Resolution No. 06-2014-68

WHITE MOUNTAIN APACHE TRIBE

A Sovereign Tribal Nation

(Approving Publication of Manuscripts relating to clinical care and prevention of RMSF, Rickettisal Zoonoses Branch, Division of Vector-borne Diseases, Centers for Disease Control)

WHEREAS, the Tribal Council of the White Mountain Apache Tribe ("Tribe") is entrusted by the Tribe's Constitution to act in all matters that concern the welfare of the Tribe, to manage all economic affairs and enterprises of the Tribe, and to regulate subordinate organizations for economic and other purposes; and

WHEREAS, the Centers for Disease Control and Prevention ("CDC") has previously received approval by Resolution of the Tribal Council to conduct certain research studies in compliance with Tribal guidelines for the improvement of community health; and

WHEREAS, publication and presentation of such information will be important and any manuscripts produced from the information discovered through this study will be presented at public forums for the purpose of increasing knowledge and treatment of RMSF, so long as publications or presentations do not result in harm to individuals or the White Mountain Apache Tribe; and

WHEREAS, the Executive Director of the Tribe's Department of Health and Human Services this day presents a request of the Centers for Disease Control's Rickettsial Zoonoses Branch, Division of Vector-borne Diseases, to publish a manuscript by Marc Traeger and others, entitled "**Differentiation of Rocky Mountain spotted fever from similar illness in a highly endemic area: Arizona, 2002-2011**," as attached and incorporated by this reference; and

WHEREAS, the Executive Director of the Tribe's Department of Health and Human Services this day presents a request of the Centers for Disease Control's Rickettsial Zoonoses Branch, Division of Vector-borne Diseases, to publish a manuscript by Joanna Regan and others, entitled "**Risk factors for fatal outcome from Rocky Mountain spotted fever in a highly endemic area: Arizona, 2002-2011**," as attached and incorporated by this reference; and

WHEREAS, the Executive Director of the Tribe's Department of Health and Human Services this day presents a request of the Centers for Disease Control's Rickettsial Zoonoses Branch, Division of Vector-borne Diseases, to publish a manuscript by Naomi Drexler and others, entitled "**Medical and indirect costs associated with a Rocky Mountain spotted fever epidemic in Arizona, 2002-2011**," as attached and incorporated by this reference; and

Resolution No. 06-2014-68

WHEREAS, the Executive Director of the Tribe's Department of Health and Human Services this day presents a request of the Centers for Disease Control's Rickettsial Zoonoses Branch, Division of Vector-borne Diseases, to share a white paper by Jennifer McQuiston and others with other tribal, state, and federal partners, entitled "**Rocky Mountain spotted fever on tribal lands in Arizona, 2003-2012: the story from emergence of a new epidemic to control and prevention**," as attached and incorporated by this reference; and

WHEREAS, the Executive Director of the Tribe's Department of Health and Human Services this day presents a request of the Centers for Disease Control's Rickettsial Zoonoses Branch, Division of Vector-borne Diseases, to publish a manuscript by Suzanne Todd and others, entitled "**No Evidence of Tooth Staining Following Doxycycline Administration in Children for Treatment of Rocky Mountain Spotted Fever**," as attached and incorporated by this reference; and

WHEREAS, the White Mountain Apache Tribe Health Advisory Board has reviewed this proposal at a Health Board meeting in May 2014; and

WHEREAS, the Tribal Council finds it in the best interest of the White Mountain Apache Tribe to approve the manuscripts listed above, as proposed by CDC.

BE IT RESOLVED by the Tribal Council of the White Mountain Apache Tribe that it hereby approves the publication of the manuscripts listed above.

BE IT FURTHER RESOLVED by the Tribal Council of the White Mountain Apache Tribe that it hereby directs that in the event that this Resolution conflicts with a prior Resolution or Policy, this Resolution shall supersede and govern over the conflicting subject matter.

BE IT FURTHER RESOLVED by the Tribal Council of the White Mountain Apache Tribe that it hereby directs that in the event this Resolution directly conflicts with the Tribal Constitution, Tribal Ordinances or Federal Laws, or any material facts concerning the issues presented are later found to be false, this Resolution shall be deemed null and void and have no legal effect.

BE IT FURTHER RESOLVED by the Tribal Council of the White Mountain Apache Tribe that the Chairman, or in his absence, the Vice-Chairman, is hereby authorized to execute any and all documents necessary to effectuate the intent of this Resolution.

The foregoing resolution was on **JUNE 6, 2014** duly adopted by a vote of **EIGHT** for and **ZERO** against with **ONE** abstaining by the Tribal Council of the White Mountain Apache Tribe, pursuant to authority vested in it under the enumerated powers listed in Article IV, Section 1 of the WMAT Constitution, so ratified on September 30, 1993, and federally recognized pursuant to Section 16 of the Indian Reorganization Act of June 18, 1934 (48 Stat. 984).

Kas 3 Vice Acting 6/10/14
Ronnie Lupe, Tribal Chairman Date

Doreen T. Numkena 6/10/2014
Doreen T. Numkena, Tribal Secretary Date

Differentiation of Rocky Mountain spotted fever from similar illness in a highly endemic area: Arizona, 2002-2011

Authors: Marc S. Traeger[1], Joanna Regan[2], Dwight Humpherys[1], Dianna Mahoney[1], Michelle Martinez[1], Ginny L. Emerson[3], Danielle Tack[4], Aimee Geissler[5], Seema Yasmin[4], Regina Lawson[6], Charlene Hamilton[7], Velda Williams[8], Craig Levy[9], Ken Komatsu[9], Jennifer McQuiston[2], David A. Yost[1]

1. Whiteriver Public Health Service Hospital, Whiteriver, AZ. 2. Rickettsial Zoonoses Branch, Division of Vectorborne Diseases, National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Centers for Disease Control and Prevention (CDC), Atlanta, Ga. 3. Pox virus and Rabies Branch, Division of High Consequence Pathogens and Pathogenicity, NCEZID, CDC, Atlanta, Ga. 4. Epidemic Intelligence Service, Division of Applied Public Health Training, Epidemiology Program Office, Centers for Disease Control and Prevention (CDC), Atlanta, Georgia. 5. DVBD 6. Student 7. Division of Health programs, White Mountain Apache Tribe, Whiteriver, AZ. 8. Department of Health & Human Services, San Carlos Apache Tribe, San Carlos, AZ. 9. Bureau of Epidemiology and Disease Control, Division of Public Health Services, Arizona Department of Health Services, Phoenix, Arizona

Keywords: Rocky Mountain spotted fever, American Indians, AIAN, Tick-borne, *Rhipicephalus sanguineus*

Running Title: Characterization of RMSF in Arizona

Corresponding Author: Marc Traeger, MD

Whiteriver Indian Health Service Hospital

200 West Hospital Drive

Whiteriver, AZ

Marc.traeger@ihs.gov 928-338-3759

Summary: Rocky Mountain spotted fever (RMSF) emerged in Arizona this past decade on several American Indian reservations. This study characterizes RMSF in this unique environment, its differences compared to other settings, and what distinguishes it from other similar illnesses.

Abstract:

Background: Rocky Mountain spotted fever (RMSF) has emerged as a significant cause of morbidity and mortality since 2002 on tribal lands in Arizona. The explosive nature of this outbreak and the recognition of an unexpected tick vector, *Rhipicephalus sanguineus,* prompted an investigation to characterize RMSF in this unique setting, and compare and differentiate RMSF cases from similar illnesses.

Methods: We compared medical records of 205 RMSF cases and 175 non-RMSF illnesses that prompted RMSF testing during 2002-2011 from two Indian reservations in Arizona.

Results: RMSF cases occurred year-round and peaked later (July-September) than RMSF cases reported from other U.S regions. Cases were younger (median age 11 years) and reported fever and rash less frequently as well as less tick exposure compared to other U.S. cases. Fever was present in 81% of cases but not significantly different from that in non-RMSF illnesses. Classic laboratory abnormalities such as low sodium and platelet counts had small and subtle differences between cases and non-RMSF illnesses. Imaging studies reflected the variability and complexity of the illness, but proved unhelpful in clarifying the early diagnosis.

Conclusions: RMSF epidemiology in this region appears different than RMSF elsewhere in the U.S. No specific pattern of signs, symptoms or laboratory findings occurred with enough frequency to consistently differentiate RMSF from other illnesses. Due to the non-specific and variable nature of RMSF presentations, clinicians in this region should aggressively treat febrile illnesses and sepsis with doxycycline for suspected RMSF.

Introduction

Rocky Mountain spotted fever (RMSF), caused by the tick-borne pathogen *Rickettsia rickettsii,* was reported only sporadically in Arizona prior to a fatal case confirmation on an American Indian reservation in 2003. An outbreak investigation uncovered cases beginning on the same reservation as early as 2002 and an unexpected vector, *Rhipicephalus sanguineus* (the brown dog tick), as responsible for this emerging infection on tribal lands [1,2]. Through 2011, 219 human RMSF cases and 16 fatalities (case fatality rate 7.3%) were reported from four Arizona reservations, and two additional reservations reported evidence of RMSF exposure in humans and/or dogs during 2012 [3,4]. All affected tribes reported *R. sanguineous* infestation and a large population of free-roaming dogs, as described in the original investigation [1,2]. In addition, during the last decade outbreaks of RMSF caused by *R. sanguineus* harbored on dogs have been documented in Mexico, and *R. sanguineus* has been reported as a vector of RMSF in South America [5,6]. Despite the almost concurrent recognition of recent outbreaks in Mexico, *R. sanguineus* ticks and the *R. rickettsii* organism found in Arizona both appear genetically distinct from those in Mexico, and the origin of the Arizona RMSF outbreak and the reasons for its recent emergence remain unclear [7,8].

RMSF is easily treated with early appropriate antibiotic therapy. Doxycycline is recommended in patients of all ages; classes of drugs other than tetracycylines, including other broad-spectrum antibiotics, are not effective [9,10,11]. Diagnostic testing lacks sensitivity when patients typically present in the first days of illness[12]. The nonspecific clinical presentation of RMSF and the necessity of choosing an antibiotic not typically used for other common illnesses or sepsis makes cases challenging to identify and manage, and also underscores the importance for physicians to have information to guide early clinical decisions. Understanding geographic patterns of infection and identifying key epidemiologic risk factors are important variables in these decisions.

The Arizona RMSF outbreak is unusual because it occurred in association with a previously unrecognized tick vector in the U.S., and emerged rapidly in a region where RMSF has not been

previously recognized. Its recent detection in tribal communities, and its high, focal incidence in a population where other multiple documented underlying health disparities exist [13,14] lends importance and urgency to characterizing the epidemiology of this outbreak. Vector, pathogen, environmental factors, and human factors may all influence the presentation and severity of RMSF in humans, including geographical location and age, race, gender and underlying health status of those infected [9,15-18]. The unique combination of host, vector, pathogen, and environmental variables within this outbreak suggest important differences in the clinical manifestations and RMSF epidemiology may exist compared to the U.S. experience with RMSF. This study describes RMSF presentation in this emerging setting to aid the differentiation of this potentially deadly disease from similar illnesses.

Methods

Data, definitions and analysis

The project was reviewed by the Centers for Disease Control and Prevention's Institutional Review Board and was judged a public health response rather than research. We performed a retrospective medical record review of patients prompting *R. rickettsii* testing from June 1, 2002-September 30, 2011 in Community A, and January 1, 2005-September 30, 2011 in Community B at community Indian Health Service (IHS) health facilities and 11 referral hospitals. Patient records were reviewed if at least one illness symptom prompted RMSF testing; those tested without symptoms following a tick bite or exposures were excluded. This broad definition was intended to capture a full spectrum of illness in patients tested for RMSF, considering that RMSF illnesses may be atypical or nonspecific.

A confirmed RMSF case was defined as a person reporting illness and:

- Serological evidence of a fourfold change in immunoglobulin G or M (IgG or IgM)-specific antibody titer reactive with *Rickettsia rickettsii* antigen by indirect immunofluorescence assay (IFA) between paired serum specimens taken after the onset of symptoms with at least one titer of 1:128 dilution or higher, or

- Detection of *R. rickettsii* DNA in a clinical specimen via amplification of a specific target by polymerase chain reaction (PCR) assay, or

- Demonstration of spotted fever group antigen in a biopsy or autopsy specimen by Immunohistochemistry staining (IHC).

A probable RMSF case was defined as a person reporting illness and who

- Did not meet criteria for confirmed case, and
- Had serologic evidence of elevated IgG or IgM antibody reactive with *R. rickettsii* antigen by IFA with at least one titer of 1:128 dilution or higher.

A non-RMSF illness was defined as a person reporting illness and

- Had at least two negative serologic titers (less than 1:64) and
- The second titer drawn no earlier than day 14 after symptom onset.

All patients who met one of these definitions were included in this review. Additional confirmation was performed on a subset of fatal case samples using sequencing and restriction fragment length polymorphism (RFLP) analysis targeting rickettsial DNA to further confirm *R. rickettsii* as the cause of death. Patients with titers of 1:64 that did not increase were excluded from the review, because this low level reactivity was considered insufficient evidence to confidently confirm or rule out recent infection.

Demographic information, medical history, history of the illness and clinical characteristics including signs, symptoms, laboratory and imaging findings, treatment, and course of illness were recorded on

anonymous case report forms. Symptoms or exposures were excluded from analysis if there was no documentation of their presence or absence. Data were analyzed using Epi Info [19]. Statistical differences in categorical variables were evaluated using a chi-square test and when the expected value of a cell was less than 5, Fisher Exact test was used. Statistical differences in continuous variables were evaluated using an ANOVA test or the Mann-Whitney/Wilcoxon Two-Sample Test when a non-parametric test was more appropriate. Statistical significance was set at alpha (α)=0.05.

Health facilities and service populations

Community A and B health facilities are rural 40-bed and 8-bed IHS hospital and outpatient facility complexes on American Indian reservations in eastern Arizona, with user populations of >16,100 and >11,900 persons respectively. Neither facility has an intensive care unit (ICU), resulting in transfers of patients for specialized care to Arizona referral facilities.

Definitions of terms

Case: A confirmed or probable RMSF case.

Children: Patients under age 18 years.

Dog contact: Dog ownership, dogs frequenting homes where patients stay or visit, feral dog feeding, etc.

Fever: Temperature ≥ 38°C (100.4°F) or a report of fever by the patient or caretaker.

Tick exposure: Acknowledgement of ticks, including but not limited to tick bites, ticks observed in the home or frequented environments, or ticks discovered on pets.

Sick contact: Documentation of a patient contact who was ill at the time of patient presentation.

Results

Demographics

We identified 205 cases and 175 non-RMSF illnesses (Table 1). Among all subjects, 52% were male and all were American Indians except one; the exception worked on tribal lands. The median age among cases was 11 years, significantly higher than that of non-RMSF illnesses (2 years, Figure 1). Among cases, 85 were confirmed RMSF and 120 were probable. Cases occurred in each month, but seasonal differences were reflected by different peak months in Community A and B (September and July respectively, Figure 2).

Exposures and historical medical conditions

Dog contact and tick exposure were significantly more frequent among cases than non-RMSF illnesses (86% vs. 69%, 55% vs. 41% respectively, Table 1). Sick contacts and travel were both significantly more frequent among cases than non-RMSF illness (17/43 [40%] vs. 8/39 [21%], 6/37 [16%] vs. 1/35[3%] respectively). The only medical history significantly more frequent among RMSF cases than non-RMSF illnesses was asthma, occurring in 8% of cases. While alcoholism and diabetes among adults were the most common underlying health conditions among cases, the frequency did not differ significantly from non-RMSF illnesses (27% vs. 23% and 22% vs. 20% respectively).

Medical care and treatment

Cases and non-RMSF illnesses both presented to health facilities a median of two times during the illness (cases range 0-9, mean=1.87; non-RMSF illness range 0-7, mean=1.94). Both first presented for care on median day 2 (cases range 1-11, non-RMSF illness range 1-12). Cases were significantly more likely to be treated with doxycycline than non-RMSF illnesses (87% vs. 78% respectively, Risk Ratio [RR]=1.69, 95% Confidence Interval [CI]=1.09-2.62), and children more often than adults (91% vs. 81% respectively, RR=2.14, CI=1.05-4.37).

Fifteen fatalities (7.3%) and 86 (42%) hospitalizations (including 29 ICU admissions [14.1%]) occurred among cases. There were no deaths and 29 (16.6%) hospitalizations (7 ICU admissions, [4.0%]) among non-RMSF illnesses. Cases were significantly more likely to result in fatality (RR undefined, p=0.0007), hospitalization (RR 2.53, 95% CI=1.75-3.66, p<0.0001), and ICU admission (RR 3.53, 95% CI=1.59-7.87, p<0.0001) compared to non-RMSF illnesses.

Signs and Symptoms

Fever was frequent but not universal among cases (81%, Table 2). Temperature maximum and range was not significantly different between cases and non-RMSF illnesses (101.8 [range 96.4-106.3] vs. 101.2 [95.8-106.4], Table 2).

Rash was present in 130/192 (68%) of cases and 92/166 (55%) of non-RMSF illnesses. Twenty of 119 cases with rash descriptions reported pruritic rash (17%); another 4% were vesicular and 2% were urticarial, descriptions not usually associated with RMSF.

The triad of fever, rash and tick exposure was significantly more frequent among cases than non-RMSF illnesses (32% vs. 16% respectively, RR 1.46, CI 1.16-1.84), but was not present in a majority of cases.

Headache occurred in a majority of cases, but was not statistically more frequent than non-RMSF illnesses (58% vs. 48%). Nausea (47%), red or draining eyes (15%), mental status change (17%), peripheral edema (12%), hepatomegaly (5%) and neck pain (11%) were all significantly more frequent among cases than non-RMSF illnesses, but occurred in a minority of patients.

Laboratory findings

Initial laboratory value means are listed in Table 3.The mean serum sodium level was significantly lower among cases than non-RMSF illnesses, but only by 2 mEq/L (136 vs. 138 respectively); chloride and potassium were similar (101 vs. 103, 3.9 vs. 4.2 respectively). Platelet count mean was significantly lower

among cases than non-RMSF illnesses, although it was not abnormally low for either group (269 $X10^3/mm^3$ vs. 350 $X10^3/mm^3$ respectively). However, initial platelet counts were low (<130 $X10^3$) in 17/141 (12%) cases, compared to only 2/144 (1.4%) among non-RMSF illnesses. White blood cell counts (WBC) were no different between cases and non-RMSF illnesses, but neutrophil count was significantly higher (67% vs. 56%) and lymphocyte and monocyte counts significantly lower (20% vs. 32%, 7% vs. 8% respectively) among cases compared to non-RMSF illnesses.

Liver test means were generally elevated among both adult and child cases with the exception of normal alkaline phosphatase levels in children and bilirubin among all patients. Only alanine transaminase (ALT) and aspartate aminotransferase (AST) among adult cases were significantly higher among cases than non-RMSF illnesses; no liver tests were significantly more elevated among child cases than non-RMSF illnesses. Tests evaluating inflammatory and coagulation status (C-reactive protein, D-dimer, PT, PTT, INR, fibrinogen levels) were infrequently performed; when performed, PT, INR, and D-dimer were significantly different among cases compared to non-RMSF illness, but these tests were usually conducted late in the course of illness.

Imaging studies

Eighty-five (41.5%) cases underwent at least one chest x-ray. Of these, 35 (41%) were initially read as normal. Chest x-ray reports from nineteen (22%) cases specifically suggested pneumonia as a diagnosis. Twenty-eight (13.6%) cases underwent at least one head computerized tomography (CT) scan, and nine chest (4.4%), eleven abdomen (5.4%), and four pelvis CTs (2.0%) were performed. Magnetic Resonance Imaging (MRI) studies were reported in six cases including five head and one lower extremity image. Ultrasound studies were performed in 21(10.2%) cases including 17 abdominal, four chest or cardiac, and two extremity ultrasounds. Nine of 17 (52.9%) abdominal ultrasounds were abnormal. Reported abnormal ultrasound findings included abnormal gallbladder with thickened wall and

pericholecystic fluid, gallstone pancreatitis, cholelithiasis with pericholecystic fluid, thickened gallbladder wall with no stones, hepatosplenomegaly, and hepatic steatosis.

Discussion

This review characterizes RMSF epidemiology since its emergence in Arizona American Indian communities a decade ago. In this series, disease patterns differed notably from reports of RMSF cases in other parts of the United States [20]. Although RMSF in most regions of the United States tends to peak in June and July in concert with seasonal activity of *Dermacentor variabilis* and *Dermacentor andersoni* ticks, in Arizona human cases peaked in July in Community B, and in September in Community A (Figure 2). Both communities exhibited a bimodal pattern of disease onset, with declines between peaks of reported cases during June, the driest month in both communities. Aggregate cases peaked during July-October (54.6%), corresponding with seasonal monsoons and indicating that climatic factors such as moisture may contribute to the ecology of tick populations and RMSF transmission in this region. These data indicate the potential for human infection with RMSF exists year-round.

While fever was frequent among both cases and non-RMSF illnesses (81% and 84% respectively), it was not universally detected in all RMSF cases, and fever among cases was less frequent than has been reported in numerous other studies, ranging from 94-100% [20-27]. Fever is a required symptom for national RMSF reporting by the national Council of State and Territorial Epidemiologists (CSTE) case definition, which likely results in an inclusion bias and higher fever frequency among U.S. reported cases than may actually occur. Thirty-eight cases (19%) in our series lacked documented fever during the course of illness (including 8 confirmed cases), suggesting that non-febrile RMSF illness occurs in this patient population.

Strikingly, almost 50% of the cases in this review occurred in patients aged 0-10 years. The mean and median age among these cases (19.8 and 11 years, respectively) is lower than the mean and median

age of RMSF among the general U.S. population (46 and 42 years, respectively) [28] and is lower than the mean age of 33 years reported among American Indians nationwide [29]. The younger age observed among cases in this review may reflect the unique vector and other environmental factors in this region. The dog plays a central role in the RMSF transmission cycle in Arizona by harboring infected ticks [3,8,30]. Children may interact with dogs and their habitats more frequently than adults, resulting in greater exposure. In this series, the median age of those with non-RMSF illnesses was significantly lower than that of cases (2 vs. 11 years respectively). This is likely because fever was considered an important indicator to result in RMSF testing, and fever occurs commonly in young children.

Rash was significantly more frequent among cases than non-RMSF illnesses (68% vs. 55%), and less common than that reported in numerous other studies [20-23, 25-27]. Although rash is often considered a hallmark of RMSF, 60% of RMSF cases in this review lacked a demonstrable rash initially and 32% failed to develop any rash while ill. Fever and rash together occurred in significantly more cases (57%) than non-RMSF illnesses (41%), but this was too infrequent to recommend it as primary criteria to consider a RMSF diagnosis. Other than fever and rash, headache was the only other symptom that consistently occurred in a majority of patients (table 2). Cough, nasal congestion, ear pain and irritability were all symptoms that occurred significantly more frequently among non-RMSF illnesses than cases, but could not be used reliably to rule out RMSF since they also occurred in cases. Of the findings significantly more likely to occur in cases than non-RMSF illness, only nausea, red or draining eyes, and headache were reported before median day 3 of symptoms among cases [11].

Although abnormal laboratory findings may raise suspicion of RMSF and their presence should trigger appropriate treatment, this study confirms that in this patient population, the values may be only slightly abnormal or may not turn abnormal until disease is advanced. Therefore, the presence or absence of abnormal laboratory values cannot be relied upon to guide early treatment decisions.

Imaging procedures were conducted frequently in this series, and likely reflect the widespread vasculitis and organ involvement that accompanies most RMSF cases, prompting evaluation and

treatment for acute abdomen, pneumonia, or neurologic syndromes. Imaging studies may provide additional clinical information, but abnormal findings indicating nonspecific inflammation may unfortunately lead the clinician away from an underlying diagnosis of RMSF, and were generally unhelpful in establishing a diagnosis of RMSF for these patients. However, because 22% percent of chest x-ray reports suggested pneumonia and 59% of all chest-x-rays were abnormal, RMSF should be viewed as a potential etiology of community-acquired pneumonia (CAP) in this region, particularly during the months of March-November. National guidelines for CAP treatment include doxycycline alone or paired with a β-lactam antibiotic [31], and clinicians should consider using doxycycline as part of standard treatment protocol for CAP in patients from Arizona Indian reservations.

In conclusion, this review characterizes RMSF during the first decade of emergence among American Indians in Arizona. We found significant differences in the clinical presentation and epidemiology of disease in this area compared to other parts of the U.S., highlighting the need for region-specific medical education for providers practicing in this area. The variability of symptom frequency in this population makes a presumptive diagnosis of RMSF difficult for the clinician. Documented or subjective fever, present in 81% of patients and 100% of fatalities, was the most reliable indicator to guide timely, effective and optimal treatment, although fever was a late symptom in some fatalities [11]. No other specific signs or symptoms, either alone or in combination, were frequent enough to consistently identify at least two thirds of RMSF cases.

Providers in this region must remain vigilant for RMSF during different months and among younger ages than previously reported in the literature. The central role the dog plays in human exposure to rickettsial-containing *R. sanguineous* ticks emphasizes the importance of community-wide animal control and pet health programs, including tick prevention. The lack of a timely diagnostic RMSF test and the high fatality rate that occurs when RMSF treatment is delayed advocates that doxycycline be used aggressively among patients in this region presenting with a febrile illness and/or sepsis. Additional

analysis has been performed to investigate the high case fatality rate seen in this population, and is published by Regan et al. in the companion article in this issue [11].

Acknowledgments: The authors wish to thank tribal health officials who wish to remain anonymous, as well as the Indian Health Service and private health care providers who care for this patient population every day. Approval for the project was obtained from participating tribes, the Indian Health Service, and the Centers for Disease Control and Prevention (CDC). The project was intended to prevent disease in response to an immediate public health threat and was therefore judged exempt from CDC IRB on a non-research basis. The study was approved by Community A and B tribal councils through resolutions 11-2010-302 and AU-11-223 respectively.

The findings and conclusions in this report are those of the authors and no do not necessarily represent the official position of the Centers for Disease Control and Prevention. Reference to specific commercial products, manufacturers, companies, or trademarks do not constitute its endorsement or recommendation by the U.S. Government, HHS, or Centers for Disease Control and Prevention.

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Table 1: Demographics, exposures and past medical history among Rocky Mountain spotted fever (RMSF) cases and non-RMSF illness patients from two tribal communities in Arizona
*** Statistically significant difference**

Demographic	Cases	Non-RMSF illness	Risk Ratio	95% CI
Number of patients	205	175		
Age: Median/mean years (range)*	11/19.8 (7 mo. – 78 years)	2/11.0 (2 mo.-79 years)	P-value=0.000	
Race	204 AI, 1 White	175 American Indian	*NA*	*NA*
Male (%)	106/205 (52%)	92/174 (53%)	0.97	0.80-1.18
Exposures				
Dog contact*	77/90 (86%)	60/87 (69%)	1.73	1.08-2.77
Tick exposure*	73/132 (55%)	48/118 (41%)	1.32	1.04-1.67
Sick contacts*	17/43 (40%)	8/39 (21%)	1.50	1.01-2.20
Travel*	6/37 (16%)	1/35 (3%)	1.80	1.21-2.67
Past Medical History				
AIDS/HIV	0/205(0%)	0/174 (0%)	undefined	

Alcoholism >17yo	22/81 (27%)	8/35 (23%)	1.07	0.83-1.38
Asthma*	17/205 (8%)	2/174 (1%)	1.71	1.43-2.06
Autoimmune disorder	2/205 (1%)	3/174 (2%)	0.74	0.25-2.16
Cancer	1/205 (1%)	1/174 (1%)	0.92	0.23-3.71
CVA/stroke	1/205 (1%)	1/174 (1%)	0.92	0.23-3.71
Diabetes >17 y/o	18/82(22%)	7/35 (20%)	1.04	0.78-1.37
Deep venous thrombosis	1/205 (1%)	1/174 (1%)	0.92	0.23-3.71
G6PD[a]	0/205 (0%)	0/174 (0%)	undefined	
Heart disease	4/205 (13%)	3/174 (2%)	1.05	0.55-2.02
Hepatitis	3/204 (2%)	3/173 (2%)	0.92	0.41-2.10
Hypertension	26/205 (13%)	13/174 (8%)	1.27	0.99-1.62
Lung disease, chronic	4/205 (2%)	5/174 (3%)	0.82	0.39-1.71
Renal iInsufficiency/failure	0/204 (0%)	3/174 (2%)	0	0-1.65
Sickle cell disease	1/205 (1%)	1/174 (1%)	0.92	0.23-3.71
Thyroid disease	6/205 (3%)	4/174 (2%)	1.11	0.66-1.86
Transplant	0/205 (0%)	0/174 (0%)	undefined	
Tuberculosis	2/204 (1%)	2/174 (1%)	0.93	0.35-2.48

a. G6PD= Glucose-6-phosphate dehydrogenase deficiency

Table 2: Symptoms among Rocky Mountain spotted fever (RMSF) cases and non-RMSF illnesses from two tribal communities in Arizona

***Statistically significant difference**

Symptom	Cases	Non-RMSF illness	Risk Ratio	95% CI
General and skin				
Fever	164/202 (81%)	142/169 (84%)	0.92	0.73-1.15
Tmax – median (Tmax range)	101.8 (98.3-106.3)	101.0 (99.0-106.4)	P-value =0.896	
Rash*	130/192 (68%)	92/166 (55%)	1.28	1.04-1.59
Fever and rash*	108/190 (57%)	71/164 (43%)	1.29	1.06-1.57
Fever and tick exposure	58/131 (44%)	40/117 (34%)	1.22	0.96-1.53
Rash and tick exposure*	48/128 (38%)	23/114 (20%)	1.44	1.15-1.81
Triad (fever/rash/tick exposure)*	41/127 (32%)	18/113 (16%)	1.46	1.16-1.84
Headache	78/135 (58%)	37/77 (48%)	1.15	0.94-1.42
Fatigue	60/130 (46%)	23/65 (35%)	1.16	0.95-1.41
Myalgia	53/129 (41%)	28/61 (46%)	0.94	0.77-1.15
Chills	47/133 (35%)	24/69 (35%)	1.01	0.82-1.24
Lethargy	24/121 (20%)	12/57 (21%)	0.98	0.75-1.26
Irritability	20/123 (16%)	38/87 (44%)*	0.51	0.35-0.74
Lymphadenopathy	5/129 (4%)	7/92 (8%)	0.70	0.36-1.38

Head/Eyes/Ears/Nose/Throat				
Nasal congestion*	43/155 (28%)	66/136 (49%)	0.64	0.49-0.83
Sore throat	27/134 (20%)	12/76 (16%)	1.11	0.87-1.41
Red or draining eyes*	22/148 (15%)	9/111 (8%)	1.28	1.01-1.65
Ear pain	13/126 (10%)	15/69 (22%)	0.69	0.45-1.04
Periorbital edema	7/147 (5%)	3/105 (3%)	1.21	0.80-1.84
Pulmonary & Cardiovascular				
Cough*	68/169 (40%)	73/138 (53%)	0.79	0.64-0.98
Peripheral edema*	18/147 (12%)	3/120 (3%)	1.63	1.32-2.02
Chest pain	12/129 (9%)	4/65 (6%)	1.17	0.86-1.58
Wheezing	9/164 (6%)	14/147 (10%)	0.73	0.43-1.22
Gastrointestinal				
Nausea*	74/156 (47%)	38/109 (35%)	1.23	1.01-1.50
Emesis	77/169 (46%)	58/144 (40%)	1.10	0.90-1.35
Anorexia	51/125 (41%)	51/106 (48%)	0.87	0.68-1.11
Diarrhea	52/163 (32%)	45/137 (33%)	0.98	0.78-1.23
Abdominal pain	48/154 (31%)	25/115 (22%)	1.22	0.99-1.50
Hepatomegaly*	7/145 (5%)	1/124 (1%)	1.65	1.24-2.20

Jaundice	6/149 (4%)	3/113 (3%)	1.18	0.73-1.90
Dysphagia	3/120 (3%)	1/51 (2%)	1.07	0.60-1.90
Splenomegaly	2/143 (1%)	4/125 (3%)	0.62	0.20-1.93
Neurologic				
Dizziness	21/110 (19%)	5/48 (10%)	1.20	0.96-1.50
Mental status change*	29/169 (17%)	5/137 (4%)	1.66	1.38-1.99
Neck pain*	16/141 (11%)	2/74 (3%)	1.40	1.15-1.70
Seizure	7/142 (5%)	3/78 (4%)	1.09	0.72-1.65
Photophobia	5/117 (4%)	1/45 (2%)	1.16	0.80-1.68

Table 3: Initial mean laboratory findings for Rocky Mountain spotted fever (RMSF) cases and non-RMSF illnesses from two tribal communities in Arizona.

Laboratory test	Case	H/WNL/L[a]	N (Mean/ median day obtained)	Non-RMSF illness	H/WNL/L[a]	N (Mean/ median day obtained)	p-value
WBC cells/mm3[b]	11	H	183 (4/3)	11	H	144 (3/2)	0.587
WBC differential Neutrophils %*	67	WNL	181	56	WNL	143	0.000
Bands %	10	WNL	83	6	WNL	43	0.975
Lymphocytes %	20 ∫	L	179	32	WNL	139	0.000
Monocytes %	7 ∫	WNL	179	8	WNL	140	0.003
Eosinophils %	1.2	WNL	179	1.4	WNL	139	0.45
Hemoglobin g/dL*	13.9	WNL	140	12.8	WNL	134	0.000
Hematocrit %*	40.4	WNL	141	38.4	WNL	134	0.002
Platelet count X10^3/mm3 ∫	269	WNL	141 (4/3)	350	WNL	144 (3/2)	0.000
Sodium mEq/L ∫	136	L	173 (4/3)	138	WNL	135 (3/3)	0.043
Potassium mEq/L ∫	3.9	WNL	134	4.2	WNL	126	0.001
Chloride mEq/L ∫	101	WNL	128	103	WNL	125	0.030
Bicarbonate mEq/L	22	WNL	135	22	WNL	125	0.371

Creatinine mEq/L	1.0	WNL	134	0.7	WNL	126	0.084
BUN mEq/L[c]	14	WNL	134	11	WNL	125	0.174
Glucose mEq/L	114	H	147	108	H	120	0.786
Adult SGPT/ALT IU/L[d]*	57.1	H	70 (4/3)	29.7	WNL	27(3/3)	0.017
Child SGPT/ALT IU/L[d]	38.5	H	92 (4/3)	27.1	WNL	90 (3/3)	0.590
Adult SGOT/AST IU/L[e]*	140.1	H	70	58.0	H	27	0.052
Child SGOT/AST IU/L[e]	91.0	H	93	56.4	H	91	0.441
Adult Alkaline phosphatase IU/L	130.2	H	69	132.2	H	26	0.862
Child Alkaline phosphatase IU/L	223.9	WNL	92	225.6	WNL	90	0.876
Adult GGT[f]	147.1	H	13	223.0	H	11	0.415
Child GGT[f]	35.8	H	16	25.7	WNL	24	0.478
Adult Total bilirubin mg/dL	1.1	WNL	57	0.7	WNL	27	0.083
Child Total bilirubin mg/dL	0.8	WNL	86	0.5	WNL	82	0.068
LDH IU/L[g]	849	H	5	401	H	4	0.364
C-reactive protein IU/L	50.0	H	11	50.0	H	16	0.983
Albumin g/dL ʃ	3.9	WNL	117	4.7	WNL	98	0.010
PT seconds[h]	15.8 ʃ	H	27	42.3	H	15	0.022

PTT seconds[i]	41.8	H	28	37.3	H	24	0.869
INR[j] ʃ	1.4	WNL	32	5.2	H	25	0.001
Fibrinogen g/L	199	H	9	102	H	1	0.602
D-dimer ng/mL*	1701	H	8	98.3	WNL	5	0.019

* Significantly higher in cases than non-RMSF illness; ʃ Significantly lower in cases than non-RMSF illness

a H/WNL/L = High/ Within Normal Limits/Low compared to expected value; b WBC = White blood cells; c BUN = Blood urea nitrogen; d SGPT/ALT = serum glutamic pyruvic transaminase/alanine transaminase; e SGOT/AST = serum glutamic oxalacetic transaminase/aspartate aminotransferase; f GGT = gamma glutamyl transferase; g LDH = Lactate dehydrogenase; h PT = prothrombin time; i PTT = Partial thromboplastin time; j INR = International normalized ratio

Figure 1: Number of Rocky Mountain spotted fever (RMSF) cases and non-RMSF illnesses by age group in two tribal communities in Arizona

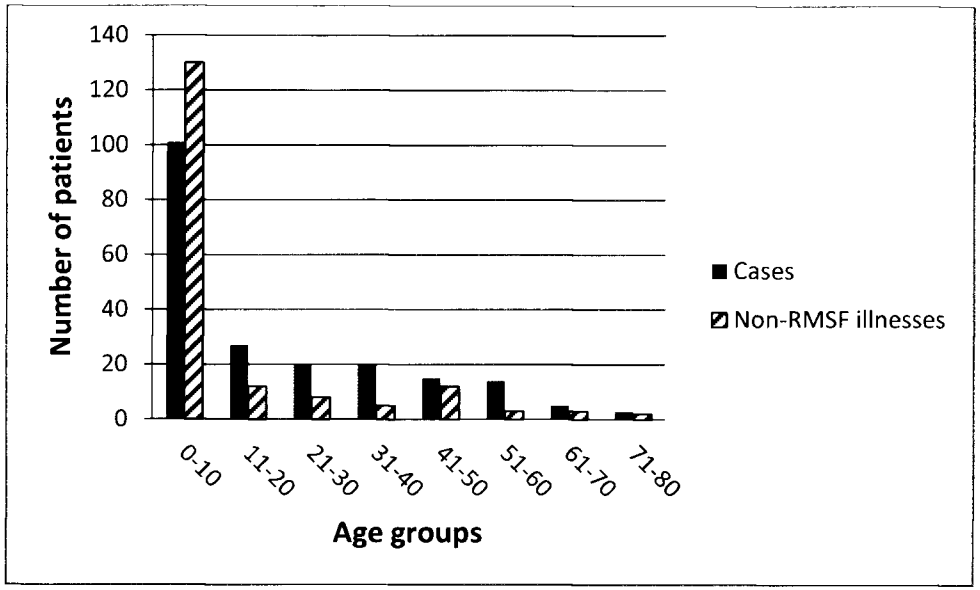
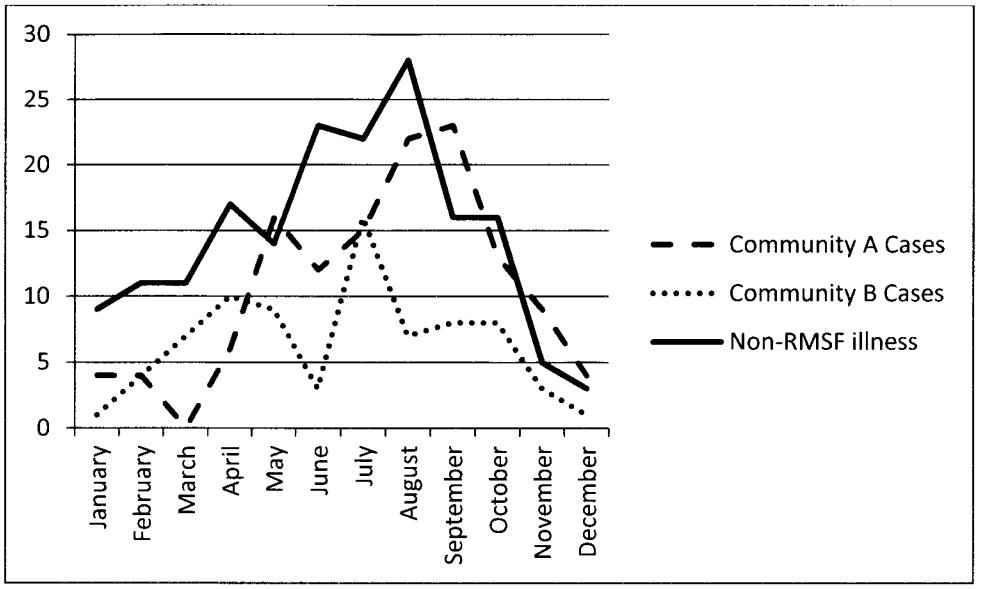


Figure 2: Month of symptom onset of Rocky Mountain spotted fever (RMSF) cases and non-RMSF illness in two tribal communities in Arizona


30
25
20
15
10
5
0
January
February
March
April
May
June
July
August
September
October
November
December
Community A Cases
Community B Cases
Non-RMSF illness

Title: Risk factors for fatal outcome from Rocky Mountain spotted fever in a highly endemic area: Arizona, 2002-2011

Authors: Joanna Regan[1], Marc Traeger[2], Dwight Humpherys[2], Dianna Mahoney[2], Michelle Martinez[2], Ginny L. Emerson[3], Danielle Tack[4], Aimee Geissler[5], Seema Yasmin[4], Regina Lawson[6], Velda Williams[7], Charlene Hamilton[8], Craig Levy[9], Ken Komatsu[9], David Yost[2], Jennifer H. McQuiston[1]

1. Rickettsial Zoonoses Branch, Division of Vector-borne Diseases, National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Centers for Disease Control and Prevention (CDC), Atlanta, GA 2. Whiteriver Public Health Service Hospital, Whiteriver, AZ 3. Poxvirus and Rabies Branch, Division of High Consequence Pathogens and Pathogenicity, NCEZID, CDC, Atlanta, GA 4. Epidemic Intelligence Service, Division of Applied Public Health Training, Epidemiology Program Office, Centers for Disease Control and Prevention (CDC), Atlanta, Georgia 5. Bacterial Diseases Branch, Division of Vectorborne Diseases, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention (CDC), Fort Collins, CO 6. Department of Population Health and Pathobiology, College of Veterinary Medicine, North Carolina State University, Raleigh, NC 7. San Carlos Apache Tribe, San Carlos, AZ 8. White Mountain Apache Tribe, Whiteriver, AZ 9. Bureau of Epidemiology and Disease Control, Division of Public Health Services, Arizona Department of Health Services, Phoenix, Arizona

Keywords: Rocky Mountain spotted fever, American Indians, Tick-borne, fatalities, *Rhipicephalus sanguineus*

Running Title: Risk factors for fatal RMSF in Arizona

Corresponding Author: Joanna Regan, MD, MPH, FAAP

Centers for Disease Control and Prevention

1600 Clifton Road NE, Mailstop C 01

Atlanta, GA 30329

jregan@cdc.gov 404-639-4341

Alternate Corresponding Author: Jennifer McQuiston, DVM (same mailing address as above)

jmcquiston@cdc.gov 404-639-0041

Summary: Rocky Mountain spotted fever has emerged as a significant health threat for American Indians in Arizona. This study examines the causes of fatal outcome in the first two tribes identified in this outbreak, and highlights points for clinical intervention.

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Abstract

Background: Rocky Mountain spotted fever (RMSF) is a treatable disease that now causes significant morbidity and mortality on several American Indian reservations in Arizona. Although the disease is treatable, reported RMSF case fatality rates from this region are high (7%) compared to the rest of the nation (<1%), suggesting a need to identify clinical points for intervention.

Methods: The first 205 cases from this region were reviewed and fatal RMSF cases were compared to non-fatal cases to determine clinical risk factors for fatal outcome.

Results: Doxycycline was initiated significantly later in fatal cases (median day 7) than non-fatal cases (median day 3), although both groups of case-patients presented for care early (median day 2). Multiple factors increased the risk of doxycycline delay and fatal outcome, such as early symptoms of nausea and diarrhea, history of alcoholism or chronic lung disease (CLD) and abnormal lab results such as elevated liver transaminases. Rash, history of tick bite, thrombocytopenia and hyponatremia were often absent at initial presentation.

Conclusions: Earlier treatment with doxycycline can decrease morbidity and mortality from RMSF in this region. Recognition of risk factors associated with doxycycline delay and fatal outcome, such as early gastrointestinal symptoms and past medical history of alcoholism or CLD, may be useful in guiding early treatment decisions. Healthcare providers should have a low threshold for initiating doxycycline whenever treating febrile or potentially septic patients from tribal lands in Arizona, even if an alternative diagnosis seems more likely and classic findings of RMSF are absent.

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Introduction

Rocky Mountain spotted fever (RMSF), caused by the tick-borne bacterium *Rickettsia rickettsii*, can be a rapidly fatal disease even in previously healthy people. Before the discovery of effective antibiotics, reported fatality rates in this country ranged from approximately 20-80% [1]. Doxycycline is the recommended treatment for suspected RMSF, regardless of patient age, and other commonly used broad spectrum antibiotics are not effective in preventing death [2-4]. When doxycycline treatment is started in the first five days of symptoms, fatal outcome is unlikely; however, treatment efficacy decreases sharply after day five of symptoms [4-6]. RMSF is difficult to diagnose during the first few days of illness because presenting symptoms are nonspecific and diagnostic testing lacks sensitivity during this time [7]. Therefore, clinicians must rely on clinical judgment and treat empirically as soon as the disease is suspected in order to prevent fatalities [2].

The epidemiology of RMSF in Arizona is different than that observed elsewhere in the United States, and the disease has emerged as a significant public health threat on multiple American Indian reservations [8]. Among 219 cases reported from tribal lands from 2003 to 2011, 16 died (7.3%) [9]; while in contrast, the reported case fatality rate among cases elsewhere in the United States was less than 1% [10]. At the request of local healthcare providers and the first two Arizona tribal communities affected, we reviewed medical records of the first 205 RMSF cases to assess risk factors for fatal outcome and identify clinical points of intervention to save lives.

Methods

Data collection, health care facilities and service populations have been previously described [8]. The project was reviewed by CDC's Institutional Review Board and judged public health response rather than research. The project was conducted with full approval of participating tribal councils. Cases included those diagnosed from 2002 through September 30, 2011. Data were analyzed using Epi Info [11].

Case Definitions

A confirmed RMSF case was defined as a person reporting illness that prompted RMSF testing and:

- Serological evidence of a fourfold change in immunoglobulin G or M (IgG or IgM)-specific antibody titer reactive with *Rickettsia rickettsii* antigen by indirect immunofluorescence assay (IFA) between paired serum specimens taken after the onset of symptoms, with at least one titer of 1:128 dilution or higher, or
- Detection of *R. rickettsii* DNA in a clinical specimen via amplification of a specific target by polymerase chain reaction (PCR) assay, or
- Demonstration of spotted fever group antigen in a biopsy or autopsy specimen by Immunohistochemistry staining (IHC).

A probable RMSF case was defined as a person reporting illness that prompted RMSF testing who

- did not meet criteria for confirmed case, and
- had serologic evidence of elevated IgG or IgM antibody reactive with *R. rickettsii* antigen by IFA with at least one titer of 1:128 dilution or higher

Definition of terms

- Tick exposure: any mention of potential tick contact in the medical record, including tick bites and ticks seen around homes or on pets.
- Dog contact: any mention of dog interaction in the medical record, including owning a pet dog or feeding strays
- Outpatient visit: visit to the clinic or the Emergency Department (ED), resulting in discharge home.
- Severe outcome: hospital admission (including intensive care unit admission) or fatality
- Late treatment: treatment with doxycycline initiated on day 5 of symptoms or later
- Late symptom: a symptom that began on day 4 of illness or later

- Abnormal laboratory test: outside noted normal values. Liver function tests were considered abnormal if they were above the age-adjusted norms [12].

Fatal cases were compared to non-fatal cases to identify risk factors for fatal outcome. Median day of symptoms on which clinical events occurred were calculated, and for selected clinically significant variables, this was compared for fatal versus non-fatal cases. Patients who received late treatment were compared to patients who were treated early (received doxycycline in the first 4 days of illness) to identify medical history variables, symptoms and laboratory findings that may be risk factors for late treatment. If there was no information regarding a specific variable documented in the medical record, the case was not included in the analyses for that variable. Statistical differences in categorical variables were evaluated using a chi-square test and when the expected value of a cell was less than 5, a Fisher Exact test was used. Statistical differences in continuous variables were evaluated using an ANOVA test or the Mann-Whitney/Wilcoxon Two-Sample Test when a non-parametric test was more appropriate. Statistical significance was set at alpha (α)=0.05.

Results

Demographics and History

Among 205 cases of RMSF included in this analysis, 190 (93%) were non-fatal cases and 15 (7%) were fatal cases (Table 1). All case-patients except one were identified as American Indians. The mean age of all case patients at the time of RMSF onset was 20 years, and mean age was not significantly different between fatal and non-fatal cases. Children ≤10 years old comprised 101/190 (53%) of non-fatal cases and 7/15 (47%) of fatal cases (Figure 1). Half of all cases (94/189) and 73% (11/15) of fatal cases occurred in males.

The months with the highest proportion of fatal cases were April (25%), August (14%) and October (14%) (Figure 2). There was no significant difference in reported tick exposure or dog contact between fatal and non-fatal cases (Table 1). Of the medical conditions collected, only a history of

alcoholism (among adults) and chronic lung disease (CLD), was a significant risk factor for fatal outcome and only a history of alcoholism (RR1.84, CI 1.14, 2.99) and CLD (RR 2.88, CI 2.34, 3.45) were significant risk factors for late treatment with doxycycline.

Symptoms

Fever (which included subjective reports) was the most common symptom (Table 2). All fatal cases included a fever at some point during the course of illness, either subjective or measured. While most of the symptoms that were more common in fatal cases occurred late in disease, gastrointestinal symptoms (abdominal pain, anorexia, nausea, vomiting and diarrhea), hepatomegaly, splenomegaly and peripheral edema typically began during the first three days of illness. Of the symptoms recorded, those significantly correlated with late treatment were headache (RR 1.82, CI 1.10-3.02), nausea (RR 1.72, CI 1.08-2.75), diarrhea (RR 1.66, CI 1.08-2.55), periorbital edema (RR 2.61, CI1.67-4.07), dizziness (RR 2.17, 1.22-3.84), and mental status change (RR 2.66, CI 1.84-3.85).

Rash occurred significantly later in the course of fatal cases of RMSF (median day 5.5, range 1-9) than non-fatal cases (day 2, range 1-14)(Table 3). Petechial rash was uncommon and late in disease course when present, occurring in 30/120 (15%) cases, on median day 7 of illness. A significantly higher proportion of fatal cases included a petechial rash with no evidence of prior maculopapular rash (6/12, 50%) compared to 12/107 (11%) non-fatal cases in which the rash was described as petechial only.

Medical care and treatment

A median of 2 outpatient visits was recorded during both fatal and non-fatal cases. In both fatal and non-fatal cases, case-patients presented on median day 2 of symptoms. However, the first notation of RMSF in the medical record occurred significantly later in fatal cases (median day 7, range 1-9) than non-fatal cases (median day 3, range 1-14) (Table 3). The median day of symptoms that doxycycline was initiated was significantly later among fatal cases (day 7, range 6-9) than non-fatal cases (day 3, range 1-14). The median interval between the first notation of RMSF in the medical record and initiation of doxycycline treatment was 0 days for both fatal and non-fatal cases.

None of the patients who died of RMSF had documentation of receiving doxycycline before day 6 of symptoms; however, most (83.9%, 52/62) of the patients with clear documentation of late treatment survived. The following antibiotics were initiated within the first 3 days of symptom onset, but were unsuccessful at preventing death: ampicillin/sulbactam, ceftriaxone, clindamycin, cefazolin, gentamycin, vancomycin, imipenum, and amoxicillin. Azithromycin was administered to two case-patients with confirmed RMSF, but mental status deterioration occurred in both and therapy was changed to doxycycline prior to day 6 of symptoms; both patients survived, but required Intensive Care Unit (ICU) care for more than 7 days.

Laboratory findings

Initial CBC, chemistry panel and liver function tests were performed significantly later in fatal cases (Table 3). Abnormalities were more frequent in fatal cases for all laboratory results except gamma-glutamyl transpeptidase (GGT) (Table 4a). Laboratory abnormalities that were significantly correlated with late treatment with doxycycline included thrombocytopenia (RR 1.98, CI 1.33-2.93), elevated AST (RR 1.75, CI 1.10-2.78), elevated ALT (RR 1.97, CI 1.31-2.95), and elevated total bilirubin (RR 2.04, CI 1.35-3.09). Urine abnormalities were noted in many RMSF cases, and having an abnormal urine finding was more frequent in fatal than non-fatal cases (Table 4b). Urine abnormalities significantly correlated to late treatment were positive leukocyte esterase (RR 1.59, CI 1.02-2.49), and the presence of white blood cells in the urine (RR 1.70, CI 1.07-2.71).

Severe Outcomes

Eighty six cases (42%) involved severe outcomes, including 15 fatalities and 71 hospitalizations. The median time of hospital admission was day 5 of symptoms for all cases (range 1-11) (Table 3) and the median duration of hospital stay was 5 days for all RMSF cases (range 1-54 days).

Patients treated early were more likely to be managed as outpatients (Table 5). However, the frequency of hospitalization and fatal outcome increased rapidly as the disease progressed without doxycycline treatment. There were 29 patients requiring admission to the ICU (Table 6). A majority of

fatal cases included a diagnosis of acute respiratory distress syndrome (ARDS), respiratory failure, disseminated intravascular coagulopathy (DIC), multisystem organ failure, renal insufficiency, and coma (Table 6), but these severe outcomes also occurred in a small number of non-fatal cases as well. A majority of deaths (13) occurred in the ICU, and 2 occurred in the Emergency Department. The median day of symptoms that death occurred was day 9 (range 6-20) (Table 3) and the most common causes of death listed in the medical record were sepsis (9), DIC (7), multisystem organ failure (5), and ARDS (3).

Among the 15 fatal cases included in this study, there were wide variations in the presenting signs and symptoms (Table 7). Three patients were afebrile when temperature was measured at the first visit, and two of these patients (a 2 year old child and 39 year old man) also had no history of subjective fever prior to presentation. The 39 year old man did develop a measured fever after admission. However, the child had a subjective fever reported by the parent only and was afebrile whenever temperature was measured by the provider. Only one fatal case-patient was diagnosed with RMSF at the first visit, and treatment initiated at time of presentation on day 7 was not effective at preventing death.

Discussion

This review of RMSF cases from two tribal communities in Arizona demonstrates the rapidly progressive nature of this disease and the need for early diagnosis and treatment. None of the fatal cases received early treatment with doxycycline, and treatment delay has been linked to increased risk of fatal outcome in numerous past publications [4-7, 13-15]. Although late treatment may not be the only cause of fatal outcome, it does represent an important factor that is potentially modifiable in the clinical setting. Therefore, analysis was performed to determine which factors were associated with late treatment and may represent signals that prompt early suspicion of the disease.

The prompt initiation of doxycycline treatment once RMSF was suspected in this patient cohort demonstrates that local providers serving these two tribes are highly aware of appropriate antibiotic

choice for RMSF. In this patient population, like others in the US [6], patients with RMSF presented to health care providers early and returned multiple times. The first notation of RMSF in the medical records was late in fatal cases (median day 7), suggesting that the problem lies in the provider's initial delay to include RMSF in the differential diagnosis for some patients. This case review identifies multiple factors that both complicate the initial presentation of RMSF, and at times, make another diagnosis appear more likely. Understanding of these factors may improve early recognition of RMSF and decrease morbidity and mortality from this disease.

Patients with a past medical history of CLD or alcoholism were at greater risk of both receiving doxycycline late and dying of the disease. It is unclear if the small number of patients with CLD identified in this review represents a true significant risk factor; however, a history of alcoholism is likely to be significant. A higher risk of fatal outcome from other rickettsial diseases in patients with a history of alcoholism has been reported in previous published studies [16]. Altered mental status, elevated transaminases and low platelets were all found to be significantly correlated with late treatment in this study, and the medical records suggested providers sometimes attributed these signs and symptoms to complications of alcoholism in patients with this history. Altered mental status frequently occurs with alcohol intoxication, and elevated liver transaminases and low platelet counts are common sequelae of alcohol related liver disease. Also, patients with a history of alcoholism are at higher risk for other severe febrile illnesses, such as aspiration pneumonia, that may appear more likely than RMSF [17]. These factors, in addition to incomplete history of present illness provided by patients acutely intoxicated, may lead to delayed diagnosis, delayed treatment, and a higher risk of fatal outcome in these patients. This finding should be used to educate providers in the region about the need to begin doxycycline early in febrile patients with a history of alcoholism, even if an alternative diagnosis seems more likely.

Other factors that may complicate presentation and result in delay include abdominal symptoms, such as nausea and diarrhea, and abnormal urine findings. Abdominal pain, anorexia, nausea, vomiting,

and diarrhea were early symptoms that occurred significantly more often in fatal cases, and nausea and diarrhea were significantly correlated with late treatment. Abdominal pain is a symptom of RMSF that has led to misdiagnosis in other published reports, resulting in cholecystectomies and appendectomies, and delayed treatment [18, 19]. Diarrhea, often seen as an indicator of a benign process, such as viral gastroenteritis, was frequently seen in RMSF patients in this study, and significantly correlated with late treatment and death. Primary abdominal complaints led to one initial diagnosis of acute gastroenteritis and two diagnoses of nonspecific abdominal pain in fatal cases (Table 7). In this review, the occurrence of abdominal pain, pyuria, and fever were initially diagnosed as pyelonephritis and resulted in delayed diagnosis of RMSF and death in 2 patients. Even in the presence of abnormal urine findings or diarrhea, which may make an alternative diagnosis seem more likely, abdominal symptoms should be considered important early clinical triggers to initiate doxycycline in patients from this region.

While the factors described above may contribute to a complicated presentation of RMSF when present, there are additional factors that complicate by their absence. Rash appeared late in fatal cases (median day 5.5 of symptoms) and this has been a documented risk factor for fatal outcome in other studies [20, 21]. In addition, although all fatal cases included fever, some patients were afebrile when temperature was measured at first presentation. Subjective reports of fever should not be discounted, and relying on the presence of a rash or clinically measured fever may lead to missed opportunities to begin treatment at the first visit.

Abnormal lab findings classically attributable to RMSF, such as thrombocytopenia, hyponatremia and elevated liver enzymes were typically observed in fatal cases, but more likely to be seen later as the disease progressed untreated. While such findings are useful treatment triggers when present, their absence should not be used to rule out RMSF.

This review is subject to several limitations. Patients with titers below 1/128 or with ELISA testing alone are included in the national case definition for reporting, but were excluded from this analysis in order to improve the stringency of our findings. Furthermore, the higher case fatality rate

seen in this region may be influenced by improved surveillance and active testing of fatal cases through PCR confirmation at CDC, a practice rarely pursued in other U.S. settings [14, 22]. Rather than the case fatality rate in this region being unusually high, the rate calculated through national surveillance may be low due to national underreporting of fatalities and over-inclusion of non-fatal cases that may not be true RMSF.

This review illustrates the significant amount of morbidity and loss of human life caused by RMSF in two small tribal communities. After the initial discovery of RMSF in this region, a high level of knowledge among providers has developed, as evidenced by high rates of doxycycline prescription among cases when RMSF is initially suspected; however, progress remains to be made. Improving early consideration of RMSF in patients with complicated presentations, such as those with history of alcoholism or signs and symptoms of another illness, and for those without classic signs and symptoms of RMSF, such as rash, will reduce mortality.

Changes in clinical practice should be encouraged through targeted provider education and healthcare facility oversight. In addition to educating local providers, extending educational efforts to tertiary care facilities receiving transferred tribal patients, should be undertaken to ensure that proper treatment is continued and proper confirmatory testing is completed. The treatment for RMSF, a short course of doxycycline, is generally well tolerated in patients, and should be used even when the likelihood of RMSF seems low, in order to prevent fatalities similar to the ones that occurred in this population. The dose and duration of doxycycline used for RMSF has not been shown to stain permanent teeth when given to pediatric patients [23], and doxycycline should be prescribed regardless of patient age based on clinical suspicion alone .

Finally, improving physician education and healthcare delivery are not the only means to deal with the ongoing epidemic in this region. Public health interventions such as animal control, vector control and veterinary care are also needed to reduce overall incidence and mortality from RMSF. Cost

analysis of medical care and loss of life and productivity caused by RMSF in this region may be helpful in illustrating that prevention measures are not only lifesaving, but cost effective.

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Table 1: Demographics, exposures and past medical history reported for fatal and non-fatal cases of Rocky Mountain spotted fever in two tribal communities in eastern Arizona

Demographics	**All cases**	**Non-fatal**	**Fatal Cases**	**RR**	**95% CI**
Number of cases	205	190/205 (93%)	15/205 (7%)		
Mean Age	19.8	19.5	23.7		ANOVA p=0.43
Child (<18years)	123/205	115/123 (94%)	8/123 (7%)	0.76	0.29-2.02
Male	46/85 (54%)	94/189 (50%)	11/15 (73%)	2.56	0.85-7.80
Exposures					
Tick Exposure	73/132 (55%)	71/125 (57%)	2/7 (29%)	0.32	0.07-1.61
Tick Bite	36/125 (29%)	34/118 (29%)	2/7 (29%)	0.99	0.18-5.34
Dog Contact	77/90 (85.6%)	72/85 (84.7%)	5/5 (100%)	*Und.*	*Und.*
Sick Contacts	17/43 (40%)	15/36 (42%)	2/5 (29%)	0.61	0.13-2.80
Travel	6/37 (16%)	6/31 (19%)	0/6 (0%)	0	*Und.*
Past Medical History					
AIDS/HIV	0/205 (0%)	0/190 (0%)	0/15 (0%)		
Immune Compromise	1/204 (0.5%)	1/189 (0.5%)	0/15 (0%)	0	*Und.*
Transplant	0/205 (0%)	0/190 (0%)	0/15 (0%)		
Asplenia	0/204 (0%)	0/189 (0%)	0/15 (0%)		
Autoimmune Ds	2/205 (1.0%)	2/190 (1.1%)	0/15 (0%)	0	*Und.*
Cancer	1/205 (0.5%)	1/190 (0.5%)	0/15 (0%)	0	*Und.*
TB	2/204 (1.0%)	2/189 (1.1%)	0/15 (0%)	0	*Und.*
Asthma	17/205 (8.3%)	16/190 (8.4%)	1/15 (6.7%)	0.79	0.11-5.65
Chronic Lung Ds	4/205 (2%)	1/190 (0.5%)	3/15 (20.0%)	12.56	5.71-27.63
Heart Disease	4/205 (2.0%)	3/190 (1.6%)	1/15 (6.7%)	3.59	0.61-21.09
Hypertension	26/205 (12.7%)	24/190 (12.6%)	2/15 (13.3%)	1.06	0.25-4.43
Stroke	1/205 (0.5%)	1/190 (0.5%)	0/15 (0%)	0	*Und.*
DVT	1/205 (0.5%)	1/190 (0.5%)	0/15 (0%)	0	*Und.*
Diabetes	18/204 (8.8%)	18/189 (9.5%)	0/15 (0%)	0	*Und.*
Sickle Cell	1/205 (0.5%)	1/190 (0.5%)	0/15 (0%)	0	*Und.*
G6PD	0/205 (0%)	0/190 (0%)	0/15 (0%)		*Und.*
Thyroid Disease	6/205 (2.9%)	6/190 (3.2%)	0/15 (0%)	0	*Und.*
Renal Failure	0/204 (0%)	0/189 (0%)	0/15 (0%)		*Und.*
Hepatitis	3/204 (1.5%)	3/189 (1.6%)	0/15 (0%)	0	*Und.*
Alcoholism	22/81 (27.2%)	16/74 (21.6%)	6/7 (85.7%)	16.09	2.05-126.20

RR=Risk Ratio, CI=Confidence interval, Und.=undefined, Transplant=solid organ and bone marrow, CLD=Chronic Lung Disease, Renal Failure=failure and insufficiency, Analysis for Alcoholism included only cases older than 17 years old

Table 2: Symptoms reported for fatal and non-fatal cases of Rocky Mountain spotted fever in two tribal communities in eastern Arizona

Symptom	All cases	Median day (range)	Non-fatal	Fatal	RR	95% CI
Fever	164/202 (81.2%)	Day 1 (1-14)	149/187 (79.7%)	15/15 (100%)	*Und.*	*Und.*
Tmax median	101.8 (96.4-106.3)		101.8 (96.4-106.3)	103.2 (100.4-105.7)	P=0.01	
Chills	47/133 (35.3%)	Day 1 (1-14)	43/123 (35%)	4/10 (40%)	1.22	0.36-4.11
Headache	78/135 (57.8%)	Day 1 (1-14)	72/126 (57.1%)	6/9 (66.7%)	1.46	0.38-5.60
Rash	130/192 (67.7%)	Day 2 (1-14)	117/178 (65.7%)	13/14 (92.9%)	6.20	0.83-46.34
Fever and Rash	78/127 (61.4%)		72/120 (60.0%)	6/7 (85.7%)	3.77	0.47-30.37
Fever and Tick	57/127 (45%)		55/120 (46%)	2/7 (29%)	0.49	0.10-2.44
Rash and Tick	47/127 (37%)		45/120 (38%)	2/7 (29%)	0.68	0.14-3.37
Clinical Triad	41/127 (32%)		39/120 (33%)	2/7 (29%)	0.84	0.17-4.14
Abdominal pain	48/154 (31.2%)	Day 3 (1-9)	41/145 (28.3%)	7/9 (77.8%)	7.73	1.67-35.84
Anorexia	51/125 (40.8%)	Day 1.5 (1-9)	43/116 (37.1%)	8/9 (88.9%)	11.61	1.50-89.99
Nausea	74/156 (47.4%)	Day 1 (1-9)	65/146 (44.5%)	9/10 (90%)	9.97	1.29-76.85
Vomiting	77/169 (45.6%)	Day 1 (1-10)	68/157 (43.3%)	9/12 (75%)	3.58	1.01-12.78
Diarrhea	52/163 (31.9%)	Day 1 (1-8)	44/151 (29.1%)	8/12 (67%)	4.27	1.35-13.54
Hepato-megaly	7/145 (4.8%)	Day 3 (1-11)	5/135 (3.7%)	2/10 (20%)	4.93	1.28-19.02
Spleno-megaly	2/143 (1.4%)	Day 1.5(0-7)	1/133 (0.8%)	1/10 (10%)	7.83	1.71-35.93
Coughing	68/169 (40.2%)	Day 1 (1-12)	62/157 (39.5%)	6/12 (50%)	1.49	0.50-4.41
Wheezing	9/164 (5.5%)	Day 2 (1-6)	9/152 (5.9%)	0/12 (0%)	*Und.*	*Und.*
Chest Pain	12/129 (9.3%)	Day 1 (1-12)	10/118 (8.5%)	2/11 (18.2%)	2.17	0.53-8.90
Nasal Congestion	43/155 (27.7%)	Day 1 (1-11)	40/145 (27.6%)	3/10 (30%)	1.12	0.30-4.12
Throat	27/134 (20.1%)	Day 1.5 (1-13)	26/126 (20.6%)	1/8 (12.5%)	0.57	0.07-4.41
Difficulty swallowing	3/120 (2.5%)	Day 2 (1-4)	2/112 (1.8%)	1/8 (12.5%)	5.57	0.96-32.19

Ear Pain	13/126 (10.3%)	Day 3 (1-7)	12/118 (10.2%)	1/8 (12.5%)	1.24	0.17-9.31
Conjunc-tivitis	22/148 (14.9%)	Day 2 (1-10)	19/137 (13.9%)	3/11 (27.3%)	2.15	0.62-7.48
Periorbital Edema	7/147 (4.8%)	Day 4 (1-9)	3/134 (2.2%)	4/13 (30.8%)	8.89	3.61-21.88
Photophobia	5/117 (4.3%)	Day 1 (1-6)	5/109 (4.6%)	0/8 (0%)	0	*Und.*
Fatigue	60/130 (46.2%)	Day 2 (1-12)	51/118 (43.2%)	9/12 (75%)	3.5	0.99-12.34
Lethargy	24/121 (19.8%)	Day 5 (1-8)	17/111 (15.3%)	7/10 (70%)	9.43	2.63
Irritability	20/123 (16.3%)	Day 3 (1-9)	17/114 (14.9%)	3/9 (33.3%)	2.58	0.70-9.45
Dizziness	21/110 (19.1%)	Day 1 (1-12)	19/103 (18.4%)	2/7 (28.6%)	1.7	0.35-8.14
Neck Pain	16/141 (11.3%)	Day 5 (1-10)	16/132 (12.1%)	0/9 (0%)	0	*Und.*
Seizures	7/142 (4.9%)	Day 6 (1-10)	4/132 (3.0%)	3/10 (30%)	8.27	2.70-25.31
MSC	29/169 (17.2%)	Day 5 (1-13)	16/155 (10.3%)	13/14 (92.9%)	62.76	8.54-461.09
Muscle Pain	53/129 (41.1%)	Day 1 (1-10)	50/118 (42.4%)	3/11 (27.3%)	0.54	0.15-1.93
Peripheral Edema	18/147 (12.2%)	Day 3 (1-10)	13/133 (9.8%)	5/14 (35.7%)	3.98	1.50-10.56
LAD	5/129 (3.9%)	Day 2.5 (1-9)	5/117 (4.3%)	0/12 (0%)	*Und.*	*Und.*
Jaundice	6/149 (4.0%)	Day 4 (1-8)	2/135 (1.5%)	4/14 (28.6%)	9.53	4.19-21.71

Median Day=Median day of symptom onset, RR=Risk Ratio, CI=Confidence interval, Und.=Undefined, Tmax=Maximum recorded temperature during course of illness, MSC=Mental status change, LAD=Lymphadenopathy

Table 3: Median day of notable clinical events for fatal and non-fatal cases of Rocky Mountain spotted fever in two tribal communities in eastern Arizona

Events	All cases	Non-fatal	Fatal	P value
Day of symptoms that rash occurred	Day 2 (1-14)	Day 2 (1-14)	Day 5.5 (1-9)	0.015
Day of symptoms that petechial rash occurred	Day 7 (2-12)	Day 7.5 (2-12)	Day 7 (6-7)	
Day of symptoms of first doctor visit	Day 2 (1-11)	Day 2 (1-11)	Day 2 (1-7)	
Day of symptoms that RMSF was first mentioned in chart	Day 3 (1-14)	Day 3 (1-14)	Day 7 (1-9)	0.005
Day of symptoms that doxycycline was started	Day 3 (1-14)	Day 3 (1-14)	Day 7 (6-9)	0.000
Duration between first mention and treatment	0 days (0-10)	0 days (0-10)	0 days (0-5)	
Day of symptoms hospitalization occurred	Day 5 (1-11)	Day 4 (1-11)	Day 5 (1-9)	
Day of symptoms first CBC was obtained	Day 3 (1-14)	Day 3 (1-14)	Day 5.5 (1-9)	0.008
Day of symptoms Sodium was first tested	Day 3 (1-12)	Day 3 (1-12)	Day 5 (1-9)	0.017
Day of symptoms AST was first tested	Day 3 (1-14)	Day 3 (1-14)	Day 7 (1-9)	0.006
Day of symptoms that death occurred	NA	NA	Day 9 (6-20)	

Table 4 a: Abnormal laboratory findings for fatal and non-fatal cases of Rocky Mountain spotted fever in two tribal communities in eastern Arizona

Lab Parameter	Non-fatal		Fatal		RR	95% CI
	Number (%)	Median Day test first abnormal (range)	Number (%)	Median Day test first abnormal (range)		
Platelets (<130)	34/160 (21.3%)	Day 5 (2-9)	14/15 (93.3%)	Day 5.5 (2-9)	37.04	5.01-274.09
Sodium (<137)	64/158 (40.5%)	Day 4 (1-12)	14/15 (93.3%)	Day 6 (1-9)	17.05	2.29-126.82
AST (Elevated)	73/148 (49.3%)	Day 4 (1-14)	15/15 (100%)	Day 7 (1-9)	*Und.*	*Und.*
ALT (Elevated)	44/147 (29.9%)	Day 4.5 (1-12)	12/15 (80.0%)	Day 7 (1-9)	7.57	2.23-25.72
Alk Phos (Elevated)	80/146 (54.8%)	Day 4 (1-14)	13/15 (86.7%)	Day 6.5 (1-9)	4.75	1.11-20.37
GGT (Elevated)	7/25 (28.0%)	Day 6.5 (3-14)	2/4 (50.0%)	Day 6.5 (6-7)	2.22	0.37-13.38
Tbili (Elevated)	15/130 (11.5%)	Day 5.5 (1-12)	10/13 (76.9%)	Day 7 (2-9)	15.73	4.66-53.08

Table 4 b: Abnormal Urine results for fatal and non-fatal cases of Rocky Mountain spotted fever in two tribal communities in eastern Arizona

Urine Finding	Non-fatal	Fatal	Risk Ratio	95% CI
Nitrate Positive	8/95 (8.5%)	2/12 (16.7%)	1.94	0.49-7.64
LE Positive	14/95 (14.7%)	1/12 (8.3%)	0.56	0.08-4.01
WBCs Present	12/52 (23.1%)	3/9 (33.3%)	1.53	0.44-5.39
RBCs Present	20/60 (33.3%)	3/8 (37.5%)	1.17	0.31-4.48
Any 1 of the 4 abn urine findings	32/96 (33.3%)	8/12 (66.7%)	3.4	1.09-10.58

RR=Risk Ratio, CI=Confidence interval, Und.=Undefined, AST= Aspartate aminotransferase, ALT= Alanine Aminotransferase , Alk Phos=Alkaline Phosphotase , GGT= gamma-glutamyl transpeptidase, Tbili= total bilirubin, LE=leukocyte esterase, WBC=White blood cells, RBC=Red blood cells, abn=abnormal

Table 4: Outcome by day of symptoms that treatment with doxycycline was started for first 9 days of symptoms for confirmed cases of Rocky Mountain spotted fever in two tribal communities in eastern Arizona

Day of symptoms treatment was started (Total number of confirmed patients treated on that day)	**Outpatient (%)**	**Hospitalized (%)**	Subset of Hospitalized **ICU (%)**	Subset of Hospitalized and ICU **Fatal (%)**
Day 1 (6)	5 (83%)	1 (17%)	0 (0%)	0 (0%)
Day 2 (11)	8 (73%)	3 (27%)	0 (0%)	0 (0%)
Day 3 (9)	4 (44%)	5 (56%)	1 (11%)	0 (0%)
Day 4 (7)	3 (43%)	4 (57%)	1 (14%)	0 (0%)
Day 5 (8)	2 (25%)	6 (75%)	4 (50%)	0 (0%)
Day 6 (9)	0 (0%)	9 (100%)	5 (55%)	3 (33%)
Day 7 (11)	0 (0%)	11 (100%)	4 (36%)	3 (27%)
Day 8 (5)	1 (20%)	4 (80%)	2 (40%)	2 (40%)
Day 9 (4)	0 (0%)	4 (100%)	4 (100%)	2 (50%)

ICU=Intensive care unit

Table 5: Interventions and notable sequelae in fatal and non-fatal cases of Rocky Mountain spotted fever in two tribal communities in eastern Arizona

Intervention	Non-fatal	Fatal	RR	95% CI
ICU Admission	16/189 (8.5%)	13/15 (86.7%)	39.22	9.33-164.88
Plasma Transfusion	4/186 (2.2%)	9/13 (69.2%)	32.19	11.44-90.62
Platelet Transfusion	5/186 (2.7%)	10/12 (83.3%)	61	14.69-253.38
PRBC Transfusion	5/185 (2.7%)	6/12 (50.0%)	16.91	6.51-43.91
Whole Blood Transfusion	4/186 (2.2%)	1/12 (8.3%)	3.51	0.55-22.20
Fluid Boluses	77/186 (41.4%)	14/14 (100)	*Und.*	*Und.*
Ventilation	6/189 (3.2%)	15/15 (100%)	*Und.*	*Und.*
Inotropic Support	7/189 (3.7%)	15/15 (100%)	*Und.*	*Und.*
Immunoglobulins	0/184 (0%)	1/12 (8.3%)	17.73	9.98-31.47
ARDS	5/189 (2.6%)	8/15 (53.3%)	16.79	7.22-39.07
Respiratory Failure	7/189 (3.7%)	15/15 (100%)	*Und.*	*Und.*
DIC	5/189 (2.6%)	13/15 (86.7%)	67.17	16.43-274.54
Multisystem Organ Failure	2/189 (1.1%)	12/15 (80.0%)	54.29	17.31-170.22
Renal Insufficiency	7/189 (3.7%)	10/14 (71.4%)	27.35	9.59-78.00
Coma	2/188 (1.1%)	9/15 (60%)	26.18	11.36-60.37
Digital Necrosis	1/186 (0.5%)	2/15 (13.3%)	10.15	3.90-26.45

RR=Risk Ratio, CI=Confidence interval, Und.=Undefined, PRBC=Packed red blood cells, ARDS=Acute respiratory distress syndrome, DIC= Disseminated intravascular coagulation

Table 6: Details on the clinical course for fatal cases of Rocky Mountain spotted fever in two tribal communities in eastern Arizona

Age in years	Day of symptoms first visit occurred	Symptoms reported at first visit	Findings from first physical	Initial (first recorded) Diagnosis
4	Day 3	Fever, chills, rhinorrhea, nasal congestion, emesis	Fever, red and bulging tympanic membrane (TM), tachycardia, otherwise normal	Otitis media and viral illness
1.2	Day 2	Fever and Rash	Fever and rash	Pneumonia, thrush (index case)
37	Unknown	Unknown, patient disoriented and unable to report symptoms	Fever, disoriented, disheveled, nits and dried blood present, pinpoint pupils, otherwise normal	Pyelonephritis, alcohol withdrawal, sepsis and mental status change secondary to withdrawal or sepsis
8	Day 2	One month history of rash, fever and ear pain	Fever, red right TM, linear punctate rash on abdomen and arms	Otitis media and scabies
2.5	Day 1	Rash with no other symptoms	Afebrile, Multiple papules in varying stages all over the body, otherwise normal	Varicella
5	Day 2	Fever, headache, flank pain, not eating and drinking well	Fever, otherwise normal	Fever with no obvious etiology
34	Day 7	Fever, shortness of breath, hallucinations	Fever, patient anxious and confused, otherwise normal	RMSF, bilateral pneumonia, myocardial infarction, sepsis
14	Day 6	Headache, fever, cough, hallucinations	Unknown	Viral upper respiratory track infection
36	Day 3	Unknown (missing)	Unknown (missing)	Upper respiratory track infection
39	Day 1	Trouble breathing and weakness	Afebrile, hypotension, pitting edema, otherwise normal	Hypotension, shortness of breath, congestive Heart Failure

3	Day 7	Vomiting, fever, decreased appetite, lethargy, diarrhea, upper abdominal pain	Afebrile, abdomen tender, no guarding, otherwise normal	Acalculus cholecystitis, thrombocytopenia
78	Day 2	Dizziness and fall	Unknown	Rhabdomyolysis, HTN, UTI, syncope, aspiration pneumonia, conjunctivitis
53	Day 4	Diarrhea, headache, tick bite	Fever, altered mental status, skin dry with poor turgor	Acute gastroenteritis, volume dehydration, hyponatremia/hypokalemia
9	Day 4	Fever and vomiting	Fever, otherwise normal	Fever and abdominal pain not otherwise specified
32	Day2	unresponsive, abnormal breathing	Fever, irregular labored breathing, unresponsive pupils, rash (fine erythematous papules over torso, not on palms and soles), human bite wound on upper arm	Cardiac arrest due to unknown etiology, sepsis vs metabolic derangement

Figure 1. Age at time of symptom onset for fatal and non-fatal cases of Rocky Mountain spotted fever in two tribal communities in eastern Arizona

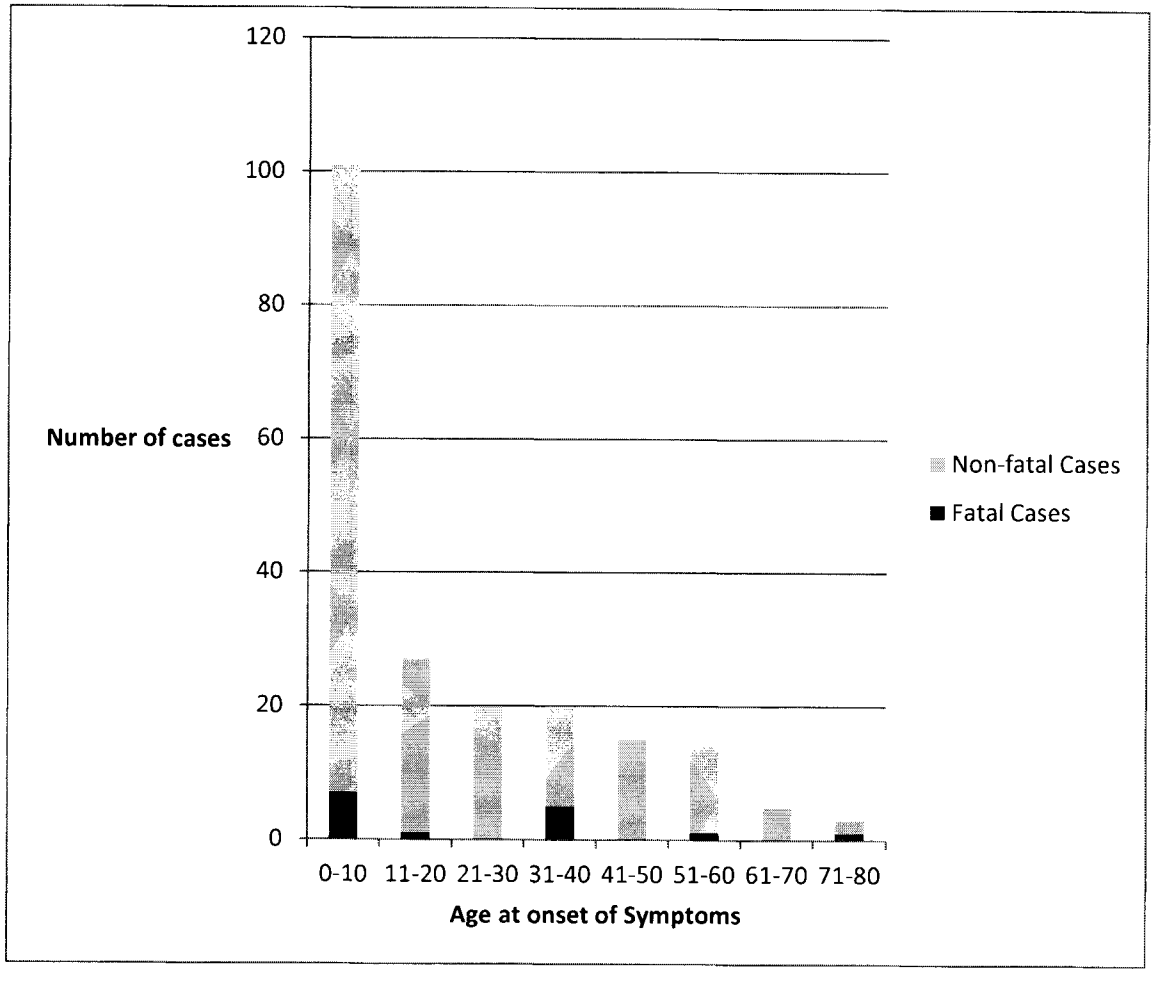
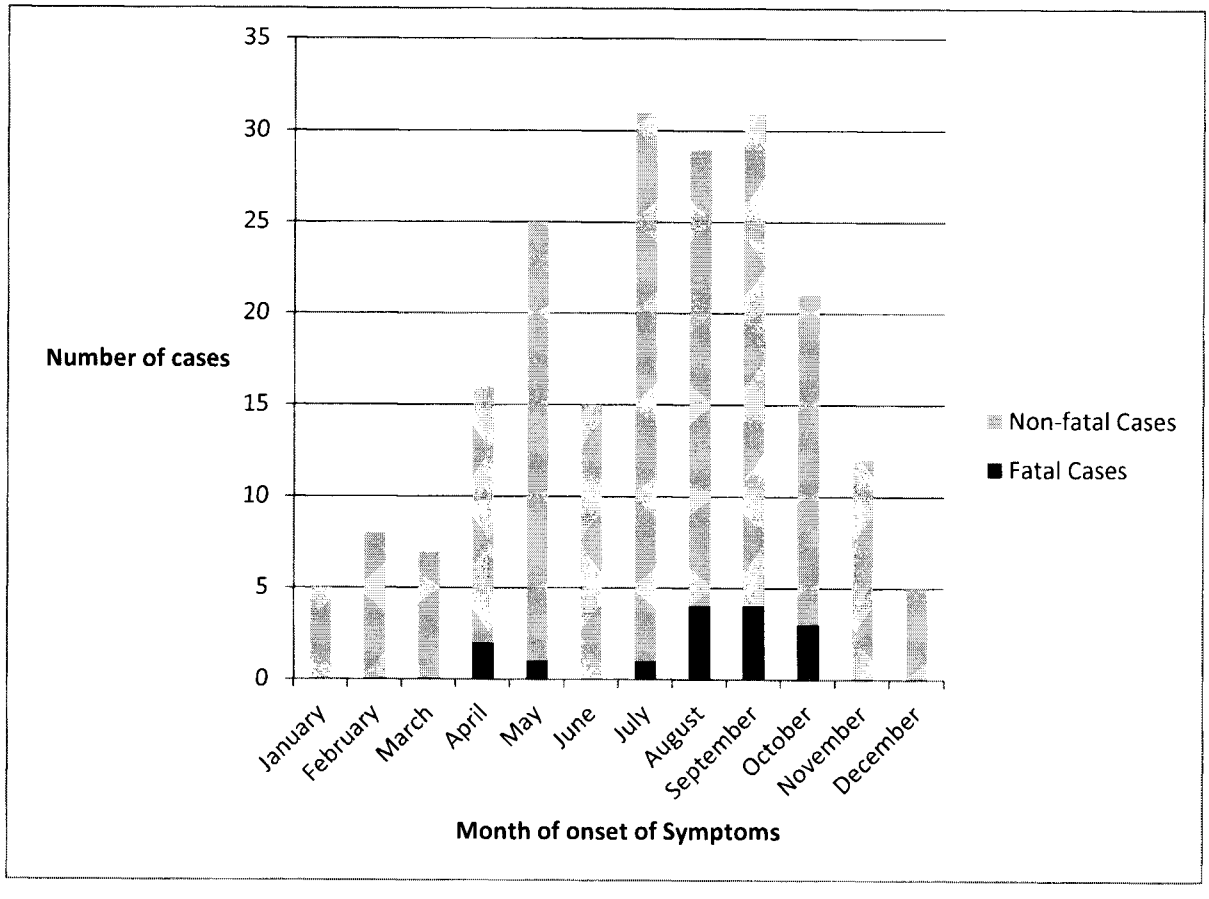


Figure 2. Month of symptom onset for fatal and non-fatal cases of Rocky Mountain spotted fever in two tribal communities in eastern Arizona



Medical and indirect costs associated with a Rocky Mountain spotted fever epidemic in Arizona, 2002-2011

Authors: N Drexler[1], J McQuiston[1], M Traeger[2], V Williams[3], C Hamilton[4], and J Regan[1]

Affiliations: 1. Rickettsial Zoonoses Branch, Division of Vector-borne Diseases, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention (CDC), Atlanta, GA 2. Whiteriver Public Health Service Hospital, Whiteriver, AZ 3. Tribe A 4. Tribe B

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Abstract

Rocky Mountain spotted fever (RMSF) is an emerging public health issue on some American Indian reservations in Arizona. RMSF causes an acute febrile illness that, if untreated, can cause long-term hospital care, permanent sequalae requiring lifelong medical support, and death. We describe costs associated with medical care, loss of productivity, and death among cases of RMSF on two American Indian reservations (est. population 20,000) between June 2001 and September 2011. Acute medical costs totaled more than $1.6 million. This study further estimated $181,000 in acute productivity lost due to illness, and $11.6 million in lifetime productivity lost from premature death. Aggregate costs of RMSF cases in Arizona 2001-2011 surmounted to $13.4 million. We believe this to be a significant underestimate of the cost of the epidemic, but it underlines the severity of the disease and need for a more comprehensive study.

Rocky Mountain spotted fever (RMSF) is a tickborne rickettsial disease caused by the bacterium *Rickettsia rickettsii.* RMSF has been endemic in parts of the United States for well over a century, but emerged on tribal lands of Arizona in 2003.[1] From 2000-2007 it was demonstrated that American Indians were experiencing a disproportionate burden of disease compared to other race groups (4 times the burden of RMSF than whites).[2]

RMSF is known to cause an acute febrile illness potentially resulting in severe sequelae or death. The case fatality rate of RMSF in the region is also markedly higher than is observed elsewhere in the United States, averaging 7% of reported cases compared to <1% nationally.[2, 3] Initial presentation can vary widely and symptoms are often non-specific in nature, making timely diagnosis difficult, Traeger et al. 2014 (in press). When treatment is delayed past day five of symptoms, severe sequelae, such as neurological deficits or damage to internal organs may occur (ref Regan fatal paper 2014). Such sequelae can cause irreparable damage requiring long-term hospital care and lifelong medical support. Disease severity, long-term or permanent sequalae, and the potential for fatal outcome all contribute to the disease burden in this region. The costs of this epidemic within the affected communities are difficult to calculate, and must take into account not only acute care medical expenses, but also potential loss of productivity due to illness or death.

A retrospective chart review was performed within two American Indian communities at the center of this epidemic. Medical charts from June 1, 2001 through September 30, 2011 from Indian Health Service (IHS) health facilities serving the affected communities were reviewed by Regan et al. 2014 (in press). The two communities in this study are home to a combined total of an estimated 25,000 people in eastern Arizona. Case definitions used in this analysis follow those initiated by Regan et al. Table I gives selected characteristics of the sample population from the analysis performed by Regan et al.

In order to assess the financial burden of RMSF within affected communities, we calculated direct medical costs associated with acute medical care and indirect costs associated with productivity lost due to premature death or disability. All estimates were adjusted to 2010 dollar values based on historic rates of inflation.[4]

The medical chart review captured every visit to IHS and non-IHS facilities attending to acute disease management of diagnosed RMSF infections. We enumerated each of the different types of visits (classifying them as outpatient, emergency room, inpatient/general admission, and inpatient/intensive care unit (ICU) admission). We applied flat rate charges billed to Medicaid according to the local IHS finance department estimates.[5] The two communities included in this study have limited on-site hospital facilities and treatment capacity for severe cases, and must transfer patients requiring intensive care. As such, cost of transfer was also included in the estimation of acute medical costs as patients were often evacuated to more advanced facilities by air ambulance. For each patient, the cost per visit was multiplied by the number of each respective visit type and added to the cost of transfer, if applicable. The sum of these values is the estimate of acute medical costs associated with RMSF in these two communities.

Costs associated with acute productivity lost due to disease were based on estimates calculated by Grosse et al.[6] The hourly rates of compensation used in the calculation of daily, annual, and lifetime production were based on national averages from the Bureau of Labor and Statistics. National averages for annual income are nearly twice as large as annual income for the population in question, so a correction factor was applied to the Grosse estimates in order to compensate for this difference. The correction factor used the gender-specific average income of the average American Indian living in Arizona[7] over the gender-specific annual income for all ages provided in the Grosse paper. It was assumed variations in compensation by age and time spent in market and household tasks did not differ between the study population and the national average.

The number of days of productivity lost due to RMSF was calculated by combining the number of days spent at each healthcare visit (this would include one day for outpatient or emergency room (ER) visits and any inpatient days) plus 4 days for recovery regardless of disease severity. For cases involving children (persons under 15 years of age) we applied the lost compensation of a 30 year old female, to serve as the productivity lost by a caregiver.

In order to calculate potential earnings lost from a premature death due to disease we used the age and gender-specific lifetime productivity estimates from Grosse et al., and adjusted them based on local annual income, as was done for acute productivity lost. Using the age at death for each of the fatal

cases we applied the proper population-adjusted age and gender-specific lifetime production lost at a 3% discount rate.

There were 205 cases identified in the medical chart review according to the probable and confirmed case definitions. 29 people were admitted to the ICU and 15 people died. Table II shows the calculations and results for acute medical costs for all 205 cases. Summary daily production value lost due to acute disease was $181,100 [95% CI: $175,954, $186,240]. On average, 1.5 (range 0-8) days were lost for non-hospital visits (outpatient and ER visits not resulting in admission), and 6.9 (range 0-55) days were lost for days spent in the hospital. Lifetime productivity lost due to premature mortality from RMSF was $11,631,998 [95% CI: $11,304,814, $11,959,182]. Median age at death from this outbreak was 14 years (range 1 to 78). Finally, aggregate economic costs of Rocky Mountain spotted fever 2001-2011 surmounted to $13,444,848 [95% CI: $13,112,518, $13,777,172], as shown in table III.

The recent emergence of Rocky Mountain spotted fever in Arizona in the last decade has left devastation in its wake. This severe, but relatively isolated outbreak has cost millions of dollars in medical costs and economic productivity lost. Lifetime productivity loss accounts for 87% of the overall cost of disease in this calculation. The average lifetime productivity lost per fatal case of RMSF ($775,467 per death) is far greater than similar estimates for pneumococcal disease ($140,862 per death).[8] This value is high in comparison to other diseases because the median age of death from RMSF in these two communities is 14 years, whereas the highest rate of case fatality in persons with pneumococcal disease are over the age of 65.[9] RMSF is striking children and young adults who were previously healthy, who would otherwise have the most potential to contribute economically to society.

Acute cost estimates provided in this study use flat rate charges billed to Medicaid, rather than itemized billing, and do not represent the sum of actual charges as direct billing information was not available for this study. These flat rate charges are not specific to the treatment of RMSF, and generally represent the minimum charges. Costly treatments such as extracorporeal membrane oxygenation (ECMO), which cost upwards of $16,000 for every 24 hours were used to treat patients in our cohort, but were not accounted for in our estimate.[10] Furthermore, since the medical chart review was cross-sectional in nature, long-term costs, such as rehabilitation and ambulatory care, as well as loss of productivity due to disability, were not included and could significantly increase the estimated costs of disease. Therefore, these calculations likely represent a gross under-estimation of the costs sustained. However, these estimates are valuable in that they underline the social and economic impact on affected communities and emphasize the need for a more comprehensive study to document the economic impact of this disease.

Acknowledgements

The authors wish to thank tribal health officials who wish to remain anonymous, as well as the Indian Health Service and private health care providers who care for this patient population every day. Approval for the study was obtained from participating tribes, the Indian Health Service, and the Centers for Disease Control and Prevention (CDC). We would also like to thank Drs. Martin Meltzer, Manjunath Shankar and Erin Staples from the Centers for Disease Control and Prevention for their mentorship in cost-analysis techniques.

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Tables

Table I. Selected characteristics of case population

Characteristic	Proportion of cases reporting (%)
Male Gender	106/205 (52%)
Median age (range)	11 yrs (7 mos-78 yrs)
History of tick exposure	73/132 (55%)
Select severe sequelae	
Respiratory Failure	22/204 (11%)
DIC	18/204 (9%)
Renal Insufficiency	17/203 (8%)
Multisystem organ failure	14/204 (7%)
ARDS	13/204 (6%)
Coma	11/203 (5%)
Digital Necrosis	3/201 (2%)
Events at discharge	
Long term sequelae	5/187 (3%)
Rehab facility	2/188 (1%)
Specialty follow-up	5/186 (3%)

Table II. Acute medical costs

Item	Number of people reporting	Number of times/length of stay	Cost per unit	Total cost
ER	170	256	$500	$128,000
Outpatient visits	81	125	$254	$31,750
Inpatient days (excluding ICU)	82	360	$1,400	$504,000
Transfers	48	48	$1,500	$72,000
ICU	29	224	$4,000	$896,000
				Bulk total $1,631,750

Table III. Summary of direct and indirect costs associated with RMSF in Arizona 2001-2011

	Point estimate	Lower bound	Upper bound
Direct costs			
Acute medical costs	$1,631,750	$1,631,750	$1,631,750
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	$13,444,848	$13,112,518	$13,777,172

NA-Not addressed in this study due to unavailability of relevant clinical information

Rocky Mountain spotted fever on Tribal Lands in Arizona, 2003-2012: The Story from Emergence of a New Epidemic to Control and Prevention

Author: Jennifer McQuiston, DVM, MS; Naomi Drexler, MPH; Rob Massung, PhD.; Justin Gerding; Mark Miller; Craig Levy; Ken Komatsu, MS; Kristen Herrick, MPH; Erica Weis, MPH; Marc Traeger, MD; Rodrigo Villar, MD; Ty Reidhead; Velda Williams; Charlene Hamilton; Stephen Piontkowski, MS

Rickettsial Zoonoses Branch, Division of Vector-borne Diseases, Centers for Disease Control and Prevention

Arizona Department of Health Services

Indian Health Service

Tribe, Reservation 1

Tribe, Reservation 2

Short title: A Decade of RMSF in Arizona

White Paper for Use in Arizona

Abstract: Ten years have passed since Rocky Mountain spotted fever (RMSF) first emerged on tribal lands in eastern Arizona, a region where RMSF had not been previously recognized. In this single decade, *Rhipicephalus sanguineus* (the brown dog tick) has been identified as the tick vector for RMSF in the southwestern United States, and American Indians have emerged as a population at significant risk for infection. During 2003-2012, 266 RMSF cases and 19 deaths

were reported in the state, from at least six different reservations. Annual incidence on the three reservations reporting consistent human cases is estimated to be 148 cases per 100,000, compared to a national rate of only 0.9 cases per 100,000. The expanding epidemic has established eastern Arizona as a region with one of the highest RMSF incidence and case fatality rates in the United States, and strongly challenged our historic understanding of RMSF transmission cycles, geographic distribution, and epidemiology. Free-roaming dogs, which are the primary blood meal source for *Rh. sanguineus*, play a pivotal role in RMSF disease ecology in Arizona, and also offer the most promising key for control of the disease. However, RMSF control on tribal lands will require financial resources beyond the capacity of most tribes, and is unlikely to be sustained without the establishment of effective animal control programs.

Introduction

Rocky Mountain spotted fever (RMSF), caused by the bacterial organism *Rickettsia rickettsii*, is a tick-borne disease that has been recognized for over a century in North and South America. RMSF presents primarily as a febrile rash illness but, if not promptly treated with tetracycline antibiotics, can progress to severe disease, including multisystem organ failure and death. Persons with occupational or recreational contact with wooded settings have long been considered at increased risk, due to contact with the primary U.S. tick vectors *Dermacentor variabilis* (the American dog tick) and *D. andersoni* (the Rocky Mountain wood tick). National surveillance data have also suggested that American Indians may be at increased risk for infection compared to other race groups.(McQuiston 2002; Dahlgren 2011; Folkema 2012; Holman 2009)

In the United States, the first cases of RMSF were reported from the Rocky Mountain region, which led to the disease being called Rocky Mountain spotted fever. However, most contemporary cases of RMSF are reported from the southeastern and south-central United States. During the last decade, five states (North Carolina, Oklahoma, Arkansas, Tennessee, and Missouri) accounted for 64% of all cases reported to the U.S. Centers for Disease Control and Prevention (CDC).(Openshaw 2010) During the period of 2009-2012, the average national annual incidence for the United States was calculated to be 0.9 cases per 100,000 persons (CDC, unpublished data), marking it as a rarely reported disease with some regional differences.

Historically, there have been few cases of RMSF reported from Arizona. During 1993-2002, only six cases of RMSF were reported to the Arizona Department of Health Services, (ADHS http://www.azdhs.gov/phs/oids/vector/rmsf/stats.htm), and many of these were associated with out-of-state travel. The traditional lack of RMSF in Arizona is not surprising, given that the majority of the state's land mass lies outside the known geographic range for *D. andersoni* and *D. variabilis.*(http://www.cdc.gov/ticks/geographic_distribution.html) In addition, much of the state boasts a dry, arid climate long considered inhospitable to ticks, which often have specific humidity and temperature requirements.
(http://www.wrcc.dri.edu/narratives/ARIZONA.htm, published by National Climatic data center)

Emergence of RMSF in Arizona

In 2003, RMSF was unexpectedly confirmed by the CDC as the cause of death in a 1 year old American Indian child from Arizona.(Demma 2005) The child's family resided on a reservation (Reservation 1, population ~12,000, Figure 1) in the eastern half of the state, and the

child had not recently travelled, implying that exposure had occurred locally. Even more concerning, one of the six RMSF cases reported to ADHS during the prior decade—a 10 year old boy who became ill in 2002 but recovered—had resided on the same reservation as the deceased child. In prospective surveillance, clinicians identified fourteen additional cases of RMSF occurring between 2003 and 2004. The annual incidence for Reservation 1 during this two year period was estimated to be 63 cases per 100,000 population, and the case fatality rate was 13%.(Demma 2005) In contrast, the U.S. annual incidence during this same period was <0.6 cases per 100,000, and the national case fatality rate was < 1%.(Openshaw 2010)

An investigation was undertaken to establish the source of RMSF exposure on Reservation 1. No *D. andersoni* or *D. variabilis* ticks were found, but numerous environmental infestations of *Rhipicephalus sanguineus* (the brown dog tick) were observed on free-roaming neighborhood dogs and in the peridomestic environment.(Demma 2005; Nicholson 2006) Laboratory testing of *Rh. sanguineus* ticks collected from the environment confirmed the presence of *R. rickettsii*; the findings implicated this vector as the source of the outbreak, and marked the first time *Rh. sanguineus* had been linked to RMSF transmission in the United States.(Demma 2005)

To better understand the extent of RMSF in this region, a serosurvey was carried out in 2004 among pediatric patients on Reservation 1; 18/184 (10%) of patients showed antibodies to *R. rickettsii*, suggesting past exposure to the organism.(Demma 2006) In addition, pediatric patients were also tested from a nearby reservation (Reservation 2, population ~9,000), which shared an extensive land border with Reservation 1. Although no human cases had been reported from Reservation #2 at the time of the serosurvey, 5/31 (16%) pediatric patients were

seropositive, suggesting that cases had likely occurred there in the past but the diagnosis had been missed. (Demma 2006)

Expansion of the Epidemic

The first human RMSF cases on Reservation 2 were reported in 2005, nearly a year after physicians and health officials were encouraged to intensify case finding in the wake of the pediatric serosurvey results.(ADHS, unpublished data) Cases have continued to be reported from both Reservation 1 and 2 every year since. From 2003-2012, 266 cases of RMSF were reported to the ADHS, the vast majority in American Indians living on tribal lands, and most from Reservations 1 and 2. (http://azdhs.gov/phs/oids/vector/rmsf/stats.htm) Nineteen deaths from RMSF were recorded, all American Indians. The tribes responded with efforts aimed at educating residents about RMSF and the risks from ticks, treating areas with heavy tick infestations with pesticides, and putting tick collars on dogs (see section on RMSF Control Challenges, below). Despite these efforts, the numbers of reported cases have varied by year, a marked increase in reported cases was observed beginning in 2010.(Figure 2)

In 2009, the first RMSF cases in American Indians residing outside of Reservation 1 and 2 were reported to the ADHS.(Baty 2014) These two patients lived in a single house on a reservation in south-central Arizona (Reservation 3, population ~ 11,000). Although the presence of *Rh. sanguineus* ticks was documented throughout the reservation, an environmental investigation identified infected *Rh.sanguineus* ticks and serologic evidence of exposure to *R. rickettsii* in dogs near the case-patients' neighborhood, but found little evidence of exposure among dogs who resided in other neighborhoods on Reservation 3.(Baty 2014) Anecdotal reports suggested that a household in the case patients' neighborhood had adopted a dog from

Reservation 1 approximately three years prior, and the clustering of seropositive dogs in the case-patients' neighborhood suggested possible localized spread from a common point source.(Baty 2014) The tribe responded to these two human cases with an aggressive tick control program, treating dogs for ticks and spraying tick-infested homes with environmental acaracides. No other human cases have been reported from Reservation 3 through the end of 2012.(Baty 2014)

By 2011, RMSF had been reported from a fourth reservation (Reservation 4, population ~11,000), located in southern Arizona (ADHS, unpublished data); enhanced surveillance was implemented, and 49 confirmed and probable human RMSF cases had been reported from Reservation 4 by the end of 2012.(ADHS, unpublished data) In 2012, a death from RMSF was confirmed by CDC in a patient with tribal affiliations to another reservation in north-central Arizona (Reservation 5, population ~ 7,000).(ADHS, unpublished data) While this patient did not live on Reservation 5, he reportedly travelled there frequently to visit family. Two additional cases were diagnosed among residents of Reservation 5 as a result of enhanced surveillance during 2012; in addition, during 2012, 3 probable cases of RMSF were diagnosed on an additional northeastern Arizona reservation (Reservation 6, population ~ 174,000), which shares an extensive land border with Reservation 5.(ADHS, unpublished data)

RMSF in Mexico

Concurrent to the appearance of RMSF on tribal lands in the American southwest, reports of RMSF have also occurred in northern Mexico, a region with similar climate, topography, and socioeconomic challenges to some parts of Arizona. In Mexicali, an urban center of nearly one million people located in Mexico's Baja California state, an RMSF outbreak involving over one

thousand suspected human cases and transmission via *Rh. sanguineus* occurred in 2009.(Sanchez 2009) Focused in a poor, densely populated neighborhood just south of the border with California, this large urban outbreak raised significant concerns about cross-border transmission. A 2010 survey of dogs and ticks at animal shelters in Calexico, just across the border with Mexico, found no evidence of *R. rickettsii*; however, *Rh. sanguineus* ticks were observed on 30% of shelter dogs, highlighting the opportunity for easy spread of disease if *R. rickettsii* were introduced.(Fritz 2012) Control efforts, including stray dog removal, euthanasia of free-roaming dogs, acaracidal spraying of homes, and public education, were implemented by Mexican government authorities. While the outbreak appeared to wane, sporadic human cases of RMSF have continued to be reported from Mexicali since that time.

During 2012, reports of human RMSF, including at least 5 pediatric fatalities that were confirmed at CDC, have been reported from Sonora state in northern Mexico.(CDC unpublished data) This suggests that the recent emergence of RMSF in this region may reflect a more widespread pattern of change or improved awareness in certain areas, and clearly demonstrates that RMSF risk extends far beyond Arizona tribal lands. Mexico's experience also proves RMSF can pose a significant threat to life when it occurs in epidemic fashion in a densely populated area.

Epidemiology of RMSF in Arizona

On the three reservations that have consistently reported human cases during the last few years (Reservations 1, 2, and 4, with a total estimated population 32,000), the estimated average annual incidence of RMSF is 148 cases per 100,000 persons. This is over 160 times the U.S.

average of 0.9 cases per 100,000 persons. This dramatic difference in incidence highlights the extreme risk for RMSF infection occurring among a relatively small population.

There are several unique features of the epidemiology of RMSF in Arizona. One of the most interesting findings from this apparently expanding epidemicis its almost exclusive focus within American Indian communities. With the exception of a few cases with suspected out-of-state exposure, nearly all of the cases reported to AZDHS during the past 10 years have occurred among persons whose race is identified as American Indian, and who live on or regularly visit tribal lands. Another feature that differentiates this epidemic from endemic RMSF transmission elsewhere in the United States is the high proportion of infected children; over 50% of cases reported to the ADHS occur in children < 18 years old, while adults make up the majority of cases elsewhere in the United States.(http://azdhs.gov/phs/oids/vector/rmsf/stats.htm; Openshaw 2010; Traeger 2014) Presumably, RMSF transmission to American Indians, and in particular, among children, is being facilitated by conditions prevalent on some Arizona reservations.

Another interesting feature of the epidemic is that RMSF occurs as community-wide outbreaks, a phenomenon which has not been observed in other parts of the United States. Although RMSF is not spread person-to-person, the occurrence of multiple cases in a single household, or at multiple households within a community, can sometimes give the misleading appearance of a communicable disease event, when in fact the circumstances occur as a result of shared environmental exposures. A review of the published literature suggests that while family clusters of RMSF do occur, sporadic RMSF cases are more the rule in other parts of the United States, due to the largely focal distribution of infected *D. variabilis* and *D. andersoni* tick populations.(CDC MMWR 2004) In contrast, the Arizona RMSF experience has been characterized by larger neighborhood outbreaks, in part due to the direct role of dogs in

propagating and spreading infected ticks, the preponderance of free-roaming (i.e. unrestrained) dogs in many neighborhoods, and the close proximity of homes to each other in many tribal housing areas.

Among the 266 RMSF cases reported in Arizona during 2003-2012, 19 died, for an overall 7% case-fatality rate.(http://azdhs.gov/phs/oids/vector/rmsf/stats.htm) This is a significant improvement over the 13% case fatality rate reported from Reservation 1 during 2003-2004, when the disease first emerged and physicians lacked awareness, and likely reflects progress in efforts to educate healthcare providers in the region.(Demma 2005) Historical perceptions of RMSF paint it as a severe and potentially fatal disease, with case fatality rates of 20-90%. While RMSF fatalities have decreased markedly during the post-antibiotic era, a 7% case fatality rate, as observed in Arizona, is still markedly different than the rate reported elsewhere in the United States, which is < 1% for all cases, and even among confirmed cases is only 3%.(Openshaw 2010) A recent medical chart review of cases from Reservations 1 and 2 identified early treatment with doxycycline as the single most important factor to avoid fatal outcome; patients who received this drug within 5 days of illness onset recovered, while the proportion of cases who died increased with each day's delay thereafter.(Regan 2014) Factors likely influencing delay in treatment for this particular patient population include an unusual proportion of patients (32%) who never developed a rash, which may be inappropriately relied upon by physicians as a diagnostic clue.(Traeger 2014; Regan 2014) In addition, alcoholism, which was a commonly reported underlying medical condition in this population, was significantly linked to fatal outcome, possibly due to underlying liver dysfunction, but also because alcoholism has symptoms that may resemble early RMSF and may therefore confuse a timely diagnosis.(Regan 2014)

Physician education has been conducted throughout the entire region, and an aggressive early treatment algorithm (Figure 4) has been recommended for healthcare facilities serving Reservations 1, 2, and 4, which have reported the highest number of human cases.(CDC, unpublished data) Although the algorithm results in a very high proportion of febrile patients receiving doxycycline (including many who may not have RMSF but who meet the inclusion criteria), in situations where the algorithm is used faithfully, case fatality rates from RMSF approach 0%.(CDC, unpublished data) Interestingly, although pediatric RMSF mortality is higher than that observed for adults in other parts of the United States (Dahlgren 2012), in Arizona, children and adults appear to have a similar risk for fatal outcome (Regan 2014). Physician reluctance to prescribe doxycycline to children because of unfounded fears of dental staining is suspected as a primary contributing cause for the higher pediatric mortality rate seen elsewhere (Zientek 2013), even though doxycycline is recommended by the CDC and American Academy of Pediatrics for the treatment of suspected RMSF in children of all ages. In Arizona, the grassroots effort to educate physicians about the emergence of RMSF in the region, as well as the high proportion of pediatric cases, has had the positive effect of ensuring a high compliance with the recommendation to give doxycycline to children when RMSF is suspected.

Understanding seasonal risk for RMSF is an important consideration for physicians, who deal with a variety of febrile patients throughout the year. With 8-10 years of observational data now complete, clear seasonal patterns can be discerned for RMSF activity on Reservations 1 and 2 (FFigure 3).(Traeger 2014) Periods of highest human risk vary by reservation and are likely directly related to tick activity that can be influenced by variables such as elevation, rainfall, and average temperatures. On Reservation 1, which is at a higher elevation and has slightly cooler seasonal temperatures than Reservation 2, human cases occurred mainly May-November, with

peak onset reported during August-September. On Reservation 2, cases appeared earlier and occurred mainly March-October, with a peak in April and July.(Traeger 2014) A dip in human cases was observed in June, corresponding with the reported driest month of the year in Arizona, and a surge in human cases was observed July-onward, corresponding roughly with the seasonal onset of monsoon rains.(Traeger 2014; http://www.wrcc.dri.edu/narratives/ARIZONA.htm, published by National Climatic data center) Despite these evidence patterns of seasonality, on both reservations, human cases and visible ticks have been reported year-round, highlighting the activity of this tick, even during the winter.

Our understanding of the epidemiology and ecology of RMSF is still evolving, especially for Reservation 4, where only a year or so of human surveillance data has been collected by the end of 2012. Due to a more southern location, a lower elevation, and differences in rainfall patterns, the ecology of RMSF on Reservation 4 is likely different from what has been reported in the other parts of the state, and early reports from one year of surveillance suggest that epidemiologic patterns (including patient age and seasonality) may also be different. Because the picture of RMSF is still early here, more research is needed.

The Role of Dogs

Dogs are highly susceptible to infection with *R. rickettsii*, and develop a febrile illness resembling that seen in humans and a robust immunologic response.(Kidd 2006; Elchos 2003; Gasser 2001;) In RMSF cycles involving *D. variabilis* and *D. andersoni*, dogs are considered more victim than villain, and when implicated in RMSF transmission to humans they are mainly considered to play the part of transport system, picking up ticks and bringing them in closer contact with people. *D. variabilis*, particularly in the adult stage, will feed on dogs as one

possible convenient blood meal source, but also more frequently feed on other mammals.(Goldberg 2002; Sonenshine 1967) In contrast, *Rh. sanguineus* prefers dogs as a blood meal source in each life stage, and adult ticks find mates and reproduce on dogs.(Dantes-Torres 2008) Therefore, the unique situation in Arizona and the involvement of *Rh. sanguineus* as a new, unexpected vector has challenged much of what we presumed about dogs and RMSF, both in their primary role in supporting tick populations, but also as potential reservoirs.

Free-roaming dogs are the most significant contributor to the perpetuation and spread of RMSF on tribal lands. When households are questioned, the majority of free-roaming dogs observed within neighborhood boundaries are claimed as pets. Dog population counts of owned dogs ranged from 0 to 13 dogs per household on Reservations 1 and 2 during 2011-2012, and averaged 1 to 2 dogs per household, depending on neighborhood and time of year.(CDC, unpublished data, from 2011 Dog Population Survey and the 2012 RMSF Rodeo project) On most tribal lands, owned dogs are often permitted to roam freely; as few as 1/3 of owners surveyed on Reservations 1 and 2 during 2011-2012 reported always or almost always restraining their dogs by fence or tether.(CDC, unpublished data, from 2011 Dog Population Survey and the 2012 RMSF Rodeo project). This equates to 70% of dogs on reservations being free-roaming. Therefore, RMSF spread between individual homes and neighborhoods likely occurs via movement of dogs (assisted by humans moving to new areas or "adopting" dogs from family and friends) and, consequently, translocation of ticks. Indeed, circumstantial evidence from Reservation 3 points to translocation of dogs from one reservation to another as a possible factor in the limited emergence of RMSF there.(Baty 2014)

Because owned dogs play an important role in RMSF transmission on tribal lands, disease ecology is heavily influenced by residents' limited access to veterinary care, and, on most

reservations, a lack of effective tribal or governmental animal control services. When RMSF first emerged on Reservation 1 and 2, only Reservation 2 had staff designated as animal control officers, and neither had standing facilities approximating a full-scale animal control program. Furthermore, both tribes lacked regular veterinary programs for spay/neuter services, a cornerstone of canine population control. Instead, tribes relied on annual, day-to-week long charity services for pet care, such as annual visits from groups like Rural Area Veterinary Services (RAVS) (http://www.ruralareavet.org/), which performs at most several hundred surgeries per year.(Tribally reported data) Additionally, annual canine rabies vaccination clinics are organized through the Indian Health Service. During a survey conducted on Reservation 2 in 2012, only 11% of male dogs were neutered, and only 10% of female dogs were spayed.(CDC unpublished data, 2012 RMSF Rodeo project) Reasons provided by residents for not neutering their pets included wanting to breed the animals, not thinking it was necessary, waiting for a scheduled sterilization clinic, and transportation issues. The low sterilization rate seen on tribal lands like Reservation 22 is in stark contrast to other parts of the U.S., where on average 83% of dogs are sterilized (http://www.humanesociety.org/issues/pet_overpopulation/facts/pet_ownership_statistics.html) . In addition to limited access to veterinary care, other inhibitors may also influence residents' ability to purchase effective tick control products, including lack of ability to acquire effective products from locally available resources (such as grocery stores and hardware stores), or inability to afford the few products that are made available.

While the literature downplays a likely role for dogs as reservoirs of RMSF, due to a limited period of rickettsemia in healthy, laboratory-raised animals (Norment 1984), the unique situation in the Arizona transmission cycle suggests that closer study may be warranted. Dogs on

tribal lands are frequently malnourished and may be immunologically compromised due to the prevalence of other canine infectious diseases and parasites; for example, a 2011 report from RAVS clinics held on Reservations 1 and 2 suggested high observed rates of parvovirus and distemper, and showed that 76% of tested dogs were positive for canine tick-transmitted diseases like anaplasmosis and ehrlichiosis. A report from Reservation 5 examining dog blood collected in 2005 and 2007 suggested rates of active *Ehrlichia canis* infection of 36%.(Diniz 2010) When exposed to RMSF, these chronically impaired dogs may well experience an extended bacteremic state beyond that observed in controlled laboratory experiments, and may contribute to the infection of new populations of feeding ticks. In particular, new and immunologically naïve puppies born each year into tick-infested environments may serve as significant amplifying hosts for *R. rickettsii*; for example, PCR positive puppies have been found in close association with areas of intense RMSF activity.(Baty 2014). However, more studies are needed to ascertain the role of dogs in general—and puppies, in particular—as possible reservoirs for RMSF in this region and unique transmission cycle.

Because *Rh. sanguineus* prefers dogs as a food source in all life stages (Dantas-Torres 2008), and because dogs are more likely to be exposed to higher numbers of ticks than people, canine serosurveys have been performed in Arizona in order to help inform health officials of local RMSF risk and, in some cases, to monitor progress toward control. Cross-reactivity is known to occur among numerous spotted fever group rickettsiae, and therefore animals positive for antibodies reactive to *R. rickettsii* may have also been exposed to other genetically related bacteria. However, as a general tool and predictor of tick exposure, these surveys have a great deal of utility, particularly if human surveillance data supports the presence of RMSF.

In many cases it is difficult to pinpoint when RMSF first appeared on affected reservations, but canine serology data suggests that for most tribes, RMSF is often already firmly established on these reservations by the time the first human case is identified. Following the identification of the initial RMSF outbreak on Reservation 1, 60/97 (62%) dogs were shown to be positive to *R. rickettsii* at titers ≥ 1:64, suggesting that RMSF was already established on the reservation by the time the first human cases were recognized (Table 1).(Demma 2006) Interestingly, an assessment of canine sera collected from Reservation 1 during a separate study in 1996 showed that only 17/329 (5%) were seropositive at titers ≥1:32 at that time.(Demma 2006) A more limited canine serosurvey was carried out on Reservation 2 in 2004, one year before the first human cases were reported, and 7/14 (50%) dogs were positive at that time.(Demma 2006) Coupled with concurrent serologic results from human pediatric serosurveys, these results helped encourage local health officials to be more aggressive in finding and diagnosing suspected cases.

Canine serosurveys have also been conducted on Reservations 3-6, most often in response to the identification of the first human cases there. Although prior published canine seroprevalence to spotted fever group rickettsiae was reported as high as66% and 53% on Reservation 5 during 2005 and 2007, respectively (Diniz 2010), a survey conducted in 2012 showed seroprevalence of 13%, and a canine seroprevalence of 16% in nearby Reservation 6. In contrast, Reservation 4, which has had the most human cases after Reservations 1 and 2, had a canine seroprevalence of 28%.(CDC, unpublished data)

Based on current trends and regional observations, human risk for infection appears greatest when local canine seroprevalence exceeds 20%. Human cases have rarely been reported from reservations where canine seroprevalence is ≤ 5% (a notable exception to this rule is

Reservation 3, where human infection and high canine seroprevalence appeared concentrated to a small radius).(CDC unpublished data; Baty 2014) A canine serosurvey was conducted outside Arizona tribal lands in 2005-2006, and evidence of prior exposure to *R. rickettsii* was seen in only 5.7% of tested dogs relinquished to Arizona county animal control shelters, although shelters in counties that shared borders with the implicated reservations did have slightly higher rates of seropositivity.(McQuiston 2009). In addition, canine sera tested in 2011-2012 from three Arizona tribes that had not had any reported human cases of RMSF showed little serologic evidence of prior exposure to *R. rickettsii* (Table 1, 3/85 positive, 4%).(CDC, unpublished data)

Although data are currently too limited to make any firm conclusions, based on these findings and current observations, a gradient of risk is observed, when human surveillance data and canine serosurvey results are examined concurrently. Based on the preponderance of human cases reported during multiple years, Reservations 1, 2, and 4 clearly have a high risk for human infection, and those reservations also have an overall canine seroprevalence > 20%. In contrast, Reservations 3, 5, and 6 have had very few human cases reported, and while positive cases have been reported, they have overall reservation-wide canine seroprevalence rates <20%.

The Role of Rh. sanguineus

Rh. sanguineus—both its feeding preferences and its ability to thrive in harsh climactic environments that would be lethal to most other tick species—lies at the heart of the RMSF epidemic in eastern Arizona. A one-host tick that preferentially acquires blood meals from domesticated dogs during each life stage (see Figure 5), *Rh. sanguineus* is one of the most common tick species throughout the world.(Dantas-Torres 2008/2010) It is found attached to people and other animals only occasionally, although wild canids like coyotes, which are found

throughout Arizona, may also provide blood meal sources and deserve further research as potential bridge hosts. Potential roles for rabbits, birds, foxes, and other wildlife species that are present in the area are also worth investigating, although iin general, *Rh. sanguineus* is considered a primary parasite of dogs, and is therefore a predominantlypredominantly urban and peridomestic pest, rather than a wildlife nuisance.(Dantas-Torres 2008/2010) While it feeds on humans only sporadically, and usually when preferred hosts are not readily present, at least one published report suggests that human predation behavior by *Rh. sanguineus* may increase at warmer ambient temperatures, a factor that may well come into play for this tick's clear role in RMSF transmission to humans in Arizona and Mexico.(Parola 2008)

Rh. sanguineus had previously been shown to be a competent vector for *R. rickettsii* in an animal model, and even before its role was identified in the current epidemic, was long considered a potential vector for RMSF in Central and South America.(da Silva Costa 2011; Piranda 2011; Parker 1933; Bustamante 1947) Molecular analysis of *R. rickettsii* strains from North and South America suggests that the variant found in Arizona appears distinct from strains circulating in other parts of the United States where *D. variabilis* and *D. andersoni* are the primary vectors, and also different from *R. rickettsii* strains in Mexico, where an *Rh. sanguineus* transmission cycle also occurs. (Eremeeva 2011)

Rh. sanguineus is also the vector for *R. conorii*, a rickettsial pathogen that causes Mediterranean spotted fever in humans in Europe, Africa, and Asia. In addition, *Rh. sanguineus* is well-recognized as a vector for *Ehrlichia canis* and *Anaplasma platys*, two rickettsial pathogens of dogs with a worldwide distribution. During the 2003-2004 investigation that was conducted on Reservation 1, at least one *Rh. sanguineus* tick was shown to be positive for *R. massiliae*, a human pathogen in Europe(Eremeeva, 2006), suggesting that other spotted fever

group rickettsiae may play a background role in human infections in Arizona. However, all human infections with accompanying PCR or culture results have been confirmed as *R. rickettsii*; no human cases of *R. massiliae* have been identified in Arizona.

Maintenance of *Rickettsia* species in *Rh. sanguineus* appears to occur through a combination of transtadial transmission (acquisition of infection through a blood meal and then transmission from one life stage to the next during the molting process), and transovarial transmission (infected females laying infected eggs).(Dantas-Torres 2008; Dantas-Torres 2010) *Rh. sanguineus* frequently co-feed in large clusters consisting of 10-100 ticks in various life stages, which may facilitate acquisition of *R. rickettsii* by uninfected ticks from infected ticks feeding nearby. In a study examining the related organism *R. conorii*, naïve ticks were observed to become infected simply by feeding next to aninfected tick, even though the dog providing the blood meal was not shown to be infected, and in some cases, was presumed "immune" to systemic infection due to high levels of circulating antibodies. (Levin 2014; Levin 2012) Notably, during the initial investigation on Reservation 1 during 2003-2004, 3% of host-seeking, non-engorged, ticks tested contained *R. rickettsii* DNA, a percentage notably higher than carriage rates in *Dermacentor* ticks, which are rarely positive for *R. rickettsii*.(Demma 2005; Stromdahl 2011; Carmichael 2010; Sexton 1976) This difference in carriage rates may be due to a variety of factors, including *Rh. sanguineus* biology, but it is interesting to speculate whether such a difference influences the high rate of RMSF transmission to humans in the region, and whether this difference may facilitate rapid spread among tick populations.

By all accounts, *Rh. sanguineus* is a very common pest of dogs on Arizona reservations, even on reservations where human RMSF has not been reported. During surveys conducted on Reservation 2 during 2012, 34% of dogs were noted to have tick infestations during March, and

63% of dogs from this reservation were observed to be infested with ticks during the month of August, including 31% of dogs with very heavy infestations of 20 ticks or more.(CDC, unpublished data, 2012 RMSF Rodeo project) *Rh. sanguineus* was also observed on nearly 7% of dogs surveys at county animal shelters outside tribal lands during November 2005-April 2006, highlighting the presence of this tick in non-tribal areas, and even in colder winter months.(McQuiston 2009)

A compounding factor for the prevalence of *Rh. sanguineus* in Arizona is the extensive availability of manufactured tick habitat around reservation home sites. Despite climatic conditions that might be considered harsh for many ticks, local home sites on reservations are frequently littered with trash and debris, which create niche environments that may retain moisture and support sustained survival of ticks. This dog-accessible habitat primarily includes discarded furniture and mattresses with soft permeable material (e.g. sofa, cushions), bags of old clothing, and dog houses with blankets or other soft bedding in them. Such materials are attractive areas for dogs who live outdoors to congregate, creating an intermingling situation that allows ticks to easy and frequent access to blood meals. These congregating spots also provide frequent opportunities for infected ticks to find new dogs as hosts, or human victims, especially children who may play in these outdoor environments. The home site issue is frequently complicated by homeowner's limited access (either physical or financial) to ready trash removal or local landfill access.

In addition to its ubiquitous presence on dogs, *Rh. sanguineus* is also a common pest in the peridomestic environment around human dwellings on reservations, presumably due to drop-off from dogs the ticks have recently fed upon (FFigure 5). On Reservation 2, a longitudinal tick population survey was carried out monthly during 2012, using a total of 15 CO^2 (dry ice - attracts

host-seeking ticks) traps each month, laid in the yards of five residences that reported evidence of ticks on dogs. Nymphs emerged first on Reservation 2 during February-April, followed by a wave of adult ticks March-April. Tick activity dropped during May and June, with all three life stages re-emerging in high numbers during July and August.(CDC, unpublished data) While high numbers of larval ticks were observed during the start of the study in November 2011, few ticks were observed a year later, in September and October, 2012. These findings may have been influenced by the fact that the tribe attempted aggressive reservation-wide acaracide spraying focused on homes with known tick activity during those months. Certainly, human data suggests human cases are often reported with onset during September and October on Reservation 2 (FFigure 3). It is not possible to discern from these data whether 2012 represented a "typical year" for Reservation 2 in terms of tick activity. Surveillance data suggest that the RMSF season started very early in 2012 for Reservation 2, with 3 confirmed human cases in March, 2 of which were fatalities. In contrast, longitudinal human surveillance data for Reservation 2 suggest that human cases more typically occur beginning in April-May.

We cannot tell from these data which stage of tick is most likely responsible for transmission of *R. rickettsii* to humans in this region. *R. rickettsii* has been demonstrated in all life stages of *Rh. sanguineus* ticks from this region, but the stage of tick most responsible for human biting behavior is less clear. With respect to *D. variabilis* and *D. andersoni*, adult ticks are most frequently implicated in human infection, and 60% of patients recall a tick bite.(Dalton 1995) Similarly, in Arizona, 55% of patients do not recall a tick bite..(Traeger 2014)

RMSF Control Challenges

If dogs are a cornerstone of RMSF ecology in this region, they are also the key to possible control. Unlike *D. variabilis* and *D. andersoni*, which feed on wildlife ranging from small

rodents to larger mammals, *Rh. sanguineus* feeds almost exclusively on dogs.(Dantas-Torres 2008; Dantas-Torres 2010) As the single most important factor blood meal host for *Rh. sanguineus*, dogs also provide an opportunity to actively kill ticks, impair tick reproduction, and break the *R. rickettsii* transmission cycle.

One positive example is found in the experience of Reservation 3. Beginning in 2010, this tribe mounted consistent and repeated tick control efforts following the identification of their first RMSF cases, focusing heavily in the neighborhood where their 2 human cases lived.(Baty 2014) This tribe was fortunate enough to already have an established animal control program and an integrated pest management plan, and so the programmatic and financial challenge of coordinating a tick control effort was easier to manage. After three years of concerted effort, no additional human cases have been reported from Reservation 3, and annual canine seroprevalence surveys have shown little evidence of spread in dogs.(Baty 2014)

The situation is markedly different on High Risk Reservations 1, 2, and 4, where both human surveillance data and canine serosurvey data suggest the widespread presence of *R. rickettsii*. During 2005-20122012, both Reservations 1 and 2conducted regular RMSF prevention campaigns to reduce ticks via the application of environmental pesticides (most commonly, permethrin or bifenthrin granules) and the placement of tick collars on some dogs (most commonly products containing propoxur, providing a few months of coverage).(IHSIHS, unpublished data) In addition, educational efforts including distribution of informational brochures, coloring book calendars, and public service announcements by print media and radio were undertaken by both tribes. Tick control campaigns were typically conducted in during the summer, and when possible were extended to multiple treatments per house. In addition, environmental cleanups to remove trash and debris from home sites were organized at various

points, usually in the spring in conjunction with Earth Day events.(IHS, unpublished data) The combined efforts were frequently carried out as a collaboration among numerous invested partners, including tribal health authorities, IHS, the Arizona Department of Health Services, the United States Department of Agriculture, and CDC, and required extensive partner collaboration to secure resources (human, financial, equipment). Work was conducted primarily by a volunteer workforce, and were generally organized ~~as only a single,~~ as a week-long annual activity, with follow-ups occurring in a sporadic fashion depending on available supply and staffing resources; because of these limitations, health officials were not always able to systematically and repeatedly target every house in a community or on a reservation. These efforts did show some success, with documented drops in tick counts following treatments. In addition, in the years following intensive control efforts conducted on Reservation 1 in 2005, lower human case counts were observedin 2006-2008 (Figure 2); however, due to the relatively recent emergence of RMSF in the region, subsequent declines in human cases may also have been due to regular variations in tick activity, relative to weather patterns and other environmental influences. As the increasing number of human RMSF cases during 2009-present demonstrates (Figure 2), these efforts have not proven successful in reducing human risk for RMSF infection long-term, although these increased case counts may also have been influenced by changes in surveillance. .

The past strategies employed by Reservation 1 and 2 have been limited, in part, because surviving eggs hatch and re-infest the environment with *R. rickettsii*-infected larvae as soon as residual pesticide levels drop below lethal levels. A single summertime application of environmental pesticides is unlikely to be successful when ticks emerge as early as February or March (Figure 5), and . In addition, summer applications timed in June are unlikely to reach large numbers of ticks, due to a natural nadir in their population cycle during dry mid-summer

weather. Tick eggs are not killed by commonly used acaracides like permethrin and bifenthrin, and ovicidal products have limited use in this UV-rich environment. Early efforts also utilized distribution of granules that required watering to be activated which is problematic in a hot, dry environment such as Arizona. Tactical application of liquid pesticide products, applied several times each year and timed for key periods of tick emergence, is likely to be a much more successful strategy.

Another factor in the lack of past sustained tick controlon Reservations 1 and 2 is the difficulty in treating the dogs themselves. Given the fact that every tick must feed on a dog at least three times during its life, strong tick control on dogs is arguably the most important piece of an effective control effort. Commonly used topical spot-ons containing fipronil, imidacloprid, and/ or permethrin are expensive, last only a month, and provide no externally visible marker that a dog has been treated. Sprays and dips are cost-effective, but have a shorter anticipated period of acaracidal activity (~ one week), and also provide no visual marker of treatment. Tick collars clearly mark a dog as treated, and currently have the longest estimated period of effectiveness (up to 5 months for some collars containing propoxur and amitraz). In order to maximize their efficacy, however, they must be properly applied and remain on the dog the entire time, no mean feat for free-roaming dogs in a rugged environment. Furthermore, anecdotal evidence from the use of propoxur collars on Reservations 1 and 2 has suggested that in most cases, less than 5 months of tick-killing activity can be expected in these harsh environments, necessitating frequent collar replacement.(CDC, unpublished data)

No matter the product selected, or the required frequency of reapplication, the single most important factor impacting a successful tick control campaign is the consistent and complete coverage of free-roaming community dogs. It is difficult to catch all dogs on the

reservation once, much less multiple times over the course of a year. All pet dogs must be treated in order for this strategy to be effective at the neighborhood-wide level, because untreated pets will wander into and drop ticks into neighbor's yards. Furthermore,unowned dogs *must* be either treated along with pets, or else permanently removed from the immediate environment, otherwise, reinfestation will be imminent. Finally, without a system to effectively track treated dogs and clearly identify unowned dogs, even the most well-intentioned efforts seem unlikely to succeed.

Sustained tick control on tribal lands will almost certainly involve more than treating dogs and yards for ticks. Effective animal control programs are urgently needed on tribal lands where RMSF exists, and without this tribal commitment, it is unlikely that stop-gap attempts to control ticks will be successful long-term. Community surveys conducted on Reservations 1 and 2 during 2012 showed a high level of support for establishing tribal animal control programs, and > 80% of residents, including elders, supported creating programs that included euthanasia for ill, unwanted, and unowned dogs.(CDC, unpublished data, 2012 RMSF Rodeo)

The high prevalence of both free-roaming dogs and *Rh. sanguineus* ticks in the peridomestic environment of most tribal households means that on reservations where RMSF is present, outdoor play and activities carries a specific risk that is not easily mitigated by commonly applied logic, such as the constant wearing of long pants and use of spray repellents. Nor is such advice practical when children live in a constant sphere of risk, with ticks infesting their pet dogs and inhabiting their play areas and, in some cases, their bedrooms. Warm temperatures and lack of air-conditioning may also result in open doors or sleeping arrangements made out-of-doors, which may increase the risk of human contact with dogs and ticks. Bites fromdogs remain a major concern on tribal lands, especially among children, and in the

Southwest, American Indian children are significantly more likely to be the victim of dog bites requiring medical care than elsewhere in the United States. (Bjork 2013) In these situations, controlling dogs and eliminating ticks has the potential to impact more than infectious disease risks: it can encourage more frequent exercise and outdoor play, and improve overall quality of life.

The RMSF Rodeo

In 2012, a small pilot project was undertaken in a 600-home neighborhood located on Reservation 2. This project, called the RMSF Rodeo, used an integrated pest management and animal control strategy to tackle tick control in a coordinated, properly timed fashion. Following the registration of project homes (~99% of which consented to participate), all dogs were registered with a tag and provided a regular collar, as well as a newly available tick collar (brand name Seresto), with the active ingredients flumethrin and imidacloprid. This collar was labelled for 8 months efficacy against ticks.

Following collar placement in April 2012, pesticide treatments were applied to all participating household yards four times, using a beta cyfluthrin-spray product approved for homeowner use, with an expected 3 week residual knock down activity against larvae, nymphs, and adult ticks. Pesticide was applied in a 3 foot high perimeter on walls and in a5 foot perimeter around houses, as well as areas where dogs bedded down or frequented. The product was applied in May, and reapplied at monthly intervals in June, July, and August. In addition, residential education regarding the program, RMSF, and ticks was undertaken through a series of pamphlets distributed to all participating households. Free spay/neuter services were provided to the neighborhood by appointment during the month of June, and animal control officers actively

removed strays from the study area. Most importantly, dogs were monitored for tick activity and checked monthly for tick collar retention, and collars were replaced if lost.

At the time of registration, 51% of homes in the RMSF Rodeo community had dogs with visible ticks. In August 2012, at the end of Year 1 of the program (and five months after tick collars were first applied), < 1% of dogs were infested with ticks. In contrast, ticks were observed on63% of dogs outside the study area on the same reservation. Furthermore, dry ice traps yielded no evidence of environmental tick presence by the end of the project. (Figures 7a and 7b). Even more impressive, although no further interventions were undertaken during September 2012-March 2013, tick numbers were still negligible in the study area in March 2013 (<3% of dogs with ticks). Subsequently, during 2013, application of the long-acting 8 month tick collar alone sufficiently controlled ticks at levels < 3% in the pilot study community. Environmental pesticide applications were only used on houses where ticks were actively observed, thus proving sustained control could be achieved with treatment of dogs alone, and with the added benefit of reducing the environmental pesticide levels during the second year of the control effort. Improved success may be facilitated by exploring methods to improve tick collar retention on dogs, as the Seresto collars were lost and needed to be quickly replaced in ~ 25-50% of dogs over the course of the program.

Costs of RMSF

The RMSF Rodeo in 2012 illustrated that strong integrated pest management programs can be highly successful in controlling ticks on a community-wide basis, which will in turn limit exposure to disease-carrying ticks and reduce human incidence of RMSF. Expanding the key components of the RMSF Rodeo across all impacted reservations is an expensive prospect

(Table 22). On Reservations 1 and 2 alone, it is estimated that it will cost $4.4 million and take 5 years to establish active animal control programs and achieve a sustainable level of tick control. Although a "safe" tick level cannot be established based on current data, a reasonable target goal is reducing ticks to < 10% of dogs, at least as a starting point. Close monitoring of dogs, tick numbers, and human illness consistent with RMSF is a vital part of any program.

In terms of benefits, investing in animal control programs and adequate tick control can be expected to save both lives and money. During the first decade of RMSF on Reservations 1 and 2, it is estimated that RMSF cost the tribes and federal government over $13 million, including direct medical costs, indirect costs of lost work time and productivity, and loss of life (Drexler, pub pending). While clearly a worthwhile investment, it will require both money and a strong commitment by tribal and public health leaders in order to be successful. Furthermore, expansion of the RMSF Rodeo activities is currently outside the financial capabilities of most tribal governments. Continuous, sustainable, outside support from government, non-profit, or philanthropic donors, is urgently needed.

Conclusions

The question of why RMSF so recently emerged on tribal lands in Arizona has many possibilities, but few definite answers. Environmental health officials with IHS report a noted increase in ticks in the years before RMSF was first reported, but the causes for this increase are unclear, and may be related to climatic, environmental, or host prevalence factors. Tribal views on community dogs may have changed during the last twenty years on tribal lands, with people more likely to keep dogs as pets and permit them closer contact with homes and children. Social and socioeconomic factors may have also shifted on tribal lands, influencing living conditions

and environmental factors that facilitate tick harborage and spread. The nearly concurrent appearance of RMSF in Mexico points to possible climactic influences across a wider geographic area. Finally, changes in diagnostic tools and surveillance may also account for the surge in reported cases, and indeed, RMSF case reports have increased nationally to an all-time high during the same decade.

Whatever the reason for its recent identification, one thing is clear: RMSF has become clearly established as a significant public health threat on Arizona reservation lands, and has the potential to spread beyond tribal and state borders. The vital conditions which have contributed to this outbreak in Arizona—including the presence of *Rh. sanguineus* ticks, prevalent free-roaming dogs, and socioeconomic challenges hampering access to effective veterinary care—are pronounced on some tribal lands, but also exist in other spheres, including some neighborhoods in large urban centers such as Phoenix and Tucson. In those cases, the introduction of a single *R. rickettsii*-infected tick or dog may be all that is needed to facilitate spread to new areas, and outbreaks in non-tribal areas remain a serious concern.

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Table 1: Rocky Mountain spotted fever on tribal lands in Arizona, 2003-2012. Human cases include those reported to the Arizona Department of Health Services (ADHS). Canine serosurvey data was reported by the Centers for Disease Control and Prevention (CDC). Dogs with *R. rickettsii* titers ≥1/64 are considered positive.

Reservation #	Year first human case of RMSF was reported	# of human cases reported through 2012	Canine seroprevalence (Year assessed)	Predicted Human Risk Level
1	2003	128	61% (2004)	High
2	2005	71	50% (2004)	High
3	2009	2	≤ 3% (2010-2012)*	Low to Moderate
4	2011	49	28% (2011-2012)	High
5	2012	2	13% (2012)	Low to Moderate
6	2012	3	16% (2012)	Low to Moderate
Other AZ tribes	No cases	--	4% (2011-2012)	Minimal
AZ, outside tribal lands	No locally acquired cases	--	6% (2005-2006)	Minimal

*Human cases reported from a single neighborhood in Reservation #3 with a 10% overall canine seropositivity during 2010.

Figure 1: Map showing Arizona reservations affected by Rocky Mountain spotted fever. Reservations are numbered in order of initial diagnosis of the first human case.

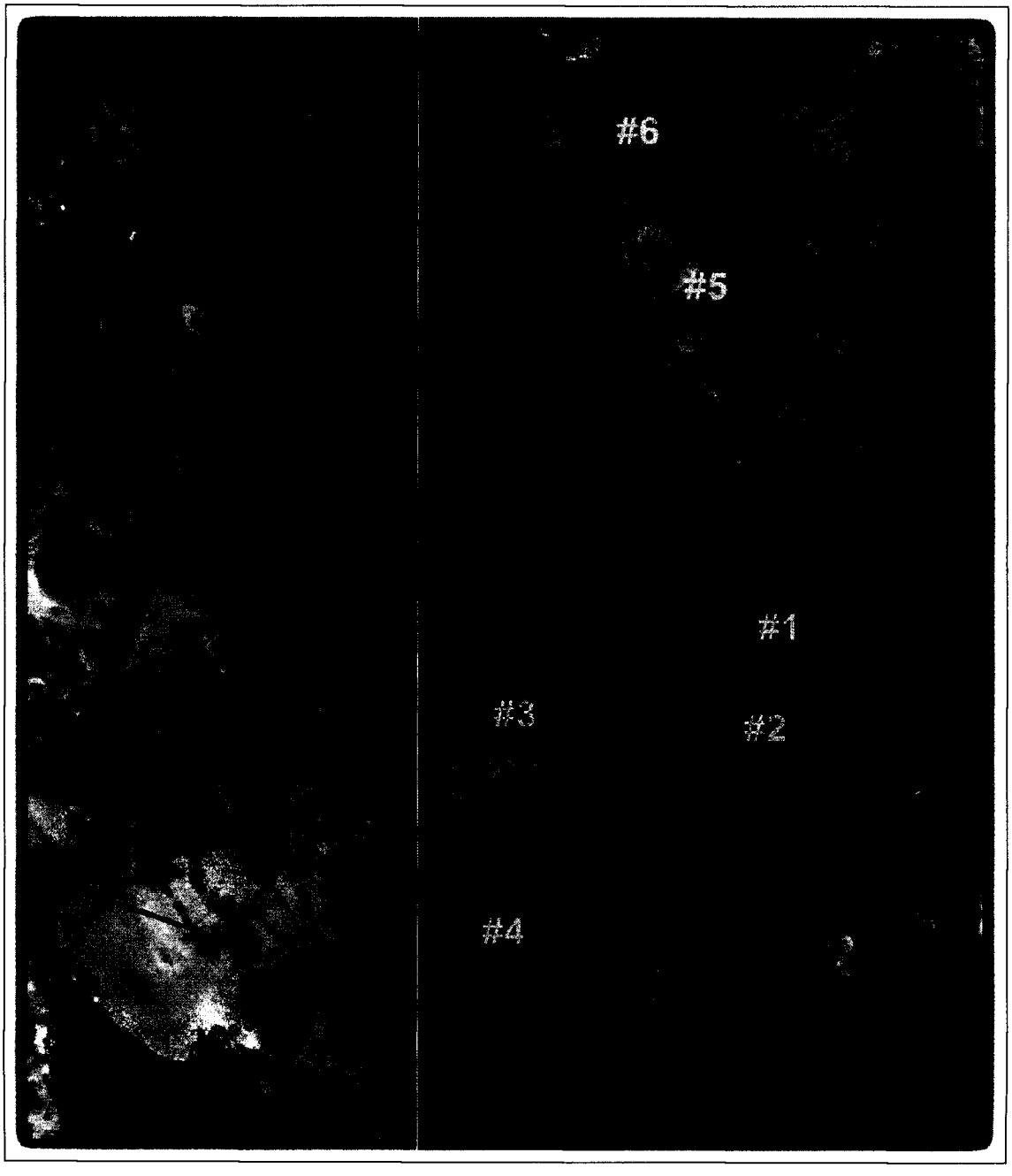


Figure 2: Annual number of reported Rocky Mountain spotted fever cases in Arizona, 1993-2012.

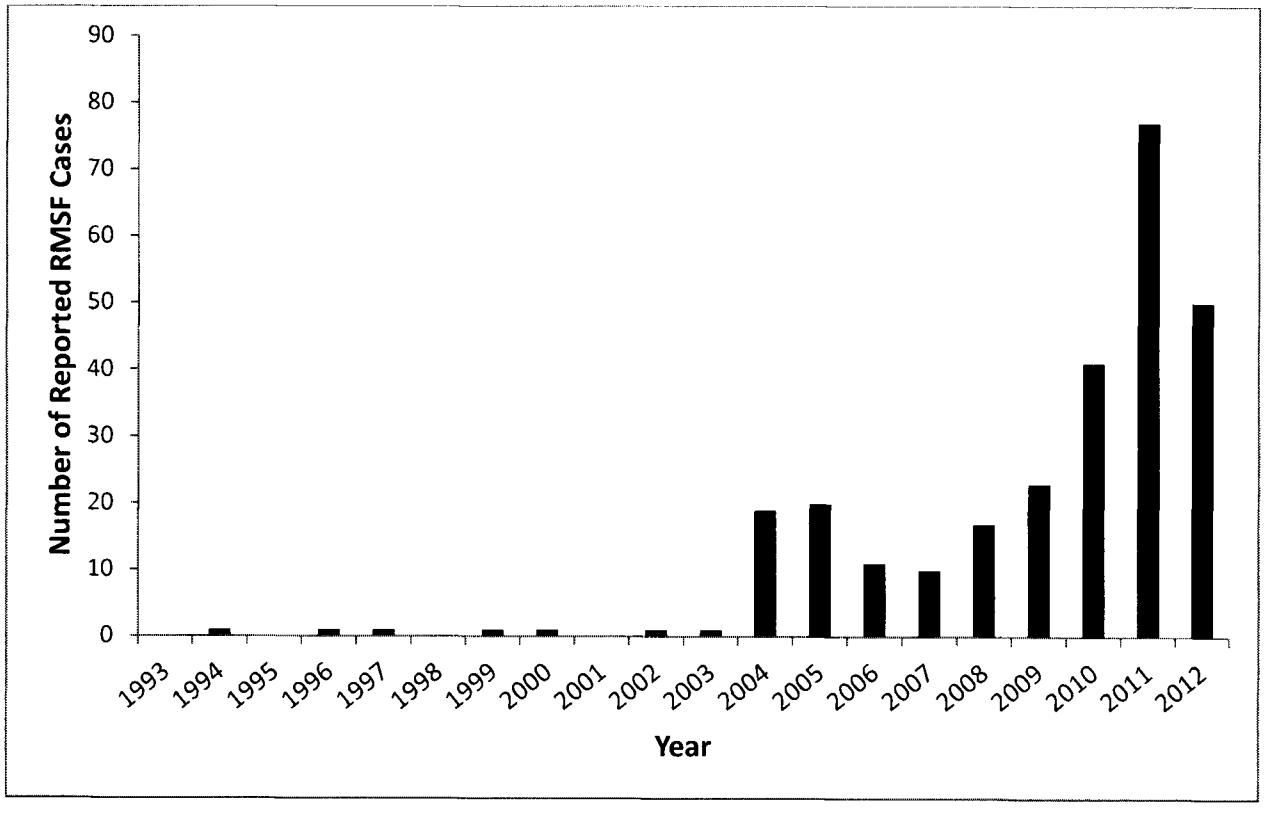


Figure 3: Month of illness onset for a subset of Rocky Mountain spotted fever cases reported from Reservations 1 (Community A) and 2 (Community B), 2003-2011.

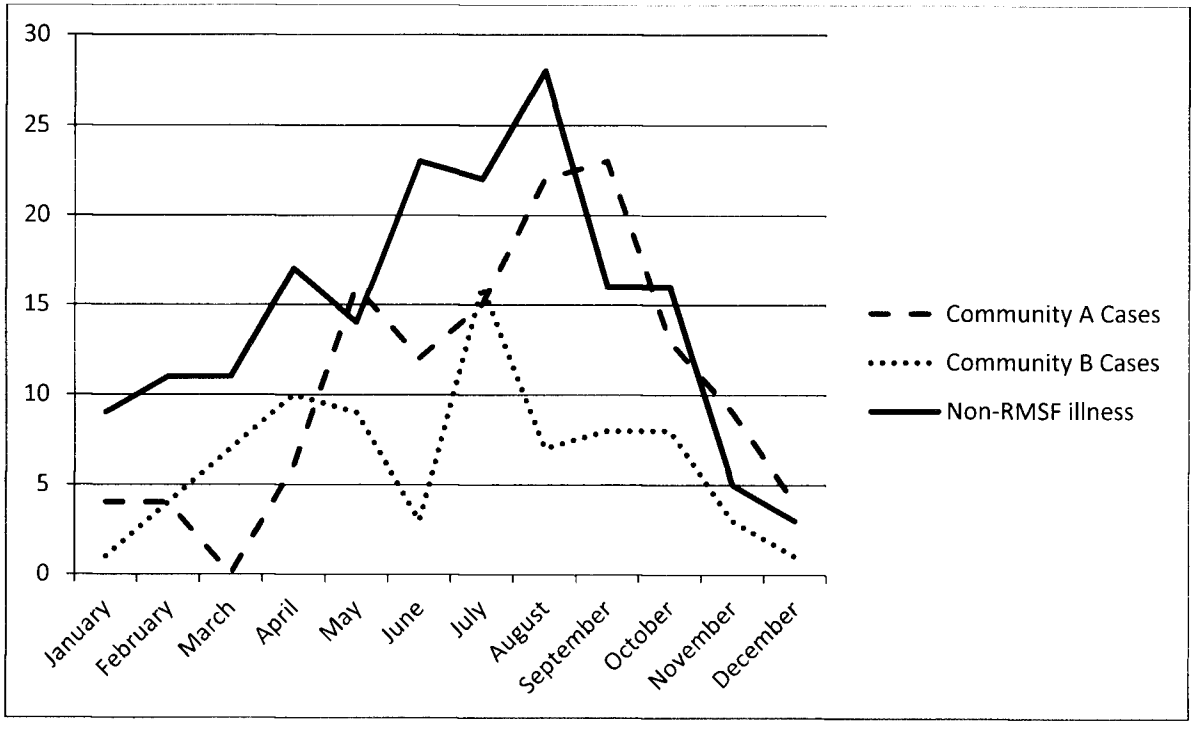


Figure 4: Algorithm for treatment of suspected Rocky Mountain spotted fever on tribal lands with a high risk for human infection (Currently reservations #1, 2, and 4).

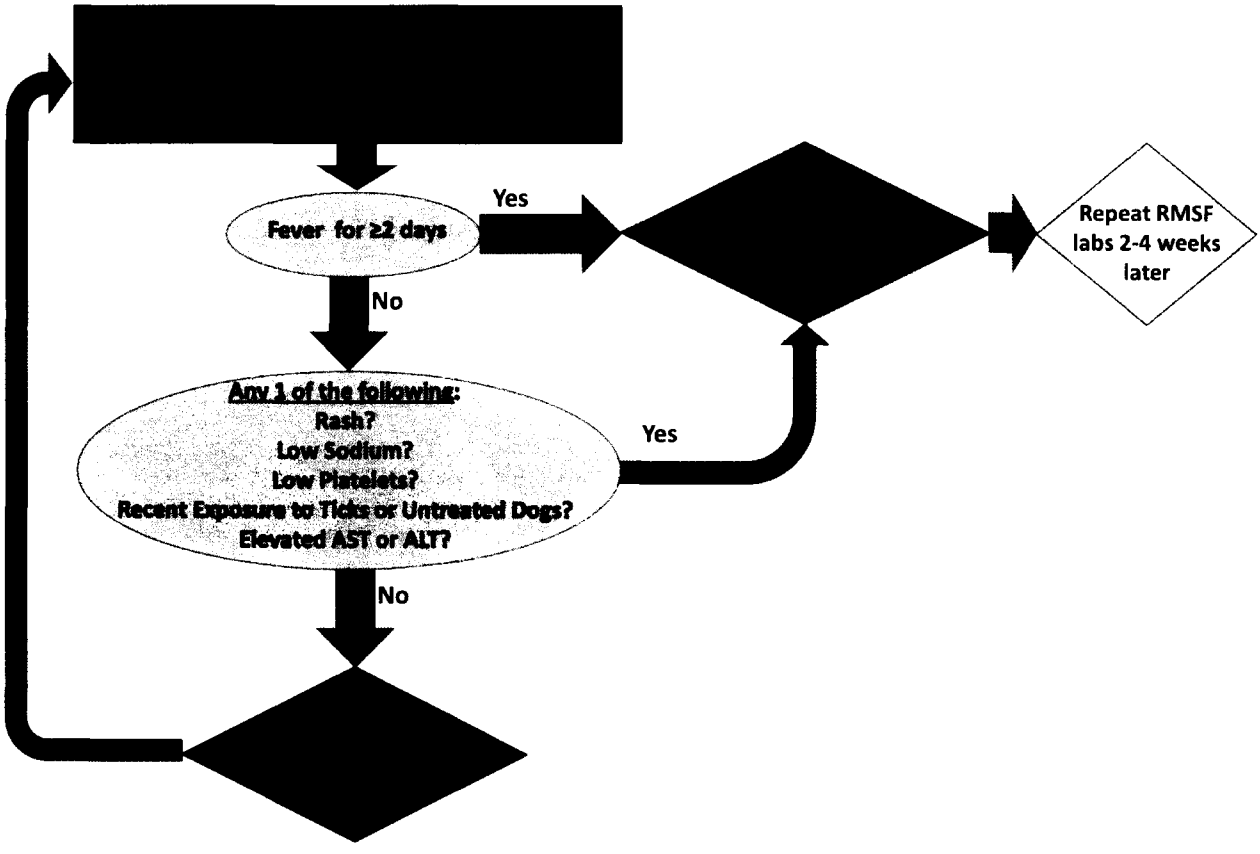


Figure 5

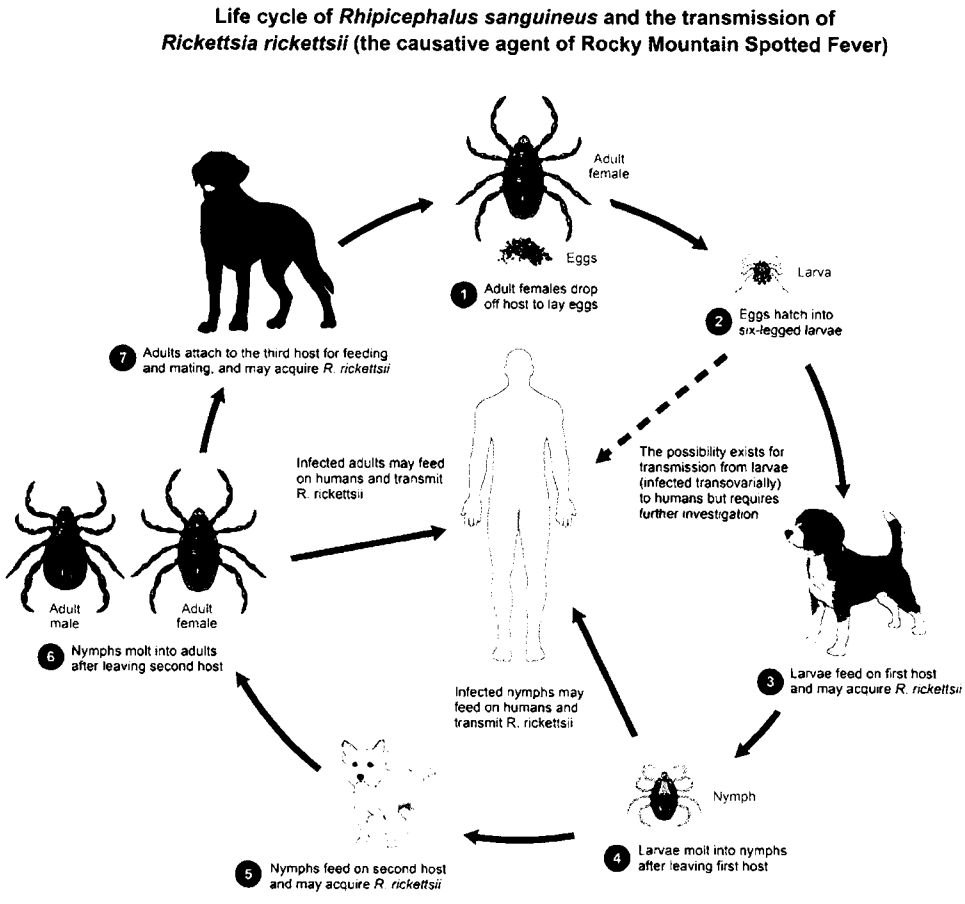

Life cycle of *Rhipicephalus sanguineus* and the transmission of *Rickettsia rickettsii* (the causative agent of Rocky Mountain Spotted Fever)
Adult female
Eggs
1 Adult females drop off host to lay eggs
Larva
2 Eggs hatch into six-legged larvae
The possibility exists for transmission from larvae (infected transovarially) to humans but requires further investigation
3 Larvae feed on first host and may acquire *R. rickettsii*
Nymph
4 Larvae molt into nymphs after leaving first host
5 Nymphs feed on second host and may acquire *R. rickettsii*
Infected nymphs may feed on humans and transmit R. rickettsii
6 Nymphs molt into adults after leaving second host
Adult male
Adult female
Infected adults may feed on humans and transmit R. rickettsii
7 Adults attach to the third host for feeding and mating, and may acquire *R. rickettsii*
Images are not drawn to scale. *R. sanguineus* can maintain *R. rickettsii* between life stages.
Humans, as well as dogs, may become infected when bitten by a tick infected with *R. rickettsii*.
CS 246081 A
CDC

Figure 6: *Rhipicephalus sanguineus* tick population survey carried out in eastern Arizona, November 2011-October 2012. 15 traps were set per month, divided between 5 houses. The houses varied by month. **Monthly results influenced by trap placement, climactic factors such as wind and rain, and recent pesticide use on the property.*

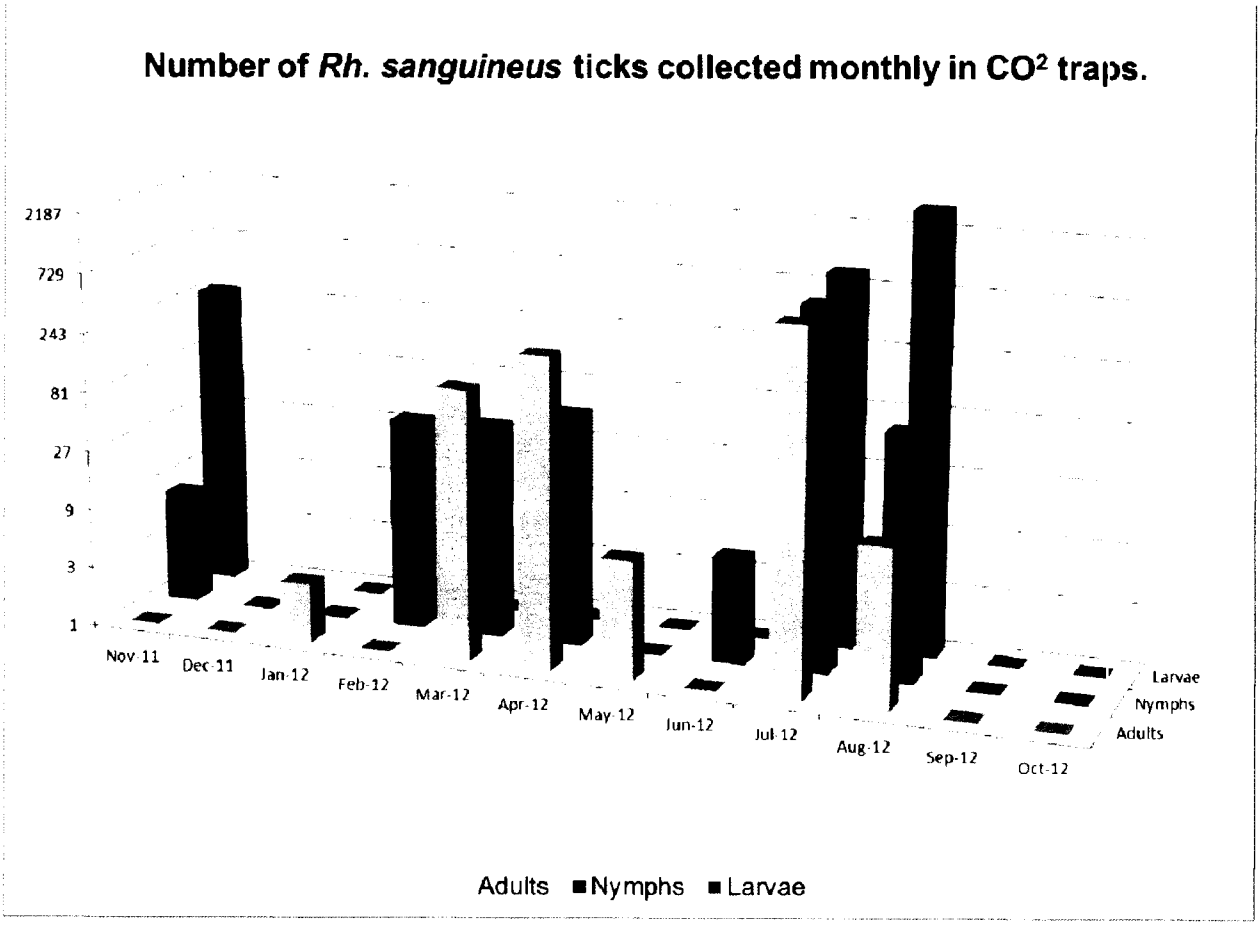
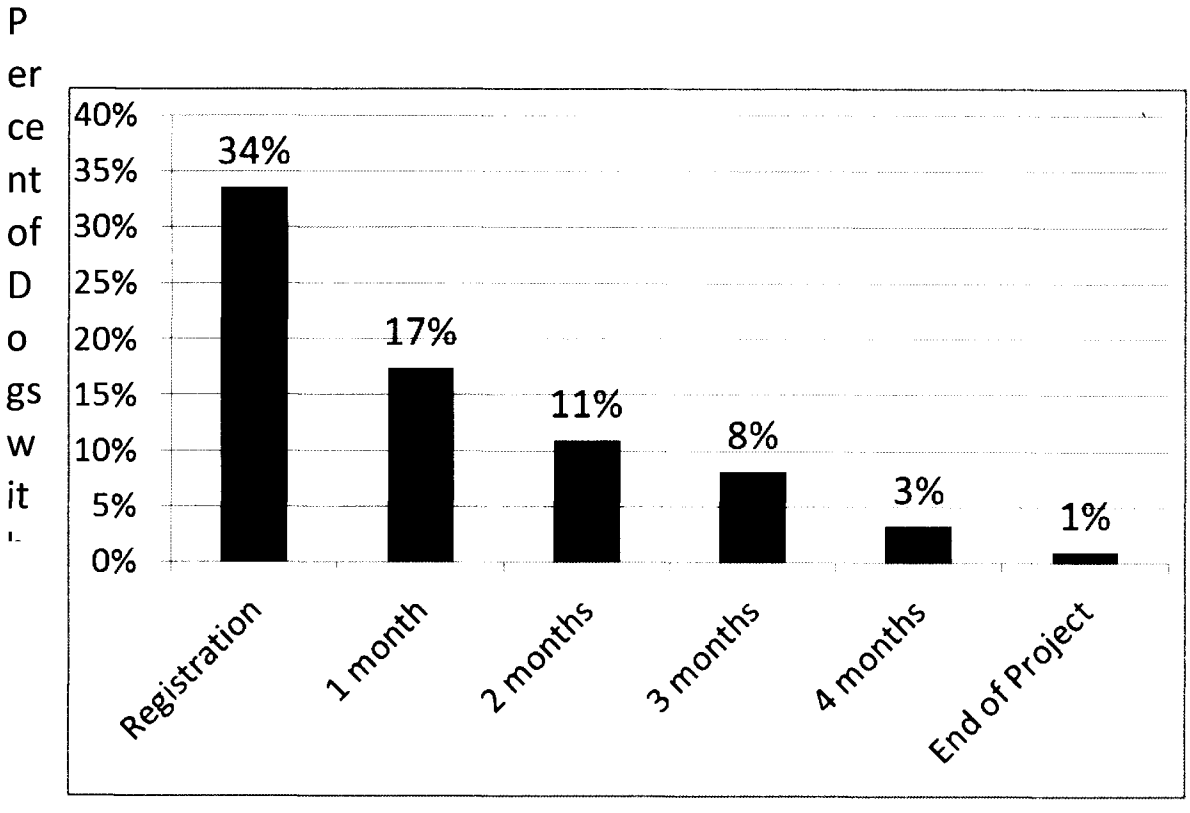


Figure 7: Tick Counts from the Rocky Mountain Spotted Fever (RMSF) Rodeo (Year 1, 2012)

7a: Tick Counts on Dogs



7b: Environmental tick counts, dry ice traps (each month featured a total of 15 traps, set at five houses. The same houses were monitored over the course of the study).

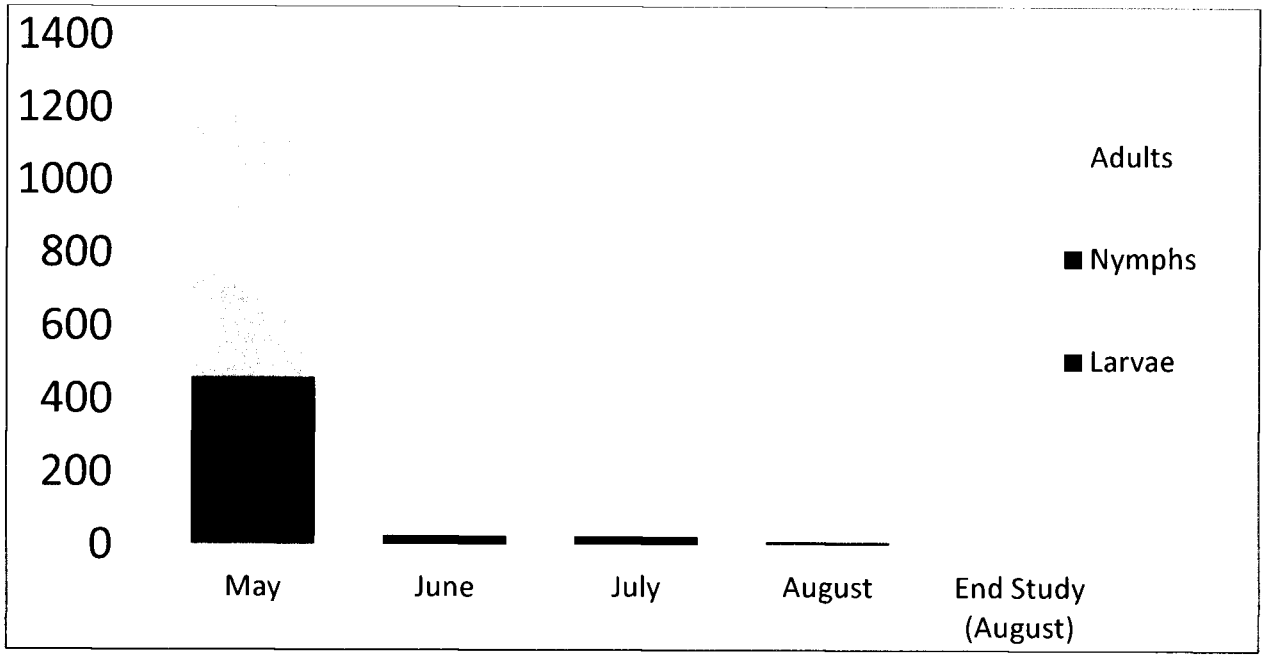


Table 2: Costs for tick control on reservations impacted by Rocky Mountain spotted fever

Tribe	Estimated number of Households	Estimated Outside Funding	Estimated Tribal Funding
Reservation 1	3,000	$1,768,415	$600,000
Reservation 2	2,000	$1,430,915	$600,000
Reservation 4	3,000	$1,768,415	$600,000
Reservation 5	2,000	$1,430,915	$600,000
Reservation 6	46,000	$16,752,115	$1,200,000
Reservation 3	3,000	$1,768,415	$600,000
State RMSF surveillance and education (for 5 years)		$375,000	
	SUBTOTAL	$25,294,190	$4,200,000

No Evidence of Tooth Staining Following Doxycycline Administration in Children for Treatment of Rocky Mountain Spotted Fever

Suzanne R. Todd, D.V.M., F. Scott Dahlgren, M.S.P.H., Marc S. Traeger, M.D., Eugenio D. Beltrán-Aguilar, D.M.D., Dr.P.H., Donald W. Marianos, D.D.S., Charlene Hamilton, Jennifer H. McQuiston, D.V.M., and Joanna J. Regan, M.D.

Abstract

Background: Doxycycline is the recommended treatment for suspected rickettsial diseases, including Rocky Mountain spotted fever (RMSF), in patients of any age. Due to the possibility of permanent staining of developing teeth, doxycycline's label warns against its use in children < 8 years of age. Reluctance to prescribe doxycycline may be one factor contributing to increased pediatric mortality from rickettsial disease.

Methods: Dentists examined visually and via spectrophotometer the permanent teeth of children who lived in a high-incidence RMSF region where doxycycline has been routinely administered to children with suspected RMSF since 2003. Children were classified as exposed or unexposed to doxycycline, based on record abstraction.

Results: Fifty-eight children, with at least one erupted permanent tooth that was calcifying at the time of doxycycline administration, were examined. The average dose of doxycycline (2.3 mg/kg twice daily for 7.1 days) was consistent with the dose and duration recommended for RMSF treatment by the American Academy of Pediatrics. Compared to 213 unexposed children who never received doxycycline, no significant difference in tooth shade was found (p=0.20). The proportion of children with enamel hypoplasia was similar in both those exposed and those unexposed to doxycycline

(p=1.0). No tetracycline-like staining patterns were visually observed in any of the exposed children's teeth (0/58, 95% confidence interval 0–5.2%).

Conclusions: This study documents an absence of tetracycline-like staining of the permanent teeth of children who received repeated short-term courses of doxycycline prior to the age of 8 years. These findings indicate that current warnings should be reconsidered.

Introduction

Tetracycline-class antibiotics (tetracyclines) were once widely used to treat a variety of infections in children, but studies beginning in the 1950s showed a link between their use in young children and staining and enamel hypoplasia of developing teeth.[1,2] Tetracyclines bind to calcium, which can lead to yellow, gray and brown staining of developing teeth if administered during tooth crown calcification, which most commonly occurs between birth and the age of 8 years for most permanent teeth except third molars.[3] Previous studies of children who received tetracyclines during odontogenesis showed visible staining in 23 to 92% (Table 1). Because of these findings, the Food and Drug Administration requires that all tetracyclines, including doxycycline, carry a label warning stating that the medication should not be used in children under the age of 8 years due to concerns about dental staining, unless no other effective antibiotics exist.[4]

Doxycycline, a newer medication in the tetracycline class, has been available since 1967 and binds to calcium less readily than other tetracyclines.[5] There are no published studies linking doxycycline to dental staining when used at the dose and

duration recommended for rickettsial diseases, and past studies have found no evidence that it causes visible staining when administered to children under the age of 8 years, even with multiple courses.[6,7] However, these studies considered small sample sizes and employed subjective methods of tooth shade evaluation.

Rocky Mountain spotted fever (RMSF), caused by the intracellular tickborne bacterium *Rickettsia rickettsii*, is a rapidly progressive and potentially fatal illness. The lack of a rapid confirmatory diagnostic test during acute illness requires healthcare providers to make early and empiric treatment decisions in order to avert severe outcomes. Doxycycline is the treatment of choice for rickettsial disease, including RMSF, in patients of any age, as recommended by the American Academy of Pediatrics (AAP) and the Centers for Disease Control and Prevention (CDC).[8,9] Chloramphenicol is less effective at preventing fatal outcome; other broad-spectrum antimicrobials typically used to treat sepsis are not effective at preventing fatal outcome.[10] Of concern, the case fatality rate of RMSF among U.S. children under the age of 10 years is five times that of cases who are older.[11] Early administration of doxycycline is one of the most important influences on survival of pediatric RMSF patients (CDC unpublished data). Despite these recommendations, U.S. healthcare providers are less likely to report treating suspected cases of RMSF with doxycycline in children under the age of 8 years than in older patients.[12,13] One possible explanation for physician reluctance to prescribe doxycycline to younger children may be due to the dental staining legacy of other tetracyclines and the current label warning.

RMSF has recently emerged as a significant public health issue in several American Indian populations of eastern Arizona.[14,15] During 2002-2013, 113 cases of

RMSF, including nine fatalities, were reported on one reservation (S. Tecle, personal communication, April 3, 2014). Due to intensive education efforts at this reservation's Indian Health Service (IHS) facility, healthcare providers there have routinely prescribed doxycycline to all suspected RMSF cases, regardless of age, since 2003. This practice resulted in a large population of children who have appropriately received one or more courses of doxycycline prior to the age of 8 years. If pediatric doxycycline administration causes dental staining, it should be detectable in this community, both visually and by means of objective measurement.

Methods

We performed a retrospective cohort study consisting of (1) a review of medical and pharmacy records and (2) a cross sectional dental examination and questionnaire. Data on tetracycline-like staining, enamel hypoplasia, and tooth shade were collected during the dental exam. Potential tooth darkening behaviors were captured through a questionnaire. Any history of receiving doxycycline was established by a review of medical and pharmacy records. The study was conducted with the approval of the Tribal Council, and the CDC and the regional IHS Institutional Review Boards.

Study Participants

The target population was all American Indian children between the ages of 8 and 16 years residing and attending schools on one reservation in eastern Arizona. This target population numbered approximately 2500 children, based on US Census data.[16] Children aged 16 years at the time of the study would have had at least one

crown still calcifying in 2003 when physicians first began using doxycycline in children for RMSF. A minimum age of 8 years was used because at this age children typically have at least one permanent maxillary anterior tooth erupted at time of examination.

Parental/guardian permission was obtained and children provided oral assent prior to participating. In addition to the dental exam, children were asked how many times daily they brushed their teeth, how frequently they drank dark colored beverages such as coffee, tea or cola and how frequently they used tobacco products.

Dental Examination

All dental examinations were performed by licensed dentists, who were blinded to the exposure status of the children. Prior to initiation of the study, five dental examiners were trained by a single experienced dentist in the recognition of the typical signs of tetracycline dental staining, using a set of color photographs displaying non-study subjects with and without tetracycline-induced defects. Training was also provided on the use and calibration of the VITA Easyshade® Compact instrument, a handheld spectrophotometer used to evaluate the shade of teeth. The Easyshade provides 16 tooth shade measures, ranging from 1 to 16, where 1 is considered the brightest shade and 16 the darkest.[17] After children brushed their teeth, a dentist performed a visual examination of fully erupted permanent maxillary central incisors, lateral incisors, cuspids and first premolars. Children without any of these teeth present were excluded. Teeth with orthodontic brackets, restoration or reconstruction work which precluded exam of the labial surface of the tooth were excluded. Dentists noted the presence of decay, fluorosis, enamel hypoplasia and presence of any tetracycline-

like staining patterns on the labial aspect of these teeth. For tetracycline-like staining, dentists looked for characteristic blue-gray coloration on the enamel with a normal tooth structure, no enamel pitting, and regular enamel glossiness. Typical lesions would have clear horizontal borders and may affect any area of the tooth, from bands to the entire surface. The dentist then utilized the VITA Easyshade® Compact spectrophotometer to obtain a single reading of tooth shade from the upper middle third of the facial aspect of each of these same teeth.[18]

In order to obtain a complete medical history on each child, parents were questioned regarding all healthcare facilities where their child received medical care. Medical and pharmacy records were obtained from the local IHS hospital. Records from off-reservation primary care providers and tertiary care centers were reviewed if applicable. Dose, duration and number of courses of all tetracyclines dispensed, including doxycycline, were abstracted from each child's medical and pharmacy record. Following record abstraction, children who had received at least one course of a tetracycline-class antibiotic were assigned to the exposed group. All others were assigned to the unexposed group.

Analysis

Only those teeth calcifying at the time of doxycycline administration, according to the calcification timeline in Table 2, were considered in our analysis of the exposed group's dental data.[3] All other remaining dental data were excluded from analysis of the exposed group. For the unexposed group, no dental data were excluded from the analysis.

All statistical analyses were performed at a significance level of α=0.05. All computations were performed using SAS, Version 9.3 © [SAS], except the confidence interval (CI) for a zero numerator proportion, calculated using the rule of 3.[19] Two sample t-tests with equal variance were used to compare pairs of means. The association between pairs of categorical variables was tested using Pearson's χ^2 test for general association; except, when any expected frequency was <5, Fisher's exact test was used. The Breslow-Day test for homogeneity of association was used to test for effect modification by age. Mantel-Haenszel estimates of the common prevalence ratio were used when adjusting for age.

Spearman's correlation coefficient was used to test the association of exposure as the total number of days of receiving doxycycline before the age of 8 years, or simply the duration of doxycycline, with two outcomes: (1) average tooth shade and (2) the proportion of teeth with enamel hypoplasia. Spearman's correlation coefficient ranges from -1 to 1, with values approaching 0 showing the least correlation. To assess potential confounding by either age at the time of study or the proportion of teeth with fluorosis, Spearman's correlation coefficient was used to test the pairwise association between these potential confounders with the duration of doxycycline and both outcomes. Controlling for potential confounders associated with the duration of doxycycline or either outcome, Spearman's partial correlation coefficients were used to test the association between the duration of doxycycline and both outcomes.

Results

Demographics and Exposure Characteristics

The records of 366 eligible children were reviewed. None had ever received a tetracycline-class antibiotic other than doxycycline. Of these, 335 children were present at school on the day of the examination and assented to participate.

Of the 335 children examined, 76 received at least one dose of doxycycline prior to the age of 8 years. However, only 58 children received doxycycline during the period of calcification of at least one tooth and had at least one of these exposed teeth fully erupted at the time of the dental examination. These 58 children were considered the exposed group for our analysis. Eighteen children who received doxycycline before the age of 8 without an erupted exposed tooth and 46 children who had received doxycycline at 8 years old or older were excluded from the analysis. The remaining 213 children who never received doxycycline were considered the unexposed group in our analysis.

The 58 children in the exposed group received a total of 120 courses of doxycycline, which is an average of 2.1 courses of doxycycline per child [range: 1–7, standard deviation s=1.4]). The mean doxycycline dose was 2.3 mg/kg (range: 0.3–2.9, s=0.37), which is not dissimilar from the recommended dose of 2.2 mg/kg. The average duration of doxycycline was 7.1 days (range 1–10, s=2.7). The average age at initial dose of doxycycline was 4.9 years old (range: 0.2–10.1, s=2.7). The route was typically oral (98%), and the frequency was typically twice daily (97%).

The mean age at time of dental exam of those who received doxycycline was 9.8 years old (range: 8.1–15.6, s=1.7), and the mean age of those who had not was 11.8 years old (range: 8.0–16.9, s=2.2). The difference between the average age of those who received doxycycline and those who did not was 2.1 years (s=2.1, $p<0.001$).

There was no significant difference between our two groups regarding whether they brushed their teeth twice daily (p=0.50), whether they drank any dark-colored beverages (p=0.36), or whether they used any tobacco (p=0.18); and, these results were qualitatively similar after adjusting for age at exam (Table 3).

Dental Examination

No visible tetracycline-like staining patterns were observed on any of the teeth of the 335 children examined, including those 58 children who received doxycycline before 8 years of age (95% CI=0–5.2%). Enamel hypoplasia was observed in 10 children (3.7%), but exposure to doxycycline was not associated with the presence of enamel hypoplasia (p=1.0, Table 3). Similarly, fluorosis-like hypomineralization was observed in 33 children (12%), but was not associated with exposure to doxycycline (p=0.35, Table 3).

Children exposed to doxycycline prior to the age of 8 years had an average tooth shade of 9.5 (range 3.0–16, s=2.5). Those never having received doxycycline had an average tooth shade of 9.0 (range 2.1–15.0, s=2.3). There was no significant difference in tooth shade between the two groups (p=0.20). The size of the groups allowed detection of a 1.0 difference in average tooth shade with a power of 0.8, and a 1.3 tooth shade difference with a power of 0.95, assuming a standard deviation of 2.5. No significant differences were observed in the average tooth shade of children when grouping by questionnaire responses or the presence of dental defects (Table 4).

Duration of doxycycline was not correlated with the proportion of teeth with enamel hypoplasia (Spearman's correlation coefficient r=-0.001, p=0.98) nor with the

average tooth shade (r=0.07, p=0.28). Those children who were younger at the time of the dental examination were more likely to have received a longer duration of doxycycline (r=-0.39, p<0.001). The proportion of teeth with fluorosis was not correlated with duration of doxycycline (r=-0.07, p=0.27), with the proportion of teeth with enamel hypoplasia (r=-0.07, p=0.23), nor with the average tooth shade (r=0.08, p=0.18). Controlling for age at examination, the duration of doxycycline was not correlated with the proportion of teeth with enamel hypoplasia (Spearman's partial correlation coefficient θ=0.04, p=0.53) nor with the average tooth shade (θ=0.09, p=0.15, Figure).

Discussion

We found no evidence of dental staining of permanent teeth in 58 children who had received doxycycline for treatment of RMSF during the period of odontogenesis. This is in stark contrast to the 23-92% prevalence of staining caused by the older tetracyclines that prompted the initiation of current warnings (Table 1). Furthermore, we found no evidence of an increased prevalence of enamel hypoplasia, and no evidence of tooth shade difference between exposed and unexposed participants. Moreover, there was no evidence that multiple doxycycline courses resulted in a significant difference in tooth shade, even when children received three or more courses of doxycycline while teeth were developing.

The most compelling finding of this study is the absence of visible characteristic tetracycline staining in this population of exposed children. When the data from this study are combined with the findings from Volovitz et al, which found no staining in 31

children exposed to doxycycline for treatment of asthma, the conclusions are strengthened, with a staining prevalence rate of 0% (0/89, 95% CI 0-3.4 %).[7]

This study is subject to several limitations. It is possible that parents did not recall all locations where a child received care; therefore, some children in the unexposed group may have received doxycycline outside of our knowledge. However, most children received care and had prescriptions dispensed at the IHS facility, and use of doxycycline in children was not common outside the reservation during this time period. Although the prescribed dosage, duration, date of administration and quantity dispensed of doxycycline recorded in the medical and pharmacy records were used in our analysis, we did not confirm whether a child completed the entire course of doxycycline prescribed to them. Children's answers to the questions on dental habits could be biased based on the child's ability to recall behaviors, to understand the question, and to admit to unhealthy behavior. The difference in the distribution of ages between those who received doxycycline and those who did not is most likely influenced by changes in clinical practice in 2009, when increasing rates of RMSF on the reservation prompted wider treatment of patients (Figure).

In addition to RMSF, there are several other infectious diseases for which a short-term course of doxycycline is the most effective treatment. These include ehrlichiosis, anaplasmosis, cholera and the other rickettsial diseases, of which RMSF is only one.[8] Additionally, short-term courses of doxycycline can be used to treat skin and soft tissue infections caused by community-acquired methicillin-resistant *Staphylococcus aureus*, as well as community-acquired pneumonia.[20,21] In contrast to other tetracyclines, our data indicate that administering multiple, short courses of

doxycycline to children whose teeth are developing does not darken the shade of teeth, cause visible staining, or increase the risk of enamel hypoplasia Short-term courses of doxycycline can be administered to children without concern of tooth staining.

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The research protocol was approved by Tribal Council and the CDC and regional IHS institutional review boards. Parents/legal guardians of study subjects gave written informed consent and children provided oral assent.

Table 1. Studies examining dental staining due to treatment with tetracyclines

Reference	Antibiotic (Duration)	Study population	Proportion (%) exposed with stained teeth
Shwachman et al (1958)[1]	Chlortetracycline and oxytetracycline (long-term)	Patients with cystic fibrosis	40/50 (80%)
Wallman and Hilton (1962)[2]	Tetracycline (short-term)	Neonates	46/50 (92%)
Swallow et al (1966)[22]	Chlortetracycline, tetracycline, and oxytetracycline (long-term)	Patients with cystic fibrosis	24/63 (38%)
Conchie et al (1970)[23]	Mixed tetracyclines (unknown duration)	Children who had received tetracycline prior to age of 6 and who are now 8-11 years	55/238 (23%)
Rebich et al (1983)[24]	Mixed tetracyclines (unknown duration)	American Indian children 4-19 years	55/137 (40%)
Volovitz et al (2007)[7]	Doxycycline (short-term)	Patients with asthma	0/31 (0%)

Table 2. Calcification timeline for anterior maxillary permanent teeth

Age	First Premolar	Cuspid	Lateral Incisor	Central Incisor
5 years and younger	X	X	X	X
6 years	X	X		
7 years		X		

Table 3: The prevalence of enamel hypoplasia, the prevalence of fluorosis, and dental hygiene habits by whether exposed to doxycycline. The crude prevalence ratio and its 95% confidence interval are presented with the age adjusted prevalence ratio, as well as the results of the Breslow-Day test for the homogeneity of the associations stratified by age as a whole number.

	Doxycycline < 8 years N (%)	No Doxycycline N (%)	Crude PR (95% CI)	Breslow-Day p-value	Age-Adjusted PR (95% CI)
Enamel Hypoplasia	2 (3.5)	8 (3.8)	0.92 (0.20–4.2)	0.79	1.6 (0.20–13.5)
Fluorosis	5 (8.6)	28 (13)	0.66 (0.27–1.6)	0.54	0.86 (0.37–2.0)
Brushes ≥2 Times Daily	40 (75)	148 (71)	1.1 (0.89–1.3)	0.32	1.1 (0.90–1.4)
Any Dark Drinks	41 (71)	163 (77)	0.92 (0.77–1.1)	0.32	0.93 (0.78–1.1)
Tobacco Use	2 (3.5)	21 (10)	0.35 (0.08–1.4)	0.64	0.75 (0.18–3.1)

Table 4: Mean tooth shade of children at dental exam, grouped by exposure to doxycycline, presence of enamel hypoplasia, presence of fluorosis, and dental hygiene habits. The standard deviation and the p-value from the two sample t-test with equal variance are also presented.

	N	Mean Tooth Shade (Standard Deviation)	p-value
Doxycycline before 8 years	58	9.5 (2.6)	0.20
No Doxycycline	213	9.0 (2.5)	
Any Enamel Hypoplasia	10	9.8 (3.1)	0.38
No Enamel Hypoplasia	261	9.1 (2.5)	
Any Fluorosis	33	9.7 (2.7)	0.16
No Fluorosis	238	9.1 (2.5)	
Brushes Teeth ≥2 Times Daily	188	8.9 (2.6)	0.10
Brushes Teeth <2 Times Daily	74	9.5 (2.3)	
Any Dark Drinks	204	9.1 (2.4)	0.98
No Dark Drinks	67	9.1 (2.8)	
Any Tobacco	23	9.1 (2.4)	0.86
No Tobacco	242	9.2 (2.6)	

Figure: A scatterplot of average tooth shade by age at exam, stratified by doxycycline exposure.

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