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Clinical and epidemiological comparison of *Rickettsia parkeri* rickettsiosis, related to *Amblyomma triste* and *Amblyomma tigrinum,* in Argentina

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ABSTRACT

The aim of this work was to compare the epidemiological and clinical characteristics of *Rickettsia parkeri* rickettsiosis related to *Amblyomma triste* and *Amblyomma tigrinum* ecological regions in Argentina. We reviewed cases of *R. parkeri* rickettsiosis from 2007 to 2017 evaluated at Muñiz Hospital, directly or through referral. Univariate analysis was used to examine the association between different variables and the disease related by each vector species. The eighteen cases of *R. parkeri* rickettsiosis included had fever, inoculation eschar and all except one had rash. Regional differences in epidemiological variables were identified, depending on the vector. There was a significantly increased risk of exposure to *A. tigrinum* in peri-domestic areas (odd ratio 12, p = 0.02), whereas an increased risk of exposure to *A. triste* was evident in wildlife areas (odd ratio 12, p = 0.02). Seasonality of *R. parkeri* rickettsiosis differed based on its vector. Cases associated with *A. triste* occurred predominantly during spring and summer, whereas those associated with *A. tigrinum* occurred during fall, winter, and springtime. Exanthema was maculopapular (13/18), maculo-vesicular (3/18) or petechial (1/18). No clinical differences were identified depending on the vector.

1. Introduction

Tick-borne rickettsioses are regional diseases with geographical dispersion in synchrony with the seasonal activity of the tick species that act as vectors. The clustered occurrence in space and time of these diseases can be modulated by different biotic and abiotic factors that influence tick habits, as well as vertebrate hosts, and by human activities that determine the exposure risk (Parola et al., 2013). *Rickettsia parkeri* rickettsiosis, a tick-borne spotted fever similar to, but less severe than Rocky Mountain spotted fever (Paddock et al., 2008b), exists throughout much of the Americas. Confirmed cases have been identified in the US, Brazil, Uruguay and Argentina (Paddock et al., 2004; Romer et al., 2011; Faccini-Martinez et al., 2018; Silva et al., 2011), although *R. parkeri*-infected ticks occur in many other countries (Mexico [Sanchez-Montes et al., 2018], Bolivia [Tomassone et al., 2010], Belize [Polsomboom et al., 2017]) which may suggest a much broader distribution of human cases. In Argentina, *R. parkeri* is transmitted by two species of ticks: *Amblyomma triste* (Nava et al., 2008; Romer et al., 2011) and *Amblyomma tigrinum* (Romer et al., 2014), both belonging to the "*Amblyomma maculatum* complex", which also includes the main vector of *R. parkeri* in North America, *Amblyomma maculatum* (Paddock et al., 2004). While *A. triste* inhabits areas close to the Paraná basin and its related tributaries and wetlands (Buenos Aires, Corrientes, Entre Ríos, Santa Fe, and Formosa Provinces), *A. tigrinum* shows a more plastic distribution, extending through different ecoregions with contrasting ecological conditions (Guglielmone et al., 2013; Nava et al., 2017) and hence is present in all phytogeographical domains in continental Argentina. This situation allows us to compare and contrast the epidemiological and clinical characteristics of *R. parkeri* rickettsiosis associated with each vector species. It is important to mention that *R.*

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parkeri strain Atlantic rainforest was identified recently in *Amblyomma ovale* ticks from Misiones province (Lamattina, et al., 2018). The significance of this finding in the scenario of human rickettsiosis in Argentina is still unknown.

2. Methods

All cases of *R. parkeri* rickettsiosis evaluated at Muñiz Hospital, either directly or through referral, were reviewed from 2007 to 2017, including some previously published cases (Romer et al., 2014, 2011; Seijo et al., 2007; Armitano et al., 2019; Borrás et al., 2017; Troglio et al., 2017; Villalba et al., 2018; Borras et al., 2018). This hospital is the main infectious diseases reference center in the country, and is located in Buenos Aires City. A suspected case was defined by the presence of fever and inoculation eschar, with or without exanthema (Angeletti et al., 2016). Laboratory confirmation was based on the detection of DNA of *R. parkeri* by conventional PCR in an eschar biopsy specimen, as described (Romer et al., 2011, 2014); otherwise, seroconversion to IgG antibodies reactive to antigens of *R. parkeri* detected by microimmunofluorescence at cut off ≥64 was considered evidence of infection with a spotted fever group (SFG) *Rickettsia* species (Romer et al., 2011). A clinically suspected case with identification of *R. parkeri* DNA from eschar biopsy specimen was considered a confirmed case. Those suspected cases with seroconversion for SFG *Rickettsia* species were classified as probable.

Different epidemiological and demographic variables were collected, including: age and sex; geographic location of the tick bite (region/province); setting during which the bite occurred (domicile and peri-domestic versus wildlife area); owning dogs; use of repellent or other personal protection measures intended to avoid tick bites; and month of occurrence of the tick bite. Clinical and diagnostic variables included: time between the moment of the tick bite and onset of fever; signs and symptoms and their relative frequencies (fever, exanthema, myalgia, headache, diarrhea, nausea, vomiting, eschar [number and anatomical distribution], adenopathy, cough, dyspnea, neurological symptoms, and hemorrhagic manifestations); results of hematological and biochemical analyses; presence of comorbidities; specific results of PCR and/or serology; and clinical outcome.

Statistical analysis: Univariate analysis was used to examine the association between each variable and the disease in both ecological regions related to *A. triste* or *A. tigrinum*. Demographic, epidemiological and clinical features were compared between the two groups of patients using Chi-squared and Fisher's exact tests. Statistical analysis was performed using SPSS software, version 22, with two-sided $p < 0.05$ considered statistically significant.

3. Results

From 2007 to 2017, 18 patients complied with the confirmed or probable definition of *R. parkeri* rickettsiosis. All of them had fever and eschar, which appeared within 1–10 days after the tick bite. Of these, 14 (78 %) were confirmed through a positive PCR on eschar biopsy specimens, and four (22 %) were classified as probable based on seroconversion of antibodies reactive with SFG *Rickettsia* species, reaching titers of up to 128, and 512 on the convalescent samples.

Table 1 summarized epidemiological, demographic and clinical features. Ten patients were women and eight were men. The average age was 49 years (SD 13, median 51.5), without significant differences between genders. Ten were exposed to tick bites in the geographical distribution area of *A. tigrinum* (Buenos Aires, Córdoba, San Luis, La Pampa, and San Juan Provinces) and eight in the distribution area of *A. triste* (Buenos Aires and Entre Ríos Provinces) (Fig. 1). Two of eight (25 %) and eight of 10 (80 %) cases were women in the distribution areas of *A. triste* and *A. tigrinum*, respectively. The age range was between 27 and 73 in the area of distribution of *A. tigrinum* (mean 49, DS 16, median 56), and between 38 and 68 in the area of distribution of *A. triste* (mean 49, DS 10, median 47.5). Six of eight (75 %) and two of 10 (20 %) cases were bitten during wildlife activities in the distribution area of *A. triste* and *A. tigrinum*, respectively. The rest of the cases were bitten in peri-domestic areas. One of eight and five of 10 cases owned dogs in the distribution area of *A. triste* and *A. tigrinum*, respectively. No patient reported the use of repellent or other preventive personal protection measures.

Table 1
Demographic, epidemiological and clinical variables of the cohort of patients.

	Disease related to *A. triste* (n = 8)		Disease related to *A. tigrinum* (n = 10)		Total (n = 18)		p	Odds Ratio
Demographic and Epidemiological variables	n	%	n	%	n	%		
Female	2	25	8	80	10	56	0.02	12
Age (years)								
average	49	N/A	49	N/A	49	N/A	N/A	N/A
SD	10	N/A	16	N/A	13	N/A	N/A	N/A
range	30	N/A	46	N/A	46	N/A	N/A	N/A
Owning dog	1	12.5	5	50	6	33	0.09	7
Repellent	0	0	0	0	0	0	*	*
Setting of the tick bite	8	100	10	100	18	100	—	—
Peri-domestic	2	25	8	80	10	56	0.02	12
Wildlife areas	6	75	2	20	8	44	0.02	12
Clinical variables								
Fever	8	100	10	100	18	100	*	*
Eschar	8	100	10	100	18	100	*	*
single	7	88	10	100	17	94	*	*
multiple	1	12	0	0	1	6	*	*
Rash	8	100	9	90	17	94	0.35	0.84
maculo-papular	7	87.5	6	60	13	72	*	*
maculo-vesicular	1	12.5	2	20	3	17	*	*
petechial	0	0	1	10	1	6	*	*
Adenopathy	1	12.5	4	40	5	28	0.19	15
Headache	8	100	5	50	13	72	0.01	0.77
Myalgia	6	75	7	70	13	72	0.81	1.2
Cough	0	0	0	0	0	0	*	*
Dyspnea	0	0	0	0	0	0	*	*
Neurological symptoms	0	0	0	0	0	0	*	*
Hemorrhagic complications	0	0	0	0	0	0	*	*
Gastrointestinal symptoms	0	0	0	0	0	0	*	*
PCR confirm	7	87.5	7	70	14	78	0.37	0.3
Seroconversion	1	12.5	3	10	4	22	0.37	3

N/A: not applicable; SD: standard derivation.
*: No statistics was computed because this variable was a constant.

Regional differences in epidemiological variables were identified, depending on the vector. For example, there was a significantly increased risk of exposure to *A. tigrinum* in peri-domestic areas (odd ratio 12, p = 0.02), whereas an increased risk of exposure to *A. triste* was evident for men in wildlife areas (odd ratio 12, p = 0.02). Cases were identified all year long except for May, June, and September. The seasonal occurrence of the cases was different between the two geographical areas corresponding to the influence of *A. triste* and *A. tigrinum*. Cases related with *A. triste* were grouped during October through March (except December), while *A. tigrinum* cases occurred during fall, winter and springtime, with a decrease in summer months (Fig. 2).

Of the 18 confirmed and probable cases, all had fever, one or more inoculation eschars, and all but one had rash. Other signs and symptoms included headache (13/18), myalgia (14/18), and adenopathy (5/18). A single eschar was present in 94 % (n = 17) of the cases (Fig. 3). One patient had three eschars. Eschars were found, in order of frequency, in limbs (n = 6, 33 %, scalp (n = 4, 22 %), chest (n = 4, 22 %), neck (n = 2, 11 %), abdomen (n = 2, 11 %), groin (n = 1, 5.6 %), and breasts (n = 1, 5.6 %). The exanthema was maculopapular (n = 13, 72

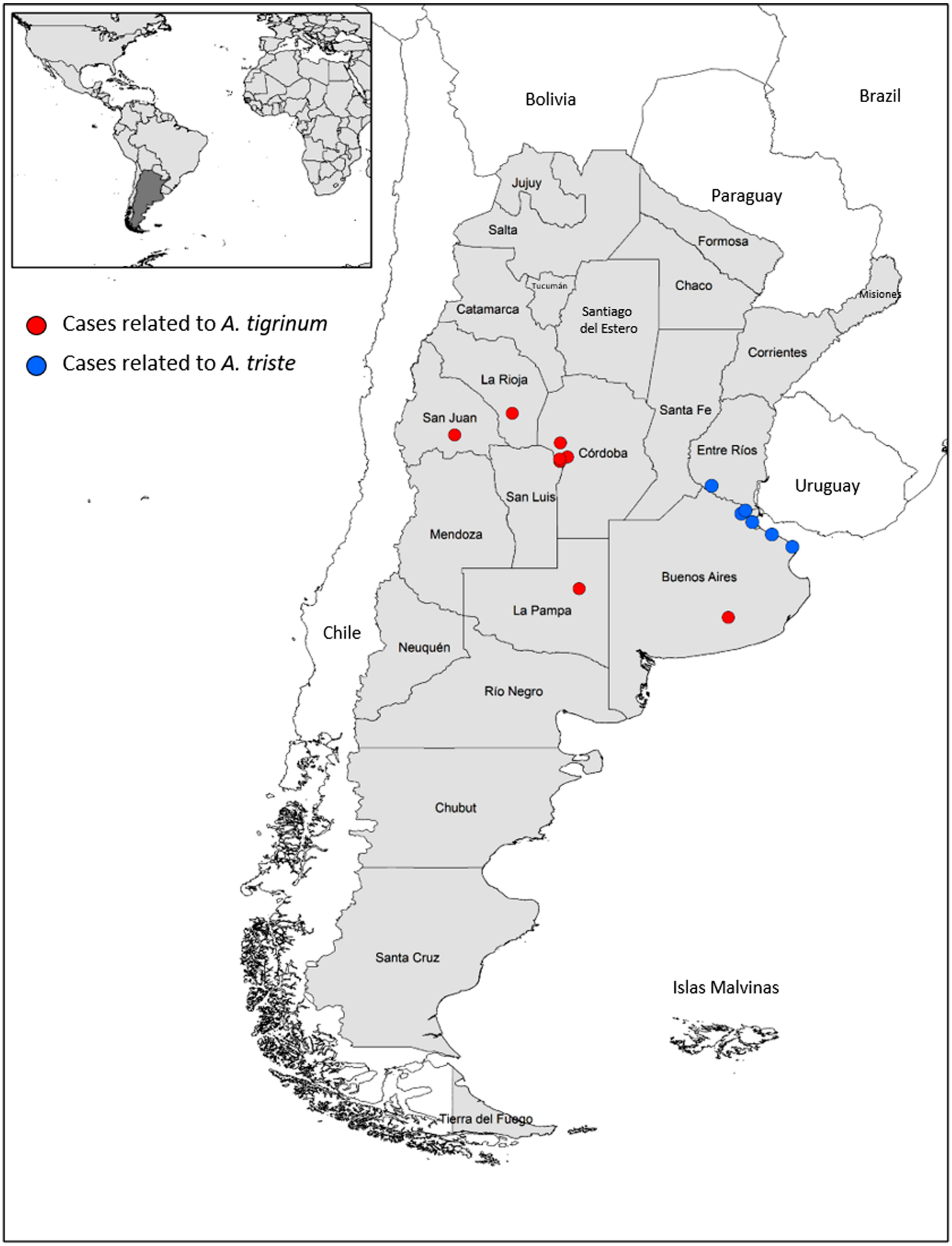

Fig. 1. Map of Argentina showing the distribution of probable and confirmed cases of *Rickettsia parkeri* rickettsiosis. Dots represent the localities of the cases, and not necessarily the number of cases. Blue circles represent localities of the *Amblyomma triste*-related cases. Red circles represent localities of the *Amblyomma tigrinum*-related cases (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

%), maculo-vesicular (n = 3, 17 %) or petechial (n = 1, 6%) (Fig. 4). It occurred in a generalized distribution in all cases, involving palms, soles, face and scalp, and was non-pruritic. The adenopathies were small (< 1.5 cm), with no inflammatory signs, and regional to the site of the bite. No patient presented with gastrointestinal, respiratory, neurological or hemorrhagic manifestations, or with evidence of severe systemic disease. Routine hematologic tests (CBC) and biochemistry panels were performed. In four cases, a low increase in hepatic transaminases was the only identified abnormality. No abnormalities were observed in leukocytes, red blood cells, or platelet counts.

All patients recovered promptly without sequelae, and none required hospitalization. Seventeen patients received antibiotic treatment with doxycycline 200 mg/day for 7 or 10 days, with complete resolution of the illness in less than two weeks. In one patient, antibiotic

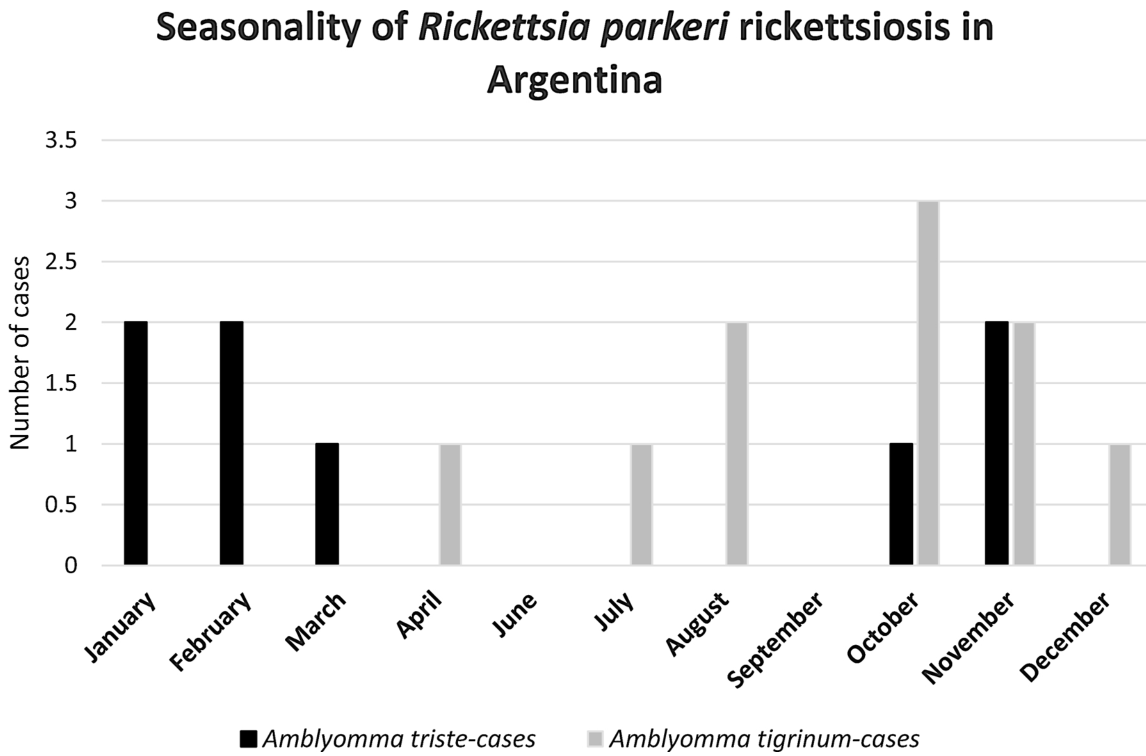

Fig. 2. Seasonal occurrence of *R. parkeri* rickettsiosis cases presented in this study. In black bars, cases related to *A. triste*. In grey bars, cases related to *A. tigrinum*. Notice how *A. triste* cases are grouped at the end and beginning of the year, while *A. tigrinum* cases occurred throughout the year, with a decrease in summer months.

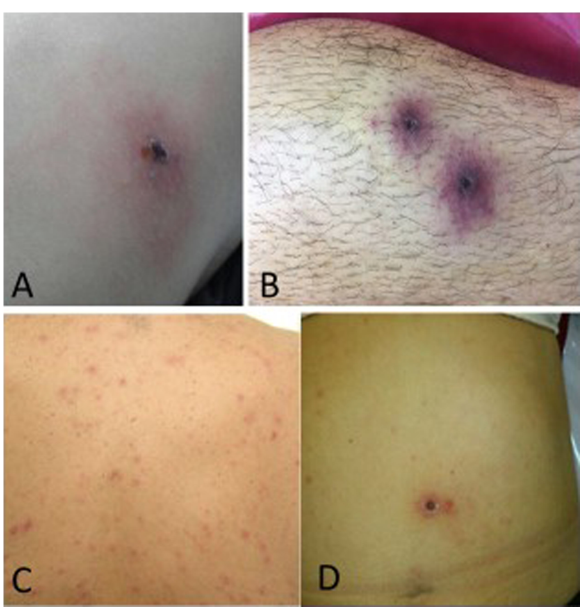

Fig. 3. (A) Eschar on thorax´ flank of a patient corresponding to *A. trigrinum* area. (B) Multiple eschars in the left leg of a patient from *A. triste* area. (C) Papulovesicular exanthema on the back of a patient from *A. triste* area (D) Eschar and maculo-papular exanthema on the abdomen of a patient from *A. tigrinum* area.

treatment was not indicated because she was in her second trimester of pregnancy, and she was closely followed up. Her symptoms resolved completely without therapy within 2 weeks and her pregnancy was otherwise uneventful. There was no statistical differences in the clinical variables between illnesses related to either *A. triste* or *A. tigrinum*.

4. Discussion

The two tick species recognized as vectors of *R. parkeri* in Argentina, *A. triste* and *A. tigrinum,* have different distributions and ecological preferences (Guglielmone et al., 2000, 2013). *R. parkeri* rickettsiosis related to *A. triste* was found in provinces linked to the Paraná River (Buenos Aires, Santa Fe, Entre Ríos, Corrientes, and Formosa); while *R. parkeri* rickettsiosis related to *A. tigrinum* was found in the provinces of Córdoba, and suggested in La Rioja, La Pampa, San Luis, and areas of Buenos Aires not related to the Parana River. Hence, the geographical location of patients with *R. parkeri* rickettsiosis can be specifically linked to a particular species.

Based on this observation, we found that the seasonality of *R. parkeri* rickettsiosis differed based on its vector. Cases associated with *A. triste* occurred predominantly during spring and summer, whereas those associated with *A. tigrinum* were distributed during most of the year, with a decrease in summer months. This phenomenon correlates with the seasonal distribution of the adults of both species, which are those stages that bite humans (Nava et al., 2017). Adults of *A. tigrinum* are active throughout the year, while adults of *A. triste* exhibit a more marked seasonality (Guglielmone et al., 2000; Nava et al., 2011, 2017). The risk of disease transmission by *A. triste* was associated with outdoor recreational or labor activities in wildlife areas. By comparison, cases associated with *A. tigrinum* were more likely linked to tick bites in the peri-domestic setting. These findings, and the broader range of age, could reflect an increased risk of contact with ticks closer to work or home residency for patients who acquired the disease from *A. tigrinum*, and allow us to propose that *A. tigrinum* prefers the peri-domestic environment.

Given that transmission of the disease to humans has been linked to the adult stages of these ticks, and because of the anthropophilic behavior of dogs, their role as a potential sentinel of this rickettsiosis must be considered, as well as their potential as transporters of ticks to the environments inhabited by humans (Grasperge et al., 2012; Labruna et al., 2007; Lado et al., 2015; Tomassone et al., 2010; Sumner et al., 2007), as occurs with *Amblyomma aureolatum* and *A. ovale* in Brazil (Szabó., et al. 2013).

The homogeneity of clinical features matches those of other series (Paddock et al., 2008a; Paddock, 2005). Fever, eschar, and exanthema are the main signs, and occur variably with other findings such as regional adenopathies, headache and myalgia. No life-threatening manifestations were identified, consistent with previous case series. The exanthema could represent the biggest challenge for clinicians as it can present as maculopapular, petechial or maculovesicular.

It is important to mention that the differential diagnosis also includes Rocky Mountain spotted fever, which is caused by *Rickettsia rickettsii* in the northern region of Argentina (Ripoll et al., 1999; Paddock et al., 2008; Seijo et al., 2016), where its potential vectors are *Amblyomma sculptum* and *Amblyomma tonelliae* (Tarragona et al., 2015, 2018). This disease shows a severe clinical course and mortality rates that can exceed 50 % (de Oliveira et al., 2016; Parola et al., 2013). The exanthema of RMSF can be maculopapular, petechial, and even purpuric, which can then evolve to necrosis; however, vesicular rashes are not reported (Paddock et al., 2008a). The disease often involves multiple organ systems (Ripoll et al., 1999; Paddock et al., 2008b). Although eschars occur only rarely in RMSF (Paddock et al., 2008a), the main findings to guide the differential diagnosis, especially during the early stages of disease, rely largely on the epidemiologic context defined by the different vector species.

One patient in this cohort did not receive antibiotic therapy. She was a woman on her second trimester of pregnancy and her clinician decided to follow her carefully without specific therapy (Troglio et al., 2017). Patients recovered completely, and not treated patients not progressed to severe disease, which is consistent with previous knowledge of *R. parkeri* rickettsiosis as a benign disease without clinical complications (Paddock et al., 2008a).

To our knowledge, this represents the first study to compare cases of *R. parkeri* rickettsiosis from areas where transmission can be attributed to one or another vector species. Moreover, *A. tigrinum* seems to prefer the peri-domestic environment, thus increasing its theoretical potential for transmission. Even though *R. parkeri* rickettsiosis has been described as a benign and self-limited disease, its low prevalence determines that, so far, we cannot predict its severity in special populations such as the aging, transplant patients, HIV, or any other form of immunocompromise. Larger series will be needed in the future to confirm these observations and shed light on these questions.

We emphasize the importance of fever, eschar, and rash to establish a presumptive diagnosis. We recommend that antibiotic therapy be initiated in those cases that meet criteria for a suspected case, and that clinical samples, including eschar biopsy or swab specimens (Myers et al., 2013) and serum, be collected to confirm the diagnosis.

The recent identification of *R. parkeri* strain Atlantic rainforest in *A. ovale* ticks from Misiones province poses a probable third ecological scenario for *R. parkeri* in Argentina (Lamattina et al., 2018), and its significance in human rickettsiosis in the country is still unknown.

It would be interesting to conduct similar studies in other countries in the region, like Brazil and Uruguay, where *A. tigrinum* along with other tick species plays a potential vectoral role (Szabó et al., 2013; Lado et al., 2014; Weck et al., 2016; Faccini-Martinez et al., 2018)

5. Conclusion

The analysis of the risk scenarios associated with *R. parkeri* rickettsiosis shows epidemiological differences between patients who reside in areas where *A. triste* prevails and those who reside in areas where *A. tigrinum* prevails. We strongly recommend diagnostic efforts to arrive to an etiological diagnosis in patients with a suspected tick-borne rickettsiosis, to effectively understand the distribution of rickettsial diseases in Argentina.

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Yamila Romer: Conceptualization, Formal analysis, Investigation, Writing - original draft, Writing - review & editing. **Pablo Borrás:** Conceptualization, Investigation, Writing - review & editing. **Francisco Govedic:** Investigation, Writing - original draft, Writing - review & editing. **Santiago Nava:** Supervision, Writing - original draft, Writing - review & editing. **José Ignacio Carranza:** Investigation, Writing - review & editing. **Soledad Santini:** Supervision, Writing - review & editing. **Rita Armitano:** Investigation, Writing - review & editing. **Susana Lloveras:** Investigation, Supervision, Writing - review & editing.

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