The Journal of Infectious Diseases

EDITORIAL COMMENTARY

Surveillance for Spotted Fever Group Rickettsial Infections: Problems, Pitfalls, and Potential Solutions

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Keywords. Rocky Mountain spotted; fever; spotted fever; group rickettsial infections;; surveillance; serologic; diagnosis; misdiagnosis.

Even experienced physicians and epidemiologists have difficulty consistently and accurately confirming or excluding a diagnosis of spotted fever group rickettsioses (SFGR). As a result, both underdiagnosis and overdiagnosis of SFGR are unresolved clinical and epidemiologic problems. The report by Straily et al in this issue of *The Journal of Infectious Diseases* sheds light on the pitfalls of using a single serologic assay to diagnose or classify a case of SFGR [1]. Their findings underscore the conclusion that rickettsial diagnostics are in dire need of modern technological advancement and that current methods for surveillance are equally in need of a major overhaul.

SFGR infections are highly variable in both their initial clinical presentation and ultimate severity [2]. Making a clinical diagnosis of SFGR infection can be fairly straightforward in patients from endemic regions who present with a history of tick bite together with skin rash, fever, and headache in the spring or summer months. However, many cases either completely escape detection or lack eventual confirmation after appropriate empiric therapy is begun. Patients who are seen in the early phases of *Rickettsia rickettsii* infection frequently have no history of a tick bite or tick contact, lack a skin rash, and have clinical findings suggestive of an undifferentiated viral illness [3]. Others have atypical symptoms that are suggestive of undifferentiated sepsis syndromes with multiorgan failure, encephalitis, myocarditis, or pneumonia, which can confound even the most attentive clinicians [2, 4, 5]. Some cases of SFGR occur "out of season" in endemic areas [6], in urban locations where SFGR are uncommon or unknown to local practitioners [7], or in travelers in whom a history of recent travel is not obtained.

Despite advances in molecular technologies, the diagnosis and classification of SFGR infections are still based largely on serologic testing. However, true convalescent titers are rarely sent, and as few as 1% of reported cases are classified as "confirmed" SFGR infection [8]. The reasons for lack of convalescent testing are numerous: Such testing is inconvenient to patients (who at that point in time are well), usually results in a fee for a clinic visit even though the actual serologic tests are provided free of charge by most state health department laboratories, and the results of convalescent testing are rarely available in a timeframe that affects clinical decision making. Further complicating surveillance is the fact that early treatment may blunt or completely abolish a typical rise in convalescent indirect fluorescent antibody (IFA) titer and/or prevent the appearance of a skin rash or other typical signs of Rocky Mountain spotted fever (RMSF) and rapidly reduce the severity and duration of illness [9–11]. Other patients may die of fulminant disease prior to the development of convalescent antibodies, in which case *R. rickettsii* infection can only be detected if pathogen-targeted approaches such as polymerase chain reaction or specific histologic staining of tissues are performed at the time of autopsy [12]. Additionally, some patients infected with *R. rickettsii* eventually recover without treatment, and it is likely that some patients infected with SFGR, such as *Rickettsia amblyommatis*, have subclinical or completely asymptomatic infections [13–15]. Thus, it is easy to understand that an unknown but probably substantial proportion of all true cases of SFGR are never reported to public health agencies.

Conversely, as Straily and colleagues show, "overdiagnosis" of SFGR is also an important problem if the presence of a single IFA immunoglobulin G titer ≥64 is used as corroborating evidence for a diagnosis of RMSF. Straily and colleagues found that 11.1% of healthy blood donors from Georgia and 6.3% of donors from Oregon and Washington had IFA titers of ≥1:64, presumably without acute RMSF as evidenced by their approval as blood donors. These authors then

Received 19 June 2019; editorial decision 19 June 2019; accepted 1 July 2019 ; published online July 3, 2019.

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The Journal of Infectious Diseases® 2019;XX:1–3

DOI: 10.1093/infdis/jiz317

sampled 243 patients who were found to be IFA seropositive by the Georgia State Health Department laboratory during 2016. Only 28% of these 243 cases met standard surveillance clinical criteria for a SFGR infection; 19% were asymptomatic, and the remaining 53% had clinical symptoms that were inconsistent with the standard case definition for RMSF [1]. Thus, under current criteria, "diagnostic" levels of rickettsial antibodies are frequently found in individuals without further evidence of active SFGR infection. Straily and colleagues appropriately conclude that "reliance on this type of supportive evidence can generate profound inaccuracies in surveillance data that define the distribution, magnitude, and clinical characteristics of spotted fever rickettsiosis in the United States."

In view of the frequency of single-IFA seropositivity in asymptomatic blood donors and various other healthy citizens, patients with various viral or nonrickettsial conditions can easily be misdiagnosed as having RMSF. In addition, patients who develop infection due to other nonrickettsial tick-borne pathogens such as *Ehrlichia chaffeensis*, *Ehrlichia ewingii*, or phlebovirus (Heartland virus) could easily be misdiagnosed as having RMSF or infection by another SFGR if they coincidentally have preexisting positive IFA titers to SFGR. As the IFA test cannot reliably distinguish infection due to *R. rickettsii* from infection with other SFGR rickettsia, such as *Rickettsia parkeri* or *R. amblyommatis*, standard testing probably also leads to an overestimate of the true incidence of RMSF and a simultaneous underestimate of the incidence of infection with these other SFGR pathogens.

Thus, despite the best efforts of countless public health employees and agencies, reliance on IFA serologic testing at a single timepoint results in both over- and underreporting of cases of RMSF and other SFGR infections. The report by Straily et al highlights that we should caution the public and the scientific community that past and recent passively collected surveillance data on the incidence of SFGR in the United States are not highly accurate. Taking into account this limitation, it may be useful to append surveillance reports with a disclaimer stating that underdiagnosis and overdiagnosis are common in clinical practice and that the true incidence of illness due to these pathogens is unknown.

In light of the above dilemma, what are some possible solutions? There certainly are accessible approaches that could improve the accuracy of current surveillance data. These approaches include improved access to existing convalescent serologic testing or PCR testing, either through intensive public health efforts (eg, targeted home visits with blood collection for convalescent testing) or improved education/training of front-line providers on the merits of pursuing confirmatory testing and availability of PCR assays. Based on the study by Straily et al, simply increasing the cutoff for single-timepoint IFA results (eg, to 1:128) would offer an increase in reporting specificity without increased burden on the system, although perhaps at some loss of sensitivity. However, many of these efforts would be time and resource-consuming, limitations that need to be weighed against the anticipated benefit over existing approaches.

Ultimately, meaningful advances in our understanding of the burden of these diseases and in our ability to identify cases of SFGR in the acute setting will require development of more sensitive, specific, and accessible diagnostic tests. A move to more objective serologic assays has merit, but ultimately suffers from the same dilemma caused by reliance on single-timepoint serologies as outlined by Straily et al. Nucleic acid amplification tests are now available for *R. rickettsii* and offer high specificity but suffer from variable (and usually low) sensitivity, as few rickettsial organisms circulate in the blood during acute illness [16, 17]. PCR testing of skin or eschar biopsy samples is equally specific and more sensitive than PCR testing of whole blood [5], although hampered by the need to obtain biopsies, which can be difficult in the outpatient setting. Metagenomic sequencing of blood and other samples offers some promise for broad detection of circulating pathogens in an agnostic fashion, but it is unclear if novel sequencing technologies (or others that are being explored) will offer sufficiently increased sensitivity compared to existing nucleic acid amplification tests. Diagnostic methods utilizing monoclonal antibodies to detect proteins induced by *Rickettsia*-infected endothelial cells warrant further investigation, particularly if such methods can be shown to be specific and sensitive in patients who are early in the course of their illness and if such testing can be quickly done at the point of care [18].

The report by Straily et al highlights that the current state of rickettsial diagnostics continues to hamstring both clinical and surveillance efforts. To this end, making enhancement of our rickettsial diagnostic armamentarium a primary focus of future research efforts in this field offers the clearest path to resolving this challenging dilemma

Note

Potential conflicts of interest. D. J. S. has received grants from the Centers for Disease Control and Prevention Epicenter Grant, other support from Johnson & Johnson, personal fees and other support from Magnolia Medical Technologies, grants from the National Football League, and personal fees from UpToDate. M. T. M. has received personal fees from UpToDate. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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