Fatal Rocky Mountain Spotted Fever in the United States, 1999–2007

F. Scott Dahlgren,* Robert C. Holman, Christopher D. Paddock, Laura S. Callinan, and Jennifer H. McQuiston

Rickettsial Zoonoses Branch, Division of Vectorborne Infectious Diseases, National Center for Emerging and Zoonotic Infectious Disease, Office of the Director, Division of High-Consequence Pathogens and Pathology, and Infectious Diseases Pathology Branch, Centers for Disease Control and Prevention, Atlanta, Georgia

Abstract. Death from Rocky Mountain spotted fever (RMSF) is preventable with prompt, appropriate treatment. Data from two independent sources were analyzed to estimate the burden of fatal RMSF and identify risk factors for fatal RMSF in the United States during 1999–2007. Despite increased reporting of RMSF cases to the Centers for Disease Control and Prevention, no significant changes in the estimated number of annual fatal RMSF cases were found. American Indians were at higher risk of fatal RMSF relative to whites (relative risk [RR] = 3.9), and children 5–9 years of age (RR = 6.0) and adults ≥ 70 years of age (RR = 3.0) were also at increased risk relative to other ages. Persons with cases of RMSF with an immunosuppressive condition were at increased risk of death (RR = 4.4). Delaying treatment of RMSF was also associated with increased deaths. These results may indicate a gap between recommendations and practice.

INTRODUCTION

Rocky Mountain spotted fever (RMSF) came to national attention as an endemic disease of the Bitter Root Valley, Montana during the turn of the last century.^{1–3} This highly virulent disease affected mainly working men during the summer months, with a case-fatality rate (CFR) upwards of 70%.⁴ This disease was also recognized in other states in the Rocky Mountains with similar epidemiology; however, the CFR appeared significantly lower.^{5–9} The cause of RMSF was identified as an obligate intracellular organism now named *Rickettsia rickettsii*.^{4,10}

By the early 1930s, physicians recognized the same disease in the eastern and southern United States, largely among children.^{11–16} Animal studies indicated the causative agent was similar if not identical across the nation.¹¹ The national CFR during the 1930s was 24%; endemic foci, such as the Bitter Root Valley, continued to display much higher virulence.¹⁷ With the discovery of antibiotics such as chloramphenicol and tetracyclines in the 1940s and with the widespread adoption of empiric treatment of fever with antibiotics, the national CFR of RMSF decreased to a low of 3% in 1955.¹⁸

National RMSF surveillance data indicated a CFR of approximately 5% through the early 1980s.^{19–22} Delayed treatment with a tetracycline or chloramphenicol was identified as a risk factor for dying during this time.^{19,20,22,23} Although reported incidence decreased through the early 1990s, deaths after delayed treatment with appropriate antibiotics continued.^{24,25} Using capture-recapture methods, Paddock and others estimated that the number of fatal cases of RMSF decreased during 1983–1998.²⁶

During 1993–2007, the reported CFR decreased to $< 1\%$, but incidence rates increased to 7 cases per million.^{27–29} Against this decreasing mortality attributable to RMSF, the reported CFR among American Indians did not decrease like the CFR among other races.³⁰ In eastern Arizona during 2002–2004, an epidemic of RMSF associated with a novel tick vector (*Rhipicephalus sanguineus*, the brown dog tick) had a CFR of 12%.³¹ The changing epidemiology of RMSF in recent reports motivated a contemporary evaluation of the incidence of fatal RMSF in the United States during 1999–2007 and the risk

factors associated with fatal RMSF by using two independent national surveillance systems.

METHODS

Multiple cause-of-death data. The National Center for Health Statistics, Centers for Disease Control and Prevention (CDC) (Atlanta, GA) maintains the U.S. national multiple cause-of-death (MCD) data by using death records for U.S. residents.³² We selected death records listing RMSF as a cause of death during 1999–2007. Rocky Mountain spotted fever was defined as a cause of death if the underlying cause of death or contributing causes of death included the International Classification of Disease, Tenth Revision code A77.0.³³ Although RMSF was listed as a cause of death, not all decedents necessarily had accompanying diagnostic laboratory evidence to support a RMSF clinical diagnosis. Other contributing causes of death listed with RMSF were examined; these categories (International Classification of Disease, Tenth Revision codes) were grouped by organ system (Table 1). The MCD data also include demographics for each decedent: state of residence, race, ethnicity, age, sex, and date of death.

Case report forms data. State and Local Public Health departments across the United States report cases of RMSF to the CDC via Tickborne Rickettsial Disease Case Report Forms (CRFs), a surveillance system supplementary to the National Notifiable Disease System for Surveillance. States are encouraged to report additional clinical and epidemiologic details of cases reported through the National Notifiable Disease System for Surveillance on paper-based CRFs. We selected CRFs with an onset of symptoms or a date of death during 1999–2007. Demographic and clinical data are collected through these forms: state of residence, age, sex, race, ethnicity, laboratory results, hospitalization, pre-existing immunosuppressive conditions (2000–2007 only), any life-threatening complications (2000–2007 only), and whether the patient died of RMSF. Identifying data, although reported to the State and Local Public Health departments, are not forwarded to the CDC. Cases are defined as probable if reporting a clinically compatible illness and if reporting serological evidence of infection. Cases are defined as confirmed if reporting a clinically compatible illness and if reporting sufficient laboratory evidence: a documented seroconversion, isolation of *R. rickettsii* in cell

*Address correspondence to F. Scott Dahlgren, Centers for Disease Control and Prevention, 1600 Clifton Road NE, Mailstop A30, Atlanta, GA 30333. E-mail: iot0@cdc.gov

TABLE 1

Summary of causes of death by International Classification of Disease, Tenth Revision (ICD-10) code for decedents listing Rocky Mountain spotted fever as a cause of death, United States, 1999–2007

Category*	ICD-10	Description of ICD-10 code	No. (%)
Systemic circulatory			22 (34.9)
	A41.9	Septicemia, unspecified	21 (33.3)
	D65	Disseminated intravascular coagulation (defibrination syndrome)	4 (6.3)
	I95.9	Hypotension, unspecified	1 (1.6)
	R23.3	Spontaneous ecchymoses	1 (1.6)
	R57.9	Shock, unspecified	1 (1.6)
Pulmonary			18 (28.6)
	J18.9	Pneumonia, unspecified	11 (17.5)
	J81	Pulmonary edema	1 (1.6)
	J96.0	Acute respiratory failure	1 (1.6)
	J96.9	Respiratory failure, unspecified	4 (6.3)
	J98.1	Pulmonary collapse	1 (1.6)
	R09.2	Respiratory arrest	2 (3.2)
	R09.8	Other specified symptoms and signs involving the circulatory and respiratory systems	1 (1.6)
Cerebral			19 (30.2)
	F06.9	Unspecified mental disorder caused by brain damage and dysfunction and to physical disease	1 (1.6)
	G04.9	Encephalitis, myelitis and encephalomyelitis, unspecified	4 (6.3)
	G93.1	Anoxic brain damage, not elsewhere classified	3 (4.8)
	G93.4	Encephalopathy, unspecified	2 (3.2)
	G93.5	Compression of brain	4 (6.3)
	G93.6	Cerebral edema	4 (6.3)
	G93.9	Disorder of brain, unspecified	1 (1.6)
	I64	Stroke, not specified as hemorrhage or infarction	1 (1.6)
	I60.9	Subarachnoid hemorrhage, unspecified	1 (1.6)
	I63.9	Cerebral infarction, unspecified	1 (1.6)
	R56.8	Other and unspecified convulsions	2 (3.2)
Renal			7 (11.1)
	N19	Unspecified renal failure	3 (4.8)
	N17.9	Acute renal failure, unspecified	4 (6.3)
Cardiac			8 (12.7)
	I48	Atrial fibrillation and flutter	1 (1.6)
	I21.9	Acute myocardial infarction, unspecified	1 (1.6)
	I46.1	Sudden cardiac death, so described	1 (1.6)
	I46.9	Cardiac arrest unspecified	2 (3.2)
	I47.2	Ventricular tachycardia	1 (1.6)
	I49.9	Cardiac arrhythmia, unspecified	1 (1.6)
	I50.0	Congestive heart failure	1 (1.6)
	I51.4	Myocarditis, unspecified	2 (3.2)
	R57.0	Cardiogenic shock	1 (1.6)
Hepatic			2 (3.2)
	K72.0	Acute and subacute hepatic failure	1 (1.6)
	K72.9	Hepatic failure, unspecified	1 (1.6)

*More than one cause of death may be listed on a decedent's record.

culture, visualization of *R. rickettsii* antigen by immunohistochemical analysis, or evidence of *R. rickettsii* nucleic acids by polymerase chain reaction.^{34,35}

Seasonality and geography. Dates of onset and death were grouped into seasons: winter from December through February, spring from March through May, summer from June through August, and autumn from September through November. Because the seasonality of RMSF depends largely on tick activity, dates were also grouped by tick season, April through September, and the remainder of the year.³⁶ The states of residence were grouped into census regions for categorical analysis.³⁷

Race. Data were analyzed based on reported race. Although the CRFs and MCD data groups American Indians and Alaskan

Natives into a single race category, *R. rickettsii* has not been reported from Alaska. Therefore, for the purposes of this report, we refer to this race grouping as American Indians.

Statistical analysis. *Case report forms.* Fisher's exact test was used to test for homogenous CFR for sex, race, and ethnicity. Wilson's confidence interval (CI) for a binomial proportion was used for CFR because of its performance with proportions near zero.³⁸ Wilcoxon rank-sum test was used to compare age and time from onset to hospitalization between fatal and non-fatal cases. The CI for the relative risk (RR) comparing CFR by sex, age, race, ethnicity, age, season of onset, region of residence, and case definition were calculated by using Wald intervals.

Capture-recapture. Capture-recapture methods have been described.²⁶ Decedents from the MCD data and fatal cases

TABLE 2

Distribution of sex, race, ethnicity, age, season of death, and region among decedents listing Rocky Mountain spotted fever as a cause of death in multiple cause of death data and among fatal cases in case report forms data, United States, 1999–2007

Demographic characteristic	MCD, no. (%)	CRFs, no. (%)	P
Sex			
Male	40 (63.5)	21 (52.5)	0.31
Female	23 (36.5)	19 (47.5)	
Race			
White	53 (84.1)	33 (82.5)	0.92
Black	4 (6.3)	2 (5.0)	
American Indian	6 (9.5)	5 (12.5)	
Ethnicity			
Hispanic	3 (4.8)	1 (2.9)	1.0
Non-Hispanic	60 (95.2)	33 (97.1)	
Age (years)			
0–9	13 (21.6)	13 (32.5)	0.57
10–19	2 (3.2)	1 (2.5)	
20–39	8 (12.7)	2 (5.0)	
40–59	21 (33.3)	13 (32.5)	
≥ 60	19 (30.2)	11 (27.5)	
Season of death*			
January–February	4 (6.3)	2 (5.1)	0.85
March–May	20 (31.7)	11 (28.2)	
June–August	29 (46.0)	17 (43.6)	
September–November	10 (15.8)	9 (23.1)	
April–September	53 (84.1)	34 (87.1)	
October–March	10 (15.9)	5 (12.8)	0.78
Region of residence ³⁷			
Northeast	3 (4.8)	1 (2.5)	0.80
Midwest	11 (17.5)	5 (12.5)	
South	46 (73.0)	31 (77.5)	
West	3 (4.8)	3 (7.5)	

*Dates of death were categorized into meteorologic seasons and tick season. In the United States, the feeding stages of tick vectors of Rocky Mountain spotted fever are most active during April through September.³⁶

MCD = multiple cause of death; CRFs = case report forms.

from the CRFs data were considered matching if the year of death, state of residence, age (± 1 year), sex, and either race or month of death (± 1 month) were equivalent between the two data. When month of death was not reported in the CRFs data, the latest of either the date of serologic analysis, the hospitalization date, or the onset date was used instead. Fisher's exact test was used to test for homogeneity of sex, race, ethnicity, age, season of death, and region of residence between the MCD and the CRFs data. Linear regression was used to test the association between the estimated number of fatal cases and the year of death.

RESULTS

Multiple cause-of-death. For 1999–2007, a total of 63 decedents with RMSF listed as a cause of death were reported. Most decedents were of white race, non-Hispanic ethnicity, and male sex (Table 2). The median age was 47 years old (range = 1–88 years). More deaths occurred in children less than 10 years old and in older adults, but fewer deaths occurred in older children and young adults (Table 2). Almost half of the deaths occurred during the summer months of June–August. Most decedents were residents who lived in the South. Septicemia was the most frequent cause of death listed with RMSF (Table 1). Approximately one-third of decedents reported systemic circulatory, pulmonary, and cerebral causes of death (Table 1). Coinfection with West Nile virus, chronic viral hepatitis C, human immunodeficiency virus,

Treponema pallidum, or *Streptococcus* species was listed as a cause of death for a single RMSF case each. Diabetes mellitus was listed as a cause of death for two RMSF decedents. Asthma, chronic obstructive pulmonary disease, and malignant neoplasm of the kidney were listed as a cause of death for a single RMSF decedent each.

Case report forms. Of the 7,738 cases of RMSF reported to CDC for 1999–2007 through CRFs, 40 case-patients (0.5%) who died were reported. Most fatal case-patients were of white race, non-Hispanic ethnicity, and male sex (Table 2). The reported median age among patients who died was 45.5 years (range = 1–82 years) with a bimodal age distribution among younger children and older adults (Table 2). Almost

TABLE 3

Number of fatal and non-fatal cases of Rocky Mountain spotted fever reported with clinical outcome through case report forms by sex, race, ethnicity, season of onset, region of residence, and case definition, United States, 1999–2007

Demographic	Fatal cases (n = 40)	Non-fatal cases (n = 7,738)	CFR (%)	RR (95% CI)
Sex				
Male	21	4,349	0.48	Ref
Female	19	3,279	0.58	1.2 (0.6–2.2)
Unknown	0	110	0	–
Age (years)				
0–4	2	198	1.00	2.0 (0.4–9.5)
5–9	11	450	2.39	4.7 (1.8–12.1)
10–19	1	770	0.13	0.3 (0.03–2.1)
20–29	1	902	0.11	0.2 (0.03–1.8)
30–39	1	1,246	0.08	0.2 (0.02–1.3)
40–49	7	1,380	0.50	Ref
50–59	6	1,285	0.46	0.9 (0.3–2.7)
60–69	3	803	0.37	0.7 (0.2–2.8)
≥ 70	8	582	1.36	2.7 (1.0–7.4)
Unknown	0	122	0	–
Race				
White	33	6,198	0.53	Ref
Black	2	607	0.33	0.62 (0.2–2.6)
American Indian	5	239	2.1	3.9 (1.5–9.8)
Asian	0	47	0	–
Unknown	0	647	0	–
Ethnicity				
Non-Hispanic	33	6,271	0.53	Ref
Hispanic	1	218	0.46	0.87 (0.1–6.3)
Unknown	6	1,249	0.48	0.91 (0.4–2.2)
Season of onset*				
Dec–Feb	0	252	0	–
March–May	18	2,179	0.82	2.3 (1.2–4.7)
June–August	14	3,978	0.35	Ref
Sept–Nov	6	1,102	0.54	1.5 (0.6–4.0)
Unknown	2	227	0.87	2.5 (0.6–10.9)
Region of residence ³⁷				
Northeast	1	289	0.34	0.72 (0.1–5.3)
Midwest	5	892	0.56	1.2 (0.5–3.0)
South	31	6,483	0.48	Ref
West	3	74	3.90	8.2 (2.6–28)
Case definition				
Confirmed	15	496	2.94	8.5 (4.6–16)
Probable	25	7,242	0.34	Ref

*Onset dates were categorized into meteorologic seasons and tick season. In the United States, the feeding stages of tick vectors of Rocky Mountain spotted fever are most active during April through September.³⁶

CFR = case-fatality rate; RR = relative risk; CI = confidence interval; Ref = referent, which indicates that the case-fatality rate for this group of cases was used as a reference when calculating the relative risk; – indicates that a RR could not be calculated for this group because no fatal cases were reported within this group.

FIGURE 1. Case-fatality rate of Rocky Mountain spotted fever cases reported through case report forms by age group, United States, 1999–2007. Error bars indicate 95% confidence intervals of the proportion of fatal cases.

half of the patients with fatal cases died during the summer months (Table 2). Most persons with fatal cases were reported to live in the South (Table 2).

The CFR decreased from 1.1% during 1999–2002 to 0.3% during 2003–2007 ($P < 0.0001$). The CFR was similar among men and women (Table 3). During 1999–2007, the CFR was similar among white, black, and Asian races, and between cases of Hispanic and non-Hispanic ethnicity (Table 3). The CFR among American Indians was 3.9 times the rate among whites (95% CI = 1.5–9.8). Among cases reported outside of Arizona, American Indians were not at significantly increased risk relative to whites (RR = 2.5, 95% CI = 0.8–8.0). Of 16 cases reported from Arizona among American Indians, 2 reported cases were fatal (CFR = 12%). The CFR was generally associated with age group ($P < 0.0001$); children less than 10 years of age (RR = 6.0, $P < 0.0001$) and adults ≥ 70 years of age (RR = 3.0, $P = 0.004$) were at greatest risk relative to all other ages (Figure 1). Children 5–9 years of age had a CFR of 2.4%; these 11 fatal cases were reported from 6 different states. The CFR differed by region (Table 3; $P = 0.02$). However, the CFR of

RMSF in Arizona was 11.8%. After removing Arizona cases from the comparison, no significant difference in the CFR was found between the regions ($P = 0.39$), and the CFR of the West was not significantly greater than the South (RR = 3.5, $P = 0.19$). The CFR was similar for cases with onset during different seasons (Table 3; $P = 0.07$). However, cases with an onset during the spring months (March–May) had a higher CFR relative to cases during the summer months (June–August) (RR = 2.3, $P = 0.01$). The CFR among confirmed cases was higher than among probable cases (RR = 8.5, $P < 0.0001$).

A total of 1,845 cases of RMSF (24%) reported being hospitalized. Hospitalized RMSF cases were 27 times as likely to die as RMSF cases not admitted to a hospital ($P < 0.0001$). The median time between onset and hospitalization among fatal cases was 6 days. However, hospitalized cases who survived were admitted a median of 3 days after onset ($P = 0.035$). A total of 325 cases (4.2%) reported an immunosuppressive condition including diabetes (60, 0.8%), cancer (33, 0.4%), arthritis (20, 0.2%), lupus (14, 0.2%), chronic obstructive pulmonary disease (10, 0.1%), Crohn's disease (8, 0.1%), human immunodeficiency virus infection or acquired immunodeficiency syndrome (7, 0.1%), and asthma (6, 0.1%). Immunosuppressed cases were 4.4 times as likely to die as immunocompetent cases ($P = 0.022$). Reported cases with adult respiratory syndrome, disseminated intravascular coagulopathy, meningitis, or encephalitis were 19 times as likely to die as cases not reporting these complications ($P < 0.0001$). The median time between onset and death was 9.5 days (range = 2–90 days), and the median time between hospitalization and death was 3 days (range = 0–48 days). Among the fatal cases, 15 cases (38%) met a confirmed RMSF case definition: 5 cases by serologic analysis, 4 cases by immunohistochemical analysis, 4 cases by polymerase chain reaction, and 2 cases by isolation of *R. rickettsii* in cell culture. The remaining 25 cases (62%) met the probable case definition on the basis of compatible serologic findings.

Capture-recapture. Fatal RMSF cases were reported by 17 states through CRFs, and 25 states reported decedents with RMSF listed as a cause of death in the MCD. The distribution of age, sex, race, and ethnicity of fatal cases reported through CRFs and of decedents in the MCD listing RMSF were similar (Table 2).

During 1999–2007, a total of 18 decedents in the MCD and fatal RMSF cases in the CRFs met the criteria for a possible

FIGURE 2. Number of annual fatal Rocky Mountain spotted fever cases reported through multiple cause-of-death (black bars) and case report form (gray bars) data, United States, 1983–2007.²⁶

match: 15 matched on all criteria exactly, 2 matched on month of death within one month, and 1 matched on age within one year. Considering the 15 pairs matching on the exact criteria, we estimated that 163 fatal RMSF cases (95% CI = 110–216) occurred during 1999–2007. Considering the 18 pairs matching on the relaxed criteria, we estimated that 137 fatal RMSF cases (95% CI = 99–175) occurred during 1999–2007.

The number of fatal cases reported through the CFR and the MCD data was lower during 1999–2007 compared with before the study period (Figure 2).²⁶ The capture-recapture analysis using all matching pairs showed that the median estimated number of annual deaths was 14 (range = 7–20). The estimated number of annual deaths did not change significantly during 1999–2007 ($P = 0.27$).

DISCUSSION

Using data from two different national surveillance systems, we estimated that the number of annual fatal cases attributable to RMSF during 1999–2007 in the United States was 14. The number of fatal RMSF cases appeared to be underreported by either system alone. Although the number of cases estimated annually appeared stable, the overall reported CFR decreased during 1999–2007 and was concurrent with an increase in the reported incidence of RMSF from 1.7 to 7.0 cases per million persons.²⁹ This paradox suggests a change in how non-fatal RMSF cases are being reported, rather than an actual change in the occurrence of fatal RMSF.

In our assessment of the CRF data, we identified several groups at increased risk of fatal RMSF. Children 5–9 years of age had the highest reported CFR (2.4%). American Indians had a higher reported CFR of RMSF than other race groups, almost 4 times as high as whites. Cases with a longer time between onset of RMSF and hospitalization had higher fatality rates, suggesting that delay in diagnosis and treatment or failure to promptly seek treatment could be linked to poor outcome. However, these data did not identify specific reasons for delayed treatment. Case-patients with an immunosuppressing condition were also at higher risk for dying.

The increased CFR among American Indians was influenced by an epidemic foci of RMSF in two American Indian communities within Arizona. In this report, there were two fatal cases reported among 16 cases of RMSF among American Indians in Arizona. When Arizona residents are excluded, the RR among American Indians decreases from 3.9 (95% CI = 1.5–9.8) to 2.5 (95% CI = 0.8–8.0), which are qualitatively different results. However, the point estimates suggest American Indians are at higher risk for fatal RMSF across the United States. Not only is the CFR increased among American Indians, but previous literature also reports that the overall incidence is 4 times greater among American Indians.³⁰

Early treatment of RMSF patients with a tetracycline-based antibiotic has been shown to improve prognosis.²³ Doxycycline is the recommended treatment of choice.³⁶ Although chloramphenicol is also rickettsiostatic, it is not recommended as a first-line therapy for persons able to tolerate tetracyclines because its use has been associated with a higher risk of death.²⁵ After the recognition of the rare but potentially fatal adverse events associated with chloramphenicol therapy, including aplastic anemia, oral formulations of chloramphenicol were withdrawn from the market and were no longer available as outpatient treatment of suspected RMSF patients

during our study period.³⁹ Because past epidemiologic studies have suggested that patients treated with chloramphenicol are twice as likely to die as those treated with tetracyclines, the American Academy of Pediatrics recommends doxycycline as a first-line therapeutic choice for children less than eight years of age with suspected RMSF, and for treatment of older children and adults.⁴⁰

Although the reported CFR among adults has decreased during the past decade, the reported CFR among children with RMSF has not seen the same improvement.^{24,25,27–29,36,41} Despite clear guidance issued by the American Academy of Pediatrics, previous literature suggests that U.S. physicians were slow to initiate therapy with doxycycline in children less than eight years of age, presumably because of unfounded concerns regarding cosmetic staining of developing permanent teeth.^{36,40,42–47} The reported CFR among children 5–9 years of age with RMSF has actually increased in recent years, despite the fact that other age groups saw reductions.^{27–29} Previous surveillance summaries did not indicate this age group was at increased risk of fatal RMSF until the early 1990s, possibly because of the availability of oral chloramphenicol.^{24,27} These fatal RMSF cases were reported from 6 states, indicating that the underlying cause of the increasing case fatality in children 5–9 years of age is geographically widely dispersed. The relatively high CFR among reported pediatric cases may be an artifact of surveillance because fatal pediatric cases may be reported more diligently than fatal adult cases.

Some of the decrease in the CFR since the 1990s may be explained by physicians treating suspected rickettsial infections with doxycycline, especially among adults and older children. Changing surveillance methods and diagnostic tests have also likely played a role, leading to increased reporting of mild RMSF or other less virulent forms of spotted fever rickettsioses to national surveillance systems.^{29,48} The large number of RMSF cases reported through CRFs with only a single IgM enzyme immunoassay may indicate the reported incidence overestimates the actual incidence: a case reported with only a single IgM enzyme immunoassay is more likely to be a false-positive positive than a case reported with more sensitive methods.^{29,49} This artifact of surveillance, and the resulting increase in reported incidence, likely contributes to the observed decrease in the reported CFR.⁵⁰ The large difference in the CFR between confirmed and probable cases (RR = 8.5) supports the conjecture that many of these probable cases are false-positive results.

The tick vectors of RMSF are most active from April through September, and most cases of RMSF occur during these months.^{36,51,52} The increased CFR during March through May, relative to June through August (RR = 2.3), suggests a decreased suspicion of tickborne disease during an interval when tick exposure is possible but less recognized. Although not statistically significant, the decreased fatality (RR = 0.42) during October through March, when RMSF is less likely to occur, relative to April through September, also suggests that many of these off-season reports are not true RMSF cases.

Under national surveillance guidelines, a fatal case of RMSF is less likely to meet the criteria for reporting under current case definitions than non-fatal cases. Patients with severe, fulminant RMSF may die before their immune system mounts an effective serologic response.⁵³ In the absence of available autopsy tissue for diagnostic testing, physicians may rely on the findings from an acute-phase serum sample to decide

whether RMSF was a cause of death, which in many cases will show a negative result. In this review, 25 fatal cases reported through CRFs met only a probable case definition, and these cases relied solely on serologic assays. More fatal cases of RMSF were likely not reported because of insufficient laboratory evidence.

The results presented in this study highlight several groups at increased risk for dying of RMSF: children 5–9 years of age, American Indians, immunosuppressed patients, and severe cases experiencing delayed diagnosis and/or treatment. Previous studies support current national recommendations that doxycycline should be used as the first-line drug against RMSF for all ages, even in children less than eight years of age.^{25,44} Labeling for doxycycline needs to explicitly indicate treatment of suspected rickettsioses in cases of all ages, and downplay the marginal risk of staining developing teeth associated with the dose and duration used to treat RMSF.^{46,47} For areas where the CFR remains high, such as eastern Arizona where local outbreaks are linked to transmission of the brown dog tick, animal control may help reduce RMSF deaths by eliminating or reducing the stray dog population.³¹ Nonetheless, these efforts may require resources unavailable to some affected communities. Continued public awareness campaigns by local public health officials may be a more economic control method in these communities. The remaining mortality attributable to RMSF may be limited by increasing early treatment with doxycycline in suspected cases of rickettsioses.

The CRFs and the MCD data have limitations. The quality of the CRFs varies greatly, and information bias exists from missing data and from misclassified demographic and clinical data. Different practices among physicians and public health departments lead to reporting bias because only cases with sufficient clinical and laboratory evidence may be reported. The MCD data may include possible coding and reporting discrepancies, and misclassification of RMSF as cause of death. The direction and magnitude of these biases are not known. The systematic misclassification of American Indian decedents in the MCD may lead to an overestimated number of fatal RMSF cases in our capture-recapture analysis.⁵⁴ The results from the CRFs are based on data from passive surveillance, and the reasons why these demographics and communities are at increased risk of fatal RMSF are beyond these data. Also, the results presented are often based upon small numbers because the overall incidence of RMSF and the corresponding CFR are relatively small. Slight variations in reporting practices may strongly bias these results. Active surveillance in disease-endemic areas may improve our understanding of risk factors for fatal RMSF and of the groups at increased risk of fatal RMSF.

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Authors' addresses: F. Scott Dahlgren, Robert C. Holman, Christopher D. Paddock, Laura S. Callinan, and Jennifer H. McQuiston, Centers for Disease Control and Prevention, Atlanta, GA, E-mails: iot0@cdc.gov, rchl1@cdc.gov, cdp9@cdc.gov, imj5@cdc.gov, and fzh7@cdc.gov.

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