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Evaluation by Geospatial and Spatiotemporal Distribution of Tularemia Cases in Arkansas

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Walden University

College of Health Sciences

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Toni Kathleen Beavers

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Walden University
2019

Abstract

Evaluation by Geospatial and Spatiotemporal Distribution of Tularemia Cases in Arkansas

by

Toni Kathleen Beavers

MPH, Walden University, 2010

BS, University of Central Arkansas, 1992

Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

Doctor of Philosophy

Public Health

Walden University

August 2019

Abstract

Tularemia is a vector-borne disease of global concern with diverse regional foci. Arkansas is an endemic state with differences in case distribution and land suitability supporting host and vector sustainment. The aim of this study was to conduct a geospatial and spatiotemporal assessment of factors associated with case distribution and timeliness and completeness of public reporting. Guided with direction from spatial epidemiology and *nidality*, referring to the association of ecology, climate, and proximity of disease, analysis included secondary data collected from the Arkansas Department of Health between 1995 and 2018. Using Poisson-based software, 2 clusters were found: a high-risk cluster encompassing 23% of the total population within 24 counties spanning an 8-year period (RR = 4.98, $p < 0.05$), and a low risk cluster that included 25% of the population within 28 counties during a 12-year period (RR 0.14, $p < 0.05$). Analysis of ecological data revealed associations between annual precipitation within the high-risk cluster and total number of cases (AUC = 0.716 and AUC = 0.726, respectively) with trends toward higher incidence rates in suitable land cover and moderate to high elevation using maximum entropy software. Analysis of timeliness and completeness revealed gaps for clinical form and transmission mode determination ($p < 0.05$), while increases in probable cases followed decreases in confirmed cases revealing gaps in laboratory diagnostics. Positive social change necessitates multidisciplinary collaboration between climatologists, clinicians, and epidemiologists to reach high-risk populations and promote educational awareness. The potential for social change includes predictive modeling optimizing funding while representing underserved populations.

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Dedication

"We must have perseverance and above all confidence in ourselves."

-Marie Curie

I want to dedicate this dissertation to my family that has supported me throughout my educational career. In particular, I dedicate this lovingly to my two sons, as I know this has been difficult giving up time with me in order for me to fulfill my dream. I hope this portrays to Hayden and Henry that education is the foundation to any dream and hope they value this journey as a beginning of support of lifelong learning.

Acknowledgments

"Let each of you look not only to his own interest, but also to the interests of others,"

-Philippians 2:4

I would like to thank my church family as being part of spiritual growth and strength in order to accomplish this journey. My sincerest thanks goes to my classmates and facility at Walden University for such an enriching and diverse learning environment. I also want to thank my employer, Becton Dickinson, & Company for valuing my benefit to the workforce and the significance of higher education as well as the ability to participate in the President's Emergency Plan for AIDS Relief (PEPFAR) during my time at Walden. A special thanks to Dr. Shanna Barnett, my Chair, and Dr. Aaron Mendelsohn, Committee Member, as without their enthusiastic support, I would not have competed this task.

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Part 1: Overview

Introduction

Tularemia is an infectious disease of global public health concern ("Tularemia', 2016). The causative agent is the bacterium *Fransciella tularensis* and it affects humans through contact with infected or colonized vectors or hosts, contaminated water or food, laboratory exposure, or bioterrorism (Berger, 2017; Mahon & Lehman, 2019; Penn, 2015; "Tularemia', 2016). While tularemia is found globally, there are regional hot spots that appear to be influenced seasonally (Desvars et al., 2015; Desvars-Larrive et al., 2017; Dupont et al., 2015; Hestvik et al., 2015; Hightower et al., 2014; Larssen, Bergh, Heier, Vold, & Afset, 2014). Within the United States, clusters of cases reported in 2015, as represented in Figure 1. 1, show a significant amount of cases within Arkansas ("Centers", 2016). Despite being a significant disease within the south central United States, tularemia has a short history compared to other vector borne diseases such as plague and malaria (Berger, 2017; Penn, 2015).

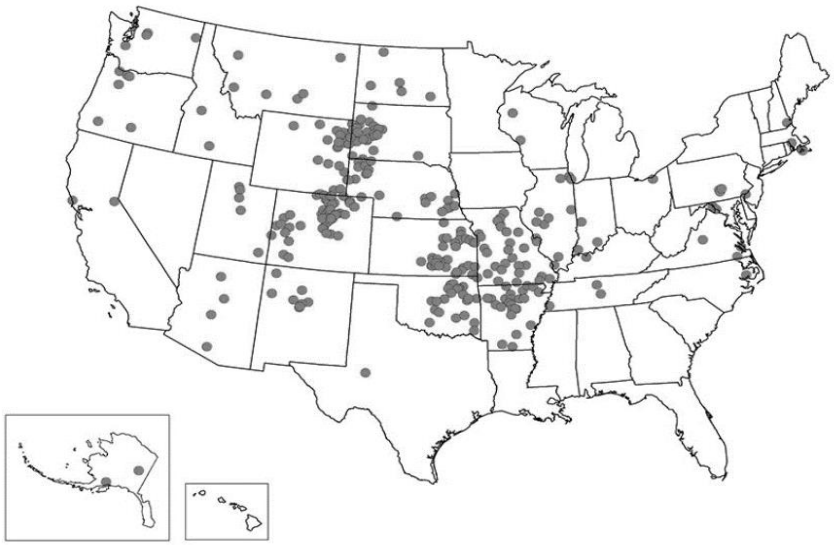

Figure 1. 1.

United States map showing tularemia cases reported in 2015. Adapted from the Centers for Disease Control and Prevention ("Arkansas Department", 2017).

A tularemia-like, hare-associated illness first described in Japan during 1818 resulted in the first reported clinical case in 1837 (Penn, 2015). In 1911, agar plates revealed a novel bacterium after a suspected plague outbreak in Tulare County, California subsequently identifying the disease tularemia (Berger, 2017; Penn, 2015). A significant epidemic occurred during World War I in Stalingrad when at least 14,000 cases reported in January of 1942 greatly influenced the health of Soviet pilots and the integrity of aircraft due to infected mice chewing through structures. In some regions, 75% of the population became affected (Croddy, 2001). Therefore, tularemia became a significant disease of national consequence (Berger, 2017; Hestvik et al., 2015).

Tularemia is endemic or possibly endemic to 48 countries and most often occurs in the northern hemisphere between 30 and 71 degrees latitude (Berger, 2017; Penn,

2015). The highest incidence occurs in Europe between the months of June and October, signifying seasonal significance (Berger, 2017). Between 1992 and 2012, 18,343 cases of tularemia reported in Europe depicted the highest percentages in Sweden (25%) and Finland (22%) and the highest incidence in Kosovo at 5.2 cases per 100,000 (Berger, 2017; Hestvik et al., 2015; Maurin & Gyuranecz, 2016). Within the United States, all states except Hawaii have documented human cases of tularemia. However, most reported cases occur within the South Central and Pacific Northwest regions as well as portions of Massachusetts as depicted in Table 1 ("Centers", 2016; Desvars-Larrive et al., 2017). Despite endemic areas within the United States, tularemia outbreaks or clustering have not been reported within the South Central region (Eisen et al., 2008; Rothfeldt, Jacobs, Wheeler, Weinstein, & Haselow, 2017).

Table 1. 1

Top 10 states with the highest incidence of tularemia between 2001 and 2010 as adapted from "Centers" (2016).

State	Number of reported cases	Incidence rate (100,000 persons per year)
South Dakota	65	0.84
Arkansas	162	0.58
Wyoming	29	0.57
Missouri	231	0.40
Nebraska	55	0.31
Oklahoma	108	0.30
Kansas	59	0.22
Montana	13	0.14
Massachusetts	84	0.13
Utah	32	0.13

Even though the number of reported tularemia cases within the United States are significantly lower than in Europe, tularemia is endemic to Arkansas ("Centers", 2016; Mani, Morton, & Clinkenbeard, 2016). One of the advantages of this study included the ability to evaluate a relatively higher number of cases as reported within Arkansas while also evaluating factors within Arkansas's diverse ecological catchment ("Arkansas Department", 2016; Eisen et al., 2008). Despite the lower number of cases as compared to areas within Europe, tularemia presentation, clinical course, and epidemiological

linkages differ necessitating the study within the catchment of Arkansas parsed within smaller regions (Eisen et al., 2008).

Problem Statement

In 2015, Arkansas reported 24 tularemia cases representing an incidence rate of 0.81 per 100,000 residents, the fifth highest among all states within the reporting system ("Centers", 2016). An Arkansas and Missouri regional analysis by Eisen et al. (2008) revealed an increased risk associated with dry forested habitats suggesting further analysis by ecoepidemiology related to county or zip codes instead of state specific incidence rates. Sporadic cases related to occupational exposure have occurred but overall a significant amount of cases within Arkansas have been associated with tick (vector) or rabbit (host) exposure (Atchley, Mudrappa, Coulter, Bradsher, & Johnson, 2015; Rothfeldt et al., 2017). Between 2005 and 2015, the total number of cases reported annually in Arkansas ranged between six and 42 ("Arkansas Department", 2017; "Centers", 2016). Seasonal variations due to climate differences representing vector life cycles or human behavior such as hunting and outdoor activities may account for monthly variation in cases but do not explain differences between years. The disproportional incidence rate over a 10-year period identifies a gap in understanding the relationship between tularemia cases, ecological factors, and suspected stagnated or mobile reservoirs within Arkansas (Desvars et al., 2015; Desvars-Larrive, et al., 2017). While Rothfeldt et al (2017) evaluated the clinical manifestations of tularemia cases within Arkansas between 2009 and 2013, results revealed a need to determine case clustering and evaluate the geospatial and spatiotemporal relationship as well as the time

to reporting of suspect or confirmed cases to public health agencies. Tularemia is a significant public health problem that has global significance as a naturally occurring infectious disease and as a potential bioterrorist threat signifying the need to comprehensively evaluate the population at-risk, environmental and climate factors, and the process and timeliness of public health reporting within Arkansas ("Arkansas Department", 2017; Caspar & Maurin, 2017; "Centers", 2016; Gopalakrishna-Remani, Brown, Shanker, & Hu, 2017).

Purpose of the Study

The purpose of this quantitative three-part study was to analyze tularemia cases by geospatial and spatiotemporal distribution, perform a cluster analysis, evaluate ecological factors of temperature, land cover, elevation, and precipitation by case distribution, and determine the process and timeliness of public health reporting of confirmed or suspected tularemia cases within Arkansas. The intent of this study was to correlate cases geospatially and spatiotemporally while analyzing contributory or relational factors. The dependent variable included the number of tularemia cases as reported to the Arkansas Department of Health ("Arkansas Department", 2017; "Centers", 2016). An ecological model integrating climate and habitat related data included relative risk of reported cases. Several studies revealed that vector and host related habitats comprise associated spatial relatability to clustering of vector-borne diseases (Desvars-Larrive et al., 2017; Eisen et al., 2008; Mailles & Vaillant, 2014; Walter et al., 2016). However, studies conducted in Texas did not find a correlation between habitat viability and case distribution of Rocky Mountain spotted fever and

Lyme disease of which both are vector-borne zoonotic diseases (Atkinson, Sarkar, Avina, Schuermann, & Williamson, 2012, 2014). By evaluating cases regionally, high-risk areas within Arkansas may be parsed from a generalized statewide area in order to provide a focus for public health funding and resources (Mackey et al., 2014; Philips, Dudik, & Schapire, 2018). By understanding climate and ecological factors related to case clustering, a predictive model may contribute to public health alerts preemptively anticipating a potential uptick while differentiating between naturally occurring cases and a potential bioterrorist event (Chen, Chughtai, & MacIntyre, 2017; Desvars-Larrive et al., 2017; Eisen et al., 2008; Mailles & Vaillant, 2014; Shacham, Nelson, Hoft, Schootman, & Garza, 2017). Thus, by performing cluster analysis and associated risk assessments, identification of at-risk populations by region provide geospatial awareness and public health focus.

Implications for Social Change

Fransciella tularensis is naturally present within some environments but tularemia cases can also be the result of an intentional biological release necessitating vigilant awareness and multifaceted preventative strategies ("Centers", 2017; Grundmann et al., 2014; Mahon & Lehman, 2019;). Collaboration between environmentalists, climatologists, entomologists, clinicians, and public health epidemiologists are necessary for prevention, management of cases, and decontamination of the environment (Dennis et al., 2001; Desvars-Larrive et al., 2017; Hestvik et al., 2015). Blackburn, Kracalik, and Fair (2016) describe the need for a well-orchestrated, systematic, and collaborative framework by using niche modeling and human and animal case recognition while

maintaining multidisciplinary cooperation. It is of utmost importance that a collaborative and cooperative approach be public policy and practice (Blackburn et al., 2016; Chen et al., 2017). This study evaluated human case data in combination with environmental and climate data that correlated information gained from multiple disciplines. The intent of this three-part study was to use a systematic interdisciplinary approach that addressed these dynamics to foster improved communication and interdisciplinary research (Bartholomew et al., 2015; Blackburn et al., 2016; Brown et al., 2015)

Another implication for social change included the need to determine occupational or behavioral risk factors. Those that work on farms and within forests as well laboratory workers have an increased risk due to occupational exposure and may be appropriate populations for focused messaging ("Centers", 2017; Rossow et al., 2014; Wiethoelter, Beltran-Alcrudo, Kock, & Mor, 2015; Wurtz et al., 2016). Exposure during environmental outbreaks due to contaminated food or water represents modifiable behavior for water gathers or seasonal hikers (Hestvik et al., 2015; Hightower et al., 2014). Within Colorado and New Mexico, public health announcements portrayed an upward trend in seasonal cases related to outdoor activities creating awareness while communicating preventive behavioral practices (Herbert, 2015; "Sante Fe", 2013; Markey, 2014). Knowledge gained from this three-part study may serve to frame public health messaging related to potential occupational or behavioral factors within Arkansas.

Background

This literature review comprises the conceptual and theoretical foundation and historical findings related to tularemia as a significant multidimensional public health

problem. Geospatial and spatiotemporal factors affecting case distribution, ecological factors related to vector-borne diseases, and the timeliness and impact of public health reporting was the focus of this three-part study. Due to the small number of cases nationally, this literature review includes data from well-documented tularemia cases, clusters, and outbreaks globally and over multiple databases and disciplines ("Arkansas Department", 2017; "Centers", 2016; Desvars-Larrive et al., 2017; Dupont et al., 2015; Hestvik et al., 2015).

Literature Search Strategy

The Walden library databases of Thoreau, ProQuest, and ScienceDirect and the National Institutes of Health (NIH) PubMed database were used for literature searches of tularemia using key terms of *tularemia, spatiotemporal, geospatial, public health reporting, surveillance, tick-borne, vector-borne,* and *reportable disease*. Multiple combinations of terms such as *surveillance* and *tularemia, geospatial* and *tularemia,* and *reportable disease* and *surveillance* narrowed focus and relevancy of the research questions. The primary sources utilized were peer-reviewed publications between 2014 and 2019. However, original research articles from historical outbreaks and significant cases necessitated understanding context and methodological thoroughness from primary publications. Websites sponsored by the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) related to tularemia were used to understand the global and national burden and collaborative perspectives as well as to define regional clusters over two or more states (e.g. "Centers", 2016, 2017; "World Health", 2018). However, within the WHO website, there were no documents,

regulations, or guidance procedures related to tularemia published after 2010 (see "World Health", 2018). The Arkansas Department of Health (ADH) website provided case definitions and unique state-specific regulations involving mandatory public health reporting of cases through 2017 (see "Arkansas Department", 2017). News reports were used to depict examples of how tularemia cases have been communicated to the public in order to gain awareness using culturally literate messaging (e.g. "Be mindful", 2015; "Market Research", 2019; "Dispatches", 2017; "Life Science", 2015; "Sante Fe", 2013; Markey, 2014). However, the framework of this three-study dissertation imparts scientific knowledge of the pathogenicity of *Fransciella tularensis* through a geospatial and spatiotemporal progression.

Causative Agent: *Fransciella tularensis*

Fransciella tularensis is a fastidious organism characterized by a difficulty to grow within a laboratory setting under normal environmental conditions but highly infectious as an aerosol once grown on agar plates (Mahon & Lehman, 2019; Wurtz et al., 2016). The morphological characteristics portray a small coccobacillus promoting phagocytosis by macrophages but the organism contains a polysaccharide-rich capsule, which evades escape from complement-mediated killing (Mahon & Lehman, 2019; Penn, 2015). *Fransciella tularensis* is always pathogenic in humans and not found as normal flora (Mahon & Lehman, 2019). However, there are no documented cases of tularemia transmitted by humans to humans (Berger, 2017; Mahon & Lehman, 2019; Penn, 2015). There are four subspecies with two causing disease in humans: subspecies *tularensis* (Type A) primarily encountered within North America and *holarctica* (Type B)

encountered in Europe (“Centers”, 2016; Desvars et al., 2015; Mailles & Vaillant, 2014). The subspecies *tularensis* causes a more severe disease and a potential bioterrorist agent prompting national and global surveillance supported by syndromic surveillance and laboratory testing (“Centers”, 2016; Desvars et al., 2015; Mailles & Vaillant, 2014; Wurtz et al., 2016).

The laboratory detection of *F. tularensis* comprises of either growing the organism on agar plates or detecting DNA within a specimen. The serological detection of antibodies using serum implies recent exposure but if paired sera is not available, a single positive antibody test cannot distinguish between recent or prior exposure (Mahon & Lehman, 2019; Nakajima et al, 2016). Tularemia case definitions have evolved based on technological improvements in laboratory detection and historical understanding of clinical presentation and confirmation of disease (“Arkansas Department”, 2016; “Centers”, 2017). Case classification is either probable or suspected (clinically compatible case with supportable laboratory results) or confirmed (clinically compatible with confirmatory laboratory results) as depicted in Table 1. 2 (“Centers”, 2017). Cases reported to the ADH by clinicians or laboratory personnel and investigated result in case categorization. Table 1.2 lists categorization of cases and cluster analysis based on historical case definitions and criteria (“Centers”, 2017).

Table 1. 2

Evolution and categorization of case definition by year ("Centers", 2017).

Year	Case Categorization	Laboratory Criteria	Epidemiological Linkage	New vs. Existing Case
2017	Ulceroglandular Glandular Oculoglandular Oropharyngeal Pneumonic Typhoidal	*Supportive* Single elevated sera in unvaccinated individual OR positive fluorescent assay or polymerase chain reaction *Confirmed* Fourfold rise in titer OR isolation of *F. tularensis*	Clinical diagnosis with history of tick or deerfly bite, exposure to *F. tularensis* by animal bite, contaminated water, or infected tissue	Diagnosis with new onset of symptoms and exposure differentiates new versus existing case
1999	Ulceroglandular Glandular Oculoglandular Oropharyngeal Intestinal Pneumonic Typhoidal	*Presumptive* Single elevated sera in unvaccinated individual OR positive fluorescent assay *Confirmed* Fourfold rise in titer OR isolation of *F. tularensis*	Exposure by clinical diagnosis supported by history of tick or deerfly bite, animal bite, contaminated water, or infected tissue	n/a
1996	Same as 1999	Same as 1999	n/a	n/a
1990	Same as 1999	*Probable* Clinically compatible case with serological titer of greater than or equal to 160 *Confirmed* Laboratory confirmation by: Fourfold rise in titer greater than or equal to two weeks apart, tested at the same time within the same laboratory, isolation in sample, or positive immunofluorescence.	n/a	n/a

Clinical and Epidemiological Manifestations

There is a wide range of clinical presentations and manifestations of individuals exposed or infected with *F. tularensis*. Tularemia may be subclinical or may exhibit a life threatening presentation within an infected individual relative to the route of infection and specific infecting species ("Centers", 2016; Desvars et al., 2015; Mailles & Vaillant, 2014; Njeru et al., 2017). This signifies the need to perform surveillance and epidemiological typing relative to severity of disease, etiology of acquisition, and transmission in order to ascertain risk factors (Hestvik et al., 2017; Maurin & Gyuranecz, 2016; Rothfeldt et al., 2017). Surveillance of tularemia requires collaboration between clinicians and epidemiologists in order to recognize cases quickly and categorize by clinical presentation to determine source of infection and public health risk ("Centers", 2017). After case recognition by clinicians, collaboration continues by means of additional expertise provided by clinical laboratory scientists using integrated diagnostic data (Mahon & Lehman, 2019; Rothfeldt et al., 2017). This three-part study included analysis of integrated data from clinical presentations and subsequent laboratory data necessary for epidemiological investigations in order to assess gaps that may potentially burden public health resources (Brown et al., 2015; Mackey et al., 2014). The iterative process of this three-part study depicts collaboration supporting case definitions during the continuum of case recognition to epidemiological investigation. Case definitions included presumptive, probable, or confirmed with modifications occurring as diagnostic tests evolved in sensitivity and specificity (see "Arkansas Department", 2017; "Centers", 2017; Mahon & Lehman, 2019; Rothfeldt et al., 2017). A presumptive case based on

clinical signs and symptoms suggestive of tularemia includes regional lymphadenopathy, influenza-like illness, fatigue, fever, chills, and myalgia ("Arkansas Department", 2017; "Centers", 2017). A confirmed case is characterized by a positive laboratory test such as a four-fold rise in serological titer after collection of two sera samples with a minimum interval of two weeks, bacterial growth of *F. tularensis*, or a positive molecular test on a biological sample ("Centers", 2017; Mahon & Lehman, 2019; Mailles & Vaillant, 2014; Rothfeldt et al., 2017). Probable cases consist of single elevations in serum samples ("Centers", 2017; Rothfeldt et al., 2017; Mailles & Vaillant, 2014). While reviewing the secondary dataset of case histories and laboratory data within this three-part study, compliance to required case categorical information determined gaps potentially identifying feedback opportunities to clinicians and laboratorians related to clinical presentation (Blackburn et al., 2016; Njeru et al., 2017; Rothfeldt et al., 2017). Within this three-part study, clinical and laboratory data considered for epidemiological review was compared to historical investigations of vector-born diseases and reportable diseases of public health risk gaging effectiveness and identifying gaps in reporting.

There are differences in clinical and epidemiological presentations of data within primary studies. Mailles and Vaillant (2014) analyzed 433 tularemia cases within France between 2002 and 2012. Annual incidence averaged 0.07 cases per 100,000 French citizens with 91% (395) occurring as sporadic cases and 9% (39) as part of 10 identifiable clusters representing differences in clinical presentation and population risk. Cases were classified based on exposure to outdoor activities (mowing, running), vectors and hosts (hares, ticks), and potential high-risk occupations (farming, forestry, laboratory)

identifying similarities of case distribution within the catchment of Arkansas (Mailles & Vaillant, 2014; Rothfeldt et al., 2017). Of the 433 cases, 70% (303) were probable cases and 30% (130) were laboratory confirmed supporting the necessity of integrating data for epidemiological analysis (Mailles & Vaillant, 2014; Rossow et al., 2014). Most cases were glandular or ulceroglandular (72%) with the remaining pneumonic (10%), oropharyngeal (6%), and oculoglandular (2%) identifying potential educational opportunities for healthcare workers related to recognition of cases (Mailles & Vaillant, 2014; Rothfeldt et al., 2017). At-risk occupations and exposures include animal, farm, forest, and laboratory exposures as well tick and mosquitoes or tabanids bites signifying focus areas for surveillance (Mailles & Vaillant, 2014; Rothfeldt et al., 2017). Males were 1.8 times more likely to acquire tularemia than females supporting increased risk among male populations (Mailles & Vaillant, 2014). Of the 10 distinctive clusters described by Mailles and Vaillant (2014) over a 10-year period, three were air borne, four were food borne, two were laboratory acquired, and the remaining cluster was an undetermined origin involving a married couple. By conducting a cluster analysis within Arkansas and determining clinical presentations and at risk populations and behaviors, communication of potential cases may increase awareness in the primary healthcare community to potentially improve case detection and promote timely epidemiological investigations (Larssen et al., 2014; Rossow et al., 2014; Rothfeldt et al., 2017). Within this complex, interplay of environment and behavior, analysis of multiple variables within different contexts support this three-part study (Brown et al., 2015).

Desvars et al (2015) conducted an epidemiological and ecological study of 4,792 tularemia cases over 29 years that occurred within Sweden. The mean incidence rate was 1.86 cases per 100,000 citizens with 58.2% of cases occurring in men. The relative risk for contracting tularemia was 1.39 times higher for males compared to females. However, the researchers omitted information related to clinical presentation, severity of disease, site of infection, and behavioral or occupational risk factors (Desvars et al., 2015). Desvars et al found that a higher prevalence in males compared to females but identified gaps in descriptive statistics and the evaluation of relational factors that this three-part study provided. Thus, completeness and accuracy of syndromic and laboratory data collected imparts a significant factor necessary for epidemiological investigations and assessment of case distribution ("Centers", 2017).

Tularemia may be underreported. Njeru et al (2017) evaluated tularemia antibodies in febrile patients presenting to two different hospitals in northeastern Kenya. Of 730 patients tested, 27 (3.7%) tested positive for *F. tularensis* antibodies despite tularemia not being considered as part of the differential diagnosis. There was no statistical difference between age groups, sex, and occupation (Njeru et al., 2017). The most common clinical presentations include lymphadenopathy, fatigue, and myalgia (Njeru et al., 2017; Rothfeldt et al., 2017). However, studies differ regarding consistency in a primary clinical presentation with differences seen nationally and regionally (see Desvars et al., 2015; Mailles et al., 2014; Maurin & Gyuranecz, 2016; Njeru et al., 2017; Rothfeldt et al., 2017). The primary focus of this three-part iterative study included environmental, behavioral, and demographic characteristics of tularemia within Arkansas

in order to assist the ADH with considerations for public health programs that are regionally relevant while identifying potential gaps in data (e.g. “Arkansas youth”, 2016; Rothfeldt et al., 2017). While there were previous reported tularemia case assessments within Arkansas, case clustering, ecological evaluation, and spatiotemporal analysis were not focus areas (Rothfeld et al., 2017; Snowden & Stovall, 2011).

Rothfeldt et al. (2017) and Snowden and Stovall (2011) evaluated tularemia cases within Arkansas to determine differences in presentation, exposure, diagnosis, treatment, sex, and age. Between 2009 and 2013, there were 284 tularemia cases reported and 138 (49%) met the probable or confirmed case definition with only 41 (30%) characterized as laboratory confirmed (Rothfeldt et al., 2017). The mean age of individuals reported as probable or confirmed cases was 47 years old (range between 1 and 83 years old) within a predominantly male population (67%; Rothfeldt et al., 2017). At-risk exposures included the following: tick, deerfly, or other fly bite (77%); lawn mowing or landscape activities (32%); hunting (13%); sick or dead animal contact (9%); soil or untreated water exposure (4%) uncooked meat ingestion (3%); and laboratory duties (1%; Rothfeldt et al., 2017). The typhoidal form was more common among older age groups while the lymphadenopathy form was more common in younger age groups (Rothfeldt et al., 2017; Snowden & Stovall, 2011). Fifty-six (42%) were hospitalized and four patients died (3%; Rothfeldt et al., 2017). Of the patients that died, two were treated with doxycycline or doxycycline and clindamycin while the other two were treated with combinations of doxycycline, vancomycin, ceftriaxone, gentamicin, and levofloxacin (Rothfeldt et al., 2017). When conducting cluster analysis and mortality rates, antibiotic treatment as well

as geospatial location may need evaluation in order to address the possible impact of mortality within Arkansas (Melchior & Neto, 2016; Rothfeldt et al., 2017). Whereas, age differences by case distribution and mortality warrant additional study. Within this three-part study, age distribution and mortality rates by cluster revealed geospatial considerations in populations at-risk while antibiotic use was not considered as a variable due to the focus on epidemiological investigation and public health risk (see "Centers", 2016, 2017; Rothfeldt et al., 2017).

Snowden and Stovall (2011) evaluated patients diagnosed with tularemia presenting to a pediatric hospital in Arkansas between 1996 and 2006. There were 30 cases with patients between 18 months and 14 years of age with most (73%) five years of age or younger and most (83%) were residents of rural areas or small towns (Snowden & Stovall, 2011). Most pediatric patients presented with ulceroglandular or glandular forms, with one patient further developing pneumonia and meningitis (Snowden & Stovall, 2011). Some antibiotic-treated patients had continuing symptoms posttreatment; however, past disease or exposure infers immune competence in immunocompentent hosts such that immunity should provide protection long term (Mahon & Lehman, 2019; Snowden & Stovall, 2011). More than 50% of patients included initial diagnoses of diseases other than tularemia supporting that tularemia may go unrecognized or result in misdiagnoses in pediatric as well as adult patients (Njeru et al., 2017; Snowden & Stovall, 2011). This three-part study included variables related to clinical presentation and mortality data by region within Arkansas while determining relational factors affecting epidemiological investigation in order to compare previous findings and

identify additional populations at risk (see Rothfeldt et al., 2017; Snowden & Stovall, 2011). It is possible that messaging to pediatricians maybe framed differently than primary care physicians caring for adult patients as clinical presentation and at-risk behaviors may be different by region (Desvars et al., 2015; Maurin & Gyuranecz, 2016; Snowden & Stovall, 2011). Differences in age-related behaviors and host and vector exposure support this three-part study approach.

Reservoirs, vectors, and hosts. Reservoirs include rabbits, as tularemia is also known as *rabbit fever*, hares, muskrats, beavers, ticks, fish, reptiles, and wild birds (Berger, 2017; Hestvik et al., 2017: Rossow et al., 2014). Domestic animals including sheep, dogs, cats, pigs, and horses are hosts but cattle appear to be resistant to the disease (Berger, 2017). Within the United States, Tamarin monkeys and orangutans, animals frequently present in zoos, have been documented as tularemia positive and two human cases of tularemia have been reported from exposure to opossums in Tasmania (Berger, 2017). Vectors include the deer fly (*Chrysops spp*.), tick, and mosquito (Berger, 2017; Maurin & Gyuranecz, 2016; Rossow et al., 2014). Vehicles and modes of infection include vector bite; direct contact of bacterium through inoculation into eye; ingestion of contaminated meat; exposure to contaminated dust, air, or water; and inhalation into the respiratory system (Berger, 2017; Maurin & Gyuranecz, 2016). However, there is no definitive reservoir characterized globally; the mode of infection within the United States appear to be by host and vector exposure (Berger, 2017; Maurin & Gyuranecz, 2016). In most regions of the United States, ticks that transmit tularemia include *Amblyoma americanum* (lonestar tick), *Dermacentor andersoni* (wood tick), and *Dermacentor*

variabilis (dog tick) and all three are endemic to Arkansas and Missouri and coincide with increased cases seen during high tick activity months between June and September ("Centers", 2017; Mani, Metcalf, & Clinkenbeard, 2015; Rothfeldt et al., 2017). However, there are no published documents related to field studies or tick counts within Arkansas.

Hightower et al (2014) analyzed field samples collected between 1941 and 2008 to determine the foci of *F. tularensis* in the Ukraine. Of 3,086 positive samples, the most common sources included arthropods (n = 2,045), mammals (n = 619), water, (n = 393) and produce (n = 29) representing an interplay between host, vector and environment and possible introduction into the food chain. The most common animal vector and host included *Dermacentor spp*. ticks (29.7%) and rodents (4.8%). Of four foci events that ranged between two and 14 years, "*nidality*" was observed, meaning that the distribution of disease and ecological characteristics in the foci areas over time were associated with forests and foothills within flood and marshlands conducive to rodents and tick habitats where farm produce and water could become contaminated (Hightower et al., 2014). Within Arkansas, there has been no documented field sample collection for direct testing of *F. tularensis* in wildlife or environmental sampling in order to assess the potential for food contamination (Rothfeldt et al., 2017; Snowden & Stovall., 2011). Therefore, indirect analysis of ecological conditions such as vegetation, humidity, and elevation was analyzed in this study to measure geospatial and spatiotemporal conditions conducive to vector and host sustainment and proliferation (see Brown, et al., 2015; Desvars et al., 2015; Jamison, Tuttle, Jensen, Bierly, & Gonser, 2015). Ecological contamination and

intentional manufacture of tularemia leads to another facet of public health concern (Dennis et al., 2001; Penn, 2015). By evaluating environmental factors conducive to the proliferation and sustainment of hosts and vectors supporting the transmission of tularemia, adjustments in surveillance points may identify opportunities for more timely recognition (Balci et al., 2014; Brown et al., 2015).

Biological warfare and laboratory exposure. *Francisella tularensis* is one of the most pathogenic and infectious bacterial agents requiring only 10 organisms to cause disease (Dennis et al., 2001; Mahon & Lehman, 2019; Penn, 2015). *F. tularensis* (Type A) was weaponized by the United States and the Soviet Union during the 1960s and manipulated to be drug resistant by Russia during the early 1990s (Berger, 2017; Dennis et al., 2001). The estimated effects of an intentional release projects 19,000 deaths in a city of 5 million while costing $5.4 billion per 100,000 exposures (Dennis et al., 2001). Symptoms may take 3-5 days postexposure and confirmation may take several more days to weeks as serology or bacterial growth of biological samples is the gold standard for case confirmation (Mahon & Lehman, 2019). This process requires time for an immune response and growth of sufficient amount of organisms for detection (Dennis et al., 2001; Mahon & Lehman, 2019; Tezer et al., 2015). In this three-part tularemia study, diagnostic laboratory testing by methodology was considered when evaluating time from case recognition to public health reporting. This process established a baseline mean time to reporting while potentially providing a feedback mechanism and baseline metric for improvement considering diagnostic test methodology and case recognition (Brown et al., 2015; Gluskin, Mavinkurve, & Varma, 2014; Kluberg et al., 2016; Revere, Hills,

Dixon, Gibson, & Grannis, 2017). As test methodology improves in both sensitivity and specificity, further analysis may reveal additional opportunities for improvement (Mahon & Lehman, 2019).

Reporting of suspect cases necessitate collaborative efforts of multiple entities within the healthcare environment ("Centers", 2017; Dennis et al., 2001; Shapiro & Schwartz, 2002; Wurtz et al., 2016). Laboratory workers should be notified in suspected cases as examination of cultures and subsequent work-up should be conducted in Biological Safety Level 3 (BSL-3) environment which is typically confined to a state public health or large reference laboratory (Dennis et al., 2001; Shapiro & Schwartz, 2002; Wurtz et al., 2016). Decontamination using an alcohol or bleach solution and the wearing of personal protective equipment (PPE) protects laboratory workers from spread of disease (Dennis et al., 2001; Mahon & Lehman, 2019). Shapiro and Schwartz (2002) described a breakdown in communication of a fatal tularemia case within Massachusetts that resulted in multiple exposures within the clinical laboratory of a hospital that prompted prophylaxis of 13 employees. The clinical staff failed to alert autopsy personnel of the suspicion of tularemia, which unnecessarily exposed individuals supporting the need for collaboration and communication (Dennis et al., 2001; Mahon & Lehman, 2019). By focusing on tularemia collaboratively, stakeholders within multiple disciplines may conduct a risk analysis at each touch point within disease recognition and transmission (see Dennis et al., 2001). In this study, case histories included exposure risk within Arkansas hospitals and health departments possibly identifying an at-risk population among total cases (see "Arkansas Department", 2016; Rothfeldt et al., 2017).

Avoidance, postexposure infection prevention, and public health response encompasses different strategies based on at-risk populations, mode of transmission, and immune competence of each individual.

Vaccination and treatment. An effective vaccine requires a protective immune response in a host or potential victim. In order for a tularemia vaccine to be effective, stimulation and protection of CD4 and CD8 T cells and cytokines such as IFN-gamma, TNF-alpha, and IL-12A pose as targets against the lipopolysaccharide (Chu et al., 2014; Oyston & Quarry, 2005). Live attenuated vaccines developed by subculturing bacterial strains repeatedly and either drying the organism or combining strains with antisera (Chu et al., 2014; Dennis et al., 2001; Oyston & Quarry, 2005). Vaccines provided within Russia serve to protect citizens living in endemic regions (Dennis et al., 2001; Oyston & Quarry, 2005). Routes of vaccine delivery have included oral administration, aerosolization, and immunization but the most widely used method is scarification (Dennis et al., 2001; Oyston & Quarry, 2005). Overall, protection has been described as "good" but not complete against typhoidal forms and incidence of ulceroglandular tularemia has not been reduced in vaccinated subjects but a lessening in severity has been described signifying lack of routine vaccination within the United States as prevention (Oyston & Quarry, 2005). Live attenuated vaccines are classified as non-approved by the United States Food and Drug Administration (USFDA) for mass immunizations due to the potential for residual virulence, adverse reactions, and inconsistencies in effectiveness and safety (Chu et al., 2014; Oyston & Quarry, 2005; Suresh et al., 2015). Chu et al (2014) evaluated a live attenuated single dose F*rancisella novicida* vaccine using two

different animal models. In both rats and cynomologus monkeys, the vaccine was fully protective in a pulmonary challenges 30-day post vaccination suggesting potential efficacy. There were no reported occurrences of side effects of the vaccine, which lends hope that a future live attenuated vaccine may be safe and effective (Chu et al., 2014). Suresh et al (2015) evaluated a killed vaccine and the protective potential of an antioxidant mutant in a secretion protein named EmrA1 and determined that the vaccine was safe and effective when aerosolized and introduced intranasally in mice when exposed to 1000 – 10,000 LD100 doses of *F. tularensis* signifying a potential use during intentional release.However bacterial clearing occurred at 14 days representing a potential delay in recovery. Therefore, during a cluster of cases or an outbreak, vaccines may not be an option for public health response (Chu et al., 2014; Oyston & Quarry, 2005; Suresh et al., 2015). Within this three-part study, assessment of populations most at risk for tularemia and determination of incidence and mortality rates by region, provided insight in order to evaluate risk versus benefit for vaccine consideration (see Dennis et al., 2001). Spatiotemporal analysis revealed relational spread of disease and factors associated with case distribution supporting public health policy development by weighing risk of disease versus benefit of vaccines geospatially (Dennis et al., 2001; Wurtz et al., 2016). Spatial considerations and risk of mortality may outweigh risk of adverse reactions in exposed individuals with predisposing factors (Dennis et al., 2001; Oyston & Quarry, 2005; Wurtz et al., 2016).

Within the United States, the use of a vaccine post exposure for laboratory workers following accidental exposure supports further study to determine efficacy

(Dennis et al., 2001). Dennis et al reports a a significant decrease in inhalation tularemia from 5.70 cases per 1,000 person-years of risk to 0.27 cases per 1,000 person-years of risk following replacement of killed vaccine by a live-attenuated vaccine in exposed individuals (Dennis et al., 2001). Whereas Schmitt et al (2012) conducted a study to determine the efficacy of a live attenuated *F. tularensis* strain related to cellular responses to cytokines by using human cells within culture media and found that human macrophages failed to illicit a proinflammatory cytokine response. These differences may reflect incomplete protection against the vaccine in human situations further supporting diversity in vaccine efficacy (Chu et al., 2014; Oyston & Quarry, 2005; Schmitt et al., 2012; Suresh et al., 2015). By evaluating mortality related to cases or clusters of tularemia, those most at-risk for death postexposure might benefit from vaccination during an intentional release (Dennis et al., 2001; Wurtz et al., 2016). There is no need for isolation or quarantine of suspect cases as there is no evidence of human-to-human transmission (Berger, 2017; "Centers", 2016). Therefore, exposed laboratory workers may continue to work and possibly be monitored more closely within the laboratory setting independent of vaccination protocols (Shapiro & Schwartz, 2002; Wurtz et al., 2016).

Prevention. Recognition between naturally occurring cases and an intentional release is the first preventative step (Chen et al., 2017; Grunow & Finke, 2002). Grunow and Finke (2002) developed a model to distinguish between naturally occurring disease outbreaks and intentional release based on 11 criteria using a three-point assessment scale and weighting factors parsed by non-conclusive and conclusive criteria. Historical

clusters and outbreaks tested the model uncovering the need to analyze ecological, biological, social, political, and clinical data within a systems approach to determine the etiology of an outbreak (Chen et al., 2017; Grunow & Finke, 2002). This three-part study includes a systems research approach to understand case distribution by complex variables involving environmental and spatial factors with behavioral and climate components collectively (see Grunow & Finke, 2002). The effects of climate and weather fluctuations impart another element to the complexity of awareness, public health notification, and epidemiological investigations (Grunow & Finke, 2002; Medlock & Leach, 2015). By benchmarking tularemia case distribution within Arkansas, differentiation between intentional release and increased cases based on fluctuations in climate potentially impart direction for prevention and control (see Grunow & Finke, 2002).

Potential Effects of Climate Change

The effects of climate change and case distribution of vector-borne diseases has been studied spatially (Hueffer, Parkinson, Gerlach, & Berner, 2013; Liang & Gong, 2017; Ogden & Lindsay, 2016; Revich, Tokarevich, & Parkinson, 2012). Case occurrence and distribution differs between vectors based on life cycles, behavioral characteristics, and species-specific metabolic adjustments to changes in climate (Ogden & Lindsay, 2016). These differences may affect the ability to survive, thrive, replicate, and transmit disease within the diverse catchment of Arkansas (Eisen et al., 2008; Ogden & Lindsay, 2016). Ticks have dependency on host density, can travel only a few meters, and are inhibited by rainfall supporting geospatial differences as depicted within the

United States (Eisen et al., 2008; Ogden & Lindsay, 2016). Dipterans such as flies and mosquitos have an increased reproduction cycle within climates of high rainfall, can travel a few miles, and are not dependent on host density signifying the necessity of studying exposure to specific host and vector as a means to understand case distribution (Ogden & Lindsay, 2016). However, ticks can seek refuge in soil litter layers during cold and wet weather that may explain case distribution primarily in rural areas implying temperature and humidity as significant factors in case distribution (Jamison et al., 2015; Ogden & Lindsay, 2016). The tick life cycle is less dependent on short-term variations in air temperature theoretically providing more stable case distribution over time provided no significant fluctuations in host (Ogden & Lindsay, 2016). This three-part iterative study included variables of land suitability, elevation, vegetation, and climate fluctuations over time as an indirect measure of habitat viability (Jamison et al., 2015; "National climatic", 2018; Ogden & Lindsay, 2016; Revich et al., 2012). The analysis of multiple complex climate factors synergistically supported "*nidality*" related to tularemia case distribution within Arkansas's catchment in order to find hot spots geospatially (see Ogden & Lindsay, 2016).

Liang and Gong (2017) conducted a review to evaluate the interplay between climate change and infectious diseases based on scientific opinions related to spatiotemporal factors of hotspots and future direction and focus as climate change occurs. Scientific opinions uncovered more uncertainty regarding differences in insect-borne infectious diseases compared to airborne, domestic zoonoses, ectoparasite zoonoses, and fecal oral diseases related to climate change supporting further analysis

(Liang & Gong, 2017). Peer reviewed publications for tickborne diseases were positive, negative, and uncertain for climate variability when predicting future associations between 1995 and 2014 (Liang & Gong, 2017). These divergent research findings reflect the need for further refined studies that include parsing factors such as socioeconomic status, land cover and usage changes over time, host movement, and differences in fluctuations by region within Arkansas (Hueffer et al., 2013; Liang & Gong, 2017; Ogden & Lindsay, 2016; Revich et al., 2012). By evaluating vector-borne diseases within a smaller region, subtle climate differences may be detected more readily and spatiotemporally when compared to case distribution within the diverse catchment of Arkansas counties (see Eisen et al., 2008). Further analysis into drastic climate changes may provide insight into effects of climate as related to differences in annual cases.

Revich et al (2012) describe climate change in the Russian Arctic as the most pronounced globally with annual average air temperatures increasing by 1.2 C between 1955 and 2000 and the upper layer of the permafrost increasing by three degrees Celsius. The Northern hemisphere permafrost exhibited a seven percent decrease in total area during the 20th century (Revich et al., 2012). At the Arctic Infectious Disease meeting in Copenhagen in 2010, scientific discussions revealed a northward shift of forest ecosystems broadening habitats conducive for infectious diseases as hosts migrate and expand (see Revich et al., 2012). Human behavior may also migrate toward these regions further introducing risk of exposure independent of climate. Serological studies conducted on animals and humans within the Soviet Union Arctic during the 1970s revealed exposure to tularemia among other infectious diseases such as leptospirosis,

brucellosis, and Q fever which included an outbreak of tularemia within a group of lemmings in 1973 (Revich et al., 2012). The authors found that tick bite exposures increased geospatially from six districts in 1999 to seventeen in 2009 with an upward migrating trend toward northern districts between 2006 and 2009 (Revich et al., 2012). Within this three-part study, history of vector and host related exposure related to case distribution provided insight into climate diversity over time geospatially related to climate fluctuations ("Centers", 2017; Hueffer et al., 2013; Revich et al., 2012).

Hueffer et al (2013) conducted a review of eight zoonotic diseases within Alaska to understand gaps in knowledge related to detection, research, prevention, and control within a shifting climate. Both *holarctica* and *tularensis* subspecies were isolated within Alaska; however, there were gaps in baseline levels of disease to determine effects of climate and potential risk over time signifying a need for benchmarked data and field studies (Hueffer et al., 2013). Gaps in field analysis exist due to cross reactivity of *F. tularensis* with other bacteria decreasing test specificity (Hueffer et al., 2013; Mahon & Lehman, 2019). This phenomenon may be a limitation within field studies as exposure to *Francisella* spp. non-tularensis may produce a false positive laboratory result decreasing test specificity falsely confirming the presence of *F. tularensis* (Hueffer et al., 2013; Mahon & Lehman, 2019). Due to this testing anomaly, reported cases were parsed into either probable or confirmed categories with corresponding laboratory diagnostic testing specific to each case geospatially (see "Centers", 2017). The method of categorizing cases based on diagnostic testing results geospatially may provide insight to unmet

diagnostic capabilities identifying opportunities to strengthen laboratory support independent of climate change (Hueffer et al., 2013; Mahon & Lehman, 2019).

Monaghan et al (2016) conducted an epidemiological and meteorological study of Lyme disease to evaluate the effect of climate change on seasonality within the United States. The authors conducted a historical analysis of cases and climate variables of gas emissions and temperature between 1992 and 2007 using secondary datasets from the National Notifiable Disease Surveillance System (NNDSS) and the North American Land Data Assimilation Systems (NALDAS) supporting diversity in annual climate (Monaghan et al., 2016). A prediction model was constructed that predicted seasonality in years 2025 to 2040 and 2065 to 2080 reflecting an overall earlier onset by 0.4 to 0.5 and 0.7 to 1.9 weeks respectively (Monaghan et al., 2016). However, changes were significantly different between states as season projections begin 3.5 weeks earlier in Virginia compared to 0.9 weeks in Maine during the 2065 to 2080 period (Monaghan et al., 2016). This prediction model supports relational evaluation between climate change and case distribution due to fluctuations geospatially in order to understand vector and host proliferation (Liang & Gong, 2017; Monaghan et al., 2016). This three-part study reflects geospatial data parsed by counties over time using datasets from NALDAS and ADH supporting reportable disease compliance geospatially using vetted datasets analyzed by climate change (see "Arkansas Department", 2016, see Monaghan et al., 2016). As climate changes, environmental conditions may change affecting host and vector habitat suggesting differences in tularemia case distribution (Balci et al., 2014; Jamison et al., 2015).

Soil moisture, periodicity of drought, humidity, and its impact on vegetation influences tickborne diseases (Jamison et al., 2015). Balci et al (2014) conducted a cross-sectional epidemiological and climate study evaluating climate variability and change during a tularemia outbreak in Kayseri Province, Turkey (Balci et al., 2014). Sporadic cases and one outbreak included 110 cases comprising an incidence rate of 8.63 per 100,000 citizens over multiple years necessitating epidemiological investigations on a case-by-case basis (Balci et al., 2014). Water, environmental, and animal samples were collected revealing contaminated water within villages following epidemiological investigation (Balci et al., 2014). Analysis of daily and annual meteorological data (humidity, rainfall, and temperature), altitude, and population associated with case distribution signifying epidemiological linkages (see Brown et al., 2015). Heavy rainfall occurred during 2009 and 2010 and resumed to average in 2011 supporting potential association of weather extremes and zoonotic diseases (Balci et al., 2014, Hueffer et al., 2013). Tularemia cases occurred in regions of high plateaus 1050 meters above sea level with clusters between December and April post rainy season and during low humidity, high temperature conditions as well as an increase in field mice occurred between 2007 and 2012 implying associations between elevation and humidity relative to host movement (Balci et al., 2014; Giles et al., 2011). Within Arkansas, reported annual case distribution fluctuated between 6 and 42 cases over a 10-year period necessitating study of differences in case distribution by year compared to climate effects (“Arkansas Department”, 2017; “Centers”, 2016).

Ryden, Sjostedt, and Johansson (2009) conducted a climate change simulation using regional climate variability and historical tularemia cases within Sweden to create a forecast model. Between 1997 and 2008, 379 cases revealed five high endemic and outbreak areas representing hotspots (Ryden et al., 2009). Historical temperature analysis and scenarios projected an average increase by two degree Celsius in monthly summer temperature between 2010 and 2100 (Ryden et al., 2009). Precipitation changes due to seasonal rains were also included in the model revealing a two-fold increase in ideal conditions for tularemia transmission even though there were only marginal changes in precipitation (Ryden et al., 2009). Models include enzootic life cycles that follow proliferation within wetlands and natural waterways that support hosts and vectors such as mosquitoes, rodents, and lagomorphs (Monaghan et al., 2016; Penn, 2015; Ryden et al., 2009). By understanding historical data and case distribution by climate variability within Arkansas, a predictive model may serve useful based on seasonal and annual weather patterns for risk awareness and disease prevention implying that small changes in climate may be associated with significant differences in case distribution of zoonotic diseases (Monaghan et al., 2016; Ryden et al., 2009).

Medlock and Leach (2015) describes the risk of vector-borne diseases as climate changes and explains possible adaptation strategies within the United Kingdom. For instance, if the annual average temperature were to increase by one degree Celsius, the expected adult mosquito activity period would increase between one to two weeks (Medlock & Leach, 2015). Furthermore, tick activity increases within urban areas after additions of green space propagating host migration, which may potentially increase

exposure to vector-borne diseases (Jamison et al., 2015). Jamison et al postulated that as the climate continues to change, zoonotic diseases might expand in range as vectors adapt and hosts travel for suitable habitat signifying the need for geospatial analysis (Jamison et al., 2015). This three-part study included analysis of case distribution geospatially and spatiotemporally by evaluating case burden within urban and rural counties with focused attention based on geographical risk and subsequent public health reporting (Jamison et al., 2015).

Public Health Surveillance and Reporting

Public reporting of infectious diseases and events affecting mortality was first described by Shattuck in 1850 with Michigan being the first state to officially mandate public reporting in 1893 (Thacker, Qualters, & Lee, 2012). Each state or territory defines public reporting policies, specific reportable diseases or conditions, and mode of communication based on public health risk (see "Arkansas Department", 2017, "Centers", 2016). Tularemia is a reportable event within Arkansas with required notification by phone call for suspected or confirmed cases ("Arkansas Department", 2017). Patient level data collected and stored based on laboratory confirmed testing is regulated by the Clinical Laboratory Amendment of 1988 (CLIA) which includes patient identification, specimen source, dates of collection and testing, test method, and testing laboratory (Castellani et al., 2015). There may be a wide range of time from clinical presentation, laboratory confirmation, and public reporting based on deviations in clinical syndrome, laboratory method, and mode of communication (Thacker et al., 2012). The CDC through the Epidemiology and Laboratory Capacity for Infectious Diseases

Cooperative Agreement supplements state funding of public reporting ("Centers", 2017). Reporting of laboratory confirmed cases for infectious diseases differs in mode of communication as in some cases 74% may be electronic for general infectious diseases while only 54% of HIV may be reported electronically (Samoff et al., 2013a;). This study evaluated the completeness and timeliness of public reporting of tularemia cases by region over time in order to benchmark and provide feedback for public policy consideration related to optimal mode of communication (see "Arkansas Department", 2017).

Accuracy, completeness, and timeliness differ by mode of communication of reportable diseases (Jakob et al., 2017; Johnson, Williams, Lee, & Bradley, 2014). Johnson et al (2014) reviewed 1,867 laboratory reports and found between 5% and 10% of electronic submissions to the Oklahoma health department contained gaps in patient demographics. However, 91% of electronically submitted reports included same day reporting compared to 87% of non-electronically submitted reports (Johnson et al., 2014). The lack of consistency and functionality within laboratory interfaces resulting from gaps in source data adds additional time for epidemiological investigations by public health personnel representing the need for additional technical resources (Johnson et al., 2014). However, Samoff et al (2013a) found that after converting from non-electronic reporting to electronic reporting within North Carolina, a four to six times decrease in return of reports due to lack of completeness was noted while case processing time improved by five days even when the total number of cases increased. Furthermore, Samoff et al (2013b) found statically significant differences in efficiencies between local health

departments based on electronic reporting status as one top performing local health unit had an average cost of $71 per case compared to a lower performing local health unit with a $124 cost per case ($p = 0.03$). By determining the accuracy and timeliness of case reporting within Arkansas, the next step in research may be to evaluate cost per case and overall operational costs by region to assess feasibility and impact of electronic reporting (see Samoff et al., 2013a, 2013b; Schumacher et al., 2017). As tularemia is a low incidence disease, cost versus benefit of laboratory interfaces and syndromic surveillance software necessitates evaluation of the burden of disease within the catchment of Arkansas (see Samoff et al., 2013a, 2013b).

The reporting of probable tularemia cases based on clinical presentation may be problematic for clinicians (Maurin & Gyuranecz, 2016; Revere et al., 2017). Revere et al (2017) found that public health professionals within an ambulatory care division in Indiana had gaps in knowledge of the reporting of public health diseases. Of 228 respondents, 86% were knowledgeable about reporting policies, 21% stated they had received training, while only 17% were knowledgeable about public reporting required policies (Revere et al., 2017). Lamb et al (2015) found that the introduction of electronic reporting decreased the time to reporting and increased efficiencies within four states per specificities listed below.

1. Iowa was able to avert the addition of staff after converting to ER during whooping cough, cryptosporidium, and *Cyclospora* outbreaks.
2. North Carolina decreased case processing by five days.

3. Kansas decreased time to public health reporting by 2.7 days as compared to facsimile.
4. California was able to interface 305 different clinical laboratories using eight different laboratory information (LIS) vendors for over 90% of laboratory reports.

The transmission of patient level data into a logical flow that pieces clinical and laboratory data is challenging as described by French's qualitative study (French, 2014). Interviews by clinical and public health professionals during the investigation of a severe acute respiratory syndrome (SARS) revealed significant gaps in source data and the perception of data dumping which negatively impacted efficiency when conducting epidemiological investigations (French, 2014). By evaluating case distribution by clinical presentation and subsequent gap analysis of tularemia case recognition in Arkansas, assessment of clinician awareness may uncover educational opportunities necessitating qualitative research through a theoretical lens (see Frankfort-Nachmias, Nachmias, & DeWaard, 2015). Lessons learned from outbreaks of other vector-borne diseases may serve as contingency models for study (Brown et al., 2015); French 2014).

Brown et al (2015) conducted a quantitative analysis of an epidemic avian influenza model that tracked and predicted spread within local government areas and subsequent transmission given optimal contact of infected hosts. The main advantage of performing surveillance and developing a multi-host surveillance model using simulations prior to disease arrival, enables public health readiness that may potentially result in resource optimization (Brown et al., 2015). A representative sample of

theoretical epidemics based on seven input parameters included clinical and subclinical stages of disease transmission based on transmission in birds and humans signifying the potential applicability of tularemia using host to vector carriage (see Brown et al., 2015). A total of 1280 simulation events with 32 sets of parameters for 40 locations evaluated chickens, backyard ducks, wild ducks, and humans as agents of transmission representing applicability within other diseases with diverse host and vector presence (Brown et al., 2015). Brown et al (2015) found that the size of the simulated epidemic was relational to number of infected animals, location of the initial cases, and time to culling operations. Multiple entry point evaluation and consideration of local and long distance surveillance are relevant with zoonotic diseases signifying relevancy of collaborative focus geospatially (Brown et al., 2015; Hightower et al., 2014). Early detection and action to control migration as represented by vector or host presence should be a critical public health priority and should not only be a function of human disease distribution (Blackburn et al., 2016; Brown et al., 2015). This three-part iterative study supported a collaborative research approach taking into account environmental factors, vector and host domains, and human case distribution fostering multiple point surveillance in order to evaluate the dynamic system contributing to case distribution (see Blackburn et al., 2016; Brown et al., 2015; Hightower et al., 2014). Timeliness may be affected by the complexities of disease recognition and global diversity in at risk populations and human behaviors based on the rapid transmission of disease within host and vector populations signifying the need for rapid disease recognition in humans (Brown et al., 2015; Hightower et al., 2014).

The differences in clinical manifestation and the lack of experience identifying tularemia by clinicians may contribute to less timely reporting of suspect cases (Njeru et al., 2017; Rothfeldt et al., 2017). Mailles and Vaillant, (2014) found the median time from clinical presentation to tularemia diagnosis was 24 days (range of 1 to 254 days) and from diagnosis to public reporting was 19 days (range of 0 to 470 days). Mailles and Vaillant found that timely recognition of clusters might not reflect timely notification of individual cases as the average days to public health notification was twice as long as the time to cluster detection (Mailles & Vaillant, 2014). Differences in disease recognition and public health notification identify a need and an opportunity to evaluate potential spatiotemporal or population differences in public health reporting within Arkansas by region and reporting entity differentiating days to recognition and public health reporting (see Mailles & Vaillant, 2014; Njeru et al., 2017; Rothfeldt et al., 2017). Understanding epidemiological linkages, spatial characteristics, and vector-borne disease transmission may provide clinicians insight into disease probability supporting more timely recognition (Brown et al., 2015; Blackburn et al., 2016).

Conceptual and Theoretical Foundation

Classical epidemiology and the application of spatial statistics constitutes the framework of this three-part study (see Blackburn et al., 2016; Snow, 1855). John Snow was one of the key contributors of epidemiological assessment by evaluating clusters of cholera (Shiode, Shiode, Rod-Thatcher, Rana, & Vinten-Johansen, 2015). Environmental considerations of water sources in which person, time, and space were key factors related to spread and disease probability (Snow, 1855). However, paper maps represented

spatial relations of cholera cases representing resource limitations when considering surveillance of infectious diseases (Shiode et al., 2015). Regional clustering can be conducted using statistical packages that can evaluate risk factors and compare case distribution within the concept of spatial epidemiology signifying relevancy in infectious disease surveillance (Blackburn et al., 2016; Kirby, Delmelle, & Eberth, 2017; Kohno et al., 2014). Spatial epidemiology implies an association between place and health within populations as contrasted to medical geography that primarily focuses on spatial patterns within context representing relevancy in vector-borne disease surveillance (Kirby et al., 2017). This three-part study included spatial statistical software within the framework of classical epidemiology to represent relationships between tularemia case distribution and ecological factors geospatially (see Blackburn et al., 2016; Snow, 1855).

Pavlovsky contributed to the early definition of spatial epidemiology in his research of "*landscape epidemiology*" (Pavlovsky, 1966). Pavlovsky's constructs centered on geographical limitations related to proximity of zoonotic diseases and associations with these differences relative to physical or biological properties supporting disease transmission by influences of vector migration and reservoirs as well as geographical prediction and risk (Pavlovsky, 1966). Pavlovsky's contributing concepts as defined by Hoare (1965) include

- Zoonotic infections are independent of man and contingent on host animals and arthropod vectors;
- Animals represent reservoirs and potential sources of human infection;

- "*Landscape epidemiology*" infers that topography, climate, vegetation, and terrain within a defined space contribute to likelihood of disease risk; and
- Parasites and their host may comprise a symbiotic relationship.

Kirby et al (2017) describe the evolution of the field of spatial epidemiology by works from Elliott, English, and Lawson. Cluster detection and geographical pattern analysis and its relation to disease incidence and mortality has progressed to studying variables relative to proximity of health aspect and well-being (Kirby et al., 2017; Qayum, Arya, Kumar, & Lynn, 2015). The focus of this three-part study included a historical perspective of the theoretical basis of spatial epidemiology combined with emerging technologies of spatial statistical software demonstrating applicability and potential reproducibility (see Hestvik et al., 2015; Larssen et al, 2014; Moinet, Decors, Mendy, Faure, & Durand, 2016).

Advancements in technology has furthered the field of spatial epidemiology as related to proximity measures, aggregation, clustering, distance adjusting, and spatial regression (Desvars-Larrive et al., 2017; Hightower et al., 2014; Rossow et al., 2014). Spatial analysis and the development of risk models rely on historical accounts of cases, vector or host data, and the ability to map or pin measurements related to some form of defined space variable (Desvars-Larrive et al., 2017; Hightower et al., 2014; Rossow et al., 2014). Within Arkansas, counties represented regional markers geospatially of documented cases (see "Arkansas Department", 2017; "Centers", 2016). Within this three-part study, historical accounts of potential risk by case using recall represented

epidemiological insights into exposure risk and behavioral factors contributing to study of association (see "Arkansas Department", 2017; "Centers", 2016).

Spatial epidemiological concepts in evaluating tularemia cases may be impacted by host and vector interactions as well as social and behavioral factors (Desvars et al., 2015; Moinet et al., 2016; Hightower et al., 2014). Residents that live or participate in activities near or among host and vector populations have a greater exposure and risk of tularemia compared to residents that have little to no exposure ("Centers", 2017; Desvars et al., 2015; Desvars-Larrive et al., 2017; Hestvik et al., 2015; Larssen et al., 2014). These risk factors may include environmental niches when evaluating vector-borne diseases (Blackburn et al., 2016). Historical perspectives include the use of a spatial epidemiology as a foundation when evaluating factors within a certain area related to a specific outcome, therefore spatial delineation may be different based on characteristics and collection methods of secondary data sources (see "Arkansas Geological", 2015; Blackburn et al., 2016; Jamison et al., 2015). Documented spatial areas studied may include one square meter as represented by relevancy of research topic and variables and availability of source data (see Jamison et al., 2015). In vector-borne diseases, zip code, county, neighborhood, state, and regional demarcations designate study regions geospatially (Kirby et al., 2017). By using spatial statistics aligned with geospatial and spatiotemporal concepts, tularemia case distribution relative to vegetation, climate, and environmental events included county demarcation based on secondary source data within this three-part study (see Atkinson et al., 2012; Atkinson et al., 2014; Blackburn et

al., 2016). Clustering served as a mapping tool geospatially and spatiotemporally characterizing risk by ecological factor (see Kirby et al., 2017).

Infectious disease cartography or mapping using geospatial technology may be approached as deterministic (primary niche of a pathogen), environmental (habitat or vegetation to support the pathogen), or geostatistical (true distribution of pathogen related to covariates) for modeling relative to at-risk populations (Kraemer et al., 2016). Geospatial tracking designates case distributions of tick-borne diseases such as Rocky Mountain spotted fever, Lyme disease, and plague relative to vector, host, and ecological factors (Abedi et al., 2018; Atkinson et al., 2012, 2014; Giles, Peterson, & Almeida, 2011). Abedi et al (2018) found that the distribution and clustering of plague cases within the Democratic Republic of Congo was associated with regions within a higher elevation, which received higher rainfall and more moderate temperatures than in lower elevations. However, Giles et al (2011) found that elevation was not a significant role in distribution of plague cases within Brazil but that case distribution included a multidimensional interplay between landscape and environment. The complex interplay between ecological factors and case occurrence supports evaluation of elevation in addition to humidity and rainfall when considering tularemia case distribution within Arkansas (see Atkinson et al., 2012, 2014; Giles et al., 2011).

Melchior and Neto (2016) conducted an epidemiological study using spatial and spatiotemporal analysis to determine malarial incidence within Acre, Brazil. The authors combined three data sets containing human cases, latitudes and longitudes, and population metrics by time to determine annual parasite incidence and case fatality rate

(Melchior & Neto, 2016). Clusters as determined by Poisson's discrete model revealed differences in incidence rates over time with one high risk cluster demonstrating significantly higher mortality rates compared to three low risk clusters within different regions supporting spatial differences in vector-borne diseases (Melchior & Neto, 2016). The authors revealed one malarial hotspot despite an overall decrease in number of cases supporting spatial analysis using a focused regional approach within Arkansas in order to determine associating factors and mortality risk geospatially (see Melchior & Neto, 2016). Studying multiple vector-borne diseases geospatially and spatiotemporally may uncover niche models appropriate for subsequent zoonotic study and geospatial risk assessment (see Blackburn et al., 2016; Melchior & Neto, 2016).

Blackburn et al (2016) conducted a review of spatiotemporal, epidemiological, and environmental patterns of anthrax, brucellosis, tularemia, and plague within Russia and the United States. Spatial mapping and identification of clusters aligned with ecological niche models conducive to tick and small mammal habitats and contaminated crops (Blackburn et al., 2016). A similar study could be beneficial as Arkansas is a farming state exhibiting ecological diversity signifying a potential risk of multiple vector-borne diseases such as Lyme, brucellosis, anthrax, and Rocky Mountain spotted fever (see "Arkansas", 2015). Research conducted related to spatial distribution of ticks compared to Lyme disease case distribution in Texas by Atkinson et al (2014) included geographical mapping of elevation, temperature, and relative humidity. The authors found low spatial concordance between habitat probability and incidence rates suggesting other factors correlated to Lyme disease case distribution (Atkinson et al., 2014). These

conflicting findings by Atkinson et al and Blackburn et al support the evaluation of tularemia case distribution within Arkansas using multiple behavioral factors relative to risk with a geospatial and environmental focus (see Atkinson et al., 2015; Blackburn et al., 2016).

Moinet et al (2016) conducted a tularemia wildlife study and evaluated tularemia cases spatiotemporally during hunting seasons within France. Post mortem, animal examination and surveillance of infectious diseases conducted by private partnerships using a veterinary laboratory network revealed significant amounts of *F. tularensis* in hares killed during hunting season (Moinet et al., 2016). Between July 2002 and June 2013, there were 693 confirmed cases of tularemia (686 hares, 4 rabbits, 2 roe deer, and 1 wild boar) with 84% occurring between October and April while peaking in January and February (Moinet et al., 2016). One high risk area and multiple elevated risk areas were noted with five clusters encompassing 127 cases with a relative risk of 2.37 and 13 secondary clusters encompassing 49 cases with a relative risk of 2.60 (Moinet et al., 2016). By evaluating tularemia cases seasonally within Arkansas in this three-part study, relevant and timely hunter's education may bring awareness to risk relational to deer hunting season (see "Arkansas youth", 2016). This three-part study included elements of climate annually and iteratively over multiple years in order to detect significant climatic events related to case distribution geospatially for focused public health policy consideration and messaging (see "Arkansas youth", 2016; Moinet et al., 2016; Jamison et al., 2015).

Jamison et al (2015) conducted a multidisciplinary review of geospatial technology and ecology of vector related diseases. The authors found that single climatic events such as increased rainfall may contribute to an outbreak of cholera or a complex event such as El Niño may contribute to multiple ecological and biodiverse changes that disrupt vector and host life cycles resulting in waxing and waning of zoonotic diseases spatially over time (Jamison et al., 2015). The growth of rubber trees, green space, and land cover diversity may also influence the spread of vector-borne diseases and outbreaks (Jamison et al., 2015). However, defining factors of scale related to microhabitat denotes further study to denote hot spots (Desvars et al., 2015; Desvars-Larrive et al., 2017; Jamison et al., 2015). This three-part study considered vegetation by case distribution and environment that may support host and vector proliferation and relational hotspots geospatially (see Desvars et al., 2015; Desvars-Larrive et al., 2017). The documentation of geospatial markers temporally necessitates accurate public health reporting of events for epidemiological investigation and risk analysis (see Desvars et al., 2015; Desvars-Larrive et al., 2017; Jamison et al., 2015; Moinet et al., 2016).

Public Health Reporting of Notifiable Diseases

Accurate and time sensitive public health reporting of notifiable infectious disease cases has been evaluated in several studies (Hoffman & Silverberg, 2018; Johnson et al., 2014; Lamb et al., 2015; Revere et al., 2017; Samoff et al., 2013a, 2013b; Troppy et al., 2014). This three-part study included individual case data for analysis of completeness and timeliness of public health reporting in order to understand data necessary for case analysis and predictive modeling (see Samoff et al., 2013a, 2013b; Troppy et al., 2014).

Using multiple studies from different vector-borne diseases contributed to the robustness of this three-part study.

Findings from Atchley et al (2015), Borde et al (2017), Desvars et al (2015), Desvars-Larrive et al (2017), Hestvik et al (2015), Mailles and Vaillant (2014), Maurin and Gyuranecz (2016), Njeru et al (2017), Rossow et al (2014), Rothfeldt et al (2017), Troppy et al (2014) and historical investigations conducted by Eisen et al (2008), Shapiro and Schwartz (2002), and Snowden and Stovall (2011) supported this three-part study. Reviews from Berger (2017), Croddy (2001), and Penn (2015) provided guidance related to the dynamics of tularemia cases and outbreaks, identified gaps in research, built research questions, and articulated significance as well as determine implications for social change. Studies of other vector-borne diseases such as Rocky Mountain spotted fever, Lyme disease, plague, and malaria were synthesized and referenced as possible method sources related to geospatial and spatiotemporal clustering, mortality, and model building (see Atkinson et al., 2012, 2014; Giles et al., 2011; Hueffer et al., 2013; Liang & Glong, 2017; Melchior & Neto, 2016; Monaghan et al., 2015; Tang et al., 2017). Peer reviewed publications evaluating the relationship between climate change, vectors and hosts contributed to understanding the diversity in annual cases (see Ogden & Lindsay, 2016; Revich et al., 2012). There was a gap in evaluating public reporting of notifiable diseases over time and by region within Arkansas (see Eisen et al., 2008; Rothfeldt et al., 2017). This study served as a benchmark using tularemia case reporting which may prompt further research evaluating other infectious diseases of public health importance

using different spatial markers by region (see Brown et al., 2015; Ogden & Lindsay, 2016).

The requirement of reporting zip code and demographic data may provide insight into mortality differences by region (see "Arkansas Department", 2017). Studies of clusters and outbreaks of vector-borne diseases have yielded differences in mortality based on demographic characteristics and spatial factors (see D'Alessandro et al., 2015; Melchior & Neto, 2016). Within Brazil, a disproportionately high mortality cluster of malaria reported within a single region, questioning the relationship to parasitic strain variances or access to health related services supports geospatial surveillance in practice (Melchior & Neto, 2016). The understanding of case distribution and mortality may provide insight on further research into spatial distribution of vector-borne diseases and access to health services. Historical tularemia clusters and outbreaks reported within the United States represent case distribution encompassing rural areas or small towns ("Centers", 2016, 2017; Eisen et al., 2008; Snowden & Stovall, 2011). One study revealed that annual mortality rates within metropolitan areas have decreased almost twice as much per year compared to nonmetropolitan areas resulting in a spatial disparity supporting the need to evaluate diseases by location (Cosby, Neaves, & Cossman, 2008). Borde et al (2017) reported that within the same region of Germany, different *F. tularensis* biovars representing significantly different potentials in pathogenicity necessitates the need to study molecular typing by region. Thus, social determinants, demographical and regional characteristics, and strain variations may all play a role in mortality (see Desvars-Larrive et al., 2017; Hestvik et al., 2015). A gap remained that

supporting systematic evaluation of geospatial factors over time and within behavioral, occupational, ecological, and climate domains as addressed in this three-part study (see Cosby et al., 2008; Desvars-Larrive et al., 2017; Hestvik et al., 2015).

Overview of the Manuscripts

The reemergence, incidence rate, and mortality rate of tularemia has been affected by multiple factors within the environment and host (Borde et al., 2017; "Centers", 2017; Eisen et al., 2008; Rothfeldt et al., 2017; Snowden & Stovall, 2011). Blackburn et al (2016) addressed the need to further expand research and explore by cooperative and collaborative approaches to surveillance, control, and eradication of zoonotic diseases by involving human and animal epidemiologists and climatologists. These multiple factors and diverse stakeholders warrant a systematic approach within a step wise manner (Blackburn et al., 2016; Eisen et al., 2008). This three-part study combined data collected from human tularemia cases reported to the ADH, ecological factors within Arkansas, and climate dynamics over time to systematically evaluate the burden of tularemia, risk factors, and time to public health reporting during the evaluation period. While this dissertation included three separate studies, the first study provided emphasis for the second and third studies by focusing on at-risk populations geospatially.

Manuscript 1

Specific problem. Arkansas had the fifth highest incidence rate of tularemia cases with 0.81 cases per 100,000 residents reported in 2015 ("Arkansas Department", 2017). Over a 10-year period, the number of annual cases of tularemia ranged between six and 42 representing a gap in understanding factors associated with case distribution

and mortality rate over time and by region ("Arkansas Department", 2017; "Centers", 2016)

Research question. What are the geospatial, spatiotemporal, and demographic characteristics of tularemia cases within Arkansas between 1995 and 2018?

Nature of study and design. This was a quantitative epidemiological study evaluating potential high-risk regions and populations (see "Centers", 2017; Mahon & Lehman, 2019). A cluster analysis was conducted and included case distribution over time within a geographical space with subsequent mortality analysis (see Desvars-Larrive, et al., 2017; Melchior & Neto, 2016).

Sources of data. Secondary data consisted of suspected cases reported by clinicians and clinical laboratories to ADH between January 1995 and December 2018 (see "Arkansas Department", 2017; "Centers", 2016; Snowden & Stovall, 2011).

Manuscript 2

Specific problem. The number and occurrence of reported cases over time within Arkansas had not been evaluated relationally to ecological factors by region conducive to host and vector "*nidality*". By evaluating annual differences and climate related variables, risk ratios may provide insights into at risk populations and relational factors (see Desvars-Larrive, et al., 2017; Eisen et al., 2008; Rothfeldt et al., 2017).

Research question. What is the relationship between ecological factors (vegetation, elevation, precipitation, temperature) and distribution of tularemia cases within Arkansas between 1995 and 2017?

Nature of study and design. This was a quantitative ecological study evaluating the relationship between tularemia case distribution and ecological factors by year (see Creswell, 2014; Melchior & Neto, 2016; Ogden & Lindsay, 2016).

Sources of data. Secondary data consisted of suspected cases reported by clinicians and clinical laboratories to ADH between January 1995 and December 2017 (see "Arkansas Department", 2017; "Centers", 2016; Snowden & Stovall, 2011). An analysis of humidity, elevation, and climate included North American Land Data Assimilation System and multiple data bases from WorldClim and PRISM Climate Group (see Atkinson et al., 2014; Desvars-Larrive, et al., 2017; Ogden & Lindsay, 2016; "Spatial distribution", 2016).

Manuscript 3

Specific problem. Timely reporting of tularemia cases may assist in differentiating naturally occurring cases versus an intentional release by bioterrorist act (Chen et al., 2017; Hightower et al., 2014). Timely detection of cases, completeness in reporting potential risk factors, and contributory elements allow timely public health promotion and preventative measures (see Herbert, 2015). Understanding these factors identifies an opportunity to benchmark timeliness of reporting and identify gaps by region or case category within Arkansas serving as improvement measurement for future studies (see Hightower et al., 2014).

Research question. What are the factors affecting timeliness and completeness of public reporting of suspect tularemia cases within Arkansas between 2009 and 2018?

Nature of study and design. This was a quantitative study evaluating time and completeness from potential case recognition to public health reporting over time (see "Arkansas Department", 2017).

Sources of data. Secondary data consisted of probable and confirmed cases reported by clinicians and clinical laboratories to ADH between January 2009 and December 2018 (see "Arkansas Department", 2017; "Centers", 2016; Snowden & Stovall, 2011).

Significance

This three-part retrospective study was an iterative and comprehensive analysis of tularemia case distribution within a 24-year period in the endemic state of Arkansas and included demographic, ecological, and behavioral factors promoting further scientific knowledge within global contexts (see Blackburn et al., 2016; Brown et al., 2015; D'Alessandro et al., 2015). Historically, there have been four global tularemia outbreaks that included more than 1,000 people within the following years: (a) Kazakhstan (1954); (b) Sweden (1966 to 1967); (c) Serbia and Montenegro (2001 to 2002); and (c) Russia (2013) with nine documented additional cases or outbreaks crossing country borders between 1971 and 2016 (Berger, 2017). Within the United States, tularemia has been a nationally notifiable disease since 1927 with updated case definitions in 1990, 1996, 1999, and 2017 as depicted in Table 1. 2. (see "Centers", 2017). The significance and complexity of evaluating the burden of tularemia cases includes the occupational risk of exposure and the threat as a biological weapon (Berger, 2017; Dennis et al., 2001). Tularemia is an occupational hazard to laboratory workers by sniffing agar plates when

grown in culture and manipulating for bacterial identification causing the creation of aerosols (see "Centers", 2017; Shapiro & Schwartz, 2002; Wurtz et al., 2016). The WHO reported in 1970 that if an intentional release of 50 kilograms of *F. tularensis* occurred over a metropolitan area of approximately 5 million people, an estimated 19,000 deaths with a total of 250,000 infected people would be expected (Dennis et al., 2001). While there has not been a documented case of intentional release of *F. tularensis*, there has been 314 naturally occurring cases within the United States in 2015 representing a 74% increase over the previous year (Adams et al., 2017). Arkansas historically has a higher than average number of cases compared to most other states as shown in Figure 1. 1 and Table 1. 2 which necessitates ongoing evaluation and drives the significance of this three-part study within contexts of financial cost, opportunities for collaborative education, and social change (see "Arkansas Department", 2017; "Centers", 2016).

Financial Considerations

The financial cost of tularemia estimates reaching $200 million globally by 2023 with an annual growth between 2017 and 2023 of 3.2% ("Market Research", 2019). Mainstream media has referenced travel to Arkansas, Missouri, and Oklahoma as an inherent risk of exposure to tick bites creating global awareness as a regional hotspot (see "Market Research", 2019). Regional business news reports have also reported increases in incidence within Colorado, Nebraska, South Dakota, and Wyoming providing regional and multidisciplinary relevancy (e.g. "Life Sciences", 2015). Press releases or mass media may negatively influence tourism creating potential financial repercussions within

Arkansas necessitating working together within one multidiscipline team for awareness and cohesive messaging (see Blackburn et al., 2016).

Collaboration and Educational Programs

Collaboration necessitates including individuals from multiple fields of study to encompass understanding the continuum corresponding to environmental, ecological, behavioral, and clinical factors associated with the public health burden of tularemia within the state of Arkansas (see Balci et al., 2014; Ogden & Lindsay, 2016; Rao et al., 2017). The ecological cycle involving the presence, replication, and transmission of *F. tularensis* includes multiple biological entities in a dynamic course supporting an integrated and collaborative systems approach (see Berger, 2017; Blackburn et al., 2016; Hightower et al., 2014; Rao et al., 2017). The Wyoming Game and Fish Department adopted a systems approach by issuing a news release that mentioned the confirmed number of human cases while alerting the public to the dangers of eating undercooked meat and drinking contaminated water ("Be mindful", 2015; Herbert, 2015; "Sante Fe", 2013). The collaborative public health team recommended using insect repellent, wearing light colored clothing, inspecting pets for ticks, avoiding sick wildlife, refraining from drinking unpurified water, wearing gloves when cleaning animal hides, and cooking meat thoroughly signifying integrated and cohesive messaging ("Be mindful", 2015). The present three-part study includes findings that may potentially benefit a collaborative public health communication approach by focusing on factors related to modifiable behavior within populations at risk of exposure (see "Centers" 2016, 2017). Additionally, public health epidemiologists require data conducive to conducting

effective investigations and related case confirmation in order to assess risk (see "Arkansas Department", 2016; "Centers", 2016, 2017).

After case confirmation, public health officials may incorporate seasonal public announcements and statements related to behaviors of increased risk geospatially (e.g. "Be mindful", 2015; Herbert, 2015; "Sante Fe", 2013). The Colorado Department of Health released a statement acknowledging a human case and offered advice on how to prevent transmission in a culturally appropriate manner using health literacy signifying single case significance and protective behaviors (see Herbert, 2015). The wearing of gloves and shoes and the wearing of dust masks during mowing as well as the practice of good hand washing was encouraged (Herbert, 2015). The Sante Fe New Mexican news source provided a statement related to a confirmed case in a publication brief to inform the public and increase seasonal awareness ("Sante Fe", 2013). Another approach is to impart creativity and entertainment in educating the public. The Blade of Toledo, Ohio mentioned "*Dracula*" while explaining the risk of tick to blood transfer and the increased risk of vector-borne infectious diseases (Markey, 2014). However, public health warnings necessitate balance when portraying the advantages of healthy summer time activities such as camping, hiking, and playing with pets while educating the public on risk of vector-borne disease in order to promote physical activity (see Markey, 2014). The CDC provided national perspectives as during the 66th Annual Epidemic Intelligence Service (EIS) conference held in Atlanta in April of 2017, which recognized tularemia as an emerging disease representing a migration of human cases northward over the previous 50 years signifying geospatial awareness and evaluation of risk (see

"Dispatches", 2017). With the collaborative and iterative framework used within this three-part study, guidance from the CDC and ADH may provide messaging opportunities from multiple scientific communities in a cohesive format using focused education geospatially (see "Arkansas Department", 2016; "Centers", 2017).

Within Arkansas, hunter education could be a focus for those at risk of exposure coinciding with potential risk of disease (see "Arkansas youth", 2016; "Centers", 2017). By understanding the relationship between tick and deer populations and weather patterns relative to tularemia risk, opportunities exist for modification of deer hunting season for vector control (Mailles & Vaillant, 2014). Consideration of combining public health messaging related to protection against ticks and gun safety during hunting season supports understanding at-risk populations (see "Arkansas youth", 2016). Another opportunity for collaborative education lies within the medical community. The risk of tularemia within a laboratory setting involves creating a biological hazard assessment and plan to decrease the risk of exposure (Shapiro & Schwartz, 2002). This three-part study included assessment of behaviors and occupational hazards related to tularemia case distribution over time within Arkansas for the potential to use focused public health awareness programs collaboratively driving social change (see "Be mindful", 2015; Herbert, 2015; "Sante Fe", 2013).

Social Change

When considering social change, direct stakeholders include those that develop tularemia, become sick, and enter the healthcare system as well as those at risk of contracting tularemia within the clinical or public health laboratory ("Centers", 2017;

Shapiro & Schwartz, 2002). Tularemia is not transmitted person-to-person but can be a significant threat to laboratory workers (Mahon & Lehman, 2019; Penn, 2015; Shapiro & Schwartz, 2002). Therefore, additional personal protective equipment (PPE) is necessary when working within the laboratory signifying the need for industrial awareness and for focused education and training (Wurtz et al., 2016). Decreasing the incidence of tularemia will decrease exposure to laboratory workers as one potential preventative measure (Mahon & Lehman, 2019). Indirect stakeholders include individuals affected by economic downstream effects of land use for hunting purposes within endemic areas suggesting balanced public health messaging campaigns (see Das & Rainey, 2010; "Sante Fe", 2013). This three-part study included relational analysis of environmental factors and modifiable behaviors within public health context that may provide identification of at risk populations and downstream financial and tourism effects identifying opportunities for appropriate public health messaging (see Das & Rainey, 2010; "Sante Fe", 2013).

Analysis of historical outbreaks reveal potential at risk behaviors and ecological factors necessitating geospatial analysis and multifaceted investigation of case distribution (Berger, 2017). The four most notable global outbreaks occurred within Kazakhstan, Sweden, Serbia, Montenegro, and Russia with an average of 1763 infected (Berger, 2017). Maurin and Gyuranecz (2016) describe two different lifecycles of *F. tularensis* subspecies *holarctica* termed aquatic and terrestrial; aquatic sources of infection are more commonly associated with large outbreaks by consumption of contaminated water, which presents as oropharyngeal tularemia. The land-based form is

associated with ticks, rodents, and lagomorphs (Berger, 2017; Maurin & Gyuranecz, 2016). Epidemiological investigations are critical to determining sentinel cases and how to stop transmission based on infecting source (Berger, 2017; Mahon & Lehman, 2019). This may require a behavior change such obtaining water from different sources when water sources become contaminated or hunting in different areas if a region is determined to be a hot zone (Rossow et al., 2014). The complexity of tularemia transmission and disease requires collaboration with individuals within multiple different fields of study such as veterinary medicine, climatology, and epidemiology in order to stop the cycle of transmission (Hestvik et al., 2014). The knowledge gained in this three-part study may explain the fluctuation in the number of cases and provide a possible model to differentiate naturally occurring cases versus intentional release of *F. tularensis* by a bioterrorist act (see Chen et al., 2017). Furthermore, by understanding factors related to seasonality and annual differences, preventative programs may be constructed preemptively based on precipitating climate related events or outdoor activities by at risk populations (see Desvars-Larrive et al., 2017; Hestvik et al., 2015; Larssen et al., 2014).

Summary

This quantitative epidemiological three-part study included the distribution of tularemia cases identifying high-risk regions and populations, the relationship between tularemia clusters, cases and ecological factors of vegetation, elevation and humidity by year, and time from laboratory result identifying a probable or confirmed tularemia case to public health reporting by notification method over time ("Centers", 2017; Mahon & Lehman, 2019). Evaluation of case distribution of tularemia within Arkansas and the

relationship of climate and ecological factors spatially over time as well as the dynamics of public health reporting of cases for collaboration supports efforts to diminish the burden of disease (see “Centers”, 2017; Eisen et al., 2008; Rothfeldt et al., 2017). While there has been regional, national, and global data related to all these factors, there has been no documented peer review study using a step wise approach of secondary data over multiple years. The wide range of incidence rates over the 24-year study period and the risk to public health supports the need to understand the interplay between vector and host factors, vegetation, climate, and human behavior (see Desvars-Larrive, et al., 2017; Rothfeldt et al., 2017). Understanding may potentially increase awareness and collaboration between animal vector epidemiologists, climatologists, and infectious disease epidemiologists to work together in tularemia control while potentially influencing social change (see Sedda et al., 2014). Part 2 includes the three separate studies for publication specific to each journal requirement.

Part 2: Manuscripts

Spatiotemporal Analysis of Tularemia: Evaluation of Clusters and Risk

Toni Beavers

Walden University

Outlet for Manuscript

The target journal for this manuscript is *Epidemiology and Infection* located within URL https://www.cambridge.org/core/journals/epidemiology-and-infection#. This journal aligns with the content of my three-study dissertation, as tularemia is a zoonotic disease that encompasses collaborative efforts from ecological, veterinary, clinical and public health entities in a multidisciplinary investigative format. The journal emphasizes primary research in the epidemiology, infection prevention, and control of global diseases using novel technology with emerging infectious diseases relevant to public health interventions. Within this study, novel scanning statistical software using Poisson distribution reflected unrecognized clusters by current public health statistical methods. The formatting expectation aligns with the International Committee of Medical Journal Editors Uniform Requirements for Manuscripts submitted for biomedical journals allowing flexibility in reference style. This manuscript has been reviewed with required edits completed yet not submitted for consideration of publication.

Abstract

Tularemia is a global zoonotic disease with differing incidence rates by region. Within North America, tularemia is predominantly associated as single cases regionally focused by seasonal exposure to vectors or hosts. In this study, within the endemic state of Arkansas, case distribution was evaluated geospatially and spatiotemporally. Between 1995 and 2018, 598 cases revealed an annual upward trend. Two clusters were unexpectedly identified using spatial scanning statistical software signifying a high-risk region in 24 of the 75 counties within Arkansas over an 8-year period (RR = 4.98, $p < 0.05$) while a low-risk cluster included 28 counties within a 12-year period (RR = 0.14, $p < 0.05$). Of the cases that were classified, most were typhoidal (28.1%) followed by glandular (17.0%), and ulceroglandular (15.8%) with less than 10%t comprising ulceroglandular, intestinal, pneumonic, oropharyngeal, and oculoglandular forms. This retrospective study and detailed statistical analysis represents focused areas of risk and may serve as a benchmark and reproducible method for prospective investigations to detect active clusters. By identifying endemic and high-risk counties within Arkansas, these regions may serve as concentrated focus areas for intervention.

Introduction

Tularemia is a zoonotic disease caused by the bacterium *Fransciella tularensis* and affects humans by exposure to vectors or hosts through multiple routes (Berger, 2017; Mahon & Lehman, 2019; Penn, 2015). There are four subspecies with two causing human disease (Berger, 2017; Penn, 2015). Type A, *Fransciella tularensis tularensis*, found predominantly in North America, is historically associated with single cases while Type B, *Fransciella tularensis holarctica* predominantly found in Europe, is associated with clusters and outbreaks (Berger, 2017; Penn, 2015). The subspecies *tularensis* causes a more severe disease and therefore a potential bioterrorist agent prompting national and global surveillance ("Centers", 2017; Desvars et al., 2015; Mailles & Vaillant, 2014; Penn, 2015; Wurtz et al., 2016). *Fransciella tularensis* is a fastidious organism characterized by a difficulty to grow within a laboratory setting under normal environmental conditions but highly infectious as an aerosol once grown on agar plates (Mahon & Lehman, 2019; Wurtz et al., 2016). The morphological characteristics are defined as a small coccobacillus which promotes phagocytosis by macrophages, but the organism contains a polysaccharide-rich capsule which evades escape from complement mediated killing contributing to the difficulty in efficacious vaccines (Chu et al., 2014; Mahon & Lehman, 2019; Oyston & Quarry, 2005; Penn, 2015; Schmitt et al., 2012; Suresh et al., 2015). *Fransciella tularensis* is highly pathogenic in humans and not found as normal flora (Mahon & Lehman, 2019; Penn, 2015). However, tularemia is not transmitted by humans to humans (Berger, 2017; Mahon & Lehman, 2019; Penn, 2015). Therefore, epidemiological investigation of suspect cases includes spatiotemporal and

geospatial evaluation of case distribution when gaging public health risk (“Centers”, 2016, 2017; Desvars et al., 2015; Desvars-Larrive et al., 2017).

Tularemia is also known as *rabbit fever* as rabbits are a significant host within the United States but muskrats, beavers, ticks, fish, reptiles, sheep, dogs, cats, pigs, horses, and wild birds can also host (Berger, 2017; Hestvik et al., 2017: Rossow et al., 2014). Vectors include the deer fly (*Chrysops spp*.), ticks, and mosquitoes with associations based on ecological factors (Berger, 2017; Maurin & Gyuranecz, 2016; Rossow et al., 2014). The vehicle and mode of infection is by bite; direct contact of bacterium; ingestion of contaminated meat; inoculation into eye; exposure to contaminated dust, air, or water; or inhalation into the respiratory system (Berger, 2017; Maurin & Gyuranecz, 2016). However, there is no definitive reservoir characterized globally (Berger, 2017; Maurin & Gyuranecz, 2016). Within the United States, ticks that transmit tularemia include *Amblyoma americanum* (lonestar tick), *Dermacentor andersoni* (wood tick), and *Dermacentor variabilis* (dog tick) and all three are endemic to Arkansas and Missouri and coincide with increased cases seen during high tick activity months between June and September (“Centers”, 2016, 2017; Rothfeldt, Jacobs, Wheeler, Weinstein, & Haselow, 2017).

While tularemia is found globally, there are regional hot spots that appear to be seasonally dynamic while differing significantly in severity (Desvars et al., 2015; Desvars-Larrive et al., 2017; Hestvik et al., 2015; Hightower et al., 2014; Larssen, Bergh, Heier, Vold, & Afset, 2014). Tularemia is endemic or possibly endemic to 48 countries, most often occurring in the northern hemisphere between 30 and 71 degrees latitude, with

the highest incidence found in Europe between the months of June and October (Berger, 2017). Between 1992 and 2012, 18,343 cases of tularemia were reported in Europe with the highest percentages in Sweden (25%) and Finland (22%) and the highest incidence in Kosovo at 5.2 cases per 100,000 (Berger, 2017; Hestvik et al., 2015; Maurin & Gyuranecz, 2016). Within the United States, tularemia has been reported from all 50 states except for Hawaii ("Centers", 2016). However, cases are more commonly found in the South Central and Pacific Northwest regions as well as portions of Massachusetts as depicted in Table 2.1 ("Centers", 2016; Desvars-Larrive et al., 2017). Even though the number of reported tularemia cases within the United States are significantly lower than in Europe, tularemia is endemic to certain states (Berger, 2017; "Centers", 2016; Eisen et al., 2008; Rothfeldt et al., 2017). Within Arkansas, tularemia remains a significant health risk post host and vector exposure ("Centers", 2016; Eisen et al., 2008; Rothfeldt et al., 2017). One of the advantages of this study included the ability to evaluate a relatively higher number of cases as reported in Arkansas while also evaluating risk factors within Arkansas's diverse catchment by county over time (see Desvars-Larrive et al., 2017; Eisen et al., 2008; Rossow et al., 2014; Rothfeldt et al., 2017).

Table 2. 1

Top 10 states with the highest incidence of tularemia between 2001 and 2010 as adapted from "Centers" (2016).

State	Number of reported cases	Incidence rate (100,000 persons per year)
South Dakota	65	0.84
Arkansas	162	0.58
Wyoming	29	0.57
Missouri	231	0.40
Nebraska	55	0.31
Oklahoma	108	0.30
Kansas	59	0.22
Montana	13	0.14
Massachusetts	84	0.13
Utah	32	0.13

In 2015, Arkansas reported 24 tularemia cases representing an incidence rate of 0.81 per 100,000 residents and the fifth highest among all states within the reporting system ("Centers", 2016). An Arkansas and Missouri regional analysis revealed an increased risk associated with dry forested habitats that may best be analyzed by ecoepidemiology related to county or zip codes instead of state specific incidence rates (Eisen et al., 2008). Sporadic cases related to occupational exposure have occurred but overall a significant amount of cases within Arkansas have been associated with tick or rabbit exposure (Atchley, Mudrappa, Coulter, Bradsher, & Johnson, 2015; Rothfeldt et

al., 2017). Between 2005 and 2015, the total number of cases reported annually in Arkansas ranged between six and 42 ("Arkansas Department", 2017; "Centers", 2016). Seasonal variations due to climate differences representing vector life cycles or human behavior such as hunting and outdoor activities may account for monthly variation in cases but does not explain differences between years ("Arkansas Department", 2017; "Centers", 2016). The disproportional incidence rate over an 11-year period identifies a gap in understanding the relationship between tularemia cases and demographic data, exposure history, clinical form, and severity of disease ("Centers", 2016; Desvars et al., 2015; Desvars-Larrive, et al., 2017; Rothfeldt et al., 2017). Clinical manifestations of tularemia within Arkansas between 2009 and 2013 revealed a predominately typhoidal form with 41% of patients requiring hospitalization and 3% mortality rate, demonstrating a need to determine case clustering while evaluating geospatial and spatiotemporal relationships and associated risks (Desvars-Larrive et al., 2017; Qayum, Arya, Kumar, & Lynn, 2015; Rothfeldt et al., 2017).

The aim of this study was to conduct a spatiotemporal analysis of tularemia cases within Arkansas to determine risk over time by county using spatial scan statistics and then evaluate demographic and potential at-risk behaviors and variables (see "Arkansas Department", 2017; "Centers", 2016; D'alessandro, Napoli, Nusca, Bella, & Funari, 2015; Desvars-Larrive et al., 2017; Qayum et al., 2015). The intent was to determine if clusters or hot spots exist which might warrant prospective analysis and risk modeling (see Desvars-Larrive et al., 2017).

Methods

The methods section outlines study participants, sampling strategy, case identification processes, sources of data, instrumentation, design, and analysis plan.

Catchment Area and Tularemia Case Data

The catchment area included the tularemia endemic state of Arkansas within the United States ("Arkansas Department", 2017; "Centers", 2016). Human tularemia cases reported between January 1995 and December 2018 were obtained from the Arkansas Department of Health (ADH) retrospectively ("Arkansas Department", 2017; "Centers", 2016). During the 24 year evaluation period, two different data collection forms were used; the tularemia case report document was created specifically for use within Arkansas and used between 1995 and 2008 while an updated form developed by the Centers for Disease Control and Prevention (CDC) for national use implemented in 2009 ("Arkansas Department", 2017; "Centers", 2016). The dataset collected between 1995 and 2008 included demographic data as well as clinical presentation, outcome, and case category (confirmed or probable) defined by county and zip code ("Arkansas Department", 2017; "Centers", 2016; Rothfeldt et al., 2017). The dataset collected between 2009 and 2018 included additional elements of occupation, potential risk factors, laboratory results, clinical data, as well as epidemiologic investigation results ("Arkansas Department", 2017; "Centers", 2016; Rothfeldt et al., 2017).

Population Data

At-risk population data consisted of residents of Arkansas during the study period totaling approximately three million as of July 2017 within 52,035 square miles

(Desvars-Larrive, 2017; “United States”, 2017). Of the 75 counties within Arkansas, demographic data characterized 79.4% White, 15.7% Black or African American, 7.3% Hispanic, 1.6%Asian, and 1% American Indian or Alaska Native while 2% reported two or more races. Females represented 50.9% while the age range included 6.4% younger than five, 23.6% younger than 18, and 16.3% over 65 years of age (“United States”, 2017). Population density within Arkansas by county included the 2010 United States Census Bureau data (USCB) from the United States Department of Commerce (“Population density”, 2018; “United States”, 2017).

Variables related to Tularemia Risk

Individual case data analyzed included demographic (age, sex, race, ethnicity), risk factors (occupational, exposure history), case category (confirmed or probable), and severity (mortality or no mortality) by county over time as depicted in Figure 2.1 (“Arkansas Department”, 2017; Desvars et al., 2015; Desvars-Larrive, 2017; Hestvik et al., 2015; Hestvik et al., 2017; Larssen et al., 2014; Rossow et al., 2014; Rothfeldt et al., 2017;). The determination of case category was categorized by testing methodology and included serology, culture confirmation (CC), polymerase chain reaction (PCR), and direct fluorescent tests (DFA) laboratory methods (Hestvik et al., 2017; Mahon & Lehman, 2019). Clusters and trends were determined, and incidence rate assessed spatiotemporally (Desvars-Larrive et al., 2017; Hestvik et al., 2017). The interplay of diverse demographic variables and evolving diagnostic analytics contributes to the complexity of case distribution (Desvars-Larrive et al., 2015). Epidemiological

investigation and subsequent case categorization relies on clinical presentation, laboratory results, and demographic data in order to assess risk ("Centers", 2016, 2017).

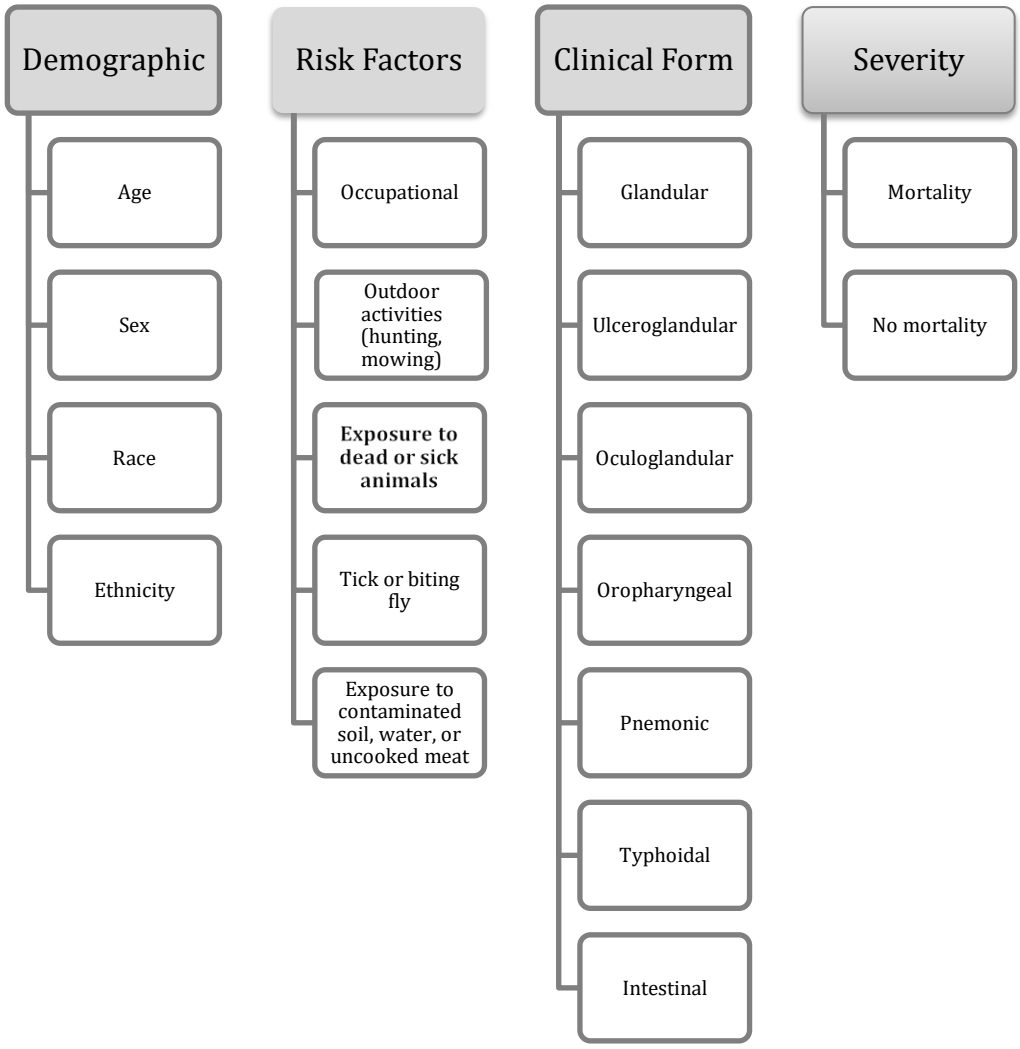

Figure 2. 1. Categorization of independent variables analyzed as related to human tularemia case distribution within Arkansas.

Instrumentation

SatScan v. 9.6 (Kulldorff and Information Management Services, Inc) was used to analyze discrete data elements spatiotemporally to detect clusters and determine

statistical differences between clusters (Desvars-Larrive et al., 2017; Kirby et al., 2016; Kulldorf, 2001). SatScan was developed by Kulldorff as a surveillance tool and has the flexibility to scan multiple data sets simultaneously to evaluate distribution of cases (Kirby et al., 2016; Kulldorf, 2001). The advantage to using SatScan is the ability to evaluate clustering when low numbers of cases are present in a heterogeneous population in order to determine regions of high and low risk while testing significance using Monte Carlo simulations (Desvars-Larrive et al., 2017; Kirby et al., 2016). With the assumption of a Poisson distribution, I analyzed covariants, trends, and missing data (see Kirby et al., 2016; Kulldorf, 2001). Statistical Package for the Social Sciences (SPSS) v. 24 (IBM, Chicago, IL) was used to descriptively analyze and depict demographic data, exposure history, case category, clinical form, laboratory data, and probable transmission mode (Green & Salkind, 2014; Larssen et al., 2014).

Design and Analysis

This quantitative design incorporated a retrospective analysis of tularemia cases over time to determine trends, peaks, and clusters within Arkansas as depicted in Figure 2.2 (see Tang et al., 2017). Regional incidence rates were determined by county (see Desvars-Larrive, 2017; "Population density", 2018; "United States", 2017). Spatiotemporal analysis using SatScan technology, according to Kulldorff's scanning statistic using a Poisson-based model, consisted of aggregating data by county by month (see Desvars-Larrive et al., 2017; Kirby et al., 2016; Kulldorf, 2001; Tang et al., 2017). Determination of clusters over time used circular shapes with a constant risk (Kulldorff et al., 1998; Tang et al., 2017). A spatial window with a maximum spatial and temporal

cluster size of 50% of the population at risk centered within each county by month and year (Desvars-Larrive et al., 2017; Kulldorff et al., 1998; Melchior & Neto, 2016; Tang et al., 2017). By limiting the testing window to 50% of the population at-risk and 50% of the geographical region, the risk of falsely decreasing the risk outside the window diminishes (Kulldorff et al., 1998). Internal and external to each circle, cases were evaluated for clustering related to the constant with significance being evaluated using 999 Monte Carlo simulation repetitions at an alpha level of 0.05 (Desvars-Larrive et al., 2017; Kulldorff et al., 1998; Tang et al., 2017). The purpose of using simulation repetitions was to increase the statistical robustness due to small numbers of cases within this study (see Green & Salkind, 2014).

For each change in space and time within the circular window, the log likelihood ratio (LLR) was calculated and the highest LLR within an area deemed a cluster (see Desvars-Larrive et al., 2017; Melchior & Neto, 2016; Tang et al., 2017). The relative risk (RR) reference was calculated as the estimated risk outside of the cluster as represented by observed divided by expected (see Green & Salkind, 2014; Tang et al., 2017).

Both high and low clusters were considered relative to statewide incidence rates. Due to the low number of cases within a cluster, descriptive statistics was analyzed by variable.

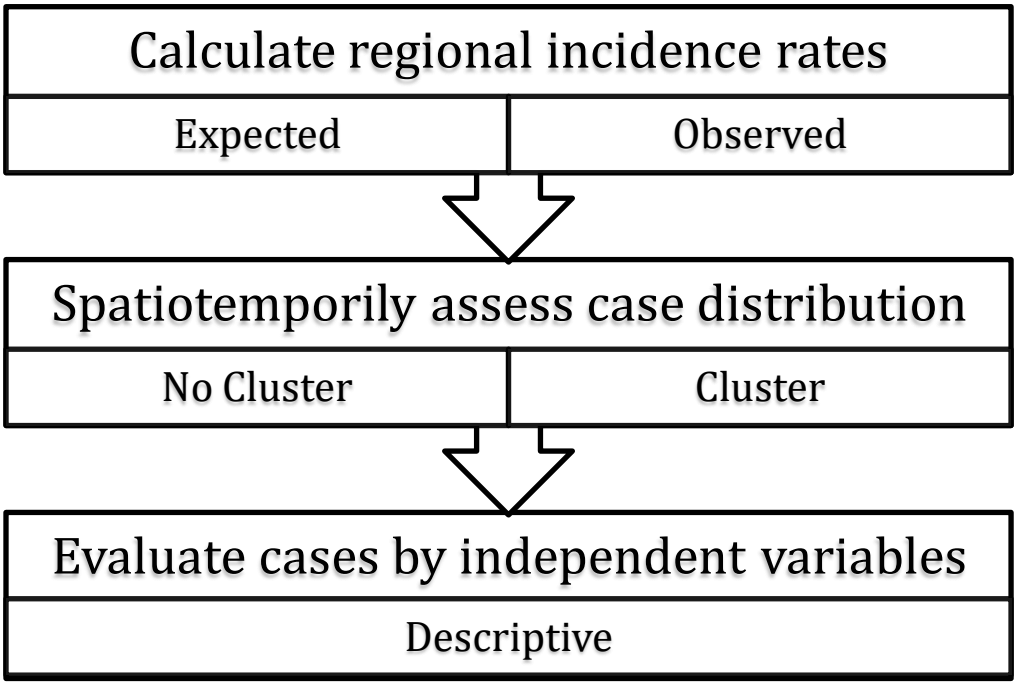

Figure 2. 2. Process depiction determining human tularemia case distribution and association of variables within Arkansas.

Ethical Considerations

This study was approved by the Scientific Advisory Committee within the Arkansas Department of Health and the Institutional Review Board of Walden University (approval # = 01-17-19-0141122).

Results

Within the study period between 1995 and 2018, there were 598 confirmed and probable tularemia cases reported and investigated within Arkansas representing an annual incidence rate of 0.9 cases per 100,000 residents. Figure 2.3 represents the total number of cases by year with a range between six (2006) and 56 (2018). Demographic

data analyzed for the entire study period revealed gaps in variable-related data that limited further analysis to cases between 2009 and 2018.

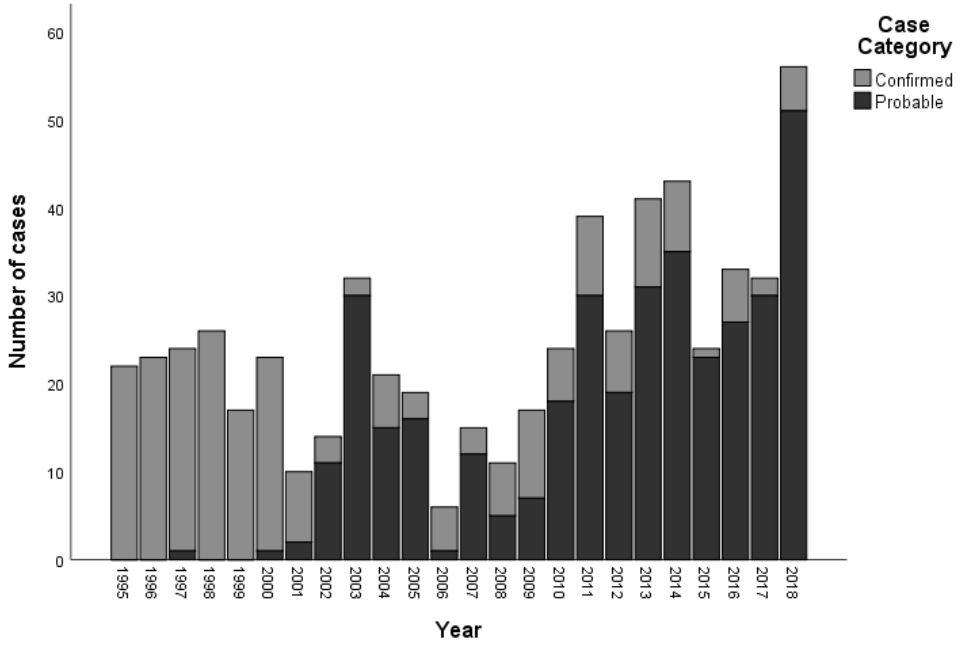

Figure 2.3. Number of confirmed and probable cases of tularemia within Arkansas by year, 1995-2018 (*n* =598)

Spatiotemporal Analysis

Calculations were conducted using SatScan v. 9.6 using 999 Monte Carlo replications that took 10 minutes on an Intel® Core (TM) i5-2467M CPU at 1.60GHz 64-bit operating system. Over the 24-year study period, two statistically significant clusters were detected (p <0 .01), one high-risk and one low-risk as represented in Figure 2.4. The high-risk cluster occurred between May 1, 2010 and October 31, 2018 and included 24 counties with a total resident population of 660,234 comprising 23% of the total population within Arkansas. Table 2.2 depicts data analyzed by county related to latitude, longitude, and resulting incidence rate within the high-risk cluster. The overall

relative risk (RR) was 4.98 within the cluster with an observed number of cases of 181 compared to an expected number of cases of 48 ($p < 0.01$). Stone county had the highest incidence rate during the 8.5-year period with 105 cases per 100,000 residents represented in Table 2.2. The low-risk cluster occurred between September 1, 2000 and August 31, 2012 and included 28 counties with a total population of 727,815 comprising 25% of the total population with expected and observed number of cases of 75 and 12, respectively depicting a RR of 0.14 ($p < 0.01$).

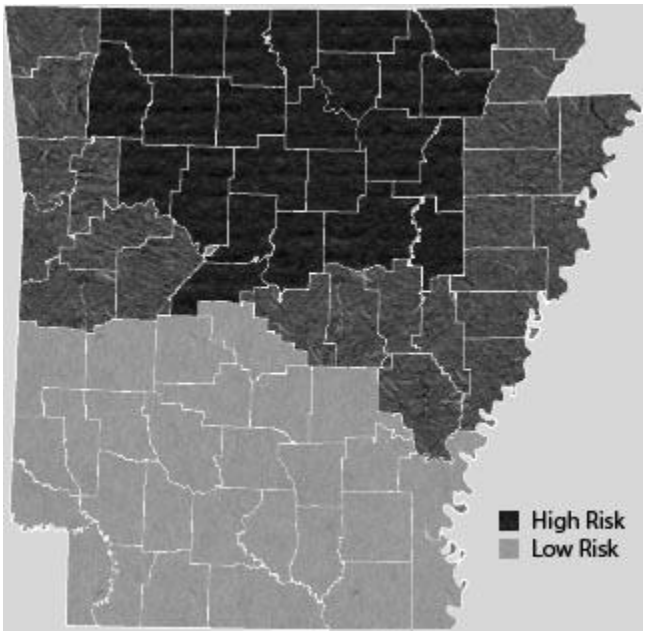

Figure 2.4. Geographical locations of high-risk and low-risk clusters of tularemia cases within Arkansas detected during spatiotemporal analysis.

Table 2. 2

Population and coordinates of high-risk cluster identified between May 1, 2010 and October 31, 2018 and corresponding incidence rate by county.

County	Latitude	Longitude	2010 Census Population	Number of Cases	Incidence rate during study period (100,000 persons during 8.5 years)
Baxter	36.3122	-92.3543	41,513	15	36
Boone	36.2852	-93.0659	36,903	4	11
Carroll	36.3641	-93.5660	27,446	2	7
Cleburne	35.5352	-92.0609	25,970	6	23
Conway	35.2077	-92.7140	21,273	9	42
Faulkner	35.1195	-92.3799	113,237	24	21
Franklin	35.4776	-93.8845	18,125	2	11
Fulton	36.3550	-91.7293	12,245	5	41
Independence	35.7575	-91.5870	36,647	8	22
Izard	36.1395	-91.8750	13,696	9	66
Jackson	35.6133	-91.2276	17,997	0	0
Johnson	35.4987	-93.4846	25,540	4	16
Lawrence	36.0706	-91.0712	17,415	6	38
Madison	36.0311	-93.7305	15,717	6	38
Marion	36.2913	-92.6814	16,653	7	42
Newton	35.9678	-93.1885	8,330	2	24
Perry	34.9827	-92.8616	10,445	2	19
Pope	35.3305	-93.0844	61,754	8	13
Randolph	36.3155	-90.9889	17,969	7	39
Searcy	35.9210	-92.6883	8,195	4	49
Sharp	36.1901	-91.4985	17,264	11	64
Stone	35.8741	-92.1699	12,394	13	105
Van Buren	35.5658	-92.4142	17,295	6	35
Washington	36.0514	-94.1987	203,065	26	13
White	35.2501	-91.7306	77,076	18	23

Descriptive Statistics

Between 1995 and 2018, a comparison of demographic data between high-risk and low-risk clusters represented showed differences of over 25 years in average age (Table 2.3). Race, ethnicity, and mortality are categorized within high-risk, low-risk, and total number of cases with a predominance of high-risk cases being male (67.4%), White (85.1%), and non-Hispanic (93.4%).

Table 2.3.

Characteristics of tularemia cases by high and low-risk cluster and total number of cases between 1995 and 2018.

Characteristic*	**High-risk (*n* = 181)**	**Low-risk (*n* = 12)**	**Total number of cases (*n* = 598)**
Age, years, mean (range, *SD*)	48 (1-83, 21.9)	22 (3-69, 21.0)	42 (1-91, 23.6)
Sex, % male	67.4	66.7	68
Race, % (category)	85.1 (White)	75.0 (White)	73.7 (White)
	0.6 (Black)	25.0 (unk)	2.7 (Black)
			0.2 (Native Hawaiian or Other Pacific Islander)
	14.4 (unk)		23.4% (unk)
Ethnicity, % (category)	93.4 (non-Hispanic)	66.7 (non-Hispanic)	80.3 (non-Hispanic)
	0.6 (Hispanic)	33.3 (unk)	1.3 (Hispanic)
	6.1 (unk)		18.6 (unk)
Mortality	0.6 (yes)	0 (yes)	1.7 (yes)
	74.0 (no)	41.7 (no)	57.2 (no)
	25.4 (unk)	58.3 (unk)	41.1 (unk)

*unk, represents unknown or missing data.

Due to the high percentage of missing or unknown variable data (34.343.6%) and diversity in missing data, risk represent intact data by risk factor. Within the high-risk

cluster, being bitten by a tick or biting fly was reported by 92.1%of 114 cases ("Centers", 2016; Rothfeldt et al., 2017). Outdoor behaviors of mowing was reported by 50.5% followed by hunting (19.8%t), and exposure to dead or sick animals (17.6%), exposure to contaminated soil or water (10.9%), and handling uncooked meat (1.9%). Within the high-risk cluster, there were no reported cases from laboratory workers compared to 1.4% of the total number of cases.

Table 2. 4

Reported risk factors by percent and number of tularemia cases between 2009 and 2018. Differences in availability of data across cases portrayed by total number of cases and high-risk cluster.

Reported Risk Factors	Total number of cases (n = 335)*		High risk cluster (n = 181)*	
	n by risk category	Percent	n by risk category	Percent
Tick or biting fly bite	220	90.9	114	92.1
Outdoor activities				
Mowing	203	52.7	105	50.5
Hunting	200	17.0	106	19.8
Exposure or handling				
Dead or sick animals	195	15.4	102	17.6
Contaminated soil or water	189	11.1	101	10.9
Uncooked meat	198	2.5	104	1.9
Laboratory worker	221	1.4	115	0.0

*Cases reviewed as total number of tularemia cases and cases within the high-risk cluster. Population *(n*) by category include cases without missing data.

The clinical forms analyzed and reported as outlined in Figure 2. 1 for years 2009 through 2018 are depicted in Table 2. 5. High percentages of cases were unclassified as 29.9% of the total number and 35.4%of the high-risk cluster exhibited gaps in data. Of

the cases that were categorized, similarities were noted between high-risk and total number of cases as the predominance comprised typhoidal (23.2, 28.1) followed by glandular (17.1, 17.0). ulceroglandular (15.5, 15.8), intestinal (3.9, 3.9), pneumonic (2.8, 3.3), oropharyngeal (1.7, 1.5), and oculoglandular (0.6, 0.6), respectively. This is similar to previous reports depicting typhoidal, ulceroglandular, and glandular representing the top three clinical forms reported within Arkansas (Rothfeldt et al., 2017).

Table 2. 5.

Clinical form of tularemia cases between 2009 and 2018 representing high-risk cluster and total number of cases.

Clinical form, % (no)	High-risk cluster (n = 181)	Total number of cases (n = 335)
Typhoidal	23.2(42)	28.1(94)
Glandlar	17.1(31)	17.0(57)
Ulceroglandular	15.5(28)	15.8(53)
Intestinal	3.9(7)	3.9(13)
Pneumonic	2.8(5)	3.3(11)
Oropharyngeal	1.7(3)	1.5(5)
Oculoglandular	0.6(1)	0.6(2)
Unclassified	35.4(64)	29.9(100)

Discussion

Using spatial statistical software, tularemia cases within Arkansas were examined spatiotemporally to determine clustering. Two previously unreported clusters were detected, one high-risk and one low-risk established by county using monthly analysis. Overall annual incidence revealed 0.9 cases per 100,000 residents representing higher incidence rates than previously reported of 0.58 and 0.81 (“Centers”, 2016). Mortality remained low (1.7%) as compared to previous studies (see Rothfeldt et al., 2017;

"Centers", 2016). This present study supports previous findings of diversity in spatial distribution of tularemia and further shows an upward trend by year (Desvars-Larrive et al., 2017; Johansson et al., 2015). Demographic and spatial differences between clusters and at-risk population may provide a baseline for targeted public health programs and interventions (Desvars-Larrive, et al., 2017; Rossow et al., 2014). While tularemia is endemic to Arkansas, the finding that diversity in incidence rate over time and space demonstrates the need to parse data spatially as the distribution was vastly different. While this was not the first published retrospective assessment of tularemia within Arkansas, this study represents the first spatiotemporal analysis using a reproducible approach to identify clusters and potential hot spots (see Desvars-Larrive et al., 2017; Rothfeldt et al., 2017). With this baseline data and spatial scan statistical model, prospective studies may be undertaken to provide regular time periodic surveillance to detect active clusters (see Kulldorf, 2001).

Limitations

Several limitations due to missing or unknown data affected this study. The ability to determine exact borders of the clusters detected was not possible as zip code data was not available for a significant amount of cases. Missing or unknown data also limited the ability to sufficiently analyze at-risk variables over the entire study period and provide subsequent risk modeling. A more timely and targeted investigation may be performed if data analysis is conducted using a prospective approach as the ability to conduct cluster analysis using SatScan near real-time is possible (see Kulldorff, 2001). Tularemia may be an ideal reportable disease to pilot prospective surveillance within

Arkansas as the requirement of public reporting of suspect tularemia cases is within 24 hours of a suspected case ("Arkansas Department", 2017). This spatiotemporal analysis did not consider compliance of reporting or analysis of subsequent investigation within a timely manner suggesting the need for further study.

As location data was limited to county of residence and not potential exposure, this limitation may reflect key differences spatially especially as related to the risk of environmental related exposure (Desvars-Larrive et al., 2017; Larssen et al., 2014; Rothfeldt et al., 2017). A more timely investigation using prospective analysis may diminish the effects of recall bias enabling a more complete history of exposure that was lacking in this study (Kulldorf, 2001). This may also improve efficiencies within the healthcare system and public health departments by improving efficiencies in data retrieval of individual cases and the required collaborative partnerships necessary for a thorough epidemiological investigation of vector-borne diseases (Blackburn, Kracalik, & Fair, 2016; Hightower et al., 2014).

During this study based on 24 years of data, changes in reporting requirements reflected technological advancements in clinical diagnostics over time ("Arkansas Department", 2017; Mahon & Lehman, 2019; Rothfeldt et al., 2017). An attempt to parse data based on these differences was conducted to minimize potential effects, but the upward trend noted within this study may be partly due to advancements in technology and public health awareness (Mahon & Lehman, 2019). During the study period, case definitions varied based on technological advancements in testing and the increased

robustness of individual case data (Mahon & Lehman, 2019; Rothfeldt et al., 2017). This may have affected the reporting and categorization of cases.

Future studies should be designed to further investigation of landscape and climate variables as individual cases and the high-risk cluster detected within the latter years of the study period and within a specific geographical location did not address potential environmental influences. The potential underreporting of tularemia as the causative agent of disease may also impact case distribution and bring to light the need for healthcare provider education for individuals that present with lymphadenopathy, generalized typhoidal symptoms, or fever of unknown origin (Njeru et al., 2017; Rothfeldt et al., 2017). Spatiotemporal analysis using spatial scan statistical software may serve as an effective surveillance tool to prospectively monitor tularemia within Arkansas in order to provide for more timely detection of clusters in order to optimize public health resources (see Kulldorf, 2001).

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Manuscript 2

Ecological and Spatiotemporal Assessment of Tularemia Cases within Arkansas

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Outlet for Manuscript

The target journal for this manuscript is Annuals of Epidemiology located within URL https://www.journals.elsevier.com/annals-of-epidemiology and is sponsored by the American College of Epidemiology. This Journal supports methodological scientific study of diverse acute and chronic diseases that encompasses understanding disease etiology and applicability within a multidisciplinary framework. Multiple types of articles are accepted for peer review include review articles, editorials, commentaries, and primary research. This study aligns with primary study and design as an original article with requirements of sections including introduction, material and methods, and results sections with option of an additional conclusion. There are no requirements for any particular reference formatting as long as style is consistent within the article. Use of DOI is encouraged but not mandatory. This manuscript has been reviewed with required edits completed yet not submitted for consideration of publication.

Abstract

Purpose: Tularemia is a zoonotic disease with diverse infecting routes and subsequent differing clinical presentations. Spatiotemporal differences corresponding to multiple environmental factors reflect complexity between ecology, climate, and case distribution. Within Arkansas's diverse ecology, tularemia case distribution portrays geospatial diversity. Methods: Population and ecological data of land suitability, elevation, precipitation, and temperature from the US Census Bureau, National Oceanic and Atmospheric Administration, and the US Geological Survey were evaluated for association to tularemia case distribution within the context of vector and host suitability using maximum entropy software. Results: Within 75 Arkansas counties over a 23-year period, correlations between annual precipitation between total number of cases and high-risk cluster were least likely due to chance (AUC = 0.716, AUC = 0.726 respectively). A historical drought precipitated an upward trend in annual cases in counties with suitable land cover. Despite fluctuations in annual temperature, associations reflected temperature as the variable of least importance. Conclusions: In Arkansas, factors related to land suitability and annual precipitation correlated with annual tularemia case distribution within the concept of *nidality*. Climate revealed as a significant factor in the ecological and spatiotemporal assessment of tularemia risk supporting multidisciplinary collaboration and opportunities for applicable public policy.

Introduction

Tularemia is a vector borne zoonotic disease of global concern caused by the bacterium *Fransciella tularensis* ("Centers', 2016). Of the four subspecies that exist within the environment, *Fransciella tularensis subspecies tularenesis* (Type A) is the primary type seen within the United States and contributes to the most severe symptoms and highest mortality (Berger, 2017; Rothfeldt et al., 2017). The inhaled or infected infective dose is 10 to 50 organisms contributing to the lethalness of weoponization (Berger, 2017; Dennis et al., 2001). Multiple infecting routes include insect or animal bites, consumption of infected meat or contaminated water, inhalation, or inoculation into mucous membranes (Berger, 2017; Mahon & Lehman, 2019; Penn, 2015; Rothfeldt et al., 2017; Schulze et al., 2016). Arkansas is an endemic state and contributes to a significant portion of cases within the United States necessitating spatiotemporal analysis in order to assess public health burden geospatially (see "Arkansas Department", 2016; "Centers", 2016).

Landscape, ecology, and climate variability have a significant influence on the occurrence of vector-borne diseases as relates to the ability to support and sustain vector and host proliferation (Balci et al., 2014; Eisen et al., 2008; Giles, Peterson, & Almeida, 2011; Jamison et al., 2015; Liang & Gong, 2017; Medlock & Leach, 2015; Moinet et al., 2016; Monaghan, Moore, Sampson, Beard, & Eisen, 2016; Ogden & Lindsay, 2016; Schulze et al., 2016). Soil moisture, periodicity of drought, humidity, and its impact on vegetation affects habitability and thus may influence transmission (Jamison et al., 2015; Schulze et al., 2017). However, conflicting studies failed to establish habitat probability

for the vectors that transmit Lyme disease and Rocky Mountain spotted fever in Texas (Atkinson et al., 2012, 2014; "Spatial distribution", 2016). The primary ticks that are capable of transmitting tularemia in Arkansas include the lonestar tick (*Amblyoma americanum*), wood tick (*Dermacentor andersoni*, and the dog tick (*Dermacentor variabilis)* with increases in tick activity during the summer and early fall seasons ("Centers", 2016; Snowden & Stovall, 2011). Publications regarding field sample collection for direct testing of *F. tularensis* in wildlife or environmental sampling in Arkansas is lacking thus indirect analysis of ecological conditions was be measured in this study to geospatially and spatiotemporally analyze conditions conducive to vector and host sustainment (Desvars et al., 2015; Jamison et al., 2015; Rothfeldt et al., 2017; Rothfeldt et al., 2017).

The concept of "*nidality*" as related to case distribution of tularemia over time implies that distribution of disease and ecological characteristics in foci regions are associated with forested areas, foothills, and regions with supportive humidity (Hightower et al., 2014; Pavlovsky, 1966). Case occurrence and distribution differs between vectors based on life cycles, behavioral characteristics, and species specific metabolic adjustments to changes in climate that affects the ability to survive, thrive, replicate, and transmit disease (Hightower et al., 2014; Ogden & Lindsay, 2016). Ticks have dependency on host density, can travel only a few meters, and are inhibited by rainfall (Ogden & Lindsay, 2016). Dipterans such as flies and mosquitos have an increased reproduction cycle within climates of high rainfall, can travel a few miles, and are not dependent on host density (Ogden & Lindsay, 2016). However, ticks can seek

refuge in soil litter layers during cold and wet weather that may explain case distribution primarily in rural areas (Jamison et al., 2015; Ogden & Lindsay, 2016). The tick life cycle is less dependent on short term variations in air temperature theoretically providing more stable case distribution over time provided no significant fluctuations in host (Ogden & Lindsay, 2016). Within Arkansas, annual case distribution has deviated between six and 42 cases over a 10-year period ("Arkansas Department", 2017; "Centers", 2016). There is a gap in understanding if temperature, differences in regional elevations, land cover, and rainfall has an impact on the diverse number of annual cases within Arkansas (see Eisen et al., 2017; Rothfeldt et al., 2017). This study evaluated annual changes in temperature and precipitation and land cover and elevation by case distribution over time and region to indirectly measure correlations to host and vector habitat variability (Jamison et al., 2015; Ogden & Lindsay, 2016). By understanding climate and ecological factors related to case clustering, a predictive model may contribute to public health alerts preemptively anticipating a potential uptick while differentiating between naturally occurring cases and a potential bioterrorist event (Chen, Chughtai, & MacIntyre, 2017; Desvars-Larrive et al., 2017; Eisen et al., 2008; Mailles & Vaillant, 2014; Monaghan et al., 2016).

Materials and Methods

Input Data

Integrating ecological data to evaluate the global effects of climate and geography on the incidence of vector borne diseases such as malaria, Lyme disease, and plague has previously been undertaken (Atkinson et al., 2014; Giles et al., 2011; Qayum, Arya,

Kumar, & Lynn, 2015; “Spatial distribution”, 2016). This study included multiple ecological data sources from the United States Census Bureau (USCB), National Oceanic and Atmospheric Administration (NOAA), United States Geological Survey (USGS), and case distribution from the Arkansas Department of Health (ADH) as depicted in Table 3. 3. 1 (see Atkinson et al., 2014; Fryxell et al., 2015; Jamison et al., 2015; Ogden & Lindsay, 2016).

Table 3. 1

Categorization, rationale, and data source by variable for inclusion of tularemia case distribution. Multiple studies have demonstrated the context of ecological factors and the incidence of vector borne diseases as related to host and vector adaptability (Eisen et al., 2008; Fryxell et al., 2015; Jamison et al., 2015; Ogden & Lindsay, 2016; “ZIPAtlas”, 2017).

Variables	Categorical or Continuous	Data Source	Rationale
Vegetation	Suitable: upland deciduous, coniferous Partially suitable: bottomland deciduous, grasssland Unsuitable: barren, wetlands, agriculture	United States Geological Survey (National Gap Analysis Project) https://viewer.nationalmap.gov/basic/	Provides cover and opportunities for vector to transfer to host; serves as refuge during temperature fluctuations
Elevation	Low: 55-500 Moderate: 500 to 2,000 High: >2,000	United States Geological Survey (National Gap Analysis Project)	Higher elevation migration and movement of hosts

		https://viewer.nationalmap.gov/basic/	occurs as climate changes
Precipitation (annual rainfall)	Continuous	National Oceanic and Atmospheric Administration (National Climatic Data Center) https://www.ncdc.noaa.gov/cdo-web/	Moderate to high humidity is conducive to habitat proliferation and habitability; high rainfall inhibits movement and activity
Temperature (Mean, Maximum, Minimum)	Continuous	National Oceanic and Atmospheric Administration (NOAA (National Climatic Data Center) https://gis.ncdc.noaa.gov/maps/ncei/indices/beta	Extremely low and extremely high temperatures slow movement and activity and increases mortality
Population Density	Continuous: Ranges between 2.6 to 4,306 residents per square mile	United States Census Bureau (USCB) https://www.census.gov/quickfacts/fact/dashboard/AR,US/PST045217	Human tularemia cases predominantly occur within rural areas

Surveillance Data

In Arkansas, suspected human tularemia cases identified by a clinician or laboratory representative are reported to the ADH for epidemiological investigation (see "Arkansas Department", 2017; Rothfeldt et al., 2017). Clinical and reference laboratories that provide human testing report positive laboratory findings directly to clinicians and provide laboratory test results to ADH for mandatory public health reporting compliance (see "Arkansas Department", 2017; Rothfeldt et al., 2017). Epidemiological investigations were conducted and cases were categorized as (1) confirmed based on clinical compatibility with culture confirmation or a >= four-fold rise in titer or (2) probable with clinical compatibility and single positive serum sample or positive non-culture based laboratory findings (see "Arkansas Department", 2017: "Centers", 2016).

Secondary data sets included confirmed and probable cases reported between January 1995 and December 2017 (see "Arkansas Department", 2017; "Centers", 2016; Rothfeldt et al., 2017). Individual case data was categorized by county to minimize privacy concerns with consideration of the Health Insurance Portability and Accountability Act (HIPAA) and aggregated (Kirby et al., 2017; Tellman et al., 2010).

Population

Arkansas has approximately 2.9 million residents within 5,000 square acres well below the United States average population of 87 residents per square mile constituting a rural state ("United States", 2017). In the 75 counties within Arkansas, population density ranges between 2.6 to 4,306 residents per square mile contributing geographical diversity (see "ZIPAtlas", 2017).

Ecological Data

Analysis of land cover, elevation, precipitation, and temperature using multiple data sets from NOAA and USGS established the ecosystem spatially by county (see Atkinson et al., 2014; Desvars-Larrive, et al., 2017; "National Climatic", 2018; Ogden & Lindsay, 2016; "Spatial distribution", 2016; "The National", 2018). Ecosystem data set used within this study represents environmental factors that support vector and host sustainment while indirectly identifying potential high-risk regions (Atkinson et al., 2014; Desvars-Larrive, et al., 2017; Kraemer et al., 2016; Samadoulougo et al., 2014)

Variables

Ecological factors as related to total number of cases and high risk and low risk clusters by county over time take into account population density (Kraemer et al., 2016). As Arkansas exhibits diverse land cover, vegetation was categorized as suitable, unsuitable, and partially suitable and further defined in Table 1 (Eisen et al., 2008). Variables were compared to determine importance of each variable related to each ecological factor (see Atkinson et al., 2014; "National Climatic", 2018; "The National", 2018). Rationale for each factor as a component for habitat probability is listed in Table 3. 1.

Instrumentation

This study utilized Maxent software capable of processing data and computing an infinitely weighted logistic regression from multiple ecological data sets while analyzing covariants of host and vector adaptability and probability distributions of tularemia cases spatially (Atkinson et al., 2012, 2014; Philips, Dudik, & Schapire, 2018). Maxent was

developed within the Center for Biodiversity and Conservation at the American Museum of Natural History for niche modeling and available as an open source software program (see Philips et al., 2018). Maxent includes a maximum entropy algorithm which compares disease occurrence to ecological covariates conditionally and marginally while using a metric of an "area under the curve" value (AUC) ranging between 0.5 to 1.0 representing complete random to best fit of correlation respectively (Atkinson et al., 2012, 2014). Distribution models depicting an AUC of 0.7 or greater represents variable correlation to case distribution (Atkinson et al., 2012, 2014; Philips et al., 2018). The following represents probability density over the domain (D):

$$P_{\lambda}(z) = \lambda(z) / \int_{D} \lambda(z) dz$$

Where Z represents tularemia cases within D using an intensity function of λ while assigning a non-negative value intensity of λ (z) to each unique point of z within D. The formula represents an inhomogeneous Poisson process (IPP) defining probability of tularemia cases by region aligned with Maxent's capabilities (Atkinson et al., 2012, 2014; Philips et al., 2018). There is an assumption of independence between cases given the predictor variables and the lack of evidence of human-to-human transmission supports this assumption (Mahon & Lehman, 2019; Penn, 2015; Philips et al., 2018).

Design and Analysis

This quantitative ecological study included the relationship between tularemia case distribution and ecological factors over the 24-year study period see (Kraemer et al., 2016; Melchior & Neto, 2016; Ogden & Lindsay, 2016). Previous analysis of tularemia cases within the Southcentral United States relied on the use of ordinal logistic regression

spatially by county for predictive modeling (Eisen et al., 2008). In this study, categorical data by county included multiple independent data sources as shown in Table 3. 1 producing an overall picture of tularemia risk by region over time (see Giles et al., 2011). By integrating multiple environmental and biological data sets over time, climate change and evolutionary effects may give insight to the fluctuations in annual cases within the complex ecological system (Jamison et al., 2015).

A high and low risk cluster by county was detected between May 2010 and December of 2018 and September 2000 and August 2012 respectively. Counties were geocoded by latitude and longitude with corresponding case distribution (see Kirby et al., 2017). Clusters represented analysis of demographic data, potential at risk behaviors, and exposures spatiotemporally and geospatially (see "Arkansas Department", 2017). Tularemia case distribution reflected individual cases following epidemiological investigation and categorization based on probable and confirmed definition at time of reporting (see "Arkansas Department", 2017). Maximum entropy software provided statistical modelling of complex interactions between ecological factors and case distribution spatiotemporally (see Kraemer et al., 2016; Philips et al., 2018). Both tularemia case database and environmental layers datasets included samples with data (SWD) format within the Maxent directory (see Phillips et al., 2018). A jackknife process termed "*training*" included evaluation of each variable together and in isolation signifying single variable consideration and potential synergistic effects (see Phillips et al., 2018).

Results

Between January 1995 and December 2017, there were 542 tularemia cases reported in 63 of the 75 counties within Arkansas as shown in Table 2. Figure 3. 1 represents an overlay map by high concentration including 26 counties representing 82% of the total number of cases and 37 counties representing low concentration of reported cases. Land cover and elevation characteristics by case distribution included the Northern part of Arkansas containing ample forested areas and moderate to high elevation. While the Southeastern part of Arkansas represented agricultural land cover in lower elevations. Most of the northern and western parts of the state includes hilly or mountainous regions that did not show consist case distribution (see "National Climatic", 2018; "Spatial distribution", 2016; "The National", 2018).

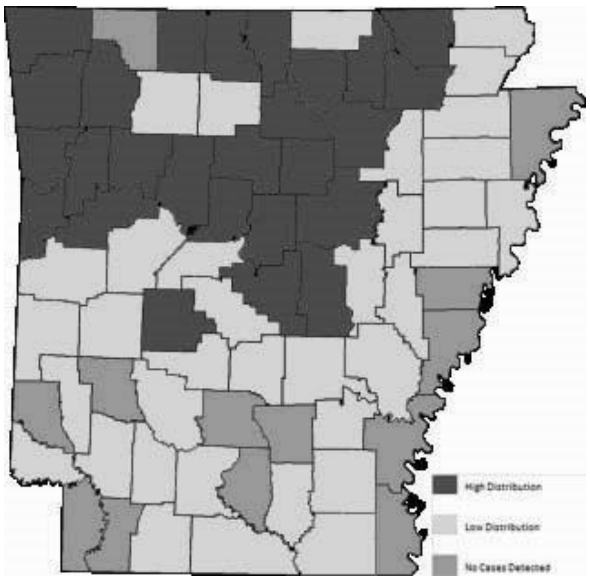


*Figure 3. 1.*Tularemia case distribution by high-concentration and low-concentration parsed by county. The high-concentration counties represent 82% of total number of cases with predominantly suitable and partially suitable land cover supporting vector and host proliferation.

Habitat Probability

As categorized in Table 3. 1, geographical habitat probability included land cover and elevation conducive to host and vector proliferation (see Atkinson et al., 2014; Desvars-Larrive, et al., 2017; Kraemer et al., 2016; Samadoulougo et al., 2014). Table 3. 2 depicts county by incidence rate, geographical location, land cover suitability, and elevation over the 23-year study period (Atkinson et al., 2014; Desvars-Larrive, et al., 2017; "National Climatic", 2018; Ogden & Lindsay, 2016; "Spatial distribution", 2016; "The National", 2018). There was a trend towards higher incidence rates within counties with elevations of moderate to high and with suitable land cover as represented in Table 3. 2.

Table 3. 1.

Tularemia incidence rate by percentage of 100,000 residents, geographical location, land cover suitability, and elevation by county within Arkansas between 1995 and 2017.

County	Latitude	Longitude	Suitability	Elevation	Population	No. of cases	Incidence rate per 100,000 residents
Sharp	36.1901	-91.4985	Yes	Moderate	17,264	23	133.2
Stone	35.8741	-92.1699	Yes	Moderate	12,394	12	96.8
Izard	36.1395	-91.8750	Yes	Moderate	13,696	12	87.6
Marion	36.2913	-92.6814	Yes	Moderate	16,653	12	72.1
Cleburne	35.5352	-92.0609	Yes	High	25,970	17	65.5
Van Buren	35.5658	-92.4142	Yes	Moderate	17,295	11	63.6
Conway	35.2077	-92.7140	Yes	Moderate	21,273	13	61.1
Searcy	35.9210	-92.6883	Yes	High	8,195	5	61.0
Fulton	36.3550	-91.7293	Yes	Moderate	12,245	7	57.2
Johnson	35.4987	-93.4846	Yes	High	25,540	14	54.8
Madison	36.0311	-93.7305	Yes	High	15,717	8	50.9
Franklin	35.4776	-93.8845	Partially	Moderate	18,125	9	49.7
Baxter	36.3122	-92.3543	Yes	Moderate	41,513	20	48.1

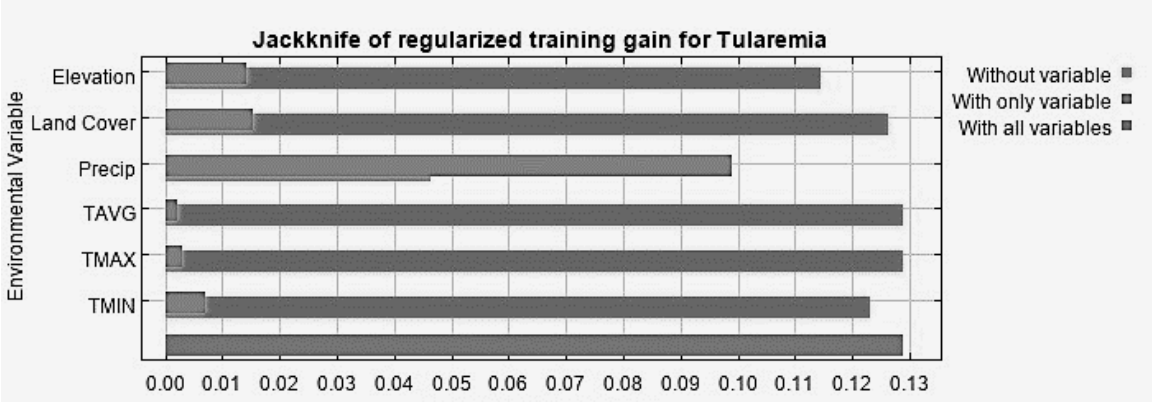
Faulkner	35.1195	-92.3799	Partially	Moderate	113,237	53	46.8
Lawrence	36.0706	-91.0712	Partially	Moderate	17,415	8	45.9
Logan	35.2208	-93.7553	Partially	High	22,353	10	44.7
Randolph	36.3155	-90.9889	Partially	Moderate	17,969	8	44.5
Woodruff	35.1962	-91.2441	No	Low	7,260	3	41.3
Independence	35.7575	-91.5870	Yes	Low	36,647	15	40.9
Newton	35.9678	-93.1885	Yes	High	8,330	3	36.0
Prairie	34.8080	-91.5341	No	Low	8,715	3	34.4
White	35.2501	-91.7306	Partially	Moderate	77,076	26	33.7
Boone	36.2852	-93.0659	Yes	Moderate	36,903	12	32.5
Perry	34.9827	-92.8616	Yes	Moderate	10,445	3	28.7
Cross	35.2796	-90.7861	No	Low	17,870	5	28.0
Lonoke	34.7791	-91.9122	No	Low	68,356	16	23.4
Yell	35.0385	-93.3621	No	Low	22,185	5	22.5
Howard	34.0503	-93.9649	Partially	Moderate	13,789	3	21.8
Arkansas	34.3600	-91.4294	No	Low	19,019	4	21.0
Clay	36.3644	-90.4006	No	Low	16,083	3	18.7
Pope	35.3305	-93.0844	Yes	Moderate	61,754	11	17.8
Washington	36.0514	-94.1987	Partially	High	203,065	36	17.7
Grant	34.3110	-92.4508	Yes	Low	17,853	3	16.8
Crawford	35.5231	-94.2602	Yes	Low	61,948	10	16.1
Little River	33.6972	-94.2205	Yes	Moderate	13,171	2	15.2
Carroll	36.3641	-93.5660	Partially	Moderate	27,446	4	14.6
Pulaski	34.7665	-92.2945	Partially	Low	382,748	47	12.3
Monroe	34.7328	-91.2078	No	Low	8,149	1	12.3
Columbia	33.2494	-93.2298	Yes	Moderate	24,552	3	12.2
Nevada	33.6894	-93.3274	yes	Low	8,997	1	11.1
Montgomery	34.5591	-93.6439	Yes	Moderate	9,487	1	10.5
Garland	33.3629	-93.7099	Yes	Moderate	96,024	10	10.4
Hot Spring	34.3375	-92.8912	Yes	Moderate	32,923	3	9.1
Benton	36.3541	94.2468	No	High	221,339	20	9.0
Scott	34.8809	-94.0897	Yes	Moderate	11,233	1	8.9
Bradley	33.5209	-92.1411	Yes	Low	11,508	1	8.7
Clark	34.0690	-93.1577	Yes	Moderate	22,995	2	8.7
Poinsett	35.5870	-90.6039	No	Low	24,583	2	8.1
Jefferson	34.2438	-91.9872	No	Low	77,435	6	7.7
Sebastian	35.2939	-94.3518	Partially	Low	125,744	9	7.2
Lincoln	33.9788	-91.7090	Partially	Low	14,134	1	7.1
Greene	36.0982	-90.5137	No	Low	42,090	3	7.1
St. Francis	35.0159	-90.7088	No	Low	28,258	2	7.1
Saline	34.6164	-92.6364	Yes	Moderate	107,118	7	6.5
Jackson	35.6133	-91.2276	No	Low	17,997	1	5.6

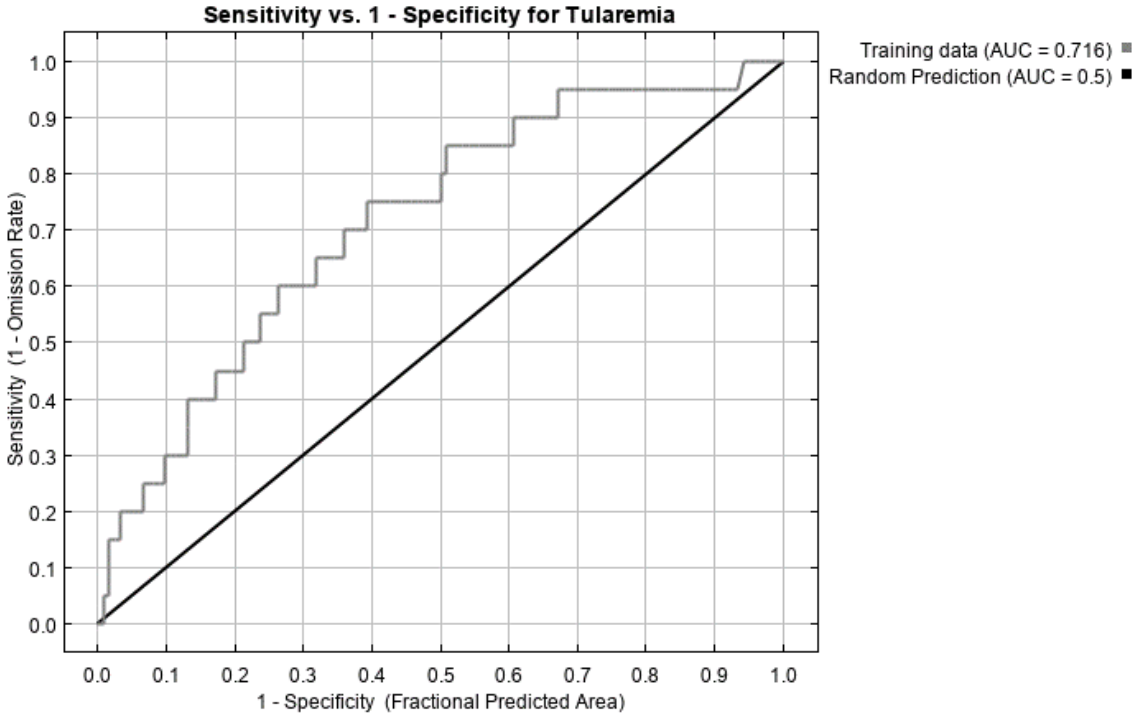
Drew	33.6006	-91.7356	Yes	Low	18,509	1	5.4
Union	33.2072	-92.6128	Yes	Low	41,639	2	4.8
Polk	34.4855	-94.2536	Yes	High	20,662	1	4.8
Ashley	33.1854	-91.7853	Yes	Low	21,853	1	4.6
Hempstead	33.7176	-93.6479	Yes	Low	22,609	1	4.4
Craighead	35.8282	-90.6320	No	Moderate	96,443	4	4.1
Ouachita	33.5740	-92.8614	Yes	Low	26,120	1	3.8
Crittenden	35.1977	-90.2728	No	Low	50,902	1	2.0
Cleveland	33.9047	-92.2163	Yes	Low	8,689	0	0.0
Sevier	34.0166	-94.2629	Yes	Low	17,058	0	0.0
Calhoun	33.5955	-92.5101	Partially	Low	5,368	0	0.0
Dallas	33.9381	-92.6082	Partially	Low	8,116	0	0.0
Lafayette	33.2723	-93.5631	Partially	Low	7,645	0	0.0
Miller	33.3847	-93.9681	Partially	Low	43,462	0	0.0
Pike	34.1773	-93.6568	Partially	Low	11,291	0	0.0
Chicot	33.3091	-91.3094	No	Low	11,800	0	0.0
Desha	33.7894	-91.3503	No	Low	13,008	0	0.0
Lee	34.7801	-90.7640	No	Low	10,424	0	0.0
Mississippi	35.8068	-90.0304	No	Low	46,480	0	0.0
Phillips	34.4684	-90.7620	No	Low	21,757	0	0.0

Climate Variability

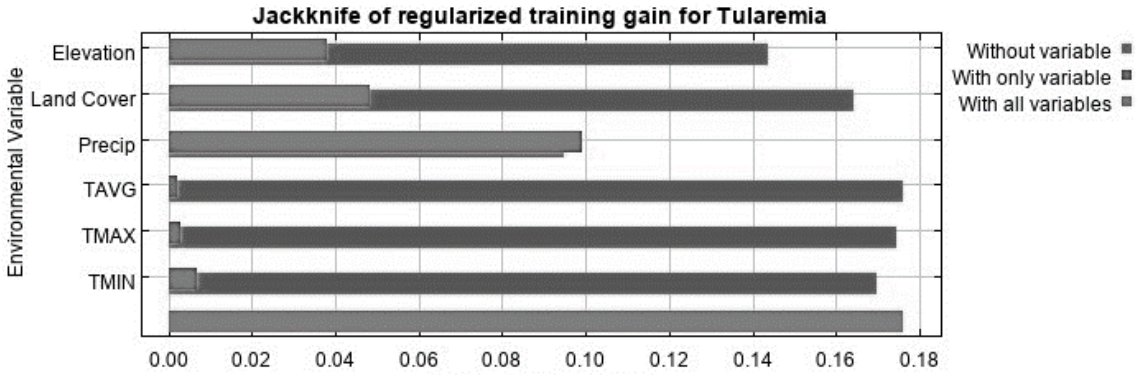
During the study period, between 135 and 216 weather stations measured climate variables within 75 counties. Annual averages represent monthly data from all stations as long as missing values did not exceed five or more days or three consecutive days within a given month (see “National”, 2018). Climate variables were analyzed using Maxent software by estimating the case distribution by latitude and longitude and finding the closest environmental conditions at the same geographical location resulting in maximizing the likelihood of the parametric exponential distribution (see Phillips et al., 2018). Analysis of total number of cases and high and low-risk clusters found differing results as represented in Figure 3. 2. In both the total number of tularemia cases and within the high risk cluster, correlation was least likely due to chance (AUC = 0.716,

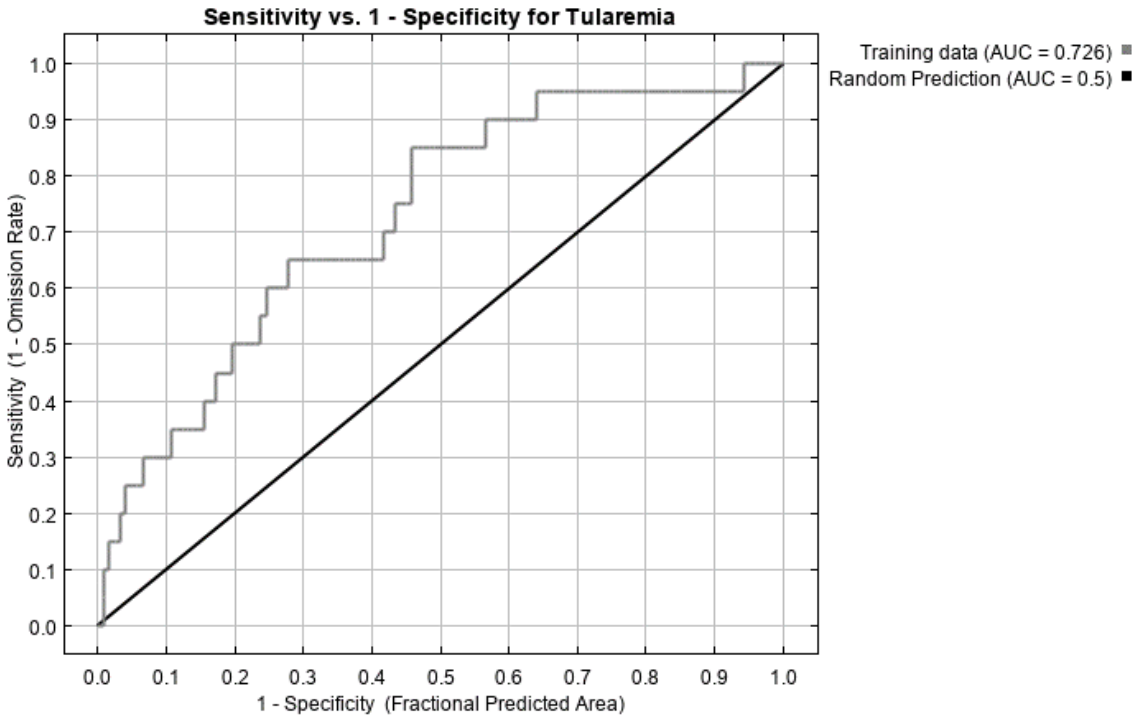
AUC = 0.726 respectively) as compared to the low-risk cluster (AUC = 0.562) represented in Figure 3. 2 revealing correlation with precipitation as a significant measure of importance by degree of gain (see Phillips et al., 2018). Within the total number of cases and the high risk cluster, land cover was also a measure of importance with elevation lower in importance but still a factor of consideration (see Phillips et al, 2018). Average annual temperature represented by mean, maximum, and minimum was of slight importance in the total number of cases and high-risk cluster but not within the low-risk cluster (see Phillips et al., 2018).



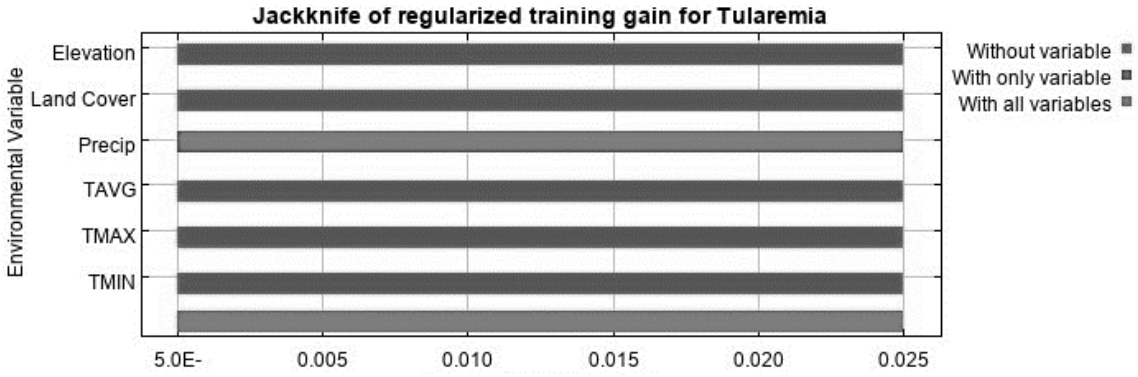


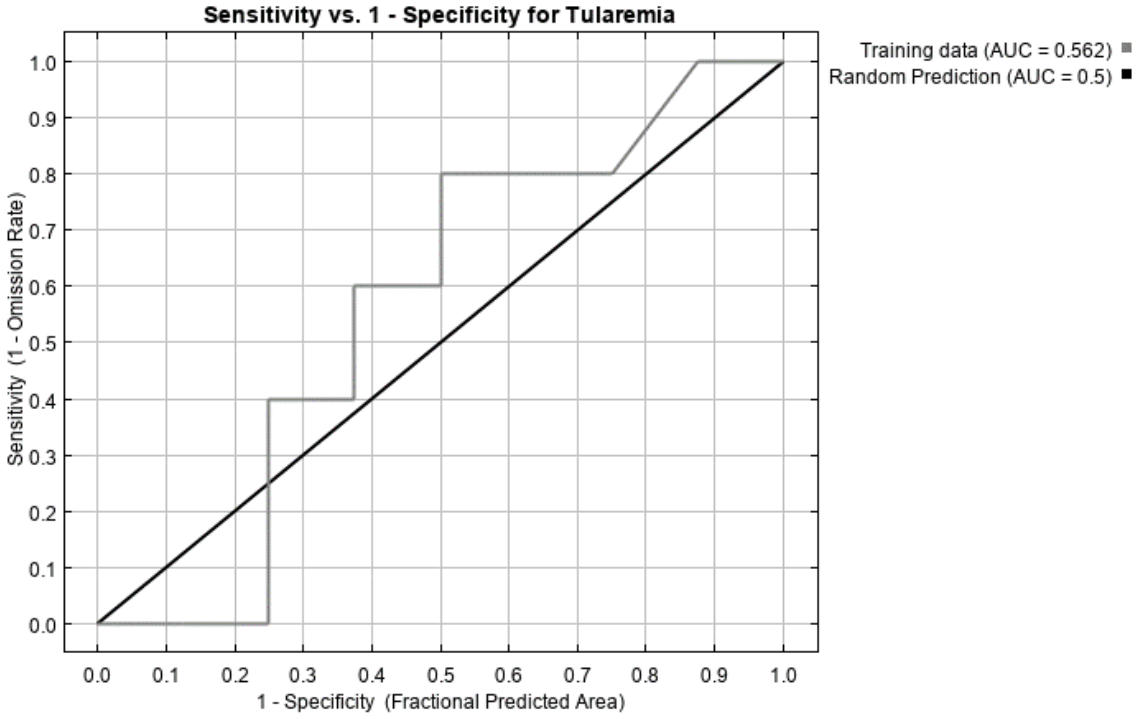
a. Total number of Tularemia cases (January, 1995 to December, 2017)





b. High-risk cluster of Tularemia cases (May 2010 to December 2017)





c. Low-risk cluster of Tularemia cases (September 2000 to August 2012)

Figure 3. 2. Measure of importance in case distribution using maximum entropy software by variable alone and in combination with all variables for total number of cases, high-risk cluster, and low-risk cluster between January 1995 and December 2017 (Phillips et al., 2018). The area under the curve (AUC) shows significance for total cases (AUC = 0.716) and the high-risk cluster (AUC = 0.726). While precipitation was a factor in the low-risk cluster, statistical significance was not met (AUC = 0.562). PRECIP = annual precipitation; TAVG = annual mean temperature; TMAX = annual mean maximum temperature; TMIN = annual mean minimum temperature.

Precipitation

Annual precipitation and case distribution within Arkansas by year shows an upward trend in cases with differing values as represented in Figure 3. 3. Two pronounced spikes in precipitation comprised between 2007 and 2009, and between 2014 and 2016 corresponding to dips in total number of cases. A documented drought lasting 101 weeks began in April 2010, continued until March 2012 affecting 53.6% of the land

mass, and comprised the longest drought in Arkansas history (“National Integrated”, 2018). During the drought and for two years post drought, there was an upward trend in annual cases.

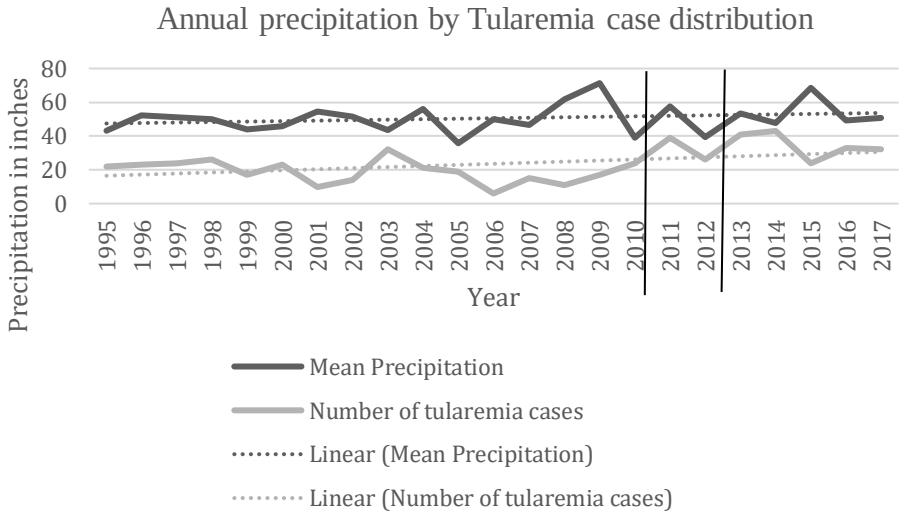


Figure 3. 3. Annual precipitation compared to tularemia case distribution within Arkansas between 1995 and 2017 showing an upward trend despite a historical drought between March 2010 and April 2012 (“National Integrated”, 2018).

Temperature

Annual temperature values remained stable throughout the study period with mean, maximum, and minimum values by tularemia case distribution depicted in Figure 3. 4. A pronounced drop in temperatures occurred between 2012 and 2014 with an upward trend in annual cases. However, maximum entropy modeling determined temperature fluctuations as the variable of least importance to annual case distribution within Arkansas during the study period as displayed in Figure 3. 2 (see Phillips et al., 2018).

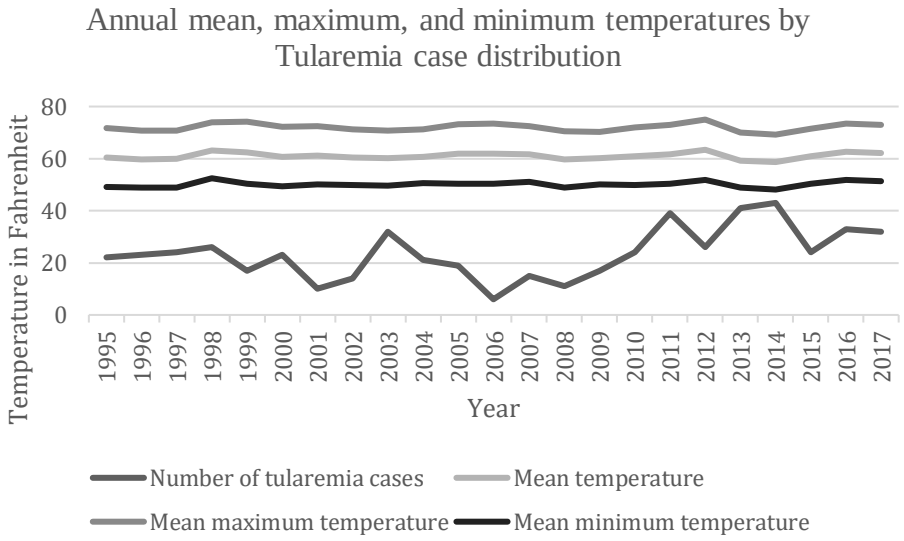


Figure 3. 4. Annual mean, maximum, and minimum temperatures compared to tularemia case distribution within Arkansas between 1995 and 2017 showing a fairly stable line with a short pronounced drop in temperatures between 2012 and 2014 with an upward trend in case distribution.

Discussion

Tularemia is a vector-borne disease endemic to Arkansas with varying incidence rates by geographical location over time. Factors that affect the sustainment and proliferation of *Francisella tularensis* include a wide range of vectors and hosts typically residing in suitable land cover and in climatic conditions that promote movement (Ogden & Lindsay, 2016; Ostfeld, Glass, & Keesing, 2005; Ryden, Sjostedt, & Johansson, 2009; Schultz et al., 2016). This study included geographical, ecological, and climate data by case distribution over time to understand impact by variable within the endemic state of Arkansas (see Ogden et al., 2016; Ostfeld et al., Ryden et al., 2009). Previous findings of other tick borne diseases such as Lyme disease and Rocky Mountain spotted fever failed to find a correlation between habitat probability and case distribution within the state of

Texas (Atkinson et al., 2012, 2014). A 23-year period was chosen to evaluate annual climate considering seasonality differences in tularemia case distribution and potential affects over multiple years within 75 Arkansas counties (see Balci et al., 2014; Desvars et al., 2015; Hestivik et al., 2015; Ryden et al., 2009).

Globally, tularemia outbreaks have been associated with increases in temperature and precipitation due to mosquitoes as being the primary vector responsible (Jamison et al., 2015; Ryden et al., 2009). Within Arkansas, this was not the case within this study as increases in cases occurred during and immediately following periods of drought and decreases in cases were associated with spikes in precipitation supporting tick proliferation and movement while heavy and sustaining rainfall likely increased tick mortality rates (see Ogden & Lindsay, 2016). Geographical areas with extreme weather events and large fluctuations in temperature and precipitation potentially influence the spread of infectious diseases and evaluation during and post weather related events are identified research gaps and opportunities that support this study (see Jamison et al., 2015; Liang & Gong, 2017; Ogden & Lindsay, 2016; Ostfeld et al., 2005).

The concept of nidality characterized by the complex symbiotic relationship of ecological systems supported precipitation as a training model representing the most meaningful variable with land cover suitability and elevation further supporting the niche model (see Hightower et al., 2014; Pavlovsky, 1966). Field studies of ticks carrying *F. tularensis* within Massachusetts demonstrated natural foci of only a few hundred meters within a four-year time span further supporting presence of niches and hot spots as demonstrated in the present study (Goethert & Telford, 2009). Human cases were used to

extrapolate the complexity of concentration of ticks, exposure, and disease due to gaps in published tick count data within Arkansas and signify research necessitating field study (see Moinet et al., 2016)

Statistical modeling using maximum entropy software allows evaluation of complex ecological systems of vector-borne diseases by variable alone and within combination over time (Kirby et al., 2017; Phillips et al., 2018). The limitation of statistical modeling includes the inability to account for environmental interventions and disease spread and therefore this design choice was used as there is no human to human spread of tularemia and little to no active interventions within Arkansas for vector and host habitat control (see Berger, 2017; Kraemer et al., 2016; Varela-Stokes, Park, Kim, & Ricke, 2017).

This study has multiple limitations. Tularemia case data was geocoded at the county level due to significant gaps in zip codes, which may have overlooked smaller niches (see Balci et al., 2014; Desvars-Larrive, 2017; Fryxell et al., 2015). Human tularemia cases geocoded within the county of residence as a surrogate for presence of *F. tularensis* did not account for behavioral variables or human movement (Desvars-Larrive et al., 2017; Fryxell et al., 2015; Schulze et al., 2016). Due to diversity in land cover, elevation, and precipitation by geographical location calculated by year, seasonal trends or hot spots potentially were missed (see Fryxell et al., 2015; Schulze et al., 2016). While mean, maximum, and minimum annual temperature was not a measureable factor within this study, no significant fluctuations tested this variable (Desvars-Larrive et al., 2017).

Retrieving ecological and climate data during case reporting of tularemia and epidemiological investigations potentially could predict changes in exposure or case distribution (Liang & Glong et al., 2017; Monghan et al., 2015). Public health messaging and targeted communication may optimize funding using geographical location and climate data with at risk behaviors such as seasonal outdoor activities (see Monaghan et al., 2015). Within this study, epidemiological investigations revealed tularemia cases as naturally occurring but *F. tularensis* can also be the consequence of an intentional biological release necessitating vigilant awareness and multifaceted preventative strategies ("Centers", 2016; Grundmann et al., 2014; Mahon & Lehman, 2019). Collaboration between ecologists, climatologists, entomologists, clinicians, and public health epidemiologists necessitate ongoing niche modeling while maintaining multidisciplinary cooperation with public policy and in practice (Blackburn et al., 2016; Chen et al., 2017).

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Manuscript 3

Evaluation of Timeliness and Completeness of Tularemia Case Reporting in Arkansas, 2009 to 2018

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Outlet for Manuscript

The target journal for this manuscript is the American Journal of Public Health (AJPH) located within URL https://ajph.aphapublications.org and is the official journal of the American Public Health Association. This journal focuses on research to advance public health within the scope of educating, supporting policy, applicability, and program evaluation. This study aligns with AJPH by focusing on the continuum and evaluation of syndromic surveillance and laboratory diagnostics using tularemia as a complex zoonotic disease requiring rapid and accurate public health reporting. The determination of underserved populations and opportunities to improve efficiency within public health organizations support this continuum allowing for focused public health policy development and education. Instructions for prospective authors include suggested topics and avenues for becoming a peer reviewer that I believe enriches diversity within this journal. In this study framework, AJPH promotes open access to further the scientific community. Instructions for submittal of this manuscript include structural requirements such as a title page, blinded manuscript for review, and cover letter addressing current knowledge, public health significance, and main message. There are no strict formatting requirements for citations or references as long as the style is consistent. This manuscript has been reviewed with required edits completed yet not submitted for consideration of publication.

Abstract

Purpose: Tularemia is caused by *Francisella tularensis*, one of the most pathogenic and infectious agents of public health significance. Public health reporting of suspect cases within Arkansas requires notification by phone within next day of recognition. Epidemiological investigations of vector borne diseases necessitate complete and timely notifications. Methods: This study evaluated data completeness and timeliness of notification by category retrospectively between 2009 and 2018. Results: Of 335 confirmed and probable cases within 53 of 75 Arkansas counties, compliance to next day notification was 9.1% with clinical form and transmission mode affecting timeliness ($p < 0.05$). Data required to assess clinical form and transmission mode represented gaps of 29.9% and 66.9% respectively. Furthermore, 80.9% of cases were categorized as probable lacking laboratory confirmation with trends including an increase in probable cases and decrease in confirmed cases over the study period. Conclusions: There is an opportunity for targeted education on recognition of suspect tularemia cases and the importance of public health reporting with applicable data necessary for epidemiological investigations. The divergence of probable versus confirmed cases over time affords an opportunity for clinical laboratory diagnostics education and the exploration of electronic reporting and syndromic surveillance.

Introduction

Within the United States, the first state to initiate public reporting of communicable diseases and events affecting mortality was Michigan in 1893 (Thacker, Qualters, & Lee, 2012). Public policy within each state and territory defines mandatory reporting of conditions and diseases by relevancy to public health and safety and by syndromic surveillance capabilities, availability of diagnostic testing, and effective preventative methods (Revere et al., 2017; Sanstead et al., 2015). Public health responsiveness to vector-borne diseases depends on accurate and timely reporting by primary healthcare professionals (PHPs) and clinical laboratory personnel (CLPs) by recognizing syndromes and communicating positive diagnostic tests results respectively (Johnson, Williams, Lee, & Bradely, 2014; Larssen et al., 2014; Revere et al., 2017). Once an individual is identified as a possible case and reported to public health officials, an epidemiological investigation is initiated to determine the origin, assess population risk, and ultimately lessen the burden of disease ("Arkansas Department", 2017, "Centers", 2016; Gopalakrishna-Remani, Brown, Shanker, & Hu, 2017).

Tularemia is a vector-borne disease endemic to Arkansas and a public health reportable event ("Arkansas Department", 2017; Rothfeldt et al., 2017). Tularemia is caused by the bacterium *Fransciella tularensis* that infects humans by contact with diseased or colonized vectors or hosts, contaminated water and food, occupational exposure, or bioterrorism (Berger, 2017; "Centers", 2016; Mahon & Lehman, 2019; Penn, 2015). Tularemia is globally distributed yet regionally focused based on environmental sustainability of vectors and hosts (Berger, 2017; Hestvik et al., 2017:

Rossow et al., 2014). Between 2005 and 2015, the number of tularemia cases reported annually in Arkansas ranged between six and 42 and in 2016, the incidence rate was 1.07 reported cases per 100,000 individuals well above the national incidence rate of 0.07 reported cases per 100,000 individuals ("Arkansas Department", 2017; "Centers", 2016).

While tularemia is not spread person-to-person, the significance to public health lies in the potential for outbreaks as a result of environmental contamination and protective behaviors that could decrease exposure risk as well as the potential for bioterrorism leading to the necessity to determine naturally occurring cases versus intentional release (Berger, 2017; Desvars et al., 2015; Mahon & Lehman, 2019; Rothfeldt et al., 2017). *Francisella tularensis* is one of the most pathogenic and infectious bacterial agents requiring only 10 organisms to cause disease and has been weaponized by the United States and the Soviet Union during the 1960s and modified to be drug resistant by the Soviet Union during the 1990s (Berger, 2017; Dennis et al., 2001; Mahon & Lehman, 2019; Penn, 2015). An intentional release is estimated to cause 19,000 deaths in a city of 5 million while costing $5.4 billion per 100,000 exposures (Dennis et al., 2001). Symptoms may take three to five days post exposure and confirmation by laboratory methods may take several more days to weeks for case confirmation contributing to the significance of timely reporting (Dennis et al., 2001; Mahon & Lehman, 2019).

In order to conduct an epidemiological investigation, reported data should be accurate and complete at the point of contact in order to effectively process and categorize suspected cases while considering national and global implications ("Centers",

2016; Rao et al., 2017; Revere et al., 2017; Rothfeldt et al., 2017). The method of reporting laboratory confirmed cases for communicable diseases maybe by phone, electronic methods, or facsimile with differing processes for different communicable diseases within the same public health agency (Samoff et al., 2013). Instances in which inaccuracy and gaps in data have caused significant delays in case investigation and closure have been reported for communicable diseases using non-electronic reporting methods and in complex vector borne diseases that rely on integrating both laboratory and syndromic data for case definitions (Gluskin, Mavinkurve, & Varma, 2014; Johnson et al., 2014; Thacker et al., 2012; Samoff, 2013). Epidemiological surveillance may necessitate and include environmental investigations to rule out drinking water and food contamination supporting the need for exposure history in addition to syndromic presentation and laboratory data ("Arkansas Department", 2017; "Centers", 2016; Blackburn et al., 2016; Rothfeldt et al., 2017). If data submitted to public health officials fails to include clinical and demographic components, case investigation may be impeded (Johnson et al., 2014; Rothfeldt et al., 2017; Troppy et al., 2014).

Timeliness of reporting may be affected by multiple factors. Troppy et al (2014) found that the use of ELR was associated with a decrease in the average time to reporting of Hepatitis C viral infections from 454 days to 26 days, however, long-term resource requirements to maintain data integrity were significant. When reporting suspected cases involving vector-borne diseases, extensive investigative time is necessary to categorize suspected cases which may necessitate chart review or additional clinical information not initially provided (Johnson, Williams, Lee, & Bradley, 2014; Larssen et al., 2014;

Rothfeldt et al., 2017). Reporting by telephone of vector-borne disease within Oklahoma has demonstrated more timely investigation of cases when compared to either ELR or communication by facsimile that may contribute to data retrieval (Johnson et al., 2014). In Arkansas, public policy requires reporting of tularemia by phone within one day of suspicion however, notifications in practice include facsimile or other electronic methods ("Arkansas Department", 2017; Rothfeldt et al., 2017). This study addresses factors associated with completeness of data necessary to conduct an epidemiological investigation and the timeliness of case recognition and public health reporting of tularemia cases within Arkansas (see Rothfeldt et al., 2017; Samoff, 2013).

Methods

Data Collection

Suspected human cases of tularemia were reported to the Arkansas Department of Health (ADH) by healthcare professionals or laboratory personnel based on clinical presentation and positive laboratory results with subsequent submission of a case report (see "Arkansas Department", 2016, 2017; "Centers", 2016). Table 4. 1 depicts case definitions and modifications historically by year (see "Centers", 2017). In 2009, an updated case document that aligned with the Centers for Disease Control and Prevention (CDC) case definitions replaced an ADH case report document (see "Arkansas Department", 2017; "Centers", 2016). Additional CDC reporting guidelines included categorization by clinical presentation, exposure history, and laboratory results (see "Arkansas Department", 2017; "Centers", 2016 Rothfeldt et al., 2017). Secondary data sets consisted of individual case reports collected between 2009 and 2018 (see "Arkansas

Department", 2017; "Centers", 2016). Statistical Package for the Social Sciences (SPSS) v. 24 (IBM, Chicago, IL) and Microsoft Excel 2013 were used to analyze the condensed data set descriptively, determine statistical significance between categories, and display results (see Green & Salkind, 2014; Larssen et al., 2014).

Table 4. 1

Characterization and categorization of tularemia case definitions by year ("Centers", 2017).

Case Definition by Year	Categories of Clinical Presentation	Laboratory Criteria	Epidemiological Linkage	New vs. Existing Case
2017	Ulceroglandular Glandular Oculoglandular Oropharyngeal Pneumonic Typhoidal	*Supportive* Single elevated sera in unvaccinated individual OR positive fluorescent assay or polymerase chain reaction *Confirmed* Fourfold rise in titer OR isolation of *F. tularensis*	Clinical diagnosis with history of tick or deerfly bite, exposure to *F. tularensis* by animal bite, contaminated water, or infected tissue	Diagnosis with new onset of symptoms and exposure differentiates new versus exisiting case
1999	Ulceroglandular Glandular Oculoglandular Oropharyngeal Intestinal Pneumonic Typhoidal	*Presumptive* Single elevated sera in unvaccinated individual OR positive fluorescent assay *Confirmed* Fourfold rise in titer OR isolation of *F. tularensis*	Exposure by clinical diagnosis supported by history of tick or deerfly bite, animal bite, contaminated water, or infected tissue	n/a
1996	Same as 1999	Same as 1999	n/a	n/a
1990	Same as 1999	*Probable* Clinically compatible case with serological titer of greater than or equal to 160 *Confirmed*	n/a	n/a

	Laboratory confirmation by: Fourfold rise in titer greater than or equal to two weeks apart, tested at the same time within the same laboratory, isolation in sample, or positive immunofluorescence.

Variables

The dependent variables included timeliness and completeness of case reporting from syndrome recognition or positive laboratory finding to notification of an ADH official (see Johnson et al., 2014; Revere et al., 2017). The independent variables for evaluating timeliness included clinical form, case recognition by entity, laboratory criteria, transmission mode, and case category to understand barriers and facilitators as outlined in Table 4. 2 (see Johnson et al., 2014; Revere et al., 2017; Samoff, Fangman, Fleischauer, Waller, & MacDonald, 2013). Completeness of case reporting evaluated compliance to demographic data, laboratory findings, exposure history, and syndromic presentation as depicted in Figure 1 (Johnson et al., 2014; Wang & DeSalvo, 2018).

Table 4. 2.
Variables by category evaluated for timeliness of public reporting of tularemia cases within Arkansas.

Transmission mode	Clinical form	Laboratory criteria	Case reporting entity	Case category
Bloodborne	Glandular	Culture positive	Healthcare provider	Confirmed
Dermal	Intestinal	Four-fold rise in titer	Self-referral	Probable
Indeterminate	Oculoglandular	PCR positive	Other	
Transplacental	Oropharyngeal	Single positive serology	Unknown or not recorded	
Vectorborne	Pneumonic	Other positive result		
Waterborne	Typhoidal	No result available		
Zoonotic	Ulceroglandular			
Other	Not initially classified			
Unknown or not recorded				

PCR= Polymerase chain reaction

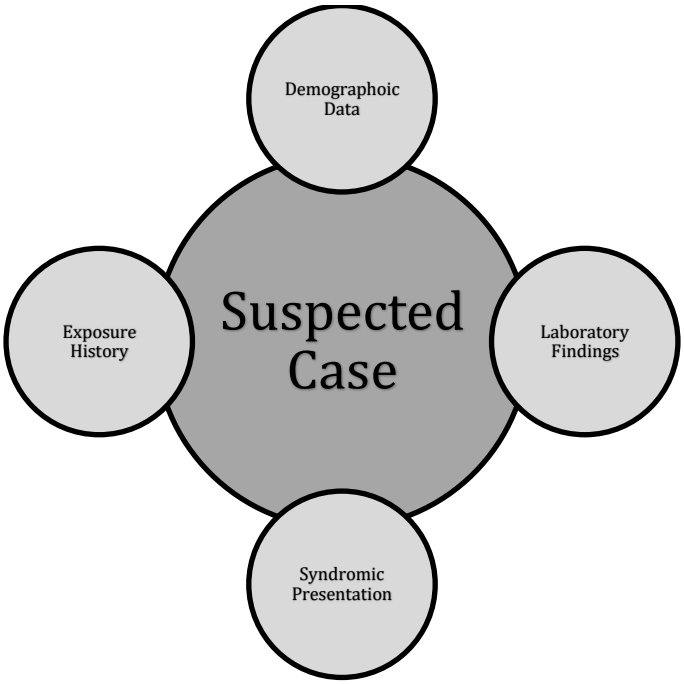

Figure 4. 1. Categorical data included to assess the timeliness and completeness of public reporting and epidemiological investigation of human tularemia cases within Arkansas (see "Arkansas Department", 2017; "Centers", 2016).

Design

This was a quantitative retrospective analysis of human tularemia cases reported to ADH between 2009 and 2018 to assess timeliness of public reporting and completeness of required data fields necessary to conduct an epidemiological investigation (see "Arkansas Department", 2017; "Centers", 2016; Johnson et al., 2014). Case categories included probable and confirmed per definitions presented in Table 4. 1 (see "Arkansas Department", 2017; "Centers", 2016). The time interval included time from event such as healthcare provider recognizing a suspected case or positive laboratory finding prompting public health notification. Time began when an individual entered the healthcare system and either tularemia was suspected by syndromic presentation or a specimen collected from the individual was culture positive for *Francisella tularensis* or other laboratory test was indicative for tularemia as presented in Table 4. 2 (see Mahon & Lehman, 2019; Penn, 2015). Completeness of data and compliance criteria depicted in Figure 4. 1 and Table 4. 2 were guided using predefined forms available online (see "Arkansas Department", 2017; "Centers", 2016).

Analysis

The time from recognition to reporting was categorized by timely (same day or next day) or delayed as greater than next day but less than seven days, greater than seven days but less than 30 days, or greater than 30 days based on the requirement of reporting tularemia within 24 hours (see "Arkansas Department", 2016, 2017; "Centers", 2016).

Evaluation of completeness of case reporting included compliance to demographic fields, laboratory test method and result, and clinical data conducive to conducting an epidemiological investigation (see "Arkansas Department", 2016, 2017; "Centers", 2016).

Results

Between January 2009 and December 2018, there were 335 confirmed and probable tularemia cases reported in 53 of 75 Arkansas counties as displayed in Figure 4. 2. Incidence rates varied by county with the highest rates seen in rural counties within the Northern region of the state as depicted in Table 4. 3. Tularemia cases classified as probable exhibited a sharp increase throughout the study period while confirmed cases steadily decreased as represented in Figure 4. 3. Transmission mode as shown in Table 4. 2 represents primary or secondary classification post epidemiological investigation and in some cases, secondary classification resulted in modification of primary classification (see "Arkansas Department", 2016, 2017; "Centers", 2016). In 2017, modifications to case definitions included discontinuing "intestinal" as a clinical form (see "Tularemia", n.d.).

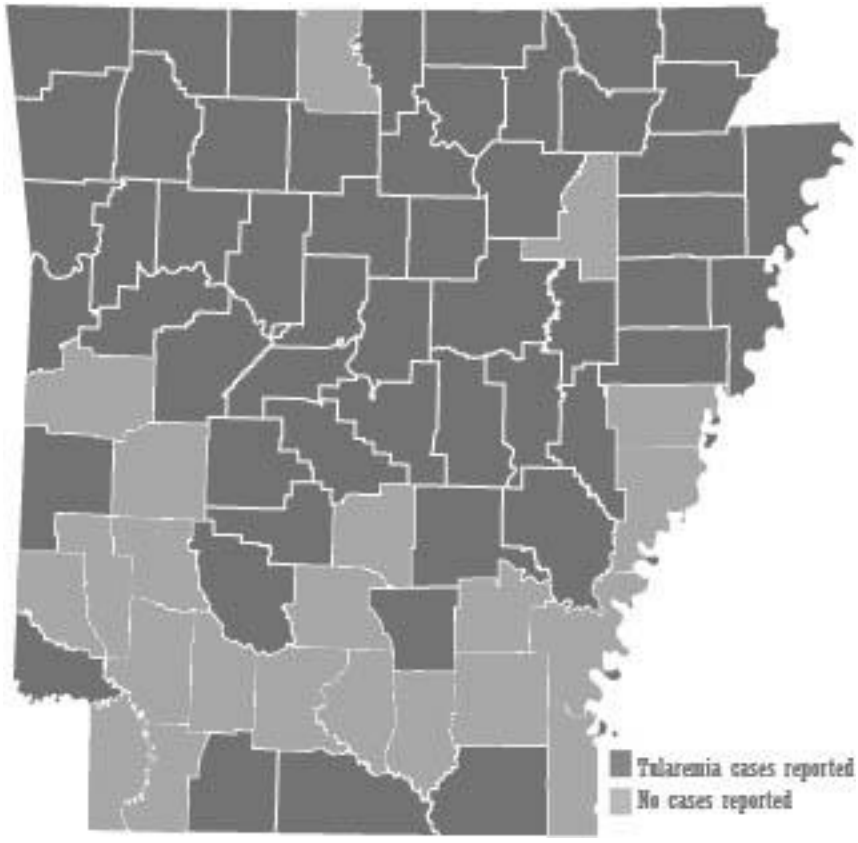

Figure 4. 2. Tularemia case distribution within Arkansas representing confirmed and probable cases between January 2009 and December 2018.

Table 4. 3.
Tularemia case distribution by incidence rate per 100,000 persons of confirmed and probable cases by county and region within Arkansas between January 2009 and December 2018.

County	Incidence per 100,000 persons	Population	Total number of cases	Region
Stone	104.9	12,394	13	North central
Sharp	69.5	17,264	12	North central
Izard	65.7	13,696	9	North central
Fulton	49	12,245	6	North central
Searcy	48.8	8,195	4	North central
Conway	42.3	21,273	9	Central
Marion	42	16,653	7	North central

Woodruff	41.3	7,260	3	Northeastern
Van Buren	40.5	17,295	7	North central
Randolph	39	17,969	7	Northeastern
Baxter	38.5	41,513	16	North central
Madison	38.2	15,717	6	Northwestern
Lawrence	34.5	17,415	6	Northeastern
Cross	28	17,870	5	Northeastern
White	24.7	77,076	19	Central
Newton	24	8,330	2	Northwestern
Cleburne	23.1	25,970	6	North central
Faulkner	23	113,237	26	Central
Cleveland	23	8,689	2	South central
Independence	21.8	36,647	8	North central
Lonoke	20.5	68,356	14	Central
Perry	19.1	10,445	2	Central
Clay	18.7	16,083	3	Northeastern
Johnson	15.7	25,540	4	Northwestern
Little River	15.2	13,171	2	Southeastern
Boone	13.5	36,903	5	Northwestern
Logan	13.4	22,353	3	West central
Washington	13.3	203,065	27	Northwestern
Pope	13	61,754	8	North central
Monroe	12.3	8,149	1	East central
Prairie	11.5	8,715	1	Central
Franklin	11	18,125	2	West central
Polk	9.7	20,662	2	West central
Ashley	9.2	21,853	2	Southeastern
Benton	8.6	221,339	19	Northwestern
Columbia	8.1	24,552	2	Southwestern
Poinsett	8.1	24,583	2	Northeastern
Carroll	7.3	27,446	2	Northwestern
Sebastian	7.2	125,744	9	West central
Pulaski	6.3	382,748	24	Central
Hot Spring	6.1	32,923	2	Central
Arkansas	5.3	19,019	1	East central
Craighead	5.2	96,443	5	Northeastern
Jefferson	5.2	77,435	4	Central
Saline	4.7	107,118	5	Central
Yell	4.5	22,185	1	East central

Clark	4.3	22,995	1	South central
Saint Francis	3.5	28,258	1	East central
Crawford	3.22	61,948	2	Northwestern
Garland	3.12	96,024	3	Central
Greene	2.4	42,090	1	Northeastern
Union	2.4	41,639	1	South central
Mississippi	2.2	46,480	1	Northeastern

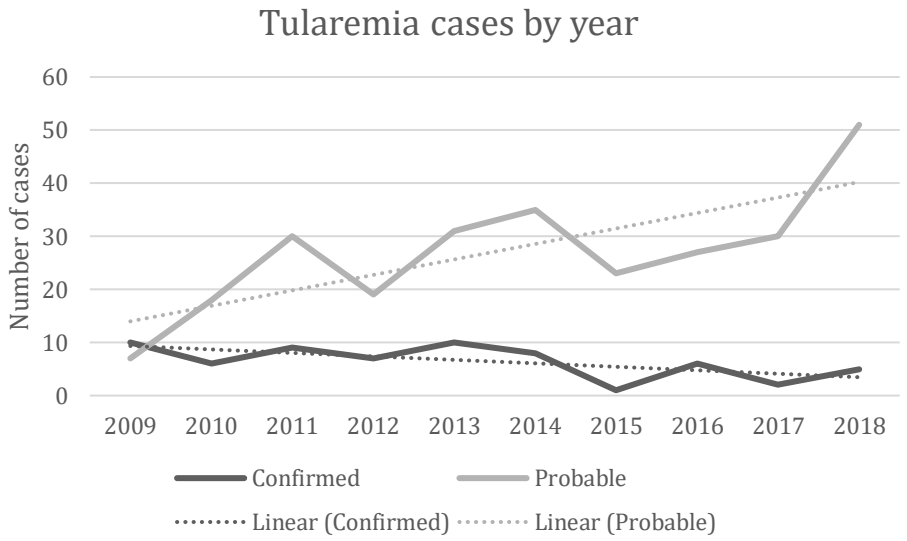

Figure 4. 3. Tularemia case distribution within Arkansas by year between January 2009 and December 2018 representing a sharp increase in probable cases and a steady decline in confirmed cases.

Timeliness

Time to reporting by category as shown in Figure 4. 3 demonstrated that compliance to next day reporting was 9.1% within this study signifying low compliance to public policy (see "Arkansas Department", 2016, 2017; "Centers", 2016). Time to reporting analysis using chi-square revealed statistically significant relationships between two of the five variables as shown in Table 4. 4 ($p < 0.05$). Clinical form and

transmission mode represent factors correlating with timeliness of public reporting (p = 0.013, p = 0.019 respectively). While laboratory criteria did not correlate with timeliness, diagnostic laboratory data are required for accurate case categorization as "confirmed" and thus may indirectly be associated with timeliness (see Penn, 2015). According to the CDC definition of "supportive" in Table 4. 1, diagnostic test results that were inconclusive of a tularemia diagnosis were considered as probable cases within this study (see "Centers", 2017).

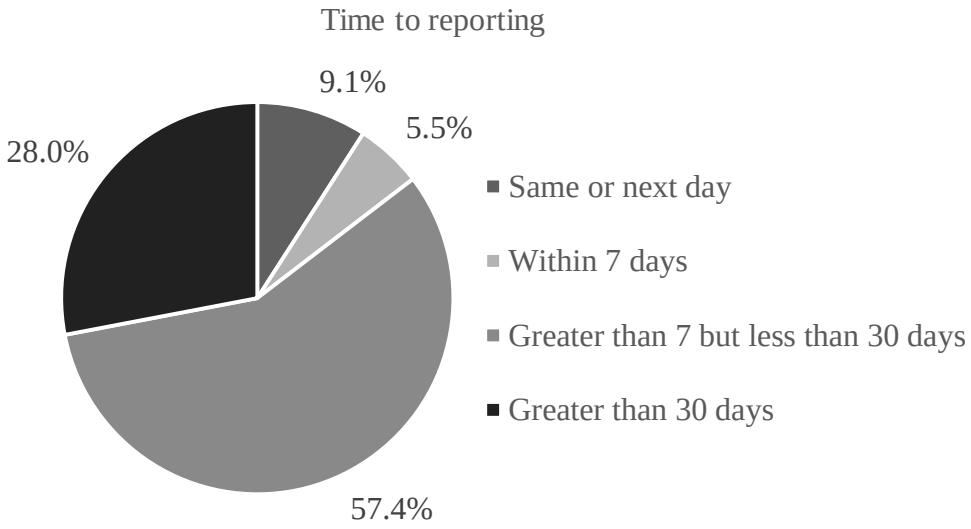

Figure 4. 4. Timeliness of reporting suspect tularemia cases by category to the Arkansas Department of Health between January 2009 and December 2018.

Table 4. 4.
Factors related to timeliness of reporting tularemia cases within Arkansas between January 2009 and December 2018. Clinical form and transmission mode were statistically significant ($p < 0.05$). After adjusting for gaps in clinical form documentation, typhoidal was added when other forms were ruled out (Racheal Odom, personal communication, May 6, 2019), there was no statistical significance between clinical form and timeliness ($p > 0.05$).

Factors	Pearson chi-square	Likelihood ratio	*df*	*p* value (Alpha)
Clinical form	38.11	37.92	21	0.013
Clinical form (adjusted)	18.66	19.73	18	0.413
Transmission mode	40.45	37.94	24	0.019
Case category	1.18	1.22	3	0.759
Case reporting entity	15.35	16.06	9	0.082
Laboratory criteria	11.70	12.64	12	0.470

Completeness

The tularemia case report provided by the CDC for state notification included questions and criteria related to patient demographics, history, clinical course, and laboratory evidence for documentation by healthcare workers or clinicians (see "Arkansas Department", 2016). Additional criteria included tularemia case status and epidemiological investigation for completion by public health officials in collaboration with the medical team and interaction with patient as necessary (see "Arkansas Department", 2016, 2017; "Centers", 2017). Completeness was assessed using demographic, clinical, and exposure data in order to determine clinical form and transmission mode (see "Arkansas Department", 2016, 2017; "Centers", 2017). Data included at risk behaviors, exposure, occupation, clinical history and course, and radiographic and laboratory results as available (see "Arkansas Department", 2016, 2017; "Centers", 2017).

Age distribution by number of cases presented in Figure 4. 4 depicts average age of 46 years (SD = 21.27, n = 334). Compliance to required demographic fields and characteristics depicted in Table 4. 5 represent gaps in documentation with 20% of race data either missing or unknown. Missing data necessary to determine clinical form and

transmission mode represent between 29.9% and 66.9% respectively meaning that gaps affected categorization of cases within these domains at the time of investigation (see "Arkansas Department", 2016, 2017; "Centers", 2017). Cases categorized as "probable" lacked sufficient laboratory data for confirmation or had inconclusive results representing a downward trend in confirmed cases by year despite an upward trend in probable cases. Over the entire study period, 80.9% of cases remained probable as shown in Table 4. 5.

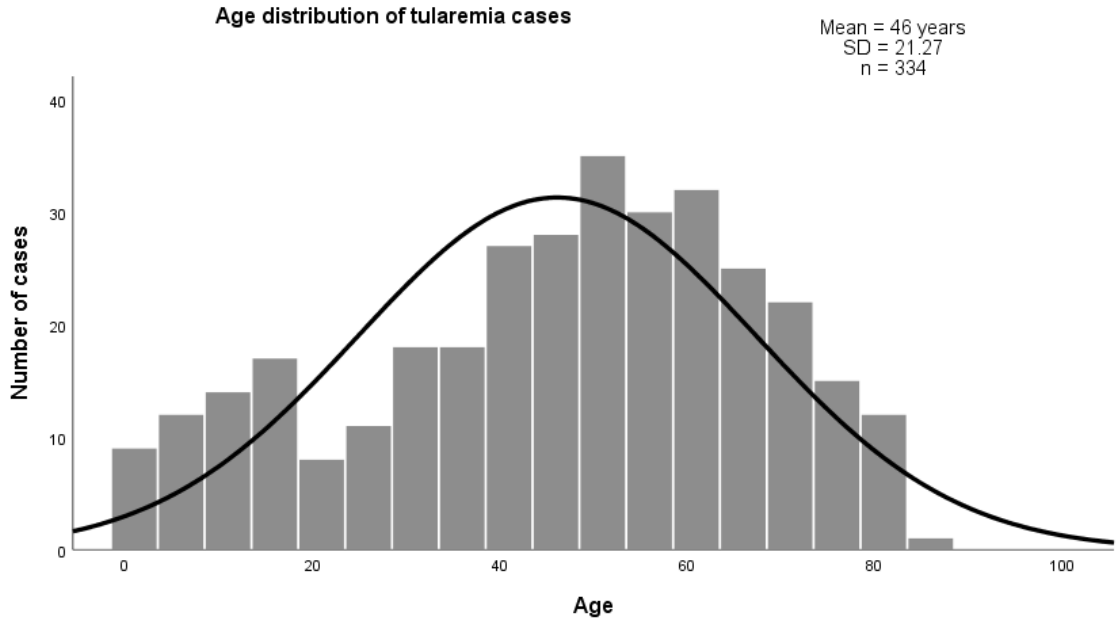

Figure 4. 5. Age distribution of tularemia cases between 2009 and 2018 representing average age of 46 years (*SD* = 21.27, *n* = 334).

Table 4. 5.
Percent of data by factor and completeness of data by category as related to tularemia case reporting and epidemiological investigations between 2009 and 2018. Percent reported is based on non-missing data.

Factor	Percent reported by category	Percent unknown or missing
Demographic data		
Average age = 46 years (range, 1-86, *n* = 334)		0.3

Sex (Male)	66.9	0.0
Race		20.0
White	78.5	
Black	1.2	
Native Hawaiian or Other Pacific Islander	0.3	
Ethnicity		5.1
Non-Hispanic	93.1	
Hispanic	1.8	
Clinical form		29.9
Glandular	17.0	
Intestinal	3.9	
Oculoglandular	0.6	
Oropharyngeal	1.5	
Pneumonic	3.3	
Typhoidal	28.1	
Ulceroglandular	15.8	
Transmission mode		66.9
Bloodborne	0.3	
Dermal	0.6	
Indeterminate	1.2	
Transplacental	0.3	
Vectorborne	26.6	
Waterborne	0.3	
Zoonotic	3.3	
Other	0.6	
Laboratory criteria		22.7
Culture positive	9.3	
Four-fold rise in titer	3.0	
PCR positive	1.2	
Single positive serology	63.9	
Case Category		n/a
Confirmed	19.1	
Probable	80.9	

Discussion

Tularemia is a reportable vector-borne disease within the state of Arkansas with aggregated data collected and reported at the national level (see "Arkansas Department", 2016, 2017; "Centers", 2016). *Francisella tularensis* is naturally occurring and endemic to Arkansas with the potential of an intentional release (Dennis et al., 2001). While *F. tularensis* does not pose significant risk person-to-person, there are occupational and behavioral risk factors based on exposure to vectors, hosts, environment, and potential aerosols within a laboratory environment (Berger, 2017; "Centers", 2016; Mahon & Lehman, 2019; Penn, 2015; Shapiro & Schwartz, 2002; Wurtz et al., 2016).

The assessment of timeliness and completeness of tularemia case reporting within Arkansas includes complex factors associated with clinical presentation and laboratory findings with reliance on timely recognition and reporting to ADH ("Arkansas Department", 2016, 2017). Most cases recorded did not adhere to the recommended time to reporting guidelines providing an opportunity for public health intervention and education (Samoff et al., 2013; Wang & DeSalvo, 2018). While there were no reported outbreaks during this study period, there was the potential for environmental influences and exposure (Balci et al., 2014; D'Alessandro et al., 2015). The sharp increase in probable cases and the decrease in confirmed cases may have uncovered an accessibility gap in laboratory services or opportunity to educate clinicians on recognition of clinical forms and the appropriateness and availability of gold standard diagnostic tests (Njeru et al., 2017: Rothfeldt et al., 2017).

Limitations

This study had several limitations. Multiple forms of communication may affect timeliness as reference laboratories used electronic reporting however, laboratories within hospitals did not have electronic reporting capabilities (R. Odom, personal communication, May 6, 2019). This might have contributed to positive tularemia test results without sufficient demographic and clinical data necessitating extensive clinical review within some instances (see Lamb et al., 2015; Overhage, Grannis, & McDonald, 2008). Factors related to timeliness and completeness did not account for potential seasonal differences or days falling on holidays or weekends that may affect compliance to public policy (Schumacher et al., 2017). Variability of investigative results did not account for perceptions, barriers, or facilitators of completeness by healthcare workers, clinicians, and public health officials (Revere et al., 2017). This study had several gaps in exposure related data over multiple years that may also be a result of recall bias due to the length of time from potential case recognition to investigation and categorization of case and underreporting (D'Alessandro et al., 2015; Feldman et al, 2003; Njeru et al., 2017).

Conclusions

Assessing factors related to timeliness and completeness of public health reporting of tularemia by HLPs and CLPs may uncover opportunities for targeted public health programs related to occupational, environmental, or behavioral exposure risk (“Centers”, 2017; Rossow et al., 2014; Wurtz et al., 2016). As case definitions evolve, an opportunity for collaboration, policy development, and communication may arise to

improve awareness and guide public policy (Blackburn et al., 2016). Public health reporting of positive laboratory results when no electronic reporting mechanisms are in place requires diligence from laboratory workers and hospital staff in order to ensure timeliness and completeness (Overhage et al., 2008). An opportunity to inform staff may lead to education and training opportunities to the potential occupational risk of aerosols for infection prevention and control (Shapiro & Schwartz, 2002). The results of this study may provide a baseline and metric to gage improvement (see Brown et al., 2015; Gluskin et al., 2014; Revere et al, 2017).

Significant gaps in documentation of transmission mode and clinical form were noted within the study period and subsequent analysis revealed the practice of using "*typhoidal*" categorically when other clinical forms were ruled out (Racheal Odom, personal communication, May 6, 2019). The practice of extrapolation presents an opportunity for using electronic reporting methods and computerized decision software that enable ongoing data integrity, feedback, and quality assessments (see Gluskin et al., 2014; Revere et al., 2017). In situations with low numbers of annual cases and complexities in clinical presentation and course, syndromic surveillance software may be helpful at the initial point of contact within the healthcare system to bring awareness to clinicians (Schumacher et al., 2017; Wang & DeSalvo, 2018). Consultative services at the patient and healthcare professional level were available and used within ADH during the study period as case reporting reflected patient initiation in some instances (L. Rothfeldt, personal communication, May 6, 2019). Recognition, timely reporting, and completeness of data necessary to conduct an epidemiological investigation using

tularemia as a model, may necessitate integrated electronic laboratory reporting and syndromic surveillance software within a collaborative framework (Gluskin et al., 2014; Schumacher et al., 2017; Wang & DeSalvo, 2018).

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Part 3: Summary

Integration of Findings

Tularemia is vector borne zoonotic infectious disease of global concern with regional differences in case distribution over time (Berger, 2017; Desvars et al., 2015; Desvars-Larrive et al., 2017; Hestvik et al., 2015; Hightower et al., 2014; Larssen, et al., 2014; "Tularemia', 2016). Tularemia has the potential of intentional release as a biological weapon and is a reportable disease within the endemic state of Arkansas ("Arkansas Department", 2017; "Centers", 2016; Dennis et al., 2001; Eisen et al., 2008). This three-part study addressed the geospatial and spatiotemporal case distribution of tularemia within Arkansas counties while also evaluating timeliness and completeness of public health reporting of suspect tularemia cases within the human population. The nature of zoonotic diseases spread by vectors and hosts relies on conditions that are favorable for the life cycle of *Fransciella tularensis*, the causative agent of tularemia, and factors that support and influence sustainability and adaptability influencing the life cycle encompassing multiple disciplines (Berger, 2017; Hestvik et al., 2017; Maurin & Gyuranecz, 2016; Rossow et al., 2014). The continuum of this complex environmental, zoonotic, and clinical process warranted this three-part study iteratively in order to focus on ecological factors spatially after determination of clustering and risk ("Centers", 2016; Dennis et al., 2001; Hightower et al., 2014; Shapiro & Schwartz, 2002; Wurtz et al., 2016). Failure to recognize tularemia and ineffective communication within this continuum may place laboratory workers at an increased risk due to aerosols, low infective dose, and high mortality rate (Dennis et al., 2001; Mahon & Lehman, 2019;

Wang & DeSalvo, 2018). By integrating the first two initial studies, descriptive statistics revealed that case distribution trended toward White males with average age range in the 40s living in the Northeastern forested part of the state within the total number of cases and high-risk cluster (see Rothfeldt et al., 2017). As there were no laboratory workers within the high-risk cluster, over half of the risks reported revealed histories of tick or biting fly bites followed by outdoor behaviors necessitating both epidemiological studies (see Eisen et al., 2008; Rothfeldt et al., 2017). This three-part study contributes to a better understanding of the complexities involved in tularemia case distribution and subsequent attributable risk within Arkansas (see Rothfeld et al., 2017).

Tularemia is a seasonal disease based on host and vector activity as related to weather fluctuations and outdoor activities ("Arkansas Department", 2017; "Centers", 2016; Desvars-Larrive et al., 2017; Hestvik et al., 2015). I found that geographical location, annual precipitation, and time by year were significant risk factors while laboratory workers were not a significant at-risk population. However, this study revealed a decrease in confirmed cases despite a sharp rise in probable cases, meaning that laboratory exposure of *F. tularensis* was minimal as cases were either diagnosed using clinical presentation or serological tests without culture confirmation which did not place laboratory workers at-risk ("Arkansas Department", 2016; Rothfeldt et al., 2017; Shapiro & Schwartz, 2002; Wurtz et al., 2016). The delay in timeliness and gaps in data supports difficulty in recognition of disease etiology and the potential opportunity for focused public health educational programs (Hoffman & Silverberg, 2018; Mailles & Vaillant, 2014; Njeru et al., 2017; Rothfeldt et al., 2017). The parsing of population by

demographic, spatial, and ecological risk may provide customized baseline data for model building (Desvars-Larrive, et al., 2017; Rossow et al., 2014).

Conceptual Framework

The conceptual framework of classical epidemiology determining person, place, and time using spatial statistics supported this three-part study by evaluating case distribution for clustering and ecological assessment (Shiode et al., 2015; Snow, 1855; Szklo & Nieto, 2014). Spatial statistical software allowed cluster analysis and ecological factor association of low number of cases using Monte Carlo simulations, Poisson distribution, and maximum entropy algorithms signifying a novel approach to epidemiological study of tularemia case distribution within the United States (see Eisen et al., 2008; Kirby et al., 2017; Kulldorf, 2001; Philips et al., 2018; Rothfeldt et al., 2017; Tang et al., 2017). After determination of high and low-risk clusters, maximum entropy analysis of habitat suitability revealed statistical significance of annual precipitation as an identified historical drought preempted an increase in annual cases lasting multiple years. Both cluster analysis and subsequent ecological assessment used contemporary geospatial tools novel to spatial epidemiology of tularemia within the United States as previous methodologies incorporated logistic regression (see Blackburn et al., 2016; Eisen et al., 2008; Kirby et al., 2017)

The concept of *nidality* signified a symbiotic interplay of land epidemiology and vector and host activity over time, supporting the results in this three-part study as tularemia case distribution was associated with forests, foothills, and exposure histories of tick bites and outdoor activities (see Hightower et al., 2014; Pavlovsky, 1966). By

using a stepwise approach, determination of clusters within the first study provided focused insight related to assessment of climate change by geospatial risk. While land suitability and annual precipitation were factors associated with case distribution, annual mean temperatures and temperature fluctuations did not contribute to the model contraindicating previous findings (Balci et al., 2014; Ogden & Lindsay, 2016; Ryden et al., 2009).

Unanticipated Findings

Within Arkansas, annual tularemia case distribution ranged between six and 56 representing low-incidence disease as compared to global occurrences and outbreaks (Berger, 2017; "Centers", 2016; Hestvik et al., 2015; Maurin & Gyuranecz, 2016). However, regional hotspots detected within this three-part study revealed diverse incidence rates spatially as one high-risk county reflected 115 times the annual average incidence within Arkansas as a whole. This resulted in the first reported occurrence of regional hotspots listed by cluster and relative risk by county and cluster ("Centers", 2016; Rothfeldt et al., 2017).

Another unanticipated finding was the detection of a historical drought followed by an increase in probable cases whereas average annual temperatures were not a significant factor in case distribution. This differed from tularemia case distribution within Europe as mosquitos serve as primary vector proliferating during rainy seasons and environmental contamination leading to water borne disease (Balci et al., 2014; Jamison et al., 2015; Ogden & Lindsay, 2016). Fluctuations in annual precipitation

correlated to case distribution by year visualized by graph representing the 23-year ecological study period despite the upward trend in cases.

Social Change

Within this three-part study, tularemia risk factors spanned behavioral, occupational, environmental, zoological, and political realms supporting systematic social awareness and change approach (see Blackburn et al., 2016; Dennis et al., 2001; Desvars-Larrive et al., 2017; Hestvik et al., 2015). Within the first study, clustering revealed spatial and behavioral risks, the second study added an element of climate as precipitation was a factor affecting case distribution; and finally, the third study revealed gaps in at-risk data influencing the ability to accomplish an effective epidemiological investigation in order to determine etiology. Knowledge gained could provide focused interdisciplinary education and cohesive communication strategies (Bartholomew et al., 2015; Blackburn et al., 2016; Brown et al., 2015). This three-part study contributed to the body of knowledge within social change aspects of collaboration, laboratory diagnostics, public health department efficiencies, disaster preparedness, policy development, and public health funding.

The iterative style of this three-part study fits together activities within multiple disciplines influencing vector borne diseases using ecologists, climatologists, primary healthcare professionals, veterinary services, and entomologists within systems research. These findings could serve as cross-functional educational opportunities with stakeholders supporting applicability of collaboration (see Rao et al., 2017; Wiethoelter et al., 2015). Collaboration between multiple disciplines to lessen the burden of

infectious diseases with globally high consequence potential has been a focus within CDC and WHO domains (Blackburn et al., 2016; “Centers”, 2017; “World”, 2018).

Gaps in laboratory diagnostics uncovered opportunities to improve access to tularemia testing and knowledge of clinicians on the appropriateness of tests for confirmation of disease. Optimizing clinical diagnostics related to sensitivity and specificity of laboratory testing and the ability to differentiate previous exposure and active disease could serve as a collaborative educational opportunity mitigating the decrease seen in confirmed cases within this three-part study (Mahon & Lehman, 2019; Nakajima et al., 2016). Awareness programs reaching multiple disciplines in an integrating and enriching environment may support early recognition (Kluberg et al., 2016; Mackey et al., 2014). Better communication and documentation of individual cases encompassing multiple disciplines may close gaps in data presented in this three-part study that affected the timeliness of public health reporting (Gopalakrishna-Remani et al., 2017; Wang et al., 2018). While all cases within this study were naturally occurring with no evidence of intentional release, progress towards rapid detection using syndromic surveillance coupled with confirmatory testing supports disaster preparedness (see Grundmann, 2014; Grunow & Finke, 2002; “World”, 2018). The implementation of electronic reporting within hospital laboratory settings may serve to improve timeliness of public reporting necessitating partnerships with informatics specialists (Castellani et al., 2015; Lamb et al., 2014).

There are many opportunities for prevention and early recognition of tularemia that span social change. With the geospatial baseline and detection of high and low-risk

clusters completed within this retrospective three-part study, a model is possible to detect clusters prospectively (see Kirby, 2017). An extension of a model may incorporate assessment criteria to determine probability of naturally occurring case distribution or intentional release using these findings as a benchmark (Chen et al., 2017; Grunow & Finke, 2002). As climate changes and extremes in weather patterns occur, climatologists may be conduits of tick warnings in endemic regions similar to warnings conducted for meningitis (Pandy et al., 2015). However, with levels of climate predictability to disease uncertainty and the balance of informing without instilling fear, a cohesive and scientific method approach within collaborative framework necessitates partnerships (Rosenbaum, 2015).

This three-part study addressed missing data and delays in reporting tularemia as a public health reportable disease. These findings contribute to scientific knowledge within a social change domain by providing information as feedback to healthcare professionals and clinical laboratories for potential improvement and the positive consequence to public health and safety. Gaps in data, inaccuracies in documentation, and delays in reporting contribute to inefficiencies within public health departments that can be mitigated (Castellani et al., 2015; Gluskin et al., 2014; Jakob et al., 2017; Johnson et al., 2014). Policy development may necessitate avenues for education and awareness within the collaborative framework of stakeholders as well as populations at-risk and the continuum of public reporting (Chen et al., 2017; Revere et al., 2017). As improvements within syndromic surveillance and laboratory testing ensue, heightened awareness within

laboratory workers may necessitate attention to this population (Grundmann, 2014; Shapiro & Schwartz, 2002).

Future Research Opportunities

Over the 24-year study period, case definitions evolved multiple times adding to the complexity of study. Prospective research and the potential impact on timeliness and accuracy of data leads to opportunities for future analysis (Desvars-Larrive et al., 2017; Jakob et al., 2017; Kulldorf, 2001). This study incorporated SatScan software that has the capability of detecting clusters near real-time, which would require interfacing clinical laboratories and healthcare databases with consideration of integrating syndromic surveillance software at the patient's initial point of contact (Desvars-Larrive et al., 2017; Kirby et al., 2017; Kulldorf, 2001). This study found that only reference laboratories used interfaced reporting leading to questions of interface feasibility to build on improvements in timeliness and completeness of data with subsequent assessment (Johnson et al., 2014; Samoff et al., 2013a).

Habitat adaptability served as a proxy for vector and host presence and sustainability (Blackburn et al., 2016; Kraemer et al., 2016). Future studies may warrant conducting tick counts and tularemia field studies as a direct measure of niche presence and areas of potential high-risk exposure (Atkinson et al., 2014; Desvars et al., 2015; Desvars-Larrive et al., 2017; Jamison et al., 2015). As land suitability changes, research into evolving host and vector viability may produce differing results (Jamison et al., 2015).

Within Arkansas, there were no published reports of underreported cases of tularemia. A point prevalence investigation of patients that enter the healthcare system using serological testing may detect previous exposure or undetected cases and serve as a baseline of exposure (Njeru et al., 2017). Assessment of feasibility and whether testing should be performed by public health laboratories warrant further consideration.

Lessoned learned include recognition of suspect tularemia cases at the point of patient contact may provide additional incentive for confirmatory laboratory testing increasing exposure for laboratory workers necessitating heightened awareness and communication (Dennis et al., 2001; Shapiro & Schwartz, 2002; Wurtz et al., 2016). The feasibility of syndromic surveillance may warrant further exploration as a means of early recognition. This may serve as an opportunity for qualitative research using a theoretical lens to understand barriers (Creswell, 2014; Frankfort-Nachmias Nachmias, & DeWaard, 2015).

Conclusions

Tularemia is a complex vector-born infectious disease of low incidence within the United States with niche-specific risk revealed within Arkansas during the 24-year study period ("Arkansas Department", 2017; Berger, 2017; "Centers", 2016). This three-part study allowed iterative research based on findings that systematically flowed into further research questions. While epidemiological investigations conducted within ADH revealed no clustering or outbreaks, novel technological software using different statistical methods uncovered different at-risk populations geospatially. Within the auspices of studying low-incidence zoonotic diseases, multiple statistical methods may

increase research robustness while working collaboratively with multidisciplinary stakeholders (Balci et al., 2014; Hestvik et al., 2014; Ogden & Lindsay, 2016; Sedda et al., 2014).

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Appendix A: Tularemia Case Report (Archived)

TULAREMIA CASE REPORT
ARKANSAS DEPARTMENT OF HEALTH

PLEASE PRINT LEGIBLY

Information has been received from _____indicating that the patient named below may have been infected with Tularemia. Please complete this form and return it to us in the envelope supplied. This information will enable the Department to provide accurate epidemiologic information and assistance to you and other healthcare workers, as well as to visitors and residents of the state.

Patient first name _____ Last name _____ DOB ___/___/_____
Street_____ City _____ Zip _____
Telephone (____)_____ Occupation _____
Sex ____ Race: __White __ Black __Asian __Amer.Indian __Other Hispanic Y N Unk
Outcome, if known: ____survived ____died Date of death ___/___/____

Name of parent or guardian if patient is a child _____

Symptom onset date ___/___/_____ Date seen by MD. ___/___/_____
Hospitalized Y N Date/Hospital_____

Fever Y N Temp. _____ Headache Y N GI symptoms Y N
Skin ulcer Y N Lymphadenopathy Y N Site_____
Pneumonia Y N X-Ray evidence Y N Clinical Y N

Culture done Y N Site_____ F. tularensis isolated Y N
Tularemia serology Y N Results/Dates_____
_____

Exposure:

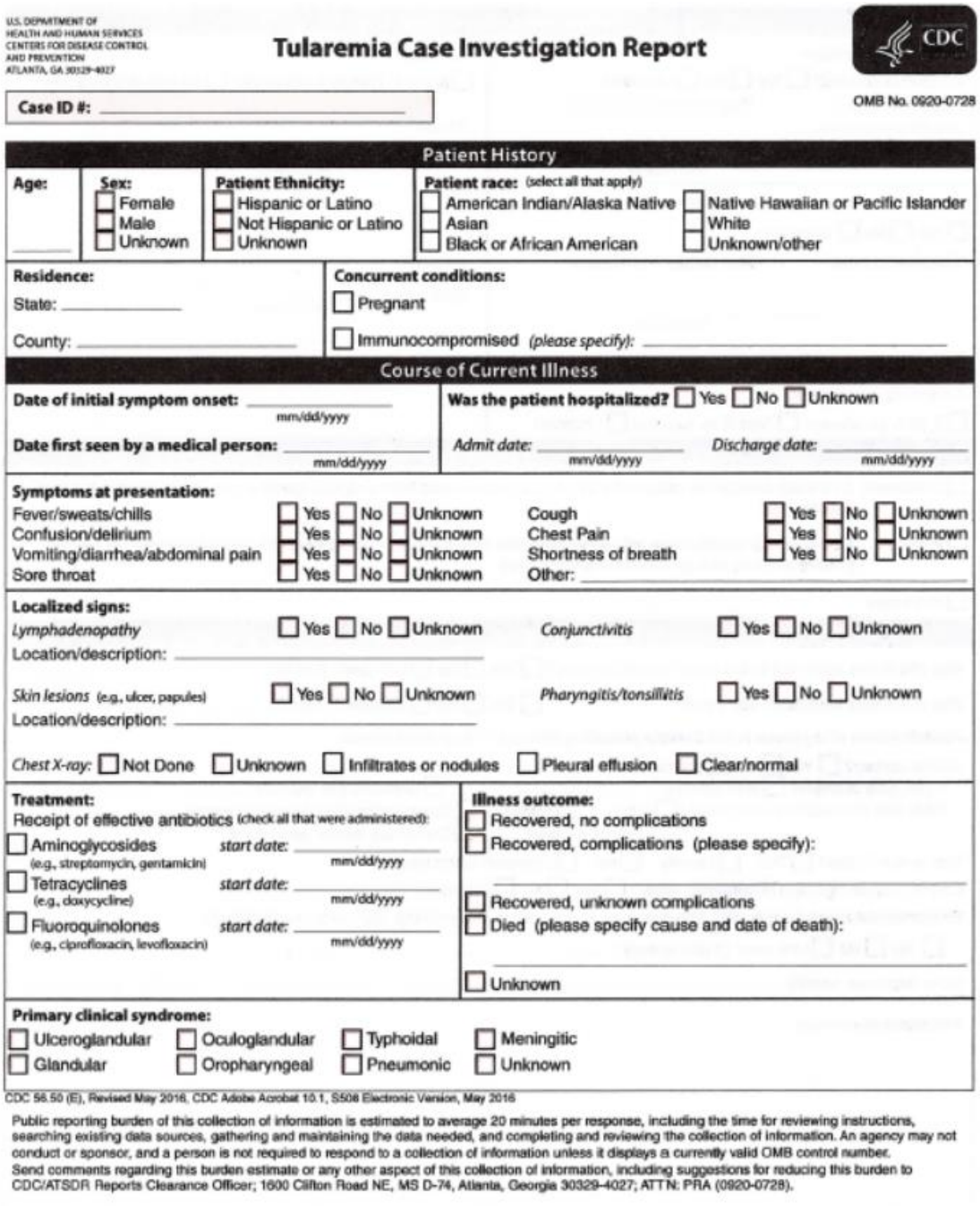
Tickbite ___/___/_____ Wild animal contact ___Rabbit ___Deer __Other_____
County of exposure_____ Date of exposure ___/___/_____
Ingestion of surface water Y N Game Y N Date ___/___/_____

Type: Ulceroglandular ___ Typhoidal___ Oculoglandular__Primary Pulmonary__

Comments_____
_____

Please attach copies of supporting laboratory test results.

Appendix B: Tularemia Case Investigation Report (Current)



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION
ATLANTA, GA 30329-4027

Tularemia Case Investigation Report

CDC

OMB No. 0920-0728

Case ID #: _____

Patient History

Age: _____

Sex: ☐ Female ☐ Male ☐ Unknown

Patient Ethnicity: ☐ Hispanic or Latino ☐ Not Hispanic or Latino ☐ Unknown

Patient race: (select all that apply)
☐ American Indian/Alaska Native ☐ Asian ☐ Black or African American ☐ Native Hawaiian or Pacific Islander ☐ White ☐ Unknown/other

Residence:
State: _____
County: _____

Concurrent conditions:
☐ Pregnant
☐ Immunocompromised *(please specify)*: _____

Course of Current Illness

Date of initial symptom onset: _____ mm/dd/yyyy

Date first seen by a medical person: _____ mm/dd/yyyy

Was the patient hospitalized? ☐ Yes ☐ No ☐ Unknown
Admit date: _____ mm/dd/yyyy *Discharge date:* _____ mm/dd/yyyy

Symptoms at presentation:

Fever/sweats/chills	☐ Yes ☐ No ☐ Unknown	Cough	☐ Yes ☐ No ☐ Unknown
Confusion/delirium	☐ Yes ☐ No ☐ Unknown	Chest Pain	☐ Yes ☐ No ☐ Unknown
Vomiting/diarrhea/abdominal pain	☐ Yes ☐ No ☐ Unknown	Shortness of breath	☐ Yes ☐ No ☐ Unknown
Sore throat	☐ Yes ☐ No ☐ Unknown	Other: _____	

Localized signs:
Lymphadenopathy ☐ Yes ☐ No ☐ Unknown *Conjunctivitis* ☐ Yes ☐ No ☐ Unknown
Location/description: _____

Skin lesions (e.g., ulcer, papules) ☐ Yes ☐ No ☐ Unknown *Pharyngitis/tonsillitis* ☐ Yes ☐ No ☐ Unknown
Location/description: _____

Chest X-ray: ☐ Not Done ☐ Unknown ☐ Infiltrates or nodules ☐ Pleural effusion ☐ Clear/normal

Treatment:
Receipt of effective antibiotics (check all that were administered):
☐ Aminoglycosides (e.g., streptomycin, gentamicin) *start date:* _____ mm/dd/yyyy
☐ Tetracyclines (e.g., doxycycline) *start date:* _____ mm/dd/yyyy
☐ Fluoroquinolones (e.g., ciprofloxacin, levofloxacin) *start date:* _____ mm/dd/yyyy

Illness outcome:
☐ Recovered, no complications
☐ Recovered, complications (please specify):
_____
☐ Recovered, unknown complications
☐ Died (please specify cause and date of death):
_____
☐ Unknown

Primary clinical syndrome:
☐ Ulceroglandular ☐ Oculoglandular ☐ Typhoidal ☐ Meningitic
☐ Glandular ☐ Oropharyngeal ☐ Pneumonic ☐ Unknown

CDC 56.50 (E), Revised May 2016, CDC Adobe Acrobat 10.1, S508 Electronic Version, May 2016

Public reporting burden of this collection of information is estimated to average 20 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to CDC/ATSDR Reports Clearance Officer; 1600 Clifton Road NE, MS D-74, Atlanta, Georgia 30329-4027; ATTN: PRA (0920-0728).

Laboratory Evidence of Infection

Detection or Isolation

F. tularensis cultured? ☐ Yes ☐ No ☐ Unknown

Specimen source (e.g., blood, wound swab) _____ Date specimen collected _____ mm/dd/yyyy

If not cultured, presence of *F. tularensis* detected?

☐ Yes ☐ No ☐ Unknown

Specimen source _____ Date specimen collected _____ mm/dd/yyyy

Test performed (e.g., DFA or PCR) _____

F. tularensis subspecies:

☐ Type A (i.e., *tularensis*) ☐ Type B (i.e., *holarctica*) ☐ Unknown

Serology:

☐ None ☐ Single positive titer ☐ ≥4-fold change in titer

Serum 1:

Date drawn _____ mm/dd/yyyy

Titer: _____

Serum 2:

Date drawn _____ mm/dd/yyyy

Titer: _____

Tularemia Case Status

☐ **Confirmed** A clinically-compatible case with either *F. tularensis* cultured from a clinical specimen or ≥4-fold change in serum antibody titer

☐ **Probable** A clinically-compatible case with either detection (not isolation) of *F. tularensis* in a clinical specimen or a single positive antibody titer (or <4-fold change in titer)

☐ **Not a case**

Epidemiologic Investigation

Was this illness epi-linked to any other tularemia cases? ☐ Yes ☐ No ☐ Unknown Specify: _____

Was this illness associated with travel? ☐ Yes ☐ No ☐ Unknown Specify: _____

Possible routes of exposure: In the 2 weeks preceding illness, did the patient report:

Animal contact? ☐ Yes ☐ No ☐ Unknown

If yes, type of animal ☐ Wild (specify: _____) ☐ Domestic pet (specify: _____)

What was the nature of the contact? ☐ Bitten ☐ Scratched ☐ Disposed/handled deceased animal ☐ Cleaned carcass ☐ Consumed hunted game meat

Tick or deerfly bite? ☐ Tick ☐ Deerfly ☐ No ☐ Unknown insect type

Contact with or ingestion of untreated water? ☐ Yes ☐ No ☐ Unknown

Environmental aerosol-generating activities (e.g., brush-cutting, lawnmowing, high-pressure spraying)?

☐ Yes ☐ No ☐ Unknown (If yes, specify: _____)

Other exposure: specify _____

Additional comments:

CDC 56.50 (E), Revised May 2016, CDC Adobe Acrobat 10.1, S508 Electronic Version, May 2016

Appendix C: Submission Confirmation of Manuscript

18-Jun-2019

Dear Ms. Beavers,

Your manuscript entitled "Spatiotemporal Analysis of Tularemia within Arkansas: Evaluation of Clusters and Risk" has been successfully submitted online and is presently being given full consideration for publication in Epidemiology and Infection.

Your manuscript ID is HYG-OM-9854-Jun-19.

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