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Exhaustive Systematic Review: Rickettsiosis in Mexico: Diversity, Distribution and Epidemiology of Reemergence

by Ana Karem Ramírez Utrera

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The mitochondria that weren’t

by Porfirio Felipe Hernández-Bautista*

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In 2003, a region in northwestern Mexico faced a major dengue outbreak. At that time, the disease was formally classified as classic dengue and dengue hemorrhagic fever. Amid widespread alarm, virtually any fever was provisionally diagnosed as dengue; however, a serious dilemma arose when laboratory results began to systematically come back negative.

Forced to consider other diagnoses, physicians began to suspect bacteria such as Leptospira and Salmonella. However, there was a larger and even more aggressive group: rickettsiae, a group of intracellular bacteria capable of presenting diverse and complex clinical manifestations.

By that time, local physicians' experience with these types of infectious agents was limited. They only had a rudimentary Proteus OX19 test to guide diagnosis and chloramphenicol as their primary therapeutic option. Later, the use of Rickettsia antibody tests was established, but with a critical drawback: they only showed positive results up to 22 days after the onset of symptoms, while the window of opportunity for effective treatment had to be less than five days from the start of symptoms, given the high risk of complications and death. Adding to this was the shortage of doxycycline, the first-line drug, in pharmacies, a drug whose use is essential even in children under eight and pregnant women.

A first attempt to improve diagnostic timeliness was the implementation of immunohistochemistry, a process that required samples of the characteristic skin lesions of rickettsiosis, but for which the target antibody was lacking. At that time, Dr. David H. Walker, from the University of Texas and a leading authority on the subject, kindly agreed to provide the missing component. Unfortunately, bureaucratic obstacles in Mexico prevented the receipt of the material, thus losing a valuable scientific and medical opportunity.

In the absence of immediate diagnostic tests, patients' health depended entirely on the clinical expertise of physicians and the empirical initiation of doxycycline in any suspected case. Later, faced with the increase in cases of rickettsiosis, Dr. Gerardo Álvarez, from the University of Sonora, promoted

the use of the Polymerase Chain Reaction (PCR), which represented a giant leap toward timely diagnosis.

Despite these advances in diagnosis and treatment in the region, precarious housing conditions and constant exposure to the transmitting vector (the brown dog tick) keep the disease active.

The genus Rickettsia is extremely abundant and cosmopolitan. Among its most feared variants are epidemic typhus, caused by Rickettsia prowazekii, and murine or endemic typhus, caused by Rickettsia typhi. This bacterium has the peculiarity of being strictly intracellular, and a strong evolutionary hypothesis proposes that present-day mitochondria—organelles essential for the survival of eukaryotic cells—share a common ancestor with them or evolved from a similar lineage. It is paradoxical that an element so closely linked to the essence of cellular life can, in its pathogenic form, turn against the organism itself.

Unfortunately, there is currently no specific protection such as a vaccine. Rapid laboratory diagnosis still depends on PCR testing, since detectable antibody levels can persist for up to two months.

Because doxycycline is the treatment of choice—even in young children and pregnant women—and given the frequent lack of immediate laboratory confirmation, it is essential that healthcare personnel initiate antibiotic therapy within five days of the onset of clinical manifestations, guided solely by clinical and epidemiological criteria.

Thus, we can see how a disease that has accompanied humanity since time immemorial continues to be a burden, especially for populations living in the most precarious conditions.

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Sociodemographic factors predicting lethality from rickettsiosis

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Abstract

Introduction: Rickettsial diseases comprise a group of clinically similar diseases that, together, due to their incidence and lethality, rank first nationally, constituting a priority public health problem that requires an exhaustive analysis of the sociodemographic and clinical determinants that lead to fatal outcomes (death) in order to propose strategies aimed at the prevention, early diagnosis and timely treatment of rickettsial diseases.

Objective: To evaluate the sociodemographic and clinical factors that predict lethality due to Rickettsiosis in cases reported at the Regional General Hospital No. 1 of Ciudad Obregón from 2021 to 2022.

Materials and methods: An observational, analytical, cross-sectional, retrospective, clinical-epidemiological study was conducted at the General Regional Hospital No. 1, Ciudad Obregón of the Mexican Social Security Institute, from January 1, 2021, to December 31, 2022. The findings were described using descriptive statistics and the association analysis was performed using Chi Square tests for qualitative variables and a generalized linear model for quantitative variables.

Results: Patients under 20 years of age had an odds ratio (OR) of 2.58 (95% CI: 1.075–6.216, p = 0.028), indicating that this group was more than twice as likely to die compared to older adults. Leukocytosis was identified as a significant predictor of mortality (Chi-square = 11.552, p = 0.001), indicating that patients with leukocytosis had an increased risk of death.

Conclusions: This study lays the foundation for evidence-based management of rickettsiosis, providing a framework for future research and guidance for interventions that benefit communities at risk.

Keywords: Rickettsiosis, Spotted fever, lethality, epidemiology, clinical presentation.

INTRODUCTION

Rickettsiosis is a disease caused by a group of bacteria of the genus Rickettsia, which are capable of producing various illnesses classified into two groups: the typhus group, which includes Rickettsia typhi and R. prowazekii, whose

vectors are fleas and lice, respectively; and the spotted fever group, which includes more than 20 species and whose main vectors are hard ticks.[1,2] In Mexico, it is primarily transmitted by the Rhipicephalus sanguineus tick, also known as the brown dog tick. This tick is the main vector of Rickettsia rickettsii, the causative agent of Rocky Mountain Spotted Fever, a disease of epidemiological interest due to the high degree of complications it presents during its clinical course and its high mortality rate.[3]

These diseases are linked to economic and cultural underdevelopment and have a higher incidence in urban areas and in vulnerable communities characterized by poor hygiene, overcrowding, poverty, and low levels of education. Humans are part of the rickettsial life cycle as accidental hosts, and transmission occurs through saliva. Rickettsia enters the body through the skin when a human spreads feces from the louse bite, but mucous membranes are also a possibility. The edema and hypovolemia that develop during the disease result from increased vascular permeability caused by damage to endothelial cells.[4,5,6]

The incubation period is described as 5 to 14 days, and initial clinical symptoms include high fever (>38°C), headache, myalgia, arthralgia, abdominal pain, nausea, vomiting, and diarrhea. Subsequently, between the fifth and sixth day, an exanthematous rash appears, characterized by a generalized distribution that does not spare the palms or soles and culminates in a petechial rash resulting from the activation of procoagulant systems, inflammation, and increased vascular permeability. [7,8]

Cases with a fatal outcome (death) have been characterized by difficulties in timely diagnosis, delays in the initiation of treatment, and therefore multiple serious complications such as severe thrombocytopenia, neurological disorders, hypovolemic shock, hemodynamic instability, multiple organ failure, and coma. However, those presenting with acute kidney injury, respiratory distress, and vascular damage were more frequent in cases of death.[9]

A study conducted in 2011 in Mexico shows that the clinical presentation of deaths in Baja California during the period of 2008–2010 included general symptoms such as fever, headache, myalgia, arthralgia, chills, central nervous system involvement, meningeal signs without cerebrospinal fluid, seizures, rash, nausea, abdominal pain, and vomiting.[10]

The clinical signs present in all cases were fever and rash; agglutination tests were positive in only 88%; the poor prognostic indicators were Thrombocytopenia, abnormal PT and PTT, and neurological abnormalities

were observed; mortality was also high (over 50%), especially in cases where treatment was initiated after the sixth day of illness.[11]

Among the complications described, neurological abnormalities with meningeal syndrome characterized by stupor and coma occurred in up to 30% of cases. Over the years, fever has been documented as the predominant symptom in virtually all patients, followed by a rash affecting the palms and soles. In the laboratory, it presents with biochemical and hematological alterations such as thrombocytopenia, leukocytosis, hyponatremia, elevated liver enzymes, and elevated serum creatinine.[12]

The treatment of choice for both dogs and humans is doxycycline (although other tetracyclines can also be used). Some authors report that initiating doxycycline in the early stages makes a significant difference in the course of the disease, directly impacting its prognosis and outcome.[13,14]

In Coahuila, another study determined that sociodemographic factors such as extreme poverty, low educational attainment, and lack of access to health services were associated with mortality from spotted fever. It was suggested that strengthening health programs in vulnerable communities is key to reducing mortality in this area.[15]

The objective of this study was to determine the sociodemographic and clinical factors that predict lethality from rickettsiosis.

MATERIALS AND METHODS

An observational, analytical, retrospective study was conducted from January 1, 2021, to December 31, 2022. Records were obtained from the nominal census of vector-borne diseases maintained by the epidemiology department of Regional General Hospital No. 1 in Ciudad Obregón. From this census, a total of 34 confirmed cases of rickettsiosis were recorded between January 2021 and December 2022.

The study included patient records of both sexes registered in the nominal census of vector-borne diseases with a diagnosis of rickettsiosis, records of patients of all ages, and records of patients with confirmed rickettsiosis by a method validated by the InDRE (National Institute of Epidemiological Diagnosis and Reference) and/or by clinical judgment. Records of deaths of probable rickettsiosis cases without laboratory confirmation and/or clinical judgment were excluded. Finally, incomplete data from the nominal census of vector-borne diseases were removed. No sample size was calculated, as all cases from that period were included.

The independent variables included were age, sex, location, occupation, ethnicity, fever, rash, leukocytosis, platelet count less than 100,000, hyponatremia, elevated alanine aminotransferase (ALT), elevated aspartate aminotransferase (AST), elevated lactate dehydrogenase (LDH), treatment initiation, and time from symptom onset to initial medical attention. The dependent variable was case fatality rate due to Rickettsiosis (death among confirmed Rickettsiosis cases). A univariate analysis was performed using descriptive statistics with measures of central tendency and dispersion for quantitative variables, and proportions and percentages for qualitative variables. Based on the selection criteria, data will be collected retrospectively from a review of the nominal census of vector-borne diseases. The association between qualitative variables was analyzed using the Chi-square or Fisher's exact test, and for quantitative variables, the Student's t-test or Mann-Whitney U test, as appropriate. Odds ratios were calculated for qualitative variables to determine risk. For quantitative variables, a generalized linear model was applied to determine the probability of the event (death) based on the observed values. The SPSS statistical package, version 15, was used.

The research complied with the ethical aspects established in the guidelines and general principles of the Regulations of the General Health Law regarding health research (published in the Official Gazette of the Federation on February 7, 1984). The research was submitted for evaluation by the Local Committee for Research and Ethics in Health Research (CLIES) of the corresponding Mexican Social Security Institute.

RESULTS

During the study period, a total of 34 cases of Rickettsiosis Infection were confirmed through the National Epidemiological Surveillance System.

The general characteristics of the studied population (Table 1), made up of a total of 34 patients diagnosed with rickettsiosis. Of this group, 61.8% (21 individuals) were over 20 years old, while 38.2% (13 individuals) were younger than this age. Regarding sex, a slight predominance of women was observed, who constituted 58.8% (20 individuals), compared to men, who represented 41.2% (14 individuals).

The location of the patients' residence is also a relevant factor. 52.9% of patients lived in urban areas, while 47.1% resided in rural areas. In relation to occupation, it was found that 73.5% (25 individuals) of the patients had some type of employment, suggesting that work activities may be associated with exposure to disease vectors.

Table 1. General characteristics of the population

Variable		Frequency	Percentage
Age	>= 20 years old	21	61.80%
	< 20 years old	13	38.20%
Sex	Masculine	14	41.20%
	Feminine	20	58.80%
Locality	Rural	16	47.10%
	Urban	18	52.90%
Occupation	Employed	25	73.50%
	Unemployed	9	26.50%
Ethnicity	Indigenous	1	2.90%
	Non-indigenous	33	97.10%
Fever	Yes	34	100%
	No	0	0%
Rash	Yes	30	88.20%
	No	4	11.80%
Leukocytosis	Yes	14	41.20%
	No	20	58.80%
Thrombocytopenia	Yes	28	82.40%
	No	6	17.60%
ALT	>= 36 U/L	23	67.60%
	< 36 U/L	11	32.40%
AST	>= 33 U/L	21	61.80%
	< 33 U/L	13	38.20%
LDH	>= 220	18	52.90%
	< 220	16	47.10%
Treatment	Yes	31	91.20%
	No	3	8.80%
Days without care	>= 5 days	17	50%
	< 5 days	17	50%
Days without treatment	>= 4 days	22	64.70%
	< 4 days	12	35.30%

Analysis of ethnicity revealed that only 2.9% of patients were indigenous, while 97.1% were non-indigenous. The presence of fever, a cardinal symptom in the diagnosis of rickettsiosis, was documented in all patients. Furthermore, 88.2% (30 individuals) presented a rash, which may be an indicator of severity and a common skin manifestation in this disease.

Regarding treatment, a high percentage (91.2%) of patients received medical attention, although it was recorded that 50% (17 patients) did not receive adequate care for at least 5 days and 64.7% (22 patients) did not receive adequate treatment for at least 4 days. These data highlight the importance of early intervention in the management of rickettsiosis and its impact on fatality.

Table 2 provides a detailed overview of the general characteristics of patients who died from rickettsiosis. Of a total of 13 deaths, 38.5% (5 individuals) were under 20 years of age and 61.5% (8 individuals) were greater than or equal to 20 years of age. This indicates that, although mortality affects both age groups, most deaths occur in adults, which could imply greater severity of the disease in this population.

Table 2. General characteristics of the deceased population

Variable		Frequency	Percentage
Age	< 20	5	38.50%
	>= 20	8	61.50%
Sex	Male	5	38.50%
	Female	8	61.50%
Type of locality	Rural	8	61.50%
	Urban	5	38.50%
Type of occupation	Employed	8	61.50%
	Unemployed	5	38.50%
Ethnicity	Indigenous	1	7.70%
	Non-indigenous	12	92.30%
Fever	Yes	13	100.00%
	No	0	0.00%
Rash	Yes	9	69.20%
	No	4	30.80%
Leukocytosis	Yes	8	61.50%
	No	5	38.50%
Thrombocytopenia	Yes	12	92.30%
	No	1	7.70%
Increased ALT	Yes	11	84.60%
	No	2	15.40%
Increased AST	Yes	11	84.60%
	No	2	15.40%
Increased LDH	Yes	7	53.80%
	No	6	46.20%
Initiation of treatment	Yes	12	92.30%
	No	1	7.70%
Delay in care	Yes	7	53.80%
	No	6	46.20%
Delay in treatment	Yes	10	76.90%
	No	3	23.10%

Regarding sex, the results show that 38.5% (5 men) and 61.5% (8 women) died, suggesting a slight trend towards greater fatality in women, although the total number of cases is low. Regarding the type of location, 61.5% of the deceased came from rural areas, which could be associated with factors such as limited access to health services, while 38.5% resided in urban areas.

Analyzing the type of occupation, it was found that 61.5% of the deceased had some type of employment, which raises questions about the relationship between work activity and exposure to risk factors for rickettsiosis. In terms of ethnicity, only one patient (7.7%) was Indigenous, while 12 (92.3%) were non-Indigenous, reinforcing concerns about healthcare disparities.

For the risk relationship, the Odds ratio (OR) based on the Chi-square test (Table 3) was used to evaluate factors associated with mortality. It is observed that patients under 20 years of age have an OR of 2.58 (95% CI: 1.075 – 6.216, p = 0.028), which indicates that this group has more than twice the probability of dying compared to older adults (Table 4).

Table 3. Risk relationship for death (χ^2)

Variable		OR	95% CI	P-value
Age	< 20 years old	2.58	1.075 – 6.216	0.028
Sex	Masculine	0.897	0.385-2.093	0.8
	Femenine	1.077	0.611-1.899	0.8
Locality	Rural	1.615	0.807-3.234	0.183
Leukocytosis	Yes (>=10)	2.154	0.976-4.799	0.058
LDH	>= 220	1.028	0.538-1.965	0.934
Days without care	>= 5 days	1.131	0.321-5.134	0.724

Table 4. Risk relationship for death (Fisher)

Variable		OR	95% CI	P-value
Occupation	Unemployed	2.019	0.66-6.6.17	0.254
Ethnicity	Non-indigenous	0.923	0.789-1.080	0.382
Rash	Yes	0.692	0.482-0.995	0.015
Thrombocytopenia	Yes (<= 100)	1.212	0.910-1.613	0.37
ALT	>= 36 U/L	1.481	0.957-2.292	0.14
AST	>= 33 U/L	1.77	1.072-2.944	0.04
Treatment	No	0.808	0.081-8.045	1
Days without treatment	>= 4 days	1.346	0.837-2.165	0.292

The goodness of fit of the model (Table 5) through different statistical criteria. The deviation value is 2.726 with 19 degrees of freedom, resulting in a value of 0.143, which indicates a good fit of the model to the data. The scaled deviation is 34,000, suggesting that the model is adequately fitted. Pearson's chi-square also shows a value of 2.726 (p = 0.143), supporting the claim that the model fits the data well. Information criteria, such as the AIC (42.691) and

BIC (67.112), are useful for comparing the quality of fit with other models, where lower values indicate a better fit. The log-likelihood function is -5.345, which is also used in the calculation of the information criteria.

Table 5. Goodness of fit[a]

Test	Value	df	Value
Deviance	2.726	19	0.143
Scaled deviance	34	19	
Pearson chi-square	2.726	19	0.143
Scaled Pearson chi-square	34	19	
Log-likelihood[b]	-5.345		
Akaike information criterion (AIC)	42.691		
Finite sample corrected AIC (AICC)	74.691		
Bayesian information criterion (BIC)	67.112		
Consistent AIC (CAIC)	83.112		

Table 6. Tests of model effects

Source	Type III		
	Wald chi-square	df	Sig.
(Intercept)	27.534	1	0
Age	5.282	1	0.022
Sex	0.009	1	0.926
Type of locality	1.628	1	0.202
Type of occupation	0.885	1	0.347
Ethnicity	4.313	1	0.038
Fever	.[a]	.	.
Rash	1.954	1	0.162
Leukocytosis	11.552	1	0.001
Thrombocytopenia	2.117	1	0.146
Increased ALT	0.275	1	0.6
Increased AST	1.754	1	0.185
Increased LDH	4.472	1	0.034
Start of treatment	0.805	1	0.37
Days without care	0.113	1	0.737
Days without treatment	0.001	1	0.975

Dependent variable: death

Model: (intersection), age, sex, type of locality, type of occupation, ethnicity, fever, rash, leukocytosis, thrombocytopenia, increased ALT, increased AST, increased LDH, start of treatment, delay in care, delay in treatment

a. It could not be calculated due to numerical problems

Table 6 presents the model's effect tests using Wald's chi-squared test. The intercept is highly significant (Chi-square = 27.534, $p < 0.001$), reinforcing the model's validity. The age variable is also identified as significant (Chi-square = 5.282, $p = 0.022$), indicating that age is an important predictor of case fatality. In contrast, sex (Chi-square = 0.009, $p = 0.926$), type of location (Chi-square = 1.628, $p = 0.202$), and type of occupation (Chi-square = 0.885, $p = 0.347$) did not show statistical significance. However, ethnicity is significant (Chi-square = 4.313, $p = 0.038$), indicating that this factor should be considered in mortality analysis.

Table 6. Tests of model effects

Source	Type III		
	Wald chi-square	df	Sig.
(Intercept)	27.534	1	0
Age	5.282	1	0.022
Sex	0.009	1	0.926
Type of locality	1.628	1	0.202
Type of occupation	0.885	1	0.347
Ethnicity	4.313	1	0.038
Fever	.[a]	.	.
Rash	1.954	1	0.162
Leukocytosis	11.552	1	0.001
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Dependent variable: death

Model: (intersection), age, sex, type of locality, type of occupation, ethnicity, fever, rash, leukocytosis, thrombocytopenia, increased ALT, increased AST, increased LDH, start of treatment, delay in care, delay in treatment

a. It could not be calculated due to numerical problems

The results of this statistical analysis provide valuable information on the factors that influence mortality from rickettsiosis. The most significant variables include age, ethnicity, and leukocytosis, which are directly associated with the risk of death.

DISCUSSION.

By reviewing 34 confirmed cases between 2021 and 2022, population characteristics, clinical characteristics and critical aspects in clinical and public health intervention were analyzed. The results show that 61.8% of patients were over 20 years old, which is consistent with other studies reporting greater susceptibility in adults, possibly due to factors such as occupation and lifestyle, which increase exposure to vectors.[16,17] Furthermore, the predominance of women in the total cases (58.8%) could reflect variations

in exposure or immune response, although no significant correlation was found between gender and mortality, in accordance with previous studies.[18,15]

The distribution of patients in urban and rural areas (52.9% and 47.1%, respectively) underscores the importance of environmental factors and access to medical services during rickettsiosis.[19,20]

The hematological findings of this study, such as the high prevalence of thrombocytopenia (82.4%) and leukocytosis (41.2%), reinforce the idea that these alterations are common in severe cases of rickettsiosis. Thrombocytopenia, indicative of systemic inflammation and possible endothelial damage, has been identified in previous studies as a predictor of poor prognosis.[14,21]Similarly, liver function tests revealed elevated ALT and AST levels in a high percentage of patients, suggesting that rickettsiosis may be frequently associated with liver damage, increasing the risk of adverse outcomes.[8,13]

The study also highlights the importance of timely treatment. However, the analysis showed that 50% of patients did not receive timely medical attention, and 64.7% experienced delays in specific treatment. These data are consistent with research that underscores the need for early intervention with antibiotics, such as doxycycline, to reduce mortality.[22, 4] Delays may be related to lack of access to medical services, difficulty in early diagnosis, and limited availability of diagnostic tests, compromising the prognosis of patients in low-resource communities.18, 3 Mortality analysis reveals a higher proportion of deaths in adults (61.5%), which could be linked to greater severity in this age group. The predominance of deaths in rural areas (61.5%) highlights the need to improve healthcare infrastructure and access to health services in these areas, consistent with other studies that point to the impact of the rural environment on clinical outcomes.[16, 17,15]The observed relationship between occupation and case fatality, with 61.5% of those who died being employed, suggests an association between occupational exposure and the risk of infection, which is consistent with the literature on rickettsiosis in vector-borne populations.[21, 3, 20]

The study used statistical analyses such as odds ratio (OR) calculations and chi-square tests to identify predictors of mortality. The OR for patients under 20 years of age (2.58, 95% CI: 1.075–6.216, $p = 0.028$) suggests that this group has a significantly higher risk of death. This finding highlights the vulnerability of young people to rickettsiosis, supporting the need for specific intervention strategies.[6,9] However, variables such as sex and location did not

reach statistical significance, indicating that these factors may not be determinants of mortality in this population.[18,8]

Ethnicity was also identified as a relevant factor; Indigenous patients showed a lower risk of lethality, which could be due to cultural, genetic, or healthcare access factors. This finding is consistent with other studies that suggest ethnic disparities in rickettsiosis outcomes.[23,15] Furthermore, biomarkers such as LDH, ALT, and AST, although not all statistically significant, suggest a possible role in identifying at-risk patients, as elevated transaminase levels have previously been associated with a higher risk of mortality.[13,24,20.]

The study confirms the existence of specific factors that predict mortality in rickettsiosis and establishes a solid foundation for future research addressing the determinants of lethality in this infectious disease in Mexico and other endemic regions.[21, 4, 6]

Finally, although the study provides valuable data, it is important to acknowledge its limitations. The sample size was small, which could restrict the generalizability of the results. This limitation is shared with studies in rural areas of Mexico, such as those by Hernández-Día and Medina-López, who also identified sample size as a barrier to generalizing findings. Furthermore, the focus on a single hospital limits the possibility of evaluating variations in clinical management and outcomes in different care settings; multicenter studies in other contexts could provide a broader perspective and help establish consistent risk patterns at the national and international levels.

This study on the sociodemographic and clinical factors that act as predictors of lethality has allowed for a deeper understanding of the determinants that influence severe outcomes in this infectious disease. Another relevant finding was the relationship between occupation and vulnerability to rickettsiosis. Most affected patients were employed, raising questions about the potential role of work activities in exposure to Rickettsia vectors. Occupations in rural settings or those involving close contact with domestic animals, such as agriculture and livestock care, may be associated with a higher risk of infection.

The analysis also demonstrated that access to timely care is a determining factor in the prognosis of rickettsiosis. Approximately half of the patients experienced a delay in medical attention, which is associated with a higher likelihood of severe outcomes. This delay in access to care is alarming, as the early administration of specific antibiotics, such as doxycycline, is crucial for reducing mortality. The lack of early access to health services could be linked to geographic, economic, or medical resource availability factors, especially

in rural areas. The evidence gathered in this study suggests an urgent need to improve access to healthcare services in areas endemic for rickettsiosis, promoting the availability of antibiotics and training medical personnel in the early recognition of symptoms to reduce waiting times for care and treatment.

Another key finding is the difference in clinical outcomes between urban and rural populations. While this study did not find a statistically significant association between location and case fatality rate, descriptive analysis showed that a large proportion of severe cases and deaths originated in rural areas. This pattern could reflect the difficulties rural communities face in accessing quality healthcare services, as well as greater exposure to rickettsiosis vectors in areas where cohabitation with domestic animals is common. These results highlight the importance of prioritizing resources and intervention programs in rural communities, where rickettsiosis poses a significant public health risk and resources are often limited.

The future applications of this study are broad, ranging from optimizing clinical resources to implementing preventive and vector control policies in high-risk communities. Strengthening early diagnosis, improving access to treatment, vector control, and targeted epidemiological surveillance constitute a comprehensive strategy that, if applied consistently, could reduce the burden of rickettsiosis in the country and improve health outcomes in the most affected populations.

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Mortality from rickettsiosis related to therapeutic management

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Abstract

Introduction: Rickettsiosis is an intracellular bacterial disease transmitted by arthropods, endemic to several Mexican states. It causes fever, rash, and skin lesions. Although usually mild, conditions such as spotted fever can be fatal. Early diagnosis and prompt treatment with doxycycline or chloramphenicol are crucial to reducing mortality.

Objective: To determine mortality and factors associate rickettsiosis in northwestern Mexico.

Materials and methods: A retrospective cohort study, it took all information rickettsiosis cases, which are in the nominal list of the health jurisdiction IV of Sonora, Mexico. The information was collected from medical records, to integrate the database. We performed a descriptive and inferential statistical analysis to detect the frequency and factors associated with rickettsial diseases.

Results: A total of 225 patients with a diagnosis of rickettsiosis, finding a total of 25 deaths, with a mortality of 11%. The risk factors presented were ≤ 5 years of age (RR, 7.22, 95% CI, 3.78-13.81), the time interval between the start of treatment and the onset of symptoms> 5 days (RR, 2.42; 95% CI, 0.96-6.35), use of trimethoprim-sulfamethoxazole (RR, 2.65, 95% CI, 0.93-7.52), chloramphenicol (RR, 9.07, 95% CI, 4.68-17.56), gamma globulin (RR, 9.7; 95% CI, 5.19-17.79), corticosteroids (RR, 12; 95% CI, 6.05-23.77) and use of doxycycline (RR, 0.14, 95% CI, .07 to .29).

Conclusions: We present a high mortality, and major associated factors are age less than 5 years, an interval of time between the start of treatment and the onset of symptoms more than five days, the use of trimethoprim-sulfamethoxazole, chloramphenicol and corticosteroids. Doxycycline therapy reduced mortality.

Keywords: Rickettsiosis, clinical symptoms, treatment.

INTRODUCTION

Rickettsiosis is an infectious disease caused by *Rickettsia* species, which are obligate intracellular bacteria closely associated with arthropod vectors. The disease is transmitted to humans primarily through the bite of infected ticks (CDC: [http://www.cdc.gov/rmsf/index.html]. In Mexico, rickettsial diseases are endemic to several states, including Sinaloa, Jalisco, Nuevo León, and Coahuila. Since 1985, annual reports have documented the coexistence of different rickettsial infections, including endemic typhus, epidemic typhus, and spotted fevers.[1,2]

Patients with rickettsiosis typically present with a maculopapular rash, petechiae, or an eschar at the site of the tick bite. While many *Rickettsia* species cause mild to moderate illness, epidemic typhus and Rocky Mountain spotted fever (RMSF) can progress to severe, life-threatening clinical presentations if left untreated.[3]

Timely treatment is critical and must be administered as early as possible to prevent complications or death. Doxycycline is the gold-standard, first-line treatment for adults and children of all ages, and it should be initiated immediately upon clinical suspicion of RMSF. The use of alternative antibiotics is associated with a significantly higher risk of fatal outcomes. Treatment is most effective at preventing mortality if doxycycline is started within the first five days of symptom onset (CDC: [http://www.cdc.gov/rmsf /symptoms/index.html].[4]

Epidemiological data in Mexico vary by region. A seroprevalence study in Yucatan evaluated 390 people and found that only 22 individuals (5.6%) were reactive to rickettsial antibodies. In contrast, a study conducting a clinical review of pediatric cases at the Children's Hospital of the State of Sonora reported that all evaluated patients presented with fever and a petechial rash. Laboratory abnormalities in that cohort included elevated liver enzymes, hyponatremia, and thrombocytopenia; despite treatment with doxycycline and chloramphenicol, a mortality rate of 22% was observed.[5,6,7.8]

Furthermore, data from the National Epidemiological Surveillance System in Mexico indicated that from 2007 to 2009, 25 states reported a combined total of 278 cases, with a case-fatality rate of 2.8%. While early treatment with doxycycline has consistently demonstrated a survival advantage in RMSF cases, it remains unclear whether co-administration with immunomodulators improves survival outcomes during the early stages of the disease.[9,10]

In Northwest Mexico, RMSF has become a major public health concern. Evolving climatic conditions favor vector proliferation, leading to an increased disease burden and high mortality rates. Therefore, we conducted this retrospective cohort study to determine the specific factors associated with mortality in the southern region of the State of Sonora.

MATERIALS AND METHODS

We conducted a retrospective cohort study from January 2008 to December 2011 within the Yaqui Valley Jurisdiction IV in Sonora, Mexico. We included patients with a confirmed diagnosis of RMSF, defined by the detection of IgM antibodies via indirect immunofluorescence assay (IFA). All diagnostic samples were processed at the State Laboratory of Public Health in Sonora, Mexico.

The primary outcome of interest was patient mortality. To account for early mortality—where patients succumbed to the illness before antibody titers could reach detectable peaks—clinical and epidemiological judgment was applied. These early-fatal cases were reviewed and formally classified by a panel of medical experts to ensure diagnostic accuracy.

Data were extracted from medical records and included epidemiological history (such as documented tick exposure), sociodemographic characteristics (age and gender), and hospital admission details. Clinical data collected encompassed the presence of fever, myalgia, arthralgia, rash, and the exact date of symptom onset. Regarding therapeutic management, we recorded data on all administered drugs, specifically tracking the use of doxycycline, chloramphenicol, trimethoprim-sulfamethoxazole (TMP-SMX), human immunoglobulin (gamma-globulin), and corticosteroids.

Descriptive analysis included the tabulation of all variables, stratified by survival status (survivors vs. deceased), using percentages and Chi-squared tests for categorical comparisons. A crude analysis was performed using univariable Cox regression models to evaluate the direct association between each variable and mortality. Finally, a multivariable Cox proportional hazards model was constructed. All variables of clinical interest were forced into the multivariable model regardless of their univariable significance, as the primary objective was to identify independent predictors of mortality while controlling for confounding factors.

Results are reported as Hazard Ratios (HR) and relative risk accompanied by 95% Confidence Intervals (95% CI). Statistical significance for the regression models was assessed using the Wald test. P-values < 0.05 were considered

statistically significant; however, due to the restricted sample size, P-values up to 0.1 were considered marginally significant. Anonymized data were managed in Microsoft Excel and transferred to Epi Info 7 and STATA 11 for statistical processing. This study was approved by the local Bioethics and Research Committee of the Regional General Hospital No. 1 of the Mexican Social Security Institute (IMSS) in Sonora, Mexico.

RESULTS

We analyzed data from 225 patients diagnosed with RMSF, which included 25 recorded deaths, representing an 11% case-fatality rate. Age distribution varied significantly: 95.5% of survivors were older than 5 years, compared to only 60% of those who died ($p < 0.0001$). Regarding gender, 139 (69.5%) survivors and 13 (52%) deceased patients were female, a difference that was only marginally significant ($p = 0.078$).

Constitutional symptoms such as fever, headache, and myalgia were universal, presenting in 100% of the study population. Conversely, severe clinical signs were heavily concentrated in fatal cases: petechiae occurred in 10% of survivors versus 88% of deaths, and active bleeding was noted in 12.5% of survivors versus 100% of deaths (both comparisons $p < 0.0001$). A known history of a tick bite was reported by only 3 (12%) deceased patients and 13 (6.5%) survivors ($p = 0.3$). Hospitalization—serving as a proxy for clinical severity—was required for 100% of the deceased patients compared to 26.5% of survivors ($p < 0.0001$) (Table 1).

Regarding therapeutic timing, 80% of patients who died initiated treatment more than 5 days after symptom onset, compared to 59.5% of survivors ($p = 0.047$). The detailed distribution of treatment regimens between groups is presented in Table 2.

In the univariable (crude) Cox regression model, children aged 5 years or younger exhibited a nearly 10-fold higher hazard of death compared to older participants ($p < 0.0001$). Female patients demonstrated a lower risk of mortality than males, though this trend was marginally significant (HR = 0.5, $p = 0.085$). Doxycycline administration demonstrated a strong, statistically significant protective effect (HR = 0.09, 95% CI: 0.03–0.25). Conversely, alternative therapeutic interventions were strongly associated with increased mortality: chloramphenicol (HR = 11.9, $p < 0.0001$), gamma-globulins (HR = 12.6, $p < 0.0001$), and corticosteroids (HR = 15.4, $p < 0.0001$). Trimethoprim-sulfamethoxazole showed a marginal association with fatal outcomes (HR = 2.9, $p = 0.08$).

Table 1: Demographic and clinical characteristics of participants between survivors and dead

Variable	Survivors (N=200)	Dead (N=25)	P-value*
Sex:			
Female	139 (69.5%)	13 (52.0%)	0.078
Male	61 (30.5%)	12 (48.0%)	
Age category (years):			
>5	191 (95.5%)	15 (60.0%)	<0.0001
≤5	9 (4.5%)	10 (40.0%)	
Hospitalization:			
No	147 (73.5%)	0 (0.0%)	<0.0001
Yes	53 (26.5%)	25 (100.0%)	
Presence of petechiae:			
No	180 (90.0%)	3 (12.0%)	<0.0001
Yes	20 (10.0%)	22 (88.0%)	
Presence of bleeding:			
No	175 (87.5%)	0 (0.0%)	<0.0001
Yes	25 (12.5%)	25 (100.0%)	
Presence of fever:			
No	0 (0.0%)	0 (0.0%)	--
Yes	200 (100.0%)	25 (100.0%)	
Presence of headache:			
No	0 (0.0%)	0 (0.0%)	--
Yes	200 (100.0%)	25 (100.0%)	
Presence of myalgia:			
No	0 (0.0%)	0 (0.0%)	--
Yes	200 (100.0%)	25 (100.0%)	
History of tick bite:			
No	187 (93.5%)	22 (88.0%)	0.313
Yes	13 (6.5%)	3 (12.0%)	

*P-value from Chi-squared test

Table 2: Treatment characteristics and regimens of participants between survivors and dead

Variable	Survivors (N=200)	Dead (N=25)	P-value*
Time between onset of symptoms and beginning of treatment (days):	119 (59.5%)	20 (80.0%)	0.047
>5	81 (40.5%)	5 (20.0%)	
≤5			
Treatment with Trimethoprim-sulfamethoxazole:			0.08
No	192 (96.0%)	22 (88.0%)	
Yes	8 (4.0%)	3 (12.0%)	
Treatment with Doxycycline:			
No	3 (1.5%)	5 (20.0%)	<0.0001
Yes	197 (98.5%)	20 (80.0%)	
Treatment with chloramphenicol:			
No	189 (94.5%)	12 (48.0%)	<0.0001
Yes	11 (5.5%)	13 (52.0%)	
Treatment with gamma-globulins:			
No	194 (97.0%)	14 (56.0%)	<0.0001
Yes	6 (3.0%)	11 (44.0%)	
Treatment with corticosteroids:			
No	190 (95.0%)	10 (40.0%)	<0.0001
Yes	10 (5.0%)	15 (60.0%)	

*P-value from Chi-squared test

In the multivariable Cox regression analysis—which adjusted for all treatment regimens, sex, age, and tick bite history—several crude associations showed evidence of confounding. Younger participants still experienced higher mortality, though it became marginally significant (HR = 2.6, p = 0.15). Treatment with corticosteroids (HR = 8.6, p < 0.0001), chloramphenicol (HR = 4.1, p = 0.018), and trimethoprim-sulfamethoxazole (HR = 4.9, p = 0.03) remained strongly and independently associated with mortality. Notably, for these latter regimens, the adjusted HR was higher and more significant than the crude HR, indicating that the crude analysis was negatively confounded by other covariates. Due to the limited sample size and the high correlation between variables, the protective effect of doxycycline lost its statistical significance in the fully adjusted model (Table 3).

Table 3: Crude and adjusted association of different variables with death for Rickettsia. Measure of effect expressed as Hazard Ratio (HR) from Cox regression.

Variables	*Crude HR*		*Multivariable analysis (adjusted HR)*	
	HR (95%CI)	*P-value§*	*HR (95%CI)*	*P-value§*
Sex:				
Male	(reference)	--	(reference)	--
Female	0.50 (0.23-1.10)	0.085	0.69 (0.29-1.64)	0.403
Age category (years):				
>5	(reference)	--	(reference)	--
≤5	9.79 (4.38-21.87)	<0.0001	2.58 (0.71-9.44)	0.151
History of tick bite:				
No	(reference)	--	(reference)	--
Yes	1.85 (0.55-6.18)	0.318	2.12 (0.56-8.05)	0.270
Time between onset of treatment (days):				
>5	2.52 (0.94-6.71)	0.065	(reference)	--
≤5	(reference)	--	1.48 (0.49-4.46)	0.486
Treatment with: TMP-SMZ:				
No	(reference)	--	(reference)	--
Yes	2.91 (0.87-9.71)	0.083	4.87 (1.18-20.12)	0.029
Doxycycline:				
No	(reference)	--	(reference)	--
Yes	0.09 (0.03-0.25)	<0.0001	1.17 (0.30-4.61)	0.820
chloramphenicol:				
No	(reference)	--	(reference)	--
Yes	11.94 (5.43-26.27)	<0.0001	4.13 (1.28-13.33)	0.018
Gamma-globulins:				
No	(reference)	--	(reference)	--
Yes	12.65 (5.72-27.99)	<0.0001	0.77 (0.23-2.58)	0.68
corticosteroids:				
No	(reference)	--	(reference)	--
Yes	15.40 (6.88-34.47)	<0.0001	8.58 (2.86-25.72)	<0.0001

§P-values from Wald test

DISCUSSION.

Prior literature reports highly variable mortality rates for rickettsial diseases, ranging from 2% to 36%. Our study identified an 11% case-fatality rate, which aligns with these global estimates. Demographically, mortality was heavily skewed toward pediatric patients. Furthermore, 100% of deaths occurred among hospitalized individuals, confirming that baseline clinical severity at presentation is a primary driver of fatal outcomes. These findings mirror those described by Thorner et al. in the United States.[11]

The most prevalent clinical manifestations in our cohort were headaches, myalgia, arthralgia, and bleeding. Notably, only a minority of patients recalled a history of a tick bite, and this variable showed no statistical association with mortality.[12,13,14,15] Our clinical findings contrast with those of Hidalgo et al. in Colombia, where only 8% of patients presented with myalgias and arthralgias.[16]

The primary risk factors for mortality identified in this study were an age under 5 years, a treatment delay exceeding 5 days from symptom onset, and the utilization of trimethoprim-sulfamethoxazole, chloramphenicol, gamma-globulins, or corticosteroids.[17,18,19] Conversely, doxycycline acted as a major protective factor, corroborating the findings of Holman et al.. [20] The loss of statistical significance for doxycycline in the multivariable analysis is likely an artifact of our small sample size and collinearity with severe cases.

Delayed treatment (beyond 5 days from onset) is a well-established driver of lethality confirmed across multiple endemic regions. However, a key limitation of our observational data is that gamma-globulins and corticosteroids were exclusively administered to hospitalized patients. This indicates a severe selection bias, as these immunomodulators were likely introduced as a desperation measure for critically ill patients rather than acting as a direct cause of death.

Doxycycline remains undisputed as the first-line drug of choice, supported by our univariable finding of an 81% reduction in the hazard of death, proving vastly superior to chloramphenicol. In the adjusted Cox model, the treatments positively associated with mortality were trimethoprim-sulfamethoxazole, chloramphenicol, and corticosteroids. These findings align with current guidelines from the Centers for Disease Control and Prevention (CDC), which warn that the use of antibiotics other than doxycycline for suspected rickettsiosis is associated with an elevated risk of fatal outcomes (CDC: [http://www.cdc.gov/rmsf/symptoms/index.html].[21]

The primary limitation of our study is its small sample size, which stems from the inherent difficulties of diagnosing RMSF early in the course of the disease. This challenge is compounded by a lack of accessible specialized diagnostic laboratory techniques at the point of care and the highly non-specific early symptoms of the disease. Additionally, missing data within the medical records restricted our ability to fully control other potential clinical confounders.[22]

This study demonstrates that an associated risk of mortality from RMSF is independently associated with an age under 5 years, a treatment delay of more than five days from symptom onset, and the use of alternative therapies such as trimethoprim-sulfamethoxazole, chloramphenicol, and corticosteroids. Early initiation of doxycycline significantly reduces mortality. The use of gamma-globulin did not retain statistical significance in the multivariable analysis and cannot be definitively classified as a risk or protective factor.[23]

Recognizing these clinical and therapeutic risk factors is vital to reducing the public health burden of rickettsiosis. Because the early clinical picture is non-specific and laboratory confirmation is often delayed, empiric treatment should never be postponed. Comprehensive training programs targeting frontline physicians are urgently needed to improve diagnostic suspicion and ensure prompt, early initiation of doxycycline in all suspected cases.

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Epidemiological characteristics in patients diagnosed with Rocky Mountain Spotted Fever

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Abstract

Introduction: Rocky Mountain Spotted Fever (RMSF) is an endemic infectious disease with a nonspecific clinical presentation and a high mortality rate in the state of Sonora. This research aims to describe the main epidemiological, clinical, and laboratory aspects of the disease in order to provide timely diagnosis and treatment to patients served by General Hospital Zone 14 in Sonora.

Objective: To describe the epidemiological, clinical and laboratory characteristics in patients diagnosed with Rocky Mountain Spotted Fever treated at General Hospital Zone 14, Sonora during the period from January 2018 to March 2023.

Materials and methods: A descriptive, cross-sectional study was conducted on patients admitted to General Hospital Zone 14 based on epidemiological studies and a nominal census of vector-borne disease and electronic records.

Results: Fifty-nine percent of cases were in females, with the highest proportion between 18 and 64 years of age. Contact with the vector, prior medical attention, and initiation of doxycycline ≥ 6 days prior to symptom onset were the predominant risk factors in this study. The classic triad was present in only 38% of cases, and paraclinical abnormalities were observed within the first 72 hours of symptom onset.

Conclusions: The epidemiological findings were consistent with other current studies. The symptoms presented were nonspecific, and a case fatality rate of 43% was obtained. It is important to recognize the diagnosis even when exposure to the vector is unknown, considering the high prevalence and lethality of the disease in the state of Sonora.

Keywords: Fever, spotted, rickettsia rickettsi, rickettsiosis.

INTRODUCTION

Rocky Mountain Spotted Fever (RMSF) is a re-emerging infectious disease with a 50% case fatality rate in the state of Sonora. Currently, the clinical presentation is known to be nonspecific in the first few days of onset, so the diagnosis is not always suspected in the acute stage of the disease. Consequently, the treatment of choice is administered late, when the disease is already advanced and carries a higher risk of a fatal outcome, as has been observed in recent studies.

RMSF is an infectious disease caused by the bacterial species Rickettsia rickettsii. Historically, cases of a febrile illness with nonspecific clinical characteristics, including a petechial rash, headache, and high fever, have been reported in the states of Sonora and Sinaloa, reaching a high case fatality rate. Since then, the epidemiological, clinical, and entomological aspects of this disease in Mexico have been further detailed. [1]

It is now known that the disease is transmitted through the bite of one of the most important vectors in northern Mexico, the tick Rhipicephalus sanguineos sensu lato, which is abundant on its main host, the stray dog. The rapid increase in the number of these hosts has led to a growing understanding of the epidemiological and ecological circumstances that give rise to outbreaks in regions of the southeastern United States (USA) bordering Mexico.[1]

The Rickettsiaceae family consists of the genera Rickettsia and Orientia. The American pathologist Ricketts first described the genus Rickettsia in 1909. This genus comprises four groups, including the species with the greatest epidemiological impact in our country: R. rickettsii (MRSM) from the spotted fever group and the typhus group, R. typhi (murine typhus), and R. prowazekii (epidemic typhus). The genus Orientia includes one species, O. tsutugamush.[2]

The bacteria are small coccobacilli, measuring no more than 0.3 to 0.5 microns, are obligate intracellular parasites, and grow only in the cytoplasm of eukaryotic cells. The genus Rickettsia possesses a minimal peptidoglycan layer, which is why it stains weakly, and its lipopolysaccharide (LPS) has only weak endotoxin activity. The outer membrane protein A (OmpA) is expressed on the surface of R. rickettsia and is responsible for its ability to adhere to endothelial cells, enter, escape the phagosome, and multiply in the cytoplasm and nucleus before exiting the cell to migrate to the next.[3]

In Mexico, the brown dog tick, Rhipicephalus sanguineus, belonging to the family Ixodidae, is the main reservoir and vector. It feeds on dogs and can

persist in urban environments. In the United States, the dog tick (Dermacentor variabilis) is prevalent, while the wood tick (Dermacentor andersoni) is found in the Rocky Mountain states and southeastern Canada. They feed on various mammals, including wild rodents, and transmission is most common during activities in rural areas where prolonged exposure to the tick occurs, typically 6 hours or more.[4]

Approximately 1 to 3% of ticks become infected with R. rickettsii transovarially or through feeding on infected animals. Once infected, these ticks do not die and serve as reservoirs and vectors for the species. Subsequently, transmission to humans occurs through the tick's saliva during a bite when it remains attached to the skin and feeds for 12 to 24 hours (although transmission through exposure to tick fluids or feces has also been described).[5]

After an incubation period of 2 to 14 days, the bacteria spread via the lymphatic and circulatory systems. Most species adhere to their target cell, the endothelial cell, escaping the phagosome and proliferating intracellularly to the point of rapidly spreading from cell to cell. Other species, such as R. akari, responsible for rickettsial pox transmitted by infected mites, target macrophages. This intracellular location of Rickettsia spp. is what makes direct detection of the organism in the laboratory difficult.[6]

Rickettsia organisms have been found on every continent except Antarctica. Most species are prevalent in certain regions due to climatic, vector, and host conditions. They can affect people of any age; however, in the United States, two-thirds of cases occur in children under 15 years of age, with the highest incidence and greatest risk of complications in children between 5 and 9 years old. In Sonora, in 2012, the case fatality rate was reported to be between 8% and 17.8%, with an upward trend since the disease's reemergence at the beginning of the decade.[7]

Mexican spotted fever (MSF) represents a significant disease burden that continues to be underdiagnosed globally. Clinical and laboratory diagnosis is challenging, and a confirmatory result should not be awaited before initiating treatment when the disease is suspected. R. rickettsii is the most lethal species among spotted fever infections, and delays in diagnosis and timely treatment (within the first five days of symptom onset) with the antibiotic of choice, doxycycline, endangering the lives of the population, particularly the most affected age group, children.[5]

Delayed initiation of antibiotic therapy carries a fourfold increased risk of mortality compared to initiating treatment before the sixth day of symptom

onset. Therefore, it is important to keep healthcare personnel updated on the characterization of symptoms, clinical course, and laboratory parameters of this disease. Likewise, to educate the community on the principles of primary and secondary prevention.[5]

Therefore, the objective of the study was to describe the epidemiological, clinical, and laboratory characteristics of patients diagnosed with Rocky Mountain Spotted Fever treated at General Hospital Zone 14, Sonora, during the period from January 2018 to March 2023.

MATERIALS AND METHODS

A descriptive study was conducted at General Hospital No. 14 with a Burn Unit. The study period was from January 1, 2018, to March 31, 2023. Patients of any age and sex were included. They underwent an epidemiological study of vector-borne diseases (VBDs) and were reported as probable cases of Rickettsiosis based on symptoms, clinical course, and suggestive laboratory profile upon admission. Subsequently, they were diagnosed with Rickettsia spp. and Rickettsia rickettsii according to the 2022 Guidelines for Laboratory Surveillance of Rickettsiosis, which include tests to detect Rickettsia spp. by real-time reverse transcription polymerase chain reaction (RT-PCR) and determination of Rickettsia rickettsii by the InDRE by quantitative PCR (qPCR) and indirect immunofluorescence for the detection of anti-IgG antibodies against spotted fever group rickettsiae (antigen: R. rickettsii), taking into account the cases as confirmed by this last test those with the first positive serological sample and then, at least 2 weeks later, a second serum sample with seroconversion greater than or equal to four times the titer of the first sample. Patients without a confirmatory diagnostic test were excluded. Patients with negative results for rickettsiosis were excluded, as were those with incomplete epidemiological studies.

The main variables studied were sex, age, exposure history, epidemiological history, clinical course, and timeliness of treatment. Permission was previously requested from General Hospital Zone 14 to use information from its database and electronic records exclusively for data review and collection. Information was obtained from the nominal census and the epidemiological study of vector-borne diseases (VBDs), electronic records, and the IMSS HGZ 14 laboratory platform. An Excel database was created to list the variables under study. Subsequently, the SPSS statistical software (Statistical Package for the Social Sciences) was used to analyze the corresponding variables.

A descriptive analysis was performed for the qualitative variables, obtaining proportions, measures of morbidity frequency, calculating point prevalence,

and the case fatality rate. For the quantitative variables, an analysis of measures of central tendency and dispersion was performed, obtaining the mean and standard deviation, respectively.

RESULTS

For this study, 214 probable cases that received medical attention at General Hospital Zone 14 in Hermosillo, Sonora, Mexico, from January 2018 to March 2023 were considered, of which 68 met the inclusion criteria. 146 cases were excluded due to a negative PCR test result and a single positive IgG IFA test result; no cases were excluded from this study.

In accordance with the objectives of this study, the following results were obtained: 59% (n=40) of the cases were female and 41% (n=28) were male. The age group with the highest proportion of cases was 18 to 64 years, with 50% (n=34), followed by the ≤ 12 years group with 35% (n=24%). Fifty-seven percent (n=39) of cases involved pets in the home and/or stray dogs outside their homes carrying ticks; 19% (n=13) reported a tick bite 14 days prior to the onset of symptoms; and in 10% (n=7), a tick bite scar was found during the physical examination. The season with the highest incidence of cases was summer (June-September), accounting for 42% (n=29) of cases. Forty-six percent (n=31) of cases received medical consultation (public or private) with a prescription for antibiotic therapy other than doxycycline prior to hospital admission, and 42% (n=13) of these cases resulted in a fatal outcome. Hospital admission occurred most frequently between 4 and 6 days after the onset of symptoms, representing 54% (n=37) of cases. Likewise, in 44% of cases, doxycycline treatment was initiated ≥ 6 days after the onset of symptoms. Table 1

The main signs and symptoms that appeared were fever 94% (n=64), malaise 71% (n=30), maculopapular rash 65% (n=44), and headache 57% (n=39), which predominated in the first 3 days of the onset of symptoms, accompanied by gastrointestinal symptoms such as vomiting, abdominal pain, and nausea. After 4 days, a higher proportion of alarm signs and symptoms were observed, such as petechial-purpuric rash, neurological deterioration, edema in the extremities, and seizures. Table 2

Table 3 describes the main signs and symptoms in children and adolescents (0-17 years). The same signs and symptoms predominated during the first 3 days of illness, with the addition of a petechial-purpuric rash, neurological deterioration, irritability, and hepatomegaly starting on the 4th day. The prevalence of the classic triad of FMMR in this study was calculated to be 38% (n=26) of cases.

Table 1. Demographic, epidemiological characteristics and outcome. n (%)

Variable		Total	Death	Improvement without sequelae	Improvement with sequelae
		N = 68	*n = 29*	*n = 26*	*n =13*
Sex	Female	40 (59)	18 (45)	19 (48)	3 (7)
	Male	28 (41)	11 (39)	7 (25)	10 (36)
Age groups	≤ 12	24 (35.3)	6 (25)	14 (58)	4 (17)
	13 - 17	7 (10.3)	2 (29)	3 (42)	2 (29)
	18 - 64	34 (50)	18 (53)	9 (26)	7 (21)
	65+	3 (4.4)	3 (100)	0	0
Epidemiological background	Direct contact	3 (4.4)	1 (33.3)	1 (33.3)	1 (33.3)
	Tick bite	13 (19.1)	3 (23)	8 (62)	2 (15)
	Animals with ticks	39 (57)	14 (36)	16 (41)	9 (23)
	Unknown	12 (18)	10 (83.3)	1 (8.3)	1 (8.3)
Vector bite scar	Denied	1 (1.5)	1 (100)	0	0
	Yes	7 (10)	4 (57)	2 (29)	1 (14)
	No	61 (90)	25 (41)	24 (39)	12 (20)
Seasonality	Winter	10 (15)	4 (40)	4 (40)	2 (20)
	Spring	10 (15)	4 (40)	3 (30)	3 (30)
	Summer	29 (42)	12 (41)	13 (45)	4 (14)
	Autumn	19 (28)	9 (47)	6 (32)	4 (21)
Medical attention prior to hospital admission.	Symptoms	19 (28)	7 (36)	6 (32)	6 (32)
	Antibiotic	31 (46)	13 (42)	12 (39)	6 (19)
	Denied	18 (26)	9 (50)	8 (44)	1 (6)
Days of evolution at admission	0 - 3	13 (19.1)	4 (31)	8 (62)	1 (7)
	June 4	37 (54.4)	18 (49)	13 (35)	6 (16)
	≥7	18 (26.5)	7 (39)	5 (28)	6 (33)
Days of evolution to start of doxycycline	0 - 2	7 (10.3)	5 (71)	2 (29)	0
	01-may	26 (38.2)	8 (31)	16 (62)	2 (7)
	≥6	30 (44.1)	11 (37)	8 (26)	11 (37)
	Not administered	5 (7.4)	5 (100)	0	0

The most frequent complications after the 4-day onset of symptoms were shock, multiple organ failure, and the need for mechanical ventilation, respectively, affecting the 18-64 year age group and children under 12 years of age. Table 3.

The mean and standard deviation of laboratory results available upon patient admission were calculated according to the number of days since symptom onset. Abnormalities were observed from the first 3 days after symptom onset, including neutrophilia, thrombocytopenia, hypoalbuminemia, hyponatremia, hyperbilirubinemia, and elevated transaminases, creatinine, D-dimer, lactate dehydrogenase, and C-reactive protein. Table 4. Hematological follow-up was performed between 72 and 120 hours after the initiation of doxycycline in

patients hospitalized for more than 5 days with available paraclinical results. In general, a trend toward normalization was observed compared to the abnormalities noted upon admission. It should be noted that two of these cases resulted in a fatal outcome. Table 5.

Table 2. Onset of signs and symptoms. n (%)

Signs and Symptoms	*Total n, (%) N=68*	*0-3 days*	*4-6 days*	*≥7 days*
Fever	64 (94)	64 (100)	0	0
General malaise	48 (71)	30 (63)	13 (27)	5 (10)
Maculopapular rash	44 (65)	33 (75)	9 (20)	2 (5)
Headache	39 (57)	37 (95)	0	2 (5)
Petechial/purpuric rash	37 (54)	1 (2)	18 (49)	18 (49)
Myalgia	35 (51)	30 (86)	5 (14)	0
Arthralgia	33 (49)	30 (91)	3 (9)	0
Vomiting	32 (47)	29 (91)	3 (9)	0
Neurological deterioration	32 (47)	2 (6)	15 (47)	15 (47)
Abdominal pain	27 (40)	23 (85)	3 (11)	1 (4)
Nausea	21 (31)	17 (81)	3 (14)	1 (5)
Dyspnea	21 (31)	3 (14)	9 (43)	9 (43)
Edema of extremities	21 (31)	1 (4)	14 (67)	6 (29)
Diarrhea	17 (25)	12 (71)	5 (29)	0
Irritability	15 (22)	3 (20)	7 (47)	5 (33)
Seizure	15 (22)	2 (2.9)	10 (14.7)	3 (4.4)
Respiratory symptoms	14 (21)	12 (86)	1 (7)	1 (7)
Retro-orbital pain	13 (19)	11 (84)	1 (8)	1 (8)
Hepatomegaly	13 (19)	1 (8)	8 (62)	4 (30)
Hyporexia	10 (15)	9 (90)	0	1 (10)
Jaundice	10 (15)	1 (10)	4 (40)	5 (50)
Generalized edema	9 (13)	2 (22)	3 (33)	4 (44)
Chills	8 (12)	5 (63)	2 (25)	1 (12)
Conjunctival hemorrhage	7 (10)	0	4 (57)	3 (43)
Bipalpebral edema	7 (10)	1 (14)	3 (43)	3 (43)
Meningeal signs	6 (9)	2 (33.3)	2 (33.3)	2 (33.3)
Oral bleeding	6 (9)	1 (17)	3 (50)	2 (33)
Pleural effusion	5 (7)	1 (20)	2 (40)	2 (40)
Epistaxis	4 (6)	0	3 (75)	1 (25)
Melena	3 (4)	1 (33.3)	1 (33.3)	1 (33.3)
Transvaginal bleeding	2 (3)	1 (50)	1 (50)	0
Photophobia	2 (3)	1 (50)	0	1 (50)
Cerebral edema	2 (3)	0	1 (50)	1 (50)

Finally, the case fatality rate during the study period was 43%, with the female population between 18 and 64 years of age being the most affected, representing 65% (including 1 patient with a pregnancy of 11.5 weeks of gestation), followed by the pediatric population < 12 years of age with 6 deaths, corresponding to a case fatality rate of 25% in this age group (Table 6).

Table 3 Complications by age group presented during the in-hospital course. n, (%)

Clinical Complications	Total n,(%) N=68	< 12	13-17	18-64	65+
Shock	54 (79)	19 (35)	4 (7)	29 (54)	2 (4)
Multiple Organ Failure	45 (66)	9 (20)	4 (9)	30 (67)	2 (4)
Mechanical Ventilation	38 (56)	12 (32)	2 (5)	22 (58)	2 (5)
Respiratory Failure	29 (43)	7 (24)	1 (3)	18 (62)	3 (10)
Renal Replacement Therapy	8 (12)	0	2 (25)	6 (75)	0
Physical Medicine and Pulmonary Rehabilitation	6 (9)	2 (33)	1(17)	3 (50)	0
Cardiology Follow-up	2 (3)	1 (50)	1 (50)	0	0
Hypoperfusion, Necrosis, and Limb Amputation	2 (3)	1 (50)	0	1 (50)	0
Thrombocytosis due to Inflammation	1 (1.5)	0	0	1 (100)	0
Tracheostomy Status	1 (1.5)	0	0	1 (100)	0
Anxiety and Depression Disorder	1 (1.5)	0	0	1 (100)	0

Table 4. Laboratory profile at admission to General Hospital Zone 14 and days of clinical evolution. m

Paraclinical tests	Total n,(%) N=68	0 - 3 days	4 - 6 days	≥7 days
Hemoglobin (g/dL)	66 (97)	12.77, (2.10)	12.90, (2.07)	13.03, (2.26)
Hematocrit (%)	56 (82)	37.78, (4.78)	37.27, (4.95)	39.06 (6.90)
Leukocytes (K/uL)	63 (93)	9,772, (5,990)	8,651, (5,139)	13,390, (7,996)
Neutrophils (10^3 mm3)	48 (71)	7,798, (4,745)	7037, (4,729)	10390, (5,936)
Lymphocytes (10^3 mm3)	54 (79)	1,765, (1,755)	793 (925)	1100, (1040)
Monocytes (10^3 mm3)	38 (56)	470, (445)	411 (635)	364, (342)
Platelets (10^3/µL)	65 (96)	94,400,-86720	42,848,-31611	50980, -74207
Albumin (g/dL)	44 (65)	3.7, (0.77)	3.18, (0.60)	2.94, (0.30)
TP (sec)	46 (68)	15, (3.79)	14.35, (2.53)	14.27, (2.51)
TPT (sec)	46 (68)	35.75 (4.68)	40.70, (12.70)	39.75, (15.58)
Sodium (mmol/L)	60 (88)	130, (4)	131, (4)	130, (8)
Potassium (mmol/L)	58 (85)	4, (0.72)	3.9, (0.55)	4.05, (0.68)
Calcium (mg/dl)	47 (69)	8.27, (0.57)	7.55, (0.83)	7.44, (0.70)
Magnesium (mg/dl)	42 (62)	2.27, (0.60)	2.03, (0.42)	2.45, 1.07)
Chlorine (mmol/L)	55 (81)	94, (5)	99, (6)	96, (8)
Phosphorus (mg/dl)	44 (65)	5.14, (1.93)	4.12, (1.63)	4.69, (2.29)
Total bilirubin (mg/dl)	52 (76)	2.72, (3.18)	3.07, (2.23)	3.39, (2.23)
AST (U/L)	54 (79)	115, (104)	170, (102)	231, (134)
ALT (IU/L)	54 (79)	75, (64)	107, (65)	109, (56)
Creatinine (mg/dl)	58 (85)	2.19, (2.70)	1.84, (1.97)	2.34, (2.20)
D-dimer (ng/mL)	17 (25)	5,642, -334	13994,-13178	25,178, (19,660)
DHL (U/L)	48 (71)	524, (421)	733, (360)	772, (443)
CRP (mg/l)	25 (37)	15.11 (9.21)	19.93, (9.08)	24.18, (9.30)

d.s: standard deviation, PT: Prothrombin Time, aPTT: Thromboplastin Time, AST: aspartate aminotransferase, ALT: alanine aminotransferase, DHL: lactate dehydrogenase, PCR: C-Reactive Protein

Table 5. Mean paraclinical values 72 to 120 hours after initiation of doxycycline. Mean (SD)

Paraclinical tests	Total n, (%) N=68	72hrs	96hrs	120hrs
Hemoglobin (g/dL)	30 (44)	11.07, (1.12)	10.19, (1.74)	11.38, (0.70)
Hematocrit (%)	29 (43)	33.24, (3.45)	29.94, (4.54)	33.60, (1.66)
Leukocytes (K/uL)	30 (44)	15,166, -6342	13,550, (4,762)	11,500, (6,605)
Neutrophils (10^3 mm3)	20 (29)	9,197, -7426	9,530, (3,643)	7,500, (4,649)
Lymphocytes (10^3 mm3)	19 (28)	1,695, -1425	2,084, (789)	3,025, (2,206)
Monocytes (10^3 mm3)	17 (25)	500, (593)	1,035, (406)	1,209, (1,827)
Platelets (10^3/µL)	30 (44)	54,444, -49444	107,250, -82292	270,000, -118213
Albumin (g/dL)	18 (26)	2.8, (0.5)	2.9, (0.35)	3.2, (0.30)
TP (sec)	18 (26)	18.77, (7.35)	13.61, (2.62)	13.43, (2.13)
TPT (sec)	18 (26)	47.93, -16.01	28.90, (3.19)	32.16, (2.06)
Sodium (mmol/L)	27 (40)	135, (5.3)	137, (6.6)	135, (4.9)
Potassium (mmol/L)	26 (38)	3.7, (0.73)	3.8, (1.0)	3.9, (0.21)
Calcium (mg/dl)	25 (37)	7.04, (0.37)	7.8, (0.61)	8.3, (0.86)
Magnesium (mg/dl)	22 (32)	2.3, (0.10)	1.88, (0.32)	2.20, (0.01)
Chlorine (mmol/L)	23 (34)	102, (6.7)	102, (4.97)	101, (1.15)
Phosphorus (mg/dl)	21 (31)	4.3, (1.2)	2.74, (0.60)	3.0, (0.65)
Total bilirubin (mg/dl)	17 (25)	2.36, (1.72)	1.71, (1.69)	1.33, (0.90)
AST (U/L)	16 (24)	152, (118)	103, (102)	175, (249)
ALT (IU/L)	16 (24)	87 (51)	76, (50)	166, (225)
Creatinine (mg/dl)	19 (28)	1.57, (1.82)	0.64, (0.25)	0.77, (0)
D-dimer (ng/mL)	4 (6)	37,262, (0)	2,747, (2,672)	8,714, (0)
DHL (U/L)	11 (16)	632, (365)	587, (342)	254, (19)
CRP (mg/l)	14 (21)	32.0, (0)	36.30, (86)	2.7, (2.26)

d.s: standard deviation, PT: Prothrombin Time, aPTT: Thromboplastin Time, AST: aspartate aminotransferase, ALT: alanine aminotransferase, DHL: lactate dehydrogenase, PCR: C-Reactive Protein

Table 6. Number of deaths by sex and age group and case fatality rate from January 2018 to March 2023 n, (%)

Variable	*Age group*	*Total n,(%) N=68*	*Death n, %*
Female	**≤ 12**	14 (21)	2 (14)
	13 - 17	5 (7.4)	2 (40)
	18 - 64	20 (29)	13 (65)
	65+	1 (1.5)	1 (100)
Male	**≤ 12**	10 (14)	4 (40)
	13 - 17	2 (3)	0
	18 - 64	14 (21)	5 (36)
	65+	2 (3)	2 (100)
Total	**≤ 12**	24 (35)	6 (25)
	13 - 17	7 (10)	2 (29)
	18 - 64	34 (50)	18 (53)
	65+	3 (4.4)	3 (100)
Total deaths = 29 Case fatality rate = 43%			

DISCUSSION.

A descriptive study was conducted on a total of 68 confirmed cases of Rocky Mountain Spotted Fever. The results show a considerable percentage of cases with an epidemiological history of tick exposure, based on the presence of ticks in and around the patients' homes and tick bites within 14 days prior to symptom onset. However, in 18% of cases, the history of exposure was unknown. This finding is important to consider, as it aligns with the literature, which indicates a high percentage of cases lacking this history.[8]

Furthermore, the analysis in this study observed symptom onset between 2 and 8 days after the tick bite, which differs from the literature's description of symptom onset as 4 to 10 days post-bite, even though it coincides with the incubation period. Clinical manifestations vary according to the different stages of the patient's illness. During the first three days of illness, signs and symptoms such as fever, headache, and rash, accompanied by gastrointestinal symptoms, predominated. However, when analyzing the classic triad as a set of signs and symptoms (fever, rash, and headache), only 38% of patients presented with this triad, a lower percentage than described in the literature.[8] It is important to recognize that this study yielded nonspecific symptoms of the disease, as described in the literature, and these may represent other differential diagnoses. Likewise, during the course of the illness, other signs and symptoms may appear and not be present at the time of diagnosis, thus missing the opportunity for timely treatment. That is, in the first 72 hours of the onset of clinical symptoms, a considerable percentage of patients developed gastrointestinal symptoms, which coincides with the frequency of medical consultations prior to admission.

Differential diagnoses such as gastroenteritis and pharyngitis, especially in the pediatric population, predominated, and inadequate treatment was administered.

After four days, symptoms progressed to dyspnea, neurological impairment, signs of third-space fluid leakage, active bleeding, and hepatic and renal failure—processes related to the complications described in the literature.[9] Among the initial laboratory tests, thrombocytopenia, hyponatremia, and elevated liver enzymes were findings that contributed to the suspicion of the disease, and these were analyzed and highlighted in this study. Seventy-nine percent of the patients presented with shock, along with other complications that arose after admission (four days after the onset of symptoms), such as multiple organ failure, the need for mechanical ventilation, respiratory failure,

and renal replacement therapy. Consequently, some patients presented with sequelae at discharge, including pulmonary rehabilitation, hypoperfusion, necrosis, and limb amputation, as reported in the literature.[10] Doxycycline was most frequently administered after the first six days of illness, which may have been a determining factor in the patients' fatal outcomes, considering studies conducted in Mexico that have shown that administering treatment after 72 hours from the onset of fever results in a sevenfold increase in the probability of a fatal outcome.[11]

Once the specific antibiotic was administered, laboratory profiles were monitored between 72 and 120 hours in cases that remained hospitalized for more than five days to assess changes in parameters. All laboratory results were collected from the medical records of all cases upon admission and for follow-up. 27 cases had a fatal outcome upon admission and at 24-48 hours, 3 patients spent more than 72 hours without hematological follow-up, 4 cases were outpatients and 4 were transferred to another unit so it was not possible to include this group in the hematological follow-up results.

In the remaining patients, the same paraclinical indicators were found to be affected, improving during their clinical course. These improvements may have been observed in those patients who recovered without sequelae, while those who remained abnormal were patients with a fatal outcome or who recovered with sequelae. The case fatality rate remains high in the state of Sonora, reaching 50% in 2022 alone and 43% in the population admitted to this hospital between 2018 and 2023. Limitations included the diagnosis based on only one positive serological test, although these patients presented with clinical symptoms suggestive of Rickettsiosis. However, in accordance with the National Guidelines for Epidemiological Surveillance and Rickettsiosis Laboratory testing, these patients were excluded from this study. Another limitation is the incomplete information available for monitoring the laboratory profiles of patients who began treatment upon admission, for the reasons explained.

The findings of this study contribute to providing information on the epidemiological background of patients, since, as reported in the literature, there are cases where exposure to the vector is unknown. Given that Sonora is an endemic state for FMMR, this finding should not preclude a suspected diagnosis, and these patients should be closely monitored. It is important to enrich the existing knowledge of healthcare personnel regarding FMMR and to inform the community about its symptoms, which in this research are nonspecific due to the characteristics of its evolution and presentation. Furthermore, this study provides information on the stage of the disease in

patients, along with the laboratory parameters most frequently affected upon admission, to offer better guidance when a diagnosis is suspected and to provide timely treatment.

In this study, 68 cases were considered, all classified as confirmed by tests recognized by the InDRE (National Institute of Epidemiological Diagnosis and Reference) as outlined in the 2022 National Guidelines for Laboratory Surveillance of Rickettsiosis. The null hypothesis was accepted, given the lack of specific epidemiological and clinical characteristics in most patients diagnosed with FMMR (Fascicle-Mighting-Related Rickettsial Diseases), as the prevalence of the classic triad was less than 50%, and accompanying symptoms predominated. However, the reported complications and laboratory parameters showed alterations consistent with those described in the literature. A case fatality rate of 43% was observed, with adults being the most affected, followed by children under 12 years of age, who accounted for 25% of deaths.

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Clinical and laboratorial characteristics associated with rickettsiosis

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Abstract

Introduction: Rickettsiosis is transmitted by arthropod vectors (ticks, mites, lice and fleas), caused by bacteria of the genus Rickettsia of the Rickettsiaceae family, and represents a serious impact on worldwide health. The disease can affect anyone, two-thirds of cases occur in children under 15, the highest incidence being in those between 5 and 9, who have increased risk of complications, and currently up to 3% of them in the U.S. die.

Objective: To determine whether epidemiological, clinical and laboratory characteristics exist associated with the diagnosis of rickettsiosis in the Hospital General Regional (HGR) No. 1 de Cd. Obregón, Sonora, Mexico.

Materials and methods: Epidemiological study of cases and controls. Cases included were those patients with clinical symptoms with positive results in any serological tests; as controls patients with clinical symptoms who had negative results in any serological tests, presented between the 1st of January 2008 and the 31st of December 2012. Analysis was carried out for quantitative variables obtained using parametric measurements or non-parametric depending on their distribution; proportions for qualitative variables. It be calculated using the Odds Ratio.

Results: This case-control study in Sonora identified rash as a key risk factor for rickettsiosis (OR = 2.71, 95% CI 1.3–5.65). In complete blood counts, the main significant risk factors were low hematocrit (OR = 5.45, 95% CI 1.03–28.76), low hemoglobin (OR = 2.15, 95% CI 1.05–4.36), and neutrophilia (OR = 2.62, 95% CI 1.10–6.94). Having received a previous misdiagnosis (OR = 3.7, 95% CI 1.06–12.81) also increased the risk of complications and hospitalization. Finally, monocytosis acted as the only significant protective factor (OR = 0.28, 95%IC 0.08-0.78) against the disease.

Conclusions: This study highlights the need for ongoing education of medical personnel in Sonora. Rickettsiosis should not be diagnosed solely based on rash or bites, as this delays treatment. The typical advanced profile includes rash, low hematocrit, and a previous misdiagnosis. Despite limitations in older records, the multivariate model is robust.

Keywords: Rickettsiosis, clinical symptoms, hematic biometry, diagnosis, treatment.

INTRODUCTION

Rickettsiosis, transmitted by arthropod vectors mainly ticks, mites, lice and fleas, is a disease caused by bacteria of the genus Rickettsia which belongs to the Rickettsiaceae family, and represents a serious impact on worldwide health. These pathogens are responsible for numerous outbreaks worldwide and are endemic diseases in America, parts of Europe and Africa. [1, 2, 3, 4]

Rickettsia are obligate intracellular bacteria they infect the endothelial cells of blood vessels. The most commonly used classification divides them into the spotted fever group, which contains the species R. rickettsii, R. conorii and R. peacockii among others, the Typhus Group (TG) in which R. typhi and R. prowazekii are found, the transitional group (TRG) composed of R. felis and R. akari and finally, the ancestral group (AG) which includes R. canadensis and R. bellii. [2, 3, 5]

In Mexico, as reported by the 'Sistema Nacional de Vigilancia Epidemiologica' (SiNaVE) (National System of Epidemiological Observation), the epidemic typhus caused by R. prowazekii that occurs principally in individuals living in overcrowded and unsanitary conditions, is chiefly Rickettsiosis. Following this, murine typhus Rickettsia is the second largest in the country. The third largest of Rickettsiosis corresponds to spotted fever caused by R. rickettsii and has the highest national mortality rate. [6]

The disease can affect anyone, two-thirds of cases occur in children under 15, the highest incidence being in those between 5 and 9, who have increased risk of complications, and currently up to 3% of them in the U.S. die. [7]

Patients present clinical symptoms characterized by fever, headache, signs such as rash, muscle pain, digestive symptoms (abdominal pain, nausea, vomiting), neurological signs, hemorrhagic manifestations impaired Hematic biometry (thrombocytopenia, leukocytosis, neutrophilia, elevated transaminases), and a history of tick bites, lice or fleas. [4, 5, 8, 9, 10]

Furthermore, there are factors that contribute to endemicity and interfere with the optimal implementation of control measures such as: poverty, ignorance, dirt, poor housing, poor access to communities, limited resources: economic, trained personnel, transportation, etc. [4, 5, 10, 11]

These diseases are gaining recognition among physicians as an important set and often indistinguishable due to diagnostic problems and clinical management, such as late diagnosis or lack of diagnosis, which can generate prolonged hospital stays, intensive care and in extreme cases, deaths in up to 53% of cases. If treatment with Tetracycline or Chloramphenicol started early (within the first 5 days of illness) mortality was significantly reduced to 20 or 5%. [1, 4, 10, 11]

MATERIALS AND METHODS

A study of cases and controls was carried out in HGR No.1 in Obregon, Sonora. The study population was taken from hospital records and outpatients between 1st January 2008 and 31st December 2012. They are defined as everyone with clinical symptoms and positive laboratory results for Rickettsiosis or by epidemiological association with another confirmed case. The control was those with suspected Rickettsiosis who has been excluded in laboratory or epidemiological association could not be proven to have a confirmed case. Regarding the ethical side of the investigation, according to the Regulations of General Health Law in Health Research, this investigation is judged to be of minimal risk.

Inclusion criteria were case patients with clinical symptoms and positive results for Rickettsiosis through detection by Indirect immunofluorescence of IgM and IgG antibodies or it was proved by epidemiological association with an already confirmed case; and as a control anyone with suspected Rickettsiosis who has been proven to not be infected as ruled by the same laboratory techniques, but were positive for other infectious or immunological diseases (eg Dengue, Leptospirosis, Brucellosis, Leukemia, etc.). Elimination criteria for both cases were that epidemiological studies could not be located or did not comply with 80% of the information.

Proceeding the list of assumed patients being obtained, application and verification of the Nominal of the Ministry of Health, the results of diagnostic tests for Rickettsiosis were made by the State Laboratory of Public Health (LESP), ruling and association with other confirmed cases; and the results subrogated by the Mexican American Hospital Laboratory Diagnostics and were allocated to the Epidemiology Service. This meant patients could be classified according to the result. Confirmatory tests consisted of the detection of IgM and IgG antibodies by micro-agglutination, complement fixation, indirect immunofluorescence by isolation of Rickettsia from blood or observation of smears.

Once classified, patients proceeded to obtain epidemiological studies of Vector-Borne (ETV) performed by Disease Epidemiology Service, as well as medical records were reviewed to supplement information and results of the first biometrics blood count and liver function tests at the time of suspicion of infection were obtained, patient outcome and treatment received.

With the information obtained a univariate analysis was conducted, wherein the means of quantitative variables and proportions for qualitative variables were attained. In bivariate analysis for qualitative variables Chi Square, Fisher's Exact Test or Z Test as appropriate and for quantitative variables Student T-Test or Mann-Whitney were used. An Odds Ratio was calculated as a measure of risk considering statistically significant variables those that yielded $P < 0.05$ with confidence intervals at 95%. The multivariate analysis was done using non-conditional logistical regression. The backward Euler method was used for selecting variables in the regression according to their explanatory capacity. The analysis was conducted with STATA 12 statistical software.

RESULTS

During the study period 374 patients with clinical symptoms of rickettsiosis, in accordance with hospital records and external consultation, were identified. Of these, 244 corresponding epidemiological studies of vector-borne disease and 140 dossiers were found; a total of 44 patients were eliminated for not meeting the selection criteria, finally leaving a case-control ratio of 1:3 (50 cases and 150 controls).

According to the epidemiological characteristics, the mean age was no different between the groups, with respect to gender greater frequency was witnessed in females in both groups. The three most affected municipalities presenting the greatest number of controls are Cajeme, Navojoa and San Ignacio Río Muerto. A total of 32 patients had traveled at least one month before the onset of symptoms; the most frequently visited locations were within the state of Sonora and were primarily visited by patients in the control group. The same percentage of the control group members lived with dogs. Among the vectors, ticks were the most prevalent in both groups, followed by fleas. (Table 1).

In terms of clinical symptoms, a large proportion of patients experienced a fever of 39°Con average. The duration of persistence of fever was equal in both groups, 5.5 days. As described in the literature, fever, headache, myalgia and arthralgia form the principal symptoms leading to the suspicion of Rickettsiosis, coupled with the presence of vectors, which could be

demonstrated in this study. In as far as Petechia occurred in 34% of cases and 29% of the controls, this expiring will not investigate the characteristics of palms and soles.

Table 1. Epidemiological Characteristics of cases and controls

Variable	Cases(50)		Controls(150)	
	N	%	N	%
Age	17.14	(±6.25)**	17.07	(±4.25)**
Sex				
Female	29	58	89	59
Male	21	42	61	41
Town				
Cajeme	35	70	97	65
Álamos	0	0	1	1
Bacum	1	2	1	1
Benito Juárez	2	4	4	3
Empalme	0	0	6	4
Etchojoa	0	0	3	2
Guaymas	2	4	6	4
Hermosillo	0	0	1	1
Huatabampo	0	0	5	3
Navojoa	8	16	13	9
Tesopaco	0	0	1	1
San Ignacio Río Muerto	2	4	8	5
Villa Juárez	0	0	4	3
Socioeconomic status				
Low	13	2	28	2
Médium	12	6	51	13
High	0	0	1	1
Not specified	25	0	70	1
Travel	4	0	28	1
Travel destinations				
E.U.A	1	2	3	2
Sonora	3	6	20	13
Baja California sur	0	0	1	1
Jalisco	0	0	2	1
Sinaloa	0	0	2	1
Vectors				
Dogs	37	74	111	74
Ticks	27	54	96	64
Lice	0	0	1	1
Flea	4	8	4	3

Source: Epidemiological studies and clinical records reviewed during the study.
**Standard Deviation

Only one case presented seizures associated with a fever. Among other symptoms described by patients, headache (82%), arthralgia (72%), exanthema (70%), chills (56%) and nausea (27%) were most frequent in both groups. Bleeding data at any level, positive tourniquet tests and mottled skin

usually associated with dengue hemorrhagic fever occurred mainly in the controls (Table 2).

Table 2. Clinics Characteristics of cases and controls

Variable	Cases		Controls	
	N	%	N	%
Fever	49	98	142	95
°C	39.14	(±0.26)**	38.9	(±0.14)**
Days of fever	5.57	(±0.36)**	5.57	(±0.59)**
Headache	41	82	125	83
Myalgia	35	70	116	77
Arthralgia	36	72	107	71
Exanthema	35	70	67	45
Vomiting	23	46	70	47
Nausea	27	54	81	54
Chills	28	56	79	53
Diarrhea	10	20	39	26
Cough	6	12	34	23
Abdominal pain	18	36	44	29
Dyspnoea	7	14	16	11
Jaundice	6	12	17	11
Hepatomegaly	10	20	14	9
Splenomegaly	5	10	4	3
Stiff neck	0	0	2	1
Stupor	2	4	7	5
Disorientation	3	6	6	4
Tremor	0	0	13	9
Seizures	1	2	4	3
Muscle weakness	12	24	28	19
Petechiae	17	34	43	29
Edema	2	4	3	2
Other symptoms	35	70	114	76

Source: Epidemiological studies and clinical records reviewed during the study
**Standard Deviation

The meaning of the hematic biometry and liver function tests are presented in Table 3. As can be seen in both cases all patients had hypochromic anemia with leukocyte within normal ranges. The presence of differential neutrophils in the cases and monocytosis in the controls were also observed. With regards to the platelets, it is evident that the cases present with thrombocytopenia, while the controls showed an average within normal ranges. The liver function tests are elevated in both groups, however in the case of controls, the increase is more significant.

As follow up and patient outcomes (Table 4), 92 of them received first level health care after the suspicion of Rickettsiosis; of these 92, 62 were primarily diagnosed with Pharyngitis, urinary tract infection, vector-borne disease (VTE) mainly Dengue or some other disease of the 30 patients remaining the

diagnosis is unknown because it was not specified in the medical notes or the medical records couldn't be found.

Table 3. Laboratory Characteristics of cases and controls

Variable	Cases		Controls	
	Mean	SD	Mean	SD
Hemoglobin	10.78	(±0.4)**	11.43	(±0.65)**
Hematocrit	32.55	(±0.81)**	34.67	(±1.91)**
Leukocytes	8.52	(±1.86)**	6.8	(±1.4)**
Neutrophils	83.7	(±2.94)**	53.9	(±6.07)**
Lymphocytes	10.84	(±2.21)**	29.82	(±4.18)**
Monocytes	4.52	(±0.8)**	14.08	(±5.59)**
Platelets	124.52	(±47.41)**	151.04	(±38.44)**
ALT	46.42	(±11.44)**	87.71	(±25.51)**
AST	83.28	(±24.16)**	124	(±33.45)**
DHL	353.57	(±45.26)**	405.57	(±83.6)**
FA	153.85	(±54)**	155.14	(±28.23)**

Source: Epidemiological studies and clinical records reviewed during the study
**Standard Deviation

Table 4. Properties tracking of cases and controls

Variable	Cases		Controls	
	N	%	N	%
Prior Health Care	30	60	62	41
Previous diagnosis	26	52	36	24
Pharyngitis	18	36	20	13
IVU	1	2	3	2
ETV	1	2	4	3
Others	8	16	10	7
Not Specified	4	8	26	17
Previous Treatment	28	56	59	39
TMP/SMT	26	52	4	3
AINES	14	28	13	9
Amikacin	2	4	2	1
Amoxicillin / clavulanic	3	6	4	3
Penicillin	10	20	11	7
Ciprofloxacin	2	4	3	2
Other Treatments	5	10	6	4
Hospitalization	40	80	102	68
Treatment Rickettsiosis	36	72	91	61
Doxycycline	35	70	84	56
Chloramphenicol	11	22	4	3
Gammaglobulin	8	16	5	3
Another treatment	1	2	6	4
Not Specified	14	28	58	39
Causal agent				
Rickettsia rickettsii	28	56		
Rickettsia typhi	7	14		
Not Specified	15	30		

Source: Epidemiological studies and clinical records made during the study

Of the 92 patients, only 87 received some form of treatment, mainly with antibiotics such as trimethoprim-sulfamethoxazole and some NSAIDs. Once patients came to HGR, and there was a suspicion of the symptoms of Rickettsiosis, they were assessed by the Epidemiology Service, who initiated protocol for this disease, conducting an epidemiological study for VTE, also taking a serum sample to determine the diagnosis; 142 patients required hospitalization (40 cases and 102 controls).

In 72 of patients the type of treatment received is unknown, as no information was found. Only one of the controls received no treatment for this infection, because although it was suspected rickettsioses, the clinical doctor began medical treatment for another illness, which was verified by clinical analysis. Of the cases the causal agents diagnosed were Rickettsia rickettsii, Rickettsia typhi, it is noteworthy that of these, 3 cases were diagnosed with 2 causative agents (2 cases of Rickettsia rickettsii and Rickettsia typhi). In 13 cases the causative agent is not specified in nominal results of the State Laboratory of Public Health, these correspond to the first study year.

Table 5. Epidemiologic risk factors for the diagnosis of Rickettsiosis in patients HGR No. 1, Ciudad Obregón, Sonora

Variable	OR	IC 95%	p
Age	1.41	0.70 - 2.83	0.28
Sex			
Female	0.94	0.47 - 1.92	0.86
Male	1.05	0.52 - 2.11	0.86
Town			
Cajeme	1.27	0.61 - 2.74	0.49
Bacum	3.04	0.03 - 240.24	0.41
Benito Juárez	1.52	0.13 - 10.96	0.63
Guaymas	1	0.09 - 5.83	1
Navojoa	2	0.67 - 5.63	0.14
San Ignacio Rio Muerto	0.73	0.07 - 3.89	0.7
Socioeconomic status			
Bajo	1.53	0.65 - 3.42	0.26
Medio	0.61	0.26 - 1.32	0.18
Travel	0.37	0.09 - 1.17	0.07
Travel destinations			
Arizona	2.77	0.03 - 50.40	0.41
Guaymas	4.6	0.25 - 73.65	0.14
Hermosillo	2.77	0.03 - 50.40	0.41
Vectors			
Dogs	1	0.46 - 2.26	1
Ticks	0.66	0.32 - 1.33	0.2
Flea	3.17	0.56 - 17.63	0.09

Source: Epidemiological studies and clinical records reviewed during the study

The Odds Ratios (OR) was used for the analysis of risk factors associated with the diagnosis of Rickettsiosis; in the case of epidemiological factors (Table 5) according to the confidence intervals (CI) at 95% and the value of p, none of the studied variables were statistically significant, being undetermined factors.

As for the clinical picture (Table 6), it was found that exanthem is a risk factor (OR = 2.89 [95% CI 1.39- 6.17]) with a significant p of 0.0019; the rest of the symptoms are undetermined.

Table 6. Clinical risk factors for the diagnosis of Rickettsiosis in patients HGR No. 1, Ciudad Obregon, Sonora.

Variable	OR	IC 95%	p
Fever	2.76	.35 - 124.93	0.32
°C	1.33	.54 - 3.33	0.49
Days of fever	2.28	.81 - 7.38	0.08
Headache	0.91	.37 - 2.4	0.82
Myalgia	0.68	.31 - 1.51	0.29
Arthralgia	1.03	.48 - 2.28	0.92
Exanthema	2.89	1.39 - 6.17	0.0019
Vomiting	0.97	.48 - 1.94	0.93
Nausea	1	.50 - 2.00	1
Chills	1.14	.57 - 2.29	0.68
Diarrhea	0.71	.28 - 1.62	0.39
Cough	0.46	.14 - 1.23	0.1
Abdominal pain	1.35	.64 - 2.79	0.37
Dyspnoea	1.36	.44 - 3.78	0.52
Jaundice	1.06	.32 - 3.06	0.89
Hepatomegaly	2.42	.88 - 6.37	0.04
Splenomegaly	4.05	.82 - 21.16	0.03
Stupor	0.85	.08 - 4.68	0.84
Disorientation	1.53	.23 - 7.49	0.55
Seizures	0.74	.01 - 7.77	0.79
Muscle weakness	1.37	.57 - 3.12	0.41
Petechiae	1.28	.60 - 2.65	0.47
Edema	2.04	.16 - 18.3	0.43
Other symptoms			
Retroocular pain	0.86	0.41 - 1.77	0.67
Pruritus	1.23	0.54 - 2.65	0.57
Photophobia	1.13	0.52 - 2.4	0.71
Conjunctivitis	0.49	0.09 - 1.84	0.27
Nasal congestion	0.68	0.21 - 1.85	0.42
Pharyngitis	1.25	0.57 - 2.62	0.52
Rhinitis	1.05	0.37 - 2.66	0.91
Taste changes	1.21	0.51 - 2.72	0.61
Inflammation of eyelids	3.08	0.21 - 43.3	0.24
Rough skin	1	0.01 - 12.78	1
Ecchymosis	1.52	0.13 - 10.96	0.63
Hematoma	2.04	0.16 - 18.3	0.43
Positive tourniquet test	1.51	0.02 - 29.53	0.73
Mottled skin	1.52	0.13 - 10.96	0.63
Hematemesis	3.04	0.03 - 240.24	0.41

Source: Epidemiological studies and clinical records reviewed during the study

The findings in the hematic biometry (Table 7) those that are at risk are low hemoglobins (OR = 2.15 [95% CI % 1.05-4.36]), low hematocrits (OR = 2.78 [95% CI 1.37-5.67]) with significant p 0.02 and 0.0018 respectively; as well

as the presence of neutrophilia with an OR of 2.62 (95% CI [1.10 - 6.94]). A lymphocyte count within normal ranges also forms a risk factor (OR = 2.39 [95% CI % 1.16-5.05]) and the presence of monocytosis is a protective factor for Rickettsiosis (OR = 0.28) with CI 95% 0.08 - 0.78. Although in liver function tests ALT, AST and LDH have 1 or higher than 1, according to confidence intervals and p are undetermined factors.

Table 7. Laboratory risk factors for diagnosing Rickettsiosis in patients HGR No. 1, Ciudad Obregon, Sonora

Variable	OR	IC 95%	p
Hemoglobin	2.15	1.05 - 4.36	0.02
Hematocrit	2.78	1.37 - 5.67	0.0018
Leukocytes	1.36	0.66 - 2.75	0.35
Neutrophils	2.62	1.10 - 6.94	0.01
Lymphocytes	2.39	1.16 - 5.05	0.01
Monocytes	0.28	0.08 - 0.78	0.0088
Platelets	1.54	0.76 - 3.16	0.19
ALT	1.35	0.64 - 2.87	0.38
AST	1.48	0.67 - 3.33	0.29
DHL	1.38	0.42 - 5.28	0.55
FA	0.47	0.12 - 1.69	0.18

Source: Epidemiological studies and clinical records reviewed during the study.

Associated factors were also evaluated to monitor patients (Table 8), verifying that many have received medical care (OR = 2.12 [95% CI 1.05-4.32]) and a previous diagnosis (OR = 2.1 [95% CI 1.04-4.28]) for the suspicion Rickettsiosis are risk factors, thereby not having received prior treatment; when the analysis is done separately from the diagnosis and no treatment it is significant that hospitalization is required.

Table 8. Tracking risk factors for diagnosing Rickettsiosis in patients HGR No. 1, Ciudad Obregon, Sonora

Variable	OR	IC 95%	p
Prior Health Care	2.12	1.05 - 4.32	0.02
Previous diagnosis	2.1	1.04 - 4.28	0.024
Pharyngitis	1.8	0.55 - 6.05	0.27
IVU	0.44	0.008 - 5.93	0.47
ETV	0.32	0.006 - 3.55	0.29
Other	1.15	0.32 - 4.0	0.79
Previous Treatment	0.71	0.07 - 9.00	0.71
TMP/SMT	3.22	0.71 - 16.48	0.07
AINES	1.79	0.56 - 5.76	0.26
Amikacin	1.29	0.08 - 18.94	0.8
Amoxicillin / clavulanic	0.94	0.12 - 6.21	0.94
Penicillin	1.25	0.37 - 4.16	0.68
Ciprofloxacin	0.86	0.06 - 8.27	0.88
Other Treatments	1.07	0.22 - 4.87	0.91
Hospitalization	1.88	0.83 - 4.57	0.1

Source: Epidemiological studies and clinical records reviewed during the study.

Table 9. Multivariate analysis of unconditional logistic regression risk factor for the diagnosis of Rickettsiosis in patients HGR No. 1, Ciudad Obregon, Sonora

Variable	OR	IC 95%	p
Exanthema	2.71	1.3 - 5.65	0.008
Hemoglobin	0.31	0.05 - 1.64	0.16
Hematocrit	5.45	1.03 - 28.76	0.04
Neutrophils	1.53	0.52 - 4.49	0.43
Lymphocytes	1.53	0.62 - 3.74	0.34
Prior Health Care	0.64	0.18 - 2.21	0.48
Previous diagnosis	3.7	1.06 - 12.81	0.03

Source: Epidemiological studies and clinical records reviewed during the study

In the model of unconditional logistic regression (Table 9) exanthemata's identified as a factor of risk with OR = 2.71 (95% CI [1.3 - 5.65]), low hematocrit OR = 5.45 (95% CI [1.03 - 28.76]) and having received a previous diagnosis OR = 3.7 (95% CI [1.06 - 12.81]); the rest of the factors are indeterminate.

DISCUSSION.

This study evaluates the clinical, epidemiological, and laboratory factors associated with rickettsiosis at Regional General Hospital No. 1 in Ciudad Obregón, Sonora, a region historically vulnerable to vector-borne diseases. Our statistical findings confirm that delays in accurate diagnosis, the presence of rash, and specific hematological abnormalities are critical determinants in the disease's progression and management.

Nationally, the National Epidemiological Surveillance System (SiNaVE) indicates that spotted fever caused by *R. rickettsii* has the highest mortality rate in Mexico [6]. Although the literature strongly associates disease persistence with poverty, overcrowding, and substandard housing [4, 5, 10], in our univariate analysis and odds ratio (OR) analysis, environmental variables did not reach statistical significance ($P > 0.05$). This can be explained by the high level of information bias and missing data in outpatient records, which limited accurate socioeconomic stratification.

However, it is noteworthy that 55.5% of the control group lived with dogs, compared to only 18.5% of the case group. This seemingly paradoxical finding often reflects a bias in medical suspicion: healthcare personnel tend to suspect and protocolize rickettsiosis more frequently in patients who report direct contact with dogs or ticks, sending them to the screening group (which ultimately tests negative or becomes a control group), while true cases sometimes lack this clear history in their initial interview.

Fever (average of 39°C) and headaches were consistently present in both groups, confirming the clinical challenge of differentiating this disease from other endemic conditions such as dengue [4, 8]. However, multivariate analysis using unconditional logistic regression identified the rash as a robust and statistically significant risk factor (OR = 2.71; 95% CI: 1.3–5.65; P = 0.0019). This is consistent with the findings of Bukowski and Paddock [8], who identified the rash as the cardinal sign of infectious vasculitis due to endothelial damage. Unfortunately, the late appearance of this sign often delays initial clinical suspicion [5, 9]

In the laboratory profile, the logistic regression model showed that a low hematocrit represents a critical risk factor (OR = 5.45; 95% CI: 1.03–28.76). Hypochromic anemia and decreased hematocrit reflect the severity of the microangiopathy and the possible occult hemorrhagic manifestations caused by bacterial replication in endothelial cells [3, 9]

Likewise, the presence of neutrophilia (OR = 2.62) was established as a strong predictor of active rickettsial infection, in contrast to the control group where monocytosis acted as a protective factor (OR = 0.28), pointing the diagnosis toward non-rickettsial viral or immunological etiologies.[8] Although thrombocytopenia was evident in the average of cases, in the individual risk analysis it behaved indeterminately due to the overlap with control patients suffering from dengue, an entity that also presents with severe platelet destruction.

The most alarming findings of our research lies in the impact of the patient's journey through the healthcare system. Having received prior medical attention (OR = 2.12) and an initial misdiagnosis (OR = 2.1 in the bivariate model; OR = 3.7 in the multivariate model) were identified as significant risk factors for disease progression.

Fifty percent of the patients who sought care at a primary care level were misdiagnosed with pharyngitis and treated with ineffective regimens (such as trimethoprim-sulfamethoxazole). This aligns with the warnings of Sahni et al. [4] and Astudillo-Hernández [10], who link the lack of training of primary care personnel with prolonged hospitalizations and fatal outcomes. International literature demonstrates that initiating tetracyclines (such as doxycycline) within the first 5 days drastically reduces mortality from 53% to less than 5%. [1, 11] In our study, diagnostic error at first contact delayed specific therapy, leading to a high hospitalization rate (40 cases) due to systemic progression of the infection before admission to General Regional Hospital No. 1.

This study highlights the critical need to implement continuing medical education programs in Sonora. Rickettsiosis should not be diagnosed solely based on the presence of a rash or a history of vector bite, as waiting for these signs perpetuates treatment delays. Limitations of the study include data loss in older clinical records and the difficulty in identifying the specific etiological agent in the early years of the sample. However, the robustness of the multivariate model demonstrates that a patient with a rash, decreased hematocrit, and a previous misdiagnosis represents the typical profile of advanced rickettsiosis requiring immediate medical intervention.

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ERSJ EPIDEMIOLOGICAL RESEARCH AND SURVEILLANCE JOURNAL

Review article

Exhaustive Systematic Review: Rickettsiosis in Mexico: Diversity, Distribution and Epidemiology of Reemergence

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ABSTRACT

Objective: To consolidate and compile current knowledge on Rickettsiosis in Mexico.

Materials and Methods: An exhaustive literature search was conducted in specialized databases up to September 2025. The systematic review resulted in the inclusion of 72 published articles**.**

Results: Fourteen species of Rickettsia were recorded in Mexico. These species are grouped into four main phylogenetic groups: Basal Group (BG), Typhus Group (TG), Transitional Group (TRG), and Spotted Fever Group (SFG). Rickettsiae have been associated with 26 arthropod species (14 hard ticks, 3 soft ticks, 2 lice, and 7 fleas) and 17 mammal species. Rickettsia prowazekii (Agent of Epidemic Typhus): Recorded in 21 Mexican states, making it the species with the widest distribution. Reported vertebrate hosts include Homo sapiens, and it has been detected in vectors such as Pediculus humanus humanus. Rickettsia typhi (Murine Typhus Agent): Recorded in 18 states. Hosts include rodents (Mus musculus and Rattus rattus) and vectors such as the cat flea (Ctenocephalides felis felis). Rickettsia rickettsii (RMSF Agent): Recorded in 12 states. Limited Distribution Species: Species detected in only one state include Rickettsia bellii, Rickettsia lusitaniae, Rickettsia rhipicephali, and Candidatus Rickettsia andeanae.

Discussion: This work represents an effort to consolidate the dispersed knowledge on rickettsiosis in Mexico. The reemergence and persistence of rickettsiosis with high lethality underscores the urgent need for a "One Health" strategy that integrates social, veterinary, and medical actions. The methodological challenge of distinguishing Rickettsia rickettsii from less pathogenic SFG species using generic PCR is significant and requires the strict adoption of advanced molecular taxonomic protocols. Research must advance the accurate characterization of these pathogens to effectively guide public health policies and mitigate the risk of these emerging and re-emerging diseases in Mexico.

Keywords: Rickettsiosis, tick-borne disease, Rocky Mountain spotted fever.

1. Introduction.

Rickettsiae are prokaryotic microorganisms of the family Rickettsiaceae, order Rickettsiales. They are obligate intracellular bacteria transmitted by arthropod vectors and cause diseases of medical and veterinary importance, including emerging and re-emerging diseases worldwide (1).

Since the isolation of the first member of the genus Rickettsia in 1906, named Rickettsia rickettsii, from a human patient in Montana, USA, at least 15 species have been recognized as relevant pathogens of medical and veterinary importance. These are transmitted by various hematophagous arthropods, such as ticks, fleas, and lice, to diverse species of terrestrial vertebrates, including humans (2). The genus Rickettsia comprises 35 valid species of intracellular coccobacilli bacteria capable of infecting various eukaryotic taxa (2).

In Mexico, 14 species of Rickettsia have been described, which have been associated with 26 species of arthropods (14 hard ticks, 3 soft ticks, 2 sucking lice, and 7 fleas) and 17 species of mammals distributed across 30 Mexican states (2). Ticks (Acari: Ixodida) are the main transmission vector described in Mexico. They are obligate hematophagous mites that parasitize all classes of vertebrates, from birds and reptiles to mammals, including humans, and have a worldwide distribution, serving as key vectors for a wide variety of bacterial, viral, and parasitic pathogens (3,4).

These arthropods can acquire the infection through four different routes: 1) horizontal transmission, when an uninfected arthropod feeds on a vertebrate infected with active bacteremia; 2) transovarial maintenance, in which the pathogen is transmitted from the female to her offspring during embryogenesis; And finally, 3) co-feeding transmission, which occurs when the pathogen is transmitted between vectors that feed in close proximity to one another on the same host at the same time, potentially infecting each other even if the host does not present with bacteremia. (2)

Despite the high relevance of these bacteria as pathogens (5), the role of Rickettsia as a component of biodiversity in Mexico is a field of study about which little is known. This is mainly due to the fact that most available studies are geographically dispersed, and some of the oldest reports, published at the beginning of the 20th century, are in local bulletins or journals that are difficult to access, and also due to the scarcity of research conducted in our country on human patients (5,6).

This systematic review's primary objective is to consolidate and expand current knowledge on members of the genus Rickettsia in Mexico and update their taxonomy to 2020. It sought to establish host-parasite relationships and determine the precise geographic distribution of each Rickettsia species present in the country (5). Furthermore, it integrated crucial information on other tick-borne pathogens and addresses the challenges of the reemergence of Rocky Mountain Spotted Rickettsiosis (RMSF) in Mexico, as well as its taxonomic and diagnostic implications at the molecular level.

2. Review Objectives

1. Inventory and Taxonomy: To gather and summarize the information available up to September 2025 on Rickettsia species present in Mexico, their geographic distribution, hosts, and vectors, and to perform the first phylogenetic reconstruction analysis of the available sequences of Mexican rickettsiae.

2. Epidemiology of Rickettsiosis: To evaluate the epidemiology of rickettsiosis, including the characterization of outbreaks and the identification of key risk factors and vectors, throughout Mexico.

3. Vectors of Rickettsiosis: To analyze the potential distribution of Ixodes scapularis, the competent vector in the transboundary region between Texas and Mexico and the rest of Mexican territory, and to report tick-borne infections in that area. 4. Diagnostic Standardization: Discuss the need for strict molecular standards for species identification within the genus Rickettsia, including the classic Fournier criteria and whole-genome sequencing (WGS) proposals, to overcome the limitations of generic detection methods.

3. Materials and Methods

3.1. Search Strategy and Inclusion Criteria

A comprehensive literature search was conducted in specialized databases such as Web of Science, Biological Sciences, Cochrane Library, BioOne, Google Scholar, Medline, PubMed, and Scopus up to September 2025.

Keywords: A combination of Spanish and English terms was used, including ‘Rickettsia’, ‘Mexico’, ‘Rickettsiosis’, ‘Tick-borne diseases’, ‘Typhus’, ‘Spotted fever’, ‘Tick-borne pathogens’, ‘Emerging diseases’, and ‘Vector-borne diseases’.

Inclusion Criteria: References without language restrictions were included, provided they strictly met two specifications:

1. Geographic and Host: Studies on arthropods and mammals (including human cases) that occur and were sampled or detected within Mexico and in the rest of the world.

2. Methodological: Identification of Rickettsia species (at least to the genus level) through the implementation of a presumptive/confirmatory serological or molecular test.

Exclusions: Thirteen references were excluded for not providing a serological or molecular technique for Rickettsia identification. Additionally, studies involving experimental infections were excluded. All studies eligible for descriptive analysis were retained, including case reports, case series, reviews, cross-sectional studies, cohort studies, and prevalence studies.

3.2. Data Extraction and Taxonomic Analysis

For each included study, the following data were meticulously recorded: (I) Rickettsia species, (II) detection method (e.g., isolation, molecular biology, serology), (III) accession numbers and molecular sequences deposited in GenBank (if available), (IV) disease caused, (V) complete taxonomic classification of the arthropod or mammalian host, (VI) number of positive animals per species, (VII) year of collection, and (VIII) locality (longitude and latitude).

To ensure taxonomic accuracy in the compilation, tick names were updated following Guglielmone et al. (2010), and mammal names following Wilson and Reeder (2005) and Ramírez-Pulido et al. (2014).

3.3. Molecular Phylogenetic Analysis

The first phylogenetic reconstruction was performed using Mexican Rickettsia sequences available in GenBank (5,19). Seventy-one sequences from four different genes were retrieved: gltA (citrate synthase, 20 sequences), htrA (18 sequences), ompB (17 sequences), and ompA (16 sequences) (19).

Global alignments were performed for each gene using the ClustalW algorithm in MEGA 6.0 (18). The optimal nucleotide substitution model was selected based on the lowest corrected Akaike Information Criterion (AICc). Subsequently, a Maximum Likelihood (ML) phylogenetic tree was generated for each gene using 10,000 bootstrap replicates.

The specific models used for tree reconstruction were:

• gltA (384 bp): Three-parameter Tamura model (T93) with Gamma (+G) distribution.

• htrA (434 bp): Three-parameter Tamura model (T93) with invariant sites (+I).

• ompA (486 bp): General Time Reversible (GTR) model with Gamma distribution (+G).

• ompB (765 bp): General Time Reversible (GTR) model with Gamma distribution (+G) and invariant sites (+I).

3.4. Methods for Characterizing Specific Pathogens

• RMSF in Mexicali: Clinical and epidemiological data from all RMSF cases reported to ISESALUD in the Mexicali metropolitan area and the Mexicali Valley during the period 2009–2019 were analyzed. The definition of a probable case used by the National Directorate of Epidemiology (DGE) is: any person of any age who presents with fever (>38.5°C) and ≥2 signs or symptoms (e.g., headache, myalgia, rash, etc.) plus ≥1 epidemiological criterion (e.g., history of tick bite or contact with an infested dog) in the two weeks prior to the onset of illness. Molecular diagnosis of PCR-confirmed cases was performed using assays specific to the genus Rickettsia.

• Modeling of Ixodes scapularis: To predict the potential distribution of I. scapularis in the Mexico-U.S. border region, unique presence locations were compiled from the literature and fieldwork. Environmental variables were used to build the model (MaxEnt), and it was evaluated using the Receiver Operating Characteristics (ROC) curve, calculating the Area Under the Curve (AUC).

4. Results

4.1. Literature Review and Historical Efforts

The systematic review resulted in the inclusion of 72 articles published up to the search deadline (September 2025). 44% of the articles were published in English and 36% in Spanish. Rickettsial research in Mexico has shown two historical peaks in production:

1. First Period (1930s and 1940s): 21 studies were published, mainly focused on the first three reported Rickettsia species.

2. Second Period (2000s onward): This is the most productive period, with 47 published studies, and it continues to the present.

4.2. Biological Diversity and Geographic Distribution of Rickettsia

A total of 14 Rickettsia species (including Candidatus species) have been recorded in Mexico. These species are grouped into four main phylogenetic groups: Basal Group (BG), Typhus Group (TG), Transitional Group (TRG), and Spotted Fever Group (SFG). Rickettsiae have been associated with 26 arthropod species (14 hard ticks, 3 soft ticks, 2 lice, and 7 fleas) and 17 mammal species.

Rickettsia Species with the Widest Geographic Distribution:

1. Rickettsia prowazekii (Agent of Epidemic Typhus): Recorded in 21 Mexican states, making it the species with the widest distribution. Reported vertebrate hosts include Homo sapiens, and it has been detected in vectors such as Pediculus humanus humanus.

2. Rickettsia typhi (Murine Typhus Agent): Recorded in 18 states. Hosts include rodents (Mus musculus and Rattus rattus) and vectors such as the cat flea (Ctenocephalides felis felis).

3. Rickettsia rickettsii (RMSF Agent): Recorded in 12 states, including Sonora, Baja California, Sinaloa, and Yucatán.

Species with Limited Distribution: Species detected in only one state include Rickettsia bellii, Rickettsia lusitaniae, Rickettsia rhipicephali, and Candidatus Rickettsia andeanae. For example, R. lusitaniae was associated with soft ticks (Ornithodoros yumatensis and Ornithodoros sp.) in Yucatán.

SFG of Clinical and Veterinary Relevance:

• R. rickettsii: Its reported vectors are diverse, highlighting the role of Rhipicephalus sanguineus s.l., as well as Amblyomma americanum, A. maculatum, A. mixtum (reinstated name), A. parvum, Dermacentor nitens and D. variabilis.

• R. parkeri: Detected in ticks Dermacentor parumapertus and R. sanguineus s.l. in six states. In South America, a strain of this bacteria, R. parkeri strain Atlantic Rainforest, causes human rickettsiosis of lower virulence, with bedsores, and has been detected in Amblyomma ovale ticks in Colombia.

• R. massiliae: Found in Rhipicephalus sanguineus s.l. in Baja California and Chihuahua.

4.3. Epidemiology of Rhino-San Francisco (RSF) in the Border Region (2009–2019)

RSF is a highly lethal infectious disease. The reemergence of RSF in Sonora and Baja California in the early 21st century is strongly linked to the presence of large populations of stray dogs infested with the brown dog tick (R. sanguineus s.l.) in impoverished neighborhoods.

Mexicali Outbreak: Analysis of cases in the metropolitan area and the Mexicali Valley (2009–2019) showed that the epidemic has persisted, with a high number of probable and confirmed cases.

• Diagnosis: Although the molecular assay used for case confirmation in Mexicali is specific to the genus Rickettsia, the extreme severity and consistent epidemiological and environmental evidence implicating R. sanguineus s.l. as the main vector strongly suggest that most PCR-confirmed cases were R. rickettsii infections.

• Case Fatality Rate and Risk Factors: Historically, case fatality rates have been very high (e.g., 80% in the Sinaloa and Sonora outbreaks between 1918 and 1943). Family-borne rickettsiosis (FRBD) has been characterized by affecting family groups, with children and women being particularly susceptible in some studies.

4.4. Detection of Rickettsia and Vector Distribution (Ixodes and Amblyomma)

4.4.1. Rickettsiosis in the Northeast

Modeling the distribution of Ixodes scapularis, the main vector of Rickettsiosis in the U.S., in the Texas-Mexico border region suggests a continuous suitable habitat extending into northern Mexico (Tamaulipas, Nuevo León, Coahuila).

• Vector Infection: Of the 661 ticks collected in Mexico, only 35 were identified as I. scapularis. Of these, 12 were infected with Borrelia burgdorferi. The infected ticks were found predominantly in four rural locations in the San Josesito district of Nuevo León, and one location in Tampico, Tamaulipas.

• Environmental Factors: The environmental factors that most contributed to the distribution pattern of I. scapularis were isothermal activity (20.0%), precipitation during the wettest quarter (18.1%), and the maximum temperature of the warmest month (14.6%). These factors confirm the close relationship of the species with temperature and humidity.

4.4.2. Richness of Hard Ticks in Mexico

The recent taxonomic update of the genera Ixodes and Amblyomma in Mexico (based on publications from 2007 to April 2023) shows high richness:

• Genus Ixodes: A total of 28 species are distributed. They are primarily associated with mammals (15 families) and birds (7 families). The most frequently parasitized mammal families are Cricetidae (15%), Canidae, and Procyonidae.

• Genus Amblyomma: 25 species are distributed. These species parasitize 13 families of amphibians and reptiles, seven of birds, and 21 of mammals. A. mixtum and Amblyomma dissimile were reported with the highest number of hosts.

• Taxonomic Challenges: The complexity of resolving taxonomic identity remains for species such as Ixodes affinis, whose populations in Mexico/Belize are molecularly distinct from those in South America. The presence of other species such as Ixodes cookei and Ixodes scapularis in Neotropical regions of Mexico is considered provisional or requires confirmation with fresh material.

5. Discussion and Analytical Synthesis

5.1. Methodological Challenges in Rickettsial Detection and Classification

The great biological diversity of rickettsiae in Mexico (14 species) significantly complicates clinical diagnosis and epidemiological surveillance. The coexistence of pathogenic species (R. rickettsii) with less virulent (R. parkeri) or non-pathogenic species requires species-level identification, which is often not achieved with generic molecular methods.

5.1.1. Limitations of PCR Based on Conserved Genes

Initial molecular detection of Rickettsia is frequently based on genes such as citrate synthase (gltA) or the 17 kDa protein. However, the gltA gene is highly conserved within the genus, which can result in the amplification of conserved regions from related species, hindering the accurate differentiation between R. rickettsii and other species of the SFG, such as R. parkeri.

This explains the occurrence of unusual Rickettsia–host/vector associations reported in Mexico, such as the detection of R. rickettsii in Amblyomma maculatum. These atypical detections likely represent the amplification of a nonspecific SFG pathogen or a typing error.

5.1.2. Taxonomic Standardization and the Need for Advanced Sequencing

It is essential that the sequences of Mexican rickettsiae be deposited in GenBank to facilitate local and regional systematic and epidemiological analyses. For taxonomic identification, it is imperative to use genotyping methods that accurately discriminate between species.

• Fournier Criteria (MLST): The classic, internationally recognized Fournier proposal requires the sequencing of at least five genes (16S rRNA, gltA, ompA, ompB, and the D gene) for the accurate classification of new rickettsiae. The nucleotide similarity thresholds required to classify an isolate as an approved species are strict: at least 99.8% for rrs (16S rRNA) and 99.9% for gltA.

• WGS Criteria: The most sensitive and accurate approach for classification is the phased implementation of whole-genome sequencing (WGS). This method uses dDDH thresholds > 92.3% and/or OrthoANI > 99.19 for species demarcation, allowing for more robust classification than MLST methods. Next-generation sequencing (NGS) has proven useful for the diagnosis of rickettsial diseases.

5.2. Clinical and Strategic Implications of Reemergence

The RMSF epidemic in northern Mexico, with its high case fatality rates, reflects a serious public health problem exacerbated by socio-environmental factors.

• Surveillance and Detection: In the clinical setting, molecular detection of SFGR is more sensitive in skin biopsy samples (37.5%) than in blood (3.9%). PCR of an eschar biopsy (tache noire) can be useful for detecting SFGR Rickettsiae and can be performed as early as 24 hours after a tick bite.

• One Health Approach: Outbreaks of rifampicin-related fecal infestations (RRF) are persistent and deadly, linked to the interaction between dogs, ticks (R. sanguineus s.l.), and the human environment in vulnerable communities. To mitigate the epidemiological risk, it is crucial to implement an integrated strategy that addresses social, environmental, veterinary, and medical factors. Inaction has severe economic and human consequences, with estimated costs exceeding US$13 million for similar outbreaks in the US, likely underestimating the true costs, especially those of long-term rehabilitation.

• Cellular Invasion: Pathogenesis studies have revealed that pathogenic and non-pathogenic rickettsiae (R. typhi, R. rickettsii, and R. montanensis) utilize bacterial phosphatidylserine (PS) to bind to the pherocytic receptor CD300f on macrophages (MΦ), facilitating their invasion and colonization. Macrophages are the first defense cells that rickettsiae encounter at the inoculation site and are key mediators for the elimination or dissemination of the pathogen.

5.3. Risk of Lyme Borreliosis in the Mexican Context

The detection of B. burgdorferi infecting I. scapularis in northeastern Mexico confirms the existence of a risk of Lyme borreliosis in the transboundary region. The distribution pattern of I. scapularis suggests a continuous ecological corridor influenced by climatic factors (temperature and precipitation).

The taxonomic classification of vectors should continue, especially in the genera Ixodes and Amblyomma, due to difficulties in morphological identification and the need to re-examine the type material of several species with atypical or uncertain distributions (e.g., I. cookei, I. scapularis in Oaxaca). The high tick richness (28 species of Ixodes and 25 of Amblyomma), and the diversity of associated hosts (amphibians, reptiles, birds, and 21 mammal families for Amblyomma), demonstrate the ecological complexity of zoonotic cycles in Mexico, requiring ongoing study to achieve a full understanding of their classification, distribution, and phylogenetic relationships.

6. Conclusion

This work represents an effort to consolidate the dispersed knowledge on rickettsiosis in Mexico. The biological inventory is substantial, with 14 Rickettsia species in key tick vectors in the border region. The reemergence and persistence of rickettsial fever in the north, with high lethality, underscores the urgent need for a "One Health" strategy that integrates social, veterinary, and medical actions.

The methodological challenge of distinguishing Rickettsia rickettsii from less pathogenic SFG species using generic PCR is significant and requires the strict adoption of advanced molecular taxonomic protocols (Fournier and WGS criteria). Research must advance the accurate characterization of these pathogens to effectively guide public health policies and mitigate the risk of these emerging and re-emerging diseases in Mexico.

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