A Case-Control Study of Risk Factors for Dog Rabies in Northeast Tunisia

Sana Kalthoum *, Raja Gharbi, Mehdi Ben Ali, Imed Ben Sliman, Nouha Haboubi, Khaoula Barrak, Khalil Fakhfekh, Rafika Ben Romdhane, Habiba El Hechri, Salma Boughanemi, Chedia Seghaier, Chokri Bahloul

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Article

A Case-Control Study of Risk Factors for Dog Rabies in Northeast Tunisia

Sana Kalthoum [1,*], Raja Gharbi [1], Mehdi Ben Ali [1], Imed Ben Sliman [1], Nouha Haboubi [2], Khaoula Barrak [2], Khalil Fakhfekh [3], Rafika Ben Romdhane [4], Habiba El Hechri [6], Salma Boughanemi [7], Chedia Seghaier [1] and Chokri Bahloul [5]

[1] National Center of Zoosanitary Vigilance, Tunisia;
[2] Regional veterinary services – governorate of Bizerte
[3] Regional veterinary services – governorate of Mannouba
[4] Regional veterinary services – governorate of Tunis
[5] Pasteur Institute of Tunis
[6] Regional veterinary services – governorate of Ariana
[7] Regional veterinary services – governorate of Ben Arous
* Correspondence: kalthoum802008@yahoo.fr

Abstract: Since 2012, the northeast of Tunisia has been experiencing an emergence of dog rabies. Published data revealed that the disease is widespread in the north of Tunisia. Even with studies on rabies, lacking knowledge on the associated risk factors was highlighted. Therefore, we conducted a case-control study on dog rabies in northeast Tunisia to identify potential risk factors for dog rabies occurrence. The cases group (n = 77) included positive dog rabies confirmed at the referral laboratory using Fluorescent Antibody Test (FAT) in 2014 and 2018. The controls group (n = 77) involved all negative cases received at the laboratory and 15-days quarantine dogs that received a certificate of absence of rabies after the observation period. Univariate and multivariate logistic regression was conducted to explore the risk factors (age, sex, breed, confinement, vaccination status, presence of bites, owned or not and origin of dogs, sector, presence of rabies cases, and slaughterhouses, etc.…) related to the occurrence of rabies. The final logistic regression model revealed that unconfined dogs were almost twice as likely to be affected as confined dogs (OR = 1.9; 95% CI: 1.17 to 3.27). The odds of rabies occurrence were 25 times higher in areas where rabies cases have been reported between 3 months and 1 year compared to the uninfected areas (25.7; 95% CI: 3.02-219.14). Similarly, the risk of rabies is significantly higher in dogs born in the home to the owner bitch (OR = 2.41; 95% CI: 1.14-5.13). Living in areas with rabies cases in the last three months increases by 2.8 times the risk of getting rabies (2.8; 95% CI: 1.16-6.77). However, vaccination reduces by 1.6 times the risk of contracting rabies (0.6; 95% CI: 0.38-0.97). Our findings provide reliable data on dog rabies that will be very useful for decision-makers and could contribute to improving the ongoing national control program of rabies.

Keywords: Rabies; dogs; Tunisia; risk factors; odds ratio; case-control study

Introduction

Rabies is a widespread disease in animals and humans. Dogs are the main vector and reservoir of the disease (1, 2, Jackson, A.C 2014, Kgaladi, J. 2013). In Africa and Asia, dogs are responsible for more than 99% of human cases (3, 4, Moges, N., 2015, Taylor, L.H 2015). World Health Organization (WHO) reported that About 59,000 people die annually due to rabies and patients under the age of 15 years are the most affected (5, N.d rabies 2020). In Africa, rabies is endemic and human deaths were estimated at 21,000-25,000. About 49 of the 54 African countries were qualified as moderate- to high-risk categories for human rabies (6, Broban A, 2018). It is a preventable disease and a multi-year mass vaccination with a high-quality vaccine can reduce the risk of human rabies (7, Jayasundara, V.K., 2016). In Tunisia, rabies is enzootic and the dog is the most important dynamic vector and reservoir. The history of rabies in Tunisia indicates that at the end of the 19th century, the disease starts its ascending phase with a lag of half a century in comparison with Europe. The first cases, which

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occurred in 1870 in the capital (Tunis), were associated with the entry of European migrants and other factors such as socio-cultural or ecological changes (8, Kmar Ben Néfissa). National Rabies Control Program (N.L.R.P.), started in 1982 under the guidance of the World Health Organization, was essentially based on awareness campaigns, parenteral vaccination of all accessible dogs, and management of "stray" dogs (9, programme national de lutte antirabique). However, the disease is still enzootic and high incidence was observed particularly since 2011 when rabies cases in animals doubled (10, Centre national de veille zoosanitaire bulletin 14). It is spread over the entire country but the northern governorates seem to be the most affected. It is shown that several factors have potentially contributed to the increase of rabies cases, such as the mishandling of waste which led to an increase in the stray dog population (11, Alescendro, R., M. J, B. R, and Z. M, 2017). In Tunisia, the current data and knowledge of the epidemiology of rabies are limited to the descriptive. Previous studies highlighted the structure and the dynamic of the dog population in Tunisia. The renewal rate ranged between 30-40% and dog densities varied distinctly between rural and urban/suburban zones. In rural zones, dog population density differed between 7 and 30 dogs per km2. In urban and suburban zones, it oscillated between 700 and 1,000 dogs per km2 (12, Wandeler AI, Matter HC, 1993). A phylogenetic study conducted between 1992 and 2003, revealed the existence of two variants of rabies virus circulating within the country. The first lineage showed nucleic affiliation with isolates from Algeria and Morocco. The second shared a strong relationship with Ethiopian and Sudanese strains (13, Amouri IK, Kharmachi H). Despite these relevant studies, rabies is still enzootic and the recent occurrence of rabies was highlighted in unusual regions in Tunisia (14, Bouslama, Z., J. Belkhiria, F. 2019). In fact, in 2012, the disease has strongly affected the northwest governorates (Governorates of Beja and Jendouba) and has progressed to the northeast governorates. A high number of outbreaks was recorded in the region of Tunis and the governorate of Bizerte for the two following years (15, Centre national de veille zoosanitaire bulletin 13, 16, Lutte contre la rage). The emergence of rabies in unusual zones in Tunisia in the last ten years raised a fundamental need to understand the disease by exploring the associated risk factors. Reliable data on the risk factors associated with dog rabies represents a fundamental key to the success of the control of the disease and can relatively explain the failure of rabies control measures in Tunisia. To eradicate rabies in humans and animals, the implemented measures of control should be updated and adjusted to the epidemiological context of the disease.

This work is the first case-control study in Tunisia on dog rabies. The main objective of this study is to clarify and identify the potential risk factors associated with dog rabies in northern Tunisia to update the strategy and the control measures for rabies.

Materials and methods

Study area and study population

The study was conducted in the northeast of Tunisia that included five governorates with an area of 3.750 km2 (2.25% of the total area of the country) and a population estimated at 568 219 inhabitants (17, INS, n.d.: RESULTATS). The dog population in these governorates was estimated at 48500 dogs (16, Lutte contre la rage) (Figure 1). These governorates were selected based on the high number of outbreaks of rabies during the period of the study. Indeed, this region has experienced a surge of rabies cases after 2012, and notifications of confirmed cases increased from 2012. The incidence of reported cases of dogs was the highest in the country (17, Kalthoum et al. 2021).

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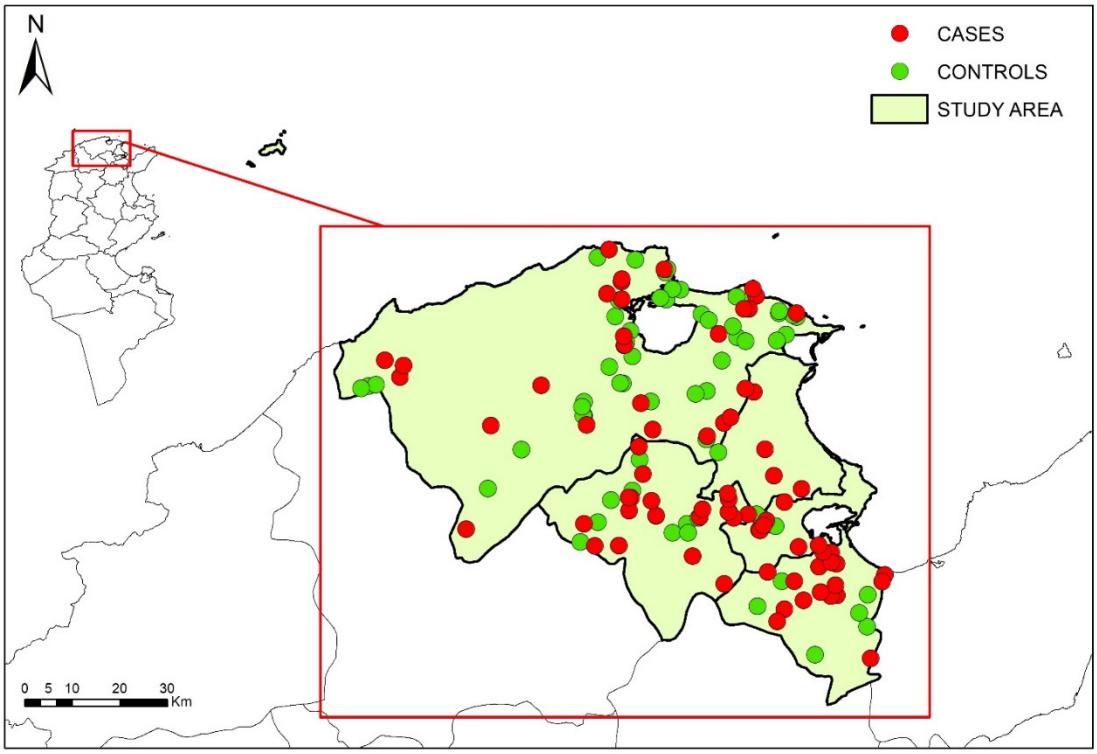

Figure 1. Map of the study area showing the geographical distribution of cases (red) and controls (green).

Study design

We conducted a case-control study in the northeast of Tunisia (Governorate of Bizerte, Tunis, Mannouba, Ben Arous, and Ariana) between 2012 and 2018 to investigate potential risk factors for dog rabies in Tunisia. The sample size was calculated using Openepi (http://www.openepi.com/SampleSize/SSCC.htm) and estimated as 154 dogs (77 control and 77 cases) with confidence level = 0.95, power = 80%, assumed odds ratio = 2.5, and expected proportion in controls = 40. The case group was recruited among the positive cases confirmed by the Fluorescent Antibody Test (FAT) in the laboratory of "Institut Pasteur de Tunis" (IPT) (Referral laboratory for the diagnosis of rabies in Tunisia) for three years (2013-2015) in the study area.

The Control group includes two categories; the first category represented negative dogs confirmed at the laboratory, which were random, selected from the recorded data of veterinary services. The second category involves suspected dogs that were observed by official veterinarians for 15 days and having a certificate of absence of rabies after three visits. Control groups were randomly selected within a 10 km radius of the cases. Control and case groups were selected taking into consideration the time of suspicion (suspected or confirmed in the same period (lag of two months)).

Data collection and risk factors

This study was carried out from 2014 to 2018. Rabies surveillance data on positive cases were retrieved from the regional veterinary services database. For each positive case confirmed at the laboratory, regional veterinary services investigated the outbreak and collect data on the rabid dog using a standard questionnaire approved by the national veterinary services. For the control group, an epidemiological investigation of all negative dogs was conducted. The same questionnaire was used for control, it included demographic and risk factors related to two groups (cases and control). The following information was gathered for both case and control: age, sex, breed, geographical localization (imada), date of suspicion, date of diagnosis, owned or free-roaming, vaccination status,

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presence of old bite, and confinement (confined, free-roaming or stray dogs). Classification of the imadas (geographical location of control and cases) into three types: urban, suburban, and rural, was provided by the regional veterinary services. To explore the impact of the municipal infrastructures, geographical positions of all red meat slaughterhouses, white meat slaughterhouses, and weekly markets were collected.

Data analysis

Data was curated validated and entered into a Microsoft Excel spreadsheet. Frequencies and proportions were calculated for the quantitative and the qualitative variables, respectively. Descriptive statistics were performed to characterize the case and control group. The variable age was studied as a categorical variable with three categories (> 3 years old, 1 - 3 years old, and < 1-year-old). Association with potential risk factors (age, vaccination status, confinement, origin, and sex) was tested in a univariable logistic regression model using the disease status (case/control) as the outcome variable. Significant risk factors with a p-value < 0.2 in the univariable model were retained for inclusion in a multivariable model. Collinearity between the explanatory variables retained after univariable analysis was then performed using the variance inflation factor (VIF) to remove variables that are correlated with each other. Results in the model were expressed as odds ratios (ORs) and 95% confidence intervals (CIs). P values < 0.05 were considered significant at the 95% confidence level .The goodness of fit of the model was tested using Hosmer–Lemeshow $\chi 2$ test (30). The area under the curve (AUC) was calculated to evaluate the predictive ability of the model. Statistical analyses were conducted using R software version 3.5.2 (https://www.r-project.org). The map was generated using ArcGIS version 10.4.

Results

Sociodemographic characteristics of cases and controls are summarized in Table 1. According to the age group classification, we found, that the age group (1-3 years old) predominates among cases and control with 45% of the total investigated dogs. Of the 154 dogs, 71% were males and 29% were females. The majority of cases and controls (83%) were owned dogs, unconfined (roam day and night) (68%). As shown in table 1, 36% of dogs were born in the household from own bitch or purchased while 64% were bought or adopted. Distribution by habitat shows that about a half of cases and control tended to come from urban areas and 29.2% and 29.9% were from rural and semi-urban areas, respectively. According to the rabies vaccination status, only 21% of the dogs were vaccinated against rabies, whereas 60% were not vaccinated and 20% had unknown status (Table 1).

Table 1. Sociodemographic characteristics of the case and control groups in northeast Tunisia.

Variable	Category	Frequency	Percentage (%)
Age group	> 3 years old	40	26%
	1 - 3 years old	69	45%
	< 1 year old	45	29%
Confinement	Confined	27	18%
	Unconfined (free all day)	105	68%
	Confined only the day or night	22	14%
Owned dog	No	27	18%
	Yes	127	83%
Vaccination status	Unknown	30	20%
	Not vaccinated	92	60%
	vaccinated	32	21%
Origin	Bought or adopted	98	64%
	From own bitch	56	36%

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Sex	Female	44	29%
	Male	110	71%
Sector	Rural	45	29.2%
	Semi-urban	46	29.9%
	Urban	63	49.9%

Univariate analysis of rabies risk factors indicated that vaccination status (p = 0.0002), confinement (p = 0.004), and the origin of the dog (p = 0.007) were potentially associated with rabies occurrence (Table 2). Similarly, the presence of rabies cases in the area in the last three months (p = 0.01) or over three months to one year (p = 0.001) showed a significant association with the disease. However, the other factors (age, sex, presence of bites, presence of a slaughterhouse or a poultry sales point, and sector type) were not significant. The final logistic regression model revealed that the risk of getting rabies is about 2 times higher for unconfined dogs that are that were allowed to roam all day (OR = 1.9; 95% CI: 1.17 to 3.27) compared to confined dogs. Dogs that are born in the home from own bitch are almost 2.5 times more likely to get rabies than dogs that are bought or adopted (OR = 2.41; 95% CI: 1.14-5.13). Living in areas with rabies cases in the last three months increases by 2.8 times the risk of getting rabies (2.8; 95% CI: 1.16-6.77). Similarly, dogs that live in areas where rabies cases have been reported between 3 months and 1 year are 25 times more likely to develop rabies (25.7; 95% CI: 3.02-219.14). However, vaccination was found to be a protective factor and it reduces the risk of contracting rabies by 1.6 times (0.6; 95% CI: 0.38-0.97) (Table 3). The Hosmer-Lemeshow goodness of fit test showed that the model fit the data well indicating that the number of predicted cases was not significantly different from the number of observed cases (X2 = 1.960, df. 8, p = 0. 659). VIF of the variables included in the model was about one. The model had a good predictive ability (ROC = 0.76).

Table 2. Univariate logistic regression analysis of potential risk factors of rabies northeast Tunisia.

Variable	Category	Témoins N (%)	Cas N (%)	p-value
Age group	> 3 years old	20 (26%)	20 (26%)	0.847
	1 - 3 years old	36 (46.8%)	33 (42.9%)	
	< 1 year old	21 (27.3%)	24 (31.2%)	
Sex	Female	19 (24.7%)	25 (32.5%)	0.286
	Male	58 (75.3%)	52 (67.5%)	
Origin	Bought or adopted	57 (74%)	41 (53.2%)	0.007
	From own bitch	20 (26%)	36 (46.8%)	
Vaccination status	Unknown	15 (19.5%)	15 (19.5%)	0.0002
	Not vaccinated	36 (46.8%)	56 (72.7%)	
	vaccinated	26 (33.8%)	6 (7.8%)	
Confinement	Confined	18 (23.4%)	9 (11.7%)	0.0041
	Unconfined (free all day)	43 (55.8%)	62 (80.5%)	
	Confined only the day or night	16 (20.8%)	6 (7.8%)	
Presence of bites	Unknown	27 (35.3%)	24 (31.6%)	0.246
	No	39 (51.3%)	34 (44.7%)	
	Yes	10 (13.2%)	18 (23.7%)	
Presence of rabies cases in the last three months	Yes	66 (85.7%)	53 (68.8%)	0.01
	No	11 (14.3%)	24 (31.2%)	
Presence of rabies cases between 3 months and one year	Yes	76 (98.7%)	65 (84.4%)	0.001
	No	1 (1.3%)	12 (15.6%)	
	No	49 (63.6%)	52 (67.5%)	0.610

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Presence of a slaughterhouse/ a poultry sales point	Yes	28 (36.3%)	25 (32.5%)	
	Yes	8 (10.4%)	15 (19.5%)	
Sector	Rural	22 (28.6%)	23 (29.9%)	0.681
	Semi-urban	21 (27.3%)	25 (32.5%)	
	Urbain	34 (44.2%)	29 (37.7%)	

Table 3. Final multivariable logistic regression model of risk factors associated with dog rabies in the northeast of Tunisia.

Variable	Odds ratio	95% CI	P-value
Vaccination status	0.614	0.389 - 0.971	0.03
Origin	2.418	1.140 - 5.130	0.02
Confinement	1.959	1.171 - 3.275	0.01
Presence of rabies cases in the last three months	2.810	1.165 - 6.777	0.02
Presence of rabies cases between 3 months and one year	25.764	3.029 - 219.144	0.002

Discussion

Rabies is endemic in Tunisia and efforts deployed to control the disease were not sufficient in eradicating rabies. On the contrary, resurgences of rabies have been observed in recent years and the disease remained confined to the north of the country (Kalthoum S. et al. 2021, Bouslema Z. et al. 2020). Historically, rabies has been circulating for a long time in northeast Tunisia which was considered an endemic area. Despite the control program and the establishment of sterilization and vaccination centers that act to reduce the risk of rabies occurrence. The northeast was chosen for the study because of the observed high incidence of dog rabies in this region and one of the objectives was to identify factors that caused the upsurge of the disease to understand the particularities of dog rabies in this region. The results of the present study provide a significant basis of information to adapt and adjust the control program for rabies. In Tunisia, there is poor knowledge about dog rabies risk factors, and to our knowledge; this study represents the first detailed research to focus on potential risk factors that are associated with the occurrence of dog rabies in Tunisia.

In this study, risk factors for rabies occurrence were age groups, sex, origin, presence of bites, vaccination status, confinement, presence of rabies cases (lag of three and nine months), presence of slaughterhouses, and type of sector (urban, suburban and rural). The univariate analysis showed that among the ten studied risk factors only five were significantly associated with the occurrence of dog rabies. No association was found between rabies and age groups and sex. Our findings suggest that dog rabies is prevalent in all age groups which is in line with previous studies in nearby countries (Khayli M et al. 2019, Yahiaoui, F.Z et al. 2018) and elsewhere in the world (Douangngeun B et al. 2017). Similarly, dog rabies was not gender specific (Ma, X et al. 2020, Medley AM et al. 2017). Additionally, our investigation showed that the type of area (rural, urban, and semi-urban) was not associated with the disease. This was an unexpected finding and disagree with studies from other countries (Noman Z. et al.2021, Gebru G et al. 2019, Knobel D.L et al. 2005), suggesting that rural areas were more exposed to the dog rabies occurrence than the urban areas. In the final logistic regression model, we found that the presence of rabies cases is a good predictor of rabies occurrence; this was not surprising since the incubation period can exceed 6 months (Consales CA et al. 2007). This result underlines the importance of outbreak management in reducing the risk of rabies occurrence (Laager M. et al 2018) and highlights the role of ring vaccination in its prevention.

We demonstrated that unconfined dogs that are that were allowed to roam all day are at a higher risk of getting rabies compared to confined dogs. The role of stray dogs in the transmission of rabies has been largely discussed and roaming behavior was found to be related to the disease propagation (Bombara CB et al. 2017, Dürr S. et al. 2014). It was demonstrated that a free-roaming dog had a

chance to be in interaction with 27 free-roaming dogs (Kazadi Kawaya E. et al. 2020). Our result confirms earlier findings by several authors that revealed that a high proportion of the owned dogs were free-roaming (Savadogo, M et al. 2021, Hergert, M. et al. 2018, Van Sittert SJ et al. 2009, Ratsitorahina M. et al.2007).

Dogs that are born in the home from own bitch were more exposed to rabies than dogs that are bought or adopted. This result may be indirectly related to the vaccination status of dogs. Previous studies showed that dogs born from owner's bitch have twice the risk of non-vaccination than dogs that would have been purchased (Flores-Ibarra M. et al. 2004, Hergert M. et al. 2016). Another explanation might be that dog owners' behaviors played a significant role in the vaccination status of their dogs. In a study conducted in KwaZulu-Natal, South Africa, more than 30% of owners think their dog is still too young to be vaccinated (Hergert M. et al. 2016). It was also reported that rabid bitches can transmit rabies to their puppies during pregnancy (Kolster KA 2022).

In this case-control study, we showed that vaccination in dogs decreased the odds of rabies occurrence compared with unvaccinated dogs. Similar findings reported that the risk to get rabies is 1.7 times higher in unvaccinated dogs than in vaccinated dogs (Thiptara, A. et al. 2011). Non-vaccination of dogs was found to be a risk factor for rabies occurrence (Chikanya E. et al. 2021, Costa LJCd et al. 2016, Davlin SL et al. 2014, Costa GB et al 2018). Indeed, the World Health Organization recommends a vaccination coverage of 70% to control dog rabies and a previous modeling essay on rabies revealed that with this vaccination coverage, rabies can be controlled and 90% of human rabies cases can be prevented (Hergert M. et al. 2016).

Finally, the risk factors investigated in our study were almost individual. The main limitations of this study were the unavailability of updated data on the dog population size and human density and the non-inclusion of environmental risk factors (accessibility, presence of garbage, presence of natural barriers (rivers and mountains) that have a very important role in propagating or stopping the spread of the disease (Tian H. et al. 2018). To properly identify potential risk factors for dog rabies, further investigation is needed and should include environmental factors. Similarly, increasing the number of cases and controls could lead to a better measure of the association between the disease and the risk factors.

Conclusion

The dog remains the main source of rabies transmission for humans and other species in Tunisia and adapting and adjusting its control strategy is a priority. Our study investigates the potential risk factors of dog rabies occurrence and shows that dog management (confinement, origin of dogs) and history of rabies (lags of three and nine months) were strongly associated with the disease. Vaccination reduces the risk to get rabies. Our study provides baseline information on rabies risk factors and further studies including environmental risk factors of rabies are recommended to improve surveillance and control of rabies in Tunisia.

Authors' Contributions: Sana kalthoum: Conceptualization; Formal analysis; Methodology; Software; Writing-original draft; Writing-review & editing. **Raja Gharbi:** Methodology and investigation. **Mehdi Ben Ali:** Methodology. **Imed Ben Sliman:** Methodology. **Nouha Haboubi :** investigation. **Khaoula Barrak :** investigation. **Khalil Fakhfekh :** investigation. **Rafika Ben Romdhane :** investigation. **Habiba El Hechri :** investigation. **Salma Boughanemi :** investigation. **Chedia Seghaier:** Validation; Writing-review & editing. Chokri Bahloul: Validation; Writing-review & editing.

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Ethics Statement: This was a national surveillance activity approved by the national and regional veterinary services. Approval by an Ethics Committee was not required. Data on animal owners were not used in the analysis.

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