Predictive Factors for Fatal Tick-Borne Spotted Fever in Brazil
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Impacts
- The severity of tick-borne spotted fever cases was demonstrated by the high frequency of hospitalization, the high case-fatality rate observed, or the increased frequency of clinical complications found in critical patients.
- The presence of predictive factors for fatal tick-borne spotted fever is important as in decision making during care, including the need for patient referrals to more complete healthcare service centres and recommendations for hospitalization in intensive care units.
- Among the epidemiological records analyzed, a report of previous exposure to ticks and residing in an urban area were associated with a lower risk of death among patients with tick-borne spotted fever.

Keywords:
Tick-borne diseases; zoonoses; rickettsial infection; Rickettsia rickettsii; case–control study

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Summary
In Brazil, two pathogenic Rickettsia species have been identified causing tick-borne spotted fever (SF). The aetiological agent Rickettsia rickettsii causes serious illness, particularly in the south-eastern region of the country. Moreover, the Rickettsia sp. strain Atlantic Rainforest cause milder clinical manifestations in south-eastern, south and north-east regions. This study has sought to analyse predictive factors for fatal SF. A case–control study was performed using disease notification records in Brazil. The cases included were individuals with laboratory confirmation and fatal progression of SF, while the controls included individuals with SF who were cured. A total of 386 cases and 415 controls were identified (1 : 1.1), and the cases and controls were similar in age. The factors identified as being protective against death were reported presence of ticks (odds ratio [OR], 0.60; 95% confidence interval [CI], 0.41–0.88), residing in urban areas (OR, 0.47, 95% CI, 0.31–0.74) and presenting lymphadenopathy (OR, 0.43; 95% CI, 0.23–0.82). Males exhibited a greater chance of death (OR, 1.57; 95% CI, 1.13–2.18), as did patients who were hospitalized (OR, 10.82; 95% CI, 6.38–18.35) and who presented hypotension or shock (OR, 10.80; 95% CI, 7.33–15.93), seizures (OR, 11.24; 95% CI, 6.49–19.45) and coma (OR of 15.16; 95% CI, 8.51–27.02). The study demonstrates the severity profile of the SF cases, defined either as the frequency of hospitalization (even in cases that were cured) or as the increased frequency of the clinical complications typically found in critical patients. Opportune clinical diagnosis, a careful evaluation of the epidemiological aspects of the disease and adequate care for patients are determining factors for reducing SF fatality rates.
Background

In Brazil, two pathogenic *Rickettsia* species have been identified as causing tick-borne spotted fever (SF), *Rickettsia rickettsii* and *Rickettsia* sp. strain Atlantic Rainforest (Parola et al., 2013; Szabó et al., 2013). Spotted fever group *rickettsiosis* (SFGR) occurs in all regions of Brazil, although its highest rates are in the southern and south-eastern regions of the country (Oliveira et al., 2016a). Due to its importance as an illness of interest to public health, the Brazilian Notifiable Diseases Information System (SINAN) must be used by all healthcare services in the country to immediately report new cases of the disease (Ministério da Saúde, 2016a,b).

In most areas within the southern region and in previously studied outbreaks confined to the north-eastern region, the disease has been found to be caused by *Rickettsia* sp. strain Atlantic Rainforest, a species closely related to *Rickettsia sibirica, Rickettsia parkeri* and *Rickettsia africae*. Its clinical manifestations are milder, and its common characteristics include the presence of inoculation eschars and lymphadenopathy (Angerami et al., 2006; Spolidorio et al., 2010; Silva et al., 2011; Vizzoni et al., 2016; Krawczak et al., 2016; Moerbeck et al., 2016). However, in the south-eastern region of Brazil, the most serious form of the disease occurs. It is caused by *R. rickettsii*. Its case-fatality rate surpasses 50% (Angerami et al., 2006, 2009b, 2012; Oliveira et al., 2016b).

The measures to be taken as part of an epidemiological investigation into SF include analyses of demographic data, clinical and laboratory profiles, and the eco-epidemiological determinants of the reported cases in an effort to define prevention and control strategies and to establish measures that can seek to reduce morbidity and mortality in Brazil (Ministério da Saúde, 2016a,b). This reduction is currently considered one of the greatest challenges of the epidemiological surveillance system of this illness in the country (Oliveira et al., 2016a).

Different factors seem to contribute to the increased case-fatality rate associated with SF. Delayed diagnosis is found in most cases overall due to the disease’s concomitant occurrence with more frequent and clinically similar illnesses, such as dengue fever and leptospirosis. This leads to treatment being started at inopportune times. Additionally, improper treatment has been observed, such as antibiotics without effective activity against *rickettsial* infections, which allows for clinical worsening and the lethal progression of these cases (Angerami et al., 2006, 2009b, 2012). The case-fatality rate for SF may be associated with the fact that doxycycline, the first-choice medication, (Chapman et al., 2006), was not available for parenteral use in Brazil. Therefore, treatment for severe cases was often a second-choice antibiotic, such as chloramphenicol (Angerami et al., 2006, 2012).

The high turnover rate of healthcare professionals and the resulting difficulty in structuring trained teams have also been mentioned as factors of influence on SF case-fatality rates. Furthermore, these factors compromise the surveillance system’s ability to obtain reliable data, and they limit our understanding of the true epidemiological situation, including factors such as incidence, case-fatality rates and risk factors (Oliveira et al., 2016c).

The difference in the pathogenicity of the Brazilian strain of *R. rickettsii* has been reported as a determining factor of the most serious form of the disease, an aspect which may explain the elevated case-fatality rates associated with SF in Brazil (Eremeeva et al., 2003; Angerami et al., 2006; Labruna et al., 2014). In the light of these questions, this case-control study sought to analyse predictive factors for fatal SF.

Methods

Type of study and data collection

This is a case–control study to analyse predictive factors for fatal SF. Cases of SF notified by SINAN between 2007 and 2015 were analysed. The records were grouped in electronic spreadsheets. Duplicate records and information out of SF laboratory-confirmed case definition proposed by Brazilian Ministry of Health (Ministério da Saúde, 2016b) were excluded from the analysis. The records considered were those from the south-eastern states of the country (São Paulo, Rio de Janeiro, Minas Gerais and Espírito Santo), the area where almost an absolute majority of deaths by the disease have been concentrated and the region where the confirmed aetiological agent, *R. rickettsii*, is prevalent (Oliveira et al., 2016a). Laboratory confirmation of the disease was established for patients who had the appropriate results on serological tests (indirect immunofluorescence reaction) and/or microbiological tests (isolation of rickettsiae in a cell culture and/or a PCR reaction) and/or anatomicopathological (immunohistochemistry) assays performed by public health reference laboratories accredited by the Brazilian Ministry of Health. The cases are confirmed considering laboratory tests identifying spotted fever group *rickettsial* infections and combined with the clinical and epidemiological data (Ministério da Saúde, 2016a,b).

Data analysis

The case was defined as each notification of a suspected case with laboratory confirmation of SF that resulted to death. The control was defined as each notification of a case with laboratory confirmation of SF that was cured.
In the analysis, the information available on the SF case notification and investigation form was used http://portalsinan.saude.gov.br/images/documentos/Agravos/Febre%20Maculosa/Febre_Maculosa_v5.pdf, accessed on 15/06/2016).

The predictive factors for fatal SF were demographic information, epidemiological information, clinical information and data on hospitalization, all of which had been standardized by the Brazilian Ministry of Health for mandatory notification of and investigation into cases of SF.

For the analysis of continuous variables (age and disease progression, which was expressed in days), the nonparametric Kruskal–Wallis test was used. For the categorical variables, the odds ratio (OR) was calculated using the univariate statistic. The analyses met a 5% level of statistical significance ($P \leq 0.05$) using Fisher’s exact test (nonparametric) and a 95% confidence interval (CI). Only the variables that demonstrated a statistically significant association have been presented. The analyses were performed in the EPI INFO 7 software, version 7.2 (Centers for Disease Control and Prevention, Atlanta, GA, USA).

**Results**

A total of 386 cases and 415 controls (1 : 1.1) were identified in the database. The cases and controls were similar in age. Table 1 shows the clinical progression of the disease in terms of the continuous variables associated with death by SF. As detailed in Table 2, the factors identified as being protective against death were the presence of the tick (OR, 0.60; 95% CI, 0.41–0.88), residing in urban areas (OR, 0.47, 95% CI, 0.31–0.74) and presenting lymphadenopathy (OR, 0.43; 95% CI, 0.23–0.82). Greater probability of death was found among males (Table 3), patients who were hospitalized, and patients who presented signs of disease severity, such as hypotension/shock, seizure and coma (Table 4).

**Discussion**

The severity of SF cases was demonstrated by the high frequency of hospitalization (even in cases that were cured), the high case-fatality rate observed, or the increased frequency of clinical complications found in critical patients (hemodynamic alterations, neurological manifestations, jaundice, oliguria and respiratory symptoms). The elevated frequency of these clinical findings is consistent with previously reported data showing the severity profile of SF attributed to *R. rickettsii* (Angerami et al., 2006, 2012).

Among the epidemiological records analysed, a report of previous exposure to ticks and residing in an urban area were associated with a lower risk of death among patients with SF. Exposure to ticks, a condition for the transmission of SF, has been observed in 73% of these cases reported in the country (Oliveira et al., 2016a). However, to a certain extent, information may have been lost due to the limitations such as the quality of the investigation and data reporting to SINAN, parasitism by vectors in the larval or nymph stage. The latter may explain why some patients did not notice the ticks (Oliveira et al., 2016a). In findings consistent with the significant proportion of patients with no reported history of previous exposure to ticks, a previous case series on SF in the state of São Paulo observed that 68.8% of patients reported exposure to the vector and that, in 17% of these cases, the information was ignored (Katz et al., 2009). Therefore, while it is important to improve measures involved in the epidemiological investigation of the disease (such as qualifying the information on tick parasitism), the data presented in this study should encourage educational measures both for people who frequent high-risk locations (locations where parasitism may occur) and for healthcare professionals. These professionals need to understand that the lack of a reported history of proven tick parasitism does not exclude the risk of infection by bites that went unnoticed.

Residing in urban areas exhibited a causal association with protection against death by SF. This fact may largely involve these inhabitants’ easier access to healthcare services. It may also be explained by the fact that, in rural areas, tick parasitism, despite being frequent and common, may still be an unknown health risk and may still be disregarded by people who reside or work in this environment (Oliveira et al., 2016a). For this reason, patients who live in or frequent high-risk areas (who are already at a higher risk of infection) do not recognize parasitism as a high-risk epidemiological event and fail to report this exposure when receiving medical attention.

The presence of lymphadenopathy as a protective factor against death should be understood as an indirect event; this clinical manifestation is more frequently associated with infection by species that are less pathogenic than *R. rickettsii*. In the context of rickettsial diseases and infections, the presence of lymphadenopathy has been described in infections by other rickettsial species, including

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case</th>
<th>Control</th>
<th>Kruskal-Wallis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>36.47</td>
<td>33.49</td>
<td>0.0270</td>
</tr>
<tr>
<td>Time between first symptoms and hospitalization</td>
<td>7.29</td>
<td>5.09</td>
<td>0.0112</td>
</tr>
<tr>
<td>Length of hospitalization</td>
<td>2.89</td>
<td>9.85</td>
<td>0.0000</td>
</tr>
</tbody>
</table>

SD, standard deviation.
R. parkeri, and the *Rickettsia* sp. strain Atlantic Rainforest of in Brazil (Spolidorio et al., 2010; Silva et al., 2011; Krawczak et al., 2016; Vizzoni et al., 2016). Lymphadenopathy has been reported in 49% of cases in an endemic region in southern Brazil, particularly in the state of Santa Catarina, where the clinical profile of SF is often one of a mild illness without reports of death (Angerami et al., 2009a). In the light of this information, one cannot dismiss the possible existence of SF cases caused by less pathogenic species being responsible for milder clinical manifestations in the population studied, even if all of the cases have been reported as confirmed cases of SF in states where *R. rickettsii* circulation is well known. This study established an inclusion criterion that cases were required to have laboratory confirmation of SF, including a serology-based laboratory diagnostic technique using an indirect immunofluorescence reaction and IgG detection in parallel samples. However, this technique does not differentiate between rickettsial species, much less among those belonging to the SFGR. Although this factor may be considered an important limitation to the current study, it is, more importantly, a flaw in the rickettsial surveillance systems used in Brazil and United States, where authors have also reported that data on mortality may not correspond to reality due to challenges in distinguishing between cases caused by the more pathogenic *R. rickettsii* and caused by less pathogenic species (Mead et al., 2015). Results based on phylogenetic analysis of *R. rickettsii* showed that the Brazilian isolates originated from a clade that is distinct from the one found in the United States. This finding suggests that the high mortality rate observed in Brazil may be the result of a more virulent strain causing infection in the country (Labruna et al., 2014).

One limitation of the study is the use of a passive epidemiological surveillance system that, among other flaws, made it impossible to obtain a relevant information predicting death by rickettsial infection, particularly by *R. rickettsii*: the adoption of adequate and timely antibiotic therapy. It is known that failure to use doxycycline and/or initiating its use too late are associated with significant risk of death among patients with Rocky Mountain spotted fever (Holman et al., 2001; Regan et al., 2015; Biggs et al., 2016).

Future studies should consider the ideal possibility of a prospective follow-up of suspected cases or at least the use of clinical and laboratory data from healthcare systems beyond those which are traditionally available in the surveillance system to assess all of the possible variables involved in the prognosis for patients with SF, including the quality of the medical care provided.

### Table 2. Categorical variables associated with a lower probability of death by tick-borne spotted fever in Brazil

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case</th>
<th>Control</th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residing in urban area</td>
<td>Yes</td>
<td>33</td>
<td>0.47</td>
<td>0.31</td>
<td>0.74</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>334</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>Yes</td>
<td>14</td>
<td>0.43</td>
<td>0.23</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>302</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reported presence of ticks</td>
<td>Yes</td>
<td>195</td>
<td>0.60</td>
<td>0.41</td>
<td>0.88</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>71</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval; n, sample size.

### Table 3. Categorical variables associated with a higher probability of death by tick-borne spotted fever in Brazil

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case</th>
<th>Control</th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Yes</td>
<td>308</td>
<td>1.57</td>
<td>1.13</td>
<td>2.18</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>78</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>Yes</td>
<td>261</td>
<td>2.25</td>
<td>1.67</td>
<td>3.04</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>105</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>Yes</td>
<td>188</td>
<td>1.90</td>
<td>1.42</td>
<td>2.54</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>161</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Yes</td>
<td>161</td>
<td>3.02</td>
<td>2.21</td>
<td>4.15</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>191</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malaise</td>
<td>Yes</td>
<td>250</td>
<td>1.67</td>
<td>1.24</td>
<td>2.26</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>109</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval; n, sample size.
Males presented greater chances of death, a finding which may be explained by males’ more frequent exposure to high-risk environments and/or by the tendency among men to fail to seek medical attention (Oliveira et al., 2016a).

As expected, greater probability of death was found among patients who were hospitalized. However, it is important to note the extensive and elevated lengths of hospital stays, even among patients who were cured (9.85 days), a finding which highlights the potential for severity even among patients who achieve favourable outcomes.

As observed in studies on other illnesses and as described for Rocky Mountain spotted fever (Walker, 1989; Chen and Sexton, 2008), cases of spotted fever that include hypotension, shock, oliguria, anuria, seizure, stupor, coma, haemorrhagic manifestations and respiratory disorders are five times more likely to result in death than controls. The presence of one or more of these manifestations during the progression of a patient suspected of having spotted fever indicates the need for their understanding not only as predictive of death but, more importantly, as a factor in decision-making during care, including the need for patient referrals to more complete healthcare service centres and recommendations for hospitalization in intensive care units. Malaise, nausea, vomiting, abdominal pain and diarrhoea were found to be associated with a greater risk of death by SF. These symptoms are not exclusively observed in SF, but also in other diseases, such as dengue fever and leptospirosis. Even so, they should be considered as potential warning signs in patients suspected of having SF, who will then need to be monitored more closely.

We discussed various predictive factors for fatal SF in Brazil. However, for an effective reduction in case-fatality rates, healthcare providers need to be aware of the occurrence of the disease. Opportune clinical diagnosis, a careful evaluation of the epidemiological aspects of the disease (risk factors) and adequate care for patients are determining factors for reducing Brazilian spotted fever fatality rates in the country.

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Competing Interests

The authors declare that they have no competing interests.

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