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# Rickettsiosis subcommittee report to the tick-borne disease working group

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ABSTRACT

Tick-borne rickettsial infections are serious, common, and difficult to diagnose. Among the most important factors leading to failure to diagnose and treat tick-borne rickettsioses effectively is a lack of consideration of the potential diagnosis by primary caregivers and emergency department physicians in patients presenting with undifferentiated acute febrile illness during tick season. This situation exists because of insufficient primary and continuing medical education of medical students, primary care and emergency medicine residents, and practicing physicians regarding tick-borne rickettsioses specific to the region where they practice. Delayed initiation of treatment with an appropriate antibiotic is associated with adverse outcomes including increased rates of hospitalization, admission to an intensive care unit, and mortality. The earliest symptoms are nonspecific, consisting of fever, headache, myalgias, and nausea and/or vomiting. Laboratory abnormalities are typically absent at this time when the therapeutic response to an appropriate antibiotic would be optimal. There is a mistaken idea among a substantial portion of physicians that the best antibiotic available, doxycycline, should not be administered to children 8 years of age or younger or during pregnancy. For all of the above reasons, there is unnecessary morbidity and mortality caused by tick-borne rickettsioses. This report proposes measures to address these critical issues regarding tick-borne rickettsioses.

## 1. Background

*Rickettsia* pathogens and associated rickettsial diseases were not a primary focus area of the first Tick-Borne Disease Working Group report; nonetheless, as a group they pose a significant impact on U.S. public health. Based on passive surveillance, more than 6000 cases of tick-borne spotted fever group (SFG) rickettsioses are reported annually, but many cases go unreported. Unfortunately, 99% of reported cases are not confirmed. At present, serologic diagnosis does not distinguish among the various SFG rickettsiae in human-biting ticks in the U.S. that stimulate antibodies, including the highly virulent *Rickettsia rickettsii*. Exposure rates are relatively high, with 10–20% of healthy persons in the lone star tick endemic region demonstrating anti-SFG rickettsial antibodies. Several hurdles exist that prevent accurate diagnosis and treatment: there is no generally available test for diagnosis of acute infection, knowledge and awareness of laboratory diagnostics and appropriate treatment by many physicians is lacking, diagnosis based on clinical manifestations early in the course of illness is very difficult, and

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only specific antibiotics are effective.

The Rickettsiosis Subcommittee identified three primary goals: 1) to describe the health impact of tick-borne rickettsial diseases in the U.S., 2) to determine obstacles to reduction of morbidity and mortality caused by tick-borne rickettsial diseases in the U.S., and 3) to identify gaps in knowledge and implementation that research may resolve. The Subcommittee identified several specific issues to be addressed including species of rickettsial pathogens in the U.S., epidemiology, surveillance (clinical and environmental), true incidence of diseases, geographical prevalence of lone star ticks, point-of-care diagnostic tests, treatment of children under 12 with doxycycline, undertreating vs overtreating, and lastly, public and clinical education.

## 2. Methods

### 2.1. Characteristics of the subcommittee

The Rickettsiosis Subcommittee was established to leverage member expertise, balance a range of perspectives, and thoroughly examine several aspects of diagnostics, treatment, and prevention of a range of tick-borne rickettsial diseases based on the published scientific literature, current research efforts, and exchanges among the Subcommittee membership.

### 2.2. Subcommittee meetings

The Subcommittee held a series of weekly/biweekly, one-hour conference calls in 2019. During the conference calls, Subcommittee members shared their expertise through presentations and discussions. Support science writers summarized the conference calls for final edits by the Co-Chairs. Meeting summaries edited and approved by the Co-Chairs are saved on the Subcommittee's SharePoint site for subcommittee members to view and use as a reference. The presentations were focused on education for physicians (medical students, residents, and continuing medical education) and other health care providers, surveillance and epidemiology, approaches to clinical diagnosis, and laboratory diagnostics.

### 2.3. Subcommittee report development

The Rickettsiosis Subcommittee developed its report to the Tick-Borne Disease Working Group based on the presentations and the subcommittee discussions. Subcommittee Co-Chair David H. Walker wrote the Background section, drafted the Overview of Rickettsial Diseases in the Results and Potential Actions section, and proposed possible actions for the Working Group to consider. David Leiby (alternate to Co-Chair Estella Jones) developed the Methods section. Other subcommittee members wrote different parts of the Results and Potential Actions section of the Subcommittee report and proposed possible actions for the Working Group to consider: Karen Bloch and Vance Fowler wrote the part on clinical management of spotted fever rickettsial infections, Lucas Blanton wrote the part on education, Hayley Yaglom and Chris Paddock wrote the section on surveillance and epidemiology, David Gaines developed the part on North American tick species. Co-Chair David H. Walker reviewed and edited all parts of the Results and Potential Actions section of the report and distributed them to the Subcommittee members for them to review, discuss, and reach consensuses.

The Subcommittee members reviewed and discussed the draft Results and Potential Actions section, consolidated possible actions to avoid redundancy, and together revised the wording of each possible action for accuracy and consistency during the conference calls. The Subcommittee members used the PICK CHART to rank the final list of possible actions between December 10 and December 17 conference calls. Different views were addressed via discussion. Votes for each of the possible actions, ranking of the possible actions, and ranking of the priority/topic areas were captured.

### 2.4. Brief for the working group

The Rickettsiosis Subcommittee developed its PowerPoint briefings for the Working Group based on existing issues, gaps, and opportunities identified, as well as possible actions proposed by the Subcommittee members.

## 3. Results and potential actions

### 3.1. Overview of rickettsial diseases

There are six species of *Rickettsia* that are potentially transmitted by ticks in the U.S.: *R. rickettsii* transmitted by *Dermacentor variabilis* (American dog tick), *Dermacentor andersoni* (Rocky Mountain wood tick), *Dermacentor occidentalis* (the Pacific Coast tick), *Rhipicephalus sanguineus* sensu lato (brown dog tick), and potentially by *Amblyomma americanum* (the lone star tick); *R. parkeri* transmitted by *Amblyomma maculatum* sensu stricto and sensu lato (Gulf Coast ticks), and potentially by *A. americanum* and *Dermacentor parumapertus; Candidatus* R. philipii transmitted by *D. occidentalis* (Pacific Coast ticks); and potentially *R. massiliae* transmitted by *R. sanguineus s.l.; R. amblyommatis* transmitted by *A. americanum*; and *R. prowazekii* transmitted by *Amblyomma tenellum*.

#### 3.1.1. Issues

- Rickettsial diseases have varied signs, symptoms, and severity, which often make them difficult to distinguish from other infections.
- There is low awareness of rickettsial diseases by physicians.
- The current diagnostic tests for rickettsioses have many limitations.

#### 3.1.2. Evidence and findings

The spectrum of illnesses ranges from life-threatening to asymptomatic (Parola et al., 2013; Walker et al., 2008). The most severe disease, Rocky Mountain spotted fever (RMSF), is caused by *R. rickettsii*. The clinical diagnosis of RMSF is hampered by appearance of rash that may not appear until two to five days after onset of fever (Helmick et al., 1984; Kaplowitz et al., 1981). In addition, those with RMSF may have symptoms that mimic a variety of other syndromes: gastrointestinal symptoms may mimic an acute surgical abdomen (Middleton, 1978), pulmonary manifestations may mimic a primary respiratory process (Donohue, 1980), and neurologic involvement may mimic meningoencephalitis by other causative infectious agents (Rosenblum et al., 1952). Finally, the absence of a history of tick exposure may dissuade a physician to consider RMSF as a diagnostic possibility.

In addition to *R. rickettsii*, other spotted fever group rickettsiae (SFGR) cause disease in the U.S. (Paddock et al., 2004; Shapiro et al., 2010). Few physicians appreciate the diseases caused by these agents. For example, the diagnosis of *R. parkeri* infection is hampered by low awareness of the disease and lack of understanding of the existence and significance of an eschar, and the usefulness of the eschar as a site for collection of diagnostic samples for molecular pathogen detection/identification by PCR (Kelman et al., 2018; Myers et al., 2013).

There are many limitations regarding the current diagnostic tests available to physicians (Fang et al., 2017). Currently, there are no rapid point-of-care diagnostic testing methods to confirm or exclude the diagnosis of a rickettsial disease during early illness. The serologic detection of anti-rickettsial antibodies is the mainstay of laboratory testing, but detectable antibodies are generally not present in the first week of illness when patients first seek evaluation (Biggs et al., 2016). The constellation of significance of the prevalence of anti-spotted fever group rickettsial antibodies in healthy persons in the lone star tick region (McCall et al., 2001; Sanchez et al., 1992; Yevich et al., 1995), tremendous exposure to *R. amblyommatis*-carrying lone star ticks (Apperson et al., 2008; Moncayo et al., 2010; Stromdahl et al., 2008), the preponderance of single sample serologic results, and the excessive

use of improper or non-quantitative serologic diagnostic assays confounds the accurate diagnosis of acute spotted fever group rickettsial infections (Dahlgren et al., 2016).

#### 3.1.3. Threats and challenges

- Life-threatening nature of Rocky Mountain spotted fever.
- Difficulty of diagnosis based on clinical manifestations and epidemiological circumstances at the time of presentation for medical attention.
- Lack of awareness, knowledge, and consideration of the diagnosis of tick-borne rickettsial diseases by primary care and emergency medicine physicians of patients early in the course of rickettsial infection when treatment is most effective.
- Lack of accurate knowledge of the true regional incidence and epidemiology of tick-borne rickettsioses.
- Lack of a sensitive and specific diagnostic test that is effective early in the course of rickettsial infection.
- Inability of current serologic tests to identify the specific *Rickettsia* infecting the patient and to determine whether the antibodies detected are pre-existing or acutely produced.
- Inadequate education of medical students, residents, and practicing physicians regarding rickettsial infections.
- Lack of knowledge regarding rickettsial infections by the general public.
- Improper use and misinterpretation of diagnostic assays for tick-borne diseases can have enormous costs, economically and to the health of the patient for whom the true cause of illness can remain undiagnosed.

#### 3.1.4. Opportunities

- Educational programs leading to enhanced awareness of and knowledge about rickettsial infections by primary care and emergency physicians leading to early institution of doxycycline treatment.
- Development of sensitive, specific point-of-care tests for diagnosis of rickettsial infections early in the clinical course.
- Development of serologic tests that are spotted fever group *Rickettsia* species-specific and distinguish pre-existing from acutely produced antibodies.
- Improved case reporting systems that provide more accurate data on the incidence, specific etiology, and geographic distribution of rickettsial infections.
- Public health information campaigns to increase public awareness of tick-borne rickettsial infections.
- Develop regional tick and tick-borne pathogen surveillance programs to identify public health risks before, rather than after tick-borne diseases become a significant public health issue.

#### 3.1.5. Possible actions for working group to consider

- Establish and fund a research program to develop sensitive, specific point-of-care tests that improve the availability of and access to species-specific molecular assays for acute Rocky Mountain spotted fever and *R. parkeri* rickettsiosis and establish serologic assays that distinguish among antibodies to *R. rickettsii, R. parkeri, Candidatus* R. philipii, and *R. amblyommatis.*
- Fund prospective clinical studies to understand the true incidence of Rocky Mountain spotted fever.
- Fund an educational outreach effort across the U.S. to inform healthcare providers, including first-line responders (primary care physicians, pediatricians, urgent care providers, emergency department providers) about the best diagnostic assays to use, best diagnostic samples to collect, and best strategies for treating patients diagnosed with or suspected of having RMSF or another tick-borne rickettsiosis (with a focus on doxycycline).

## 4. Priority 1: clinical management of spotted fever rickettsia infections

### 4.1. Summary

Delayed initiation of treatment for Rocky Mountain spotted fever/spotted fever rickettsiae (SFR) is associated with adverse outcomes, including increased rates of hospitalization, ICU care, loss of limbs, and/or mortality. Studies suggest that the most important factor in failure to prescribe empiric doxycycline is not a delay in seeking health care but rather a failure of providers to consider the diagnosis of SFR infection. Potential reasons for delay in prescription of doxycycline are listed below.

### 4.2. Issues

Failure on the part of clinicians to consider the diagnosis, recognize the signs and symptoms, and initiate empiric doxycycline in patients with SFR/RMSF

### 4.3. Evidence and findings

#### 4.3.1. Varied epidemiology

- The highest incidence of human infection with spotted fever group agents occurs in the so-called RMSF belt, extending from North Carolina to Oklahoma. However, sporadic cases of SFR occur throughout the continental U.S., and clinicians in areas of low endemicity may be less familiar with the presentation.
- ~x223C 90% of reported cases of SFR have onset between April and September; however, infection can occur year-round, especially in sites of emerging endemicity such as Arizona.
- A history of tick exposure is not universally present, and absence of this should not dissuade providers from considering a diagnosis of SFR.

#### 4.3.2. Diverse clinical presentations

- The earliest symptoms of SFR are nonspecific, consisting of fever, headache, and myalgias. Laboratory abnormalities are typically absent at this stage.
- By days 2 to 4 of illness, approximately 50% of patients will have developed a rash, which is often subtle at this stage (macular lesions around ankles and wrists). Laboratory findings suggestive of the diagnosis such as thrombocytopenia and elevated liver enzymes may be present.
- By days 5 to 7 the fever and constitutional symptoms persist, the rash becomes petechial and generalized, and laboratory abnormalities become more pronounced.
- Untreated, after 5 days of symptoms, life-threatening complications can occur, such as sepsis, meningoencephalitis, purpura fulminans, renal insufficiency, acute respiratory distress syndrome or other devastating complications of this infection.
- Mortality in the absence of treatment exceeds 20%, and sequelae such as cognitive impairment, seizures, renal dysfunction, and limb amputation may be seen among survivors.
- Atypical presentations (acute abdomen and meningoencephalitis) are not infrequent, and providers may consider alternative diagnoses when focal symptoms predominate.

#### 4.3.3. Knowledge gaps

- Provider surveys have demonstrated striking disparities in first choice of treatment for RMSF between children ≤ age 8 (30–51% would give doxycycline) compared to older children or adults (69–93% would give doxycycline).
- Ongoing misplaced concern for doxycycline causing staining of pediatric teeth, despite the American Academy of Pediatrics recommendation that doxycycline is safe for all ages.

#### 4.3.4. Opportunities

- Improve provider recognition and empiric treatment of RMSF/SFR at early stages of the illness (e.g., prior to onset of rash).
- Educate providers on updated recommendations for use of doxycycline in children ≤ age 8.

#### 4.3.5. Threats or challenges

- Mandated training modules that indiscriminately target clinicians who do not provide primary care or urgent care will be burdensome and low-yield.
- Development of overly-broad training materials that emphasize aspects of tick-borne illness that are not relevant to recognition and treatment of infection (e.g., epidemiology, entomology, or retrospective diagnostics).

#### 4.3.6. Possible actions for working group to consider

- Fund seasonal educational outreach efforts in endemic regions to raise public awareness about rickettsial diseases.

## 5. Priority 2: education on rickettsial diseases

### 5.1. Summary

Severe manifestations, sequelae, and death attributed to RMSF can be avoided with the initiation of doxycycline during the first few days of illness (Kirkland et al., 1995). Unfortunately, the difficulty of recognizing the disease clinically, misconceptions that erroneously anchor physician beliefs regarding doxycycline, failure to recognize the severity of the disease, and misconceptions regarding laboratory testing often lead to the failure of prescribing appropriate antimicrobial therapy (Alvarez-Hernandez et al., 2018; Mosites et al., 2013; Zientek et al., 2014). Even in less severe rickettsial infections, such as those with *R. parkeri*, failure to recognize and treat can lead to an unnecessarily prolonged febrile illness (Paddock et al., 2008). Many factors may contribute to the failure to recognize the disease and misconceptions regarding its treatment. These include busy clinical practices and the growing complexity of medicine, which all compete for physicians' time. In addition, waning knowledge of less prevalent diseases (i.e., RMSF), compared to more common illnesses, may play a role. Although the realities of clinical practice patterns that contribute to the failure to recognize RMSF are not possible to address, the issues that contribute to the failure of the timely prescribing of doxycycline can be addressed through enhanced educational efforts. Opportunities exist at all levels of education, training, and practice.

#### 5.1.1. Issues

The failure to clinically recognize RMSF as a possible diagnosis and misconceptions regarding the timing/appropriateness of doxycycline therapy can lead to severe illness and death.

### 5.2. Evidence and findings

#### 5.2.1. Evidence that gaps in knowledge exist

- Studies of physician knowledge regarding Rocky Mountain spotted fever have revealed the following (Alvarez-Hernandez et al., 2018; Mosites et al., 2013; Zientek et al., 2014):
- Physicians often fail to recognize that doxycycline should be initiated prior to the results of laboratory testing.
- Many physicians would not consider the diagnosis in the absence of rash.
- Physicians often fail to recognize that doxycycline is the drug of choice in children.
- Physicians often fail to recognize the potential for death.

### 5.3. Threats or challenges

#### 5.3.1. Why are there gaps in clinician knowledge

- Medical school curricula must prepare students for a great breadth of material over a short period of time. Rapid advances in all fields of medicine have led to increasing specialization.
- During residency, physicians in training often have massive and hectic workloads. For infections that vary regionally, physicians training in one part of the country may not obtain the clinical experiences to optimally prepare them for practicing in a different region.
- Clinicians in practice are extremely busy. Physicians often have little time to gather the necessary clinical information and formulate a plan of care, and this may contribute to missing an important diagnosis. Those on the front line of care (primary care physicians and emergency medicine physicians) deal with a great variety of medical problems.

### 5.4. Opportunities

#### 5.4.1. Problem areas that could potentially be addressed by education

- The signs and symptoms of rickettsial diseases are largely undifferentiated and mimic a variety of other infectious syndromes. Therefore, it can be difficult for physicians to recognize the illness (Biggs et al., 2016).
- It is important for practitioners to realize that rash, which is frequently considered characteristic for a rickettsiosis, is often absent during the early stages of illness (Helmick et al., 1984; Kaplowitz et al., 1981).
- Unfortunately, there are no rapid point-of-care diagnostic tests available to accurately diagnose rickettsioses (Fang et al., 2017). Antibodies reactive to rickettsial antigens are not present during the early stages of illness (Paris and Dumler, 2016). It is important to recognize that treatment should not wait for results of laboratory testing (Kirkland et al., 1995).
- Although most clinicians recognize that doxycycline is the drug of choice for rickettsial diseases, some are often hesitant to prescribe it, especially in children (Alvarez-Hernandez et al., 2018; Mosites et al., 2013; Zientek et al., 2014) and during pregnancy (Cross et al., 2016).

### 5.5. Potential actions for working group to consider

#### 5.5.1. Potential actions to fill gaps in knowledge

- Encourage accrediting bodies to ensure tick-borne education in medical school curricula and graduate medical education and recommend that there be a greater presence of tick-borne disease material on licensing examinations and specialty board examinations.

## 6. Priority 3: surveillance and epidemiology

### 6.1. Summary

Rocky Mountain spotted fever, caused by *R. rickettsii,* remains the most severe tick-borne rickettsial illness, and has been a nationally notifiable condition since the early 1920s. In 2010, the reportable diseases list was updated to capture two additional tick-borne spotted fevers discovered during the first decade of the 21st century *(R. parkeri* rickettsiosis and Pacific Coast tick fever). These three diseases are now included collectively as nationally notifiable conditions under the general heading of "spotted fever rickettsiosis."

### 6.2. Issues

Because national surveillance for spotted fever rickettsiosis is based exclusively on passive reporting of cases that are largely confirmed by non-specific serologic tests that often detect background seroprevalence rather than confirm active disease, these data are unlikely to accurately describe the magnitude of these diseases or identify the specific agent responsible for the actual illness. In this context, existing surveillance is susceptible to under and over representation. We need to determine more accurately the true contribution of undetected or under-detected spotted fever group rickettsial pathogens, as well as the contribution caused by remote exposures to non-pathogenic or possibly minimally pathogenic agents such as *R. amblyommatis, R. montanensis*, or *Candidatus* R. andeanae that result in non-specific background seroprevalence.

### 6.3. Evidence and findings

The number of cases of SFGR reported to the Centers for Disease Control and Prevention (CDC) per year has increased significantly during the last two decades, 495 cases reported in 2000, and more than 6200 cases reported in 2017 (Heitman et al., 2019).

Factors that complicate surveillance include the following.

- Approximately 82% of all cases identified by national surveillance are identified by a single antibody titer to spotted fever group *Rickettsia* determined by indirect immunofluorescence antibody assay (IFA) (Binder et al., 2019).
- Baseline seropositivity to SFGR in healthy blood donors is as high as 11% in some areas of the U.S. (Straily et al., 2019).
- Many other spotted fever group *Rickettsia* species of uncertain pathogenicity are found in North American human-biting ticks that could elicit cross-reactive antibodies (Dahlgren et al., 2016).
- Improper interpretation of serologic tests can significantly affect accuracy of national surveillance estimates and obscure recognition of the true etiologic agent of disease, particularly those caused by other tick-borne pathogens, such as *Ehrlichia chaffeensis, Ehrlichia ewingii,* Heartland virus, and Bourbon virus (Egizi et al., 2017; McClain & Sexton, 2019).

### 6.4. Opportunities

The Council of State and Territorial Epidemiologists adopted a revised case definition for SFGR in June 2019, most notably by requiring an IgG titer of 128 or greater as serological evidence of a probable case. This represents a two-fold greater antibody titer than required by the previous surveillance case definition. Because approximately 45% of all recently reported cases of spotted fever rickettsiosis in the U.S. were based on a single IgG antibody titer of 64 (Heitman et al., 2019), this change will likely decrease the over-diagnosis of non-cases, particularly in high incidence states. Nonetheless, recent studies indicate that a single antibody titer is an unreliable measure of diagnosis and could inaccurately affect surveillance estimates that define magnitude and clinical characteristics of RMSF and other spotted fever rickettsioses (Straily et al., 2019), to emphasize that many opportunities exist to develop improved diagnostic assays that more accurately corroborate acute rickettsial disease.

### 6.5. Challenges

- Cross-reactive antigens of spotted fever group *Rickettsia* species generally preclude assignment of the specific etiologic agent by current serological methods.
- During the early stages of illness relatively small amounts of pathogen nucleic acid are found in circulation, making molecular detection particularly challenging during the first few days of disease.
- Appropriate use of the IFA assay requires tandem analysis of serum samples to detect a 4-fold rise in IgG titer in specimens collected during the acute and the convalescent phases of illness. Nonetheless, a convalescent specimen is collected infrequently, and only 1% of reported cases of spotted fever are supported by this method.

### 6.6. Possible actions for working group to consider

- Establish programs on active surveillance to understand the true geographic representations of rickettsial diseases including programs that survey for changing distributions of medically important tick species and rickettsial pathogens within these species.

## 7. Priority 4: North American tick species associated with the transmission of spotted fever group rickettsial agents to people in North America

### 7.1. Summary

Currently, there are six tick species in the U.S. that are thought to transmit pathogenic and/or non-pathogenic spotted fever group rickettsiae (SFGR) to people. These include three *Dermacentor* species (*D. andersoni, D. variabilis*, and *D. occidentalis*), two *Amblyomma* species (*A. americanum* and *A. maculatum*), and one *Rhipicephalus* species (*R. sanguineus s.l.*). Although these six tick species occur in distinct regions, some regions overlap and, therefore, cover most of the U.S.

*Dermacentor* tick species were the first ticks to be associated with the transmission of RMSF to people in the early 1900s, starting with *D. andersoni* (the Rocky Mountain wood tick) in the Rocky Mountain region of the U.S. where there were as many as 50 or more fatalities per year due to RMSF in the Bitter Root Valley of Montana. Subsequently RMSF also became associated with the American dog tick (*D. variabilis*), which can be found in every U.S. state east of the Rocky Mountains, as well as in some areas of California.

Although presumed agents of *R. rickettsii* were found in *D. andersoni* ticks collected in areas of Montana in the early 1900s when there were large annual outbreaks of RMSF causing high rates of human mortality, there are no recent published molecular studies reporting *R. rickettsii* in *D. andersoni*. In a recent study (Dergousoff et al., 2009) collected *D. andersoni* across an area of Canada just north of Montana, but the only SFGR agent detected by PCR was a tick endosymbiont (*Rickettsia peacockii*), which was found in 76% of 506 adult ticks collected and tested.

Numerous studies have been published on the role of *D. variabilis* as an RMSF vector. A recent survey of *D. variabilis* ticks in North Carolina (Kakumanu et al., 2018) used PCR to test a collection of 532 adult ticks for eight different SFGR, and *R. rickettsii* was detected in five (0.9%) of the tested ticks. Two other known SFGR pathogens, *R. parkeri* and *R. massiliae* were found in 7.8 and 3.8% of these tested ticks. *R. parkeri* and *R. massiliae* may cause a relatively mild, non-fatal illness in people, but may not always cause an overt illness in infected persons. Additionally, a number of other SFGR were found in these 532 tested ticks but are not currently known as, or not thought to be pathogenic to

people. These other SFGR included *R. amblyommatis,* found in 29.3% of the tested ticks, *R. montanensis* in 7.7%, an *R. conorii*-like agent in 3.8%, *R. bellii* in 1.9%, and *R. rhipicephali* in 0.4% of tested ticks. Human exposure to any one of these SFGR could potentially cause a cross-reactive immune response detectable by serological testing for RMSF. In another recent molecular study of SFGR in *Dermacentor* ticks in California, Wikswo et al. (2008), tested 365 *D. occidentalis,* (Pacific Coast tick) by PCR for a variety of SFGR. *R. rickettsii* was found in only one (0.3%) of the tested ticks, but *Candidatus* R. philipii, a recently discovered mild human pathogen, was identified in 7.7% of the tested ticks, and *R. rhipicephali*, a presumptively non-pathogenic agent, was found in 24.7% of the tested ticks.

In recent decades, the great majority of spotted fever rickettsiosis (SFR) cases diagnosed in the U.S. have been concentrated in the southeastern U.S. where the lone star tick, (*A. americanum*) predominates. Lone star ticks are an aggressive biter of people and are, by far, the most common cause of tick bites to people in this region. A study across nine states of the eastern U.S. from Oklahoma to Florida to New York to Iowa and five states in between (Mixson et al., 2006) found that 41% of adult lone star ticks were infected with *R. amblyommatis*. Another study in Maryland (Stromdahl et al., 2008) found that *A. americanum* larvae, which commonly bite people, had a "high prevalence" of infection with *R. amblyommatis* (no percentage value given). Gaines et al. (2014) also found *R. amblyommatis* in 55.9% of 1381 nymph stage and in 72.8% of 206 adult stage *A. americanum* ticks collected from 25 sites across Eastern Virginia. Although *R. parkeri* was also found in 1% of the 206 adult ticks and 0.4% of the 1581 nymph-stage lone star ticks tested in Virginia, *R. rickettsii* was not found. Therefore, due to the very high *R. amblyommatis* infection rates seen in lone star ticks, it is likely that most patients with SFR positive serology test results in the southeastern U.S. result from exposure to *R. amblyommatis* through lone star tick bites. There is only one published account of *R. rickettsii* transmitted to a person in North Carolina by a lone star tick (Breitschwerdt et al., 2011). However, recently *A. americanum* was shown to be capable of acquiring two different strains of *R. rickettsii* and transmitting each strain to laboratory animals. Therefore, it is evident that lone star ticks can contribute to some RMSF transmission (Levin et al., 2017).

*Amblyomma maculatum*, the Gulf Coast tick, has been collected as far north as Coastal and Piedmont regions of Northern Virginia, but it generally occupies a more restricted and more southerly region of the southeastern U.S than the lone star tick. In 2002, *A. maculatum* was first associated with the transmission of *R. parkeri* to people in southeastern Virginia (Paddock et al., 2004). Several recent studies have tested *A. maculatum* collected from North Carolina, Virginia, Kansas, and Oklahoma. In North Carolina, a total of 234 *A. maculatum* collected from 23 counties had a 29.1% infection rate with *R. parkeri,* and a 3.8% infection rate with *Candidatus* R. andeanae, which is not known as a human pathogen (Varela-Stokes et al., 2011). Of the 301 *A. maculatum* ticks collected in southeastern VA (Nadolny et al., 2014), 51% were infected with *R. parkeri* whereas only 0.33% were carrying *Candidatus* R. andeanae. Among *A. maculatum* totaling 122 and 94 ticks that were collected from nine counties in Oklahoma and nine counties in Kansas, respectively, none tested positive for *R. parkeri*; (Paddock et al., 2015). However, the same ticks from Oklahoma and Kansas had 73% and 47% infection rates with *Candidatus* R. andeanae, respectively. Although *Candidatus* R. andeanae is not known as a human pathogen, persons exposed to it through tick bites might subsequently test positive on a serological test for RMSF.

*Rhipicephalus sanguineus s.l.*, the brown dog tick, is primarily associated with dogs, but will bite people and is a competent vector for *R. rickettsii.* This tick lives primarily on dogs and can be found in and around the structures or dens that dogs live in. Brown dog ticks can be found in association with dogs and dog habitats, throughout the U.S. and Mexico, but are only common where dogs are not regularly treated with tick or flea prevention measures and where such dogs can range freely to associate with other dogs. In 2005 several large outbreaks of RMSF occurred on Indian Reservations in Arizona where dogs typically ranged freely and were rarely treated for ticks or fleas. Brown dog ticks were the only tick species found in the Reservation environments where people were contracting *R. rickettsii* infections. In 2005, persons from the Georgia Department of Health and the CDC-Rickettsial Zoonosis Branch initiated tick surveys around Gordon County, GA in response to multiple human cases of RMSF that had been identified from that county. Tick collections around one residence in that county yielded, eight brown dog ticks, and when these were tested, one (12.5%) tested PCR positive for *R. rickettsii* (Garrison et al., 2007). In the early 2000s pathogen studies of brown dog ticks by Eremeeva in Arizona (Eremeeva et al., 2006), Beeler in California (Beeler et al., 2011), and Forandel in Virginia (Fornadel et al., 2013) did not find *R. rickettsii* in the tested ticks, but did find *R. massiliae*, another known human pathogen. *Rickettsia massiliae* was found in 25% of 20 brown dog ticks collected from the environment in Arizona, in 72% of the ticks collected from dogs in California, and in 33% of the ticks collected from dogs in Virginia, respectively. In a study in Mexicali, Mexico (Eremeeva et al., 2011) found *R. rickettsii* in 31.3% of 96 *R. sanguineus s.l.* ticks, and although this Mexicali strain of *R. rickettsii* was genetically different from the strain of *R. rickettsii* causing disease outbreaks in Arizona, it was also identified as a human pathogen in Mexico. Finally, Owen et al. (Owen et al., 2019) collected *R. sanguineus s.l.* from multiple sites in Northern Mexico and Arizona, and *R. rickettsii* infection rates in these ticks ranged from 0% to 43% among multiple collection sites. These findings indicate that the brown dog tick can be an important vector of *R. rickettsii* in locations where domestic dogs roam freely and can also act as a vector of *R. massiliae* in some locations.

### 7.2. Issues

The prevalence of *R. amblyommatis* in lone star ticks in the southeastern U.S. may have a significant influence on the over-diagnosis of RMSF in the U.S. Lone star ticks are aggressive biters of people and are the most common human-biting tick in the southeastern U.S. Unlike other *Amblyomma* tick species, all stages of the lone star tick (i.e., larvae, nymphs, and adults) readily bite and feed on people, and several studies have determined that lone star tick nymphs can have *R. amblyommatis* infection rates in the 40 to 60% range (Gaines et al., 2014), and up to 84% of adult stage ticks may be infected (Mixson et al., 2006). Larval stage lone star ticks can also acquire *R. amblyommatis* transovarially and may bite people in large numbers during the mid to late summer months (Stromdahl et al., 2008). Given that lone star tick larvae may be abundant on the ground from mid-July through August and can crawl through the weave in most socks to bite ankles, it is likely that many people are bitten by larval lone star ticks each year without knowing that it was a tick that bit them. Their multiple bites on ankles are often mistaken as "chigger bites." Therefore, people in the southeastern U.S., whose occupations or outdoor activities make them prone to tick bites, are likely to be exposed to *R. amblyommatis* from lone star tick bites on a yearly basis and could subsequently test positive on serological assays for RMSF for a year of more after their tick bites. It is also evident that *A. americanum* ticks may occasionally carry *R. rickettsii*, are competent vectors, and could be an important vector of RMSF due to their biting prevalence.

### 7.3. Evidence and findings

Reviewed literature showed that various SFGR agents are detected in collections of each of the six tick species. However, with the exception of rates in brown dog ticks (*R. sanguineus s.l.*), the majority of the SFR agents found in the other five tick species were identified as being moderately to mildly pathogenic, or non-pathogenic, with the presumptive non-pathogenic SFGR agents accounting for most of what has been found in the various studied tick species. *Rickettsia parkeri* appeared to be the most commonly identified pathogenic SFGR agent

but was only common in *A. maculatum*, which do not bite people frequently, may have painful bites, and only bite people as adult stage ticks.

Among the 11 identified SFGR agents carried by these six tick species, four agents (*R. rickettsii, R. parkeri, R. massiliae*, and *Candidatus* R. philipii) are proven human pathogens. Although *R. rickettsii* infections are clearly known to cause fatal illnesses in people, the other three agents are not. Additionally, although *R. amblyommatis* and the less common *R. montanensis* have occasionally been suspected of causing mild illness symptoms in a few of the people exposed to them, there is relatively little evidence of disease causation (McQuiston et al., 2012).

In the recent studies using molecular pathogen identification techniques, *R. rickettsii* was detected in all but one of the six tick species examined. It was present in up to 1% of two *Dermacentor* species and had only been detected once in *A. americanum.* but was found in relatively high proportions of some of the *Rhipicephalus sanguineus s.l.* populations tested in Mexico and Arizona. Furthermore, large RMSF outbreaks in Mexico and Arizona suggest that *R. sanguineus s.l.* is an important vector of RMSF, particularly in areas where there are free-roaming, poorly maintained dog populations. After large outbreaks of RMSF and its discovery in *D. andersoni* ticks in Montana in the early 1900s, most of the focus on RMSF transmission over the past century has been on *Dermacentor* species, which also have an affinity for dogs as hosts. In the early 1900s era when RMSF was first discovered in the communities of western Montana, dogs roamed freely, were poorly cared for, and there were no available acaricides to use for tick prevention on dogs, so it is not inconceivable that *R. sanguineus s.l.* might have also played some role in that outbreak.

## 8. Challenges and opportunities

As the ticks that are suspected of being RMSF vectors to people commonly carry a variety of non-pathogenic, or low pathogenic spotted fever rickettsial (SFR) agents, and infection with these agents may cause seropositive results in people who are tested for exposure to RMSF, the diagnosis of human illnesses related to SFR exposure is prone to over-diagnosis and overtreatment. Therefore, the development of agent-specific diagnostic assays for diagnosis of suspected SFGR illnesses could help define the actual prevalence of SFR illnesses and prevent over-diagnosis and treatment.

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## Supplementary materials

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