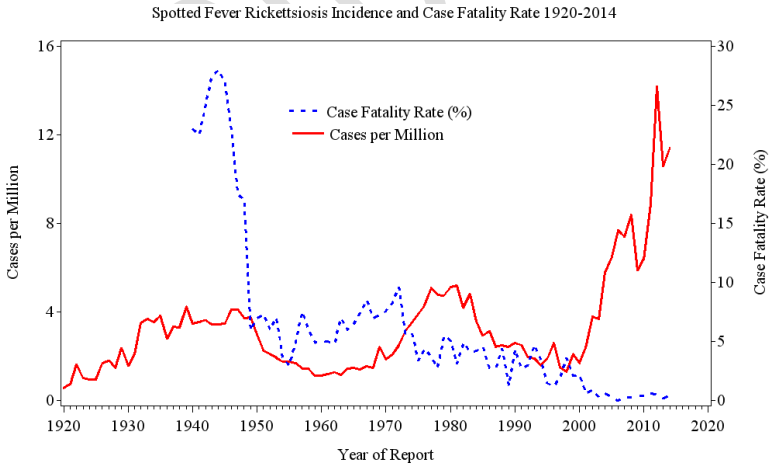
Spotted Fever Rickettsioses in the United States

Background

- Spotted fever rickettsioses (SFR) are a group of diseases caused by closely related bacteria in the spotted fever group *Rickettsia* (SFGR). These pathogens cause acute febrile illnesses, with headache, malaise, thrombocytopenia, as well as rash and occasional eschars (dark scab at the site of tick or mite bite).
- The most well-known SFR is Rocky Mountain spotted fever (RMSF), caused by *Rickettsia rickettsii.* RMSF is the deadliest tickborne disease in the Americas, with a case fatality rate of up to 30% in some areas despite availability of treatment.
- RMSF has been nationally notifiable since the 1920s. In 2010, cases of RMSF became reportable under the category Spotted Fever Rickettsiosis (SFR). This category captures cases of RMSF, *Rickettsia parkeri* rickettsiosis, Pacific Coast tick fever, rickettsialpox, and likely others as well. The change is a response to recognition that commonly available serologic tests are unable to differentiate between SFGR species. These other SFR were likely already being captured under RMSF case classifications prior to the case definition change.

Burden

- SFR cases have generally been increasing since they were first notifiable with a significant spike in cases in the last decade.
- The annual incidence of SFR saw a sharp increase from 1.7 to 9 cases per million persons from 2000 to 2012.
- Increasing trends appear to be continuing with 4,269 cases reported in 2016 and preliminary reports indicating over 5,300 cases provisionally reported in 2017.



Diagnostic challenges

- Closely related species of SFGR have cross-reactive antigens and cannot be definitively distinguished using commonly available serologic assays. Most commercial labs are unable to differentiate the species using these serologic methods.
- Antibodies can rise in the first week of illness and elevation can persist for months or years following infection.
- Accurate diagnosis of SFR using serologic methods requires paired serum specimens taken from the first week of illness and a second sample taken 2–4 weeks later.
- The current case definition for SFR allows for other, non-specific serologic testing, such as indirect immunofluorescence antibody (IFA) assays to detect immunoglobulin M (IgM), latex agglutination, enzyme-linked immunosorbent assay (ELISA), and dot-ELISA testing, as supportive laboratory evidence. These tests have significant limitations and may cloud our understanding of SFR burden.
- There is increasing suspicion that other less pathogenic SFGR may be responsible for many of the SFR cases, including diseases associated with other tickborne agents including *R. parkeri, R. amblyommatis, R. montanensis,* and *Rickettsia* 364D.
- Molecular methods are rarely used to confirm SFR, and due to the reliance on serologic methods, the causative agent is seldom identified.
- PCR detects rickettsial DNA in whole blood and can be used when a patient is experiencing symptoms. PCR is highly specific for *Rickettsia* DNA, and can result in a diagnosis to the species-level in some cases. However, a negative PCR

result does not rule out rickettsial infection. While molecular methods cannot be the only tool in our diagnostic toolkit, they provide a unique opportunity to better understand the pathogen diversity of spotted fever rickettsioses in the United States.

New developments

- Researchers at the CDC are nearing the end of a study looking at the prevalence of SFGR antibodies in approximately 3,000 healthy blood donors from Georgia, Washington, and Oregon, from serum collected during May–July 2016. Preliminary results indicate that approximately 11% of the donors from Georgia and 6% of those from the Pacific Northwest have IgG antibodies reactive with *R. rickettsii* at titers ≥1:64 when tested by IFA.
- Previous seroprevalence studies have estimated 4–6% seropositivity for SFR in the total U.S. population. More localized seroprevalence studies have found rates as high as 22% in areas of Arkansas. Seroprevalence studies using higher titer cut-offs of 1:256, ranged in seroprevalence from 7.7% in Tennessee to 1.8% in North Carolina. These studies suggest that background seroprevalence may be greater than previously thought.
- Real-time *Rickettsia* species PCR assays are now available through the Laboratory Response Network in participating state and local public health labs. Increased use of these assays is important for detecting true infections with SFR, as well as identifying the specific infecting agent.

Acknowledgments

A special thank you to Anne Straily, Chris Paddock, F. Scott Dahlgren, Stephanie Shields, Joseph Singleton, Cecilia Kato, Laura Tonnetti, and Susan Stramer, for allowing us to share results from their unfinished work.

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