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An Evidence Based Rationale for Making Tick - borne Relapsing Fever a Nationally Notifiable Disease

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DEDICATION

To those in the pursuit, understanding, and advancement of scientific knowledge, and to those who might benefit from its exploration.

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ABSTRACT

Tick – borne relapsing fever (TBRF) is globally dispersed, and within the United States is found primarily in the mid – west, south - west, and north – west portions of the country. TBRF is a disease which causes patients to experience flu – like symptoms and is distinguished by multiple relapses of high fever which can cause individuals to be hospitalized multiple times over months. TBRF is caused by *Borrelia* spp. spirochetes and spread by *Onthidoros* spp. soft – shelled ticks. First diagnosed in the early 20th century, the disease has gone underdiagnosed and has attracted little attention for over a century despite being the cause of illness in multiple outbreaks. Previous reviews on the subject have been limited in scope and focused on state – specific reports in localized regions of the country. The primary and secondary objectives of our review were to describe the epidemiology, scope, and clinical outcomes of TBRF to update the medical community on its impact and also to establish an evidence - based reasoning for inclusion of TBRF in the NNDSS. We present our review of TBRF as the most expansive in regard to years covered and sample size. As well, this is the only review, to our knowledge, which has collected and analyzed data by infection type. Papers selected for review had to be original case reports of TBRF infections, published in English, and have occurred in the United States. Data from similar reviews were not included nor were those papers used for analysis. Added criteria were used to collect data on cases which could be used for logistic and Poisson regressions analyzing the likelihood of clinical outcomes. After

the review process was complete, 80 papers were used for the primary analysis and 40 papers used to collect data for regression analyses. Results showed that most of TBRF infections took place in adults and children. Men were statistically more likely to be infected than women ($p = <0.0001$). Symptom profiles for causative agents confirmed flu-like symptoms as the most reported (headaches, vomiting, chills/sweats) but revealed that many symptoms were statistically more likely to be found in *B. turicatae* infections compared to *B. hermsii* infections, indicating that infection type influences clinical presentation of the disease. Modeling febrile episodes and Jarisch – Herxheimer reactions on treatment type hinted that some treatments are better than others but no statistically significant claims can be drawn from this analysis. In conclusion, this review highlights important differences between our results and prior published literature reviews, as well as provides recommendations on reporting practices, treatment protocols, and future work while arguing that TBRF should be a nationally notifiable disease and reported to the NNDSS.

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LIST OF ABBREVIATIONS

BH……...*Borrelia hermsii*

BT…….….....*Borrelia turicatae*

CDC……...…United States Centers for Disease Control and Prevention

CSTE…….Council of State and Territorial Epidemiologists

IRR……. ....Incidence rate ratio

NNDSS……....National Notifiable Disease Surveillance System

OH……..*Ornthidoros hermsi*

OT…….*Ornthidoros turicata*

TBRF……...Tick - borne Relapsing Fever

CHAPTER 1

INTRODUCTION

The National Notifiable Diseases Surveillance System (NNDSS) is a network of systems run by the United States Centers for Disease Control (CDC) and Prevention which works on a national level to compile data on disease incidence, distribution, disease agents, and host factors. The NNDSS works in conjunction with the Council of State and Territorial Epidemiologists (CSTE), whose job it is to provide a recommended list of nationally notifiable diseases and coordinate with state and local health departments and health agencies, which provide case data for informing periodical updates to the list of nationally notifiable diseases.[1]

Disease reporting begins on the state and local level with cases identified by health providers, hospitals, and laboratories. State legislatures, on recommendation from health agencies and health professionals, dictate which diseases are mandatorily reported allowing for state funds to be utilized accordingly.[2] There are many diseases which are universally reported, such as salmonella outbreaks and highly contagious vaccine-preventable infectious diseases. Other diseases, which are found regionally, are sporadically reported depending on the incidence of disease. Because there are no federal laws which dictate disease reporting, conveying information to the CDC on the federal level is technically voluntary. Despite being non-compulsory, every U.S. state health department, five territorial health departments, and two local health departments (New York City and D.C.) report to the CDC for diseases which are nationally

notifiable.[3] Diseases on the nationally notifiable list are those of particular concern for public health, thus justifying allocation of state tax revenue and health department resources for tackling of these priority conditions. This criterion includes emerging pathogens or any other disease which is deemed a large enough health concern. If properly addressed, the incidence of these diseases and health hazards are reduced, and if at some point the incidence is reduced enough or its surveillance is not seen as justifiably beneficial, a disease may be taken off the notifiable list. Some of the benefits of having a disease on the nationally notifiable list is that it receives more exposure to the health community and local resources, making identification and treatment easier and more efficient. Further, it helps establish and/or create a federal database on all reported cases in the United States.[4–6] Additionally, the infrastructure created by surveillance reporting laws ensures the maintenance of strong working relationships between physicians and public health entities that are critical for effective infectious disease outbreak response.[7] Centralized and formatted data is incredibly useful for conducting research on diseases and coming up with strategies to prevent further incidence. One of the diseases not currently on the nationally notifiable list is Tick – borne Relapsing Fever (TBRF).

Relapsing fever is a global vector-borne disease caused by infection with *Borrelia* spp. spirochetes. Louse and tick – borne relapsing fevers are epidemic and endemic, respectively.[8,9] While the primary foci of louse-borne relapsing fever is east Africa, a true understanding of TBRF is less known yet of public health importance, and early identification of endemic areas can prevent future outbreaks.[10,11] Global estimates of TBRF are lacking, but the disease has been reported in Africa, Asia, Europe, and North America.[12] In Asia, specifically in Japan, various Ixodes ticks are responsible for

infection with *Borriella miyamatoi* spirochetes,[13] whereas in Africa, several *Ornthidoros* spp. soft ticks, such as *Ornthidoros moubata*, transmit *Borrelia duttoni*, *B. crocidurae*, and *B. hispanica*.[12,14] Our understanding of endemic TBRF in the United States is still in its infancy with only two major reviews done on the disease, both published in the last 15 years.[15,16]

In the United States, TBRF is most commonly found in the south-west, mid-west, and pacific north-west, with California and Colorado being the biggest contributors to disease incidence.[16] TBRF, as the name suggests, is a disease which causes intermittent febrile episodes and is contracted after a tick vector has taken a blood meal from a human host. Those infected can expect, on average, to experience two to four febrile episodes with fevers ranging from 103 degrees to 108 degrees Fahrenheit. Pregnant women are particularly vulnerable to TBRF and can experience spontaneous miscarriage, hepatic involvement, neonatal asphyxia, preterm delivery, and death. Transmission of the spirochete from mother to infant can occur prenatally via the placenta or during labor and birth.[17] Less serious complications caused by TBRF include chills/sweats, nausea, malaise, and headaches. Standard treatment varies from single to multiple rounds of antibiotics including tetracycline, doxycycline, and macrolides (e.g. erythromycin). Patients treated with antibiotics for TBRF have a 50% chance of experiencing a Jarisch – Herxheimer reaction where their symptoms worsen along with rigors, hypotension, and high fever.[15] TBRF has been treated with many different types of antibiotics in the past and present, most likely due to the lack of treatment guidelines for TBRF which would standardize treatment protocols for the disease.[18]

The causative agents of TBRF are bacterial spirochetes of the genus *Borrelia* and species in the United States are *B. hermsii,* and *B. turicatae*. Similar to other spirochetes, *B. hermsii* and *B. turicatae* bacteria manipulate surface antigens to avoid detection from host defenses.[18–20] This ability to change surface proteins lets them hide out in hosts and cause bouts of high-grade fever when proliferation of the bacteria becomes high enough. The spirochete (corkscrew) shaped bacteria are problematic for diagnosis using microscopy because their shape is similar to other bacteria such as *Helicobacter,* for example.[18] Serological testing also presents some challenges because false positives on tests for Lyme disease are common due to the similarity of proteins between the *Borrelia* spp.[21–23] Knowing the geographic region the patient was exposed along with other contextual pieces of clinical and epidemiological information is important for proper identification, diagnosis, and treatment.

The ticks which bear these bacteria are argasid (soft-bodied) ticks of the genus *Ornithodoros*. In the United States, the bacteria species are named for the tick which bears them. *O. hermsi* ticks are typically found in high elevation areas (>5000ft) along the Western US mountain ranges whereas *O. turicata* ticks are found in low elevation areas such as Texas, Florida, and Nevada.[16] Sylvatic transmission occurs during bloodmeal feeding between ticks and reservoir species, primarily squirrels, chipmunks, and other rodents. Humans are not typical reservoir hosts but can be infected and serve as competent mammalian reservoirs if bloodmeals are taken during the febrile bacteremia period. Spirochetes are transmitted via tick saliva, and once in the human blood stream they begin to proliferate in the human host causing disease.[24] Vector characteristics play an important role in transmission. To illustrate this, compare the differences between

Ixodidae (hard) and Argasidae (soft) bodied ticks. Besides having different physical appearances, the ticks also have different life cycles and feeding strategies.[25] Hard ticks have only three life stages, a larval stage, a nymphal stage, and an adult stage whereas soft ticks have several nymphal stages as well as the larval and adult stage. The increased number of nymphal stages translates to greater pathogen transmission opportunities as soft ticks require bloodmeal to complete each molting.[26] Hard ticks seek out prey and are active during daylight and nighttime hours while soft ticks lie in wait for their prey and are primarily nocturnal. Lastly, feeding time for hard ticks is much longer (hours to weeks) than soft ticks (15 – 90 minutes).[25]

Hard ticks are responsible for transmitting Lyme disease, Rocky Mountain spotted fever, tularemia, Colorado tick fever, etc. while soft ticks are known only to transmit TBRF.[27,28] This may be in part to the types of hosts the ticks feed on and the ubiquity with which hard ticks are found allowing them to come into contact with a larger variety of species. Their predator habits, seeking out their prey, add to this fact but also show why people are more likely to come into contact with hard ticks. Soft ticks come into contact with human hosts most commonly in remote caves, cabins, or camping sites, and because they feed at night, they are less active than hard ticks.

While hard ticks are responsible for most of the disease burden caused by tick species, however, there are two characteristics of soft ticks which makes them especially worth considering as a public health issue. Unlike the hard tick which can only transmit the spirochete bacteria during its adult life state, soft ticks can pass on the bacteria throughout all nymphal stages as well as their adult stage. While more limited in activity than hard ticks, they are more dangerous over their lifespans respectively because they

can transmit the bacteria earlier than hard ticks and for a longer period of time. Soft ticks not only feed for a shorter period of time, their time to transmit the bacteria is also much shorter than the hard ticks. Soft ticks have been shown to transmit spirochetes within 30 seconds, much less than the hours it takes a hard tick to transmit a pathogen like the one that causes Lyme disease.[29] If a person is bitten by a tick which carries *B. burgdorfi*, there is a good chance that individual will not be infected as long as they notice the tick feeding within an hour or two.[30] Yet, if an individual is fed on by an *O. hemsi* tick, the time it takes to notice the tick feeding is almost inconsequential as it is likely long passed the time necessary to transmit the bacteria. Lastly, *Ornithodoros* spp. ticks can live up to 10-20 years and go years without a bloodmeal source, which is significantly longer on both accords than its hard tick comparator.

TBRF is often overshadowed by other louse/tick borne infections because it accounts for less of the disease burden in this category than other diseases. Between 1990 and 2011 there were only 504 cases of TBRF reported to state and local agencies.[16] For comparison, over 30,000 cases of Lyme disease are reported to the CDC every year with estimates that the true burden of disease is between 296,000–376,000 cases/year.[31,32] But incidence alone does not tell the whole story. Because there is no national reporting recommendation for TBRF, it is likely that the amount of cases reported is much lower than the actual burden. Difficulty in identifying the causative agent with microscopy and laboratory techniques might also be a contributing factor to underreporting. Those who become infected by TBRF experience reoccurring episodes of debilitating fevers, headaches, and pains. In more extreme cases TBRF can cause death, especially in childbearing mothers and neonatal infants. Overall disease burden might not be high, but

morbidity associated with TBRF is extreme. TBRF is an easily acquired, dangerous infection which requires more attention. Making TBRF a nationally notifiable condition, along with constructing standardized treatment guidelines will help prevent future cases of the disease, decrease mortality, and mitigate morbidity.

Despite a suspected knowledge gap among United States physicians, cases have been consistently reported since 1922.[9,15] The primary goal of this historical review is to inform the medical community of TBRF clinical characteristics and epidemiologic associations in an effort to identify areas of high disease burden and enhance differential diagnosis of high-risk populations. We theorize that the lack of notifiable disease status has resulted in low knowledge among healthcare providers possibly translating to an underdiagnosis of these important pathogens. The secondary aim is to compare the *Borrelia* species responsible for TBRF to identify potential differences in infection prevalence, clinical manifestation of disease, transmission of risk factors, risk of Jarisch-Herxheimer reaction and mortality rate. The last aim of this paper is to use the information gathered in the systematic review to determine a potential need, rational and justification for inclusion of TBRF on the national notifiable list.

CHAPTER 2

METHODS

A systematic review was conducted in compliance with Preferred reporting items for systematic reviews and meta-analyses (PRISMA).[33] Our initial literature search was conducted utilizing Medline and PubMed using the following search terms: tick borne relapsing fever, *Borrelia turicatae, Ornithodoros turicata, Borrelia hermsii, Ornithodoros hermsi,* and United States. *Ornthidoros parkeri* and *Borrelia parkerii* were excluded from this review, as they were only added to the list of TBRF causative agents within the last three years and would not have adequate representation in our historical review. In an effort to include all historical manuscripts that might not be included in current electronic format, a second trace-back search of included manuscripts' reference lists was also conducted. Manuscripts were excluded if transmission was suspected outside the geographic United States, not published in English, or if the article was not clinical or human health related. In order to gather sufficient sample sizes and maintain data quality, information from each article was screened on the basis of each variable. If a paper included an appropriate amount of data concerning method or place of infection, duration of sickness, and risk factors then it was included in the analysis. For example, if a paper reported infections on 100 patients but only had symptom data for two then only the symptom data for those two cases would be analyzed while the other 98 would be discounted from inclusion in a denominator on symptom frequency so as to avoid zero inflation. However, those other 98 cases could still be used in geospatial clustering. The

guiding principle in this exercise was to make sure that the total number for the article had corresponding, matching data on the variable which statistics were gathered on. The second literature collection, a sub grouping of the original, was gathered in order to perform a regression analyses on two clinical outcomes as well as descriptive statistics on infection characteristics. The added criteria for inclusion in this collection required that the data be matched to a particular ID. Whereas the larger dataset included aggregate and specific data, the smaller dataset only included data which had matching participants. To be matching, data on prognosis, symptoms, treatment, and risk factors must be related to an identified patient with information on age and sex available.

Information extracted from each article included clinical history and presenting illness, clinical laboratory values, diagnostic test used, patient prognosis and course of illness, and epidemiologic risk factors. Descriptive statistics summarized each of these categories' variables. Chi-squared tests were used to test for independence between proportions of individuals with *B. hermsii* or *B. turicatae* infections on the basis of sex, age, and symptom frequency. In instances with small frequency counts (≤ 5), Fisher's exact test was used in place of a Chi-squared test. Disease prognosis by infection type, including average incubation days, average febrile and afebrile days, and average number of febrile episodes was analyzed via a T-test under normal theory assumptions. In addition to these analyses, a multivariable logistic model was used to estimate the risk of a Jarisch – Herxheimer reaction using treatment comparisons as the predictor of interest with standard statistical assumptions. Poisson regression was used to analyze the association between number of febrile episodes and treatment type and other standard predictors. Other covariates for both regressions were sex and age. All statistical analyses

were performed using SAS 9.4 software (SAS Institute Inc., Cary, North Carolina). Finally, geospatial cluster analysis was performed on cumulative clinical records by location to identify hotspots for disease incidence, using ArcGIS Pro v.2 (ESRI Corporation, Redlands, CA).

CHAPTER 3

RESULTS

The original literature search and subsequent search done by reviewing sources included in the first search yielded 190 articles. After screening by titles and abstracts, three were found to contain duplicate data and removed from the review. 187 articles were screened through full text and 111 were excluded leaving 76 papers for the primary analysis. Of those 76, 40 met the requirements for inclusion in the secondary analysis and were included therein (Figure 3.1).

Primary Analysis Findings

The total number of cases included was 1241 (*B. hermsii* = 493 | *B. turicatae* = 748), ranging in years from 1915 to 2016. Both *B. hermsii* and *B. turicatae* infections occurred primarily in adults and children. Combining both age categories, adults and children accounted for 95% of *B. hermsii* infections and 99% *B. turicatae* infections. Age data was analyzed categorically. Four discrete age groups were constructed (adult ≥ 18 years, pediatric 1 – 17 years, infant < 1 year, elderly ≥ 60 years). There were no significant differences in the proportion of infections comparing all age groups (p=0.4288), nor were there significant differences in proportions of infections comparing adults to children (p=0.3363), adults to infants (p=0.3239), or adults to elderly (p=0.6762). The percentage

of males with *B. hermsii* or *B. turicatae* infections was significantly higher (p= <0.0001) than females (Table 3.1).

Aggregated symptom data was available for 433 patients (*B. hermsii* = 391 | *B. turicatae* = 42). Fever, chills/sweats, headache, nausea, vomiting, myalgia, weakness, and malaise were the most reported symptoms among both infections combined, with each being reported 18% – 77% of the time. Clinical symptoms were recorded dichotomously, even if symptoms reoccurred during multiple relapses. Symptoms indicative of serious complications, including splenic enlargement and tachycardia were reported for combined infections 13% and 8% of the time. Other serious complications, including tachypnea, jaundice, hypoxia and syncope were reported less than 5% of the time. There were statistically significant differences between infection types for most of the symptoms (symptoms reported >5% of the time). Compared to *B. hermsii*, those infected with *B. turicatae* were more likely to report fever (p=0.0012), headache (p=0.0007), nausea (<0.0001), vomiting (p=0.0004), myalgia (p=0.0365), weakness (p=0.0004), arthralgia (p=0.0012), malaise (p=<0.0001), rash (p=<0.0001), tachycardia (p=<0.0001), and back pain (p=<0.0001) (Table 3.2). Conversely, *B. hermsii* patients were more likely to present with anorexia (p=0.0071) than *B. turicatae* patients.

Aggregated data for other prognostic indicators including incubation period, febrile days (how many days total experiencing fever), afebrile days (how many days total without fever between febrile periods), and total febrile episodes (instance of a febrile period or episode) was collected for 929 patients. Overall, the average amount of incubation days was 8, with a range from 1 – 25 days. Patients experienced an average of

4 febrile days and 4 febrile periods and 7 afebrile days. No significant differences between infection types were noted for each of these variables (Table 3.3).

Published reports on year of incidence was available for 1241 patients. The primary dataset found that most case data were for infections which occurred in the early to mid – 20th century, specifically in the 1930s and 1960s. Some of that data that was collected was on a range of years. For those infections the midpoint in the range of years was selected as year of infection (Figure 3.2). Data on month when infection occurred was collected for 1485 patients. Most cases take place in the summer months and trails off in the fall and winter while gradually increasing through the spring. The months of June, July, and August are roughly responsible for a combined 60% of the total incidence observed in the study (Figure 3.3). Incidence by state where infection was either confirmed or suspected to have occurred was included for 1110 people in 14 states. Over 50% of these cases took place in Texas which means that the causative agent in these TBRF infections was most likely *B. turicatae*. This is in contrast to recent literature which typically sties cases in California and Colorado as having the highest incidence for TBRF. California and Colorado were the next highest states for TBRF infections, besides Arizona, with 619 and 63 cases each, respectively. A single case was noted in Ohio, far from the endemic areas where *Ornthidoros* spp. ticks are typically found (Figure 3.4).

Secondary Analysis Findings

The following are the findings presented from the case files with matching data. The total number of cases included in this analysis was 67 (*B. hermsii* = 51 | *B. turicatae* = 16) with data on cases from 1961 to 2016. Characteristics of infection were recorded for all

67 cases. Only 25% of patients reported observing a tick bite and evidence of tick infestation was found in only 22% of cases. Most infections occurred in either cabins (34%), caves (17%), and the general outdoors (8%). *Borellia* positive ticks and *Borellia* positive reservoir animals were located at the site of infection 18% and 13% of the time, respectively. In almost half of all cases (41%), the sleeping structure where infection occurred was uninhabited at times, often for months (Table 3.4).

Using case specific data collected in the secondary analysis, two regressions were generated to describe possible relationships between treatment type and either risk of Jarisch – Herxheimer reactions or number of febrile episodes. The first outcome was analyzed using a logistic regression with age and sex as co-predictors along with treatment type. In current literature, tetracycline is often cited as the preferred treatment for TBRF, thus in our analysis tetracycline was used as the referent group comparing doxycycline, penicillin, or combination/other treatments. Odds ratios show that penicillin and combination/other treatment was less likely (OR = 0.90 and 0.66, respectively) than tetracycline alone to result in a Jarisch – Herxheimer reaction. However, doxycycline was 2.56 times as likely to result in a Jarisch – Herxheimer reaction than tetracycline (Table 3.5).

To evaluate the association between treatment type and number of febrile episodes, a Poisson regression was used. Compared to tetracycline treatment, the incidence rate ratios for number of febrile episodes were 1.24, 1.11, and 0.79 for combination/other, doxycycline, and penicillin, respectively. This means that the incident rate of febrile episodes for combination/other treatment was 1.24 times the incident rate of the same outcome for tetracycline treatment, meaning that only penicillin resulted in a

lower incident rate of febrile episodes compared to tetracycline use (Table 3.6). Note that the results of the logistic and Poisson regressions are not statistically significant, as the inferences associated with the outputs have wide confidence intervals that include one, indicating the possibility that there were no differences in either measured outcome based on treatment type.

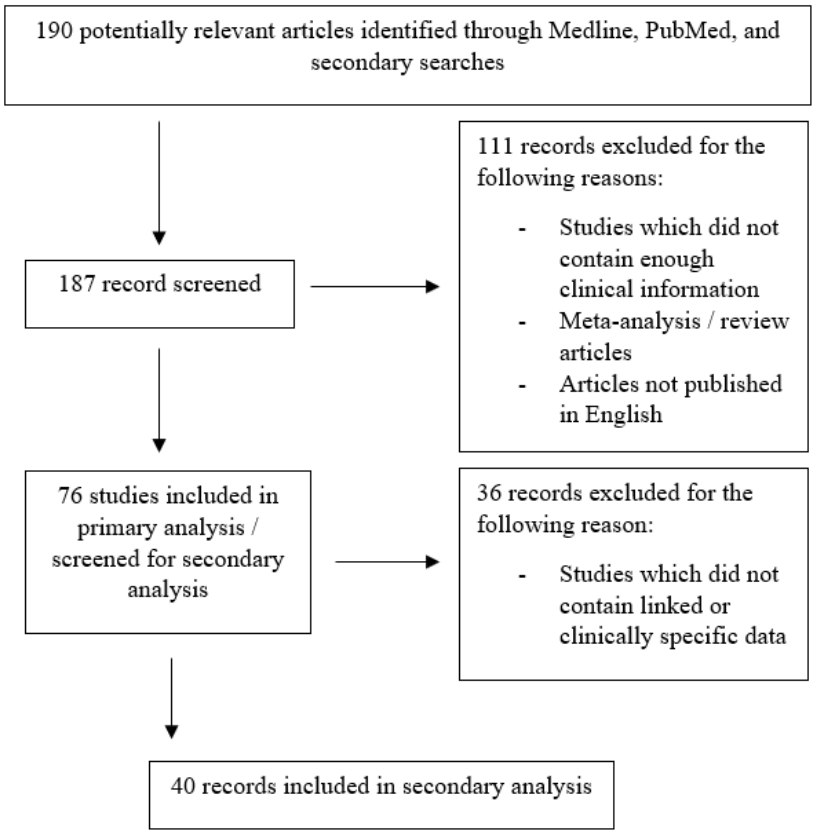

Figure 3.1 Flowchart displaying search process and record selection for analysis.

Table 3.1 Demographic characteristics of TBRF cases.

Variable	*B. hermsii* (N=308)	*B. turicatae* (N=100)	p-value
Age (%)			0.4288
Adult (18-60)	126 (56)	55 (65)	
Pediatric (1-17)	86 (39)	29 (34)	
Infant (<1 yr)	5 (2)	0 (0)	
Elderly (60+yrs)	6 (3)	1 (1)	
Sex (%)			<.0001
Male	194 (63)	259 (87)	
Female	114 (37)	40 (13)	

Note. Adult (18-60), Pediatric (1-17), Infant (<1yr), Elderly (60yrs+)

Table 3.2 Symptom profile of TBRF cases.

Symptom	Overall N (%) N = 433	*B. hermsii* n (%) n = 391	*B. turicatae* n (%) n = 42	p-value
Fever	337 (77)	296 (76)	41 (98)	0.0012
Chills/Sweats	212 (50)	193 (49)	25 (60)	0.2106
Headache	223 (53)	200 (51)	33 (79)	0.0007
Nausea	148 (35)	122 (31)	26 (62)	<0.0001
Vomiting	132 (32)	118 (30)	24 (57)	0.0004
Myalgia	202 (48)	185 (47)	27 (64)	0.0365
Weakness	93 (22)	75 (19)	18 (43)	0.0004
Arthralgia	46 (11)	43 (11)	12 (29)	0.0012
Anorexia	69 (16)	67 (17)	1 (2)	0.0071
Malaise	78 (18)	55 (14)	23 (55)	<0.0001
Abdominal Pain	44 (10)	51 (13)	0 (0)	NA
Rash	42 (10)	21 (5)	23 (55)	<0.0001
Splenic Enlargement	57 (13)	50 (13)	7 (17)	0.4799
Tachycardia	35 (8)	21 (5)	14 (33)	<0.0001
Eye pain	34 (8)	34 (9)	0 (0)	NA
Back pain	33 (8)	8 (2)	25 (60)	<0.0001
Red eyes	33 (8)	33 (8)	0 (0)	NA
Diarrhea	26 (6)	26 (7)	0 (0)	NA

Note. Rest of symptoms including blurred vision, congestion, confusion, dehydration, dizziness, dyspnea, epigastric pain, fatigue, hypotension, hypoxia, jaundice, lethargy, leg pain, meningitis (suspected), photophobia, retrobulbar pain, rhinorrhea, sore throat, syncope, tachypnea, and weight loss each accounted for ≤ 5% of symptom occurrence.

Table 3.3 Prognostic indicators of RF by causative agent.

	Overall avg. (range)	*B. hermsii* avg. (range)	*B. turicatae* avg. (range)	p-value
Incubation Days	9 (1-25)	8 (1-15)	10 (6-25)	0.588
Febrile Days	4 (1-17)	4 (1-17)	4 (1-9)	0.978
Afebrile Days	7 (1-20)	7 (1-20)	8 (5-10)	0.446
Febrile Episodes	3 (1-15)	3 (1-8)	5 (2-15)	0.204

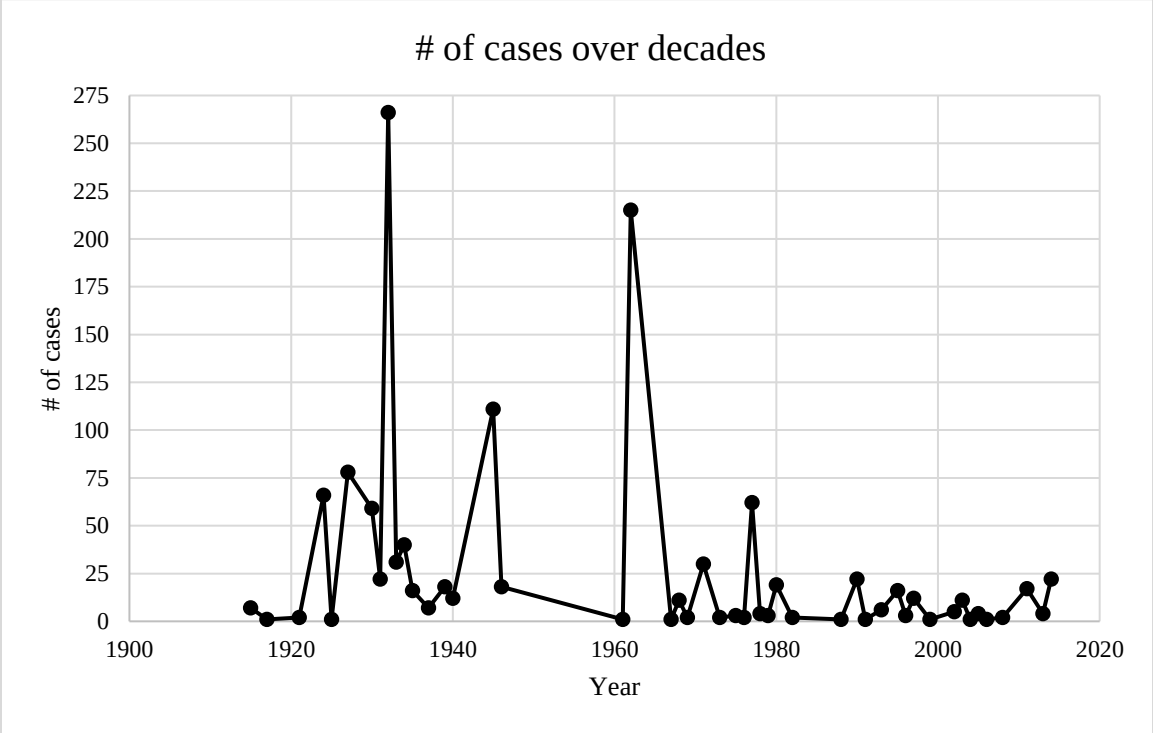

Figure 3.2 Incidence of infections described over the decades.

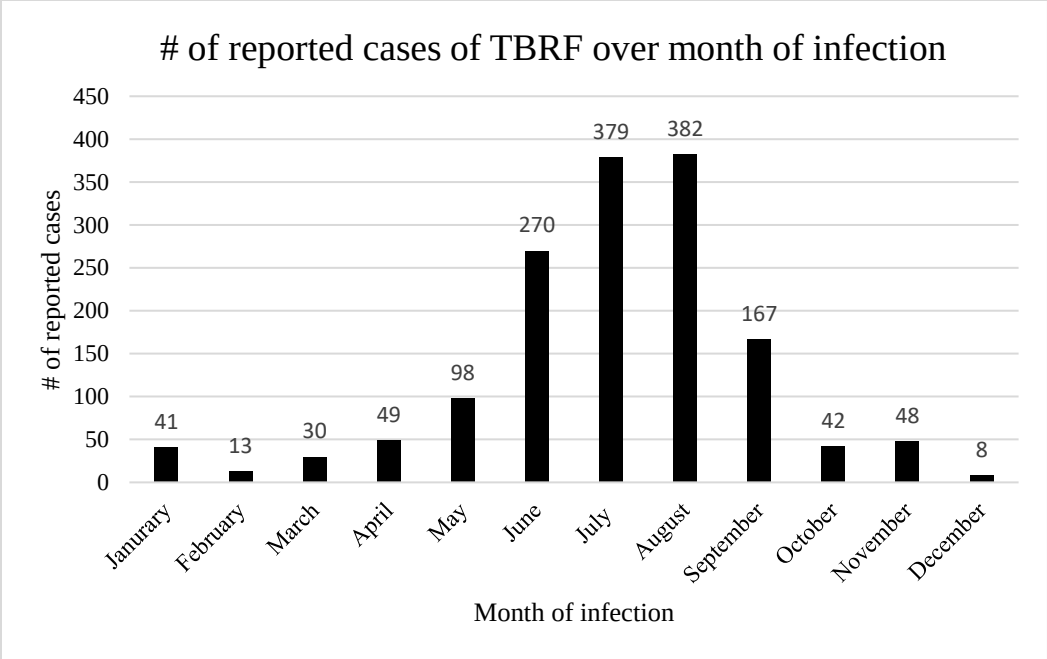

Figure 3.3 Incidence of infections by month.

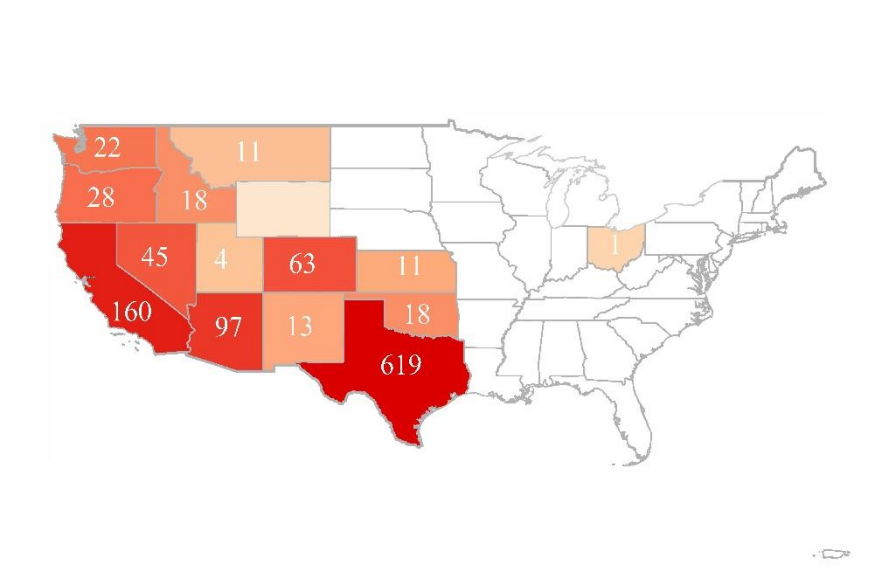

Figure 3.4 Shaded map of confirmed or suspected TBRF cases identified in the final analysis.

Table 3.4 Characteristics of infection.

Characteristic	**% cases reported**
Patient reported tick bite	25%
Cabin associated	34%
Trailer Associated	1%
Camping Associated	4%
Evidence of tick infestation	22%
Ticks recovered from site	21%
Cave site	17%
Condominium	4%
General outdoors	8%
B+ ticks found at site	18%
B+ animals found at site	13%
Pregnancy associated	5%
Sleeping structure uninhabited at times	41%

Table 3.5 Results of logistic regression modeling Jarisch - Herxheimer reaction and treatment comparison.

Treatment Comparison	Estimate	OR (95% CI)
Combination/other vs. Tetracycline	-0.5218	0.66 (0.048 – 9.03)
Doxycycline vs. Tetracycline	0.8387	2.56 (0.173 – 38.4)
Penicillin vs. Tetracycline	-0.2096	0.90 (0.044 – 18.5)

Note. Confidence intervals calculated with alpha at 0.05.

Table 3.6 Results of Poisson logistic regression modeling number of febrile episodes and treatment type.

Treatment	Estimate	IRR (95% CI)
Combination/other	0.212	1.237 (0.736 – 2.076)
Doxycycline	0.111	1.117 (0.574 – 2.175)
Penicillin	-0.239	0.788 (0.358 – 1.735)

Note. Confidence intervals calculated with alpha at 0.05. Treatment tetracycline used as referent group.

CHAPTER 4
DISCUSSION

This review reports on TBRF clinical epidemiology based upon published reports spreading over a century cumulating 1200 cases originating from 14 states. The methodology of this report, unlike similar published reviews which use state reported data, uses previously published cases. This methodological difference can result in less precise measurements but one of the advantages of our approach is an increased amount of information over more years which shows not only a current report on the state of the disease but also a historical perspective. Our data collection method also resulted in unique variables which have not been previously described and provides a basis for advanced statistical models which can be used to describe disease presentation and duration.

Currently, this is the only review at present knowledge which has looked through case reports and generated this type of data. Data from the CDC is limited and most of the clinical information is abstracted from a single report by Dworkin et.al.[34] To our knowledge, our sample size represents the largest of its kind and most geographically represented as well. In the Dworkin et.al paper used by the CDC, information was gathered on only 4 different states, limited to the most north-west part of the United States. Given its geographical niche, it is reasonable to infer that this data might be limited to *B. hermsii* infections only which might describe some differences in findings. Clinical presentation of the disease is presented as a single entity, but our review has

showed differences in clinical presentation based on infection type. Symptom frequency found in our review is similar to CDC reported data.[18] Specific frequency percentages of symptoms vary marginally but the relative frequencies are identical (i.e. the same symptoms present the most frequently in our review and previous work, such as headaches, myalgia, and chills being reported most often). In our analysis, which contained clinical information on 337 patients, *B. turicatae* infections were found to have significantly higher incidences of fever, headache, nausea, emesis, weakness, and more symptoms despite being much less representative in our sample. This suggests quite possibly that *B. turicatae* infections clinically manifest differently from *B. hermsii* infections and that treatment and symptom management practices for each disease should be approached separately instead of how they are currently treated as one.

Profiling this disease is challenging due to the wide array of symptomology and clinical presentation. The pathogen was found in individuals without fever, suggesting that infections can occur which do not cause fever but still cause other flu-like symptoms. Those asymptomatic infections noted in our review were identified in outbreak investigations, suggesting that all persons with exposures should be tested for infection. While the majority of cases did report fever and flu-like illness described above, symptoms were not consistently grouped together between patient populations or within the individual patient. Within a single individual, different febrile relapse episodes could be accompanied by a multitude of other symptoms and rarely were they consistent. While febrile episodes typically lessened in duration after the initial episode, this was not always true. At present, this review, nor any other articles have been able to identify clinically reproducible trends as this disease runs its course. One of the main indicators of

TBRF, besides relapsing episodes, is fever temperature which averaged over 103 degrees Fahrenheit. From data collected it was not possible to determine a statistical relationship between the number of febrile relapses and temperature. Because temperature was typically recorded for only the first febrile episode, there was not enough data to make any inference on whether temperature wanes or increases with repeated febrile relapses. The current position on febrile periods typically site three days for any one febrile period but it is not clear how this number was determined. In our study, febrile periods were usually one or two days, and subsequent relapses usually had shorter febrile periods, but this was not always the case. In our study we used relapse data to not only look at the expected number of febrile days a patient might experience for any one episode, but we looked at how many days total an individual would be expected to experience fever during the entire course of the disease. Our analyses found the expected number of febrile episodes to be three and expected number of total febrile episodes for both infections' types combined to be six days. This indicates that febrile periods might be shorter than previously described but they might also be different depending on infection type. While not statistically different, our analysis showed the average number of febrile episodes for *B. turicatae* infections was two days less than its *B. hermsii* counterpart. Afebrile periods have not been previously described but were included in this review to shed light on how long the disease can endure. Afebrile periods, which averaged 7 days overall, and were higher (albeit not statistically) in *B. turicatae* infections. One extreme case noted afebrile periods accumulating 48 days resulting in relapsing fevers for months. There were relatively wide ranges in each of these variables and were often different between

infections, adding to the complications in characterizing the disease's clinical presentation.

Our results indicate that *B. turicatae* infections are clinically different from *B. hermsii* infections and in many cases are associated with increased morbidity. Incubation days for *B. turicatae* infections were longer, number of febrile episodes higher, and reported higher proportions of various symptoms. Some of these differences may be due to physicians not being aware that TBRF infections have two different causative agents. This could lead to delayed diagnosis and in turn could cause a delay in treatment leading to more febrile episodes, febrile days, and afebrile days.

TBRF treatment has evolved over the years with the advent of different antibiotics but there seems to be little guidance in how these treatments are selected. To analyze treatment effectiveness, we ran regressions to see if certain treatments resulted in better outcomes. The current position in the medical community indicates that tetracycline is the preferred treatment but there is little data to support why that is the case, even so, tetracycline was used in our analyses as the referent group for this reason. Our data does not support the hypothesis that other antibiotics or treatments, such as penicillin or combination therapies might be more effective in reducing the risk of Jarisch – Herxheimer reactions compared to tetracycline treatments alone but we note that due to a small sample size, our ability to detect such a difference is limited. We cannot, at this time, make any statistically sound inference on the association between treatment type and risk of Jarisch – Herxheimer reaction. To analyze the number of febrile episodes we used a Poisson regression. In this analysis, tetracycline results in lower incidence rate of febrile episodes compared to other treatments, save for penicillin. Once again, these

results are not statistically sound but both regressions provide the basis for the type of analyses which can be used in the future on larger data sets to infer better and more efficient treatment options for TBRF.

Consistent with prior assumptions, we found TBRF is primarily found in traditionally healthy populations, occurring in summer months when vacationing to remote cabins is most likely to occur. Sites which are older, have less regular upkeep, and are uninhabited at times during the year present the most likely areas in which risk of infection is higher.[35] Temperature plays a catalytic role in the epidemiology of this disease; hot weather encourages reservoir mammals to venture out of the tick's habitat while simultaneously attracting naïve humans into the habitat. During the fall and winter months, rodent species turn to indoor or sheltered habitats to wait out the cold and harshness of the outside conditions. *Ornthidoros* spp. ticks lie in wait to take blood meals and ingest infected blood from rodent species which act as reservoirs and harbor the *Borellia* bacteria. It is possible that *Borellia hermsii* and or *Borellia turicate* spirochetes can be vertically transmitted during birth resulting in some ticks being born as vectors, hosting the bacteria in their saliva.[36] While rarely obsreced there is alos another route for vector infection. Hyperparasitism between *O. hermsi* ticks has been observed which resulted in previously uninfected *O. hermsi* ticks becoming infected with *B. hermsii* spirochetes after being fed on by infected ticks.[37] As the temperature increases during the spring in summer, the rodents leave their nests to forage in the more hospitable climate while outdoor enthusiasts move indoors to enjoy seasonal respites and become new hosts to ticks. These seasonal movements are not just affected by temperature but also reservoirs and people. Our review showed that ticks were recovered from infection sites

only 21% of the time. This low number is partly due to the fact that not all sites were investigated for tick infestations, but many which were still turned up no ticks. A special report published in 2009 by Gaither, et.al provides a possible explanation for this.[38] Gaither posits that tick movements are influenced by which host they are attempting to feed on. Their research group originally began looking for ticks where one might assume them to be found, in the nests of rodents, but soon found out that they were nowhere to be seen. When widening their scope, they found black tar residues which turned out to be blood as well as live and dead ticks in the cracks along window, near pictures close to windows, crevices of walls, and near sleeping areas. Gaither mentions that finding soft shelled ticks in these locations is unusual, so her team hypothesized that the ticks make accommodations for host type and were moving within their area to increase the likelihood of blood meals when humans were present. This hypothesis is not only interesting because it gives researchers a better idea of where to locate these ticks but also it shows that these, mostly nidicolous ticks, can become mobile and adapt to their hosts making them far more resourceful than previously considered.

While most cases occurred in males there is no particular reason noted in this review or any other literature source to indicate this is anything more than incidental. It might be the case that areas where infection risk is higher might be visited more often by males than females but there is no evidence of sex inherently increasing risk of infection. Many of our cases took place in boys' camps, caves, and forest cabins. It might be that *Ornthidoros* spp. ticks inhabit areas frequented more my males compared to females.[39] There is evidence to support this. We spoke to The National Speleological Society which told us that among their 8000 members, the ratio of men to women was 2:1. This review

also found no evidence to indicate that individuals might be more prone to infection based on age, as infection was found in all age groups. Although mostly found in adults and children, these groups most likely represent those coming into contact with these nesting ticks due to their active lifestyles.

TBRF incidence is virtually impossible to measure due to lack of surveillance and different reporting practices in 12 states that consider TBRF a notifiable condition. State health department websites vary widely in which diseases have publicly available data from year to year. TBRF is often left off the infectious disease surveillance reports for years at time and there is no information on discerning infection type. The only major reviews covering TBRF are an MMWR report published in 2015 with data on 504 cases collected from 1990 - 2011 and the aforementioned article by Dworkin, et.al published in 1998 with information on 182 cases from 1980 – 1995.[15,16] While their reviews have similar findings to this one, one major difference is noted in respect to the occurrence of Jarisch-Herxheimer reactions. Dworkin, et. al reported that Jarisch-Herxheimer reactions occurred roughly 50% of the time in their 1998 review with 34 of the 66 cases which had data on this outcome included in that review. Our review, which spans published reports over a 100 - year span did not note nearly as many cases. There are a couple possible solutions to resolve this discrepancy. One possibility is that the published reports did not often have access to the complete details of the medical records which record which described treatment and reaction. Another might be lack of awareness of the reaction led to a lack of recognition when reviewing case files and misconstrued for the disease itself instead of a response to treatment. By looking at medical records, Dworkin and his team were able to identify Jarisch-Herxheimer reactions even when they weren't explicitly

reported due to the patients notes and symptom descriptions after treatment. It is possible that disease management today is better than it was when Dworkin was collecting data for his review 20 years ago but there is no formal treatment recommendation and despite prevailing advice suggesting that tetracycline treatment is the best course for adults and unpregnant women, our review noted cases of Jarisch-Herxhemier reactions in response to that antibiotic as well as others. Regardless, the sample size from which this statistic was derived is probably inflating how often this reaction is actually occurring but the observations from both of these studies show why this outcome is of particular interest in TBRF treatment.

This review highlights a number of reasons why TBRF should be a nationally notifiable disease. Firstly, no major published works has summarized the current state of the disease in the United States for over a decade. Secondly, the quality of data on the topic and access to it are unreliable and leave much to be desired. California's state health department has arguably the best information publicly available on the disease but lacks crucial information on treatment, number of relapses, and duration of disease. In other states where TBRF is reportable, yearly incidence is not even reported in their surveillance reports consistently, sometimes skipping years entirely. This leads to inconsistent data, missing data, and a lack of not only public but professional awareness which causes the disease to go mistreated and underdiagnosed. Even with standardized reporting measures, universal reporting criteria, and increased awareness, this disease will be challenging to address due to its multifaceted and unique clinical presentations, similarities to viruses or other more common bacterial infections, and various incubation periods.

TBRF is a traveler's disease. Most of our cases show that individuals or families were vacationing or staying in remote wooded areas when they were infected. TBRF is difficult to diagnose on its own but is more likely to be diagnosed in states where the disease is endemic because physicians are more likely to look for it. For traveler's which return home to states where TBRF is not normally found and is not a reported disease, a correct diagnosis might never be confirmed. The disease will usually run a self-limiting course, but improper treatment and management will prolong patient suffering and discomfort. To showcase this issue, consider the following evidence which was found in during our review. TBRF was identified in travelers from Nebraska, Kansas, Florida, and Texas in one report where all travelers had stayed in the same cabin located in the Rocky Mountains in Colorado in 1995.[40] While TBRF is found frequently in Texas it is not in the other states mentioned. Upon returning home, the individuals from Texas were more likely to be diagnosed correctly sooner. Without knowing what diseases are endemic in certain areas, knowing which area a patient stayed in does little good. In another case from 1967, a woman who had visited western states where TBRF is commonly found returned to Boston and presented with multiple relapses of fever.[41] This was originally treated as a viral infection and the patient was discharged from the hospital when her fever waned. When her fever recrudesced, she was readmitted and eventually received tetracycline treatment until her fever and other symptoms reduced and was discharged again. Had her doctor been aware of TBRF and the areas which it is endemic he or she might have diagnosed TBRF sooner and saved the patient a return to the hospital.

This scenario where an outdoor enthusiast travels to an endemic area, becomes infected while on vacation, incubates the infection during the trip, develops symptoms upon return

to their home state, and has an extended course of disease due to a lack of physician knowledge is not conjecture but shown to be likely common. The current state of knowledge on the disease is such that physicians in non-endemic regions of the United States are more likely to allow for greater periods of patient distress and continue to contribute to underreporting of the disease.

TBRF is rarely fatal and over the course of a century, only two published case reports resulted in mortality. The first, an elderly individual close to 70 years of age had a heart attack while experiencing a febrile episode and subsequently died.[42] Her symptom profile reported one of the highest fevers collected in our review (105 degrees Fahrenheit) and she also experienced hepatic enlargement which was one of the more advanced, yet less common, symptoms. The second individual, a newborn infant, died quickly after birth after acquiring a TBRF infection via transplacental means from the mother.[43] The only symptom reported were seizures and a low-grade fever before the infant was found unresponsive. Both fatal cases had been identified as having a *B. hermsei* infection. TBRF mortality is likely rare due to TBRF infections typically occurring in younger, more robust individuals in good health. Despite the low mortality rate, TBRF should still be considered especially dangerous to infant and elderly populations and appropriate treatment is crucial to prevent death. Additionally, a higher number of clinically advanced cases were seen. Meningitis cases, hepatosplenomegaly, tachycardia, dyspnea and tachypnea and even jaundice. These are associated with much worse outcomes and can be risk factors for disease later in life.

While not communicable from person to person, the disease has the potential to be incredibly infectious on a large scale due to its short transmission time and clustered

incidence. Three of our papers included in this review highlight this potential. On two separate occasions, once in 1973, and again in 1990, outbreaks of TBRF occurred at the Grand Canyon National Park in Arizona. In the first instance, 10 individuals were infected between June and July of 1973. In almost the exact same location 17 years later another 17 individuals were positively diagnosed with TBRF indicating that there are hotspots for the tick vectors and their reservoirs where the pathogen maintains a stable presence in the area. As recently as 2014, an outbreak occurred at an outdoor education camp in Arizona where six confirmed cases and five probable cases of TBRF were identified. The camps were often uninhabited save for the warmer months when campers took up residence in older cabins.[44–46] These examples are likely to become more commonplace as accommodations and dwellings age and deteriorate, constructing hospitable vector and mammalian reservoir habitats. The climate might begin to play more of a factor as well. With warmer temperatures due to global warming, spring and summer seasons are likely to see longer durations which will increase the window in which infections are most likely to occur. Warmer climate might influence tick movements as well. Although they are nesting ticks, the *Ornthidoros* species riding on the backs of rodents or birds might find themselves in new areas if their hosts are able to cover more ground for longer periods of time.[47] If the ecological niche of these ticks expands then a rise in incidence would be expected. Having a national reporting recommendation would result in increased awareness for states which are currently not experiencing TBRF infections but might begin to develop some. This would lead to quicker recognition and better treatment plans for patients. The severity of the disease, while varied, also presents potential for excruciating pain because of its cyclical progress.

The reoccurrence rate derived from the secondary analysis was 75%, meaning that patients are very likely to experience more than one febrile episode with an unpredictable accompaniment of debilitating symptoms as well as a high fever. This can hospitalize patients for days, keeping them from work, accumulating considerable personal and hospital economic burdens.

This review summarizes a large period of time on published data and gives an idea as to the scope of not only the disease itself but the difficulty in studying and treating it. The major limitations of this study are the relatively small sample size, missing data, and data quality. Although, this being a review, is a reflection of the quality and quantity of published data available and a reflection of the overall limitations in studying the disease. This review, while expansive in both years, as well as the amount of information included does have a number of limitations. The first of which is the data collection process. While other reviews had requested state specific data from health departments and accompanying medical records, our review was conducted using only published literature. The accuracy of our data is dependent on the various methodologies utilized in the published reports we used to construct our data set and often these reports shared varying degrees of information, some detailed and ordinal, others less so. In places where exact data was not available, best estimates were used for analysis. Some of the years listed for reviews gave a range but did not associate their cases with precise years, in this instance we chose to take the midpoint of the range as the year of incidence. Overlapping cases is a possible issue. While we diligently reviewed the papers chosen so as not to include duplicate data there is still the possibility that some of these cases might have been reported on in multiple papers. With large sample sizes taken from a range of years

it is difficult to tell if those cases overlap with any on other reports on cases in those areas within those years.

Generalizability is another possible issue. Due to the unique methodology presented here, making comparisons between previous works must be taken with some considerations in mind on how data was collected in those papers vs. this one. Comparisons within this paper should also be thought of in the same light given the added criteria for inclusion in the secondary analysis. This difference can help explain some possible notable discrepancies in the data presented here.

Despite its limitations, we note that this review has a number of strengths. This is the only review, to our knowledge, that has reported on TBRF and analyzed differences in clinical presentation and prognosis by infection type. Another strength of this study is its sample size and geographic range, including data on 14 states. This review also highlights trends and updates the medical and epidemiological community with the largest study on the topic in many years. This study was able to show that there are differences in clinical presentation of this disease based on infection type and these differences are worth further exploring to standardize treatment protocols and diagnosis, lower morbidity and mortality, and help preventions efforts by targeting endemic areas and hotspots as well as increase the public awareness of the disease. With increased awareness and standardized reporting measures, physicians and public health professionals can more readily identify a relapsing fever infection and treat it. Increased treatment not only leads to better health outcomes and reduced morbidity for patients but also increases the amount of data available on treatment which can improve treatment practices and help develop personalized treatment plans.

This review can be seen as a template for the type of information and reporting which would be useful in the NNDSS. Data on infection type is crucial to understanding how and where the pathogen spreads and how this results in different clinical presentations. Furthermore, understanding which treatments work best requires precise data on which antibiotics were used, their dosage, and treatment course with an emphasis on lowering the number of relapses and incidence of Jarisch-Herxheimer reactions. In addition, modeling data can be improved by inclusion of more covariates. In this review, data on only sex and age was available but race, body mass index, socioeconomic status, etc. might be important for developing reliable models. In conclusion, TBRF should be a nationally notifiable disease because it is vastly underreported, lacks awareness in the medical community, especially in non-endemic states, is reported infrequently and inconsistently which results in poor data pertaining to the disease and its pathogen, and because best treatment practices which limit morbidity and other unfavorable outcomes is impossible to determine with the current data available. An inclusion on the list of nationally notifiable conditions will push TBRF to the forefront of clinician concerns, create better data quality on this disease, and limit future infections and outbreaks while lowering morbidity and mortality for those who are infected.

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Records of Ixodes affinis (Acari: Ixodidae) Parasitizing Avian Hosts in Southeastern Virginia . *J Med Entomol*. 2015;53(2):441-445. doi:10.1093/jme/tjv175

APPENDIX A: LIST OF PAPERS USED IN FINAL ANALYSIS IN ALPHABETICAL ORDER BY AUTHOR

Author	Paper	Journal	Year
Badger et.al	Tick talk: Unusually severe case of tick-borne relapsing fever with acute respiatory distress syndrome-case report and review of the literature	Wilderness and Environmental Medicine	2008
Bannister et.al	Relapsing fever	Southwestern Medicine	1930
Bohls et.al	Relapsing fever in Texas and the laboratory method of diagnosis	Texas State Journal of Medicine	1933
Boyer et.al	Tick-borne relapsing fever: An interstate outbreak originating at Grand Canyon National Park	American Journal of Epidemiology	1977
Briggs et.al	Relapsing fever in California	Journal of the American Medical Association	1922
Briggs et.al	Relapsing fever	Califonria & Western Medicine	1935
Burns et.al	Relapsing fever in California	California and Western Medicine	1936
Christensen et.al	Tickborne relapsing fever, Bitterroot Valley, Montana, USA	Emerging Infectious Diseases	2015
Closson et.al	Relapsing fever	The Journal of the Kansas Medical Society	1934
Cole et.al	Elgin medical group first to find bacteria unseen in humans	Elgin Air Force Base Public Affairs	2016
Curtis and Bronson	Isolation and Characterization of Borrelia hermsii Associated with Two Foci of Tick-Borne Relapsing Fever in California	Journal of Clinical Microbiology	2004
Davis et.al	Ornithodoros turicata and relapsing fever spirochetes in New Mexico	Public Health Reports	1941
Davis et.al	Relapsing fever associated with ARDS in a parturient woman: a case report and review of the literature	Chest	1992
Davis et.al	Tick-borne relapsing fever caused by Borrelia turicatae	Journal of Pediatric Infectious Diseases	2002
Dennis et.al	Commentary	California and Western Medicine	1936
Eads et.al	Relapsing fever in Texas: distribution of laboratory confirmed cases and the arthropod reservoirs	The American Journal of Tropical Medicine and Hygiene	1950
Edell et.al	Tick-borne relapsing fever in Colorado	Journal of the American Medical Association	1979
Espinoza et.al	Relapsing fever in New Mexico: report of two cases	Rocky Mountain Medical Journal	1977
Ettestad et.al	Tickborne relapsing fever outbreak after a family gathering-New Mexico, August 2012	Morbidity and Mortality Weekly Report	2003
Felder et.al	Borrelia hermsii relapsing fever	Blood	2014
Fihn et.al	Tick-borne relapsing fever in the Pacific Northwest: An underdiagnosed illness?	Western Journal of Medicine	1980
Fischer et.al	Present distribution of relapsing fever in oklahoma	Publication of the American Association for the Advancement of Science	1942
Frazier et.al	Abstract of Discussion	Texas State Journal of Medicine	1931
Fuchs et.al	Neonatal relapsing fever due to transplancental transmission of Borrelia	Journal of the American Medical Association	1969
Gaither et.al	Where are the ticks? Solving the mystery of a tickborne relapsing fever outbreak at a youth camp	Journal of Environmental Health	2016
Gholkar et.al	Borrelia hermsii (relapsing fever)	New England Journal of Medicine	2013
Gillespie et.al	Relapsing fever in the United States	Journal of the American Medical Association	1935
Goodman et.al	Borrelia in Boston	Journal of the American Medical Association	1969
Graham et.al	Relapsing fever in Texas: Possibility of an animal reservoir	Texas State Journal of Medicine	1931
Guggenheim et.al	Tick-borne relapsing fever during pregnancy: a case report	Journal of Reproductive Medicine	2005
Hemingway et.al	Ornithodoros hermsi and relapsing fever in Oregon	Northwestern Medicine	1940
Horton et.al	The spectrum of relapsing fever in the Rocky Mountains	Archives of Internal Medicine	1985
Jones et.al	Tick - Borne Relapsing Fever Outbreak among a High School Football Team at an Outdoor Education Camping Trip, Arizona, 2014	Morbidity and Mortality Weekly Report	2015
Kemp et.al	Relapsing fever in Texas: V. A survey of the epidemiology and clinical manifestations of the disease as it occurs in Texas	The American Journal of Tropical Medicine and Hygiene	1934
Klein et.al	Relapsing fever-successful treatment with demethylchlortetracycline (Declomycin)	California Medicine	1964
Lakin et.al	Epidemiologic notes and reports outbreak of relapsing fever--Grand Canyon National Park, Arizona, 1990	Morbidity and Mortality Weekly Report	1991
Lawaczeck et.al	Tickborne relapsing fever in a mother and newborn child-Colorado 2011	Morbidity and Mortality Weekly Report	2012
Le CT	Tick-borne relapsing fever in children	The Journal of Pediatrics	1980
Legge et.al	A new etiologic observation: with case report of a field worker	California and Western Medicine	1933
Liles & Spach	Late relapse of tick-borne relapsing fever following treatment with doxycline	Western Journal of Medicine	1993
Linneman et.al	Tick-borne relapsing fever in the Eastern United States	American Journal of Diseases of Children	1978
Lovett et.al	Fever in a couple vacationing in the mountains of Southern California	Journal of Clinical Infectious Diseases	1992
Luckey et.al	Epidemiologic notes and reports relapsing fever-Georgia, Arizona	Morbidity and Mortality Weekly Report	1973
Malison et.al	Relapsing fever	Journal of the American Medical Association	1979
McIntosh et.al	Zoonoses at Henry Ford Hospital: clinical, epidemiological and therapeutic aspects	Henry Ford Hospital Medical Journal	1982
Meader et.al	Five cases of relapsing fever originating in Colorado, with positive blood findings in two	Colorado Medicine	1915

Mohr et.al	Relapsing fever	Journal of the Oklahoma State Medical Association	1979
Morrison et.al	Relapsing fever: report of three cases, one in a six day old infant	Journal of the American Medical Association	1941
Murphy et.al	Acute respiratory distress syndrome in persons with tickborne relapsing fever-three states, 2004-2005	Morbidity and Mortality Weekly Report	2007
Neilson et.al	Report of a case of relapsing fever	Journal of the American Medical Association	1940
Newton et.al	Relapsing fever	New England Journal of Medicine	1996
Parsons et.al	Discussion	California and Western Medicine	1937
Paul et.al	Outbreak of tick-borne relapsing fever at the north rim of the grand canyon: evidence for effectiveness of preventive measures	The American Journal of Tropical Medicine and Hygiene	2002
Philip et.al	Relapsing fever: data implicating Ornithodoros hermsi as a vector in northern Idaho	Public Health Reports	1940
Porter et.al	Relapsing fever in California	American Journal of Public Health	1932
Rawlings et.al	An overview of tick-borne relapsing fever with emphasis on outbreaks in Texas	Texas Medicine	1995
Raymond et.al	Case of relapsing fever in Arizona	Southwestern Medicine	1926
Reynold et.al	Relapsing fever: comments on its incidence in Nevada	California and Western Medicine	1937
Roscoe et.al	Tick-borne relapsing fever	American Family Physician	2005
Schwan et.al	Tick-borne relapsing fever caused by Borrelia hermsii, Montana	Emerging Infectious Diseases	2003
Schwan et.al	Tick-borne relapsing fever and Borrelia hermsii, Los Angeles County, California, USA	Emerging Infectious Diseases	2009
Steenbarger et.al	Congenital tick-borne relapsing fever: report of a case with first documentation of transplacental transmission	The Journal of Birth Defects	1982
Taft et.al	Relapsing fever: report of a sporadic outbreak, including treatment with penicillin	Journal of the American Medical Association	1945
Terrell et.al	Abstract of Discussion	Texas State Journal of Medicine	1931
Thayer et.al	Relapsing fever	Southwestern Medicine	1940
Thompson et.al	Outbreak of tick-borne relapsing fever in Spokane County, Washington	Journal of the American Medical Association	1969
Tilley et.al	Three cases of relapsing fever associated with lakeside cabin	Canada Communicable Disease Report	1994
Todd et.al	Tick-transmitted diseases in the Rocky Mountain States	Rocky Mountain Medical Journal	1974
Tollefsen et.al	Relapsing fever	Medical Bulletin of the Veterns' Administration	1935
Trevejo et.al	An interstate outbreak of tick-borne relapsing fever among vacationers at a rocky mountain cabin	The American Journal of Tropical Medicine and Hygiene	1998
Varden et.al	Relapsing fever in children	California and Western Medicine	1932
Varden et.al	Relapsing fever in children	American Journal of Diseases of Children	1934
Waring et.al	Relapsing fever endemic in Colorado	Colorado Medicine	1918
Weller et.al	Relapsing fever in central texas	Journal of the American Medical Association	1930
Wilder et.al	Case report: A retrospective serological analysis indicating human exposure to tick-borne relapsing fever spirochetes in Texas	PLOS Neglected Tropical Diseases	2015
Wynns et.al	Epidemiologic studies on relapsing fever in California	American Journal of Public Health	1935