Expanding Range of *Amblyomma americanum* and Simultaneous Changes in the Epidemiology of Spotted Fever Group Rickettsiosis in the United States

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Abstract. Spotted fever group (SFG) *Rickettsia* species are etiologic agents of a wide range of human infections from asymptomatic or mild infections to severe, life-threatening disease. In the United States, recent passive surveillance for SFG rickettsiosis shows an increased incidence and decreased severity of reported cases. The reasons for this are not well understood; however, we hypothesize that less pathogenic rickettsiae are causing more human infections, while the incidence of disease caused by more pathogenic rickettsiae, particularly *Rickettsia rickettsii*, is relatively stable. During the same period, the range of *Amblyomma americanum* has expanded. *Amblyomma americanum* is frequently infected with "*Candidatus* Rickettsia amblyommii", a SFG *Rickettsia* of unknown pathogenicity. We tested our hypothesis by modeling incidence rates from 1993 to 2013, hospitalization rates from 1981 to 2013, and case fatality rates from 1981 to 2013 regressed against the presence of *A. americanum*, the decade of onset of symptoms, and the county of residence. Our results support the hypothesis, and we show that the expanding range of *A. americanum* is associated with changes in epidemiology reported through passive surveillance. We believe epidemiological and acarological data collected on individual cases from enhanced surveillance may further elucidate the reasons for the changing epidemiology of SFG rickettsiosis.

INTRODUCTION

Rocky Mountain spotted fever (RMSF) is a severe, life-threatening illness caused by infection with *Rickettsia rickettsii*, the most virulent of all known spotted fever group (SFG) *Rickettsia* species. Early treatment with doxycycline typically results in rapid recovery; but, after the fifth day of illness, untreated cases have high chances of severe illness, including disseminated intravascular coagulopathy and multisystem organ failure, potentially leading to permanent disabilities or death.[1–6] Confirmed cases of RMSF occur sporadically across the United States with concentration in the south central and southeastern states.[3,7,8]

In the United States, several other SFG *Rickettsia* species cause human disease, but these are characteristically far milder infections compared with RMSF and are not associated with deaths. *Rickettsia akari* causes rickettsialpox, a febrile illness with a rash, associated with mites and house mice.[9,10] *Rickettsia parkeri* causes a febrile illness with a characteristic eschar.[11,12] The Gulf Coast tick (*Amblyomma maculatum*) was the first discovered vector of *R. parkeri*, but the lone star tick (*Amblyomma americanum*) is also a potential vector.[13,14] In California, *Rickettsia* species 364D causes a febrile illness associated with an eschar, and the cases reported to date have not required hospitalization.[15,16] The Pacific Coast tick (*Dermacentor occidentalis*) is the suspected vector of *Rickettsia* species 364D, and reported cases have so far been within its range.[16]

Serological evidence suggests other SFG *Rickettsia* species may cause mild or abortive infections. *Rickettsia montanensis* has historically been considered nonpathogenic to humans because of the absence of human cases and the high prevalence of *R. montanensis* in the American dog tick (*Dermacentor variabilis*), which is also the primary vector of *R. rickettsii*.[17] However, a single case report associated *R. montanensis* with a mild, afebrile illness.[18] Cases of SFG rickettsiosis reported through public health surveillance systems in North Carolina may be attributed to "*Candidatus* Rickettsia amblyommii".[19] Using polymerase chain reaction, researchers demonstrated the presence of "*Ca*. Rickettsia amblyommii" in ticks removed from humans, including a case with a rash localized to the site of tick attachment.[20,21] In addition, a longitudinal study of dogs in Oklahoma demonstrated rickettsemia and seroconversion to several *Rickettsia* species following tick exposure, despite no clinical illness.[22] These various rickettsiae are antigenically related, and serologic assays developed for the diagnosis of RMSF may react nonspecifically with antigens of less pathogenic SFG *Rickettsia* species.[7] In this context, it is not possible to differentiate SFG rickettsioses by serology alone.

Passive surveillance for SFG rickettsiosis in the United States began in 1920.[23] The case fatality rate (CFR) for RMSF, which was 1–10% in the United States during 1950–2000, dropped precipitously in 2001, and has remained under 1% for 12 consecutive years (Figure 1).[3,8] Accompanying this trend was a sizeable increase in reported incidence, with the reported annual incidence rate (IR) topping historical highs of six cases per million persons, reaching into cases per 100,000 for the first time in recorded history (Figure 1).[3,8] Possible explanations for these changes in reported epidemiology include changes in public health surveillance, clinical practice, use of enzyme-linked immunosorbent assay, and the underlying epidemiology of RMSF and other SFG rickettsiosis.[3] Determining whether this trend observed in passive surveillance is a result of changes in the epidemiology of SFG rickettsiosis or an artifact of surveillance is a matter of public health importance.

A regional study suggests that changes in the epidemiology of SFG rickettsiosis may be unrelated to changes in the ecology of the American dog tick, historically identified as the principal vector of *R. rickettsii* in the United States.[24] Another study mapped the approximate distribution of the American dog tick, the lone star tick, the brown dog tick (*Rhipicephalus sanguineus*), the Gulf Coast tick, and the area with the highest

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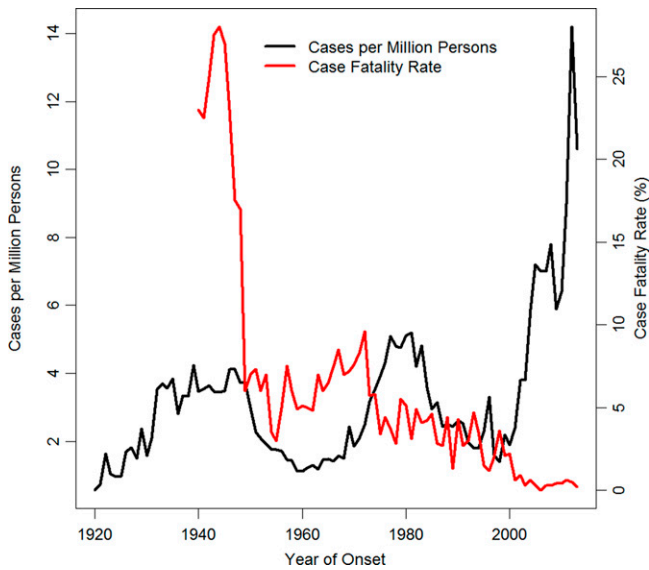
FIGURE 1. Historical incidence rate and case fatality rate of spotted fever group rickettsiosis in the United States, 1920–2013 (2013 CDC unpublished data).[3,8] The two measures are negatively correlated (Spearman's $\rho = -0.37$, $P = 0.001$).

reported RMSF incidence during 2001–2005 to illustrate the overlap of reported RMSF with the ranges of the lone star tick, the brown dog tick, and the Gulf Coast tick populations, suggesting most cases reported as RMSF might be other SFG rickettsiosis.[17] The range of the lone star tick is expanding into areas previously thought uninhabited by the tick, which may affect changes in the epidemiology of SFG rickettsiosis.[25,26] We hypothesize that less pathogenic rickettsiae are causing more human infections, while the incidence of disease caused by *R. rickettsii* is relatively stable. Here, we use data from passive surveillance for human SFG rickettsiosis and data on the presence of the lone star tick to test our hypothesis by investigating the association of the widening range of the lone star tick with an increase in incidence, a decrease in CFR, and a decrease in hospitalization.[27]

METHODS

Tick data. We used county-level distribution data for *A. americanum* from 1980 to 2013 adopted from the work of Springer and others,[27] maintaining the designations of established, reported, or absent as defined by the authors. Counties were designated as

- established, if at least six ticks from one life stage or at least two life stages were found,
- reported, if one to five ticks of a single life stage were found, or
- absent otherwise.

Springer and others used the years the ticks were collected to tie reports in the literature to decades, and when absent, the year of publication was used as a proxy. We allowed each decade to inherit the previous decades' evidence for the tick's status in our data, as investigators may not have been interested in reestablishing the presence of the tick decade after decade in the literature.

Human data. The Centers for Disease Control and Prevention (CDC) has two passive surveillance systems that collect data for SFG rickettsiosis. Since 1981, state and territorial public health departments report cases of SFG rickettsiosis to the CDC by case report forms (CRFs) (http://www.cdc.gov/ticks/forms/2010_tbrd_crf.pdf), and these CRFs include the county of residence, year of onset, and data regarding hospitalization and survival or death from disease. Since 1993, public health departments report cases of SFG rickettsiosis to the CDC through the Nationally Notifiable Disease Surveillance System (NNDSS), and these data also include the county of residence and onset date (http://wwwn.cdc.gov/NNDSS/). Incidence rates were computed using county population estimates from the U.S. Census Bureau, Population Division, for 1993–2013. Because *Rickettsia* species 364D, *R. parkeri*, and *R. akari* are not known to cause fatal SFG rickettsiosis, we used the CFR as a marker for the presence of RMSF in the passive surveillance data. Similarly, we used hospitalization as a softer marker for the presence of RMSF, as cases of *R. parkeri* rickettsiosis may be diagnosed as RMSF and subsequently hospitalized.[12]

Statistical methods. We used three generalized additive models to investigate the relationship between SFG rickettsiosis and the status of *A. americanum* populations: absent, reported, or established. Cases were assigned latitude and longitude based on the centroid of their county of residence, and this spatial component was included in our models using thin plate splines with a basis of dimension 40.[28,29] The parametric part of each model included the distribution status of *A. americanum*, the decade of onset of symptoms, and an interaction term between the main effects. A log-binomial model was constructed for both the hospitalization rate (HR) and the CFR. Data from 1981 to 2013 were included in these analyses using the CRFs. A Poisson model was constructed for the number of reported cases from the NNDSS using population estimates from the U.S. Census Bureau, Population Division, to compute the offset for each county for each decade. Data from 1993 to 2013 were used in this analysis. Nonparametric models were regressed only on thin plate splines to generate maps. We used the Wald χ^2 test for linear hypotheses from our regression models at $\alpha = 0.05$, and we used the Wald interval to construct 95% confidence intervals (CIs). Because the interaction terms in our model were all significant, we did not perform hypothesis testing or construct CIs for results outside our models. Analysis was performed using SAS software (Version 9.3 of the SAS System for Windows; Copyright 2010, SAS Institute Inc., Cary, NC) and R software (Version 3.1.1; Copyright 2014, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

From 1993 to 2013, 31,234 cases of SFG rickettsiosis were reported through NNDSS, which included a county of residence, for an IR of 5.20 cases per million persons per year. The reported IR increased each decade and increased with the strength of evidence (absent < reported < established) for the presence of *A. americanum* (Table 1). The estimated IR was highest, up to 94 cases per million persons per year, in a region spanning from Arkansas and Missouri to Virginia (Figure 2). From 1981 to 2013, 21,483 cases of SFG rickettsiosis were reported through CRFs, which included hospitalization

TABLE 1

The IR, HR, and CFR of reported cases of spotted fever group rickettsiosis by status of *Amblyomma americanum* within a county and decade of onset of symptoms

	IR*	HR (%)	CFR (%)
Amblyomma americanum within county			
Absent	2.28	48.6	1.68
Reported	6.07	33.2	0.74
Established	10.3	27.8	0.65
Decade of onset of symptoms			
1980s	–	72.0	2.80
1990s	1.68	51.0	2.03
2000s	5.38	24.4	0.43
2010s	10.0	27.3	0.47

CFR = case fatality rate; HR = hospitalization rate; IR = incidence rate.
The IRs were calculated using case counts from the Nationally Notifiable Disease Surveillance System and population estimates from the United States Census Bureau, Population Division, for 1993–2013. The HRs and CFRs were calculated using the case report form data for 1981–2013. The statistics in this table are crude statistics, not adjusted statistics from our regression models.
*Cases per million persons per year.

status and county of residence. Of these cases, 7,597 were hospitalized (HR = 35.4%). In general, the reported HR decreased with time and with the presence of *A. americanum* (Table 1). The estimated HR was high along the Gulf of Mexico, from 65% to 85% (Figure 3). From 1981 to 2013, 21,443 cases of SFG rickettsiosis were reported through CRFs with data on whether the case survived or died and county of residence, and 210 of these cases were fatal (CFR = 0.98%). In general, the reported CFR decreased with time and decreased with the presence of *A. americanum* (Table 1). The estimated CFR was high in a region spanning Arizona to Montana, from 2.4% to 9.3% (Figure 4). *Amblyomma americanum* was either reported or established in much of the South, parts of the Midwest, and parts of the Northeast by the 2010s (Figure 5).

Our full model of the IR of SFG rickettsiosis was statistically significant ($P < 0.0001$). The effect of the presence of the lone star tick and IRs was not the same for each decade ($P = 0.0007$; Figure 6). In the 1990s, the estimated IR was greater in counties where *A. americanum* was reported than counties where *A. americanum* was absent (IR ratio [IRR] = 1.08, 95% CI = 1.01–1.16), and the estimated IR in counties where *A. americanum* was established was greater than counties where *A. americanum* was absent (IRR = 1.10, CI = 1.03–1.17). By the 2010s, counties where *A. americanum* was

reported had a higher IR than counties where *A. americanum* was absent (IRR = 1.15, CI = 1.09–1.21) and counties where *A. americanum* was established had a higher IR than counties where *A. americanum* was absent (IRR = 1.28, CI = 1.22–1.34). The IR increased between decades (IRR = 2.08, CI = 2.02–2.16). The correlation between regression parameters for the decade of onset with *A. americanum* being reported was 0.65 and with *A. americanum* being established was 0.71.

Our model of the HR was statistically significant ($P < 0.0001$). The effect of *A. americanum* populations and HR was not the same for each decade ($P = 0.004$, Figure 7). In the 1980s, whether *A. americanum* was absent, reported, or established within a county was not associated with HR ($P = 0.31$). By the 2010s, the HR in counties where *A. americanum* was reported was similar to counties where *A. americanum* was absent (risk ratio [RR] = 0.92, CI = 0.83–1.01), and the HR in counties where *A. americanum* was established was lower than counties where *A. americanum* was absent (RR = 0.82, CI = 0.74–0.90). The HR decreased each decade (RR = 0.70, CI = 0.68–0.73). The correlation between the regression parameters for the decade of onset with *A. americanum* being reported was 0.16 and with *A. americanum* being established was 0.16.

Our model of the CFR was statistically significant ($P < 0.0001$). The effect of the presence of *A. americanum* on CFR was not the same for each decade ($P = 0.03$; Figure 8). In the 1980s, whether *A. americanum* was absent, reported, or established was not associated with CFR ($P = 0.15$). By the 2010s, the CFR among counties where *A. americanum* was reported was similar to that among counties where *A. americanum* was absent (RR = 0.68, CI = 0.46–1.01), and the CFR among counties where *A. americanum* was established was lower than counties where *A. americanum* was absent (RR = 0.38, CI = 0.26–0.56). The CFR decreased each decade (RR = 0.58, CI = 0.47–0.72). The correlation between the regression parameters for the decade of onset with *A. americanum* being reported was 0.20 and with *A. americanum* being established was 0.24.

DISCUSSION

Our results support the hypothesis that the expanding range of the lone star tick contributes to the increasing incidence and decreasing severity, as measured by HR and CFR, of reported SFG rickettsiosis because of a decreasing proportion
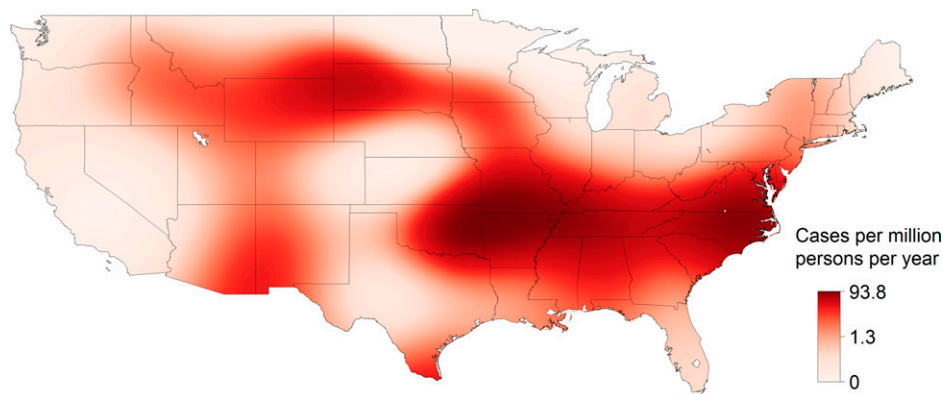

FIGURE 2. The incidence rate (IR) of spotted fever group rickettsiosis in the United States, 1993–2013. IRs were estimated from a nonparametric Poisson model using thin plate splines ($P < 0.0001$), with case counts from the Nationally Notifiable Disease Surveillance System and population estimates from the U.S. Census Bureau, Population Division.
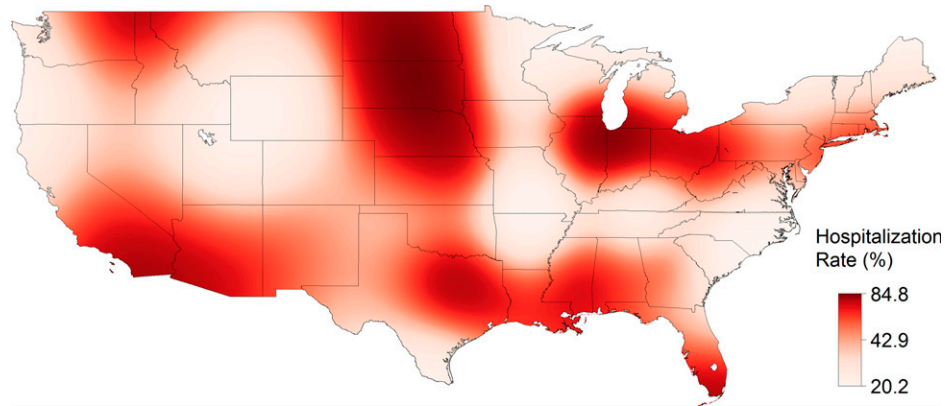
FIGURE 3.   The hospitalization rate (HR) of spotted fever group rickettsiosis in the United States, 1981–2013. HRs were estimated from a non-parametric log-binomial model using thin plate splines ($P < 0.0001$). Data are from case report forms.

of reported cases being RMSF. However, other factors may also play an important role, because the effect of time in our models was always stronger than the effects of the presence of the lone star tick. From our model of incidence, the IR was highest in counties with an established presence of the lone star tick each decade. But, counties with no reports of the lone star tick in the literature, largely in the western United States, also saw large increases in incidence over time (Figure 6). Similarly, the HR was lowest in counties with an established presence of the lone star tick each decade (Figure 7). The trend was not as simple for the CFR. The presence of the lone star tick was not associated with CFR in the 1980s, but by the 2010s, the CFR was lower in counties with stronger evidence of the lone star tick (Figure 8). Yet, the primary factor explaining the decrease in CFR in our model is again time, as the differences in the presence of the lone star tick within a decade are much less than the differences between decades (Figure 8). Generally, the dose–response relationship of the strength of evidence for the presence of the lone star tick with both the incidence and the severity of SFG rickettsiosis supports the hypothesis that the expanding range of the lone star tick is responsible for some of the changes in the epidemiology of SFG rickettsiosis.

Doxycycline has been a recommended treatment of RMSF and other SFG rickettsiosis for decades, and the association between treatment with chloramphenicol and an increased

risk of fatal outcome led to doxycycline becoming the single recommended treatment.[2] This discovery alone may be sufficient to explain the decreased CFR of SFG rickettsiosis between the 1990s and the 2000s (Table 1). However, oral chloramphenicol was no longer manufactured in the United States by 1991, so only the intravenous formulations—exclusive to the hospital setting—were available for treating SFG rickettsiosis.[30] Removal of chloramphenicol as a treatment for SFG rickettsiosis could not have decreased the HR between the 1990s and the 2000s. Either preventing severe illness by appropriate, early treatment or a change in the distribution of the etiologic agents causing SFG rickettsiosis could explain the reported changes.

In most regions of the United States, several distinct etiologic agents contribute to the epidemiology of SFG rickettsiosis. An exception is Arizona, where peridomestic RMSF is associated with pet dogs and the brown dog tick.[31] No other tick vectors or SFG *Rickettsia* have been associated conclusively with human disease in this state. Here, the IR, HR, and CFR are all higher than the national average (Figures 2–4). These trends in Arizona are consistent with the historical epidemiology of RMSF. Our maps also suggest that a similar phenomenon continues in Idaho and Montana, where the first reports originated, giving RMSF its namesake.[32,33]

While the prevalence of *R. rickettsii* in *D. variabilis* is typically under 1%, the prevalence of "*Ca*. Rickettsia amblyommii"
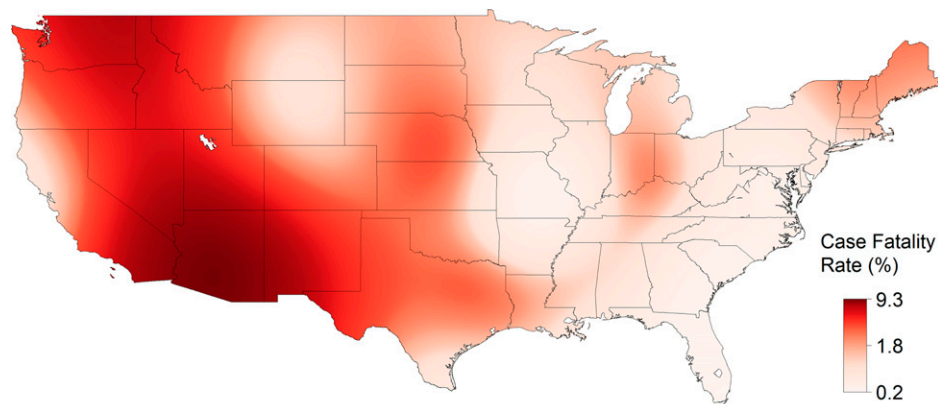

FIGURE 4.   The case fatality rate (CFR) of spotted fever group rickettsiosis in the United States, 1981–2013. CFRs were estimated from a non-parametric log-binomial model using thin plate splines ($P < 0.0001$). Data are from case report forms.
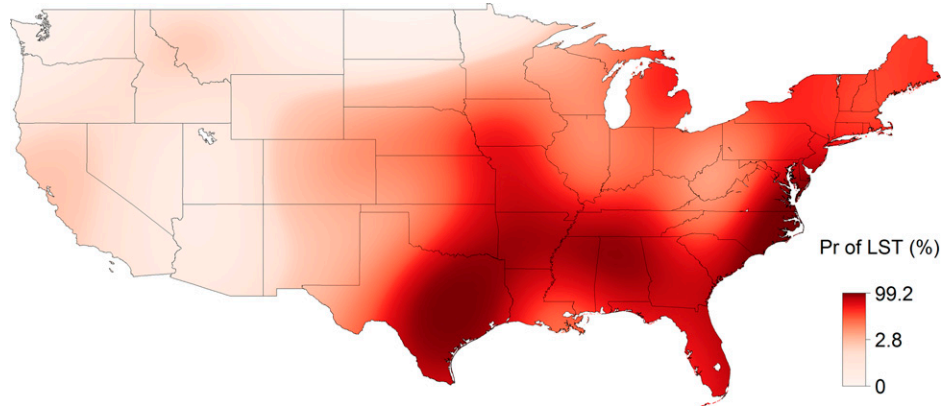
FIGURE 5. The distribution of the lone star tick (*Amblyomma americanum*) in the United States, 2013. The probability of the lone star tick being reported or established (vs. absent) was estimated from a nonparametric binomial logistic regression model using thin plate splines ($P < 0.0001$). Data are from Springer and others.[27]

in *A. americanum* is often over 50%.[17,20,34–44] Because of these large differences in prevalence, exposure to *R. rickettsii* may be rare relative to exposure to "*Ca*. Rickettsia amblyommii". A prospective case series in North Carolina demonstrated that most reported cases of RMSF were another SFG rickettsiosis, as these illnesses were milder than classical RMSF and serological titers were generally higher for "*Ca*. Rickettsia amblyommii" than for *R. rickettsii*.[19] A similar study at Fort Chaffee, Arkansas, produced similar results: National Guardsmen who seroconverted to *R. rickettsii* often did not have an illness compatible with a tickborne disease.[45] The association of the presence of the lone star tick with both decreased severity and increased incidence of SFG rickettsiosis supports these findings, and most cases of SFG rickettsiosis reported through

passive surveillance are unlikely to be RMSF. Besides the lone star tick and "*Ca*. Rickettsia amblyommii", other vectors and SFG *Rickettsia* species may contribute to the changes in epidemiology of SFG rickettsiosis, as the temporal trend toward less severe disease and higher incidence is only partly explained by changes in the range of the lone star tick.

The ecology of *R. parkeri*, which is thought to be transmitted primarily by the Gulf Coast tick, may also play an important role in the changes of the epidemiology of SFG rickettsiosis.[12] The Gulf Coast tick is an aggressive biter of humans, and the prevalence of *R. parkeri* in the Gulf Coast tick is often > 20%.[46] Despite its name, the range of the Gulf Coast tick has expanded beyond the coast of the Gulf of Mexico.[47] Our results suggest a contribution of the Gulf Coast tick to the national statistics for SFG rickettsiosis. In the United States, the HR is high along the Gulf Coast (between the Brazos River and the Chattahoochee River) relative to the areas with highest
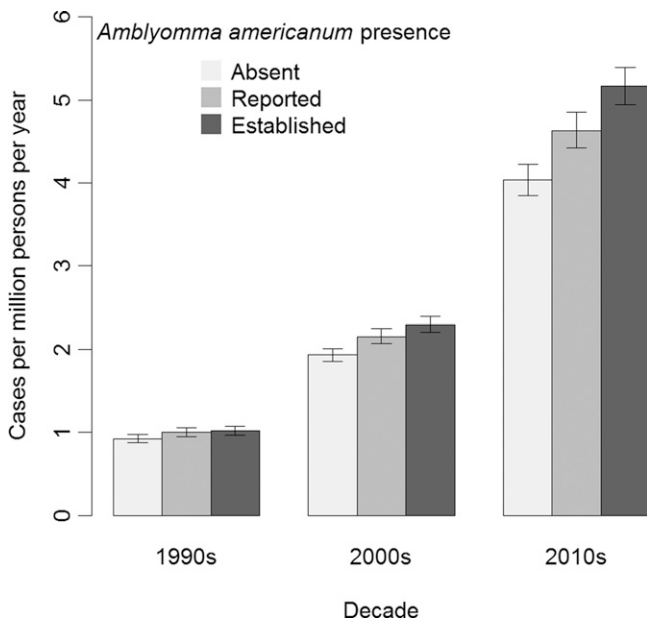

FIGURE 6. A plot of the incidence rate (IR) of spotted fever group rickettsiosis vs. decade of report by *Amblyomma americanum* presence, 1993–2013. The estimates are from our Poisson model of the IR using case counts from the Nationally Notifiable Disease Surveillance System and population estimates from the U.S. Census Bureau, Population Division. The error bars represent Wald 95% confidence intervals.
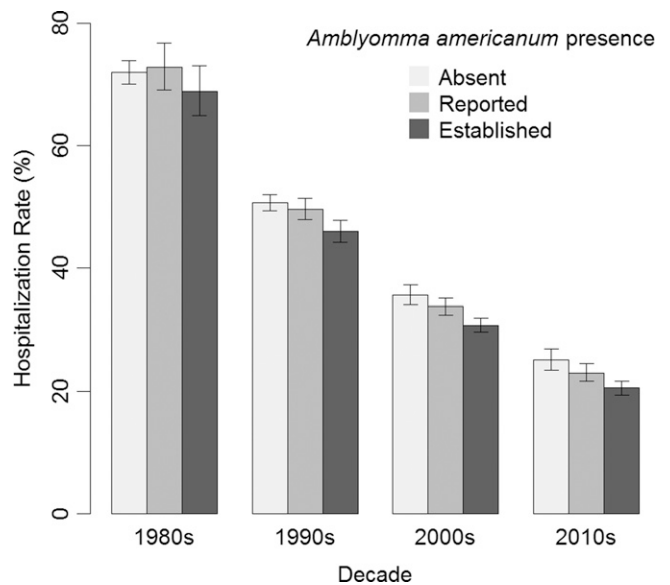

FIGURE 7. A plot of the hospitalization rate of spotted fever group rickettsiosis vs. decade of report by *Amblyomma americanum* presence, 1981–2013. The estimates are from our log-binomial model of the hospitalization rate using data from case report forms. The error bars represent Wald 95% confidence intervals.
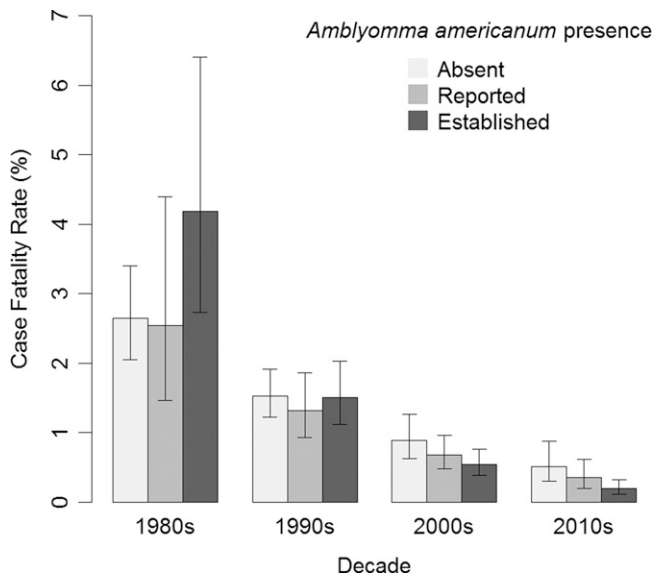
FIGURE 8.   A plot of the case fatality rate (CFR) of spotted fever group rickettsiosis vs. decade of report by *Amblyomma americanum* presence, 1981–2013. The estimates are from our log-binomial model of the CFR using data from case report forms. The error bars represent Wald 95% confidence intervals.

incidence, while the CFR is not (Figures 3 and 4). This finding is more consistent with *R. parkeri* rickettsiosis than with either RMSF or infections with less pathogenic SFG *Rickettsia* species, suggesting the importance of *R. parkeri* and its vector may be underappreciated.[46] In Kansas and Oklahoma, the Gulf Coast tick may not carry *R. parkeri* because of high prevalence of "*Candidatus* Rickettsia andeanae", an agent of unknown human pathogenicity.[48] In our results, the HR in Kansas and Oklahoma was lower than other parts of the Gulf Coast tick's range, suggesting that the Gulf Coast tick may not be a vector associated with severe SFG rickettsiosis in these states.

The lone star tick is also the vector of *Ehrlichia chaffeensis*, the agent of human monocytic ehrlichiosis (HME).[25] The CFR of HME is low (< 2%), but the HR of HME is 50%.[49,50] The maps in Figure 2 show an elevated IR from Missouri and Arkansas to Virginia. However, the HR in these areas is well below the reported HR of HME (Figure 3). Although the difference is less striking, the CFR in these areas is also below the reported CFR of HME (Figure 4). While the serological assays for *R. rickettsii* may cross-react with *E. chaffeensis*, the reported epidemiology of SFG rickettsiosis in this region is not severe enough to be consistent with reported epidemiology of HME.[7]

Our results are subject to limitations. Importantly, our methods are limited by the ecological fallacy: the associations we report at the county level do not imply that the lone star tick is responsible for any human disease. This limitation is particularly problematic in studies involving data generated through passive surveillance, as identifying the tick vector responsible for a representative sample of cases of SFG rickettsiosis is not feasible. Without epidemiological and acarological data on individual case-patients, inference is limited to the county level. A challenge to interpreting the results from our model is whether the observed associations with the changing epidemiology of SFG rickettsiosis and the expanding range of the lone star tick are collinear. When modeling hospitalization and fatality, the presence of the lone star tick is

not correlated with the decade of onset. When modeling incidence, the two are highly correlated; although, our methods should be sufficiently robust to a correlation of 0.71 and 0.66 between regression parameters. This implies that as the range of the tick vector expands with time and the IR of SFG rickettsiosis increases with time, teasing out the effects of the expanding tick vector on IR is subject to more uncertainty. We observed no other issues with multicollinearity (data not shown). The human data presented here are based on passive surveillance, which is subject to a variety of artifacts. Similarly, the tick data are based on the interests of individual investigators. Especially, investigators may have found the lone star tick incidentally during extensive investigations into the ecology of *Ixodes scapularis*. Altogether, our data are less than ideal, with systematic gaps in coverage and completeness. Further, the degree of completeness at any particular location may change over time. Given the length of the periods we investigated, we expect these limitations to contribute to bias toward the null. The lone star tick data do not exactly match periods of the human data. For the analysis of IR, we included data on the lone star tick from 1980 to 2013 and human data from 1981 to 2013. For the analysis of HR and CFR, we included data on the lone star tick from 1990 to 2013 and human data from 1993 to 2013. However, we felt this discrepancy was preferable to using only data from 2000 to 2013 in the analysis of IR and using only data from 1990 to 2013 for the analyses of HR and CFR.

Despite the limitations of our data and methods, we have demonstrated that the expansion of the lone star tick is associated with increasing incidence and decreasing severity of reported SFG rickettsiosis in the United States. As a variety of SFG *Rickettsia* species, vectors, and reservoirs drive the epidemiology of SFG rickettsiosis in the United States, we are not surprised that our models were able to explain only a fraction of the trends observed in passive surveillance. Including the status of other tick vectors, such as the Gulf Coast tick, as well as the prevalence of SFG *Rickettsia* in these vectors in our models may also expand our understanding; however, such an analysis will still be inferior to a study at the individual case-patient level. Enhanced surveillance for tickborne rickettsial diseases at endemic sites may provide the ecological, clinical, epidemiological, and laboratory data needed to further elucidate the complex, dynamic natural history of SFG rickettsiosis in the United States.

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