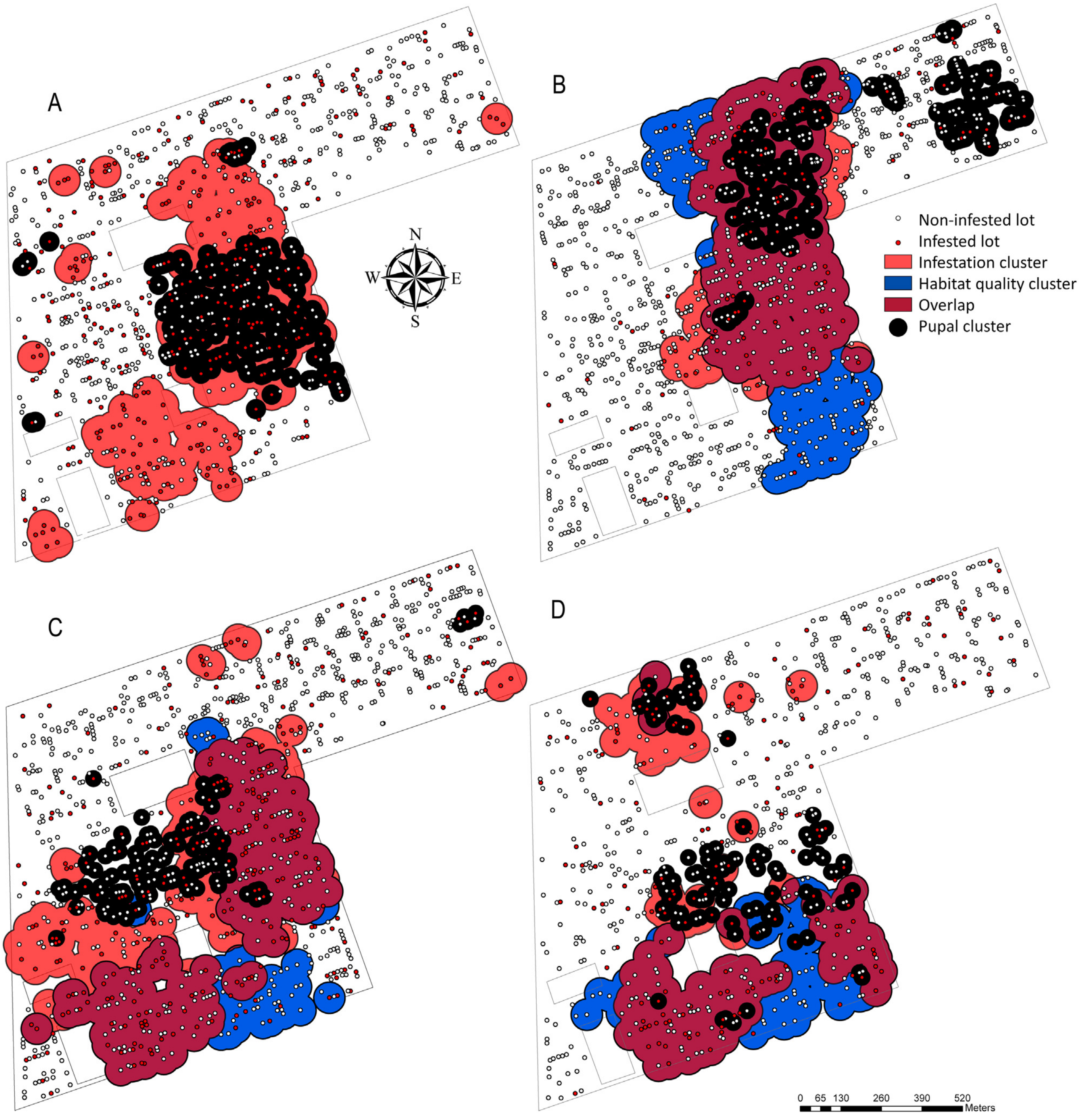

**Fig. 2.** Maps for each lot and location of clusters of infestation status, habitat quality and *Ae. aegypti* pupal production according to local analyses for every survey. Overlap is the intersection between infestation and habitat quality clusters. (A) Fall 2007. (B) Spring 2007. (C) Fall 2008. (D) Spring 2008. Clorinda, 2007–2008.

and endogenous processes (dispersal) explaining the observed patterns of larger-scale infestation. Also, in some of the surveys, aggregation was intermittently significant, evidencing aggregation at several scales; therefore, the resulting large-scale clustering was a result of an aggregated distribution of clusters.

We recorded between-survey variability of every aspect considered of the spatial patterns (scales of aggregation, location of clusters and relation between patterns of different data types). Spatio-temporal statistics showed weak associations between infestation in pairs of successive surveys. This was also consistent with the fact that only 6% of the lots inspected were infested in 75% or more of the surveys.

Clusters moved through a portion of the neighborhood (from the center to its southernmost part) that was too large to pinpoint as an area suitable for cost-effective spatially targeted control at the neighborhood scale, where smaller areas with key premises would need to be identified. Rather, these results suggest that city-scale spatial targeting, aiming at whole neighborhoods or large parts of neighborhoods, may be recommended. Identifying higher risk areas for reinforcing control in Clorinda is beyond the scope of this study but is consistent with reported heterogeneity in infestation indices between neighborhoods (Gürtler et al., 2009).

Several putative causes for the temporal instability of clusters emerge from our results. One possibility is instability in habitat conditions, e.g., changes not only in climatic conditions but also on the profile of containers and water use practices. According to Table 2, this seems to be occurring in Clorinda, however the determinants of these changes remain unknown. A second possible cause

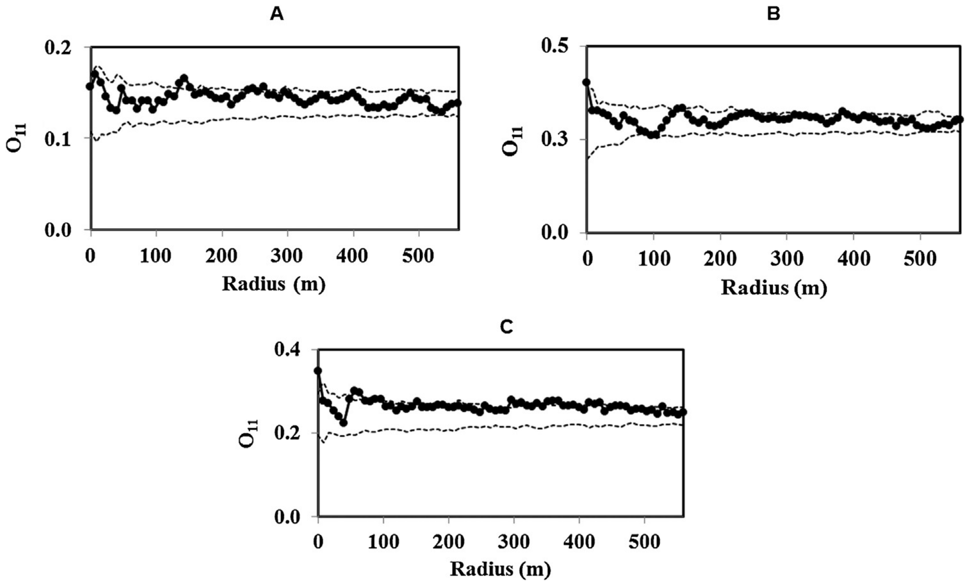

**Fig. 3.** Spatio-temporal global analysis of the relation between *Ae. aegypti* infested sites in subsequent surveys. (A) Fall 2007–Spring 2007. (B) Spring 2007–Fall 2008. (C) Fall 2008–Spring 2008. Clorinda, 2007–2008.

is the intermittence of putative key premises, responsible for high mosquito production. Lots with over 100 pupae production almost every time reduced their production to zero between surveys. If these lots were in fact "key premises", this effect could be determinant for the patterns found and may have been produced by the treatment of lots, either by the chemical treatment itself or by changes in the behavior of inhabitants due to the impact of having health promotors collect so many pupae from their containers.

The temporal dynamics of all study variables probably changed at a much higher rate than what could be recorded in our four surveys, which occurred approximately every 6 months. Temporally finer-grained longitudinal studies are needed to better understand the drivers of variation of both habitat quality and *Ae. aegypti* abundance in Clorinda, as well as many other aspects of the current dengue agenda (Scott and Morrison, 2010).

The number of pupae was much less aggregated than infestation status and their patterns of aggregation only partially overlapped. This is consistent with the low correlation found between pupal indices and other indices based on presence/absence of infestation (Garelli et al., 2009). The importance of highly productive sites for vector and transmission dynamics remains a topic for further study.

This study was performed in a context of temephos-based focal control which co-occurred with pupal surveys. There is some evidence that vector control actions could modify the spatial distribution of the vector (Barrera, 2012). In our study area, variables directly related to the control strategy did not show spatial structure, i.e., the control status of lots (e.g., treated, closed or refusing inspection) was randomly distributed throughout the study area. Also, a multivariate statistical model did not find effects of temephos-based larval control between successive surveys in the infestation status of containers (Garelli et al., 2012). However, effects of control actions on putative "key premises" cannot be excluded, as it has been pointed out earlier.

Other studies involving spatial point pattern analysis investigated the occurrence of dengue cases and not vector distribution (e.g., Vazquez-Prokopec et al., 2010; Liebman et al., 2012; Yoon et al., 2012). Unfortunately, this type of data was not available in Clorinda, limiting the scope of our study. In addition, the lack of information regarding adult mosquitoes was another limitation of the present study, alongside the coarse temporal grain used. Adults are much more difficult to collect, a problem that has led to an emphasis on indices based on immature stages (Focks, 2003).

The search for cost-effective control has directed interest toward increasingly focused strategies, such as those targeting specific container types or areas like key premises. According to our results, a control strategy in Clorinda would need to cope with spatial heterogeneity over time and relatively large clusters. Therefore, at the neighborhood scale, spatial targeting would not be as efficient as it might be in other settings were stable smaller-scale clusters permit the identification of key premises. Future analyses should be centered on identifying the city-scale areas where control is more needed. This information could be coupled with a focus on well-characterized containers that are responsible for most of mosquito production (Garelli et al., 2012), and considering the high importance of water use practices, the involvement of the community in order to attain more cost-effective integrated vector 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.2013.07.019.

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