Rocky Mountain spotted fever in Mexico: past, present, and future

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Rocky Mountain spotted fever, a tick-borne zoonosis caused by *Rickettsia rickettsii*, is among the most lethal of all infectious diseases in the Americas. In Mexico, the disease was first described during the early 1940s by scientists who carefully documented specific environmental determinants responsible for devastating outbreaks in several communities in the states of Sinaloa, Sonora, Durango, and Coahuila. These investigators also described the pivotal roles of domesticated dogs and *Rhipicephalus sanguineus sensu lato* (brown dog ticks) as drivers of epidemic levels of Rocky Mountain spotted fever. After several decades of quiescence, the disease re-emerged in Sonora and Baja California during the early 21st century, driven by the same environmental circumstances that perpetuated outbreaks in Mexico during the 1940s. This Review explores the history of Rocky Mountain spotted fever in Mexico, current epidemiology, and the multiple clinical, economic, and social challenges that must be considered in the control and prevention of this life-threatening illness.

Introduction

On April 24, 2015, the National Center for Preventive Programs and Disease Control (CENAPRECE) in the Mexican Ministry of Health issued a Declaration of Epidemiological Emergency to highlight looming public health concerns regarding Rocky Mountain spotted fever in the northern regions of Mexico, particularly in the states of Baja California and Sonora. To put this action into perspective, national surveillance in the USA identified 40 cases of fatal Rocky Mountain spotted fever during 1999–2007, whereas Sonora reported 80 fatal cases of this zoonotic disease in 2015 alone (Epidemiological Surveillance System of the Ministry of Health of Sonora; data provided by G Álvarez-Hernández). Rocky Mountain spotted fever is a tick-borne infectious disease caused by *Rickettsia rickettsii* that occurs sporadically and typically as isolated cases throughout most of the Americas. Nonetheless, specific ecological and epidemiological circumstances can trigger and perpetuate epidemic levels of disease, as exemplified by recent outbreaks in southern and eastern regions of the US state of Arizona caused by rapid and steep increases in the numbers of free-roaming dogs and host-seeking *Rhipicephalus sanguineus sensu lato* (brown dog ticks) in impoverished communities. Nearly identical circumstances were described in detail by Mexican epidemiologists who investigated multiple epidemics of Rocky Mountain spotted fever in several states of Mexico during the 1940s. More than 70 years later, these conditions continue to drive contemporary outbreaks across multiple regions of southwestern USA and northern Mexico.

During the past 100 years, case fatality rates from outbreaks of Rocky Mountain spotted fever in Mexico ranged from approximately 30% to 80% (table), rivalling or exceeding those described for other deadly infectious diseases in the Americas, including plague (13%), meningococcaemia (17%), and yellow fever (48%). Medical and indirect costs associated with severe disease can be enormous, since critically ill patients often develop compromise or failure of multiple organ systems and therefore require admission to an intensive care unit and various interventions, including mechanical ventilation, inotropic support, or dialysis. Some patients who recover from severe Rocky Mountain spotted fever can develop long-term or permanent disabilities such as cognitive deficits, ataxia, hemiparesis, blindness, deafness, or amputation following gangrene. Clinical diagnosis is challenging, particularly during the early stages of the illness when signs and symptoms are non-specific, and in regions where health-care providers' awareness of the disease is low. An accurate and early diagnosis, and early, specific treatment, are crucial to a successful patient outcome; nonetheless, correct diagnosis of Rocky Mountain spotted fever is further complicated by its clinical similarity to many other infectious diseases endemic to Mexico, including dengue, leptospirosis, and, most recently, chikungunya and Zika virus infections.

Resurgence of Rocky Mountain spotted fever in Mexico, beginning in the mid-2000s, has expanded in scope and magnitude and now summons extensive medical, social, and epidemiological resources of local, state, and national public health programmes. The rising incidence of the disease also represents an important social issue since most patients live in poverty and the highest case fatality rates are associated with children younger than 10 years. Rocky Mountain spotted fever also poses a health concern along the USA–Mexico border since the incidence of this disease is greatest in several states of northern Mexico (figure 1).

Here we summarise various historical aspects of Rocky Mountain spotted fever and the current epidemiology of this disease in Mexico, and define several fundamental challenges to prevent and control future outbreaks. This Review also incorporates the convergence of several contemporary themes in public health, including the importance of a One Health approach to effectively address human, animal, and environmental health determinants that contribute to the multiple and profound consequences of this life-threatening zoonotic disease.
Historical Review

Past
Anecdotal reports of a severe febrile illness with high mortality in the states of Sonora and Sinaloa existed for many decades before formal recognition of Rocky Mountain spotted fever in Mexico in 1943. Medical descriptions of a lethal illness from this region, associated with a petechial rash and designated malignant scarlet fever, were first published in 1903. This disease generated considerable panic among afflicted villages, and inhabitants often burned the households of sick individuals. In 1923, an unusual and frequently fatal disease that resembled Rocky Mountain spotted fever was described in Sinaloa. The illness, coined Choix spotted fever in reference to the municipality where the outbreaks occurred, was associated with R. sanguineus sensu lato ticks found abundantly on dogs in the vicinity of case-patient households. However, no confirmatory tests were done and the disease remained incompletely characterised.

In 1943, epidemiologists Miguel Bustamante and Gerardo Varela from the Institute of Health and Tropical Diseases in Mexico City provided the first detailed clinical, epidemiological, and entomological findings on Rocky Mountain spotted fever in Mexico. Data summarised from more than 200 cases revealed a highly lethal infectious disease that occurred during 1918–43 in several rural areas in the municipalities of El Fuerte and Choix in Sinaloa, and Alamos in Sonora. The disease was associated with high fever (≥40°C), severe headache, a generalised petechial rash, and a cumulative case fatality rate of 80%. These investigators determined that most cases occurred from March to October, which coincided with the period of highest yearly temperatures and rainfall, and that many cases occurred in family clusters.

With support provided by the Rocky Mountain Laboratory in Hamilton, MT, USA, the investigators confirmed the disease as Rocky Mountain spotted fever. They also described salient epidemiological features of the disease paralleled by contemporary outbreaks of Rocky Mountain spotted fever in southwestern USA and northern Mexico, including the vulnerability of economically disadvantaged populations in rural areas and the high frequency of cases in children. Studies subsequently established Rocky Mountain spotted fever in a border region shared by the

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**Table: Historical and contemporary case fatality rates of Rocky Mountain spotted fever in Mexico, 1918-2016**

<table>
<thead>
<tr>
<th>Period</th>
<th>States</th>
<th>Number of cases (case fatality rate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bustamante and Varela (1943)†</td>
<td>Sinaloa</td>
<td>215 (80%)</td>
</tr>
<tr>
<td>Silva-Goytia and Elizondo (1952)†</td>
<td>Sinaloa, Sonora</td>
<td>45 (27%)</td>
</tr>
<tr>
<td>De Lara Huerta and Barragán (2008)†</td>
<td>Coahuila, Durango*</td>
<td>115 (55%)</td>
</tr>
<tr>
<td>Zavala-Castro and colleagues (2008)†</td>
<td>Yucatán</td>
<td>9 (33%)</td>
</tr>
<tr>
<td>Álvarez-Hernández and colleagues (2015)†</td>
<td>Sonora*</td>
<td>210 (30%)</td>
</tr>
<tr>
<td>Milan (2016)†</td>
<td>Baja California</td>
<td>255 (29%)</td>
</tr>
</tbody>
</table>

*Paediatric series. †Department of Epidemiology, Institute of Public Health Services of the State of Baja California; data provided by NSH Milan.

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![Figure 1: Locations of historical and contemporary outbreaks of Rocky Mountain spotted fever in Mexico and collection sites of ticks infected with *Rickettsia rickettsii*](http://dx.doi.org/10.1016/S1473-3099(17)30173-1)
states of Durango and Coahuila, known as La Laguna (figure 1), where an outbreak of severe illness was diagnosed initially as typhus. These investigators also noted that the geographical distribution of Rocky Mountain spotted fever in Mexico was more limited than that of typhus but mortality was far greater.6

Seminal contributions by these investigators established the role of *R. sanguineus* sensu lato as an important vector of *R. rickettsii* in northern Mexico. In affected communities, local dogs were consistently infested with *R. sanguineus* sensu lato and these ticks were frequently observed on the adobe (sun-dried brick) walls, earth floors, and mattresses of patients’ households. It was further recognised that domesticated dogs transported ticks around and into patients’ homes, and that the peridomestic nature of *R. sanguineus* sensu lato explained the occurrence of family clusters of disease and high attack rates among women and children,7,8,42,44 which accounted for an epidemiological profile in Mexico that differed notably from that of Rocky Mountain spotted fever in the USA at that time.42 During these and subsequent investigations by other scientists, multiple isolates of *R. rickettsii,* were obtained from *R. sanguineus* sensu lato ticks collected from sites in Coahuila, Durango, Michoacán, Nuevo León, and Sonora.7,8,42,44 These and additional isolates of *R. rickettsii* obtained from patients in Coahuila, Durango, Sinaloa, and Sonora were highly pathogenic when inoculated into guinea pigs, similarly to the most virulent strains of *R. rickettsii* isolated from western regions of the USA.6,8,42,44 Other *R. rickettsii* strains of lower virulence were isolated from *R. sanguineus* sensu lato ticks in the state of San Luis Potosí and from ticks identified as *Amblyomma cajennense* in the state of Veracruz.6,8,42 Studies done during an outbreak of Rocky Mountain spotted fever in La Laguna during 1951–52 corroborated earlier observations of Bustamante and colleagues, including the role of *R. sanguineus* sensu lato as the vector, the predominance of cases involving children, the relation with social deprivation, the occurrence of family clusters of illness, and the profound lethality of the disease.7,8,42,45

There were no formal reports of Rocky Mountain spotted fever in Mexico for several decades following the outbreaks described during the middle of the 20th century. The reasons for this occurrence are unknown; however, a steady decrease in the incidence of Rocky Mountain spotted fever was also described in the USA between the late 1940s and 1970.29 Several hypotheses have been proposed for the decline in reported cases during this period, but among the most compelling is the impact of the pesticide dichlorodiphenyltrichloroethane (DDT). Between 1950 and 1959, an estimated 26–36 million kg of DDT was applied annually around the world, and used widely in campaigns against malaria in Mexico. Some investigators have suggested that an unintended but fortuitous consequence of its intense and broad-scale use was an extensive reduction of tick vectors of Rocky Mountain spotted fever.49 Irrespective of a specific cause or causes, increased incidence of tick-borne spotted fever group rickettsioses was recognised in many countries around the world, including the USA, Spain, Italy, and Israel, beginning in the early 1970s.29

Present

Beginning in the mid-2000s, many investigators documented the re-emergence of Rocky Mountain spotted fever in several states throughout northern and central Mexico.23,24,26–31,36,37 These contemporary outbreaks share several similarities with those described during the 1940s and early 1950s, including the frequent involvement of children and the economically disadvantaged, high case fatality rates, and strong epidemiological associations with large numbers of free-roaming, tick-infested dogs.23,24,27,28

From 2003 to 2016, 1394 total cases with 247 deaths were identified in Sonora, with an aggregate case fatality rate of 18%, greater than that of other endemic diseases such as dengue (1%), pertussis (9%), and influenza (11%); Epidemiological Surveillance System of the Sonora Ministry of Health; data provided by G. Álvarez-Hernández). Patients younger than 19 years accounted for 58% of all cases and 60% of deaths. During this period, annual numbers of cases of Rocky Mountain spotted fever and the frequency of fatal disease increased drastically (figure 2). Various socioeconomic circumstances have influenced the rapid growth of this epidemic, and approximately 75% of identified patients originated from poor neighbourhoods characterised by many free-roaming dogs and large numbers of *R. sanguineus* sensu lato ticks in peridomestic areas. A summary of 210 patients
consecutively referred to the largest children’s hospital in the state of Sonora during 2004–15 identified an overall case fatality rate of 30%, with the greatest number of deaths occurring among children younger than 10 years. The median time from symptom onset to initial evaluation was 2 days, and only 13% of patients received a correct diagnosis at the first evaluation. The median time from onset to presentation at the referral hospital was 5 days, by which time most patients exhibited advanced disease (figure 3). In this context, 88% of these children developed generalised petechial rashes involving palms and soles, 16% developed pulmonary oedema, 25% developed renal failure, and 14% had convulsions.16

During 2009–10, a large outbreak of Rocky Mountain spotted fever occurred in the city of Mexicali, Baja California, drawing additional attention to the re-emergence of the disease in Mexico. From 2009 to 2016, there have been 967 cases with 132 deaths (figure 4), and the aggregate case fatality rate during this period (14%) was greater than that of several other infectious diseases of regional importance, including dengue (2%), influenza (2%), and pertussis (11%; Department of Epidemiology, Institute of Public Health Services of the State of Baja California; data provided by NSH Milan). The emergence and persistence of Rocky Mountain spotted fever in Mexicali has been largely driven by previously recognised factors that include poor living conditions and an abundance of dogs infested with R sanguineus sensu lato.13

The ecology and natural history of Rocky Mountain spotted fever in Mexico is most likely to involve several species of ixodid ticks, although R sanguineus sensu lato is the only one associated historically and contemporaneously with large-scale outbreaks of the disease. The taxonomic status of R sanguineus sensu stricto is unresolved and data suggest that ticks identified collectively as R sanguineus comprise a group of genetically distinct taxa that is likely to include multiple sibling species. Because distinct populations of R sanguineus sensu lato often differ in vector competence with other infectious agents, it is possible that some populations of R sanguineus sensu lato ticks in Mexico are more effective vectors of R rickettsii than are populations in other regions of the Americas. R rickettsii has been identified in several other species of human-biting ticks throughout Mexico, including Amblyomma parvum and Amblyomma imitator. Naturally occurring R rickettsii infections in A cajennense ticks have also been described; however, modern taxonomic assessment suggests that specimens of Amblyomma mixtum in Mexico were incorrectly synonymised as A cajennense, suggesting that A mixtum is another potential vector of Rocky Mountain spotted fever in Mexico.

**Future**

“Those who cannot remember the past are condemned to repeat it.”

George Santayana, 1905

Rocky Mountain spotted fever remains an expanding public health problem in Mexico despite recognition of the various factors that perpetuate epidemic levels of this
disease. The remarkably high case fatality rates and long-term morbidity are largely preventable, but require sustained and coordinated efforts at local, state, and national levels to improve the collective wellbeing of affected communities. In this context, immediate actions need to focus on effective diagnosis, treatment, and prevention strategies, but must also be coupled with long-term efforts to address social and environmental determinants that contribute to epidemic levels of Rocky Mountain spotted fever. Additionally, the geographical distribution of this outbreak necessitates binational consideration between the USA and Mexico, since an estimated 14 million people reside within 100 km on each side of the 3100 km USA–Mexico border, including many who live in socioeconomic and environmental conditions similar to those identified in contemporary epidemics of Rocky Mountain spotted fever. Indeed, there are several instances of patients acquiring the infection in northern Mexico and subsequently presenting to hospitals in US border cities in California and Arizona for medical attention (Centers for Disease Control and Prevention [NA Drexler, CD Paddock], unpublished). In this context, it is crucial for US health-care providers along the USA–Mexico border to recognise that Rocky Mountain spotted fever is endemic to this region.

Because of the rapid evolution of disease severity, infected patients who do not receive doxycycline by day 5 of their illness are at 2.5–3.5-times greater risk of fatal outcome than those receiving this antibiotic before day 5 in patients for whom therapy is delayed until day 6 or longer, the risk of death is more than four times greater than for those receiving doxycycline before day 6. In this context, it is important to educate community health practitioners, particularly those in rural areas, of the early signs and symptoms of this disease and the necessity for prompt administration of doxycycline to prevent potentially irreversible damage to multiple organ systems. Providing access to intravenous doxycycline to treat critically ill patients who are obtunded or vomiting, as well as an oral suspension of this antibiotic to facilitate administration of therapy to very young children, is an urgent necessity; however, neither formulation is available in hospital pharmacies in Mexico.

Finally, it is imperative that primary-care providers recognise the appropriateness of doxycycline as primary therapy for Rocky Mountain spotted fever in children of any age. Despite many studies suggesting the absence of tooth staining and enamel hypoplasia in children receiving short courses of doxycycline before the age of 8 years, most primary-care physicians in the USA remain reluctant to use this antibiotic as first-line therapy in very young children. This issue is also relevant in Mexico, where a cross-sectional study of 343 doctors from different specialties and levels of medical care in five municipalities of Sonora revealed that almost half of primary-care physicians are reluctant to provide doxycycline to children younger than 10 years (G Álvarez-Hernández, unpublished). These findings might explain, in part, the frequency of fatal disease, particularly among young children, and highlight the need to educate clinicians about the diagnosis and treatment of Rocky Mountain spotted fever in areas where the disease is endemic.

There are few clinical and public health laboratories in Mexico with the capability to provide confirmatory diagnostic testing for Rocky Mountain spotted fever. Validated and standardised serological and molecular assays are needed in states with large case counts to support national surveillance for the disease and to more accurately document the burden of disease in the country. Promoting awareness of Rocky Mountain spotted fever among communities, particularly its association with ticks and dogs, and the rapidity with which fatal disease can occur, is a fundamental component of early treatment and prevention efforts.
prevention campaigns. Because people who speak indigenous languages and are not fluent in Spanish inhabit some affected communities, education and outreach efforts require health-care providers who can converse in the particular languages of these communities.

The intersecting components of human, animal, and environmental health collectively form the foundation of One Health, and Rocky Mountain spotted fever in Mexico provides a salient example of this concept. The health of canine populations in communities where *R* rickettsii is endemic directly affects the risk of Rocky Mountain spotted fever in human beings. In this context, a comprehensive strategy to control the epidemic of this zoonotic disease in Mexico could be used effectively through a One Health approach. Dogs represent the principal host for each feeding stage of brown dog ticks and therefore contribute directly to the density of *R* sanguineus sensu lato within a community. In many regions of Mexico, environmental conditions favour the development and maintenance of *R* sanguineus sensu lato ticks throughout the year, allowing for as many as 2-5 generations annually. As exemplified recently in southwestern USA and northern Mexico, unchecked populations of free-roaming pets and stray dogs contribute to massive and concentrated proliferations of *R* sanguineus sensu lato, spread of ticks infected with *R* rickettsii to new areas, and transportation of infected ticks in and around households, contributing to the high incidence of disease among young children who become infected while playing in their yards or homes. Young, immunologically naive dogs are likely to represent amplifier hosts for *R* rickettsii, and help perpetuate Rocky Mountain spotted fever in impoverished communities where these animals rarely receive routine or preventive veterinary care and are seldom spayed or neutered. Improving the health of dogs in these settings can reduce exposure of human beings to circumstances that adversely affect their health. Short-term solutions involve animal control programmes that promote responsible pet ownership, including spaying and neutering, as well as widespread access to effective acaricides that include topical treatments and long-acting tick collars. These methods can be highly effective, as exemplified recently by a community-based campaign in a small town in Sonora where 56 cases of Rocky Mountain spotted fever and 22 deaths were reported during 2009–15. Following placement of acaricide-impregnated collars on approximately 750 dogs from 530 households and application of deltamethrin spray to the homes, no new cases were reported from this community between March and November, 2016. However, these interventions are prohibitively expensive for the impoverished communities from which most cases of Rocky Mountain spotted fever in Mexico originate, and therefore funding from state, national, and even international agencies is needed to initiate and maintain these endeavours. Long-term solutions for prevention of Rocky Mountain spotted fever should also focus on development of a canine vaccine against *R* rickettsii to block transmission between ticks and canines.

Throughout the Americas an expansive catalogue exists of re-emerging and newly recognised tick-borne diseases, including many potentially lethal infections in addition to Rocky Mountain spotted fever. *Ehrlichia chaffeensis*, an agent of human ehrlichiosis, has been detected in amblyomma ticks in various regions of Mexico and was identified as the cause of death in a patient from the State of Mexico. At least 68 species of ixodid (hard) ticks are distributed across Mexico, and the distribution and complexity of tick-borne agents contained within these species continues to expand. Indeed, investigators during the 1940s isolated a pathogen from *R* sanguineus sensu lato ticks collected in Michoacán that produced an illness in guineapigs clinically similar to Rocky Mountain spotted fever, but could not be further characterised by serological techniques available at that time. In this context, it is likely that several other tick-borne infectious agents remain to be discovered throughout this region of North America.

Despite varied and complex challenges, immense public health benefits can be achieved by diminishing the incidence of Rocky Mountain spotted fever in Mexico through an integrated and multidisciplinary response to mitigate the various social, environmental, veterinary, and medical factors that stoke epidemic levels of this lethal and debilitating infectious disease. The public health, moral,
and economic gains provided by effective control and prevention programmes are similarly profound, as shown in a study examining costs associated with medical care, loss of productivity, and death among 205 cases of Rocky Mountain spotted fever from two rural communities in Arizona during 2002–11. The medical and indirect costs estimated from this evaluation exceeded US$13 million, and probably underestimated the actual sustained costs since long-term expenses for rehabilitation and ambulatory care were not included. These are crucial considerations for the many resource-limited communities affected by Rocky Mountain spotted fever in Mexico; the consequences of inaction could be severe, and grimly reflected by the growing numbers of those who die or become disabled permanently by this devastating disease.

Contributors
G AH and CDP conceptualised, researched, wrote, and revised the manuscript. GAH and NSHM provided epidemiological data for the states of Sonora and Baja California. GAH and CDP provided clinical and pathology images for figures. RRL, CDP, and GAH created the figures. GAH, JFGR, NSHM, RRL, CBB, and CDP reviewed and provided input to the entire manuscript.

Declaration of interests
We declare no competing interests.

Acknowledgments
The findings and conclusions are our own and do not necessarily reflect the views of the US Department of Health and Human Services or the Ministry of Health of Mexico.

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