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Temporal Trends in Tularemia Incidence In The United States From 2010 to 2020. Are Age And Sex Associated With These Changing Trends?

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TEMPORAL TRENDS IN TULAREMIA INCIDENCE IN THE UNITED STATES FROM 2013 TO 2019 ARE AGE AND SEX ASSOCIATED WITH THESE CHANGING TRENDS?

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PUBLIC HEALH

ABSTRACT

Background: Tularemia or Rabbit Fever was discovered in 1911 in a plague-like outbreak among rodents in Tulare County, California. Tularemia in the US has expanded from rural to more metropolitan areas, which may be potentially correlated with the escalating exposure of humans to animal vectors. There has not been a recent study evaluating trends in Tularemia, especially one that has evaluated if the trends in Tularemia over time differ by demographic characteristics.

Methods: This is an ecological study to evaluate the temporal trends and if trends Tularemia incidence over time differs by age and sex in the United States from 2010-2019. The National Notifiable Diseases Surveillance System database was used to obtain tularemia data, and incidence rates were calculated based on annual US Census data. A generalized linear model was used to assess temporal trends in Tularemia and if trends differed by age and sex using interaction terms.

Results: When analyzing temporal trends, the average Tularemia incidence between 2010 – 2019 was 0.07 per 100,000 people, with the highest incidence of 0.10 in 2015 and the lowest incidence of 0.04 in 2010. The generalized linear model showed that over the study period, Tularemia incidence increased by 0.004 per 100,000 persons (p = 0.001). Men had the highest incidence of Tularemia, ranging from 0.05 in 2010 to 0.11 in 2019 compared to 0.03 in 2010 and 0.07 in 2019 in women. However, there was no difference in temporal trends by sex (p = 0.24). Tularemia incidence was highest in those 65 years of age and older, especially in the 2015 spike, but there were no differences in temporal trends by age group (p = 0.08).

Conclusion: Overall Tularemia incidence increased slightly during the study period, with no difference in trends by sex and age. Future studies should focus on the increased risk presented by domestic pets and if vaccines could be helpful.

Keywords: tularemia, vector

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LIST OF ABBREVIATIONS

CDC	Center for Disease Control & Prevention
NNDSS	National Notifiable Diseases Surveillance System

INTRODUCTION

Caused by a small gram-negative bacterium, Tularemia or Rabbit Fever was identified in 1911 in a plague-like outbreak among rodents in Tulare County, California (Ellis, JR et al, 2002). The bacteria are found in mammals, primarily rabbits, and amphibians. Subsequently named *Bacterium tularensis* (Ellis, JR et al, 2002), the bacteria can be transmitted from animals to humans (Zargar, Afsaneh et al 2015). In 1947 Tularensis became part of its own genus called Francicella, which was characterized into four subspecies – tularensis, holartica, mediasiatica, and novicida inhalation (Fooladfar, Z et al 2023). Tularensis and holartica are the main bacteria that spread the disease, with tularensis, the most dangerous, being the organism traditionally found in the US and holartica in the remainder of the world (*Factsheet on Tularaemia*, 2017).

Once encountering the organism, the incubation period averages 3-5 days but can occur anywhere between 1-21 days (*Tularemia for Public Health Officials | CDC*, 2022). All cases of Tularemia have the same generalized signs and symptoms – fever, chills, headache, malaise and fatigue. Different routes of transmission determine the presentation of the remaining signs and symptoms (*Tularemia for Clinicians | CDC*, 2022). Table 1 describes the six different possible presentations/syndromes of Tularemia.

Tularemia is exclusive to the northern hemisphere (Ellis JR et al, 2002). It thrives during the warmer months but is still a threat in the winter. Most, if not all cases during the winter, occur in rural areas to people who encounter infected animals (e.g., hunters, butchers, and those who skin animals for trade). European countries report around 800 cases a year, with Sweden and Finland reporting the highest numbers. However, there are countries with no reports of Tularemia including Iceland, Ireland and the United Kingdom (*Factsheet on Tularaemia*, 2017). The US averages about 200 cases per year (CDC, 2018) in all states except Hawaii (the brown

TYPE	TRANSMISSION	SIGNS AND SYMPTOMS
Ulceroglandular *	usually a bite - tick or deer fly, handling an infected animal	ulcer at site of infection, swelling of regionl glands - groin or armpit
Glandular	same as above	no visual ulcer, swelling of regionl glands - groin or armpit
Oculoglandular	bacteria enter through eye(s) after handling an infected animal	irritation and inflammaion of the eye with swelling of lymph glands in front of the ear.
Oropharyngeal	eating or drinking contaminated food or water	sore throat, mouth ulcers, tonsillitis, and swelling of lymph glands in the neck
Pneumonic **	breathing dusts or aerosols containing the organism	cough, chest pain, and difficulty breathing
Typhoidal	possibly - eating or drinking contaminated food or water	combination of generalized symptoms without localized symptoms noted above.

*most common
**most dangerous

Table 1. Tularemia Transmission Routes with Signs & Symptoms

dog tick and the spinose ear tick found in Hawaii do not prefer human contact Allred (2022). In the warmer months, the mode of transmission can be through inhalation of airborne particles, ingestion of contaminated water, tick bites and deer flies. To date, there has been no evidence of human-to-human contact.

In the summer of 2000, a Tularemia outbreak occurred on Martha's Vineyard ("Tularemia Cases on Martha's Vineyard Puzzle Experts," 2004). A construction worker reported to the island hospital complaining of chest pain, general malaise, a high fever, and a terrible cough. Soon others began to arrive with the same symptoms. There was no known vector on the island that could produce such symptoms, which puzzled health care providers. Once testing began, all the patients appeared to have pneumonic tularemia. This was alarming as *Francisella tularensis* had been classified as a Category A biological weapon (*Tularemia Facts*, n.d.), the most dangerous biological weapons, in the 1950's, because the aerosolization of as few as 10 microparticles can lead to pneumonic Tularemia and can be deadly if intervention is not received in time. Through this outbreak, researchers discovered that in certain areas the bacterium had become naturally airborne.

Cases of Tularemia in the US have expanded from rural to more metropolitan areas, which may be potentially correlated with the escalating human and animal population. A 2018 study found that between 2013-2016, at least 13 reported human cases were linked to contact with domestic dogs (e.g., family pets) that were only allowed outside a few times a day (Kwit et al., 2019). While Tularemia cases appeared to have remained stable, researchers realized that Tularemia was no longer just a "rural" occurrence. ("Tularemia Cases on Martha's Vineyard Puzzle Experts," 2004), potentially increasing the exposure to the bacterium in other urban or suburban areas, as well as in different age and sexes. However, to our knowledge, there has not been a recent evaluation trends in Tularemia, specifically focusing on differences by demographic groups. Thus, this study aims to evaluate trends in Tularemia between 2010 and 2019, and to determine if trends differ by age and sex.

METHODS

Study Design and Setting

An ecological study was designed to evaluate temporal trends in US Tularemia incidence from 2010 – 2019 using the National Notifiable Diseases Surveillance System (NNDSS). Sponsored by the Centers for Disease Control and Prevention (CDC), the NNDSS conducts surveillance to better understand, track, and respond to health threats. (*NNDSS - TABLE 1JJ. Tuberculosis to Tularemia | Data | Centers for Disease Control and Prevention*, 2021). In partnership with the Council of State and Territorial Epidemiologists, NNDSS determines which conditions reported to local, state, and territorial public health departments are nationally notifiable. The role of the NNDSS is to collect, analyze and report data on national notifiable diseases to programs across CDC. The data are compiled weekly, and then the aggregate data are posted annually.

Identifying tularemia

Every US state and territory has access to the CDC Tularemia Case Report Form (Appendix 1). Once doctors have identified the presence of the bacteria, the form is completed and forwarded to local public health offices. Public health officials then send the information back to the CDC. The form allows for the local public health department to relay signs and symptoms and designates the type of Tularemia the patient may have. The form also allows for the method of determination to be identified – either an actual specimen or if a blood titer was performed. The NNDSS then compiles weekly confirmed cases tabulating overall incidence and by age, sex, state, and region. The NNDSS makes note of whether the cases involve residents of the locality or if they are non-residents who may be traveling and become ill.

Statistical Analysis

Tularemia incidence was calculated by year as well as stratified by sex and age. The age ranges were pre-determined by the CDC as the following: 0, 1-4, 5-14, 25-39, 40-64 and 65+ (*Tularemia Home | CDC*, 2018). The youngest two categories were combined based on sample size. The US population for each year, based on census data, was used to calculate incidence per 100,000 persons (*Tularemia Home | CDC*, 2018). We used PROC GENMOD to evaluate trends in Tularemia over the study period. PROC GENMOD is a generalized linear modeling procedure that estimates parameters by maximum likelihood and can fit models to binary and ordinal outcomes (SAS Help Center, n.d.). This model was used since a typical linear regression could not accommodate the incidence being a continuous variable while age and sex were both categorical variables. We used a year*age and year*sex interaction term to evaluate if trends in tularemia incidence over the study period differed by age and/or sex groups. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC), with the alpha level set at 0.05.

RESULTS

During the study period (2010-2019), the average annual number of cases was 211 cases per year. The highest number of cases occurred in 2015 with 314 cases, while the lowest occurred in 2014 with 124 (Figure 1). There appeared to be a spike between 2014-2015. This spike was primarily isolated to six midwestern states (Figure 2).

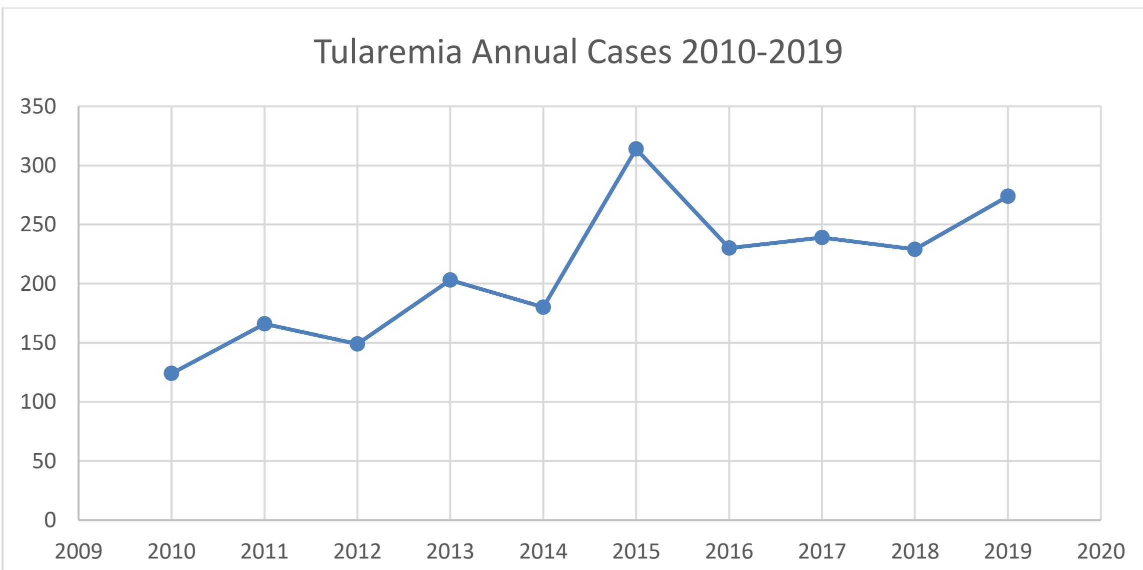

Figure 1. Tularemia Annual Cases 2010-2019

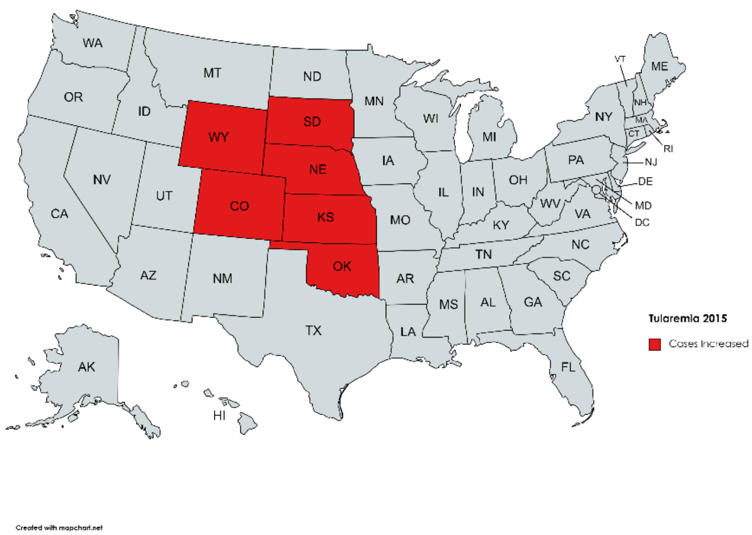

Figure 2: States contributing to the 2015 spike in Tularemia incidence

The average Tularemia incidence was 0.07 per 100,000 people during 2010 - 2019. The highest incidence of 0.10 was in 2015, while the lowest incidence of 0.04 was in 2010 (Figure 3). The annual incidence appeared to increase throughout the study period. Despite the spike in 2015 that deviated from the linear trend, overall Tularemia incidence only increased by 0.004 per 100,000 people.

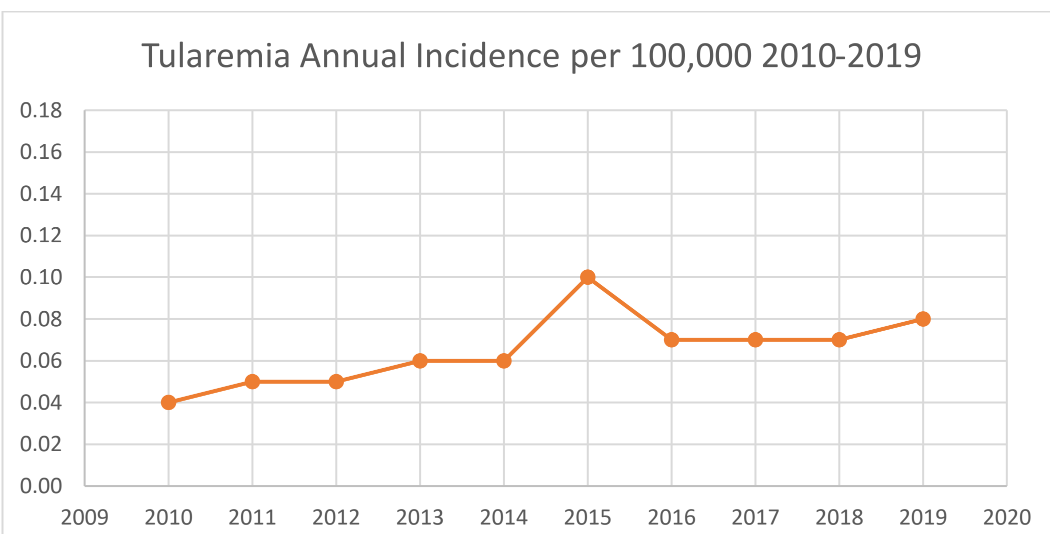

Figure 3. Tularemia Annual Incidence per 100,000 2010-2019

Evaluating if trends in Tularemia differ by sex

The average incidence of Tularemia was 0.09 for males and 0.05 for females per 100,000 people during the study period. In 2015 the highest incidence per 100,000 was 0.14 for males compared to only 0.06 in females (Figure 4). For both males and females, the lowest incidence was in 2010. The modeling results showed that there was no difference in the trends in Tularemia incidence by sex (p = 0.24).

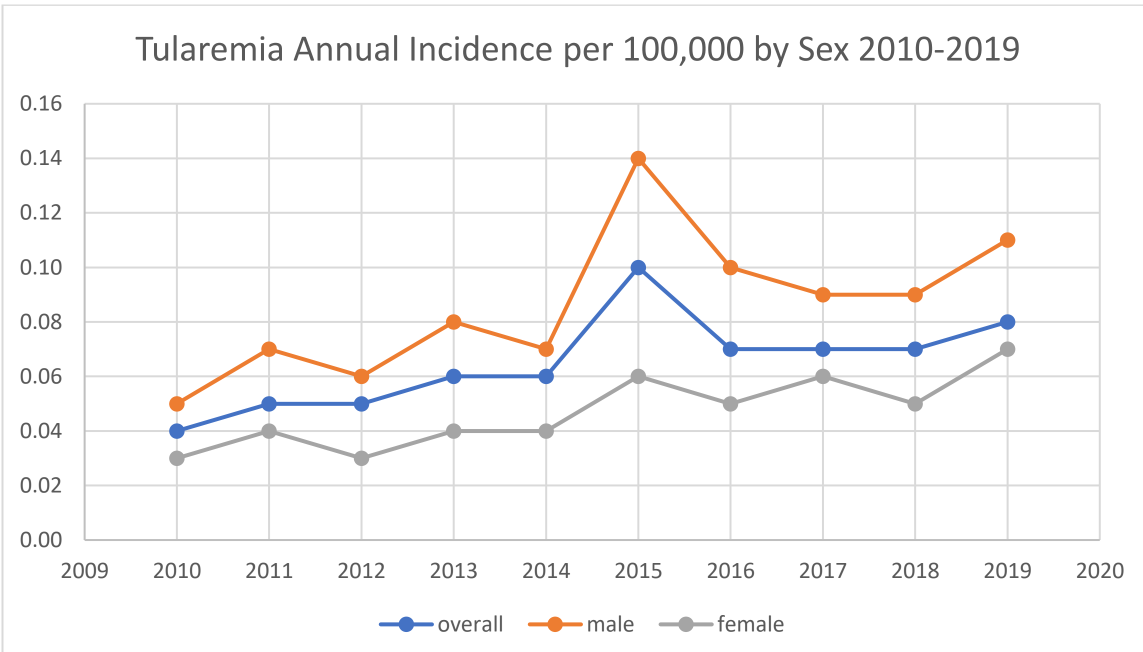

Figure 4. Tularemia Annual Incidence per 100,000 by Sex 2010-2019

Evaluating if trends in Tularemia differ by age

Figure 5 shows the annual incidence of Tularemia per 100,000 people by age group. The highest incidence per 100,000 of Tularemia was in the ≥65 years age group at 0.17, then followed by the 40-64 age group at 0.13. The ≥65 had an annual average incidence which ranged from 0.05-0.17 per 100,000. The highest incidence shown in

2015. The 40-64 age group showed an average annual incidence of 0.08 per 100,000 with their highest incidence in 2015 at 0.13. The lowest incidence per 100,000 was in the 15-24 age group at 0.03. During the study period, the average incidence per 100,000 for this group ranged between 0.02-0.07. The 25-39 age group had a slightly higher annual incidence of 0.04 per 100,000. This age group showed the least amount of fluctuation with the highest annual incidence of 0.06 per 100,000 in 2015, 2018 and 2019. The 0-4 and 5-14 age groups had an annual average incidence of 0.07 per 100,000. Their highest incidence was also similar with the 0-4 age group peaking at 0.10 per 100,000 while the 5-14 age group peaking at 0.09 per 100,000. Again, the modeling results showed that trends in Tularemia incidence per 100,000 did not differ significantly by age group (p = 0.08).

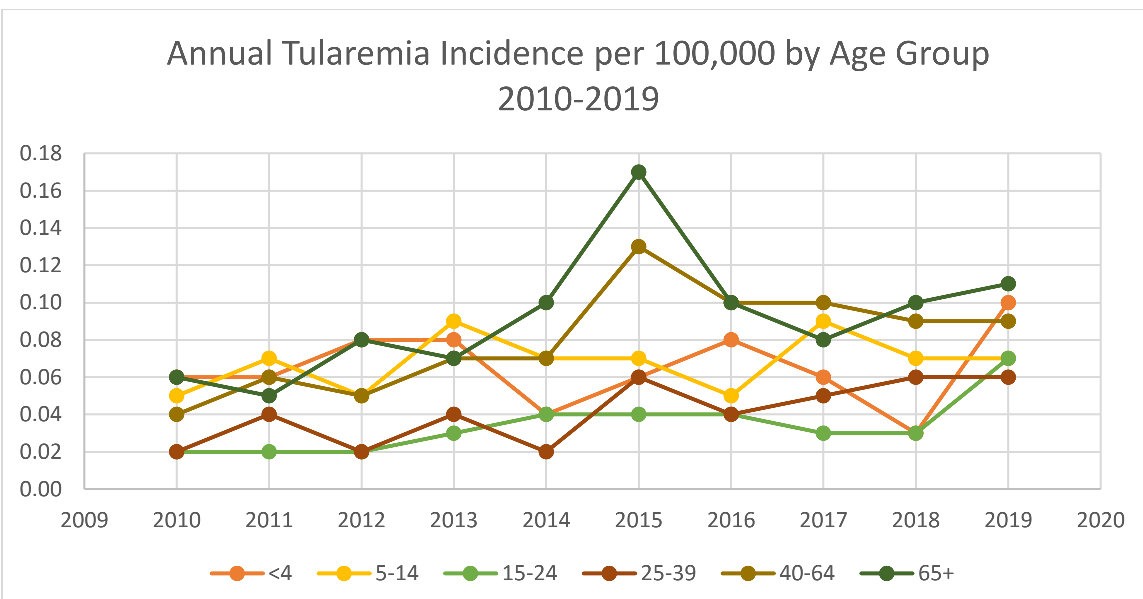

Figure 5. Annual Tularemia Incidence per 100,000 by Age Group 2010-2019

DISCUSSION

In summary, between the 2010-2019 study period, the overall incidence of Tularemia increased by 0.004 per 100,000 people, with no differences in trends by age or sex. Between 1930-1989 Tularemia cases steadily declined from approximately 2000 cases annually to about 200 cases annually (Yeni et al., 2021), and from 1990-2009 the average annual cases decreased to a low of 123(CDC, 2018). These declines have been contributed to the fact that hunting and gathering as main mode of obtaining food for consumption declined, thus people were no longer readily exposed to rabbits and hares, the predominant vector initially responsible for most cases after the discovery of the bacteria. Also, given advances in building development and pest control, houses and/or offices no longer have large rodent and/or small animal encroachment. Using the most contemporary Tularemia data, this study showed an increase in cases and incidence from 2010 – 2019. This could be attributed to an increase in the incidence of Tularemia cases in domestic pets. As previously mentioned, a 2018 study reported that at least 13 reported human cases were linked to contact with domestic dogs. These were not hunting/hiking dogs, they were family pets that were only allowed outside a few times a day. Another study, in Anchorage AL found an increase in incidence in Tularemia cases related to transmission of bacteria from pet cats (*Tularemia From Domestic Cats*, 1993). Future studies should explore the role domestic animals plays as an emerging Tularemia vector.

Between 2014-2015, annual cases spiked, primarily driven by increases in cases in six midwestern states – Oklahoma, Wyoming, Colorado, South Dakota, Nebraska, and Kansas (CDC, 2018); however, the literature does not point to any specific events that precipitated this spike. Consistent with the literature, this study also found that the highest incidence in Tularemia cases were in males. Higher cases in males have been attributed to outdoor professions – landscapers, construction workers and hunters (Stidham et al., 2018). The 2015 spike saw double the cases in males than that in females. Although causation has not been evaluated, this spike, particularly in males in the Midwest could be contributed to farming, a popular occupation in the region or pipeline related jobs. Both occupations require an extensive amount of digging and disruption of the earth potentially disturbing territories of small animals allowing bacteria like Tularemia to be more present than before. These findings emphasize the need for ongoing surveillance of temporal changes in Tularemia incidence by sex to continue to characterize this epidemiological data. Future studies should explore the encroachment of humans into undeveloped urban areas and the impact it may have on Tularemia incidence in nearby communities.

With respect to age, Tularemia incidence was highest in those 65 years of age and older followed closely by the 45-64 age group. These findings are not consistent with the literature, as studies that included multiple age groups saw higher incidence in smaller children (Ellis et al., 2002) (Fooladfar & Moradi, 2023). This could be due to the predisposition of children to play in the grass and dirt and place things in their mouths that may be exposed to the bacteria. One potential reason this study observed higher tularemia incidence in older adults is that older adults have more time to spend time in nature increasing their susceptibility to experience ticks and deerfly bites. Despite the different incidences by age, this study did not find any significant differences in trends in tularemia incidence over the study period. Efforts should continue to better identify the high-risk population given the higher prevalence of Tularemia risk in this age group. Focusing on time spent outdoors could help increase awareness of these risks and identify prevention interventions to minimize future incidence.

LIMITATIONS

As with all epidemiological studies, this study has limitations. First, this study was limited by the available NNDSS data, which is aggregated country wide data. The NNDSS does provide information regarding age, sex, and location of cases, but did not provide aggregate data by other demographic characteristics like race and ethnicity, which could have different Tularemia incidences and/or trends. Secondly, given the aggregate data, this study was limited to an ecologic study design. Having individualized data could have allowed the use of cross-sectional designs, which would allow for calculating prevalence in high incidence areas. Thirdly, NNDSS only provides information on confirmed cases, despite the case report form collecting information on both “confirmed” and “probable” diagnoses. The addition of the probable cases could allow one to determine virulence in areas that may not necessarily report cases of Tularemia. Since it is understood that Tularemia does not build immunity and a person can be infected multiple times, perhaps a longitudinal study could be done to identify the impact on overall incidence in populations and all potential repeated incidences. Also, the severity of repeated incidences could be an important discovery. Lastly, the Tularemia case report form collects more information regarding the circumstances around the cases, and having this individual level data could answer important questions. For example, individual level data at the county and state level would allow one to identify hot spots, vulnerable population, and community level risk. Such data could lead to the development of community-specific Tularemia prevention and tick awareness campaigns that can be disseminated through multiple platforms to reach the target audience.

The case report form also has a section devoted to Epidemiological Investigation that is not publicly available. Of interest, these data could be used to identify trends in vectors and exposure to Tularemia. As previously mentioned, domestic pets can be an important vector of this disease. Studies focusing on animal vectors can lead to pet safety, like cleaning of pet areas and supplies inside the home and extra bathing of pets to remove potential bacteria, and deceased animal awareness campaigns like proper procedures for the disposal of deceased animals with appropriate personal protection equipment.

Lastly, if individual information on cases based on contact or ingestion of contaminated water were publicly available, one could evaluate the incidence and trends of Tularemia due to contaminate water. This could also lead to community awareness campaigns that limit access to these water sources as well as cleaning and/or eliminating these sources depending on the size.

CONCLUSION

This study found that Tularemia incidence has increased over time, with no significant differences in Tularemia incidence trends over time by age and sex. If these trends continue, more Tularemia cases could overwhelm the health system, particularly if outbreaks occur like the one on Martha's Vineyard in 2000 and 2001 ("Tularemia Cases on Martha's Vineyard Puzzle Experts," 2004). While Tularemia is understood to be extremely contagious, there is very limited information regarding transmission through domestic pets and/or contaminated water. Further studies should be done to understand not only incidence trends but trends in vectors leading to conditions and the effectiveness of various prevention interventions to mitigate infection. Although not the primary objective of this study, currently, there are no Tularemia vaccines to prevent infection. Such vaccines could be used in domestic pets against to prevent human Tularemia transmission.

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APPENDIX

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

Tularemia Case Investigation Report

Case ID #: ____________

OMB No. 0920-0728

Reset Form

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
Location/description: ____________

Conjunctivitis ☐ Yes ☐ No ☐ Unknown

Skin lesions (e.g., ulcer, papules) ☐ Yes ☐ No ☐ Unknown
Location/description: ____________

Pharyngitis/tonsillitis ☐ Yes ☐ No ☐ Unknown

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

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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:

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