



Spatio-temporal evolution of canine rabies in Tunisia, 2011–2016

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1 **Title**

2 Spatio-temporal evolution of canine rabies in Tunisia, 2011-2016

3

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27

Abstract

28

29 Tunisia is an endemic country for dog mediated rabies. An increase in canine rabies
30 cases during the last decade has been suspected. Since no studies have been
31 conducted on rabies spatial distribution, the present work was focused on
32 spatiotemporal evolution of rabies in Tunisia during the 2011 – 2016 period with a
33 special focus on the reservoir species. Data collected concerned suspected dogs
34 that originate from the whole country. Surveillance indicators such as positive
35 fractions and number of suspected dogs received at the laboratory have been
36 calculated. Spatiotemporal hotspots were then mapped, spatial and spatio-temporal
37 analysis were carried out using discrete Poisson spatial model and space-time
38 permutation models available in SaTScan9 software. The study revealed that an
39 actual increase in canine rabies incidence occurred in Tunisia since 2012. Spatial
40 and spatio-temporal analysis identified clusters centered in the North and in the
41 Center East of the country. Spatio-temporal clusters were non overlapping, indicating
42 that this spatial distribution is not fixed through time. A large heterogeneity in
43 surveillance indicators such as number of suspected dogs was associated to the
44 distance to the laboratory or to insufficient coordination between governorates.

45

46 **Keywords**

47 Canine Rabies; spatial epidemiology; Tunisia; spatio-temporal analysis; SaTScan; Dogs

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52 **Introduction**

53

54 Rabies is a zoonotic disease caused by a virus of the *Lyssavirus* genus [1]. It is
55 transmitted through direct contact between infected saliva and wounded skin or
56 mucosa. Most mammals can be infected by rabies including humans and the
57 outcome is usually fatal. In most North African countries, dogs are the main reservoir
58 and vector of rabies [2,3].

59 In Tunisia, rabies surveillance is conducted through the National Rabies Control
60 Program (NRCP) under supervision by three ministries (Ministry of Health, Ministry of
61 Agriculture and Ministry of Interior). Surveillance and control include laboratory
62 testing of all suspected animals at the National Reference Rabies laboratory of the
63 Institut Pasteur of Tunis (IPT). Animal rabies surveillance is managed via veterinary
64 services' units present in all Tunisian governorates.

65 Rabies control and surveillance efforts in Tunisia show high indicators compared to
66 North Africa and Mediterranean regions and cost approximately 5.2 million US
67 Dollars over a five year period (2012 – 2016) [4]. In fact, Tunisia's dogs vaccination
68 coverage is among the highest, comparing all Mediterranean countries [5,6].
69 Moreover, the number of suspected animals tested at the laboratory (all species
70 included) in Tunisia is high compared to other African and Mediterranean countries
71 [6]. For instance, 1148 animals were tested in Tunisia in 2014 with only one
72 laboratory available for rabies diagnostics. Conversely, although rabies is endemic in
73 Morocco, only 310 animals had been tested for rabies in 2014 even though they
74 retain seven national laboratories [5,6].

75 However, despite continuous efforts to control rabies, a rapid increase in incidence
76 has been observed in Tunisia since 2012 resulting in multiple human rabies cases as
77 well as a high cost for post exposition prophylaxis (PEP). In fact, although no human
78 cases have been recorded in 2009, human rabies reemerged with a peak of 6 human
79 cases in 2013 and in 2015 increasing PEP cost from 1,99 million TND (720,000 USD)
80 in 2010 to 3,48 million TND (1,27 million USD) in 2016 [16].

81 The increase in animal rabies incidence occurred in multiple geographic regions in
82 the country. Multiple factors are suspected for this recent rise, particularly low
83 vaccination coverage and mismanagement of household waste [7].

84 Even though rabies is endemic in Tunisia, few studies have been published on rabies
85 and none aimed to assess the geographical distribution of the disease in animal
86 reservoir which is dogs [2,3]. The aim of this study is to describe and analyze the
87 epidemiological situation of dog rabies in Tunisia during the six-year period (2011–
88 2016), when an incidence increase was observed. Furthermore, a spatio-temporal
89 analysis of rabies evolution over the study period will be presented. Total number of
90 suspected dogs tested and the number of rabies cases together with positive
91 fractions, were calculated and spatially represented, since they are good indicators
92 for evaluation of passive rabies surveillance [8]. Therefore, the present work aims to
93 evaluate passive surveillance through an accurate analysis of rabies distribution, in
94 order to provide veterinary services with targeted recommendations to eliminate
95 rabies.

96 **Materials and methods**

97 **Study area**

98 Tunisia is an upper-middle income country in North Africa. It is administratively
99 divided into 24 departments named governorates, which are further subdivided into

100 264 delegations. Tunisian territory is geographically divided into different regions
101 based on their bioclimatic stages and demographical characteristics. The most
102 densely populated regions are the North East and Center East. The South is less
103 populated because of its arid Saharian climate [9,10]. The study area covered the
104 whole country of Tunisia. Delegations were used as the smallest unit for spatial and
105 spatio-temporal analysis, since all of the 264 delegations were represented by
106 veterinary services for epidemiological surveillance in those areas.

107 **Data collection**

108 In suspected cases of rabies in dogs, specimen of dead bodies were sent to the
109 rabies laboratory for brain extraction and diagnostic testing. These specimen were
110 collected by governmental veterinary services or private veterinaries within national
111 rabies surveillance network according to international standards of specimen
112 collection [11]. An information sheet accompanying the specimen was then registered
113 into the IPT rabies laboratory database. Variables used in the study were extracted
114 from the rabies database and included suspected dog's location (at the delegation
115 level), date of death, specie and rabies Fluorescent Antibody Test (FAT) result. The
116 centroid of each delegation was calculated using ArcGIS 10.2 [12] to approximate
117 suspect dog's exact location.

118

119 **Inclusion criteria**

120 Only rabies suspected dog specimens that were sent to the rabies laboratory from
121 2011 to 2016 were included in this study. Dogs were selected independently of their
122 vaccination status, age or breed. A dog was considered as a rabid case only if it was
123 positive to FAT on extracted brain specimens, as recommended by the WHO and the
124 OIE standards [11,13].

125

126 **Descriptive analysis**

127 Three indicators were evaluated to assess rabies' epidemiological status in Tunisia:
128 number of suspected rabid dogs, number of actual positive rabies cases and positive
129 fraction per delegation. To measure these variables, we calculated the number of
130 suspected rabid dogs at the delegation level. Also, we used the number of dogs
131 revealed positive to rabies at the delegation level as cases. Positive fraction (PF) is is
132 the proportion of suspected dogs that tested positive to rabies. This measure is more
133 accurate because it reflects the actual rabies status without being biased by the
134 number of collected specimen. A country level PF was calculated for each year of the
135 6-year study period (2011– 2016) taking into account the total number of cases and
136 specimens received at IPT. In order to test for significant difference in number of
137 cases, Chi square for trends has been carried using R 3.5.2 software. This test
138 concerned number cases and number of suspected dogs from 2011 to 2014, where
139 an observable increase is noticeable. A value of $p < 0.05$ was used to define
140 statistical significance.

141 **Spatial and spatio-temporal analysis**

142 Spatial analysis was conducted using discrete Poisson spatial model [14] available
143 in SaTScan v9.4.4 software [15].The Poisson approach in SaTScan calculates
144 clusters compared with dog population statistics, to determine potential clustering of
145 rabies cases. Dog population size is estimated according to a calculation made by
146 General Direction of Veterinary Services based on a model taking into account the
147 human population size and the categorization of territory [22-24] and published in the
148 Rabies Control Program Newsletter [16]. SaTScan calculates the expected number
149 of cases within a scanning window based on a Poisson distribution. Spatial analysis

150 scanned for areas with high rates within a spatial window, which was selected with a
151 maximum spatial cluster size of 25 percent of the population at risk as the best
152 window size providing relevant cluster information with enough accuracy. Then, each
153 model was evaluated with an inference of 1000 replications. A value of $p < 0.05$ was
154 used throughout the analyses to define statistical significance. Spatial hotspots were
155 then mapped at the country level using ArcGIS 10.2 [12].

156 The space-time permutation model [17] was used to detect the presence of areas
157 and time periods with significant aggregation of rabies cases in dogs, via SaTScan
158 software [15]. Scanning for clusters included spatial and temporal dimensions
159 ranging from 0 up to 25% of the study area, with an inference of 1000 replications.
160 The selected time precision for temporal analyses was 1 month. Temporal precision
161 was chosen because it offers an optimal balance between computing time and
162 precision in results.

163

164 **Results**

165

166 **Descriptive analysis**

167 Number of suspected dogs and number of rabies cases from 2011 – 2016 are
168 represented in Figure 1 (fig 1). Overall, both metrics have been following the same
169 evolution trends over the study period. An increase is noticed beginning in 2012.
170 A total number of 2,666 suspected dogs were tested at the IPT rabies laboratory over
171 the study period, and 1181 (44.3%) tested positive for rabies. Number of cases rose
172 from 54 in 2011 to 167 in 2012 then reached 280 cases in 2014 and then plateaued
173 in 2015-2016 (approximately 200 dog rabies cases / year). Similarly, there was an
174 increase in positive fractions along with an increase in incidence. Indeed, even

175 though a large number of dogs (548) was tested in 2014, 280 (51%) were positive for
176 rabies, unlike in 2013 when 199 (42%) tested positive.

177 Chi square for trends showed results indicating a strong evidence of trend for an
178 increasing number of cases from 2011 to 2014 (χ^2 = 13.432, p-value =
179 0.0002473).

180

181 *Fig 1: Canine rabies incidence during a 6 year period 2011-2016*

182

183 Figure 2 (fig 2) represents spatial distribution of rabies cases. Most cases were found
184 in the North and in the Center East of the country. Delegations with the highest
185 number of cases were Sbikha (35 cases; 2.9% of total number of cases). Nefza (25
186 cases; 2.1% of total number of cases) Jendouba Nord (24 cases; 2% of total number
187 of cases) and Jebeniana (22 cases; 1.7% of total number of cases). Very few cases
188 were identified in the South, with only 38 (3.2%) cases total recorded in all 48
189 Southern delegations.

190

191 *Fig 2: Spatial distribution of dog rabies cases, 2011-2016*

192

193 Spatial representation of suspected dogs specimens collected per region show an
194 important disparity between delegations in neighboring governorates and even
195 between delegations within the same governorate (Fig 3). Only 29 delegations over
196 264 have collected on average more than three suspected dogs per year, while 110

197 delegations over 264 have collected less than 5 suspected dogs specimens during
198 the whole 6 year time period.

199

200 *Fig 3: Spatial representation of suspected dogs specimens collected per delegation*

201

202 **Spatial analysis**

203 Spatial analysis identified four statistically significant clusters located in the North and
204 in the Center East (fig 4). The most likely cluster (Cluster 3, $p < 0.001$) contained 132
205 cases and was centered around delegation of El Jem (Governorate of Mahdia) and
206 included delegations of Souassi (Mahdia) and EL Hencha (Sfax). Cluster 1 was
207 centered around delegation of Joumine, in South East Bizerte governorate, including
208 also delegations from Beja governorate (119 cases). Cluster 2 included governorate
209 of Tunis and its suburbs (152 cases). Cluster 4 included only one delegation which is
210 Sbikha in Kairouan governorate (42 cases).

211

212 *Fig 4: Spatial clusters of dog rabies cases in Tunisia*

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214

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Table 1 : List of spatial clusters

Cluster Number	p value	Main delegations	Center location	Number of cases	Expected number of cases
1	<10 ⁻³	Sejnane, Ghazala, Joumine (Bizerte) Beja Amdoun (Beja)	Joumine (Bizerte)	119	57
2	<10 ⁻³	Tunis – Ben Arous	Ben Arous	152	33
3	<10 ⁻³	Sbikha (Kairouan)	Sbikha (Kairouan)	42	13
		Nadhour (Zaghouan)			
4	<10 ⁻³	El Jem, Souassi, El hemcha (Sfax)	El Jem (Mahdia)	132	56.7

222

223 Spatio-temporal analysis

224 The space-time permutation model in SaTScan identified six clusters that emerged in
 225 different time periods. Clusters are spread over the Northern and in the Center
 226 Eastern regions, similar to the spatial clusters. Spatio-temporal clusters were non-
 227 overlapping.

228 The largest cluster (42 cases) occurred in 2012 and centered on the delegations of
 229 Jendouba Nord, Ain Draham and Fernana from Jendouba governorate, situated in
 230 the North West of Tunisia. Two other clusters appeared in the North West in 2013
 231 then in 2016, but did not appear in the same governorate. The 2013 cluster (43
 232 cases) included delegations from the governorates of Beja and Bizerte, that are
 233 located to the East of governorate of Jendouba. The 2016 cluster (18 cases) included
 234 Eastern delegations of the governorate of Bizerte (Fig 5).

235

236

237 Fig 5 :Spatio-temporal clusters of dog rabies in Tunisia

238

239 **Discussion**

240 This study is the first to evaluate dog rabies in Tunisia, using spatial, temporal and
241 cluster analysis methods. The results describe epidemiological characteristics of
242 rabies in Tunisia for 2011-2016. Particularly, results demonstrated unequal
243 suspected dogs specimens collection distribution across the country and a
244 statistically significant increase in rabies cases from 2011 to 2014. Rabies is one of
245 the most important health burdens Tunisia faces. Analyzing spatial cluster dynamics
246 over time allowed us to identify areas of high incidence that, compared to
247 surveillance indicators provided valuable information thus to suggest
248 recommendations that might help improve rabies control.

249 Prior to the 2014 rabies peak, a high number of canine rabies was observed in 1992
250 (350 canine rabies cases) explained by a stoppage of mass vaccination between
251 1988 and 1992 [7]. However during the 2014 outbreak season, vaccination had been
252 high and stable, reaching more than 423,000 domestic and semi stray dogs (63%)
253 [16].

254 Spatial clusters were identified in governorates in the North and the Center East of
255 Tunisia.

256 Veterinary units in these governorates have also been sending more suspected dog
257 specimens to the IPT laboratory, accounting for 77.9% of the total suspected dogs
258 cases over the entire study period. Northern and Central-Eastern governorates are
259 the most densely populated as they contain 50% of the total Tunisian human

260 population [10]. Also they are located only a short distance from the laboratory and
261 connected to it by highways.

262 No clusters were identified in the Southern and West Central governorates.
263 Veterinary services from these governorates shipped fewer suspected dogs
264 specimens to the laboratory, which can possibly be explained by two reasons. First,
265 shipping specimens to the only reference laboratory, located in Tunis can sometimes
266 be more complicated for veterinary units that are geographically distant from the IPT
267 laboratory and less connected by roads and highways. The second reason is that
268 Southern governorates are less densely populated [10]. For instance, South West of
269 Tunisia is part of the Sahara desert with both smaller human and dog populations
270 which might explain the lower number of suspected dogs specimens shipped to the
271 laboratory.

272 Large heterogeneity in specimens collection is observed not only between
273 governorates but also at the delegation level. Delegations in the identified clusters,
274 such as Jendouba and Sbikha, have a high suspected dogs specimens collection.
275 Most likely rabies surveillance is intensified in these delegations in response to an
276 increase in the number of laboratory confirmed cases in the delegation itself.
277 Interestingly, a low number of suspected dogs specimens was observed in some
278 delegations located around identified clusters. For instance, only 5 specimens were
279 collected over the study period in Testour (less than 1 specimen per year), which
280 neighbors the Beja cluster. Moreover, less than one specimen per year was collected
281 in nine out of 11 delegations in the governorate of Siliana (neighboring to Beja). If a
282 strong coordination between delegations and governorates is correctly applied, we would
283 have noticed a high number of suspected dogs shipped to the laboratory from delegations
284 neighboring to Beja. Hence, we can suspect that rabies surveillance in delegations
285 neighboring to clusters of high incidence may not have been reinforced in a firm timely

286 manner to stop spread of the disease from one delegation to another. The discrepancy in
287 suspected dog's specimen collection indicates that there might be a heterogeneity in
288 rabies surveillance efforts during the study period, with possible underreporting in
289 some regions.

290 Collecting suspected dogs specimens around cluster confirmed cases is highly
291 recommended and this would require a better coordination between surveillance
292 units from governorates where clusters occurred and including bordering delegations.

293 A robust and active surveillance system should prioritize data collection, recognizing
294 the need for cooperation between government and veterinary units [18]. This
295 recommendation includes others suggested to the NRCP in previous studies, such as
296 better coordination between ministries, to raise public awareness and to increase
297 vaccination coverage [7].

298 Spatial patterns after 2012 show a clear shift when North-Eastern governorates that
299 where rabies-free in 2011(such as Bizerte) became endemic (Fig 2). Although all
300 spatio-temporal clusters identified were located in the North and the Center East,
301 locations of rabies cases have shifted significantly from one year to another (Fig 5).
302 Thus, spatial clusters of rabies cases in dogs are not fixed through time and one
303 might expect a shift in cluster locations in the future. Disease spread could be
304 explained by a potential rabies resurgence in certain governorates or a viral
305 transmission from neighboring governorates. According to previous studies, rabies
306 virus can spread long distances, from 30 to 50 km/year in North African, in countries
307 such as Algeria and Morocco [19].

308

309

310 Canine rabies virus isolates in Tunisia are divided into two geographically
311 independent phylogenetic variants; one situated in the North West and one in the
312 North East, Center and South[2]. Thus, non-overlapping clusters could be either
313 independent phylogenetic variants or a change in spatial patterns of previously
314 identified phylogenetic variants. Ideally, a phylogeographical study of 2011-2016
315 canine rabies isolates, specifically in the North and Center East, could confirm this
316 hypothesis. This hypothesis is consistent with results from previous studies where
317 different spatio-temporal patterns were explained by different phylogenetic rabies
318 virus variants or strains [20,21].

319 The main limitation in this study was the inability to access the actual dog population
320 size in Tunisia, which is an important parameter in the spatial methods presented in
321 this study. Dog population size was estimated by number of dogs vaccinated by
322 veterinary services, which is based on a model taking into account the human
323 population size and the categorization of territory which are: rural, urban and semi-
324 urban [22-24]. Territory categorization may have shifted over time and an updated
325 model taking into consideration shifts in categories could improve accuracy of the
326 results. Another limitation could be the geographic location of each rabies case.
327 Using exact geographic coordinates for each confirmed case could improve results.

328

329

330 **Conclusion**

331 In summary, an increase in canine rabies incidence occurred starting in 2012 with a
332 large number of cases distributed in the North and the Center East of the country.
333 Spatial clusters of high incidence have been identified in specific delegations of the
334 north and the center east. Nevertheless, if rabies surveillance was evenly conducted

335 in the territory, even more clusters of incidence perhaps could have showed up. This
336 way, heterogeneity in surveillance efforts has been highlighted and may be caused
337 by distance to the rabies IPT laboratory or to other factors, such as a lack of
338 coordination between surveillance units. This irregular disparity in rabies surveillance
339 could be an additional factor of the spread of the disease from one governorate to
340 another. Overall, we recommend increasing vigilance in the governorates of the
341 Center West and in the South and most importantly to standardize surveillance and
342 testing protocols and more efficient coordination between surveillance units, by
343 improving information systems and real time notifications. The potential to control
344 rabies spread relies not only on the vaccination coverage, but also on the quality of
345 surveillance.

346

347

348

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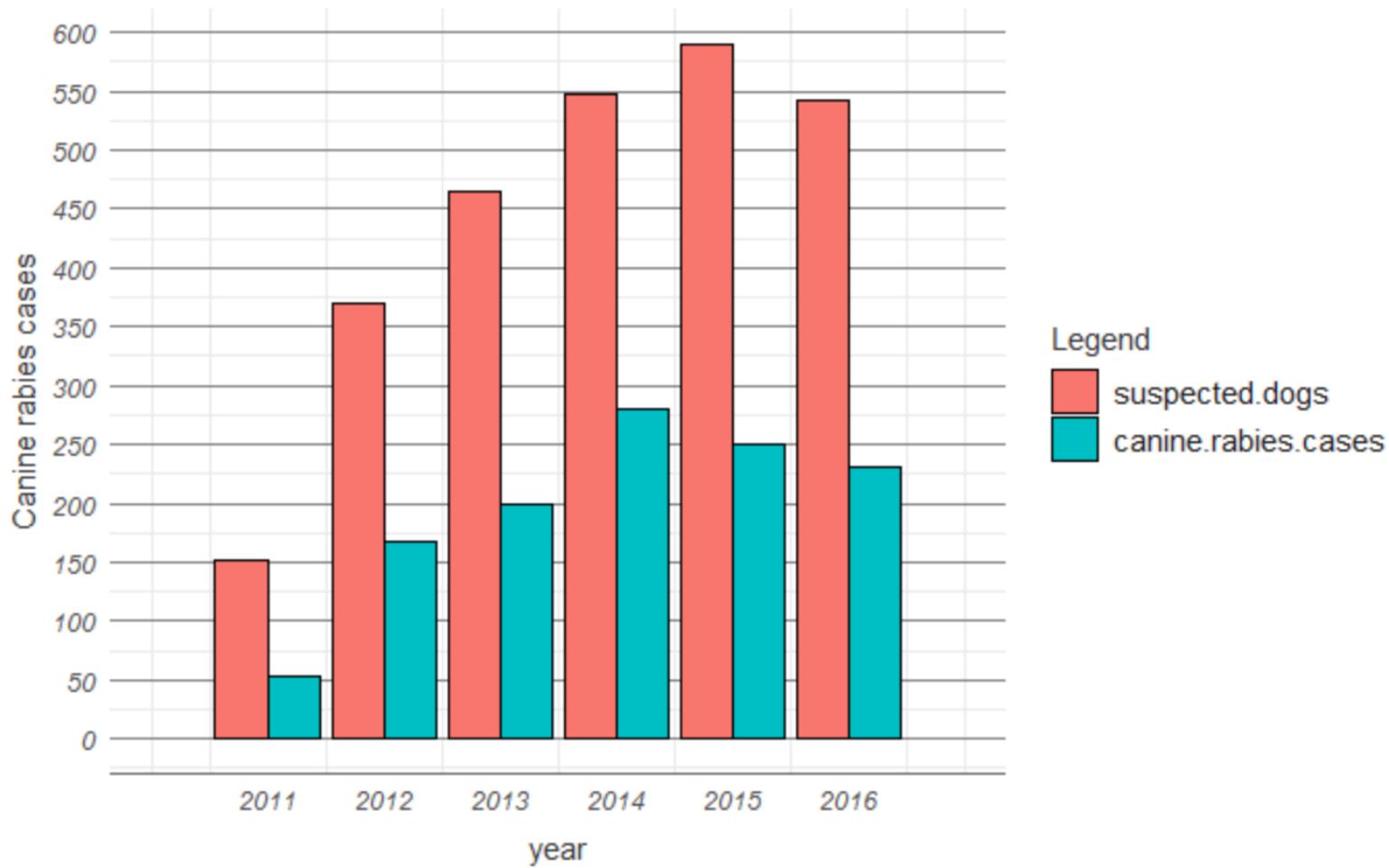
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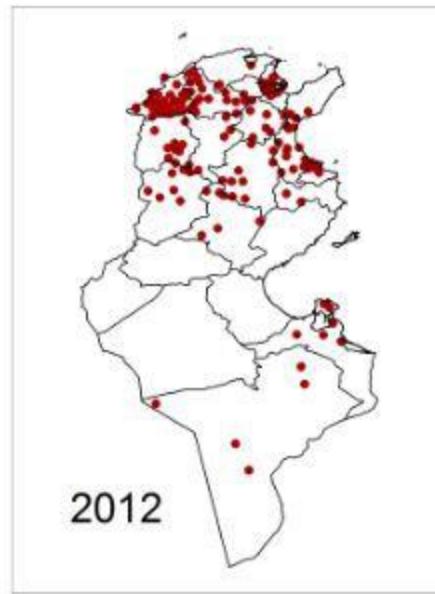
Canine rabies cases in Tunisia, 2011 - 2016



Evolution of canine Rabies cases 2011 - 2016



2011



2012



2013



2014

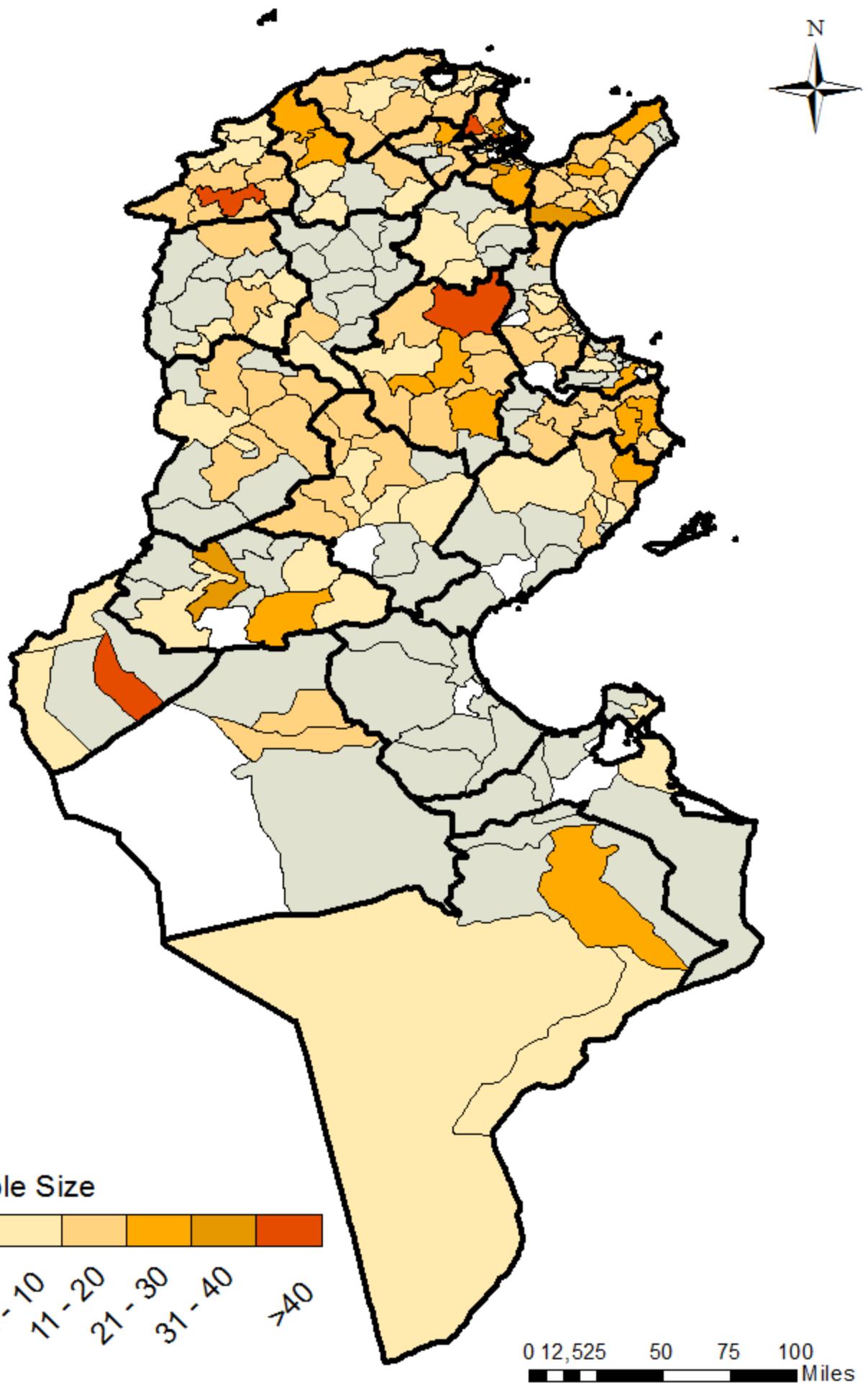


2015

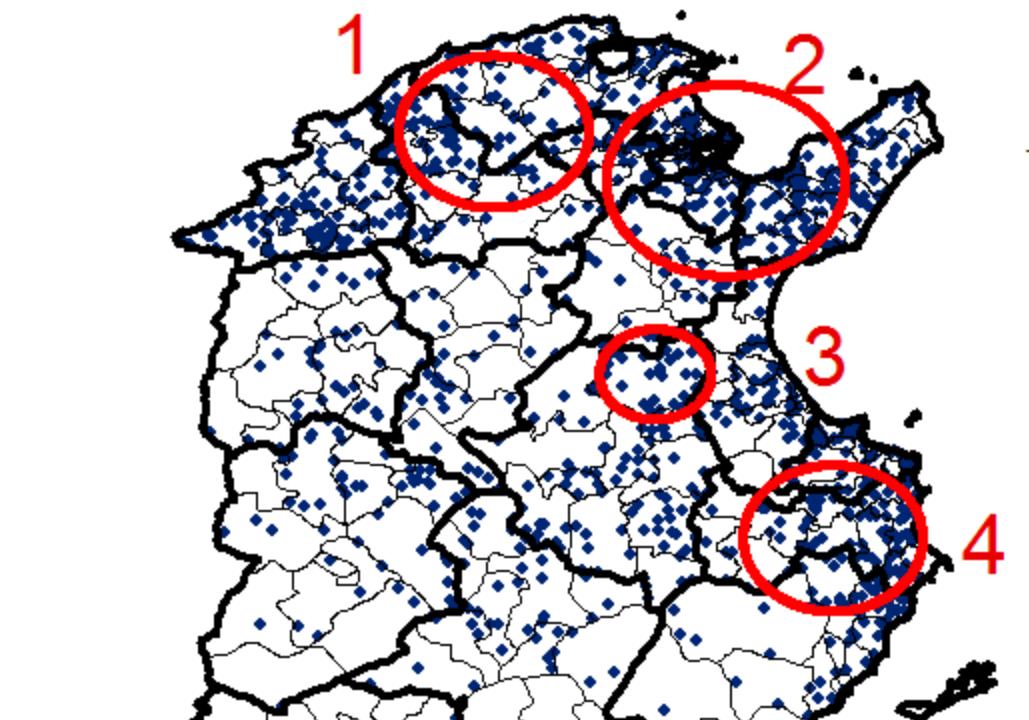


2016

Spatial representation of sample size per delegation



Canine rabies spatial clusters, 2011-2016



Legend

spatial clusters

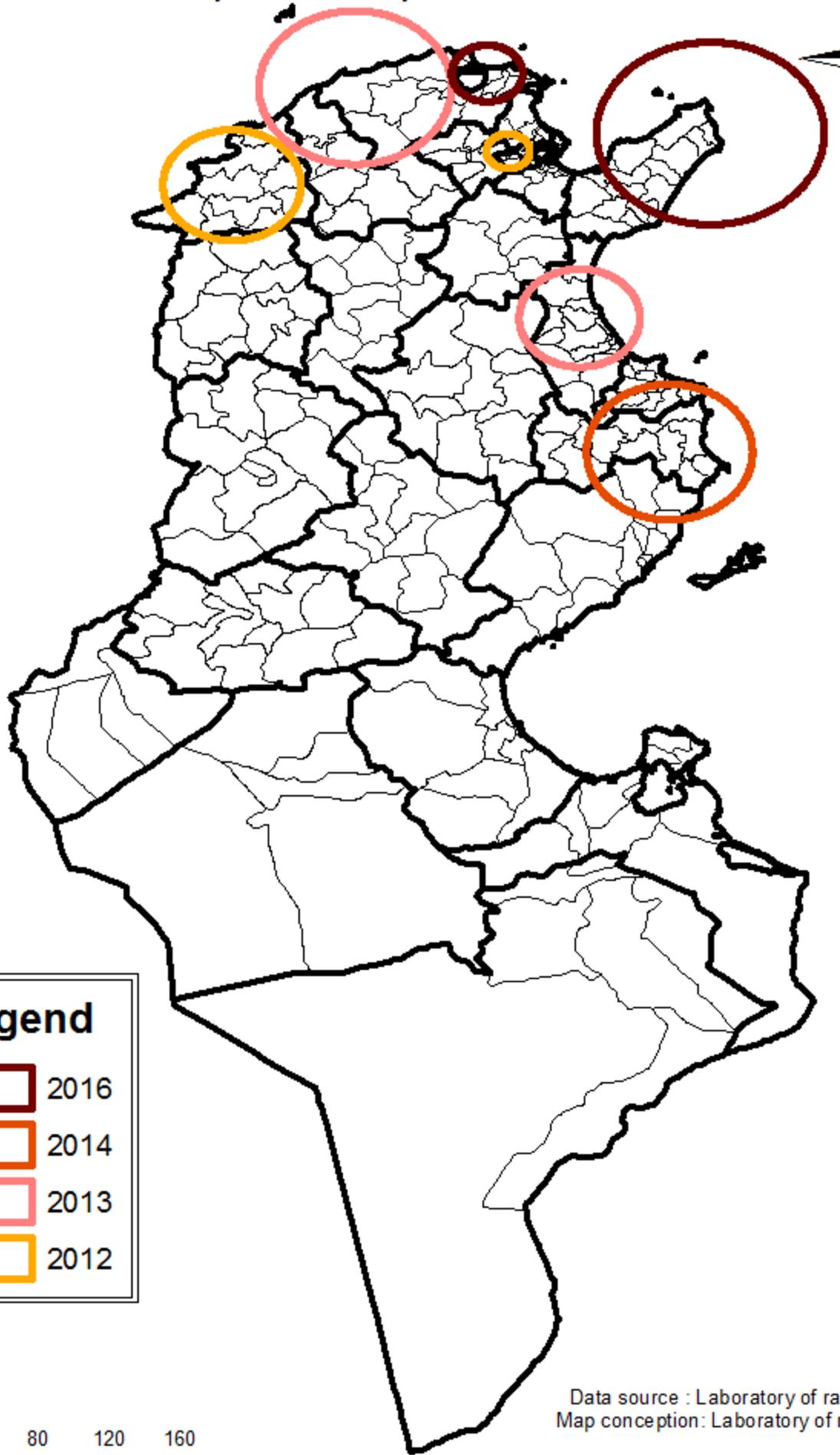
• rabies cases

0 15 30 60 90 120 Miles

Data Source : Laboratory of rabies, IPT

Spatio-temporal clusters

N



Legend

- 2016
- 2014
- 2013
- 2012

0 20 40 80 120 160 Kilometers

Data source : Laboratory of rabies, IPT
Map conception: Laboratory of rabies, IPT