PERSISTENT SEQUELAE OF ROCKY MOUNTAIN SPOTTED FEVER: CLINICAL EVIDENCE, COST, AND PUBLIC HEALTH IMPLICATIONS FOR ARIZONA TRIBAL COMMUNITIES

by

NAOMI ADRIEL DREXLER

(Under the Direction of Brittani Harmon)

ABSTRACT

Rocky Mountain spotted fever (RMSF) is a life-threatening tickborne disease, caused by the bacterium *Rickettsia rickettsii*. Illness begins with non-specific symptoms, such as fever, headache, and muscle pain, but progresses rapidly. When left unmitigated, the bacteria can damage the cells lining small blood vessels resulting in organ failure, sepsis, and ultimately death. Patients who survive severe RMSF infections may be left with permanent disability including organ damage, necrosis of extremities requiring amputation, and neurologic deficits. Few studies have described the long-term sequelae (LTS) from RMSF and little is known about the persistence of such sequelae nor the impact of such disabilities on patients and families. This dissertation describes a cohort of individuals hospitalized for RMSF in two Arizona communities to assess the presence, persistence, and relative cost of neurologic sequelae years following infection. Acute disease is described from medical records. Surviving individuals were interviewed about their disease recovery and individuals reporting ongoing symptoms were assessed by a neurologic exam. Twenty-three percent of individuals interviewed showed signs of LTS on exam. Delayed antibiotic therapy was the single most important predictor of LTS.

Evidence of long-term disability following RMSF emphasizes the severe and potentially life-long consequences of delayed recognition and treatment. Furthermore, such evidence draws attention to the potential long-term care required to support individuals during their recovery. Arizona tribal communities have been substantially impacted by RMSF but may lack the resources for long-term morbidity management in the wake of epidemic disease. A second study compares the cost of acute care using flat-rate charges in the Arizona tribal cohort and to medical billing information from two large national databases. Average direct costs per hospitalized case of RMSF ranged from $16,894-$25,573 among the three sources. Finally, total disease impact is described in terms of disability-adjusted life years (DALYs) lost from RMSF. Estimates for the Arizona cohort included 516 DALYs lost, representing substantial morbidity and mortality in small tribal communities. Descriptions of disease burden can help policy makers evaluate the relative importance of RMSF prevention and may help prioritization of long-term medical support systems for highly impacted communities.

INDEX WORDS: Rocky Mountain spotted fever, tickborne, rickettsial, cost analysis, disability, tribal communities

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NAOMI ADRIEL DREXLER

BS, Pacific Lutheran University, 2008

MPH, Emory University, 2011

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NAOMI ADRIEL DREXLER

Major Professor:	Brittani Harmon, DrPH
Committee:	George Khalil, DrPH
	Paige Armstrong, MD, MHS

Electronic Version Approved:

Ron Walcott
Interim Dean of the Graduate School
The University of Georgia
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CHAPTER 1

INTRODUCTION

OVERVIEW

Rocky Mountain spotted fever (RMSF) is a bacterial infection spread by the bite of an infected tick and is considered the most deadly tickborne disease in the Western hemisphere (Álvarez-Hernández et al., 2017). RMSF is a rapidly progressing disease, starting with non-specific symptoms, such as fever, headache, and muscle pain, but quickly degrading to organ failure, sepsis and death in a matter of days. Doxycycline is the recommended treatment of choice in adults and children of all ages according to the Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics (2018; Biggs et al., 2016). The number of days elapsed from illness onset to initiation of doxycycline is the single most important predictor of severe and fatal outcomes; significantly higher rates of severe disease and death occur if doxycycline is started after 5 days of illness (Holman et al., 2001a; Regan et al., 2015). Patients who are treated earlier, are less likely to be hospitalized and are less likely to require time in the intensive care unit (ICU) (Regan et al., 2015). Early signs and symptoms of RMSF may be difficult for healthcare providers to discern in the first few days of illness, presenting clear dilemma: treat all cases as possible RMSF, or risk advancing disease and potential critical outcomes. Treatment decisions are made based on signs, symptoms, and patient history, without the advantage of rapid diagnostic tests. Decisions are largely evaluated on a risk-benefit assessment of immediate (short-term) consequences, and do not consider the life-long

impact of disease. Evidence of long-term disability from delayed treatment may provide further evidence to healthcare providers to consider early administration of doxycycline.

RMSF has been well described in the United States since the late 1800s with most literature focusing on the acute disease process; however, severe sequelae were recognized early on to confer substantial morbidity. Long-term sequelae (LTS) refer to persistent disability relating to acute RMSF illness. Previous literature suggests that LTS from RMSF are primarily neurologic in nature. Small case series have documented LTS in 3–55% of RMSF cases including: loss of hearing, changes in movement and cognition, as well as behavioral disturbances, incontinence, chronic pain and other neurologic dysfunctions (Archibald & Sexton, 1995; Berlin & Thomas, 1948; Gorman et al., 1981; Rosenblum et al., 1952). While these severe complications are known to occur, limited information is available on the timeline of persistence the likelihood of improvement, and no studies include discussion of patient-centered outcomes such as perceived changes in function and impact on daily activities. A handful of case series have suggested that the damage caused by the bacteria during the acute disease process may persist for months or years, but no large-scale, systematic collection of LTS have been undertaken. Better understanding of the types of LTS, risk factors for developing LTS, and the potential duration of LTS will allow practitioners, patients, and families to make informed decisions about the long-term management and treatment needs of patients following their discharge. When indicated, resources such as behavioral, physical, or occupational therapy could be made available to better support patients and families.

Epidemic levels of RMSF have been reported in several Arizona tribal communities since 2002. High disease incidence and relatively stable patient populations makes this the largest contemporary U.S. cohort of RMSF survivors in which LTS can be assessed. The research

presented herein describes an evaluation of LTS following severe RMSF in two tribal communities. Evidence of LTS are subsequently used to update estimates of the total cost of RMSF. Economic evaluations have already described the high acute indirect and medical costs associated with the Arizona RMSF epidemic, totaling more than $13.1 million during 2002–2011 (Drexler et al., 2015). These descriptions however, were unable to address the potential costs associated with supporting the long-term management of RMSF-related disability. Description of the short, medium, and long-term impacts of disease and provide critical information to policy makers, healthcare providers, and communities about the global impact of RMSF.

PURPOSE STATEMENT

The purpose of this research is to better understand the existence of long-term neurologic sequelae following RMSF illness among hospitalized patients, and to describe the economic and social impact of this disease on Arizona tribal communities. This study was conducted in order to provide actionable information to three parties: 1. healthcare providers treating and supporting cases of RMSF in Arizona tribal communities, 2. policy makers prioritizing resources for tribal communities, and 3. community members, patients, and families. While the conclusions of this study are truly only representative of the disease in Arizona tribal communities, the results can provide preliminary evidence for the broader picture of severe RMSF in the Western hemisphere.

OUTLINE

This thesis is organized into five chapters, a bibliography, and relevant appendices including a statistical appendix. Chapter 1 includes an introduction to the topic, problem statement, and overview of the study methods. Chapter 2 serves as review of related literature to date including: a history of RMSF, descriptions of the epidemiology and clinical manifestations

(including the current evidence for long-term sequela), the emergence of RMSF in Arizona (including current prevention practices), and descriptions of healthcare and health disparities among American Indians. Chapter 3 serves as a drafted manuscript on the evaluation of long-term neurologic sequelae in the Arizona cohort and was formatted for submission to the Clinical Infectious Diseases Journal. Chapter 4 will serve as a second manuscript surrounding the economic impact of RMSF including long-term care estimates, and disability indicators. Chapter 4 is formatted for submission to the American Journal of Public Health. Lastly, chapter 5 draws these concepts together to assess the public health implications of these analyses. The dissertation concludes with a bibliography and appendices including data collection tools.

BRIEF OVERVIEW OF METHODS

The research described in this dissertation evaluates a group of individuals hospitalized with RMSF between 1–15 years following their acute illness and includes three data collection elements: a medical chart abstraction of acute illness; a patient interview about recovery, ongoing symptoms, and impact on daily activities; and a neurologic exam for individuals reporting persistent symptoms. Chapter 3 of this thesis utilizes quantitative approaches to describe the occurrence of long-term neurologic sequelae following severe RMSF infection in hospitalized cases between 2002–2017. Neurologic LTS were assessed in individuals reporting decline in function or incomplete recovery from initial RMSF illness using a comprehensive neurologic exam, including a global assessment of cognitive function, using the Montreal Cognitive Assessment administered by a licensed medical provider. Individuals reporting neurologic sequelae are compared to non-fatal cases without LTS. Patient characteristics are described using univariate and bivariate analyses according to length of time from RMSF illness,

date of doxycycline administration, and severity of RMSF illness (as indicated, for example, by the presence of intubation, severe thrombocytopenia, organ failure, or tissue damage).

The second portion of the thesis, presented in chapter 4, focuses on describing the economic and social impact of RMSF in Arizona by estimating the total costs of disease. Results of the long-term sequelae study in chapter 3, provide a more detailed description of the long-term consequences of RMSF including time to recovery and supportive care required following discharge. Such information was used to fill gaps in understanding of the long-term costs of disease. Direct costs for the cohort are described using flat-rate charges by visit type and are compared to two national medical claims databases. Information on disability and mortality are further combined into a single indicator, the disability-adjusted life year (DALYs) lost due to disease. DALYs are comparable across diseases and can be used to prioritize important health issues.

Finally, results on the long-term sequelae of RMSF and cost analysis are placed into context of public health action; describing implications for healthcare providers, hospital and regional policy makers, as well as communities.

CHAPTER 2

LITERATURE REVIEW

HISTORY OF ROCKY MOUNTAIN SPOTTED FEVER

Rocky Mountain spotted fever (RMSF) is an acute febrile illness caused by the bacterium *Rickettsia rickettsii,* a member of the spotted fever group of *Rickettsiae*. Rickettsial diseases are widespread throughout the world and range in pathogenicity from innocuous species like *R. bellii,* to the most deadly species, *R. rickettsii* (Parola et al., 2013). RMSF was first described by a Surgeon General of the Army in 1896, listing several accounts of a "spotted fever" of unknown origin occurring in spring months in Idaho (Wood, 1896). Wood noted however, that cases were likely to have been occurring in tribal communities of the Bitter Root Valley since the 1860s. Later reports by another Army Surgeon, E.E. Maxey further describe residents on the mountainous hillside of the Snake River Valley developing sudden onset of purpuritic fever with rapidly progressing disease (1899). Residents noticed that cases occurred during spring and summer months, initially attributing its occurrence to contaminated water from snow runoff. Early investigations into the source of the spotted fever by the Montana Board of Health, however, proposed possible tick transmission based on exposure histories of local patients (Wolbach, 1919). It wasn't until 1906 that researcher Howard Ricketts was able to successfully document transmission to guinea pigs through the bite of Rocky Mountain wood ticks, *Dermacentor venustus (*later clarified as *D. andersoni)* (Ricketts, 1906).

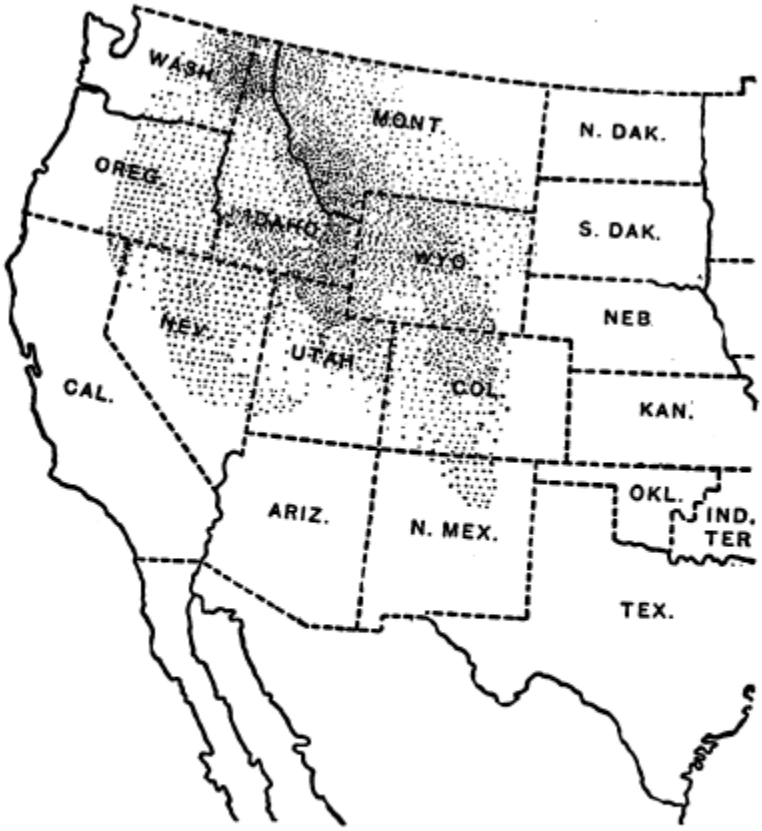
EPIDEMIOLOGY OF RMSF

Enzootic cycles

Early cases in the Rocky Mountain regions were all associated with transmission from *D. andersoni.* Rabbit ticks, *Haemaphysalis leporis-palustris*, were also shown to be capable of carrying *R. rickettsii* in the early 1900s, however they are not believed to have a substantial impact on the human disease cycle (Parker et al., 1951). All life stages of both tick vectors were shown to harbor the bacteria and there was evidence of transovarial transmission (passage of the bacteria from the adult female to her offspring). Today, *R. rickettsii* is known to be vectored by a variety of Ixodid (hard bodied) ticks including *D. variabilis* and *D. andersoni* in the U.S., and *Amblyomma cajennense, A. aureolatum,* and *Rhipicephalus sanguineus* in Mexico and Central America (Álvarez-Hernández et al., 2017; Azad & Beard, 1998; Dantas-Torres, 2007; Drexler et al., 2016). Other tick species have been identified as capable vectors but have not yet been implicated as principal components to maintenance of *R. rickettsii* in the environment, nor drivers of human infection. *R. rickettsii* are generally found in low burdens in these tick populations (<1% of ticks per geographic unit), resulting in sporadic human cases (Azad & Beard, 1998; Stromdahl et al., 2011). Animal hosts for these ticks include small and medium sized mammals, including canids, rodents, and rabbits; humans are incidental, dead-end hosts (Azad & Beard, 1998; Spencer, 1929; Wolbach, 1919).

Early Epidemiology

Following initial discovery and reporting of RMSF, cases were described throughout the Rocky Mountain region (Figure 2.1), with early cases also reported in Nevada, Wyoming and Idaho, California, Oregon, Washington, and Colorado (Wolbach, 1919).



MAP 1.

Map showing the distribution of the Rocky Mountain spotted fever tick (*Dermacentor venustus*). The degree of shading indicates the relative abundance of the tick in different sections.

Reproduced from Hunter and Bishopp. United States Department of Agriculture, Bureau of Entomology, Bulletin No. 105.

Figure 2.1: Early distribution of RMSF in the West (Wolbach, 1919).

Annual reporting of RMSF cases were tracked in key western locations since the early 1900s, and the disease became nationally reportable in 1920s (Hattwick, 1971). Cases were most commonly reported in the spring and summer months, with the majority of cases occurring among adult men (Spencer, 1929). Occupational and recreational risk factors were apparent with hunters, foresters, surveyors, fisherman, and cattleman highly impacted (Spencer, 1929). Beginning in the 1930s, cases emerged in the southern United States; concurrent with a

precipitous decline in cases reported out of western states (Hattwick, 1971). Incidence of RMSF in the 1930s–1940s gradually increased and high case fatality rates (10–30%) were experienced during these periods before antibiotic therapy was available, (Figure 2.2).

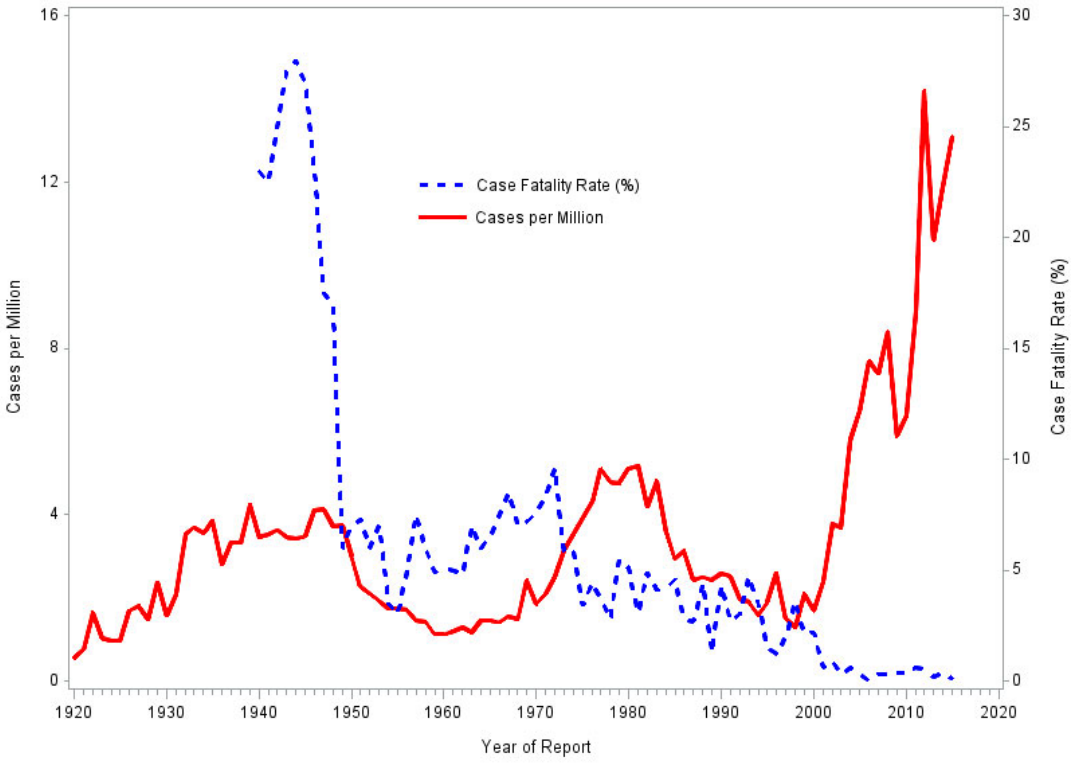


Figure 2.2: Incidence and case fatality rate of spotted fever rickettsioses in the United States, 1920–2015 (Centers for Disease Control and Prevention;, 2019)

Modern Epidemiology

Since 2010, RMSF has been tracked for surveillance purposes under the broader category "Spotted fever rickettsiosis" (CSTE, 2009). Illnesses within this group are clinically similar and cannot be distinguished using common serologic assays (Drexler et al., 2016). Spotted fever rickettsioses are reported throughout the contiguous United States, with 60% of cases being reported from five states: Arkansas, Missouri, North Carolina, Oklahoma and Tennessee, Figure

2.3 (Drexler et al., 2016). A higher proportion of cases are still reported among men, with the majority being white and non-Hispanic (Drexler et al., 2016).

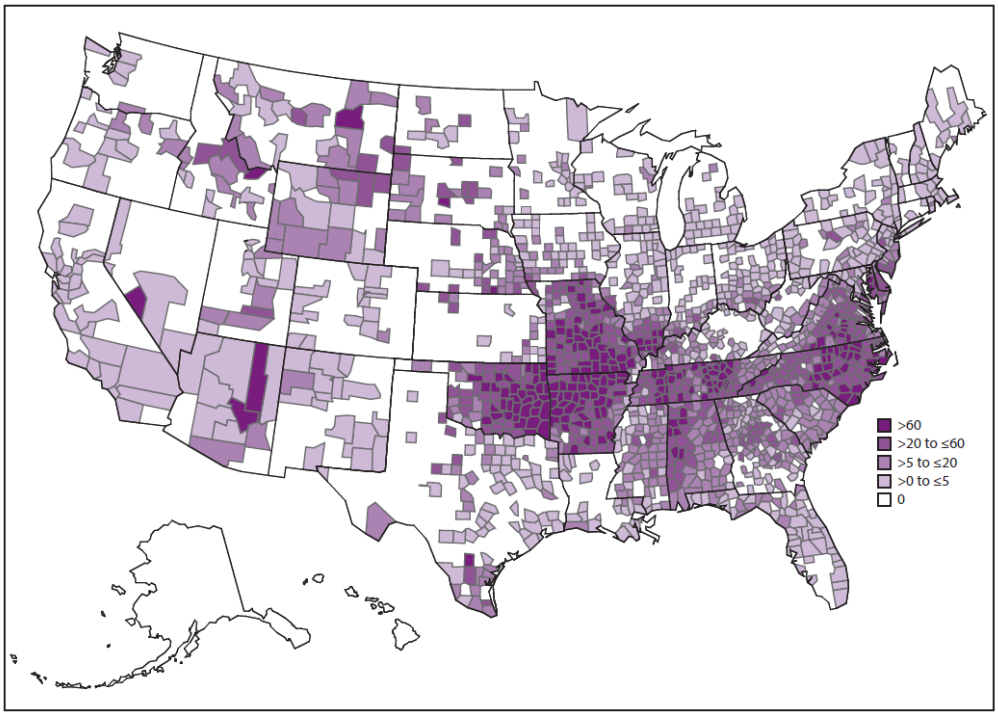


Figure 2.3: Distribution of spotted fever rickettsiosis, 2000–2013 (Biggs et al., 2016).

Modern-day case fatality rates of spotted fever rickettsiosis using national surveillance data report deaths in less than 1% of cases, which is considerably less than what would be expected from a summary of true RMSF cases (modern clinical case series typically report fatalities in 5–10% of true RMSF cases) (Biggs et al., 2016; Buckingham et al., 2007; Traeger et al., 2015). As with disease incidence and distribution patterns, descriptions of case fatality rates using national surveillance data likely capture other, less pathogenic spotted fever group *Rickettsia*, including *R. parkeri* rickettsiosis and Pacific Coast tick fever, leading to a skewed representation of disease mortality (Dahlgren et al., 2016; Drexler et al., 2016; Heitman et al., 2019).

PATHOGENESIS AND CLINICAL MANIFESTATIONS OF RMSF

Rickettsia rickettsii infect the endothelial cells that line the small blood vessels throughout the body resulting in cell injury leading to increased permeability of vessels, microvascular hemorrhages and infarcts (Valbuena & Walker, 2009). Damage to vital organ systems can be caused by direct tissue damage, or, secondarily by edema and inflammatory responses such as increasing permeability in the lungs leading to non-cardiogenic edema (Walker et al., 2003).

Descriptions of clinical disease have remained largely consistent throughout the history of RMSF in the United States (Biggs et al., 2016; Buckingham et al., 2007; Helmick et al., 1984; Traeger et al., 2015; Wolbach, 1919). Illness typically begins 3–12 days following the bite of an infected tick. Unlike other, commonly known tick borne pathogens, *Rickettsiae* can be transmitted in less than 2 hours of tick attachment (Levin et al., 2019; Spencer & Parker, 1923). The first sign of illness is often sudden onset of fever, accompanied by headache, chills, malaise and myalgia. Patients may also experience stomach pain, leg pain, nausea or vomiting. Complete blood count and chemistries are typically normal during early stages of illness (days 1–3). A rash classically appears between day 2–4 of illness, and begins as a faint, macular or maculopapular eruption on the writs or forearms spreading centrally. It typically spares the face, but can include the palms of the hands and soles of the feet (Biggs et al., 2016; Helmick et al., 1984; Traeger et al., 2015; Walker, 1995). The majority of RMSF cases initially present to a healthcare provider within the first 2–3 days of illness, when clinical signs and symptoms are non-specific and easily attributed to other febrile prodromes (Helmick et al., 1984; Traeger et al., 2015).

During intermediate stages of illness, days 4–5, patients begin to experience more profound systemic illness: high fever, often unresponsive to antipyretics, severe abdominal pain,

altered mental status, hepatomegaly, or splenomegaly. At this time, laboratory values will begin to appear abnormal including downward trending platelet count, mild leukocytosis, and slight elevations in hepatic transaminases, which are signs of increased damage to organ systems and platelet consumption. As disease advances, macular rash eruptions progress into petechiae, a reflection of vasculitis in the skin; petechiae may fuse and become confluent. Purpura and dusky, mottled regions may appear on the extremities. When infection is allowed to progress to severe stages (beyond 5 days from illness onset), the bacteria will cause advancing damage to vital organ systems including meningoencephalitis, acute renal failure, acute respiratory distress syndrome (ARDS), severe hypotension, and coagulopathy. Necrosis accompanied by gangrene may occur in the extremities and digits from lack of profusion, oftentimes requiring intensive wound care, debridement, or amputation. Roughly half of RMSF deaths occur within the first 8 days of illness (Paddock et al., 1999). Death typically occurs from irreparable damage to organ systems resulting in cardiopulmonary failure, shock, and hypovolemia. Until tetracycline antibiotics were invented in the 1940s RMSF was associated with case fatality rates as high as 90% (Wilson & Chowning, 1904). Once tetracycline-class antibiotics were readily used for the treatment of RMSF case fatality rates of disease decreased to less than 10% of cases (Hattwick, 1971). Chloramphenicol is the only alternative treatment effective against *R. rickettsii,* however, use of chloramphenicol is associated with higher rates of severe illness and death (Holman et al., 2001a).

Diagnosis of RMSF

There are no rapid diagnostic tests to confirm RMSF and treatment decisions must be based on clinical signs, symptoms, and exposure history. Laboratory confirmation may occur days to weeks following initial illness. The most commonly used diagnostic tests include

molecular assays, including polymerase chain reaction (PCR) and immunologic (serologic) assays such as indirect immunofluorescence assays (IFA). Molecular assays look for rickettsial DNA or RNA in the blood, while immunologic assays look for antibodies. Serologic assays are best evaluated in pairs, one sample drawn within the first week of illness to serve as a baseline response, and a second sample taken weeks later to demonstrate a clear antibody response to a recent infection; single samples are unable to confirm a recent rickettsial illness. Molecular assays are not widely available, leading to a larger reliance on serologic assays. Serologic assays convey a high degree of cross-reactivity among spotted fever group *Rickettsiae* and are unable to provide reliable species specificity. The lack of paired serum samples in reported cases of spotted fever rickettsiosis (less than 10% of cases reporting paired samples) and notable cross reactivity, even among non-pathogenic agents, calls into question our true understanding of spotted fever rickettsiosis burden and epidemiology (Binder et al., 2019).

Neurologic Sequelae of RMSF

Symptoms suggestive of neurologic involvement during acute RMSF infection are frequent; headache (>80%), stupor (20%), meningitis (>20%), ataxia (20%), coma (20%), seizures (10%), decreased hearing (10%), and papilledema (<10%) were reported from one clinical summary (Lisak et al., 2016). Focal signs likely result from endothelial damage leading to infarcts or hemorrhages in the brain. Several publications highlight a classic “starry sky” appearance of numerous micro-hemorrhages in the perivascular space of the brain, captured on MRI (Crapp et al., 2012; Sun et al., 2015). Cell damage can also cause perivascular leakage, resulting in edema, swelling of the brain, and increased pressure in the central nervous system (CNS) resulting in decreased oxygenation and cell death. Demyelination has been noted in post-mortem evaluations of the CNS in proximity to vascular damage (Archibald & Sexton, 1995;

Berlin & Thomas, 1948). Most notations of neurologic damage are reported in the 1–2 weeks of illness, with the greatest involvement at the time of systemic illness and are usually accompanied by damage to other organ systems (Figures 2.4a and 2.4b). Following treatment with effective antibiotic therapy, endothelial damage is halted. However, the state of cell damage at the time of treatment may impact the likelihood of recovery. Over time, cells throughout the body replicate, damaged cells in tissue and organs are replaced and organ function recovers. However, neurons are often slow or unable to regenerate, and damage to tissue within the CNS may be irreversible.

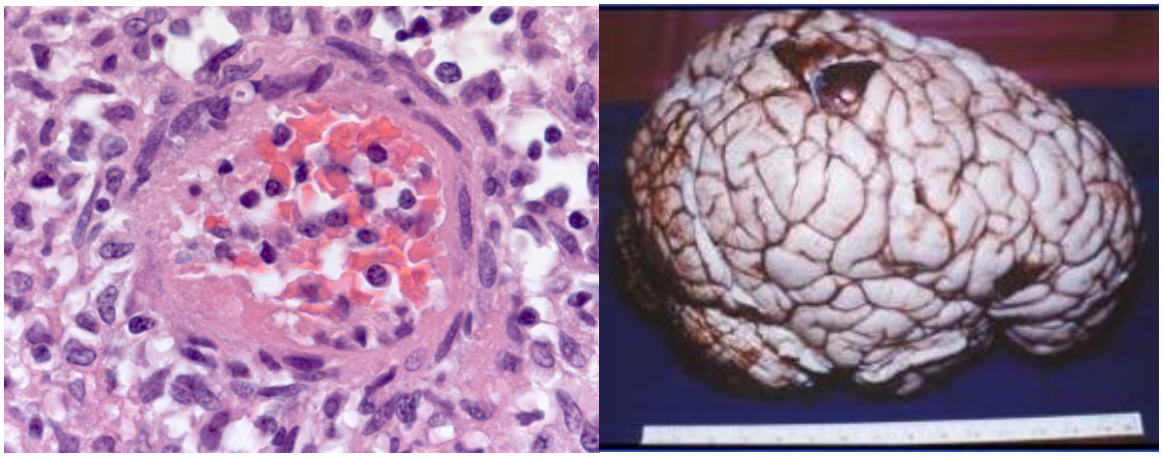


Figure 2.4: Evidence of cellular damage from *Rickettsia rickettsii* (a) using immunohistochemistry in a cross section of lung tissue; (b) in gross pathology of the brain during autopsy showing subarachnoid hemorrhages (Armstrong & Drexler, 2018).

Descriptions of neurologic symptoms are scattered throughout the literature (Table 2.1). A publication from the 1930s referenced persisting seizure activity in a single case of RMSF from Iowa with seizures lasting years following illness (Jordan, 1938). In 1948, Berlin and Thomas made a more global conclusion about persistent neurologic sequelae following acute disease recovery (Berlin & Thomas, 1948): “Although the involvement of the central nervous

system in Rocky Mountain spotted fever usually either is followed by complete recovery or results in death during the acute stage, in rare cases significant neurologic sequelae may remain." This publication documented profound mental deterioration, behavior changes, and paraplegia 19 months following RMSF illness.

To our knowledge, the first publication to systematically evaluate long-term neurologic consequences following RMSF, were published by Rosenblum et al. (1952). This study describes 37 patients previously diagnosed with RMSF. LTS were evaluated by patient history, clinical exam and some with additional electroencephalogram (EEG) one to eight years following illness (Rosenblum et al., 1952). Sequelae were documented in 21 of the 37 patients: 14 indicated sequelae in their patient history, 12 had clearly abnormal EEG, and 6 showed signs of neurodysfunction including motor dysfunctions and hyperreflexia. Patients also reported memory loss, changes in personality, confusion, ataxia, and dizziness. Half of the patients showing neurologic abnormalities reported CNS symptoms during their acute illness, while the others did not. EEG results showed 12 patients with abnormal values, however only a single case was considered to have residual neurologic damage from RMSF. Abnormal EEG results could not be associated with disease severity, but a high proportion of individuals who had abnormal EEGs were noted to have had fever for more than 10 days during their acute illness.

The largest body of evidence relating to long-term neurologic outcomes from RMSF comes from a Gorman et al. in 1981, which evaluated 42 patients, all children, following RMSF (Gorman et al., 1981). Gorman and colleagues observed behavioral disturbances and learning disabilities; this was the first study aimed at grading the level of disability using standard cognitive measures. Patients were grouped into clusters with mild, moderate, and severe illness. Individuals with more severe disease had substantially higher rates of learning disability. The

authors further observed a higher likelihood of intellectual deterioration in those experiencing coma during acute illness.

A later study by Archibald & Sexton (1995) documents the long-term outcomes of 20 individuals following an RMSF illness, nine of which reported the presence of long-term sequelae. This evaluation provides the longest period of follow-up ranging from one year to 18 years (mean 11 years) following illness onset. The patients participating in this study were categorized as having severe, but non-fatal illness with the median length of hospital stay of 47 days (range 14–117 days). The primary sequelae noted included difficulties with speech, deafness, weakness, bowel and bladder incontinence; paraparesis; peripheral neuropathy; cerebellar, vestibular and motor dysfunction; as well as language disorders (Archibald & Sexton, 1995). Evaluations of 11 patients who did not report persistent sequelae showed no appreciable difference in encephalopathy, thrombocytopenia, or renal failure during acute illness. There was also no significant difference observed in length of time to treatment.

More recent case studies have reported the occurrence of LTS, including a publication in early 2019 about persistent sequelae in a Mexican patient evaluated ten years following acute illness, however no further systematic evaluations have been reported to date (Dzul-Rosado et al., 2019). While these publications demonstrate that RMSF has been associated with long-term neurologic damage, they are incomplete in their evaluation of common types of sequelae, impact on quality of life, and persistence of symptoms. It is hoped that the subsequent research presented herein may provide valuable information to close those knowledge gaps and provide clear and actionable data for local healthcare providers.

Table 2.1: Evidence of long-term neurologic sequelae following RMSF

Publication	**Patient population**	**Duration of follow-up**	**Proportion of individuals with long-term sequela**	**Types of long-term sequela**
Rosenblum et al 1952	All ages	1–8 years	21/37 (56%)	Motor dysfunctions, hyperreflexia, memory loss, changes in personality, confusion, ataxia and dizziness
Gorman et al. 1981	Children	1–10 years	2/42 (5%)	Mental disability and intellectual deterioration
Archibald & Sexton 1995	All ages	1–18 years	9/20 (45%)	Hearing loss, peripheral neuropathy, bladder and bowel incontinence, weakness, dysarthria, cerebellar, vestibular and motor dysfunction

Table 2.2: Sequelae at discharge from large clinical reviews

Publication	**Patient population**	**Proportion of individuals with sequelae at discharge**	**Sequelae at discharge**
Buckingham 2007	Children	13/92 (14%)	Speech dysfunction, ataxia, blindness, amputation
Traeger 2015	All ages	5/187 (3%)	Amputation, seizures, coma

ROCKY MOUNTAIN SPOTTED FEVER IN ARIZONA

Historically, few cases of RMSF were reported in Arizona; during 1993–2002, only six cases of RMSF were reported to the Arizona Department of Health Services (ADHS) (Arizona Department of Health Services, n.d.), and many of these were associated with out-of-state travel (personal communication ADHS). The absence of cases was not considered abnormal as Arizona is largely unoccupied by the principal vectors of RMSF, *D. andersoni* and *D. variabilis.* Only small populations of *D. andersoni* have been reported from areas of northern Arizona, in deciduous forests above 8,000 ft (James et al., 2006).

In 2003, ADHS received notification that a one year old child living on an American Indian reservation in Eastern Arizona had died from what was suspected to be RMSF (Demma et al., 2005). The child was brought into the emergency room with a high fever, maculopapular rash and quickly decompensated developing sepsis, eventual multi-organ system failure, and died. Blood and tissue samples were sent to the Centers for Disease Control and Prevention (CDC), where RMSF was confirmed using PCR. Medical chart abstractions from the local health facility revealed that a similar case was diagnosed using serologic assays in 2002 from the same tribal community but survived; this is believed to be the first autochthonous case of RMSF in Arizona (Demma et al., 2005). Subsequent ecologic investigations at the homes of both children confirmed an absence of *Dermacentor* species in the tribal community, but a considerable burden, including peri domestic infestation, of *Rhipicephalus sanguineus,* the brown dog tick (Demma et al., 2005; Nicholson et al., 2006). PCR of ticks collected from the patient's home site, neighborhood dogs, and surrounding areas showed these ticks to be carrying *R. rickettsii* (Nicholson et al., 2006). Laboratory research has subsequently shown *Rh. sanguineus* to be an extremely efficient vector for *R. rickettsii*, with possible transmission from all life stages (larva,

nymph, adult) of this species (Labruna et al., 2008). Unlike *Dermacentor* species, which typically engage in a wildlife-based enzootic cycle, *Rh. sanguineus* primarily feed on domestic dogs at each life stage and are uniquely adapted for living in and around domestic spaces (Dantas-Torres, 2008). Free-roaming dog populations provide an accelerating factor in RMSF in tribal communities, they serve as transporters of ticks and with the ticks themselves, are likely the primary hosts for *R. rickettsii*. The reservation community in which initial cases were reported is isolated and lacks permanent veterinary services allowing stray dog populations to proliferate.

During 2002–2005, 27 cases of RMSF were diagnosed from this same community (Arizona Department of Health Services, n.d.). Beginning in 2005, cases began to appear in a second tribal community with subsequent identification in other tribal areas; a total of six tribal communities have been impacted to-date (Arizona Department of Health Services, 2015). Index cases within each new area were followed by ecologic investigations identifying *Rh. sanguineus* as the primary vector and noting substantial populations of free-roaming dogs heavily parasitized by *Rh. sanguineus* (CDC investigations not published). More than 425 cases of RMSF have been diagnosed in Arizona tribal communities (ADHS) during 2002–2018; with an incidence rate in the three most highly impacted areas 150 times higher than the national average (N. Drexler et al., 2014). Dynamics of RMSF epidemics are different in each tribal community; some have experienced only a handful of cases, while others continue to report numerous critical cases and deaths every year. The reasons for such differences are not fully understood, but may include virulence factors, number of susceptible hosts, density of ticks, and may be influenced by local control responses following case identification. Prompt and thorough tick control protocols (including free provision of tick control treatment for community dogs) immediately following

the first human cases, is the current standard approach to limiting further spread of RMSF (Alvarez-Hernandez et al., 2019). Concurrent to the appearance of RMSF on tribal lands in the American southwest, reports of RMSF were also reported in northern Mexico, a region with similar climate and socioeconomic challenges to some parts of Arizona (Álvarez-Hernández et al., 2017). These areas also continue to experience peri-domestic exposure to *R. rickettsii* by brown dog ticks, resulting in epidemic rates of RMSF. RMSF in northern Mexico has resulted in thousands of cases and hundreds of deaths (Álvarez-Hernández et al., 2017; Sanchez et al., 2009).

Prevention and Control of RMSF in Arizona

The single host preference of *Rh. sanguineus* in Arizona and Mexico transmission cycles presents an opportunity for targeted prevention and control. Prevention recommendations for *Dermacentor*-transmitted RMSF focuses on avoidance of tick habitats; personal protective measures, such as used of DEET and permethrin products; and thorough tick checks (Piesman & Eisen, 2008). Reduction of tick populations in forested and grassy areas, or host-targeted control to wildlife are impractical and are considered ineffective. However, the peri-domestic focus of *Rh. sanguineus* and the preferred domestic dog host creates an opportunity for host-targeted prevention efforts. Early control efforts in Arizona tribal communities included application of granular pesticide and provision of tick control products to owned dogs. These efforts were largely ineffective; not all dogs received preventative treatments, and granular acaricides had limited use in hot, arid climates. In 2012, state, federal, and tribal partners initiated a community-based integrated prevention project called the RMSF Rodeo (N. Drexler et al., 2014). Integrated efforts included application of long-lasting Seresto ® tick collars to all community dogs, monthly environmental acaricide applications to homes and yards, increased spay and neuter

activities, and community education. The project achieved rapid success; tick burdens observed on dogs were reduced from 63% to less than 5% and environmental sampling of ticks was reduced beyond detectable limits within the first three months of the program. Most importantly, human incidence of RMSF decreased in the project community by 43% in the 2 years following the intervention. These prevention practices were subsequently adapted and implemented in several impacted communities in Arizona and still serve as the gold standard for RMSF prevention and control in Arizona. Similar, integrated practices have been further implemented in one small community in Sonora (Straily, 2016). Results of the Sonora study indicate similar, rapid reduction of tick burdens on dogs and in the environment, and fewer human cases and deaths in the project area (Alvarez-Hernandez et al., 2019; Straily, 2016). The integrated prevention efforts are undoubtedly effective in reducing the incidence of disease but require intensive personnel and material resources to produce and sustain. While tribal communities are committed to preventing this dangerous disease in their communities, they are limited by lack of resources and infrastructure such as vector control programs and veterinary services.

Clinical and Epidemiological Factors Associated with RMSF in Arizona

Clinical and epidemiologic characteristics of RMSF cases in Arizona were described in a 2011 study (Regan et al., 2015; Traeger et al., 2015). This retrospective chart review summarized 205 cases from two highly impacted reservations during 2002–2011. The review provided critical information on a variety of topics including description of clinical characteristics and epidemiologic risk factors. Largely, the clinical progression of Arizona cases was like previous clinical summaries; patients sought care early in clinical illness (median first care on day 2) with non-specific signs and symptoms. The vast majority (81%) of patients reported a fever, and while rash was a common finding among patients in this series (68% at any point during their

illness), the presentation of rash varied widely (including pruritic, urticarial and vesicular). The review by Traeger et al. further noted distinct epidemiologic factors differentiating RMSF in Arizona from that reported elsewhere in the United States; cases were reported in every month of the year, there was a high preponderance of pediatric cases (50% of cases were 10 years or younger), and while tick bites were moderately frequent (55%), exposure to free-roaming and tick infested dogs was common (86%). The medical chart review data published by Traeger et. al represent the largest body of evidence about RMSF in Arizona, but long-term effects following hospital discharge were unable to be described and have, as of yet, not been addressed by subsequent publications.

Medical and Indirect Costs of RMSF in Arizona

The data obtained from the Regan and Traeger clinical reviews were secondarily used to describe the medical and indirect costs associated with the Arizona RMSF epidemic (Drexler et al., 2015). Cases in the original chart abstraction included individuals from two tribal communities, receiving direct care at facilities run by the Indian Health Services (IHS), or purchased care at outside facilities paid by IHS and Medicaid. Direct billing information was unavailable, so healthcare visits were enumerated by visit type (classifying them as outpatient, emergency, inpatient/general admission, and inpatient/intensive care unit (ICU) admission). Direct costs of acute care were then calculated using 2011 flat-rate charges billed to Medicaid by IHS based on type of visit and length of stay (Table 2.3). Indirect costs of RMSF included both acute and lifetime productivity lost due to illness (Table 2.4). Productivity costs were derived from estimates provided by Grosse et al., a commonly used source for productivity estimates in the United States (2009) based on age and gender. Grosse estimates of productivity were

adjusted proportionately for the average annual income of American Indians in Arizona using annual income reported in the 2010 Census (N. A. Drexler et al., 2015).

Arizona cases described in this study were severe, resulting in high direct and indirect medical expenses associated with acute disease; over 80% of RMSF cases required emergency room visits, 14% were admitted to the intensive care unit for severe illness, and 7% were fatal. On average 1.5 days (range 0–8 days) were lost for outpatient visits, 6.9 day (0–55 days) were lost for inpatient days, and 4 days were added to productivity estimates to account for home convalescence.

Table 2.3: Acute medical costs associated with RMSF, 2002–2011 (Drexler et al., 2015)

Acute medical costs based on IHS all-inclusive reimbursement rates from Medicaid

Item	Number of people reporting at least one	Total number of encounters or days	Cost per unit ($)	Total cost ($)
ER visits	170	256	294	75,264
Outpatient or clinic visits*	81	125	294	36,750
Inpatient days†	82	360	2,034	732,240
Transfers	48	48	1,500	72,000
ICU days	29	224	2,034	455,616
				Bulk total 1,371,870

ER = emergency room; ICU = intensive care unit; IHS = Indian Health Service.
*Visit not resulting in an admission, excluding visits to ER.
†Excludes days spent in the ICU.

Table 2.4: Medical and indirect costs associate with RMSF in Arizona, 2002–2011 (Drexler et al., 2015)

Summary of direct and indirect costs associated with RMSF in Arizona, 2002–2011

	Point estimate	Lower bound	Upper bound
Direct costs			
Acute medical costs	$1,371,870	$1,371,870	$1,371,870
Long-term medical costs	NA	–	–
Indirect costs			
Acute loss to productivity	$181,100	$175,954	$186,240
Long-term loss of productivity due to disability	NA	–	–
Lifetime lost due to death	$11,631,998	$11,304,814	$11,959,182
Total	$13,184,968	$12,852,638	$13,517,292

NA = not addressed in this study due to unavailability of relevant clinical information; RMSF = Rocky Mountain spotted fever.

A total of nearly $13.2 million in losses linked to the epidemic of RMSF during 2002–2011. On average, each death cost $775,467 in direct medical expenses and lifetime productivity lost, more than five times that of pneumococcal disease ($140,862) in the United States (Drexler et al., 2015). The high cost per life lost likely related to the substantial number of children who died from RMSF.

Medical chart abstractions sourced for this study only related to acute care and no costs were estimated for the cost of long-term care, representing a notable gap in the current economic burden of RMSF in Arizona. One of the intended outcomes of the data described in this dissertation is to obtain descriptions and relative abundance of severe disability, length of time to recovery, and impact on daily function to better assess the overall economic burden of disease.

HEALTHCARE IN AMERICAN INDIAN COMMUNITIES

The U.S. government has a unique responsibility in providing healthcare and preventive health services to American Indians and Alaska Natives, in fulfillment of the Federal Trust responsibilities. Between 1781 and 1841 the U.S. government entered into nearly four hundred treatises with American Indian tribes in which the U.S. government promised protections of sovereignty, healthcare, and reservations, in exchange for land (Pfefferbaum et al., 1995; Warne, 2006). IHS was established in 1955 to provide direct healthcare services to American Indians and Alaska Natives at IHS facilities or tribally run facilities. Healthcare services for American Indians and Alaska Natives have been renegotiated at several points in history with varying coverages for services but was permanently appropriated in 2009 (Warne & Frizzell, 2014). However, American Indian health programs are often dramatically underfunded. A 2003 study documented a 59% shortfall in funding for American Indians and Alaska Natives resulting in lack of access to critical services (U.S. Commission on Civil Rights, 2003)

Health Disparities in Tribal Communities

American Indians have been experiencing health disparities for more than 500 years (Jones, 2006). On average, American Indians have a life expectancy more than 5 years less than all other races (*Indian Health Disparities*, 2018). Publications from the last few decades have documented health disparities relative to other races, in rates of suicide (1.9 times), cardiovascular disease (CVD) (1.2 times), diabetes (4.2 times), and infectious diseases such as tuberculosis (7.5 times) and death from chronic liver disease (4 times) (Barnes et al., 2010; *Indian Health Disparities*, 2018; Jones, 2006). Rickettsial diseases, including RMSF have been documented to differentially impact American Indians, with one analysis estimating four times higher rates of RMSF among American Indians than whites (Dahlgren et al., 2011). Higher rates

of RMSF are thought to be related to the predominance of American Indians in parts of the United States where transmission rates are known to be higher, including Oklahoma, Arizona, and California.

Most studies attribute the increased rates of disease and disability to lack of primary care resources, limited health screenings, and limited access to healthy foods and key services. Other studies have implied the root of health disparities goes beyond socioeconomic factors, and may additionally involve genetic and cultural differences (North et al., 2003; Pettitt et al., 1990; Warne, 2006). One study in Minnesota described additional barriers to health program utilization relating to distrust, discrimination, and lack of respect for cultural beliefs from non-Native healthcare providers (Call et al., 2006). No one reason has been predictive of all health disparities, and the problem is likely multi-factorial (Jones, 2006; Warne, 2006). Nationwide, American Indians are twice as likely to be unemployed with more than 50% of the AI population living 200% below the federal poverty line (compared to 29% of the general population) and experience a significantly higher rate of disability than the general population (Castor et al., 2006; Zuckerman et al., 2004).

In 2010, roughly 22% of American Indians (alone or in combination with other race groups) resided in reservation communities, often in rural and remote portions of the country, with a potential lack to critical health services (Norris et al., 2012). Although many rural communities do have provisions for primary healthcare within reservation communities (either provided by the Indian Health Service or through tribally run health programs) the availability of specialty services and critical care units is severely lacking in many areas, including the Southwest. Beyond direct access, one survey documented far fewer American Indian and Alaska Natives having access health insurance beyond IHS services with almost 35% uninsured (rates

three times higher than that of whites) (Zuckerman et al., 2004). This study suggested that overall healthcare access issues were more related to lack of insurance coverage, rather than race. Regardless of the causes of health disparities, differential rates of morbidity and mortality have been documented among American Indians (Castor et al., 2006; *Indian Health Disparities*, 2018; Jones, 2006; Norris et al., 2012; Zuckerman et al., 2004). American Indians living in remote tribal communities may be dually impacted both by increased rates of exposure to diseases like RMSF, and increased rates of disability and death from limited infrastructure and medical resources (Cunningham, 1993; Probst et al., 2004). Documenting high rates of disability requiring supportive care could be used to advocate for increased resources at tribal health facilities.

Social Impacts of Death and Disease in Tribal Communities

Beginning in 1830s, American Indians were systematically removed from their ancestral homelands in southeastern U.S. under the Indian Removal Act of 1830, signed by President Andrew Jackson. This act offered territory west of the Mississippi River in a series of relocations including the forceful movement of more than 70,000 tribal members from the Southeast U.S. during the Trail of Tears. During this movement thousands of American Indians died from disease, malnutrition, and exposure to the elements. Once relocated, American Indian communities were further denigrated as children were removed from their homes and forcibly place in boarding schools in an effort to assimilate tribal identity, language, and traditions to western norms (Pfefferbaum et al., 1995). It is during this period that most historians feel the greatest damage to Tribal culture occurred in the form of physical, cultural, and emotional abuse. Many experts believe that the multi-generational subjugation of Native peoples have resulted in additive traumatic experiences called “historical traumas” (Brave Heart & DeBruyn, 1998). The

concept of historical trauma has been applied to the families of Holocaust and people imprisoned in Japanese internment camps but was only recently applied to the American Indian experience. Social scientists argue that generations of systematic losses of tradition and culture to targeted groups because of race, religion or other demographic traits, may lead to compounded experiences of oppression.

In addition to historical trauma and lack of health resources, American Indians in the Southwest have a higher lifetime prevalence of individual trauma. One study estimates more than 60% (62% among women, 66% among men) of American Indians in the Southwest have exposure to one or more traumas in a lifetime, this is notably higher than the 60% and 51% for women and men in the general U.S. population (Manson et al., 2005). Traumas in this study include molestation, assault, being involved in a disaster event, or being witness to trauma are combined to one measure. The authors of this study remark on the possible connection of trauma to adverse health effects, mental illness, and overall health disparities. Although not a specific component of the trauma calculation, witnessing a sudden and dramatic death due to disease could logically be included as a source of trauma. When taken in context to of other individual and group traumas experienced in American Indian communities, it is a reasonable extension that numerous deaths in small tribal areas (such as those occurring from RMSF) may increase the overall social impact of death.

CHAPTER 3

MORBIDITY AND FUNCTIONAL OUTCOMES FOLLOWING ROCKY MOUNTAIN SPOTTED FEVER HOSPITALIZATION— ARIZONA, 2002–2017[1]

[1] Drexler et al. To be submitted to *Clinical Infectious Diseases.*

ABSTRACT

Background: Rocky Mountain spotted fever (RMSF) is a deadly tickborne disease disproportionately affecting Arizona tribal communities. While the acute clinical effects of RMSF are well-documented, a more complete understanding of the long-term health consequences is needed to provide guidance for providers and patients in highly impacted areas.

Methods: We performed a retrospective review of hospitalized RMSF cases from two tribal communities in Arizona during 2002–2017. Medical charts from acute illness were abstracted for information on clinical presentation, treatment, and status at discharge. Surviving patients were interviewed about disease recovery and patients reporting incomplete recovery were eligible for a neurologic exam.

Results: 80 hospitalized cases of RMSF met our inclusion criteria and were reviewed. Of these, 17 (21%) resulted in a fatal outcome. Among surviving cases who were interviewed, most (62%) reported full recovery, 15 (38%) reported ongoing symptoms or reduced function following RMSF illness, and 9 (23%) had evidence of neurologic sequelae at the time of exam. Sequelae included impaired cognition, weakness, decreased deep tendon reflexes, seizures, and cranial nerve dysfunction. Longer hospitalization (25.5 days vs 6.2 days, $p<0.001$), a higher degree of disability at discharge (median modified Rankin score 1 vs 0, $p= 0.03$), and delayed doxycycline administration (6.2 days vs 4.1 days, $p=0.12$) were associated with long-term sequelae.

Conclusion: Although the etiology of sequelae is not able to be determined using this study design, life-altering sequelae were common among patients surviving severe RMSF illness. Delayed administration of the antibiotic doxycycline after day five was the strongest predictor of morbidity.

INTRODUCTION

Rocky Mountain spotted fever (RMSF) is a potentially deadly tickborne disease caused by the bacterium *Rickettsia rickettsii.* RMSF is a rapidly progressing illness; bacteria invade endothelial cells throughout the body resulting in disrupted organ perfusion, sepsis, and sometimes death (Walker et al., 2003). Prior to antibiotic therapy, case fatality rates from RMSF were as high as 60% (Hattwick, 1971; Wolbach, 1919). However, with advances in critical care and widespread availability of tetracycline class antibiotics, case fatality rates have dropped significantly to 5–10% in the United States (Biggs et al., 2016; Buckingham et al., 2007; Regan et al., 2015). Delayed treatment beyond day five of illness is the single most important predictor of severe and fatal outcomes from RMSF (Holman et al., 2001a; Regan et al., 2015).

RMSF is characterized initially as an acute febrile illness with non-specific symptoms such as fever, headache, and muscle pain. A disseminated rash usually appears between day 2–4 of illness. Beyond day five of illness, patients may begin experiencing severe abdominal pain, respiratory distress, and acute neurologic signs and symptoms. Neurologic symptoms are thought to result from blood vessel injury in the central nervous system or by the resulting inflammatory process (Rosenblum et al., 1952; Walker et al., 2003). Early accounts of neurologic impairment included persistent changes in neurologic function, loss of motor control, and behavior change (Berlin & Thomas, 1948; Jordan, 1938). Subsequent case series similarly documented neurologic dysfunction years after acute disease recovery, although many included small sample sizes and varying types of neurologic evaluations (Archibald & Sexton, 1995; Gorman et al., 1981; Rosenblum et al., 1952).

Arizona tribal communities have experienced epidemic levels of RMSF since 2002, with some areas reporting incidence rates 150 times higher than the national average (Drexler et al.,

2015). In the years following the initial surge in cases, families and providers began reporting persistent impairment among patients surviving acute illness. In this study, we review hospitalized cases in a large cohort to better understand sequelae following RMSF, the frequency and duration with which symptoms persist, potential of improvement, and the expected degree of disability.

METHODS

We used a convenience sample of individuals hospitalized with RMSF during 2002–2017 from two highly impacted communities in Arizona. Cases were identified using data reported to the Arizona Department of Health Services (ADHS). For the purposes of this study, long-term sequelae (LTS) are defined as symptoms reported by patients or signs identified on exam following acute RMSF illness and lasting more than one year. Data for this study were obtained from three separate sources: 1) abstraction of medical chart from acute RMSF illness; 2) interview of surviving patients and; 3) neurologic exam of patients reporting persistent sequelae. All cases meeting the case criteria were included in the medical chart abstraction, and all individuals who could be contacted were eligible for patient interview.

Inclusion Criteria

Cases were included based on criteria adapted from the Council of State and Territorial Epidemiologists case definition for Spotted fever rickettsiosis (including RMSF) used in national disease surveillance (CSTE, 2009). Clinical criteria include fever with one or more of the following: rash, eschar, headache, myalgia, anemia, thrombocytopenia, or elevated hepatic transaminases. Afebrile cases with laboratory evidence and a clinical presentation otherwise consistent with RMSF were also included in this analysis. Only hospitalized individuals were included. Additionally, cases were required to have at least one of the following pieces of

laboratory evidence: 1) elevated immunoglobulin G (IgG)-specific antibodies reactive to *R. rickettsii* by indirect immunofluorescence antibody (IFA) assay with titer value ≥1:128; 2) detection of *R. rickettsii* by polymerase chain reaction (PCR) assay; or 3) demonstration of spotted fever group *Rickettsia* (SFGR) antigen by immunohistochemistry. Serologic cross-reactivity among SFGR is known to occur, but all cases of spotted fever rickettsiosis from these two tribal communities with PCR confirmation have been speciated to *R. rickettsii.* Therefore, RMSF is presumed to be the predominant cause of spotted fever rickettsiosis in this area. Due to anticipated high background prevalence of IgG antibodies at low titer values, a higher titer threshold was used than the CSTE definition, this is consistent with previous Arizona publications (Regan et al., 2015; Traeger et al., 2015).

Medical Chart Abstraction

Clinical information was abstracted from the inpatient record during acute illness. Data collected included signs and symptoms of acute illness, neuroimaging studies, assessments on the severity of illness, time to treatment, co-morbid conditions at the time of admission (including previously diagnosed neurologic dysfunction), and condition at the time of discharge (including disposition, documented neurologic status, referrals for follow-up or rehabilitation, and any identified disability). Severe illness was defined as one or more of the following: evidence of shock or use of vasopressors, ARDS, multiorgan failure, renal failure, cerebral edema, coma, digital necrosis, severe thrombocytopenia (<50 x10^3 platelets/uL), or use of mechanical ventilation. The modified Rankin scale was estimated by trained abstractors based on information provided in the medical chart to provide an objective measure of neurologic disability at the time of discharge (Banks & Marotta, 2007).

Patient Interviews

Surviving RMSF cases who could be contacted were eligible for interviews. Surveys included perceived disease recovery and functional capacity (using a 5-point Likert scale) before and after RMSF illness. Surveys were administered by a trained member of the tribal health department or hospital staff. Patients were asked about other neurologic diagnoses since their RMSF illness to control for unrelated, intervening causes of neurologic dysfunction. Individuals reporting decline in function from baseline, persistent symptoms, or difficulty completing tasks were eligible for a neurologic exam.

Neurologic Exam

Neurologic exams were conducted either by a board-certified neurologist or a licensed physician under the supervision of a board-certified neurologist. A standard neurologic exam included evaluation of mental status, cranial nerve function, motor and sensory function, reflexes, coordination, and gait. Additionally, cognitive impairment was further evaluated using the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005), and results were compared to reference standards in the overall population (Rossetti et al, 2011). Cognitive impairment was defined as scoring less than 26 on the MoCA. In cases where MoCA could not be completed, overall cognitive function was assessed during the mental status portion of the neurologic exam. Level of disability was again assessed using the modified Rankin scale at the time of neurologic assessment and compared to the score at the time of discharge. No imaging or laboratory tests were performed as part of this study. Patients were considered to have neurologic sequelae if the neurologic exam showed abnormal neurologic findings or if patients self-reported changes in function or the existence of neurologic abnormalities (such as seizures, changes in

vision, hearing, bowel or bladder incontinence, or behavioral disturbances) at the time of neurologic exam.

Ethical Considerations

This protocol was reviewed and approved by the Institutional Review Board (IRB) at the Centers for Disease Control and Prevention, the Phoenix Area Indian Health Service IRB, and was approved by the tribal council or appropriate tribal governing body at each of the participating locations. The University of Georgia and ADHS IRB deferred to CDC's determination. This study was further evaluated for burden under the paperwork reduction act. The data collection tools were approved by the Office of Management and Budget (0920-1267).

Data Collection and Analysis

Data for each activity were recorded on paper forms and deidentified data were subsequently entered into an encrypted Microsoft Access database on a CDC secure server. Data collections from each of the three sources were reviewed for completeness by the site supervisor at the end of each day. Statistical analyses were performed using SAS version 9.4 (Cary, NC). Demographic characteristics and key clinical indicators of the study population were shown using descriptive statistics. Bivariate associations were further assessed with the primary outcome of the presence or absence of LTS among surviving patients using Fisher's exact tests, the Student's t-test for normally distributed data, and Mann-Whitney test for ordinal, non-normally distributed data. Unadjusted odds ratios obtained through logistic regression are reported for key associations. Significance was assessed at $p<0.05$.

RESULTS

Medical charts from 80 hospitalized cases of RMSF with illness during 2002–2017 were evaluated (Figure 3.1). Half of the patients (n=40, 50%) were female, and median age was 14.5 years (IQR 4–42). Seventeen cases (21%) resulted in a fatal outcome.

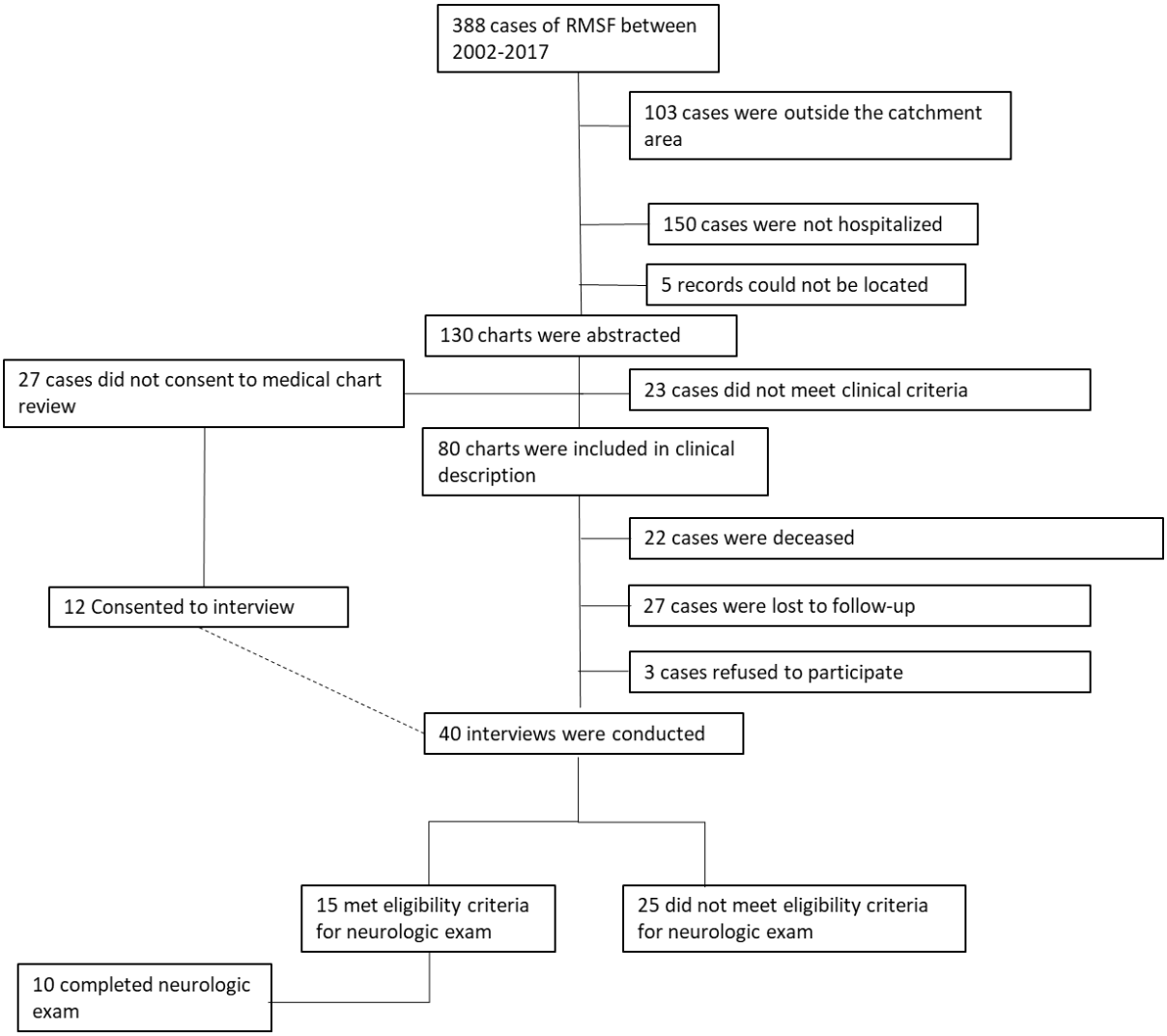


Figure 3.1: Flow diagram for study inclusion evaluating long-term neurologic sequelae following Rocky Mountain spotted fever hospitalization —Arizona, 2002–2017

Medical Chart Review

Hospitalized patients in this cohort experienced a wide range of clinical signs and symptoms, with the majority reporting fever (59%), and rash (66%) at some point during their illness; history of tick exposure was less common (31%) (Table 3.1). Sixty-one percent of cases reported illness onset July–October. Patients were hospitalized for a median of 4 days (IQR 3–7, range 1–60) with 40% requiring admission to an intensive care unit; severe illness was reported in 44% of cases. Twenty-eight (35%) individuals were discharged from the hospital with documented neurologic sequelae including weakness, pain, hearing loss, seizures, ataxia or balance problems, visual impairment, speech or swallowing dysfunction, coma, anxiety or depression. Other, less commonly reported sequelae included paresthesia, incontinence, tremors, or hyporeflexia.

Table 3.1: Characteristics of hospitalized cases of Rocky Mountain spotted fever —Arizona, 2002–2017, N=80

Variable	**N (%)**
Median age (IQR)	15 (5-42)
Female sex	40 (50)
Month of illness onset	
January–March	13 (16)
April–June	14 (17)
July–September	37 (46)
October–December	16 (20)
Median days to first doxycycline administration (IQR)	4 (2-6)
Comorbid medical condition	
Diabetes mellitus	15 (19)
Neurologic condition	13 (16)
Psychiatric illness	12 (15)
Report of tick bite	25 (31)
Rash	53 (66)
Fever	47 (59)
Admission to Intensive Care Unit	32 (40)
One or more severe signs±	35 (44)
Neurologic sequela at discharge	28 (35)
Disposition at discharge	
In-hospital death	17 (21)
Non-fatal impairment*	54 (68)
No impairment	9 (11)

±One or more of the following: evidence of shock or use of vasopressors, ARDS, multiorgan failure, renal failure, cerebral edema, coma, digital necrosis, severe thrombocytopenia (<50 $x10^3$ platelets/uL), or use of mechanical ventilation
*Based on modified Rankin score 1–5

Patient Interview

Twelve individuals consented for interview but did not approve of inclusion of their medical chart information, therefore, 40 survivors of acute infection (63%) were successfully contacted following their illness for the patient questionnaire. Most patients interviewed (62%) experienced full recovery from their disease; 15 cases (38%) reported ongoing symptoms or reduced function following their RMSF illness. The median score of self-reported functionality

on the 5-point Likert Scale following RMSF illness was significantly lower among persons reporting incomplete recovery (4, IQR 4) than among those who recovered completely (5, IQR 5) (U-test p=0.01). A score of five indicated the individual was “perfectly able to function.” Among those who reported recovering from illness, the mean time to normal function was 12.7 days (range 1–30 days).

Neurologic Exam

Fifteen individuals qualified for the neurologic exam based on interview responses. Twenty-three percent (9/40) of RMSF survivors reported symptoms or showed signs of LTS. Sequelae observed during the exam included impaired cognition, decreased deep tendon reflexes, cranial nerve dysfunction including visual impairment, weakness, abnormal gait, station and coordination, and paresthesia (Table 3.2). Additional LTS reported by patients at the time of neurologic exam included seizures, pain, photosensitivity, behavioral concerns, and fecal urgency. Median age of patients with LTS was 38 years (IQR, 4–40) at the time of illness, and clinical evaluation was a median of 6 years (IQR 1–11) following acute illness.

Bivariate analyses of severe clinical manifestations during acute disease and subsequent development of LTS produced no statistically significant associations. Three of the nine patients (33%) with LTS did not have neurologic sequelae recorded at the time of discharge. Patients with LTS had twice the odds of experiencing severe symptoms during acute illness, although this finding was not statistically significant (OR: 2.1, 95% CI, 0.5–9.0). Seizures were the most commonly reported sequela (33%) at discharge among individuals with LTS. Of the three individuals with LTS reporting seizures at discharge, two continued to experience seizures at six- and 11-years post-infection. There were statistically significant differences in modified Rankin scores at discharge among patients with LTS and those without (median 1 and 0, respectively,

U-test p= 0.03) (Table 3.3, Table 3.4). Furthermore, patients with LTS experienced significantly longer duration of hospitalization (mean 25.5 days vs 6.2 days, t-test $p<0.001$), and initiated doxycycline later than patients without LTS (6.2 days vs 4.1 days, t-test p=0.12) (Figure 3.2). In fact, patients with LTS had 19 times higher odds of initiating doxycycline after day 5 of illness (OR 19.5, 95% CI, 2.3–167.9).

Table 3. 2: Description of hospitalized cases of Rocky Mountain spotted fever with long-term sequelae — Arizona, 2002–2017, n=9

ID	Age at acute illness (years)	Time from illness onset to initiation of doxycycline (days)	Duration of inpatient stay (days)	Significant clinical findings during hospitalization*	Results of neurologic diagnostic testing during hospitalization	Sequelae at time of discharge	Time from discharge to neurologic exam (years)	Long-term sequelae
1	1	10	15	ARDS, altered mental status/encephalopathy, mechanical ventilation, DIC, petechial rash, cerebral infarcts	MRI: Punctate infarcts in inferior cerebellum and focal lesions in corpus callosum	Disorientation/altered mental status, hearing loss, visual impairment, seizures, dysarthria, dysphagia, weakness, tremors, ataxia, reported decline in function	6	Altered mental status (E); dysphagia (E); decreased muscle tone in extremities (E); MoCA unable to be assessed, but grossly impaired in all domains (E); seizures (S); behavioral concerns (S)
2	54	8	12	Diffuse macular rash	None performed	Weakness and numbness	1	Impaired cognitive function with challenges in abstraction, recall and language (M); slow motor finger taps and foot taps (E); decreased reflexes (E); positive Babinski (E); fatigue (S)
3	57	2	4	Systemic inflammatory response syndrome	None performed	None	5	Impaired cognitive function with challenges in language, attention and abstraction (M); decreased visual acuity (E); decreased reflexes in upper extremities and absent in lower extremities (E)
4	1	5	7	Organ failure, coma, altered mental status, shock, severe thrombocytopenia, papular rash, mechanical ventilation, global encephalopathy	CT: Normal EEG: global encephalopathy (diffuse slowing and disorganization)	Seizures	10	Language impairment (M); abnormal visual acuity (E); decreased upper extremity reflexes (E); pain (S); delayed developmental milestones (S)
5	4	6	1	Diffuse maculopapular rash	None performed	None	1	MoCA unable to be assessed, attention issues (E,S); difficulties with problem solving compared to level expected for age (E); non-aphasic, non-

								dysphasic speech issues (E, S)
6	39	5	7	Petechial rash	None performed	None	11	Paresthesia and numbness in lower and upper extremities (E); decreased reflexes in upper extremities and absent in lower extremities (E); fatigue (S); imbalance (S); fecal urgency (S)
7	40	5	4	Maculopapular rash, frontal cerebral infarcts	MRI: Punctate infarcts in peduncular and frontal white matter	None	1	Decreased reflexes (E); pain (S); photosensitivity (S)
8	4	5	60	Sepsis, ARDS, renal insufficiency, multiorgan failure, DIC, petechial rash, mechanical ventilation, cerebral atrophy	Multiple MRIs: Progressive cerebral atrophy.	Dysarthria, Dysphagia, seizures, ataxia	11	Significantly impaired cognition (limited attention, language, recall and executive functions) (M); decreased reflexes bilaterally (E); bilateral weakness (E); expressive and receptive aphasia (E); decreased visual acuity (E); slow finger taps and foot taps (E); seizures (S)
9	39	11	7	Renal insufficiency, altered mental status, petechial rash	CT: Normal	Visual and auditory changes not specified	11	Abnormal language and recall (M); altered mental status (E); decreased visual acuity (E); decreased auditory function (cranial nerve VIII impairment) (E); unilateral numbness (E); absent and decreased reflexes (E); abnormal station (E); positive Romberg (E)

*Excluding comorbidities prior to RMSF
†Unclear speech, but not aphasic, some delays prior to RMSF, but family noted decline following RMSF
(S) self-reported finding
(E) clinical finding based on neurologic exam
(M) abnormal MoCA result

ARDS: Acute Respiratory Distress Syndrome
CT: Computed Tomography Scan
DIC: Disseminated Intravascular Coagulation
EEG: Electroencephalogram
MoCA: Montreal Cognitive Assessment
MRI: Magnetic Resonance Imaging

Table 3.3: Clinical findings during hospitalization for Rocky Mountain spotted fever cases with and without long-term sequelae — Arizona, 2002–2017, n=73

	Long-term sequelae N=9	No long-term sequelae n=64	P-value
Non-neurologic			
Shock or vasopressor use	1 (11)	6 (11)	0.25
Acute Respiratory Distress Syndrome	2 (22)	5 (6)	0.14
Multiorgan failure	2 (22)	6 (11)	0.31
Renal insufficiency	2 (22)	8 (15)	0.62
Necrosis	0 (0)	2 (4)	1
Severe thrombocytopenia	2 (22)	9 (16)	0.65
Rash	8 (89)	34 (62)	0.15
Supportive care procedures			
Transfusion	2 (22)	4 (7)	0.2
Hemodialysis	0 (0)	2 (4)	1
Amputation	0 (0)	0 (0)	-
Mechanical ventilation	3 (33)	6 (11)	0.11
Neurologic			
Coma	1 (11)	2 (4)	0.37
Mental status change†	3 (33)	16 (20)	0.39
Cerebral edema	0 (0)	1 (2)	1
Any neurological sequelae at discharge	6 (67)	21 (38)	0.43
Any severe signs±	4 (44)	15 (27)	0.24
Modified Rankin score (median, IQR)	1 (1)	0 (0—1)	0.07

†As reported from family or documented by medical staff at admission or during hospitalization
±One or more of the following: evidence of shock or use of vasopressors, ARDS, multiorgan failure, renal failure, cerebral edema, coma, digital necrosis, severe thrombocytopenia (<50 x10^3 platelets/uL), or use of mechanical ventilation
*Statistically significant finding

Table 3.4: Characterization of neurologic findings observed during exam among individuals with long-term sequelae — Arizona, 2002–2017, n=9

	Frequency abnormal*	Notes on abnormal findings
Mental status (MoCA)±	6/7 (86%)	Mean score=19.1, SD 6.7
Modified Rankin scale at exam†	7/9 (78%)	Median score=1, IQR 1, range 1—3
Reflexes	8/9 (89%)	Most had decreased deep tendon reflexes, one patient with hyperreflexia
Cranial nerve function	4/7 (57%)	CNII was most frequently affected showing decreased visual acuity. Facial sensory deficits (CN V), and hearing loss (CN VIII) were also noted. One additional individual couldn't be formally assessed for all cranial nerve function but had clear dysarthria.
Strength	4/7 (57%)	Reduced strength in the 3–4/5 range; all results were bilateral
Gait and station	3/9 (33%)	Wide-based gait or inability to walk on toes were the most common findings
Motor function	3/9 (33%)	Two patients experienced bilateral slowing of finger taps, one showed decreased tone in upper and lower extremities
Coordination	2/8 (25%)	Bilateral dysmetria on upper extremity past-pointing
Sensory function	2/9 (22%)	Numbness and paresthesia were reported
Language	1/9 (11%)	Receptive and expressive aphasia

*Formal assessment of function could not be performed in some cases due to age and cooperation of patient. Unless otherwise noted, those not formally assessed were deemed to be grossly normal by the assessing physician
±Normative value for MoCA is 26
†Normative value for modified Rankin is 0

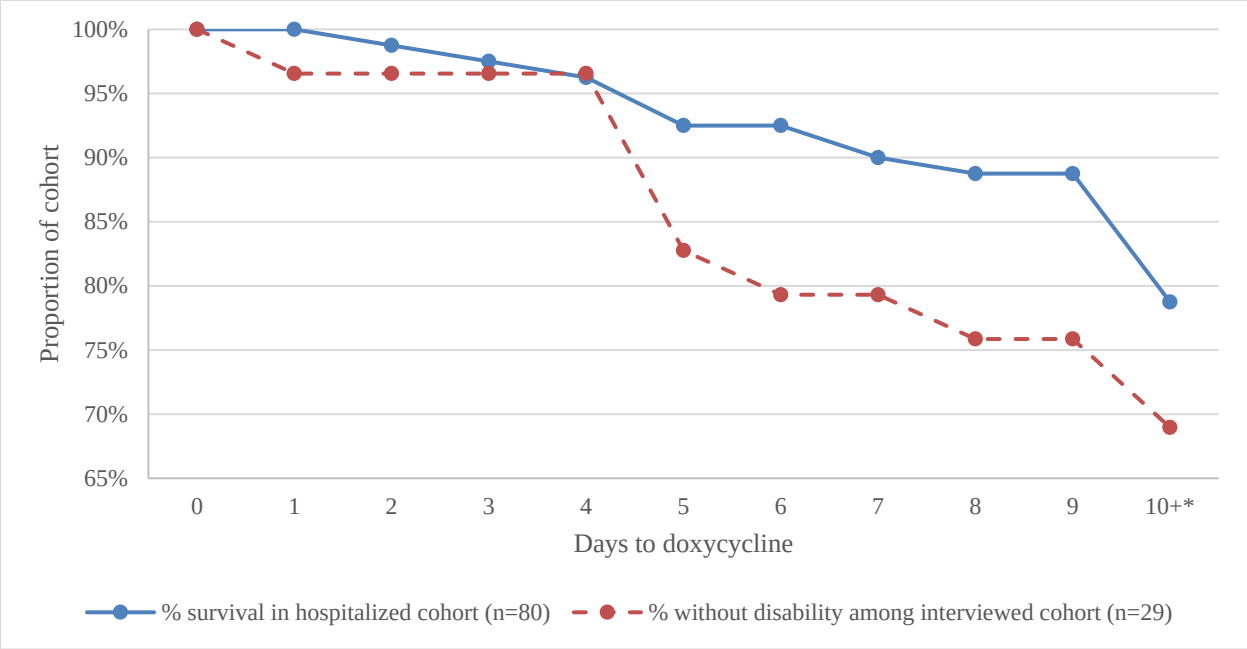


Figure 3.2. Survival curve for death and disability among Rocky Mountain spotted fever cases — Arizona, 2002–2017

±Includes only cases where medical charts were available

*Includes those who never received doxycycline

DISCUSSION

Acute Disease Findings

Our findings provide further evidence of the severe and fatal nature of RMSF. The case fatality rate (CFR) was 21% in our cohort, which is higher than the estimated 5–10% for the United States (Biggs et al., 2016). However, since we included only hospitalized cases, it is likely we captured those with more severe disease. The clinical descriptions of RMSF cases were similar to what has been reported in previous summaries from Arizona (Regan et al., 2015; Traeger et al., 2015). Younger populations were heavily impacted in this cohort (nearly 44% of cases were among children < 10 years of age). Rash was the most frequently clinical sign (67%) and was similar to previous studies [68%, (Traeger et al., 2015)], though in a lower proportion

than is reported nationally (88-97%) (Buckingham et al., 2007; Helmick et al., 1984). Fever was reported in less than 60% of cases, which is the lowest proportion in the published literature and lower than was reported in the previous Arizona study (81%) (Traeger et al., 2015). Advanced illness with hypothermia at the time of first presentation may account for absence of fever in some cases as well as numerous accounts of antipyretic use at first visit. History of tick bite was infrequently reported (31%) in this cohort; lower than national reports (49-60%) and the previous Arizona study (55%) (Buckingham et al., 2007; Helmick et al., 1984; Traeger et al., 2015). Compared with the previous literature (15%), this study reports a profoundly higher proportion (35%) of individuals with neurologic sequelae at the time of discharge (Buckingham et al., 2007).

Recovery and Long-term Sequelae

Nearly half of the surviving individuals agreed to participate in the patient survey, providing key insight into disease recovery. Most patients reported full recovery with a mean time of 12 days to normal function. While time to defervesence and discharge have been previously reported, to our knowledge this is the first report on time to disease recovery. A substantial proportion (23%) of individuals had evidence of long-term sequelae from RMSF based on neurologic exam and reported neurologic symptoms. These estimates are consistent with previous studies on neurologic sequelae following RMSF (5–56%), and represent the largest and most complete evaluation of LTS (Archibald & Sexton, 1995; Berlin & Thomas, 1948; Gorman et al., 1981; Rosenblum et al., 1952). Although a wide range of ages experienced long-term sequelae, the median age of at first illness among individuals with long-term sequelae (38 years) is significantly older than the median age of the overall hospitalized cohort (15 years). Cognitive impairments occurred frequently (86%), with the most impairment reported in areas of

recall, language, and attention. Other common LTS included decreased deep tendon reflexes, decreased motor function, visual impairments and other cranial nerve dysfunction, weakness, changes to gait and station, and report of seizure activity. Paresthesias, language impairments, and abnormal coordination were reported, but less frequent.

Predictors of Long-term Sequelae

Individual clinical findings during hospitalization, presence of one or more elements of severe disease, and presence of neurologic sequelae at discharge were not significantly predictive of the development of LTS. Our ability to identify statistically significant predictors of LTS may, however, be limited by the small sample size of individuals with LTS. Delay in doxycycline administration is the strongest predictor of LTS. Survival analysis demonstrates an increase in adverse outcome (death or disability) if treatment is delayed. Further, patients receiving doxycycline after day five of illness were significantly more likely to experience LTS and death. Increased morbidity and mortality following a delay in treatment past five days defines a critical time period, consistent with previous literature (Holman et al., 2001b; Regan et al., 2015). Furthermore, the curve showing frequency of individuals with disability showed a steep decline once treatment was delayed past day 4 of illness onset, whereas mortality lagged by 1–2 days. This suggests a critical window where treatment delay may not cause death but can contribute substantially to disability and decreased functional outcome. Patients with LTS also experienced longer hospitalizations and were discharged with significantly more disability as denoted by the modified Rankin exam.

Many of the cases with documented LTS did not have reported neurologic sequelae at the time of discharge. This disconnect with disposition at the time of discharge with ultimate development of neurologic sequelae were previously documented (Rosenblum et al., 1952).

Researchers theorized that neurologic damage was possible even in patients not experiencing severe illness or that sequelae were subclinical at the time of discharge, so development of neurologic sequelae following RMSF should not be ruled out solely based on discharge status. Neurologic imaging can be a helpful adjunct in the assessment of patients with RMSF, however, a thorough exam at discharge is equally valuable in identifying deficits and disability that may benefit from rehabilitation. If sequelae are identified at the time of discharge, supportive and rehabilitative care can be initiated to improve function.

LIMITATIONS

This study relies on convenience sampling RMSF patients; while not externally valid, this cohort is the largest group of patients with RMSF known in the United States and provides substantial evidence of severe disability following RMSF. Focus on hospitalized cases allowed us to ensure true illness with RMSF and not background seropositivity, but oversamples severe cases, which may bias our estimates of frequency of LTS. Medical chart abstractions represent secondary reviews of information collected at the time of illness; the quality and completeness of records was highly variable. Neurologic exams were also subject to several biases. Although largely objective, neurologic exams may be subject to some inter-rater differences; we attempted to reduce that variability by having only three physicians conduct exams, and all were trained and supervised by a single board-certified neurologist. MoCA assessments are validated for English-speaking populations in individuals 8 years and older. All participants were offered the use of a certified health translator into their Native dialect. No individuals used this option, however, MoCA results may have been impacted by the administration of the test in their non-primary language (Hu et al., 2013). Finally, while effort was made to identify intervening

neurologic diagnoses during the patient survey, we are unable to rule out the contributions of other more common causes of neurologic impairment, such as uncontrolled diabetes mellitus.

CONCLUSION

RMSF is a deadly and debilitating illness. While most individuals with severe RMSF experience complete recovery in 1 to 2 weeks following illness, roughly one in four patients may experience persistent, or even permanent neurologic sequelae. We documented neurologic sequelae up to 11 years following acute disease. While most of the patients with LTS had one or more neurologic sequelae at discharge from their acute hospitalization, we also identified patients with LTS that were not appreciated to have deficits at time of discharge. This study provides the most comprehensive description of long-term neurologic sequelae following severe RMSF to date. While we are unable to attribute a specific cause of neurologic sequelae, we demonstrate that specific neurologic impairments, such as seizures, cognitive impairment, weakness, and damages to specific cranial nerves are consistently found in patients recovering from severe RMSF. Such results provide important and actionable information for patients, families, and healthcare providers in areas endemic for RMSF. Like patient recovery from other neurologic insults, such as stroke, patients who have been treated for severe RMSF would benefit from a complete neurologic examination at the time of discharge and potential use of neuroimaging studies to identify acute and sub-acute neurologic injury. Anticipation and early identification of neurologic injury can direct the use of rehabilitative services such as physical, behavioral and occupational therapy in the months and years following acute disease to improve outcomes. Recognizing the full burden of RMSF can assist affected communities regarding planning, prevention, and outreach.

CHAPTER 4

THE BURDEN OF ROCKY MOUNTINA POSTTED FEVER IN ARIZONA TRIBAL COMMUNITIES[2]

[2] Drexler et al. To be submitted to the *American Journal of Public Health.*

ABSTRACT

Objective: Tribal communities in Arizona are now surpassing 15 years of hyperendemic rates of the deadly tickborne disease Rocky Mountain spotted fever (RMSF). Medical and indirect costs have been estimated, but do not account for long-term healthcare or disability implications for tribal communities.

Methods: Costs associated with hospitalization among an Arizona cohort were estimated from flat-rate charges billed from the Indian Health Service to Medicaid. Costs were then compared to two national datasets (MarketScan and the Healthcare Cost and Utilization Project, National Inpatient Survey). Total burden of disease was estimated using disability-adjusted life years (DALYs) lost to account for the compounded effects of morbidity and mortality.

Results: Direct costs of RMSF hospitalizations were estimated between $16,894–$25,573 per case using the three data sources. Direct cost increased by length of stay with costs increasing $4,200–$6,300 per day. More than 500 years of healthy life have been lost from RMSF between 2002–2017 in two communities, with nearly two-thirds (66%) contributed by individuals 14 years or younger.

Conclusions: RMSF may have a greater impact on Arizona tribal communities than was previously recognized. Effective prevention programs have been identified and could be further prioritized to avert preventable death and disability in tribal communities.

INTRODUCTION

Rocky Mountain spotted fever (RMSF) is a severe and potentially fatal tickborne disease caused by the bacterium *Rickettsia rickettsii*. RMSF is a rapidly progressing illness that begins with non-specific symptoms such as fever, headache, and body aches. Without early treatment,

the disease then progresses to a severe, systemic infection potentially causing organ failure, digital necrosis, and death (Biggs et al., 2016). Patients who are not treated early, with the antibiotic doxycycline, are more likely to require hospitalization, intensive care treatment, and have an increased risk of death from RMSF (Regan et al., 2015). Roughly half of RMSF cases are hospitalized, and up to 25% of cases result in a fatal outcome (Álvarez-Hernández et al., 2017; Dalton et al., 1995). RMSF is relatively uncommon in the United States, with sporadic cases occurring nationally (Drexler et al., 2016). However, since 2002, epidemic rates of RMSF have been reported in American Indian communities of Arizona (Demma et al., 2005). Recent studies have identified increasing incidence of RMSF among American Indians in the southwest from nearly zero in 2001 to more than 115 per million persons in 2008 indicating an alarming issue of public health importance (Folkema et al., 2012).

Economic estimations are a tool used to evaluate the impact of potentially serious public health issues and allow for the prioritization of limited resources. Costs of RMSF have been described in previous publications relating to the epidemic of RMSF in Arizona, documenting more than $13.1 million in acute medical costs, productivity lost during acute illness, and lifetime productivity lost from premature death (Drexler et al., 2015). However, these previous estimates do not address long-term health costs and disability indicators, so the full economic impact is likely to be far higher. Moreover, disease burden is not only felt in dollars and cents of direct medical costs but are also felt in the lives lost and years of healthy life deprived by preventable disease. Disability-adjusted life years (DALYs) lost are a commonly used economic estimate which combines loss of life and time lost due to disability into a single metric. These metrics can then be compared across multiple diseases and issues of public health and safety. This manuscript is designed to estimate the full economic and social impact of RMSF using

DALYs and facilitate prioritization of public health concerns in Arizona tribal communities. Integrated prevention programs have been proven to be an effective means of reducing RMSF cases and deaths, however, they are resource intensive (Alvarez-Hernandez et al., 2019; Drexler et al., 2014). Analysis of disease burden can help affected communities weigh the benefits and disadvantages of intensive prevention efforts for their respective communities.

METHODS

The economic analysis described herein represents a cohort of individuals with severe RMSF requiring hospitalization from two tribal communities during 2002–2017. Medical records of eighty cases were described in chapter 3 of this dissertation. As with previous studies looking at the economic impact of RMSF in this epidemic, acute medical costs were estimated by summing enumerated healthcare days for the patient population (Drexler et al., 2015). Healthcare days were stratified by type of healthcare visit (outpatient visits, emergency room visits, inpatient days and days in step-down facilities). Flat-rate charges billed to Medicaid were applied for each visit-type using 2017 Indian Health Service (IHS) reimbursement values for the lower 48 states (Folwer, Elizabeth, 2017). This study additionally accounts for costs of long-term care facilities and referrals for rehabilitation based on costs estimated by the Arizona Healthcare Cost Containment System (AHCCCS) fee-for-service rates as of October 1, 2017 (Arizona Healthcare Cost Containment System, n.d.). Direct medical costs are described by length of stay and day of illness on which doxycycline was first administered. See supplemental material 1 for detailed statistical appendix.

Total direct costs per patient for the Arizona cohort were compared to national medical billing data from two sources: the Healthcare Cost and Utilization Project (HCUP) using the National Inpatient Survey (NIS) and MarketScan® (Truven) inpatient database. HCUP is a

nationally representative database of clinical encounters including individuals with public insurance (Medicare, Medicaid), some private insurance providers, as well as uninsured individuals. NIS is a stratified subsample, representing roughly 20% of inpatient visits at community hospitals, it does not include Veterans Affairs or Indian Health Service hospital data. MarketScan uses medical billing data from large employer-sponsored health programs and Medicare supplemental programs. Both datasets are based on the International Classification of Disease (ICD)-9 or ICD-10 codes. Average cost of care is described for sample populations listing ICD-9 or ICD-10 codes for RMSF (082.0 and A77.0) up to 30 days post discharge. Mean and total costs were calculated for each data source for all data years, differences in the mean are assessed using analysis of variance (ANOVA), and differences in proportions are compared using chi-square statistics. Significance was assessed at $p<0.05$.

Disability-adjusted life years (DALYs) were calculated by summing the number of years lost due to death (YLL), with the number of healthy years lost due to disability (YLD) (DALY=YLL+YLD) (Murray, 1994). YLL reflects the difference between age at death and the average life expectancy of American Indian populations in Arizona and multiplies this value by the annual mortality rate in the United States (U.S. Census Bureau, 2010). YLD is calculated by the incident number of cases with a certain disability multiplied by the disability weight. DALY estimates for RMSF were calculated using severity indicators from the study of long-term sequelae (chapter 3) as detailed in the outcome tree in Figure 4.1. Disability weights were based on those listed by WHO (Salomon et al., 2012). Since there were no direct indicators of RMSF illness provided by WHO we used selected disability weights to serve as proxies, Table 4.1. Stroke with persistent deficits was used as a model for long-term neurologic damage from RMSF. Uncomplicated RMSF, not requiring hospitalization was considered a moderate acute

infection. Incidence and duration for each potential outcome of RMSF are based on data presented in the original study of long-term sequelae presented in chapter 3. DALYs were calculated using a 3% discount rate and standard age-weighting (β=0.04, C=0.1658) using the DALY calculation worksheet provided by WHO (Colin Mathers, 2001), see statistical appendix for further detail.

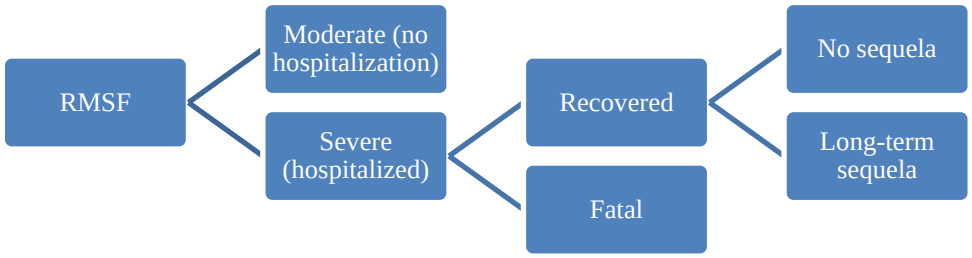


Figure 4.1: Possible outcomes of hospitalized cases of RMSF used in calculating disability-adjusted life years lost

Table 4.1 Disability measures for calculating years of life disabled

Outcome	**Cumulative incidence (per 1000)***	**Disability weight proxy**	**Disability weight used**	**Duration (years)**
Moderate illness (non-hospitalized)	6.39	Infectious disease: acute episode, moderate 0・053 (0・033–0・081)	0.053	0.08†
Severe illness (hospitalized) no LTS	2.30	Infectious disease: acute episode, severe 0・210 (0・139–0・298)	0.210	0.03*
Severe illness (hospitalized) with LTS	0.38	Stroke: long-term consequences, moderate plus cognition problems (0.312 (0.211-0.433))	0.426	10*

*Based on LTS study presented in chapter 3
†Based on Drexler et al. 2015

Data from HCUP and MarketScan were analyzed using SAS 9.4 (Cary, NC), and DALY calculations were tabulated in Microsoft Excel. Economic analysis using secondary data and publicly available data were not considered human subjects research and were not subject to review by an institutional review board. The original study of long-term sequelae was approved by institutional review boards of the Centers for Disease Control and Prevention, Arizona Department of Health Services, IHS, University of Georgia, and received tribal council approvals.

RESULTS

Direct Costs

During 2003–2017 there were 1,392 discharges listing ICD codes for RMSF from the MarketScan dataset and 3,373 discharges among individuals in the NIS sample. Eighty cases were reviewed from the long-term sequelae study with 25 outpatient visits, 118 ER visits, 348 general admission days, 161 ICU days, and 90 step-down days and 300 occupational, physical or speech therapy days (based on fulfillment of 30-day referrals per patient). Direct costs associated with hospitalized cases in the Arizona epidemic are estimated to be more than $2 million (average cost per patient $24,885) with substantial contributions from general admission and intensive care days as well as time in step-down facilities for severely ill patients. National estimates of direct medical costs from MarketScan and HCUP databases produced comparable estimates of direct cost per patient among hospitalized patients with estimates of $16,894 per case and $25,573 per case, respectively, Table 4.2. Demographic characterization of RMSF cases from the two national sources were similar in terms of sex composition, and disposition at discharge (X^2 $p<0.05$). While there was a statistically significant difference between the mean

values from all three samples in terms of cost ($F=16.59$, $p<0.0001$), length of stay ($F=6.22$, $p=0.002$), and age ($F=44.79$, $p<0.0001$), the values demonstrate similar overall trends in costs of disease. Limited clinical data were available for national datasets, however total cost by average length of stay was able to be plotted, demonstrating that costs incrementally increased by length of stay and were consistent among the three data sources. For each additional day of hospitalization, there were more than $4,200 in additional direct costs in the Arizona cohort ($R^2 = 0.951$), more than $5,300 in MarketScan ($R^2 = 0.5559$) and more than $6,300 in HCUP ($R^2 =0.5889$). Additionally, total cost by day of doxycycline administration was assessed for the Arizona cohort (data not available in national datasets). While this comparison led to a general observation of increased cost per day of delayed doxycycline, this model had poor fit ($R^2 = 0.0171$) to the data and could not be used to reliably predict direct medical expenditure indicating that there may be additional factors influencing the cost of disease severity secondary to delayed treatment.

Table 4.2: Estimated direct medical costs of hospitalized cases of RMSF cases from three sources

	MarketScan	**HCUP***	**Arizona cohort**
Date range	2003–2017	2002–2016	2002–2017
Number of cases	1392	3373	80
Female	521 (37.4%)	1297 (38.5%)	40 (50%)
Age			
Mean age in years (SD)†	37.2 (19.4)	42.4 (23.7)	25.0 (23.0)
Age less than or equal to 10 years±	182 (13.1%)	438 (13.0%)	37 (46.3%)
Length of Stay			
Mean length of stay in days (SD)†	4.4 (6.0)	4.9 (6.0)	6.4 (8.0)
Cost			
Mean total cost per person (SD)†	$16,894 ($42,736)	$25,573 ($49,411)	$24,885 ($34,862)
Total cost observed per data source	$23,516,448	$86,257,729	$1,990,800
Discharge status after first admission			
Home	1173 (84.3%)	2879 (85.4%)	59 (73.8%)
Died	2 (0.2%)	23 (0.7%)	17 (21.3%)
Transfer to SNF or other facility	42 (3.0%)	186 (5.5%)	4 (5.0%)
Home health service	36 (2.6%)	157 (4.7%)	-
Readmissions**	42 (3.0%)	111 (3.3%)	-
Other	2 (0.2%)	15 (0.4%)	-
Unknown	95 (6.8%)	2 (0.05%)	-

*Represents unweighted data only representative of survey results, not national estimates
†Statistically significant difference in the means using ANOVA
±Statistically significant difference among proportions using Chi square
**Readmission within 30 days of original admission

Disease Incidence and Recovery

During 2002–2017 there were 285 cases of RMSF reported from two Arizona tribal communities. In a recent study, 80 hospitalized cases were described, of those 17 died, nine

developed long-term sequelae, and 54 recovered from their illness (chapter 3). Duration of morbidity for non-hospitalized cases was estimated to be 4 days for recovery as used in previous descriptions for non-complicated illness (Drexler et al., 2015). Duration of morbidity for severe, hospitalized cases without long-term sequelae are based on self-reported time to recovery (12.7 days) (chapter 3). Duration of long-term sequelae are based on current time to evaluation (up to 11 years), although actual duration of sequelae may be lifelong.

Disability-adjusted Life Years Lost

Total impact of disease using the baseline model of DALYs lost estimated a total of 22 DALYs per 1000 persons, totaling more than 516 years of healthy life lost from RMSF in two tribal communities between 2002–2017. DALYs were evenly split among men and women. Young individuals were heavy contributors to the overall DALY burden with nearly two-thirds (66%) in persons less than 14 years of age. Much of the total disease burden (93%) result from years of life lost from premature death, with some contributions (6%) coming from the long-term sequelae and negligible contributions from non-morbid illness, Figure 4.2. Average annual DALY calculations from RMSF for these two tribal communities is estimated to be 1.4 DALYs lost per 1,000 persons.

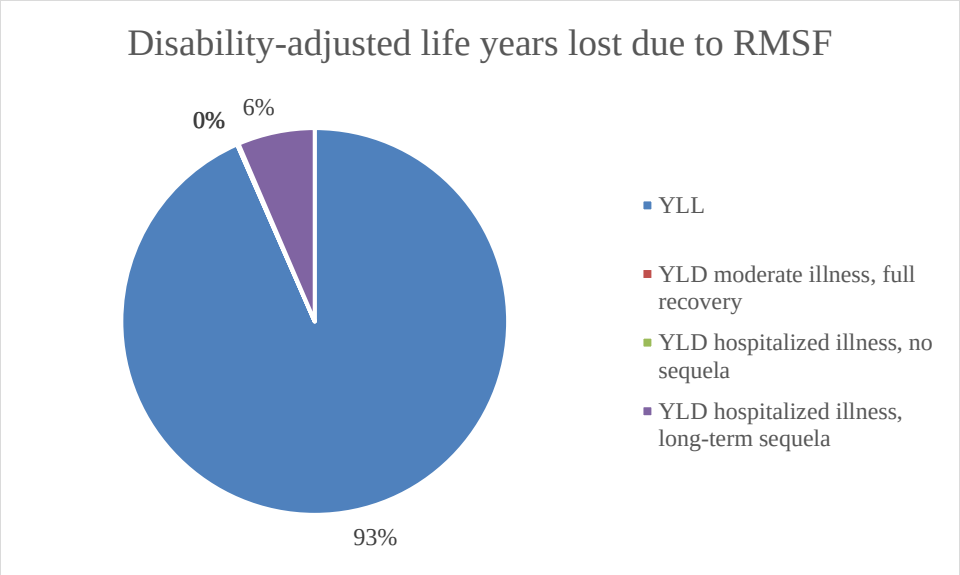


Figure 4.2: Contributions to disability-adjusted life years lost due to RMSF, Arizona 2002–2017

DISCUSSION

The results of this study demonstrate high direct costs related to RMSF hospitalizations in local and national samples. Direct cost per case using large, national databases produced estimates that were consistent with the flat-rate charges of the Arizona cohort indicating that economic burden calculated from Arizona surveys are reasonably representative of the average cost per case throughout the United States. The two national databases showed consistent estimates of length of hospitalization and disposition at discharge compared to one another, however, the Arizona cohort is notably more severe in their makeup with a higher proportion of cases with fatal outcome, and an overall longer mean length of stay. The Arizona cohort was also far younger than the national samples (mean age 25.4 years, compared to 37.2 and 42.4 for MarketScan and HCUP respectively) meaning that Arizona tribal communities may sustain larger indirect costs from heavy RMSF impact in the younger, more productive ages. Disease severity indicators, such as mortality and hospitalization rates, obtained from national surveillance are typically lower than those noted in Arizona as they are often include records of

less severe rickettsioses (such as *Rickettsia parkeri* rickettsiosis), whereas we believe all rickettsioses occurring in Arizona tribal communities represent true RMSF (Drexler et al., 2016). Thus, we believe the direct costs per case in Arizona likely is more indicative of economic burden for RMSF specifically.

We assessed overall disease burden using DALYs to account for the effects of morbidity and mortality. Total disease burden of RMSF in two tribal communities was 22 DALYs per 1,000 persons, totaling 516 DALYs for cases during 2002–2017. This means more than 500 years of healthy life lost due to preventable disease. To our knowledge, this is the first estimate of RMSF burden using DALYs and the first economic analysis to include disability contributions. This estimate demonstrates heavy contributions of premature mortality from this epidemic; while DALYs from long-term sequelae contributed less to overall DALYs, this morbidity may be substantially increased if the duration of sequelae proves to be lifelong. Comparable estimates of disease burden for these two specific communities have not been made for other infectious and non-infectious causes, however, DALY estimates in the United States were estimated by McKenna and colleagues and stratified by race (McKenna et al., 2005). All-cause DALY loss during 1996 among Native Americans was roughly 295,000 DALYs nationally, the equivalent of 766 DALYs per 1,000 population (McKenna et al., 2005). According to McKenna and colleagues, diabetes mellitus contributes an estimated 9,100 DALYs annually (23.6 DALYs/1,000 persons per year). While not directly comparable, if these rates and disability contributions applied to our two tribal communities, it would implicate RMSF as a substantial public health issue and an underappreciated contributor to local morbidity and mortality.

This cost analysis is subject to several limitations. First, direct cost estimates from Arizona are based on flat-rate charges by visit type, rather than direct billing information. The close estimation of costs from national samples, however, indicates that little is lost by use of this crude technique. RMSF cases in national databases were identified using ICD codes consistent with RMSF regardless of their ranking in diagnostic criteria; numerous codes could be listed for any hospitalization and inclusion does not indicate that RMSF was the primary reason for hospitalization. Next, key indicators for DALY calculations are based on estimates from a small portion of the population in the study of long-term sequelae and may not reflect actual rates of disease or disability. Finally, disability weights are based on a survey of healthcare providers in 14 countries and do not reflect self-reported impact of disability on persons suffering from such morbidities (Arnesen & Nord, 1999; Salomon et al., 2012). Such surveys have not, to our knowledge, been undertaken in Native American communities to describe the relative value of health and disability. Therefore, assumptions of relative cost of disability may not be appropriate to local priorities. Due to the use of local incidence data, the result of DALY calculations are not likely to be representative of the RMSF burden nationally. Instead, these values should be used by local policy makers in prioritizing health resources.

PUBLIC HEALTH IMPLICATIONS

American Indians across the United States have documented lower life expectancy and higher prevalence of chronic and infectious conditions (Arias et al., 2014; Barnes et al., 2010; Cobb et al., 2014; Jones, 2006). Burdens of reportable diseases are routinely reported in national surveillance reports; however, the incidence of disease rarely represents the true cost to individual communities. We observe substantial disease burden from direct medical expenses and disability-adjusted life years lost in Arizona tribal communities from RMSF. Clear

identification of RMSF as an issue of public health concern can direct the prioritization of key prevention measures. RMSF is a preventable disease in hyperendemic settings, such as those in Arizona tribal communities. Evidence-based prevention strategies have been identified through community-based studies and include community-wide treatment of dogs, education, and acaricidal product administration (Drexler et al., 2014). However, such activities are resource intensive. The findings of this study should serve as a resource to local health policy makers to understand the true cost of disease to tribal communities and evaluate if costly prevention practices are worth investment.

CHAPTER 5

CONCLUSIONS AND PUBLIC HEALTH IMPLICATIONS

INTRODUCTION

This chapter presents a summary of the combined findings of chapters 3 and 4, and addresses the implications for public health professionals, policy makers, and communities for the betterment of health and wellness of people in Indian country. Evidence from these Arizona-based studies will be placed into the context of the larger public health problem surrounding Rocky Mountain spotted fever (RMSF) in Arizona tribal lands. The final chapter will further reflect on how these results might impact the treatment and management of RMSF throughout the world. Finally, the dissertation will conclude with discussions of limitations and recommendations for future studies.

SUMMARY OF FINDINGS

Certain Arizona tribal communities have experienced epidemic levels of RMSF since 2002, with an incidence 150 times higher than the national average (Drexler et al., 2014). While still not common, this disease has had an undoubtable impact on communities resulting in high rates of death and disability. Infection with *Rickettsia rickettsii*, the bacteria that causes RMSF, results in the sudden onset of rapidly progressing disease starting with fever and headache, and progressing to systemic illness, organ failure, and eventually death (Biggs et al., 2016). RMSF can be difficult to diagnose in its early stages due to the predominance of non-specific signs and symptoms and lack of sensitive rapid diagnostic testing. Yet evidence in the peer-reviewed literature clearly shows early administration of antibiotic therapy is critical for the prevention of

morbidity and mortality, requiring healthcare providers to act quickly (Holman et al., 2001a; Masters et al., 2003; Traeger et al., 2015). Delay in diagnosis and treatment can result in death and severe illness in a matter of days. Long-term disability and impact on quality of life have largely been unexplored and therefore do not currently factor into clinical and policy decision making. The purpose of this dissertation is to provide evidence of the long-term neurologic sequelae following severe RMSF illness and discuss the potential economic and social costs of disease resulting from delayed treatment.

The study presented in chapter 3 identified the occurrence of neurologic sequelae following RMSF infection in nearly a quarter of the surviving population. Among the 40 patients that were able to be contacted following their acute disease recovery, nine showed signs of neurological dysfunction including cognitive disruption, weakness, abnormal reflexes and motor function, hearing and vision loss, seizures, and paresthesias. Such disabling factors were identified up to 11 years following acute RMSF illness and may, in-fact, be permanent. On average, patients that recovered from RMSF reported a return to normal function 12.7 days following hospital discharge, indicating a longer period of convalescence than was previously reported. Thus, even individuals that experience a full recovery may have longer indirect effects (inability to resume work, school, or daily function as a result of their illness) than previously described. No individual clinical signs during acute illness were predictive of neurologic sequelae; in fact, this study identified that a third of patients with long-term sequelae (LTS) had no neurologic impairment at discharge following acute RMSF. This indicates that some disability may be subclinical during early convalescence, making close follow-up of patients important. Overall, this study provides strong evidence of neurologic sequelae following severe RMSF, describes a range of neurologic consequences, and highlights the potential longevity of

resulting disability. The degree of disability and impact on general productivity varied by individual, with some reporting an inability to return to work, difficulties in school, and diminished life quality. Such impacts on life-quality, using patient-centered indicators have not been previously described for RMSF and point to a larger societal impact of the disease.

In order to better quantify the true burden of this devastating, but preventable disease the authors undertook an economic description of the medical costs associated with treatment as well as the disability-adjusted life years (DALY) lost from disease. While economic analysis cannot truly measure the impact of disease on a population, it is a commonly used technique for policy makers to evaluate the relative costs and consequences of disease. Medical and indirect costs of RMSF from acute and fatal disease were previously estimated to cost $13.1 million in Arizona tribal communities between 2002–2011 (Drexler et al., 2015). Such numbers already describe the enormous economic burden placed on communities impacted by RMSF in terms of medical expenses and potential life lost. Additional calculations presented in chapter 4 address the possible contributions of disability and long-term care. Long-term direct care costs relate to follow-up visits; outpatient physical, occupational and speech therapy; behavioral therapy; and care provided in step-down facilities following RMSF hospitalization. Mean direct healthcare costs were estimated to be roughly $24,885 per Arizona case during 2002–2017. Similar estimates per case were obtained using national inpatient databases and direct medical billing information, showing that the per capita impact experienced in the Arizona cohort may be reflective of the cost of RMSF nationally.

To compare the relative burden of disease including morbidity and mortality, DALYs were calculated. Using data collected in the hospitalized Arizona cohort described in chapter 3, an estimated 516 DALYs were lost from RMSF in two tribal communities between 2002–2017.

When compared to national disease burden estimates among Native Americans, RMSF would rank as the second highest health impact after alcohol use (McKenna et al., 2005). Such descriptions show RMSF to be a major contributor to preventable morbidity and mortality in Arizona tribal communities.

IMPLICATIONS OF RESEARCH FINDINGS

Research outlined within this dissertation are assessed in terms of overall health impact for RMSF in Arizona tribal communities using the Frieden Health Impact Pyramid developed by former CDC Director Thomas Frieden, Figure 5.1 (2010). This framework outlines tiers of interventions contrasting the potential impact to disease incidence, as well as the tradeoff costs from intensive activities. RMSF in Arizona is a multi-faceted issue requiring a coordination of interdisciplinary action at every level of the health impact framework. Using this framework, evidence based RMSF prevention activities are described in terms of their impact and relative cost including developments identified in chapters 3 and 4 of this dissertation.

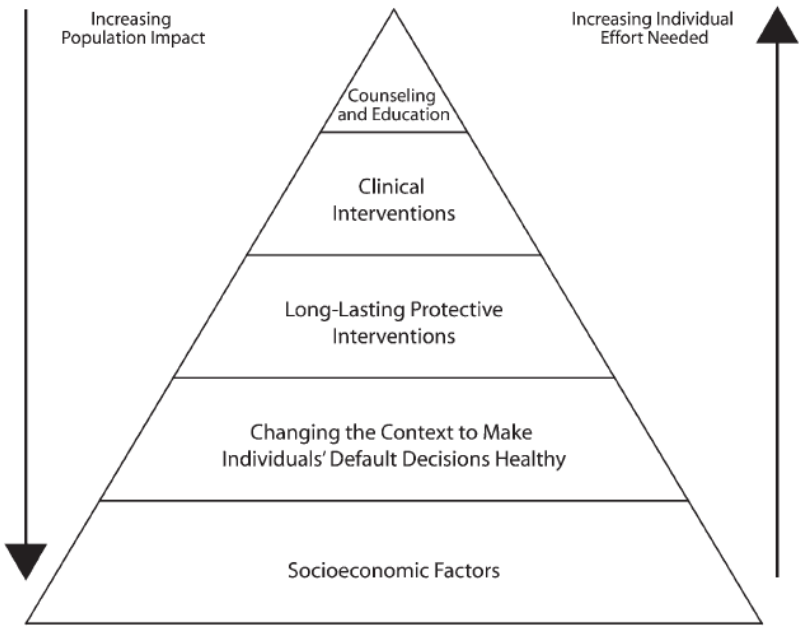


FIGURE 1—The health impact pyramid.

Figure 5.1 Frieden Health Impact Pyramid (Frieden, 2010)

The base of the Frieden Health Impact Pyramid represents interventions addressing socioeconomic factors. In chapter 2 social inequities of health of American Indian communities were discussed, including higher rates of suicide, chronic disease, and infectious diseases (Barnes et al., 2010; *Indian Health Disparities*, 2018; Jones, 2006). As highlighted in earlier chapters, unemployment is high in American Indian communities with more than half of American Indians living below 200% of the federal poverty line (Castor et al., 2006; Zuckerman et al., 2004). Low socioeconomic status is accompanied by overall low access to services, healthy foods, and health resources. Services which impact risk for RMSF include, but are not limited to, waste management, animal control, veterinary care, and vector control services. Lack of access to each of these elements allows for ticks to proliferate in Arizona tribal communities

in ways not experienced by more economically advantaged areas. While raising the overall socioeconomic status of Arizona tribal communities would have the broadest implication for population health in the area, this is also the most difficult public health intervention to achieve and sustain. Dr. Frieden himself noted that such action needs to be undertaken from a governmental or societal perspective, and that the lack of progress is at times due to the lack of political will (Frieden, 2010).

The second and third tiers in the Frieden Health Impact Pyramid relate to healthy decision making and long-lasting interventions, respectively. Chapter 2 of this dissertation highlights the key role of domestic dogs which are free roaming in many of the affected tribal communities. The widespread nature of free-roaming dogs necessitates prevention on a community-scale. Door-to-door campaigns provided by tribal governments exemplified in the RMSF Rodeo reduce the barriers to accessing tick preventives by bringing them to households directly and eliminating any cost barriers (Drexler et al., 2014). In these integrated programs, all homes in a tribal community are treated for ticks by members of the tribal health department. Further, all dogs, owned or unowned, are provided long-lasting tick preventives. Not only are these services provided free-of-cost to the community members, but they also limit the need for homeowner training in pest management techniques—another potential barrier to healthy practices. In the situation of tribal door-to-door campaigns, residents must opt out of treatment, making it easier for the default towards healthy action.

Integrated prevention activities for RMSF arguably also act at the third level of prevention discussed by Dr. Frieden, providing long-lasting protection. Implementation of these practices in Mexico resulted in zero fatalities inside the intervention communities for the entire year following application (Alvarez-Hernandez, G, 2019). The Frieden model envisions long-

lasting protections to require infrequent efforts such as mass drug administrations or male circumcisions used to prevent HIV transmission; thus, serving as cost-efficient prevention mechanisms. Integrated RMSF prevention practices currently require monthly (or at minimum bi-monthly) activity, and therefore may fall short of the envisaged long-lasting protection, however, they introduce some level of protection beyond immediate impact. Other long-lasting interventions for RMSF include *Rickettsia* vaccines for dogs (the amplifying host) as well as anti-tick vaccines which could be used on dogs to prevent tick infestations altogether. Such activities, however, are only theoretical based on current scientific literature (Dantas-Torres et al., 2012; Merino et al., 2013; Samish et al., 2008).

The long-term sequelae study presented in chapter 3 provides clear action at the fourth tier of the Frieden model as clinical intervention. Doxycycline has been proven though multiple studies as an effective treatment for RMSF with evident superiority to other medications when administered within the first five days of illness (Holman et al., 2001a; Regan et al., 2015). Research in chapter 3 describes further evidence of this critical time period in preventing life-altering disability and death. Evidence of the impact of effective treatment with relatively few adverse effects have led to the development of strong treatment recommendations for healthcare providers in areas highly endemic for RMSF. Following the peak of the epidemic, some highly impacted communities implemented treatment algorithms to encourage early treatment following only two days of fever. While arguably not appropriate for non-epidemic areas (where positive predictive value of RMSF as the cause of fever of two or more days may be much lower) this clinical recommendation produced a clear and effective means of reducing severe and fatal outcomes (Bezold et al., 2018). Local policy makers have further implemented flags to electronic health records to cue healthcare providers to initiate treatment for certain clinical signs, history

of tick bite, or when tests are ordered for RMSF. Such interventions interact at a tertiary prevention level; they do not prevent disease, or allow for early diagnosis, but prevent the severe ill-effects of the disease with a clear point of action for healthcare providers.

Finally, the last and lowest yield mode of prevention highlighted in the Frieden model focuses on counselling and education of persons at risk. Current educational activities in impacted communities of Arizona focus in three areas: 1. prevention of RMSF, including treatment of dogs and homes; 2. personal protection activities, such as use of repellents, frequent tick checks, and tick removal; and 3. education about RMSF signs and symptoms to encourage early recognition and care. These educational activities, while important, are the last line of defense, and are particularly challenging in settings of Arizona RMSF where ticks may be encountered daily in and around homes. In some communities where door-to-door prevention practices are unavailable or impractical, education may be the only viable protection against this deadly disease.

All in all, the point illustrated by Dr. Frieden in the presentation of the health prevention pyramid is that comprehensive disease prevention requires action at all levels. While interventions targeting the bottom of the pyramid have the greatest potential to improve health, they are often the most difficult to achieve and the most indirect impact on a specific health topic. Cost-effective RMSF prevention should be targeting the second and third tiers, implementing universal prevention practices as defaults for care, and ideally with long-lasting effects. While the silver bullet for such action has not yet been identified, economic analyses may be used to describe the overall cost-effectiveness of widespread prevention efforts rather than relying on higher tiers on the prevention pyramid.

Implications for Regional Policymakers

Effective prevention strategies for RMSF have been identified using integrated vector control techniques (Drexler et al., 2014). However, scaled implementation of such techniques are slow and are hindered from lack of basic animal control, veterinary, sanitation, and vector control infrastructure in many tribal areas. Previous studies provide strong documentation of the substantial impact that RMSF prevention can have on a community resulting in measurable decreased incidence and death (Drexler et al., 2014; Straily, 2016). Such interventions have proven to have a 43% reduction in human disease incidence on smaller community scales (Drexler et al., 2014). For the two communities in the Arizona cohort, costs of implementation have been estimated at roughly $4 million for 5 years (CDC). If 43% case reduction could be applied to current epidemic rates of disease (285 cases between 2002–2017 from the two communities), this would imply 122 cases of those cases could have been averted. Using previous net disease costs of $13.1 million, cost-effectiveness analyses (measured by net costs, over the change in health):

Net cost= cost of implementation-cost averted through prevention

$4 million-$13.1 million=$9.1 million saved

Change in health outcomes: 285*43%=122 cases averted

Cost effectiveness ratio= net cost/change in outcomes=$74,590 cost savings per case averted

Information from these studies can be used to advocate to public and private health partners for increased investment in RMSF prevention. While the current prevention practices require a substantial amount of monetary and personnel resources, this estimate is in fact providing cost-savings compared to the result of disease, with total disease costs more than five times that of prevention.

Implications for Hospital Policymakers

Hospital-based policy makers must prioritize use of finite resources. Results in chapter 3 have identified that a substantial portion of individuals with severe RMSF may have long-term disability resulting from vascular damage. Like other vascular injuries, such as heart attack or stroke, patients experiencing RMSF-related sequelae may benefit from long-term follow-up and specialty care for months or years following illness. Hospitals in epidemic regions could assess their need for supportive care resources such as occupational, physical, and behavioral therapy based on their local risk of disease using values from the long-term sequelae study.

Implications for Healthcare Providers

Previous studies have described the outcomes of hospitalization, intensive care stays, and death by date of doxycycline administration (Regan et al., 2015). Information now includes evidence that delay in doxycycline administration may be associated with increased rates of disability. The total evidence demonstrates that death, severe disease, and disability can all be averted with early doxycycline administration within the first 5 days of illness. Increasing amounts of vascular damage may occur when the bacteria are allowed to proliferate past this point and may result in irreparable damage to the neurologic vasculature. The best clinical outcomes are associated with earlier treatment. RMSF is difficult to diagnose in the early stages of illness because of non-specific clinical findings and lack of definitive acute phase diagnostic tests (Sexton & Kaye, 2002). Rash is often considered to be the hallmark sign of RMSF; however, patients typically seek care for the first time in the first 2–3 days of illness, when rash may not yet be present. Rash does not typically occur until day 3–4 of illness and may be faint in early stages (Biggs et al., 2016; Buckingham et al., 2007). “Classic” petechial rash involving the

palms of the hands and the soles of the feet may not be present until day 5 or later of illness, thus if providers are waiting for rash prior to treatment, they will undoubtably miss the critical window to avoid severe impacts. Recent knowledge, attitudes and practices surveys of healthcare providers documented nearly 20% of providers choosing to treat for RMSF only after a rash appeared (Mosites et al., 2013). Without the confidence in diagnosis and awareness of the importance of early treatment, providers may hesitate to aggressively use of doxycycline, leading to preventable death and disability. Evidence of long-term sequelae may a further impact healthcare provider follow-up for severe cases of RMSF. One third of patients had no neurological dysfunction at the time of hospital discharge but went on to develop long-term neurological sequelae. Close monitoring of patient populations following a severe episode of RMSF may help identify neurologic consequences as they become apparent. Although neurologic imaging was not available for all cases with LTS, vascular damage including punctate lesions could be identified using MRI or CT and may facilitate early identification of neurologic damage.

Implications for Communities

This dissertation provides a substantial understanding of functional outcomes following severe disease and, as far as the investigators are aware, the first account of RMSF recovery from a patient perspective, detailing times to recovery and perceived changes in function. While most patients interviewed reported complete recovery from RMSF illness, there was a substantial proportion (23%) reporting long-term sequelae. Accounts of time to recovery, and direct life impact are imperative for patients and family members to understand when making plans following a severe illness.

RMSF has already been highlighted as a dangerous, and potentially life-threatening disease in impacted Arizona communities, and will now be described as a potential source of severe disability. Information about death and disability may underline the importance of prevention strategies in communities at risk for RMSF. One recommendation made to community leaders following this research is to consider using survivor and family stories of RMSF death and disability. By demonstrating a range of outcomes, patient and family testimonials can penetrate a deeper level of understanding and self-identification. “Tips from former smokers” is perhaps one of the greatest examples of survivor testimonies successfully used to drive health promotion (Neff et al., 2016). Such campaigns have been deeply successful in calling direct attention to death and disability, while emphasizing people’s ability (self-efficacy) to take preventative action. Storytelling is a key feature in many American Indian communities and has been effectively used to promote prevention strategies and empowering communities to health action (Hodge et al., 2002; Wexler et al., 2013). Community educators can use community conversations surrounding RMSF, including testimonies, to reignite the perceived threat of RMSF and remind community members of continued vigilance and early care.

LIMITATIONS

Limitations of Study Design

The primary limitation in the documentation of long-term sequelae comes from the cross-sectional study design. Neurologic exams were conducted years following acute RMSF illness, with no longitudinal follow-up to recognize when and if disability developed or identify intervening factors. Researchers attempted to minimize the potential of such intervening factors by documenting preexisting neurological illness during our medical chart review, and asked

cases to self-identify new neurologic illness during survey. However, these results may be incomplete.

The image below represents the possible outcomes of the neurologic assessment unable to differentiated in the current study design.

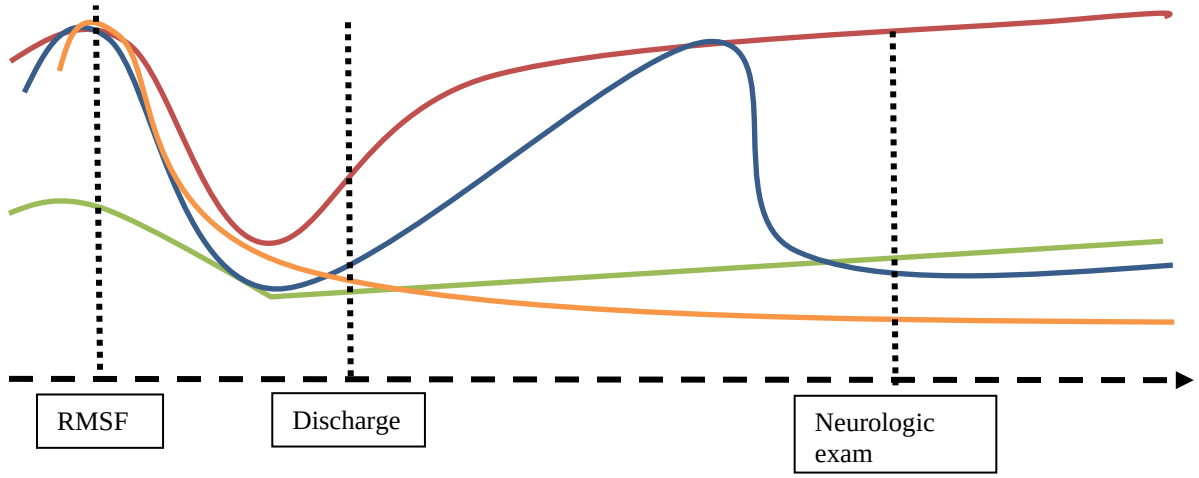


Figure 5.2: Potential outcomes of neurologic assessment, Arizona 2002–2017

( ) patient 1: normal function prior to RMSF, functional recovery, no long-term sequela

( ) patient 2: normal function prior to RMSF, no functional recovery, abnormal neurologic exam indicating long-term sequela(e) potentially due to RMSF

( ) patient 3: normal function prior to RMSF, functional recovery, intervening neurologic event, abnormal neurologic documenting sequela(e) likely unrelated to RMSF

( ) patient 4: abnormal function prior to RMSF, functional recovery, abnormal neurologic exam, long-term sequela(e) likely unrelated to RMSF

As demonstrated in the image, the findings of this study represent a snapshot of disability with several iterations of recovery paths and how those might be seen during the neurologic exam. Without following patients from their time of illness to the time of sequela development,

the study has no ability to conclude that sequelae are directly caused from their acute RMSF experience.

This study represents a large-scale, non-probabilistic convenience sampling of hospitalized cases in Arizona. Convenience sampling limits our ability to extrapolate findings to the general population of individuals with RMSF. The authors were unable to evaluate how representative the study findings were to the overall RMSF community but provides key description of methods and overall conclusions which could be replicated in national or international settings.

Limitations of Study Methods

Several additional limitations are identified from specific study methods. Patient accounts of recovery times are highly subject to recall bias years following acute illness. Furthermore, clinical factors are described secondarily using medical chart abstraction, records may not have been complete, and the availability of information regarding sequelae at discharge varied widely. The Montreal Cognitive Assessment (MoCA), is a commonly used clinical tool to assess cognitive function, however, the MoCA has not been validated in this specific community. Normative values for this specific population are unknown and the authors are unaware if preference for native language may have skewed results, as has been described for other populations (Hu et al., 2013).

Further limitations result from the economic analysis in chapter 4. Estimates for the Arizona cohort are based on flat-rate charges as direct billing data were not available. The direct costs of hospitalized cases, therefore, reflect estimated, rather than actual costs. Complicated, and costly procedures and repeat visits associated with chronic disease management may not be captured accurately from flat-rate charges. However, direct medical costs estimated from the

Arizona cohort were close to those estimated from national medical billing databases, suggesting that flat-rate estimates may not be an inappropriate proxy.

Disability-adjusted life years (DALYs) lost from disease are commonly used techniques to estimate the burden of disease morbidity and mortality by the World Health Organization and World Bank but are not typically used in more developed countries like the United States which tend to use quality-adjusted life years lost. DALYs assume less value for disabled life-years and estimates of disability are based on expert panels, not patient accounts; thus, although DALYs are widely used and supported, some experts believe that their use may lead to over estimation of disease cost (Arnesen & Nord, 1999). Calculations of DALYs associated with RMSF in Arizona tribal communities are based on a small subset of cases in the study of long-term sequelae, and therefore are not likely to be representative of RMSF.

RECOMMENDATIONS FOR FUTURE RESEARCH

The data presented herein represent a summary of experiences from a convenience sample of persons hospitalized for RMSF in hyperendemic communities of Arizona. The cohort includes data only from hospitalized cases of RMSF, likely leading to the over estimation of neurologic sequelae in the general RMSF-impacted population. While these data can be useful in evaluating the presence or absence of neurologic sequelae following severe RMSF illness, it cannot be used to address the likelihood of developing sequelae and is unable to evaluate true risk factors for predicting neurologic sequelae. Future studies should target two areas: 1. A case-control evaluation of neurologic sequelae in RMSF related hospitalizations compared to non-RMSF related hospitalizations. 2. True causation would need to be established using a longitudinal study, taking individuals from before their RMSF illness, following them through

their illness manifestations, and then following them for several years to track occurrence and resolution of neurologic sequelae compared to other hospitalized controls.

Economic analysis for Arizona tribal communities relating to RMSF are now thoroughly documented. This dissertation has established the short and long-term consequences of disease and have preliminarily discussed cost-effectiveness of using integrated prevention protocols to avert RMSF death and disability. Translational studies could scale these findings for national or even international settings in order to describe the cost of RMSF throughout the Western hemisphere where RMSF is endemic. Future studies could further address the social impact of disease in tribal communities. In-depth socio-behavioral research could be used to address community-level impact of disease, as well as expand on the relative value of health, social structure, and the impact of disability and death on small tribal communities. Lastly, research could also describe the innate protective factors of deep-seeded cultural practices and how they increase resiliency to disease and disability.

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APPENDICES

Appendix A: IRB Determination

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Centers for Disease Control
and Prevention (CDC)

Memorandum

Date April 1, 2019

From Jerrell Little
IRB-Committee 2 Administrator
Human Research Protection Office

Subject CDC IRB Approval of Continuation #1 of CDC Protocol #7100, "Long term sequela of Rocky Mountain spotted fever" (Expedited)

To Naomi Drexler, MPH
NCEZID/DVBD

CDC's IRB-Committee 2 has reviewed and approved your request to continue protocol #7100 for the maximum allowable period of one year and it will expire on **4/10/2020**. The protocol was reviewed in accordance with the expedited review process outlined in 45 CFR 46.110(b)(1), under categories 4, 5, and 7. Contact with participants has begun and continues; this may include follow-up for debriefing or notification of results.

If other institutions involved in this protocol are being awarded CDC funds through the CDC Office Financial Resources (OFR), you are required to send a copy of this IRB approval to the CDC OFR award specialist handling the award. You are also required to verify with the award specialist that the awardee has provided OFR with the required documentation and has approval to begin or continue research involving human subjects as described in this protocol.

As a reminder, the IRB must review and approve all human subjects' research protocols at intervals appropriate to the degree of risk, but not less than once per year. There is no grace period beyond one year from the last IRB approval date. It is ultimately your responsibility to submit your research protocol for continuation review and approval by the IRB along with available IRB approvals from all collaborators. Please keep this approval in your protocol file as proof of IRB approval and as a reminder of the expiration date. **To avoid lapses in approval of your research and the possible suspension of subject enrollment and/or termination of the protocol, please submit your continuation request along with all completed supporting documentation at least six weeks before the protocol's expiration date of 4/10/2020.**

Any problems of a serious nature must be brought to the immediate attention of the CDC IRB, and any proposed changes to the protocol should be submitted as an amendment to the protocol for CDC IRB approval before they are implemented.

If you have any questions, please contact your National Center Human Subjects Contact or the CDC Human Research Protection Office (404) 639-7570 or e-mail: huma@cdc.gov.

cc: NCEZID Human Studies Review (CDC)

Appendix B: Medical Chart Abstraction Tools

RMSF LONG TERM SEQUELA STUDY: CHART ABSTRACTION FORM

Patient information (remove top page following abstraction)	PATIENT ID ___ ___ ___ ___ ___
Patient's Name: _____ (Last Names) _____ (First Name)	
Date of Birth: ____/____/____ (MM DD YYYY) Abstractor initials: _____	

FINAL

1

RMSF LONG TERM SEQUELA STUDY: CHART ABSTRACTION FORM

PATIENT ID _ _ _ _ _ _

I. Patient data

Gender: ☐ M ☐ F Date of Birth: _____/_____/_____ (MM/DD/YYYY)

Tribal community: _____ Tribal affiliation: _____

II. Chart abstraction info

Abstractor initials: _____ Date of chart abstraction: _____/_____/_____ (MM/DD/YYYY) Location of primary abstraction: _____

III. Dates of care

Not available

Date of first symptoms: _____/_____/_____ (MM/DD/YYYY) ☐

Symptoms at first provider visit: _____

Date of fever onset (if different): _____/_____/_____ (MM/DD/YYYY)

Date of first provider visit: _____/_____/_____ (MM/DD/YYYY) ☐

ICD-9 or ICD-10 codes used at first provider visit: _____

Tick bite or tick contact noted in first visit? ☐ Yes ☐ No ☐ Unk

Healthcare facilities visited during RMSF illness:

Name of facility	Dates of care	Type of visit (ED, outpatient, inpatient)
_____	From: _____/_____/_____ To: _____/_____/_____ (MM/DD/YYYY)	_____
_____	From: _____/_____/_____ To: _____/_____/_____ (MM/DD/YYYY)	_____
_____	From: _____/_____/_____ To: _____/_____/_____ (MM/DD/YYYY)	_____
_____	From: _____/_____/_____ To: _____/_____/_____ (MM/DD/YYYY)	_____
_____	From: _____/_____/_____ To: _____/_____/_____ (MM/DD/YYYY)	_____

Admitted to ICU? ☐ Yes ☐ No From: _____/_____/_____ To: _____/_____/_____ (MM/DD/YYYY)

Date of first RMSF mention in chart: _____/_____/_____ (MM/DD/YYYY) ☐

Date of first tetracycline therapy: _____/_____/_____ (MM/DD/YYYY) ☐

Date of fever resolution: _____/_____/_____ (MM/DD/YYYY) ☐

Number of ER visits: _____

Number of outpatient visits: _____

Number of general admission days: _____

Number of ICU days: _____

IV. Medical history prior to hospitalization *(check if yes)*

☐ Diabetes ☐ Hx of drug abuse ☐ Hx of alcohol abuse

V. Medical history during hospitalization *(check if yes)*

☐ Evidence of shock or use of vasopressors
☐ ARDS
☐ Multiorgan failure
☐ Renal insufficiency
☐ Cerebral edema
☐ Coma
☐ Altered mental status
☐ Digital necrosis
If yes, specify body parts involved: _____
☐ Severe thrombocytopenia (<50 10^3 uL)
If yes, list date of first result <50 10^3 uL: _____/_____/_____ (MM/DD/YYYY)
☐ Rash and/or eschar
If yes, please describe onset (including dates), location, and evolution: _____

RMSF LONG TERM SEQUELA STUDY: CHART ABSTRACTION FORM

PATIENT ID ___ ___ ___ ___ ___

VI. Treatment and procedures during hospitalization

Antibiotic (including tetracycline therapy)	Start date	End date
_____	____/____/____ MM DD YYYY	____/____/____ MM DD YYYY
_____	____/____/____ MM DD YYYY	____/____/____ MM DD YYYY
_____	____/____/____ MM DD YYYY	____/____/____ MM DD YYYY
_____	____/____/____ MM DD YYYY	____/____/____ MM DD YYYY

☐ Vassopressors (which:_____)
From ____/____/____ MM DD YYYY to ____/____/____ MM DD YYYY

☐ Transfusion (products an quantity:_____)
Date1 ____/____/____ MM DD YYYY Date2 ____/____/____ MM DD YYYY

☐ Mechanical Ventilation (eg. Intubation)
From ____/____/____ MM DD YYYY to ____/____/____ MM DD YYYY

☐ Hemodialysis (e.g. CRRT)
From ____/____/____ MM DD YYYY to ____/____/____ MM DD YYYY

☐ Amputation
If yes, specify body parts involved: _____

☐ Other surgical procedures
Describe: _____

VII. Neurologic and psychiatric history prior to RMSF

Did patient have any documented neurologic impairments (including concussion or TBI, fetal alcohol syndrome, Parkinson's, etc.) prior to RMSF illness?

☐ Yes ☐ No ☐ Unknown

If yes, specify type: _____

Date of diganosis ____/____/____ MM DD YYYY ☐ Unknown

Did patient have any documented psychiatric impairments prior to RMSF illness?

☐ Yes ☐ No ☐ Unknown

If yes, specify type: _____

Date of diganosis ____/____/____ MM DD YYYY ☐ Unknown

For children <8 years, were there any previously documented developmental delays noted prior to RMSF illness?

☐ Yes ☐ No ☐ Unknown

If yes, describe: _____

VIII. Neurologic and psychiatric history at discharge

	YES	NO	Unknown
Behavioral/personality change	☐	☐	☐
Memory problems	☐	☐	☐
Anxiety	☐	☐	☐
Depression	☐	☐	☐
Confusion/disorientation/coma	☐	☐	☐
Headache	☐	☐	☐
Pain	☐	☐	☐
Dysarthria/slurred speech	☐	☐	☐
Dysphagia/difficulty swallowing	☐	☐	☐
Hearing loss	☐	☐	☐
Blindness/visual impairment	☐	☐	☐
Diplopia/opnthalmoplegia	☐	☐	☐

	YES	NO	Unknown
Numbness/parasthesias	☐	☐	☐
Myoclonus	☐	☐	☐
Seizures	☐	☐	☐
Bowel/bladder incontinence	☐	☐	☐
Weakness	☐	☐	☐
Difficulty breathing	☐	☐	☐
Tremors	☐	☐	☐
Ataxia/problems with balance	☐	☐	☐
Hyporeflexia/areflexia	☐	☐	☐
Decline in functional capacity from baseline	☐	☐	☐

If yes, describe: _____

3

RMSF LONG TERM SEQUELA STUDY: CHART ABSTRACTION FORM

PATIENT ID ___ ___ ___ ___ ___

IX. RMSF Testing

Specimen type: _____ _____/_____/_____ (MM DD YYYY) Test: _____ Result: _____

Specimen type: _____ _____/_____/_____ (MM DD YYYY) Test: _____ Result: _____

Specimen type: _____ _____/_____/_____ (MM DD YYYY) Test: _____ Result: _____

Specimen type: _____ _____/_____/_____ (MM DD YYYY) Test: _____ Result: _____

Specimen type: _____ _____/_____/_____ (MM DD YYYY) Test: _____ Result: _____

X. Other infectious etiology testing

Was a secondary infection documented (discharge summary, chart, labs)?

☐ Yes ☐ No ☐ Unknown

If yes, please describe the nature of the infection and corroborating laboratory evidence:

_____

_____

_____

_____

XI. Lumbar puncture *(leave blank if not performed)*

Note, if multiple LPs were performed please use earliest result _____/_____/_____ (MM DD YYYY)

WBCs/mm^3 _____ Protein (mg/dL) _____ Gram stain _____

WBC diff: ___%PMN ___%Lymp ___%Eos ___%Mon Glucose (mg/dL) _____ Color (eg.xanthochromia) _____

RBCs/mm^3 _____ Culture _____

XII. Neurologic and imaging studies:

	Performed	*Not performed*	*Date of finding*	*Impression (if unremarkable, write "normal")*
Head CT	☐	☐	_____/_____/_____ (MM DD YYYY)	_____ List substantial changes in subsequent series: _____
Head MRI	☐	☐	_____/_____/_____ (MM DD YYYY)	_____ List substantial changes in subsequent series: _____
Spinal MRI	☐	☐	_____/_____/_____ (MM DD YYYY)	_____ List substantial changes in subsequent series: _____
Specify: _____				
EEG or other neurologic study	☐	☐	_____/_____/_____ (MM DD YYYY)	_____ List substantial changes in subsequent series: _____
Specify: _____				

4

RMSF LONG TERM SEQUELA STUDY: CHART ABSTRACTION FORM

PATIENT ID ___ ___ ___ ___ ___

XIII. Outcome

Final disposition:

☐ Died

Date of death: _____/_____/_____ (MM DD YYYY)

☐ Transferred to another facility

Date of transfer: _____/_____/_____ (MM DD YYYY)

Date of discharge, if known: _____/_____/_____ (MM DD YYYY)

Type of facility:

- ☐ Acute rehabilitation
- ☐ Sub-acute rehabilitation
- ☐ Skilled nursing/long term care
- ☐ Hospice
- ☐ Other: _____

Name of facility: _____

☐ Home

Date of discharge: _____/_____/_____ (MM DD YYYY)

Was patient referred for any of the following supportive care at discharge?

For each type of supportive care note referral status and list length of referral (days)

Physical therapy	☐ Yes	☐ No	☐ Unknown	_____ days
Occupational therapy	☐ Yes	☐ No	☐ Unknown	_____ days
Speech therapy	☐ Yes	☐ No	☐ Unknown	_____ days
Behavioral therapy	☐ Yes	☐ No	☐ Unknown	_____ days

Other, please describe _____

XIIII. Modified Rankin Scale at discharge *(based on discharge summary) use pediatric modified Rankin for children less than 8 years of age*

0 = No symptoms at all

1 = No significant disability despite symptoms; able to carry our all usual duties and activities

2 = Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance

3 = Moderate disability; requiring some help, but able to walk without assistance

4 = Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance

5 = Severe disability; bedridden, incontinent and requiring constant nursing care and attention

6 = Dead

SCORE (0 – 6): _____

Additional notes from previous sections *(please note page number, section and item continued)*

5

Appendix C: Patient Survey

Answers are being provided on behalf of:

□ Self

□ Child

□ Deceased

Please answer the questions to the best of your ability. It is ok to say you don't know.

1. As discussed earlier, our records show that you (your child) was diagnosed with RMSF in (mm/yyyy). Is this correct?
   Yes / No / Don't know

   --If no, please provide us with the approximate date in which you (your child) had RMSF: (mm/yyyy)

2. Our records also indicate that you (your child) left the hospital on (MM/DD/YYY). Is this correct?
   Yes / No / Don't know

3. After you left the hospital, where did you (your child) go?
   □ Home □ Another hospital

   □ Nursing home □ Rehabilitation facility

   □ Other

   □ Don't remember

   Name of facility:

   _____

   How long were you there? _____

4. On a scale of 1 to 5 how would you rate your (your child's) overall ability to function prior to your RMSF illness?
   (Unable to function in my daily life) 1—2—3—4—5 (perfectly able to function)

5. Do you feel like you (your child) have recovered fully from your RMSF illness?
   Yes / No / Don't know

   --If yes:

   how long did it take to get back to normal? _____

   --If no:

   have your (your child's) symptoms improved over time?

   Yes / No / Don't know

   what symptoms are you (your child) still experiencing?

   _____

   _____

   --If don't know, proceed to next question.

6. On a scale of 1 to 5 how would you rate your (your child's) overall ability to function since your (their) RMSF illness?
   (Unable to function in my daily life) 1—2—3—4—5 (perfectly able to function)

7. Have you (your child) been diagnosed with neurologic illness since your (their) RMSF illness (such as a stroke, dementia, Parkinson's Disease, etc.)
   Yes / No / Don't know

   --If yes:

   what was the illness? _____

   when was it diagnosed? _____

8. Are there any activities which you (your child) used to do before your RMSF illness that you (they) are unable to do at this time?
   Yes / No / Don't know

   --If yes:

   please specify which activities:

   _____

   _____

   do you think this change is due to your (their) RMSF illness?

   Yes / No / Don't know

Appendix D: Neurologic Exam Form

RMSF LONG TERM SEQUELA STUDY: NEUROLOGIC EXAM FORM

Patient data (remove top page following exam)

Patient's Name: _____ (Last Name) _____ (First Name)

PATIENT ID ___ ___ ___ ___

Date of Birth: ____/____/____ (MM/DD/YYYY)

Gender: M ☐ F ☐

Tribal community: _____

Tribal affiliation: _____

FINAL

RMSF LONG TERM SEQUELA STUDY: NEUROLOGIC EXAM FORM

PATIENT ID ___ ___ ___ ___

Date of RMSF onset: _____/_____/_____ (MM/DD/YYYY) Age at illness (years):_____ Current age (years):____

Neurologic exam completed? ☐ Yes ☐ No

If yes, Date of exam: _____/_____/_____ (MM/DD/YYYY) Provider performing exam: _____

If no, why not? ☐ Deceased ☐ Lost to follow up ☐ Did not consent ☐ Other, describe: _____

I. Altered mental status ☐ Altered ☐ Normal ☐ Unknown/Unable to determine

(If altered or unknown, proceed to 2. Mental status examination, otherwise skip to 3. Language)

II. Mental status (8 years and older) *(as determined by the Montreal Cognitive Assessment (MOCA)). See appendix A for children ≤ 5 years.*

Visuospatial/executive: _____ (5) Attention: _____ (6) Abstraction: _____ (2) Orientation _____ (6)

Naming: _____ (3) Language: _____ (3) Delayed recall _____ (5) TOTAL: _____ (30)

☐ Check if patient ≤ 5 years of age (see Appendix A)

☐ Check if patient > 5 years, ≤ 8 years (continue to section IV)

III. Language (8 years and older) *See appendix A for children ≤ 5 years.*

☐ Normal ☐ Expressive aphasia ☐ Receptive aphasia ☐ Global aphasia ☐ Dysarthria

Description of difficulty: _____

IV. Cranial nerves

CN I ☐ Normal ☐ Abnormal, describe: _____

CN II

Pupil exam ☐ Normal ☐ Abnormal, describe: _____

Accommodation ☐ Normal ☐ Abnormal, describe: _____

Visual field ☐ Normal ☐ Abnormal, describe: _____

Visual acuity ☐ Normal ☐ Abnormal, describe: _____

Fundoscopic exam ☐ Normal ☐ Abnormal, describe: _____

CN III ☐ Normal ☐ Abnormal, describe: _____

CN IV ☐ Normal ☐ Abnormal, describe: _____

CN V ☐ Normal ☐ Abnormal, describe: _____

CN VI ☐ Normal ☐ Abnormal, describe: _____

CN VII ☐ Normal ☐ Abnormal, describe: _____

CN VIII ☐ Normal ☐ Abnormal, describe: _____

CN IX ☐ Normal ☐ Abnormal, describe: _____

CN X ☐ Normal ☐ Abnormal, describe: _____

CN XI ☐ Normal ☐ Abnormal, describe: _____

CN XII ☐ Normal ☐ Abnormal, describe: _____

V. Sensory

Upper extremities ☐ Normal ☐ Numbness ☐ Paresthesias Other, describe: _____

Lower extremities ☐ Normal ☐ Numbness ☐ Paresthesias Other, describe: _____

Core ☐ Normal ☐ Numbness ☐ Paresthesias Other, describe: _____

Face ☐ Normal ☐ Numbness ☐ Paresthesias Other, describe: _____

VI. Motor

A. Abnormal movements

Fasciculations ☐ Yes ☐ No Comments: _____

Tremor ☐ Yes ☐ No Comments: _____

Chorea/dyskinesias ☐ Yes ☐ No Comments: _____

Myoclonus ☐ Yes ☐ No Comments: _____

B. Bulk

Atrophy ☐ Yes ☐ No Comments: _____

C. Tone

Upper extremities ☐ Normal ☐ Increased (spastic or rigid) ☐ Decreased Comments: _____

Lower extremities ☐ Normal ☐ Increased (spastic or rigid) ☐ Decreased Comments: _____

Core ☐ Normal ☐ Increased (spastic or rigid) ☐ Decreased Comments: _____

D. Other upper motor neuro signs

	R		L		
Pronator drift	☐ Yes	☐ No	☐ Yes	☐ No	Comments: _____
Finger tap speed	☐ Normal	☐ Slow	☐ Normal	☐ Slow	Comments: _____
Foot tap speed	☐ Normal	☐ Slow	☐ Normal	☐ Slow	Comments: _____

RMSF LONG TERM SEQUELA STUDY: NEUROLOGIC EXAM FORM

PATIENT ID ___ ___ ___ ___

E. Strength *(0 = No movement; 1 = Barely discernable movement; 2 = Movement along plane of gravity; 3 = Movement against gravity; 4 = Movement against resistance; **5 = Normal**)*

Neck flexors _____

Neck extensors _____

Upper extremity:

R		L
	Deltoids	
	Biceps	
	Triceps	
	Wrist extensors	
	Wrist flexors	
	Finger extensors	
	Finger flexors	
	Abductor pollicis brevis	
	Opponens pollicis	
	Interossei	

Lower extremity:

R		L
	Hip flexors	
	Hip extensors	
	Hip abduction	
	Hip adduction	
	Quadriceps	
	Hamstrings	
	Plantarflexors	
	Dorsiflexors	
	Foot evertors	
	Foot invertors	
	Extensor hallucis longus	
	Toe flexors	
	Toe extensors	

VII. Reflexes *(0 = Absent; 1 = Decreased; **2 = Normal**; 3 = Increased/hyperactive; 4 = sustained clonus)*

R		L
	Brachioradialis	
	Biceps	
	Triceps	
	Patellar	
	Ankle jerk	

Excessive jaw jerk ☐ Yes ☐ No

	R		L	
Sustained ankle clonus	☐ Yes	☐ No	☐ Yes	☐ No
Plantar response (Babinski)	☐ Up ☐ Down ☐ Unclear		☐ Up ☐ Down ☐ Unclear	

VIII. Coordination

	R			L			Comments:
Finger-to-nose	☐ Normal	☐ Dysmetric	☐ Other	☐ Normal	☐ Dysmetric	☐ Other	_____
Heel-knee-shin	☐ Normal	☐ Dysmetric	☐ Other	☐ Normal	☐ Dysmetric	☐ Other	_____
Past-pointing	☐ Normal	☐ Overshoot	☐ Other	☐ Normal	☐ Overshoot	☐ Other	_____
Check reflex	☐ Normal	☐ Loss of check reflex	☐ Other	☐ Normal	☐ Loss of check reifex	☐ Other	_____

IX. Gait and station

Spontaneous gait ☐ Normal ☐ Hemiplegic ☐ Steppage ☐ Shuffling ☐ Other, describe: _____

Able to walk on toes ☐ Yes ☐ No

Able to walk on heels ☐ Yes ☐ No

Able to tandem ☐ Yes ☐ No

Romberg ☐ Positive ☐ Negative ☐ Unable to assess

X. Additional narrative/comments:

Modified Rankin Scale *(at exam), use pediatric modified Rankin for children less than 8 years of age*

0 = No symptoms at all

1 = No significant disability despite symptoms; able to carry our all usual duties and activities

2 = Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance

3 = Moderate disability; requiring some help, but able to walk without assistance

4 = Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance

5 = Severe disability; bedridden, incontinent and requiring constant nursing care and attention

6 = Dead

SCORE (0 – 6): _____

RMSF LONG TERM SEQUELA STUDY: NEUROLOGIC EXAM FORM

PATIENT ID ___ ___ ___ ___

Appendix A: Ages and stages exam for modified mental and cognitive assessment in children ≤ 5 years

Example attached.
21-age appropriate questionnaires are available for children 1 month to 5 .5 years of age. Questionnaire will be facilitated by study staff and parents. Evaluations take 10-15 minutes to complete and 2-3 minutes to score. ASQ-3 has been validated with age-appropriate normative results available for reference.

Category	Score	Comments
Communications		
Gross motor skills		
Fine motor skills		
Problem solving		
Personal-social		
Overall		

RMSF LONG TERM SEQUELA STUDY: NEUROLOGIC EXAM FORM

PATIENT ID ___ ___ ___ ___

Appendix B: Modified Rankin Scale for children

RMSF LONG TERM SEQUELA STUDY: NEUROLOGIC EXAM FORM

PATIENT ID ___ ___ ___ ___

Appendix C: Neurologic notes:

For cases in which neurologic sequela are suspected please provide summary of any notes on neurologic history since RMSF episode. Records may be obtained from school evaluations, behavioral health referrals or neurologist exams.

Appendix E: Data Appendix for Economic Analysis

This appendix provides further description of the economic analyses in chapter 4 of this dissertation. Herein, we provide methods, data and manipulations used in calculating direct costs from the Arizona cohort, as well as supplemental data and calculations used in assessing the disability-adjusted life years lost (DALY).

ESTIMATING DIRECT COSTS OF RMSF FROM AN ARIZONA COHORT

Data sources

Chapter 4 provides a brief overview of calculations of indirect costs. Data were obtained from the long-term sequelae (LTS) study described in chapter 3 in which hospitalized cases of RMSF during 2002–2017 from two tribal communities in Arizona are described. Eighty cases in total were included in this analysis. Healthcare in tribal communities of Arizona are largely provided directly by the Indian Health Service (IHS) or by tribally run healthcare facilities. Under Public Law 93-638 tribes can receive the money that IHS would have used to provide direct health services for tribal members and directly manage healthcare services for themselves. These services are largely governed by the same reimbursement rates as the IHS; thus, all charges are assumed to align with those published by IHS. Direct billing information was not available for patients in this cohort.

Calculations

In order to describe estimated direct costs of these patients the authors used an enumeration of the healthcare visits during the course of their RMSF illness by visit type including: outpatient visits, emergency room (ER) visits, days of general admission, days of intensive care unit (ICU) admission, days in step-down or skilled nursing facility following

hospital discharge, and number of occupational or physical therapy appointments referred at hospital discharge. Frequency of visit type was multiplied by either all-inclusive reimbursement rates billed by IHS to Medicaid (general admission days and outpatient visits), or costs described in a fee-for-service rate (Arizona Healthcare Cost Containment System, n.d.; Folwer, Elizabeth, 2017). Table 1 summarizes each of the types of visits and the enumerated costs per visit type from the Arizona cohort.

Table 1: Direct costs of RMSF care among a hospitalized cohort, Arizona, 2002–2017 (n=80)

Item	*Number of people reporting*	*Number of times/length of stay*	*Cost per unit**	*Total cost*
ER†	72	118	$221	$26,078
Outpatient visits	19	25	$391	$9,775
General Admission days	60	348	$2,933	$1,020,684
ICU days†	30	161	$5,295	$852,495
SNF or step-down facility days†	4	90	$1,010	$90,900
Occupational therapy visits referred†	10	300	$111	$33,300
				Bulk total $2,033,232

*2017 Reimbursement values
†2017 Fee-for-service

Limitations of direct costs estimates

Direct cost estimates from Arizona are based on flat-rate charges by visit type, rather than direct billing information, these estimates do not account for specialized treatment, medications, and services. They are generally viewed as a lower-bound of possible clinical costs. Several of the cases included in the cohort experienced severe illness requiring critical care procedures, such as extracorporeal oxygenation, wound debridement in a surgical facility, and amputation of digits; such procedures likely experienced direct medical costs far exceeding the flat-rate estimate. However, the close estimation of costs per case from national databases including

HCUP and MarketScan indicates that little is lost by use of this crude technique to describe direct costs from the Arizona cohort.

ESTIMATING DALYS LOST RMSF IN AN ARIZONA COHORT

Total disease cost for RMSF in the Arizona cohort was estimated using disability-adjusted life years (DALYs) lost. DALY are the sum of years of life lost (YLL) from premature death as well as years of life lost due to disability (YLD) [DALY=YLL+YLD]. Cumulative incidence rates of each possible outcome were derived from the LTS study using the observations in figure 3.1 of RMSF cases in the two communities during 2002–2017, over the total population of the two communities as per the 2010 Demographic Profile Data (U.S. Census Bureau, 2010). Moderate illness included all cases not hospitalized in the two communities (150 cases), severe illness without LTS (54 cases), severe illness resulting in LTS (9 cases), and severe illness resulting in death (17 cases). DALY calculations were performed using the DALY calculation Excel spreadsheet provided by the World Health Organization using the following DALY parameters: discount rates (r= 0.03), β=0.04, constant (C=0.168), and age-weighting component (K=1). Formulae embedded in the worksheet are provided in the National Burden of Disease Manual (https://www.who.int/healthinfo/nationalburdenofdiseasemanual.pdf?ua=1) and adapted from Murray and Lopez (1996).

$$YLL = N\,Ce^{(ra)} / (\beta+r)^2 \left[e^{-(\beta+r)(L+a)} [-(\beta+r)(L+a)-1] - e^{-(\beta+r)a} [-(\beta+r)a-1]\right]$$

$$YLD = I\,DW\,Ce^{(ra)} / (\beta+r)^2 \left[e^{-(\beta+r)(L+a)} [-(\beta+r)(L+a)-1] - e^{-(\beta+r)a} [-(\beta+r)a-1]\right]$$

Where a is the age of onset. DALY calculations for RMSF had component elements of YLL, YLD_1 (individuals with moderate illness who were not hospitalized), YLD_2 (individuals with

severe illness who had no sequelae), and YLD_3 (individuals with severe illness who developed LTS).

Raw data calculations:
Y LL calculations:

DISEASE:	***Rocky Mountain spotted fever***	Updated:	*8-Feb-20*
REGION:	***Arizona tribal communities***	By:	*Naomi Drexler*
PERIOD:	***2002-2017***	Status:	*Final*

THIS TEMPLATE ENABLES CALCULATION OF YLL (See Part A below in rows 25 to 102)
YLD (See Part B below in rows 105 to 133)
DALYs (See Part C below in rows136 to 150)

IF YOU HAVE MORE THAN ONE SEQUELA FOR A DISEASE, CREATE A COPY OF THIS TEMPLATE FOR EACH SEQUELA AND ADD THE DALYs FOR ALL SEQUELAE.

1. Enter disease name, region and period in the yellow cells above.
2. Enter update information in the purple cells above right.
3. If required, change discount and age weight parameters for DALY calculation in the grey box below.
4. If required, change age groups (insert additional rows if needed, and adjust lookup formulae for standard LE)

DALY Parameters		
0.03	Discount rate (r)	Standard discount rate is 0.03
0.04	Beta (b)	Standard age weights use beta=0.04
0.1658	Constant (C)	Standard age weights use C=0.1658
-0.07	-(b+r)	
1	K	K=0 (no age weights) to 1 (full age weights)

A. YLL template

A1.Enter population data in yellow cells below.
A2. Enter numbers of deaths for 5 year age groups in green cells below. (or death rates in next column and calculate numbers of deaths)
A3. If necessary, modify average ages at death (blue column). This may be important for lowest and highest age groups.

	Population	Deaths	Deaths per 1,000	Av. Age at death	Standard LE		YLLs	YLL per 1,000
Males								
Less than 5 years	1,435	2	1.39	3.5	76.9	1.000	71	49.8
5-9	1,210	2	1.65	7.5	72.9	1.000	74	61.5
10-14	1,065	0	0.00	12.9	67.5	1.000	-	0.0
15-19	1,266	0	0.00	18.1	62.4	1.000	-	0.0
20-24	1,054	0	0.00	22.5	57.9	1.000	-	0.0
25-29	856	0	0.00	27.5	53.0	1.000	-	0.0
30-34	624	1	1.60	34.0	46.6	1.000	27	43.5
35-39	569	3	5.27	37.3	43.3	1.000	75	132.0
40-44	697	0	0.00	42.6	38.1	1.000	-	0.0
45-49	670	0	0.00	47.7	33.2	1.000	-	0.0
50-54	606	1	1.65	51.0	30.1	1.000	17	27.3
55-59	477	0	0.00	57.6	23.9	1.000	-	0.0
60-64	374	0	0.00	62.7	19.5	1.000	-	0.0
65-69	226	0	0.00	67.7	15.4	1.000	-	0.0
70-74	163	0	0.00	72.6	11.8	1.000	-	0.0
75-79	94	1	10.64	78.0	8.5	1.000	4	41.0
80-84	40	0	0.00	82.4	6.4	1.000	-	0.0
85+	26	0	0.00	89.0	3.9	1.000	-	0.0
Total	11,452	10	0.87	29.7	51.5		269	23.4
Females								
Less than 5 years	1,464	2	1.37	4.0	78.9	1.000	72	49.4
5-9	1,175	2	1.70	5.5	77.5	1.000	74	62.6
10-14	1,062	1	0.94	14.0	69.0	1.000	37	35.0
15-19	1,250	0	0.00	17.9	65.2	1.000	-	0.0
20-24	1,089	0	0.00	22.6	60.5	1.000	-	0.0
25-29	878	0	0.00	27.5	55.7	1.000	-	0.0
30-34	650	0	0.00	32.6	50.7	1.000	-	0.0
35-39	617	0	0.00	37.5	45.9	1.000	-	0.0
40-44	773	0	0.00	42.7	41.0	1.000	-	0.0
45-49	720	0	0.00	47.7	36.2	1.000	-	0.0
50-54	650	1	1.54	53.0	31.2	1.000	16	24.6
55-59	528	1	1.89	55.0	29.4	1.000	15	28.2
60-64	394	0	0.00	62.6	22.5	1.000	-	0.0
65-69	291	0	0.00	67.6	18.2	1.000	-	0.0
70-74	229	0	0.00	72.6	14.1	1.000	-	0.0
75-79	145	0	0.00	77.6	10.5	1.000	-	0.0
80-84	72	0	0.00	82.6	7.5	1.000	-	0.0
85+	38	0	0.00	90.0	4.3	1.000	-	0.0
Total	12,025	7	0	20.1	63.2		214	17.8

A1. YLL in study age groups

	Population	Deaths	Deaths per 1,000	Av. Age at death			YLLs	YLL per 1,000
Males								
0-4	1,435	2	1.4	3.5			71	49.8
5-14	2,275	2	0.9	7.5			74	32.7
15-29	3,176	-	0.0				-	0.0
30-44	1,890	4	2.1	36.5			102	54.1
45-59	1,753	1	0.6	51.0			17	9.4
60-69	600	-	0.0				-	0.0
70-79	257	1	3.9	78.0			4	15.0
80+	66	-	0.0				-	0.0
Total	11,452	10	0.9	29.7			269	23.4
Females								
0-4	1,464	2	1.4	4.0			72	49.4
5-14	2,237	3	1.3	8.3			111	49.5
15-29	3,217	-	0.0				-	0.0
30-44	2,040	-	0.0				-	0.0
45-59	1,898	2	1.1	54.0			31	16.3
60-69	685	-	0.0				-	0.0
70-79	374	-	0.0				-	0.0
80+	110	-	0.0				-	0.0
Total	12,025	7	0.6	20.1			214	17.8

YLD from moderate illness:

As non-hospitalized cases were not included in the LTS study, the authors used the age distribution of cases of all RMSF cases in Arizona 2002–2011(Traeger et al., 2015).

DISEASE:	***Rocky Mountain spotted fever***	Updated:	*8-Feb-20*
REGION:	***Arizona tribal communities***	By:	*Naomi Drexler*
PERIOD:	***2002-2017***	Status:	*Final*

THIS TEMPLATE ENABLES CALCULATION OF YLL (See Part A below in rows 25 to 102)
YLD (See Part B below in rows 105 to 133)
DALYs (See Part C below in rows136 to 150)

IF YOU HAVE MORE THAN ONE SEQUELA FOR A DISEASE, CREATE A COPY OF THIS TEMPLATE FOR EACH SEQUELA AND ADD THE DALYs FOR ALL SEQUELAE.

1. Enter disease name, region and period in the yellow cells above.
2. Enter update information in the purple cells above right.
3. If required, change discount and age weight parameters for DALY calculation in the grey box below.
4. If required, change age groups (insert additional rows if needed, and adjust lookup formulae for standard LE)

DALY Parameters

0.03	Discount rate (r)	Standard discount rate is 0.03
0.04	Beta (b)	Standard age weights use beta=0.04
0.1658	Constant (C)	Standard age weights use C=0.1658
-0.07	-(b+r)	
1	K	K=0 (no age weights) to 1 (full age weights)

B. YLD template

B1. Enter population data in yellow cells below (if have not entered them above for YLL).
B2. Enter incidence rates, age at onset and duration in green cells
B3. Enter disability weights in blue cells below.

*Based on proportion by age Traeger et al. in all RMSF cases

	Population	Incidence	Incidence* per 1,000	Age at onset	Duration (years)	Disability Weight	YLDs	YLD per 1,000
Males								
0-4	1,435	20	0	2.1	0.0	0.053	0.0	0.0
5-14	2,275	19	0	8.0	0.0	0.053	0.0	0.0
15-29	3,176	12	0	22.2	0.0	0.053	0.0	0.0
30-44	1,890	8	0	38.0	0.0	0.053	0.0	0.0
45-59	1,753	6	0	52.9	0.0	0.053	0.0	0.0
60-69	600	3	2	64.7	0.0	0.053	0.0	0.0
70-79	257	2	10	75.0	0.0	0.053	0.0	0.0
80+	66	0	30	85.0	0.0	0.053	-	0.0
Total	11,452	70	6.1	20.4	0.0	0.05	0.0	0.0
Females								
0-4	1,464	23	16	2.2	0.0	0.053	0.0	0.0
5-14	2,237	18	8	8.5	0.0	0.053	0.0	0.0
15-29	3,217	13	4	21.4	0.0	0.053	0.0	0.0
30-44	2,040	13	6	36.4	0.0	0.053	0.0	0.0
45-59	1,898	8	4	50.7	0.0	0.053	0.0	0.0
60-69	685	3	4	62.7	0.0	0.053	0.0	0.0
70-79	374	2	5	74.0	0.0	0.053	0.0	0.0
80+	110	0	0	85.0	0.0	0.053	-	0.0
Total	12,025	80	6.7	21.2	0.0	0.05	0.1	0.0

YLD from severe illness without LTS:

DISEASE:	***Rocky Mountain spotted fever***	Updated:	*8-Feb-20*
REGION:	***Arizona tribal communities***	By:	*Naomi Drexler*
PERIOD:	***2002-2017***	Status:	*Final*

THIS TEMPLATE ENABLES CALCULATION OF YLL (See Part A below in rows 25 to 102)
YLD (See Part B below in rows 105 to 133)
DALYs (See Part C below in rows136 to 150)

IF YOU HAVE MORE THAN ONE SEQUELA FOR A DISEASE, CREATE A COPY OF THIS TEMPLATE FOR EACH SEQUELA AND ADD THE DALYs FOR ALL SEQUELAE.

1. Enter disease name, region and period in the yellow cells above.
2. Enter update information in the purple cells above right.
3. If required, change discount and age weight parameters for DALY calculation in the grey box below.
4. If required, change age groups (insert additional rows if needed, and adjust lookup formulae for standard LE)

DALY Parameters

0.03	Discount rate (r)	Standard discount rate is 0.03
0.04	Beta (b)	Standard age weights use beta=0.04
0.1658	Constant (C)	Standard age weights use C=0.1658
-0.07	-(b+r)	
1	K	K=0 (no age weights) to 1 (full age weights)

B. YLD template

B1. Enter population data in yellow cells below (if have not entered them above for YLL).
B2. Enter incidence rates, age at onset and duration in green cells
B3. Enter disability weights in blue cells below.

	Population	Incidence* (*Based on LTS study)	Incidence per 1,000	Age at onset	Duration (years)	Disability Weight	YLDs	YLD per 1,000
Males								
0-4	1,435	5	3	1.6	0.0	0.210	0.0	0.0
5-14	2,275	11	5	7.7	0.0	0.210	0.1	0.0
15-29	3,176	4	1	20.5	0.0	0.210	0.0	0.0
30-44	1,890	3	2	35.6	0.0	0.210	0.0	0.0
45-59	1,753	1	1	59.0	0.0	0.210	0.0	0.0
60-69	600	2	3	63.5	0.0	0.210	0.0	0.0
70-79	257	1	4	70.0	0.0	0.210	0.0	0.0
80+	66	0	0	85.0	0.0	0.210	-	0.0
Total	11,452	27	2.4	19.9	0.0	0.21	0.2	0.0
Females								
0-4	1,464	6	4	2.0	0.0	0.210	0.0	0.0
5-14	2,237	5	2	6.6	0.0	0.210	0.0	0.0
15-29	3,217	1	0	29.0	0.0	0.210	0.0	0.0
30-44	2,040	6	3	37.3	0.0	0.210	0.1	0.0
45-59	1,898	7	4	53.2	0.0	0.210	0.1	0.0
60-69	685	1	1	68.0	0.0	0.210	0.0	0.0
70-79	374	1	3	74.0	0.0	0.210	0.0	0.0
80+	110	0	0	85.0	0.0	0.210	-	0.0
Total	12,025	27	2.2	30.1	0.0	0.21	0.2	0.0

YLD from severe illness with LTS:

DISEASE:	***Rocky Mountain spotted fever***	Updated: *8-Feb-20*
REGION:	***Arizona tribal communities***	By: *Naomi Drexler*
PERIOD:	***2002-2017***	Status: *Final*

THIS TEMPLATE ENABLES CALCULATION OF YLL (See Part A below in rows 25 to 102)
YLD (See Part B below in rows 105 to 133)
DALYs (See Part C below in rows136 to 150)

IF YOU HAVE MORE THAN ONE SEQUELA FOR A DISEASE, CREATE A COPY OF THIS TEMPLATE FOR EACH SEQUELA AND ADD THE DALYs FOR ALL SEQUELAE.

1. Enter disease name, region and period in the yellow cells above.
2. Enter update information in the purple cells above right.
3. If required, change discount and age weight parameters for DALY calculation in the grey box below.
4. If required, change age groups (insert additional rows if needed, and adjust lookup formulae for standard LE)

DALY Parameters

0.03	Discount rate (r)	Standard discount rate is 0.03
0.04	Beta (b)	Standard age weights use beta=0.04
0.1658	Constant (C)	Standard age weights use C=0.1658
-0.07	-(b+r)	
1	K	K=0 (no age weights) to 1 (full age weights)

B. YLD template

B1. Enter population data in yellow cells below (if have not entered them above for YLL).
B2. Enter incidence rates, age at onset and duration in green cells
B3. Enter disability weights in blue cells below.

	Population	*Based on LTS study Incidence*	Incidence per 1,000	Age at onset	Duration (years)	Disability Weight	YLDs	YLD per 1,000
Males								
0-4	1,435	1	1	2.0	10.0	0.426	3	2.1
5-14	2,275	0	0	10.0	10.0	0.426	-	0.0
15-29	3,176	0	0	22.5	10.0	0.426	-	0.0
30-44	1,890	1	1	39.0	10.0	0.426	5	2.5
45-59	1,753	1	1	57.0	10.0	0.426	3	1.8
60-69	600	0	0	65.0	10.0	0.426	-	0.0
70-79	257	0	0	75.0	10.0	0.426	-	0.0
80+	66	0	0	85.0	10.0	0.426	-	0.0
Total	11,452	3	0.3	32.7	10.0	0.43	11	0.9
Females								
0-4	1,464	3	2	2.8	10.0	0.426	10	6.7
5-14	2,237	0	0	10.0	10.0	0.426	-	0.0
15-29	3,217	0	0	22.5	10.0	0.426	-	0.0
30-44	2,040	2	1	39.0	10.0	0.426	9	4.5
45-59	1,898	1	1	54.0	10.0	0.426	3	1.8
60-69	685	0	0	65.0	10.0	0.426	-	0.0
70-79	374	0	0	75.0	10.0	0.426	-	0.0
80+	110	0	0	85.0	10.0	0.426	-	0.0
Total	12,025	6	0.5	23.4	10.0	0.43	22	1.9

Total DALYs:

C. Total DALYS = YLL+YLD1+YLD2+YLD3									
		Males			*Females*			*Persons*	
	Population	DALYs	DALYs per 1,000	population	DALYs	DALYs per 1,000	Population	DALYs	DALYs per 1,000
Age									
0-4	1435	74	51.9	1464	82	56.1	2899	157	54.0
5-14	2275	75	32.8	2237	111	49.6	4512	185	41.1
15-29	3176	0	0.0	3217	0	0.0	6393	0	0.0
30-44	1890	107	56.6	2040	9	4.6	3930	116	29.6
45-59	1753	20	11.3	1898	34	18.1	3651	54	14.8
60-69	600	0	0.0	685	0	0.0	1285	0	0.0
70-79	257	4	15.0	374	0	0.0	631	4	6.1
80+	66	0	0.0	110	0	0.0	176	0	0.0
Total	11452	280	24.4	12025	237	19.7	23477	516	22.0

Limitations of DALY calculations

Overall, DALY calculations are based on a small cohort of individuals and may not accurately reflect the burden of disease more broadly. Years of life lost (YLL) were the most substantial contributor to DALYs from RMSF. Incident deaths captured in this study are likely a good representation of the number of deaths during the specified time periods as there was a high acuity during this time for investigating suspicious deaths with fever and rash for RMSF. Years of life disabled (YLD) are a function of the incidence of each outcome within a prescribed population, the disability weight, and the duration of disability. Each of these values were estimated based on available data. Incidence of disability were obtained from the LTS study in chapter 3. As non-hospitalized cases were not described in this study, age distributions were based on distributions of all RMSF cases (Traeger et al., 2015); the most thorough description of Arizona RMSF cases to date. Number and age distribution of individuals hospitalized for RMSF with and without LTS were obtained from the study described in chapter 3. While the description of hospitalizations are likely accurate, the incidence of sequelae may be incomplete as not all individuals who survived their RMSF experience agreed to be evaluated for neurologic sequelae.

Duration of disability were based on previous studies 5 days for non-hospitalized cases, assuming treatment within the first 2 days and 3 days of convalescence; duration of disability among hospitalized individuals without sequelae were based on self-reported time to recovery in the long-term sequalae study (2 days of illness and 12 days of recovery), and duration of LTS was estimated at 10 years following longest duration observed in the Arizona cohort. Lastly, disability weights specific for RMSF and RMSF-related sequelae are not available in the peer-reviewed literature. Study authors used the disability weights of moderate and severe infectious diseases, and disability weight ascribed to stroke with moderate and severe long-term consequences to estimate a comparable result for RMSF-related disability. Differences in these values may impact the burden calculation. YLD made only moderate contributions to overall disease burden, thus the authors do not believe these limitations of substantially inflate our calculations.