PASSIVE SURVEILLANCE AS AN INSTRUMENT TO IDENTIFY RISK FACTORS FOR FATAL ROCKY MOUNTAIN SPOTTED FEVER: IS THERE MORE TO LEARN?

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Abstract. National surveillance for Rocky Mountain spotted fever (RMSF) dates from 1920; however, the collection of detailed epidemiologic, clinical, and laboratory data on RMSF by using case report forms began in 1970. Despite issues with compliance and changes in case definitions, surveillance data have permitted researchers to assess risk factors for fatal RMSF quantitatively. Factors consistently associated with increased risk of death include severity of disease, older age, lack of tick bite, absence of classic symptoms, delay in diagnosis and initiation of appropriate antibiotic treatment, and treatment with chloramphenicol only. In several studies, treatment with a tetracycline has been shown to be protective. The continuation of current passive surveillance activities may allow researchers to refine their estimates of risk but is unlikely to produce novel results. Modified surveillance activities could focus on evaluating the risk for fatal RMSF among special populations, monitoring appropriate antibiotic use, and assessing new diagnostic tests.

INTRODUCTION

Systematic collection, collation, and reporting of the national incidence of Rocky Mountain spotted fever (RMSF) in the United States began in 1920 at the Rocky Mountain Laboratory (RML) of the National Institutes of Health. The date is linked to the transferral of Ralph R. Parker to the U.S. Public Health Service (PHS) from the Montana Board of Entomology. The profound lethality of RMSF has been a defining feature of this disease since its initial description near the beginning of the 20th century: from 1873 to 1920, 431 RMSF cases and 283 deaths, representing a case-fatality ratio (CFR) of approximately 66%, were reported in western Montana alone. Accordingly, it was this feature that precipitated Parker’s appointment, which followed closely after the death of state Senator Tyler Warden and his wife from RMSF in Lolo, Montana, in 1921. Before 1920, case reports of RMSF and RMSF CFRs were summarized only sporadically, and they either did not consistently indicate whether patients survived or died or in other ways left the clinical outcome ambiguous. A case file established and compiled by Parker until his death in 1949 (the “Parker file”) is the most complete record of RMSF cases occurring during the first 75 years after the identification of the disease and is now reposited in the National Archives in Washington, DC.

Various geographic, temporal, and demographic features of RMSF have been delineated, primarily from analyses of data collected through passive surveillance. During the past 30 years, surveillance data have also been gathered and used to identify risk factors associated with fatal RMSF. The mechanisms of surveillance, the laboratory methods used to confirm the diagnosis, and the analytic tools applied to the data collected on RMSF have changed markedly over the past 120 years. Also during this period, there has been a progressive evolution in the medical management of this disease. Epidemiologists and biologists have attempted repeatedly to extract meaningful information about long-term trends in the occurrence of RMSF and have speculated about the factors contributing to real or apparent changes in disease incidence and the CFR. The purpose of this review is to assess critically the proposed risk factors for fatal RMSF gleaned from passive surveillance and to evaluate the information that might be gained from continuing these surveillance efforts in their current or modified form.

A PRIMER ON RMSF SURVEILLANCE

Temporal variation. Interpreting and predicting temporal trends in the incidence of RMSF by using national surveillance data are dually complicated by variability in how the data have been collected and reported and by periodic alterations in how cases have been defined. For example, laboratory tests to confirm the diagnosis of RMSF did not become widely available until the 1940s, and routine application of these laboratory assays as a criterion for defining a case of RMSF has been commonplace only since the 1970s. In some cases, reconsideration of the specificity of a “confirmatory” assay has led to changes in the categorization of patients. A positive Weil-Felix test (i.e., antibody reactive to Proteus antigens OX-19 and OX-2) was used as one of several laboratory criteria to confirm a case of RMSF through 1979, however, beginning in 1981, a positive Weil-Felix reaction was considered, at best, evidence of “probable” RMSF.

Even allowing for the effect that imperfections and variations in RMSF surveillance efforts may have had on the reported disease incidence, the annual number of RMSF cases in the United States has shown dramatic swings since 1920 (Figure 1). The reasons suggested for the major periods of increase and decrease in RMSF cases have, with few exceptions, been difficult to investigate and even more difficult to corroborate (Table 1). Fortunately, several of the factors that have influenced the CFR for RMSF are known with greater certainty.

What passes for passive surveillance. The history of RMSF surveillance can be divided approximately into four periods (Table 2). The first period ran from 1873 through 1920, when efforts to collect national statistics on disease incidence and associated fatalities were relatively incomplete and nonsystematic. Recognizing the existing limitations to accurate reporting of RMSF, Assistant Surgeon General W. C. Rucker recommended in 1912 that RMSF be added to the list of nationally reportable diseases. The second phase during which national RMSF surveillance data began to be compiled lasted from 1920 through 1949. A national summary of RMSF cases reported during this interval was published; however, it
does not include information on fatalities. Although detailed data on patient outcome during this interval are contained within the Parker file, a complete description of these data has never been published. A transitional period began in 1949 and lasted through approximately 1970. During this third period, the mission of RML changed, and the focus of epidemiologic research on RMSF shifted to the southeastern and mid-Atlantic United States. In 1948, the responsibility for collecting and reporting morbidity and mortality figures (including those for RMSF) was officially transferred to the National Office of Vital Statistics of the PHS. In 1961, the responsibility for publishing weekly summaries of morbidity and mortality data was transferred to the Communicable Disease Center (now the Centers for Disease Control and Prevention [CDC]). It was during this transition period, which followed closely after the death of R. R. Parker, that the national incidence of reported RMSF reached its modern-era nadir in 1959, with 199 cases and 10 deaths. At least one authority suggested that Parker’s death and the cessation of RMSF surveillance activities at RML led to the precipitous decrease in reported cases.

### Table 1

Factors suggested as increasing or decreasing the incidence of RMSF over time in the United States

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Suggested factor</th>
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<tr>
<td>Surveillance</td>
<td>Improved education and disease reporting&lt;sup&gt;15,16,40&lt;/sup&gt;&lt;br&gt;Recognition of RMSF in the eastern U.S.&lt;sup&gt;25,50&lt;/sup&gt;&lt;br&gt;Increase in false-positive diagnoses&lt;sup&gt;15&lt;/sup&gt;&lt;br&gt;Death of R. R. Parker&lt;sup&gt;40&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pathogen</td>
<td>Spread or translocation <em>R. rickettsii</em> from Rocky Mountain region to eastern U.S.&lt;sup&gt;1,23,50-52a&lt;/sup&gt;&lt;br&gt;Variation in virulence of <em>R. rickettsii</em>&lt;sup&gt;23&lt;/sup&gt;</td>
</tr>
<tr>
<td>Vector or vertebrate reservoir</td>
<td>Emergence of novel transmission cycles in the eastern U.S.&lt;sup&gt;25,53,54&lt;/sup&gt;&lt;br&gt;Cyclical change in vectors or infecting organism&lt;sup&gt;13&lt;/sup&gt;&lt;br&gt;Diminished use of pesticides (specifically DDT)&lt;sup&gt;55&lt;/sup&gt;&lt;br&gt;Tick (<em>D. variabilis</em>) infestation of household pets in eastern U.S. increases infection rate of women and children&lt;sup&gt;16,23,54,56&lt;/sup&gt;</td>
</tr>
<tr>
<td>Human demography or behaviors (especially in the East)</td>
<td>Change in vectors or infecting organism, including lethal effect of <em>R. rickettsii</em> on tick&lt;sup&gt;15,57&lt;/sup&gt;&lt;br&gt;Competition/interference by East side agent (<em>Rickettsia peacockii</em>)&lt;sup&gt;58,59&lt;/sup&gt;&lt;br&gt;Increased use of DDT&lt;sup&gt;55&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

* Mentioned by these authorities but not necessarily endorsed.

DDT = dichlorodiphenyltrichloroethane.
decline in RMSF cases and deaths detected by national surveillance.16

The fourth, and current, period in RMSF surveillance activities has been characterized by focused efforts to collect information on the clinical and epidemiologic features as well as the diagnostic laboratory test results of nationally reported cases of RMSF.17 Beginning in 1970 and continuing to the present, case report forms (CRFs) have been used to obtain supplemental information on RMSF cases. These forms have undergone several revisions, but since 1981 the CDC has used the same CRF. This effort has required increasingly close collaborations between CDC and state health departments and local health providers. Routine surveillance data on RMSF had been collected by the forerunner of the PHS, which had been authorized by Congress in 1878 to collect morbidity statistics on cholera, smallpox, plague, and yellow fever. By 1989, all 50 states began submitting data collected as part of the National Notifiable Disease Surveillance System electronically through the National Electronic Telecommunications Surveillance System (NETSS).17,18 These data are tabulated weekly in CDC’s Morbidity and Mortality Weekly Reports. However, NETSS collects only limited information on individual cases (the location and date of disease occurrence and the age, sex, and race of the person affected), and these data are inadequate for investigating specific epidemiologic features of RMSF.

**Limitations to surveillance data.** Efforts to improve the quantity and quality of nationally reported RMSF data have been hampered by the nature of passive surveillance. Completion of CRFs requires the submitter to have detailed knowledge of the clinical history of the patient and the results of the patient’s clinical and diagnostic laboratory tests. Although CRFs are submitted to CDC as separate reports independent of the weekly NETSS reports, one can roughly estimate the completeness of data available for analysis by determining the percentage of cases reported through NETSS for which a CRF has been submitted. Compliance with the request to submit CRFs has proven problematic (Figure 2). In 1975, only 44% of RMSF cases reported weekly from state health departments were accompanied by a CRF. In 1979, after a national effort to improve compliance, more than 90% of RMSF cases were complemented by CRFs.10 However, that high level of compliance has not been sustainable (see Figure 2). From 1981 through 1996, the number of CRFs submitted was 81.5% of the 11,536 RMSF cases reported through NETSS.19–21

In addition to CRFs not being submitted, those that have been submitted often lack the requested information necessary to confirm a diagnosis of RMSF on the basis of case definitions approved by the Council of State and Territorial Epidemiologists and CDC.22 In 1981, only 35% of the RMSF cases submitted to CDC on CRFs were confirmable on the basis of the information supplied on clinical presentation and laboratory testing.21 From 1981 through 1996, RMSF was considered confirmed or probable in 5,470 (58%) of the 9,402 cases described by CRFs received at CDC.19,20 The nonsubmission of CRFs and the incompleteness of CRF data mean that fewer than half of the RMSF cases reported through NETSS are available for detailed analysis, including the analysis of risk factors for death (see Figure 2).

### MORTALITY ASSOCIATED WITH RMSF

**General trends.** Despite the vagaries and inconsistencies inherent to national RMSF reporting, the data are sufficient to permit detection of unambiguous changes in the CFR associated with RMSF over time (see Figure 1). At the beginning of the 20th century, RMSF was fatal in approximately 65 to 80% of cases.3,4 However, early reports also noted substantial variation in disease severity across geographic regions, such as a CFR for RMSF of less than 4% in Idaho compared with 75% in Montana.4 In 1938, Parker reiterated this observation, noting that the “virulence of infection in man” varied with locality.23 Epidemiologic explanations for some of the geographic differences in CFRs are explored later; however, significant genetic and phenotypic variation among isolates of *Rickettsia rickettsii* presumably contributes to the observed differences in severity of disease.24

From 1935 through 1944, the annual CFR for RMSF was consistently above 20% and averaged 22%.25 Beginning in 1944, the CFR declined steadily to less than 10% in 1949, a drop attributed to improvements in supportive therapy derived from a more complete understanding of the pathophysiology of RMSF and to the introduction of para-aminobenzoic acid as therapy for RMSF.25,26 From 1949 through 1962, after the discoveries and expanded use of chloramphenicol and tetracyclines as therapy for rickettsial diseases, the CFR declined to an average of 5.5%.27 Since 1962, annual CFRs have fluctuated between 2 and 6%.10,19,20,28 The CFR for RMSF from 1990 through 1998 was 2.8%, significantly lower than the 3.7% for the 9-year period from 1981 through 1989.29 Although the reasons for the continued decline in the CFR are uncertain, the greater awareness of tick-borne diseases in general (e.g., Lyme disease and the ehrlichioses) may prompt both patients and treating physicians to consider these pathogens and to initiate appropriate antibiotic treatment earlier than they might have previously. In addition, more RMSF patients are now being treated with the drug of choice: doxycycline.29 Because of the underlying severity of RMSF, the difficulty of making an early diagnosis, and the frequent lack

### Table 2

Categorization and attributes of surveillance systems used for collecting information on Rocky Mountain spotted fever in the United States

<table>
<thead>
<tr>
<th>Period</th>
<th>System</th>
<th>Strengths</th>
<th>Weaknesses</th>
<th>CFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1873–1920</td>
<td>Case reports</td>
<td>National coverage</td>
<td>Sporadic, nonsystematic</td>
<td>60–80%</td>
</tr>
<tr>
<td>1920–1949</td>
<td>Parker File</td>
<td>Continuity</td>
<td>No laboratory confirmation, never fully described</td>
<td>20–70%</td>
</tr>
<tr>
<td>1949–1970</td>
<td>NOVS/CDC</td>
<td>Availability of data for long-term trend analysis</td>
<td>No epidemiologic, clinical or laboratory information</td>
<td>2–7%</td>
</tr>
<tr>
<td>1970–present</td>
<td>CDC case report form</td>
<td>Epidemiologic, clinical, and laboratory data</td>
<td>Moderate to low submission rates</td>
<td>2–7%</td>
</tr>
</tbody>
</table>

of awareness of this illness among some health care providers, the CFR of RMSF is unlikely to fall much lower.

**Quantitative analyses of risk factors.** In 1976, Hattwick and colleagues published a landmark study of RMSF in which they rigorously analyzed a comprehensive data set acquired through standardized CRFs that applied a strict case definition requiring laboratory confirmation of disease. Not surprisingly, they found that the risk for fatal RMSF was strongly associated with factors reflective of increased severity of illness, as indicated by splenomegaly, pneumonia, stupor, coma, shock, and a history of hospitalization. More importantly, through statistical analysis, they identified several epidemiologic risk factors for death among patients with RMSF, including older age (most notably among individuals /H11350), no history of tick bite, and failure to treat with a tetracycline or chloramphenicol (Table 3).

Hattwick et al. also found a significantly higher CFR among males, black males in particular, findings also identified by some subsequent investigators but not with the consistency of other risk factors (see Table 3). In a case–control study based on 1974 surveillance data, researchers compared 44 fatal cases with 50 nonfatal cases of RMSF and found the same suite of significant risk factors (increasing age, initial nonspecific symptoms, no history of tick bite) for fatal outcome. However, although the CFRs were elevated among men and blacks, these results were not statistically significant.

The increased risk for death among adults with RMSF may be attributable to impaired immune function (“immunosenescence”) or to delays in diagnosis and treatment initiation among older patients. Because the age-specific incidence of RMSF is highest among children and young adults, one might suspect that delays in diagnosis occur more frequently among older patients than among younger patients. However, analyses controlling for treatment delays and type of antibiotic therapy have demonstrated an independent increased risk for fatal outcome among persons older than 40 years. It should be stressed that dichotomization of RMSF cases into age groups of less than and greater than 40 years reflects an apparent natural breakpoint in the age-specific CFR from a case series of RMSF patients. In actuality, the CFR of RMSF increases steadily from approximately 4.5% in patients in the 40- to 49-year age group to more than 7.5% in patients older than 70 years. Other rickettsial diseases, such as epidemic typhus and murine typhus, are also more severe in older patients, suggesting that host factors uniquely associated with aging may be important determinants for fatal outcome.

Two additional risk factors for fatal RMSF identified by most epidemiologic studies are inappropriate antimicrobial drug treatment (i.e., no therapy or therapy with an antibiotic other than a tetracycline or chloramphenicol) and no history of a tick bite. The latter finding is one of a suite of risk factors, including atypical presentation and delay in diagnosis, that presumably increase a patient’s risk for a fatal outcome by causing the treating physician to delay initiating appropriate antibiotic therapy.
 Delay in appropriate treatment is the leading cause of
death among RMSF patients. A case–control study conduced in 1974 compared fatal and nonfatal RMSF cases among individuals of similar age, sex, and date of onset and documented the effect of treatment delay on a patient’s risk for death: the interval between disease onset and the diagnosis of RMSF among patients who died was 6.7 days compared with 4.5 days for those who survived. Similarly, a temporally related increase in CFR was observed among 155 deaths from RMSF occurring during 1981 and 1992: patients treated with appropriate therapy within the first 4 days of disease were 3.1 times less likely to die than those treated 5 or more days after onset.

Male gender has not been a consistently identified risk factor for fatal RMSF for the last 3 decades (see Table 3). In earlier times, RMSF was an occupational disease of adult males, particularly shepherds, woodsmen, and hunters in the western states, where infections resulted from exposure to the wood tick, Derma centor andersoni. The convergence of the CFRs for males and females was driven by the decline of RMSF as an occupational disease in the West and by the increased recognition of RMSF among women and children in the eastern United States. In the eastern United States, exposure to R. rickettsii results primarily from encounters with the American dog tick, Derma centor variabilis, which can be very common in peridomestic and suburban environments.

The historical higher rates of RMSF fatalities reported from western states can be largely explained by the age structure of the population affected rather than by predictable geographic patterns in the virulence of R. rickettsii or the gender of the afflicted. In 1947, Topping noted that among children younger than 12 years, the CFR for RMSF over a 10-year period was the same in Maryland and Virginia (12%) as it was in Montana and Idaho. Furthermore, whereas 50% of all RMSF cases in the eastern states occurred among children younger than 12 years, most RMSF cases in the West were among men older than 40 years, the age group with the greatest risk for fatal outcome. Before the 1940s, most RMSF cases were reported from the mountain states (this surveillance category includes Arizona, Colorado, Idaho, Montana, New Mexico, Nevada, Utah, and Wyoming, but not all of these states have reported many RMSF cases). However, since then, more cases have been from the southern Atlantic states (Delaware, Georgia, Florida, North Carolina, Maryland, District of Columbia, South Carolina, Virginia, and West Virginia). For example, from 1981 through 1996, 5,368 cases of RMSF were reported in the southern Atlantic states (46.5% of the national total) compared with only 234 from the mountain states (2.0% of the total).

The possible association between CFR and race is more vexing, because the mechanisms by which race could be associated with fatal RMSF outcome include both the sociologic (e.g., less access to or substandard medical care) and the genetic (e.g., greater susceptibility to fatal disease among individuals with glucose-6-phosphate dehydrogenase deficiency). A higher CFR for blacks was a consistent finding in epidemiologic studies of RMSF through the 1970s (see Table 3). Since 1981, however, although CFRs for blacks have been somewhat higher than those for whites, the differences have not been statistically significant.

When discussing race as an independent risk factor for a fatal outcome among patients with RMSF, one must simultaneously control for the effects of other potential risk factors. Dark skin can make detection of an attached tick or the presence of a rash more difficult to ascertain, and both of these effects have been identified as risk factors for death among RMSF patients because they hinder prompt diagnosis and treatment (see Table 3). The initial epidemiologic studies reporting race as a risk factor for fatal outcome of RMSF did not use multivariate statistical techniques to assess whether race acted independently of other risk factors; results from analyses indicate that race does not act independently, and both of these effects have been identified as risk factors for death among RMSF patients because they hinder prompt diagnosis and treatment (see Table 3).
ties in diagnosing RMSF in the absence of a discernible rash or tick bite history have led to recommendations to presumptively use antimicrobial drugs to treat anyone in endemic locations who presents during warm months with “atypical” manifestations (e.g., no tick bite, diarrhea, jaundice) if RMSF cannot be ruled out.44

An important finding to emerge from risk factor analyses of fatal RMSF cases was the difference in CFRs between patient groups treated with the two antibiotics of choice. In 1990, Fishbein et al.31 first reported that patients treated with chloramphenicol only had a significantly higher CFR (7.7%) than those treated with a tetracycline antibiotic only (2.2%). Subsequent studies with larger series of RMSF cases have confirmed and refined this observation,20,29 although one must consider several caveats when interpreting these findings and translating them into formal treatment recommendations.

One such caveat is that information on the severity of RMSF contained on CRFs is limited, and the possibility exists that antibiotic treatment varied systematically with disease severity. However, results from three studies showed that controlling for hospitalization as a marker of disease severity did not eliminate the increased risk for death associated with chloramphenicol treatment alone.20,29,43 In a multivariate analysis, increasing age, treatment delays of 5 days or more, and treatment by chloramphenicol alone were each shown to be independent risk factors for death among RMSF patients, whereas treatment with tetracyclines only was protective.29 In part because of these findings, the American Academy of Pediatrics and CDC currently recommend that doxycycline be considered the drug of choice in treating RMSF, irrespective of the patient’s age.37,45 However compelling, statistical associations alone cannot provide definitive answers to the question of relative therapeutic value of these two drugs for treating RMSF. Controlled clinical trials would be required for this purpose, but given the severity and rarity of RMSF and the existence of an effective and safe drug (i.e., doxycycline), such an effort appears unlikely and unwarranted.

THE FUTURE OF PASSIVE SURVEILLANCE

Is there more to learn from current systems? It is unlikely that continued passive surveillance for RMSF by using data collected with current CRFs will provide significant new epidemiologic insights into the risk factors for fatal outcome or that additional studies based on the same information will further strengthen the well-established statistical associations (see Table 3). Other surveillance activities, such as the collection of long-term data on RMSF by NETSS, provide the raw material needed to quantitatively assess changes in disease incidence. If fluctuations in RMSF incidence (see Figure 1) are due to factors other than variation in surveillance and reporting, then long-term surveillance remains essential for providing the data necessary for continued study.

Future objectives. At least three major areas for assessment or study may be best approached by the use of newly designed CRFs: (1) studies of disease in special populations at risk; (2) assessments of programs to enhance the appropriate use of antibiotics for treating RMSF; and (3) evaluations of new diagnostic methods as they become available. To help address these goals, CDC introduced a new generic tick-borne rickettsioses CRF in 2000. The new CRF seeks to obtain novel information about RMSF and other tick-borne diseases, such as the presence of underlying medical conditions and the specific diagnostic laboratory tests used to differentiate between rickettsial and ehrlichial infection. However, inherent limitations remain to designing a single-page form that collects relevant facts and maximizes compliance.

The occurrence of RMSF among special populations with underlying chronic conditions that may predispose them to more severe disease may be best addressed by national reporting systems that can collect data on rare conditions. Examples include persons with immunosuppressive conditions, such as transplant recipients, patients infected with HIV, or chronic ethanol abusers, all of whom may be more prone to severe rickettsial diseases.35,46 Individuals with genetic conditions that predispose them to fatal RMSF (e.g., glucose-6-phosphate dehydrogenase deficiency) form another category of interest.42

CRFs can be used to assess trends in antibiotic treatment for RMSF and the effectiveness of education programs aimed at informing public health practitioners about the recommended use of doxycycline for treatment of nearly all RMSF patients. Although overall use of tetracyclines was higher in the 1990s than in the 1980s, children younger than 10 years with RMSF continued to be treated with chloramphenicol more often than any other age group29 despite current recommendations.37,45 Through their monitoring of antimicrobial drug use, CRFs can also be used to assess the impact of education and public health campaigns on medical practices.

Finally, passive surveillance data have been used to assess the sensitivity and utility of different serologic and immunohistochemical tests for the diagnosis of RMSF.30,47 New diagnostic tests for RMSF will continue to be developed, and surveillance will provide an important means of collecting sufficient data to examine the relative merits of different assays. The need for sensitive tests capable of identifying RMSF in those infected before they develop antibodies is well illustrated by cases of rapidly fatal disease, when death occurs within the first week of illness.30 Although currently of limited value,48 polymerase chain reaction-based diagnostics will certainly be refined and introduced as complements to early diagnostic efforts.

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