New Approaches for an Old Disease:

Surveillance and Epidemiology of Flea-borne Typhus in California

By

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To my family

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ABSTRACT

Flea-borne typhus (FBT) is a febrile rickettsial disease caused by the bacteria *Rickettsia typhi*. In the United States, rats, opossums, and cats act as reservoir hosts of *R. typhi* and can readily transmit the bacteria to feeding flea vectors (*Xenopsylla cheopis* and *Ctenocephalides felis*). Formerly referred to as murine typhus, FBT was historically among the most common vector-borne diseases in the U.S. before nationwide public health practices effectively controlled FBT through pest control. In recent years, however, reported cases of FBT have risen in California, Texas, and Hawai'i. Understanding the current epidemiology of FBT is becoming ever more important to interpret and respond to the changing trends in FBT. This dissertation aimed to contribute to the body of knowledge regarding FBT epidemiology and ecology in California.

In Chapter 1, we characterized FBT epidemiology in California from 2011 to 2019 by reviewing incidence, clinical course, and exposure histories collected in surveillance reports. Eight spatiotemporal clusters and areas with persistent FBT transmission were highlighted in Los Angeles County and Orange County using SatScan.

Chapter 2 used a Bayesian hierarchical zero-inflated Poisson model with a spatially conditional autoregressive random effect to assess the relationship between population-level socioeconomic and built environment variables and FBT surveillance reporting. As measured by the Healthy Places Index, census tracts with greater socioeconomic advantage were associated with higher rates of FBT surveillance reporting (IRR = 1.34; 95% CI [1.07, 1.69]). Census tract demographics, economic variables, housing characteristics, and land use were also discussed.

In Chapter 3, we constructed a novel mathematical transmission model of FBT using ordinary differential equations (ODEs) resembling the ecology of *R. typhi* in California. Sensitivity tests were performed using Latin hypercube sampling and partial rank correlation coefficients to identify parameters influential to human *R. typhi* infections. Sensitivity analyses highlighted human-opossum exposure and opossum-flea index as highly influential to the predicted proportion of humans infected in a population. Scenario analyses representing possible intervention activities were evaluated and discussed to demonstrate practical applications of the model.

The results of these chapters characterize the recent epidemiology of FBT in California, provide context for public health FBT surveillance practices, and present a mathematical framework to model *R. typhi* transmission. Together, these will improve our understanding of FBT epidemiology and ecology and inform local-level public health intervention activities.

INTRODUCTION: EPIDEMIOLOGY AND ECOLOGY OF FLEA-BORNE TYPHUS

The pathogen: *Rickettsia typhi*

In general, rickettsial diseases (rickettsiae) are described as genetically related obligate intracellular bacteria that infect an arthropod host for a period of their zoonotic cycle.[1] Rickettsiae bacteria belong to the genera *Rickettsia, Ehrlichia, Orentia, Coxiella, Anaplasma, Neorickettsia, Neoerlichia,* and *Wolbachia* in the order Rickettsiales.[2] *Rickettsia* spp. belong to one of three groups: spotted fever group (SFG; e.g., *Rickettsia rickettsii*), typhus group (TGR; e.g., *Rickettsia typhi* and *Rickettsia prowazekii*), and scrub typhus group (STG; *Orientia tsutsugamushi*). A fourth group, transitional group rickettsiae (TRG), has been proposed as a taxonomic status for species designation but has not yet been recognized.

Flea-borne rickettsioses are a grouping of rickettsiae that are maintained and vectored by flea species. The two diseases classified as flea-borne rickettsioses are flea-borne typhus (FBT) and flea-borne spotted fever (FBSF), caused by the bacteria *R. typhi* and *R. felis,* respectively.

Rickettsia typhi is the causative agent of flea-borne typhus (FBT), a vector-borne human febrile disease, and the subject of this thesis. *R. typhi* is a member of the TGR rickettsiae and is closely related to *R. prowazekii,* the causative agent of louse-borne typhus (epidemic typhus). Historically, FBT has also been referred to as endemic typhus or murine typhus.

Hosts, vectors, and transmission of *R. typhi*

Rickettsia typhi is commonly observed in coastal, subtropic regions globally where capable mammal reservoirs and flea vectors are available. While many vertebrate host species have been documented with infection naturally or in laboratory settings, the most important components of the classical flea-borne typhus life cycle are commensal rat species, such as the

black rat (*Rattus rattus*) and the Norway rat (*Rattus norvegicus*).[3] Rats and their fleas, particularly the oriental rat flea (*Xenopsylla cheopis*) maintain and vector FBT worldwide. This rat-flea-rat transmission cycle is considered truly commensal as neither the flea nor rat are harmed by *R. typhi* infection.

Other peridomestic animals may also serve as competent reservoirs to *R. typhi*. Past FBT case series indicated an association with seropositive domestic cats and opossums in Los Angeles County, California.[4] While fleas were not tested for *R. typhi* in the study, heavy infestations of the cat flea (*Ctenocephalides felis*) were observed on opossums and cats. *C. felis* is a competent vector of *R. typhi* in laboratory and natural settings.[3,5] Further research in southern California and Texas confirmed the role of opossums and *C. felis* as an alternate FBT transmission cycle for FBT in the United States.[6–9]

Two sylvatic cycles are often described in regions where opossums are present in endemic regions of the United States (e.g., southern Texas, Los Angeles and Orange Counties in California). The traditional rat-flea-rat cycle is colloquially named the “urban cycle” while the opossum-flea cycle is called the "suburban cycle”. The premise behind these designations is that transmission involving rats generally occurs in metropolitan environments while transmission involving opossums likely occur outside of densely urban areas.[10] Even so, these cycles are not likely to be mutually exclusive despite generally specific host preferences among varying flea species. *C. felis* is an uncommonly cosmopolitan vector that will also feed on rat species if available. As such, the two cycles may overlap in environments where hosts and vectors coexist or share home ranges.

In nature, transmission of *R. typhi* occurs when susceptive vertebrate hosts are inoculated with *R. typhi* through contaminated flea feces. This typically occurs at the site of the bite wound,

where fleas may shed *R. typhi* contaminated feces shortly after feeding. However, inoculation can also occur on different sites of exposed skin, respiratory tracts, conjunctivae (i.e., eye exposure), or other mucous membranes to a lesser extent. Once infected, the vertebrate host will maintain the rickettsia as it undergoes intracellular multiplication. The rickettsia eventually spread to the host's blood stream where adult fleas may become infected after taking a blood meal. *R. typhi* is extremely efficient at evading host and vector immune responses. In fleas, only a few rickettsial organisms are need to result in infection.[11] The rickettsia undergo significant intracellular multiplication again within the flea vector and, approximately 10 days (extrinsic incubation period) later, the flea will become infectious to naïve vertebrate hosts.[3,12] Vertical (i.e., transovarial) transmission of *R. typhi* from fleas to their progeny is possible for *X. cheopis*, but uncharacterized for *C. felis*. Furthermore, fleas remain infected for life and with uninhibited reproductive capacity and life span.[13]

Humans are incidental hosts of *R. typhi* and cannot transmit the bacteria to fleas, vertebrate hosts, or other humans. Transmission also occurs through inoculation of infected flea feces to a bite wound or other mucous membranes. There is limited laboratory evidence that it is possible for an infectious flea bite alone to successfully transmit *R. typhi* to humans, but it is unlikely to occur in nature.[14]

Clinical characteristics of flea-borne typhus

Disease is commonly characterized by headaches, fever, and body aches that develop 7-14 days after inoculation. This febrile triad of symptoms may also be accompanied by rash, though it occurs in less than 50% of case-patients.[15] Serological findings include thrombocytopenia, elevated liver enzymes (e.g., ALT, AST), and leukopenia. Prior case series note that complications may occur in approximately 25% of cases. Complications were less

common among children being noted in 15.3% in one review.[15,16] Common FBT complications include pneumonia, central nervous system dysfunction (e.g., altered level of consciousness), acute kidney injury, and meningitis.

Despite a significant proportion of cases with recorded complications, FBT mortality is low (0.4%).[10,17] One contributing factor to this is availability of antibiotic treatment, specifically doxycycline, a common tetracycline antibiotic. There is no evidence of chronic FBT infection post-treatment.

Taxonomy Considerations: R. felis, R. typhi, and Flea-borne Typhus

Despite not belonging to the TGR, *R. felis* is often referenced in literature as the secondary agent of FBT. This taxonomical discrepancy is partially due to its shared flea vectors, reservoirs, and clinical signs. Cross-reactivity of serological antibody tests and failure to successfully isolate *R. felis* in samples from infected patients also hinder efforts to differentiating the two diseases worldwide for public health purposes.[18] No human cases of flea-borne rickettsioses have been attributed to *R. felis* or FBSF in the United States to-date. In turn, it should be clarified that this dissertation recognizes *R. typhi* and *R. felis* (or other RFLOs) as two similar rickettsia that cause similar, but separate diseases. The subject of this dissertation is *R. typhi* and FBT.

FBT history and epidemiology in the U.S.

The first test to distinguish *R. prowazekii* and *R. typhi* was established in 1917 by Dr. Hermann Mooser who first isolated *R. typhi* from fleas on rats. Though, it is likely that FBT was a common, undiagnosed disease for at least a century before this. Cases of FBT in the United States peaked in 1944 when over 5,000 cases were reported nationally. The implementation of vector control programs decreased the number of cases in the U.S. through host removal (rodent

trapping) and dichlorodiphenyltrichloroethane (DDT) use in and around households.[8,19] In the 1950s, fewer than 100 cases were reported in the United States annually.[8,10] The successful typhus control campaigns changed the epidemiology and ecology of FBT over the following forty years. During which, investigations into the persistence of FBT in parts of Texas would lead to identifying opossums and cats as key reservoirs.[8]

Currently, FBT is considered a resurging disease with most human cases in the United States are reported from southern Texas, southern California, and Hawai'i.[17] A total of 1,762 TGR cases were reported to the Texas Department of State Health Services during 2003-2013. TGR was used as the disease classification instead of FBT at the time due the IFA test's inability to differentiate between *R. prowazekii* and *R. typhi*. However, it is likely that very few of these cases were caused by *R. prowazekii*. Case counts ranged from 27 in 2003 to 222 in 2013, the majority of which peaked in June and July. Most cases occurred in southern Texas (e.g., Nueces County) but geographical expansion was also observed.[20] Similar trends have been observed in southern California. From 1984 to 1994, 75 reports of FBT in Los Angeles County were reported.[21] This is in stark contrast to the 479 cases of FBT were reported in Los Angeles County and 1,142 in Orange County during 2001-2015.[22] Even more recently, 318 cases were reported in a two-year period from 2020 to 2021 despite using a stricter, more specific case definition. Of which, 209 cases were reported in 2021 alone making it the highest number of cases reported for a single year in recent history.

Scope and Objectives of Thesis

The objective of this dissertation is to assess the public health surveillance and ecology of FBT in California. More specifically, this dissertation aims to 1) characterize FBT epidemiology and disease surveillance in California, 2) assess socioeconomic and environmental variables

associated with FBT surveillance reporting in California , and 3) develop a mathematical model to study transmission dynamics of FBT. Together, these three chapters will incrementally improve our understanding of FBT epidemiology and surveillance with approaches that have not been used for this disease.

1. Surveillance of Flea-borne Typhus in California, 2011-2019

Abstract

Flea-borne typhus (FBT), formerly referred to as murine typhus, is an acute febrile disease in humans caused by the bacteria *Rickettsia typhi*. Currently, cases of flea-borne typhus are reported for public health surveillance purposes (i.e., to detect incidence and outbreaks) in a few U.S. states. In California, healthcare providers and testing laboratories are mandated to report to their respective local public health jurisdictions whenever *R. typhi* is detected in a patient, who then report cases to state health department. In this study, we characterize the epidemiology of flea-borne typhus cases in California from 2011 to 2019. A total of 881 cases were reported during this period, with most cases reported among residents of Los Angeles and Orange counties (97%). Demographics, animal exposures, and clinical courses for case patients were summarized. Additionally, spatiotemporal cluster analyses pointed to five areas in southern California with persistent FBT transmission.

Introduction

Flea-borne typhus (FBT), formerly known as endemic typhus or murine typhus, is a febrile disease caused by *Rickettsia typhi*. The gram-negative, intracellular bacterium is a member of the typhus group rickettsiae and is closely related to epidemic typhus (*R. prowazekii)*.[23] Like other *Rickettsia* species, *R. typhi* relies on arthropods and mammalian hosts to maintain its life cycle. *Rickettsia felis*, a species in the spotted fever *Rickettsia* group, has also been suggested as an agent of FBT. However, *R. felis* has not been identified in human infections in California.

The FBT transmission cycle revolves around the primary mammalian host (*Rattus* spp.) and arthropod vector, the rat flea (*Xenopsylla cheopis*). This cycle is often referred to as the urban cycle. In Texas and California, an additional cycle of transmission involves opossums (*Didelphis virginiana*) as a potential reservoir to *R. typhi* and the cat flea (*Ctenocephalides felis)* as the principal arthropod vector.[4,6] This cycle is often referred to as the suburban cycle due to the ecological overlap between opossums, cats, and humans outside major city centers. Fleas may acquire the bacteria while feeding on rickettsemic hosts. The bacteria reside in the midgut epithelium of the flea, where they can be transmitted to humans or other hosts by introducing infected feces onto flea bite wounds or mucous membranes.[18]

Most human infections are self-limiting and mild, characterized by non-specific symptoms, including fever, headache, myalgia, and rash. A review of typhus group rickettsioses surveillance in Texas noted that 59.6% of case patients were hospitalized from 2003 to 2013.[20] While the mortality rate of FBT is relatively low (0.4%), FBT may progress to severe disease in 10-25% of cases.[15,23,24] Clinical severity of FBT is associated with older age, delayed diagnosis, and conditions compromising hepatic, renal, pulmonary, or central nervous system functions.[16,18]

Complications have been reported to occur in 28% of cases.[25] Complications may include shock, bronchiolitis, pneumonia, encephalitis, renal failure, and sepsis.[16,24–26]

FBT occurs worldwide, particularly in tropical or subtropical coastal regions. Cases of FBT in the United States peaked in 1944 when over 5,000 cases were reported nationally. The implementation of vector control programs decreased the number of cases in the U.S. through host removal (rodent trapping) and dichlorodiphenyltrichloroethane (DDT) use in and around households.[8,19] In the 1950s, fewer than 100 cases were reported in the United States annually.[8,10] Currently, most human cases in the United States are reported from Hawai'i, southern Texas, and southern California.[17]

Flea-borne typhus is not nationally notifiable, though FBT cases in California have been reportable since 1916. Mandatory electronic laboratory reporting (ELR) of *R. typhi*-positive samples began in 2011.[27,28] Reported cases in California have increased in recent years, particularly in southern California, where an endemic focus has emerged in a region within Los Angeles and Orange counties. For this study, data for FBT cases were captured using a single case definition from 2011 to 2019, facilitating a standardized collection of demographics, clinical, and laboratory information. This paper aims to summarize FBT surveillance data from this period to characterize the current epidemiology of the disease in California. Furthermore, this report outlines spatiotemporal clusters of FBT detected in Los Angeles County. Assessing these data may improve local public health response and highlight areas for improvement in FBT surveillance.

Materials and Methods

Data sources

The California Department of Public Health (CDPH) receives reports of notifiable disease incidence case report forms (CRFs) electronically through the California Reportable Disease Information Exchange (CalREDIE) or directly from local health jurisdictions (LHJ; i.e., county or city health departments). Most typhus cases are identified after case-patients seek medical care for their symptoms. Serologic assays detect immunoglobulin antibodies (i.e., IgG or IgM) or *R. typhi* DNA in a patient's serum. LHJs receive notifications from providers or laboratories of positive FBT case-patients. The LHJs collect case-patient information using an FBT-specific case report form. Reports include basic demographic information such as residence, place of work, race/ethnicity, age, and gender, as well as more detailed data describing the clinical course, diagnostic test results, possible exposures, and illness resolution. The CRF data are submitted electronically to CDPH directly or via CalREDIE.

This report summarized surveillance data following the California surveillance case definition used between 2011 and 2019 to describe the epidemiology of reported cases. This surveillance case definition classified reports as confirmed, probable, or suspect. Briefly, confirmed cases must be clinically compatible (e.g., experienced fever, headache, myalgia, or rash) with laboratory confirmed evidence (i.e., IgM and IgG positive for *R. typhi* antigen by IFA $\geq$ 1:128 without convalescent titer or positive RT-PCR). Reactive acute convalescent antibody tests with a fourfold titer increase compared to the acute sample or detection of DNA for *Rickettsia typhi* or other *Rickettsia sp.* by RT-PCR, excluding *R. rickettsii,* the causative agent of Rocky Mountain Spotted Fever (RMSF) also serve as laboratory confirmed evidence with greater specificity. Probable cases have clinically compatible symptomatology and supportive

laboratory evidence (i.e., either IgM or IgG positive for *R. typhi* antigen by IFA ≥ 1:128 without convalescent titer or positive RT-PCR). Suspect cases lack clinical evidence of disease or are without documentation of disease course (e.g., clinical assessments not performed, or no medical records are available) and have supportive laboratory evidence. Only confirmed and probable reports were considered cases of FBT and analyzed in this study (Supplemental Table 1).

Race and ethnicity were combined to form a new variable, *race/ethnicity*, to evaluate the demographics of reported cases. Hispanic or Latino ethnicity was collapsed into the race category. For example, if a person identified ethnicity as Hispanic or Latino and white race on their case report form (CRF), their *race/ethnicity* record was reflected as *Hispanic or Latino*. A person without indication of Hispanic or Latino ethnicity on their CRF was recorded as their race alone (e.g., *non-Hispanic Asian* was recorded as *Asian*).

Animal exposures (e.g., fleas, opossums, rats, cats, dogs, etc.) were collected from fields on the CRF and supplemental forms. Frequencies of exposures were tabulated if the infected person reported the animal in or near their home residence or place of work.

Some CRFs included supplemental hematology results. Thrombocytopenia was classified as a platelet count less than normal human platelet count range lower limit (< 150,000 platelets per microliter of blood), leukopenia as a reduction in white blood cell (WBC) count less than 3.5/mcL. Elevated liver enzymes were classified if either aspartate transaminase (AST) levels exceeded 40 IU/L or alanine transaminase (ALT) levels were above conventionally accepted upper normal limits for adults, 40 IU/L.[29–32]

County population and demographic data were retrieved from corresponding one-year American Community Survey (ACS) estimates. *Racial/ethnic* and gender composition of typhus

cases in Los Angeles County and Orange County were compared to their respective proportion of the county population using ACS population demographic estimates. County race and ethnicity estimates followed the same combination criteria as used in the FBT *race/ethnicity* variable combination. Cumulative incidence rates (i.e., reported cases per population) were calculated per 100,000 population at risk from 2011 through 2019 using the average estimated population for Los Angeles and Orange counties.

Household addresses were mapped for cases reported from each jurisdiction, assuming these served as the primary exposure location. Records of FBT cases among persons experiencing homelessness (PEH) were reviewed to identify the location of their encampment by address or general location. Coordinates corresponding to the centroid of a given neighborhood were assigned to PEH if the individual acknowledged living in that area at the likely time of exposure (e.g., a PEH without an address acknowledging they lived in Central City East ("Skid Row") would be assigned the coordinates corresponding to the centroid of Central City East, Los Angeles). Household addresses were included in the spatiotemporal cluster analysis if 1) location was obtainable, including latitude and longitude, 2) location could be geocoded to a census tract upon case record review if household addresses were not available, 3) location was within a census tract with a population greater than zero, and 4) date of episode was available in the case record.

During the surveillance period, the population did not fluctuate greatly for Los Angeles and Orange counties. The total population in these counties increased by approximately 2.9% from 2010-2020, with an estimated average increase of 1% year-to-year from 2011 to 2019 [33,34]. Therefore, the 2017 ACS 5-year census tract population estimates were used to represent all years under study. Population data were downloaded from the 2017 ACS 5-year estimates for

each census tract in Los Angeles and Orange counties. County and census tract shapefiles for 2017 were accessed using California Open Data Portal. California city shapefiles for 2017 originate from the U.S. Census Bureaus' TIGER/Line database and are publicly available from the United States Open Data portal.

Spatiotemporal cluster analysis

Case addresses were aggregated by census tracts to retrieve the number of cases per tract per month for the surveillance period. Census tracts were chosen as the unit of analysis due to 1) the availability of underlying population data for each census tract to standardize the raw count data; 2) the ability to create zero-count data, observations with zero cases, otherwise unavailable while using case-only FBT typhus data; and 3) maintenance of privacy for patients by not directly disclosing their location. To correctly model count data at the census tract level, a discrete Poisson model was used for the spatiotemporal cluster analysis. A maximum cluster radius of 2.3 kilometers was specified to provide practical value (i.e., development of prevention and intervention efforts in smaller localities) to identified clusters and determined by calculating the median area of cities in Los Angeles and Orange counties in square meters (Supplemental Table 2). Cluster centers were restricted from geographically overlapping. With case counts temporally aggregated to monthly case counts per census tract, the minimum temporal cluster size was set to 1 month and the default maximum temporal cluster size (50% of period under study) was used in SatScan. Relative risks for retrospective spatiotemporal clusters were calculated by estimating the risk within the cluster divided by the estimated risk outside the cluster conditioned on the cumulative number of cases observed in the specified time and space[35]. Spatiotemporal cluster analyses were conducted using SatScan v9.7. Maps and plots were created using ArcGIS Pro 2.7.0.

This study was considered exempt for human subjects review by the California Health and Human Services Agency's Federal wide assurance #00000681; approval was obtained from the Office of Human Research Protections, Committee for the Protection of Human Subjects (Project: 2020-117).

Results

Surveillance summaries

From 2011 to 2019, 881 cases of FBT were reported to CDPH; 529 (54.9%) met the case definition for confirmed and 352 (36.6%) were probable. The number of cases reported each year within the timeframe ranged from 47 in 2011 to a peak of 164 cases in 2018 (Figure 1). Cases were reported from 16 local health jurisdictions. Most cases were reported from Los Angeles County (n = 685, 77.8%) and Orange County (n = 169, 19.2%). The cumulative incidence rate was 6.82 cases per 100,000 in Los Angeles County and 5.38 cases per 100,000 in Orange County during the nine-year surveillance period. Sporadic cases were reported in other southern California counties, including San Diego (5), San Bernardino (4), and Riverside (1). Cases occur throughout the year, but approximately half (n = 439, 49.8%) occur during the summer months June through September (Figure 2).

The distribution of clinical and laboratory findings was similar for both classifications and thus were combined in Tables 1 (demographics) and 2 (clinical and laboratory findings). Most cases were reported among males (n = 504, 57.2%). The median age among reported cases was 43 (0 – 93; Table 1). White (n = 374, 42.5%) and Hispanic or Latino (n = 291, 33.0%) race and ethnicity were most frequently reported. Forty-nine (5.6%) case patients identified as Asian, 30 (3.4%) as Black or African American, 5 (0.6%) as Native Hawaiian or Pacific Islander, and 4

(0.5%) as American Indian or Alaskan Native. Race and ethnicity data were unknown for 128 (14.5%) case-patients.

A total of 733 (83.2%) case-patients reported receiving inpatient care. Among those with hospitalization admission and discharge dates available (n = 659, 74.8%), the median length of initial stay was 4 (range 0-84) days. Twenty-nine (3.29%) case-patients were readmitted for a median period of 3 (range 0-8) days following their initial hospitalization. The average time between the onset of symptoms and collection of positive antibody test was 12.6 (SD= 23.4) days. Reported clinically compatible signs and symptoms were fever (n = 865, 98.2%), headache (n = 651, 73.9%), myalgia (n = 494, 56.1%), and rash (n = 379, 43.0%). Other commonly reported symptoms included nausea or vomiting (n = 453, 51.4%) and cough (n = 314, 35.6%). Thrombocytopenia was reported in 194 (22.0%) case-patients, leukopenia in 227 (25.8%) case-patients, and elevated liver enzymes (aspartate transaminase [AST] or alanine transaminase [ALT]) in 169 (19.2%) case-patients (Table 2).

Of the self-reported animal exposures to cats, dogs, opossums, rodents, and fleas around the case patient's household or at the employment location, cat exposures were most frequently reported by case-patients (n = 466, 52.9%) throughout the surveillance period (Table 3). Exposures to dogs (n = 436, 49.5%), opossums (n = 333, 37.8%), rodents (n = 230, 26.1%), and fleas (n = 188, 21.3%) were also noted by cases. History of bug bites during the incubation period (within 14 days prior to the onset of symptoms) was recalled in 199 (22.6%) case-patients.

Spatiotemporal clusters

Out of all reported FBT cases reported in Los Angeles and Orange counties between 2011 and 2019 (N = 854), 830 were included in the spatiotemporal clustering analysis. Twenty-four cases were excluded from further analysis because of missing or unobtainable location data. There was a total of 8,057 census tracts analyzed from Los Angeles and Orange counties with a mean tract area (SD) of 50.08 km^2 (416.99 km^2) and a mean (SD) population of 4,858.97 (2,234.59). Eight spatiotemporal clusters were detected (Figure 3). Most of these clusters were in communities in the City of Los Angeles (Table 4). Two geographically and temporally limited clusters with high relative risks were identified in Willowbrook (RR = 102.9; n = 11), a community in south central Los Angeles County, and San Gabriel Valley (RR = 232.37; n = 5). The combination of smaller temporal window and high RR in these clusters provide evidence of past outbreaks. On the other hand, the most cases reported in a single cluster were identified in Long Beach (RR = 7.54; n = 29) in a temporal window over four years long.

Discussion

FBT cases in California have reached the highest levels measured in decades. Los Angeles County reported 75 cases of FBT between 1984 and 1994.[21] Between 2002 and 2010, 185 cases of FBT were reported in California.[36] The present study totaled 881 cases reported, 4.8 times more than that of the previous nine-year period, with an average of 97.8 cases per year. Reported cases show the specificity of FBT to the Los Angeles Basin in California, with a greater frequency of cases occurring during summer months. Considering that flea reproduction, feeding, and maturation are all increased during warm weather, it is reasonable to infer that the seasonality of FBT transmission is related to flea biology.[37–40]

Most demographic findings were similar to those of prior studies. More case-patients were male, which is consistent with prior FBT case series in Colombia (58%),[41] Spain (55%),[42] Greece (57-61%),[43–45] and Texas (55%).[26,46] Interestingly, when considering only Los Angeles and Orange County cases, non-Hispanic white case-patients were overrepresented, and Hispanic or Latino case-patients were underrepresented when compared to the population distribution in Los Angeles and Orange counties (Figure 4). This contradicts race and ethnicity among TGR cases in Texas, in which 64% of TGR cases were Hispanic or Latino.[20] In an ideal disease surveillance system, the demographics of disease reports (including non-cases) would reflect those of the population at risk. Discrepancies between observed and expected demographics among cases could then be tested to indicate high-risk groups. Unfortunately, we cannot make this comparison without comprehensive demographic data for suspect and non-cases. In the context of passive disease surveillance for FBT, it is difficult to describe disease risk due to unmeasured confounding in the surveillance system. For example, the underrepresentation of Hispanic or Latino persons among FBT cases may not necessarily point to a lower risk for this population but a lower likelihood of being tested and diagnosed with FBT. This inconsistency signals a potential gap in FBT surveillance that requires further investigation.

The percentage of cases reporting fever, myalgia, and rash in our study was similar to that of prior studies.[20] Prevalence of alanine or aspartate transaminase (ALT/AST) elevation were lower than previously reported.[15] However, it is important to note that slight elevation in liver enzymes above normal levels may be transient and not indicate acute liver injury. Also, upper normal limits may also depend on various factors including age, sex, race or ethnicity, pre-existing conditions, and location of testing laboratory.[47–50] A higher proportion of case-patients in our study reported nausea or vomiting (51.4%), diarrhea (29.4%), and abdominal pain (31.6%)

than in prior studies (26.7%, 18.6%, and 18.8%, respectively).[15] Thrombocytopenia (22.0%) was also less common than in a systematic review of FBT cases (42.2%).[15] Clinical serological tests (e.g., platelet counts, white blood cell counts) were unavailable for a high proportion of case records (22%) in the current study. Hospitalization was reported for 83.2% of case-patients in the present study. The proportion hospitalized (83.2%) is higher than that reported for typhus group rickettsioses in Texas from 2003 to 2013 (59.6%) and in a case series of 29 patients in Germany (64%).[20,51]

At least one animal exposure was recorded for most cases (99.1%). The reported exposures were consistent with animal exposures reported in Texas, except for a lower proportion of reported exposure to fleas in the present study.[20] Animal exposure data collected via case-patient recall are problematic for elucidating the role of urban animals in FBT transmission cycles. These data are predicated on what the person sees, thus potentially underreporting animals that are more active at night, such as rodents and opossums. Domestic animals such as dogs and cats may also be overrepresented due to pet ownership. A limitation of the exposure data presented is that differentiates between free-roaming animals, pets owned by the case household, or pets belonging to others in the community. The surveillance data do not account for flea-control medication use, either. While the findings may direct general hypotheses on reservoirs and vectors, better characterization would be gained from on-the-ground ecological studies or standardized improvements in exposure data collection.

Geographically and temporally smaller clusters with larger relative risks detected in SatScan are highly indicative of potential health hazards. Two resulting spatiotemporal clusters relate to outbreaks (e.g., five or more cases within one months to one year in a defined area) of flea-borne typhus determined by local health jurisdictions. The Willowbrook (cluster 1) and

downtown Los Angeles (cluster 8) clusters each included a time frame that fits with previously reported outbreaks in Los Angeles County.[52] The extremely high relative risk estimates in the resulting spatiotemporal clusters are because these outbreaks were geographically confined and occurred over a relatively short time frame. Similarly, the San Gabriel Valley cluster (cluster 4) corresponds with a brief but well-documented outbreak in a mobile home park.[53]

Long periods, such as periods extending multiple years, observed in most of the clusters (clusters 2, 3, and 5-7; Table 4) may reflect populations or areas with persistent FBT transmission rather than emerging health hazards. The Pasadena Public Health Department reports localized hotspots year-to-year and reported epidemic levels of FBT reported in 2018.[54] The resulting high RR and long temporal period in Cluster 3 is likely due to combining effects of FBT persistence in independent hotspots annually and outbreaks in 2018. Cluster 2 (i.e., Long Beach) had relatively low relative risk and higher number of cases in a period over four years long and may be attributed to FBT endemicity in the City of Long Beach.[55] The remaining clusters (5-7) in communities within the City of Los Angeles have lower relative risks, fewer cases, and long temporal intervals. These may point to areas where cases are periodically reported or where risk is higher than expected. In other words, FBT cases arise from these areas frequently enough to suggest association with some underlying process, but elucidating specific reasons will require further research.

The combination of significant high transmission areas in Pasadena and Long Beach and the absence of spatiotemporal clusters in Orange County despite a significant disease burden warrant further attention. Long Beach and Pasadena are two of three state-recognized city-level health jurisdictions in California. All other local health jurisdictions operate at the county level. It is worth considering whether these findings are driven by differential public health activities

improving knowledge and awareness of FBT in high-risk locations, resulting in differences in FBT surveillance ascertainment between each of the four jurisdictions included in the region.

These data present potential biases and limitations. Because most cases are identified after seeking health care, the data captured here likely represent relatively severe infections of *R. typhi*. The discrepancy between lower rates of severe cases historically (10-25%) and the relatively high proportion of cases receiving inpatient care in the present data (83.2%) point to potential selection bias.[15,23,24] The surveillance system's reliance on a person to seek out medical attention to receive adequate testing and subsequently being identified as a case may cause an underestimation in FBT cases, especially in the context of typically moderate clinical signs and symptoms of FBT. Furthermore, social and economic pressures such as income, health care access, and health insurance play a significant role in an individual's cost-benefit perception when considering seeking a health care provider. This is further supported by the overrepresentation of non-Hispanic white individuals and underrepresentation of Hispanic or Latino individuals in the present data, as health disparities in Hispanic or Latino communities may act as a barrier to being identified as a case.[56] As such, it is warranted to evaluate socioeconomic variables in future reported FBT cases. While the association with summer months may indicate a change in animal or vector activity, it could be confounded by increased outdoor activity among people in the summer relative to the winter. In the spatiotemporal cluster analysis, using static population estimates for all census tracts in the study period corresponding to the 2017 5-year ACS estimates may not accurately measure the underlying population at risk. However, this issue may be nominal considering that the estimated population change from 2010 to 2019 is estimated to be only 2.0% in the area where clusters were detected.[33] Using FBT case count data by census tract may introduce aggregation bias by assuming all persons within a tract

are at equal risk and may not reflect reality when evaluated with more granularity or at the individual-level. Similarly, PEH are at considerably higher risk for exposure to FBT due to increased time spent outdoors, living conditions that attract rodents and free-roaming animals, and less access to flea-control for pets but may not be captured in census tract population estimates. This parallels findings for other vector-borne diseases such as bartonella.[57,58] Therefore, it is likely that the cluster including the downtown Los Angeles outbreak underestimates the relative risk of FBT among PEH and overestimates that of the general public in the area. Lastly, misclassification of cases may exist in the surveillance data. The ability to detect rickettsial disease immune response fluctuates during the time course of infection. Serological testing for antibody response (i.e., IgM and IgG) may not appear in detectable levels until 5-10 days after an individual presents symptoms.[59] Therefore, a sample collected early in disease course (i.e., less than 14 days post-inoculation) from a truly infected individual may result in low antibody titers (i.e., IgM or IgG $\leq$ 1:64) that do not meet the case definition. Suspected cases with low initial titers should have a convalescent sample collected and tested 10-20 days later or be tested by RT-PCR.[59,60]

In 2020, the case definition for FBT in California was amended to align with other reporting states. This study aimed to characterize reported FBT case data in California using the preceding case definition active from 2011 to 2019. During this surveillance period, data show a substantial and concerning increase in reported FBT cases even while underestimating the true burden of disease. FBT is a significant vector-borne disease endemic to Los Angeles and Orange counties in California with sporadic outbreak potential. Additionally, a high percentage of severe cases observed warrant targeted health education and improvements in pest control particularly in areas identified with persistent localized risk. This information adds to the modern metadata

about FBT as research continues to show FBT is a potentially serious disease. FBT public health surveillance would greatly benefit from further research in host and vector ecology in this region of California.

Tables and Figures

Figure 1: Reported FBT cases by year, California, 2011-2019.

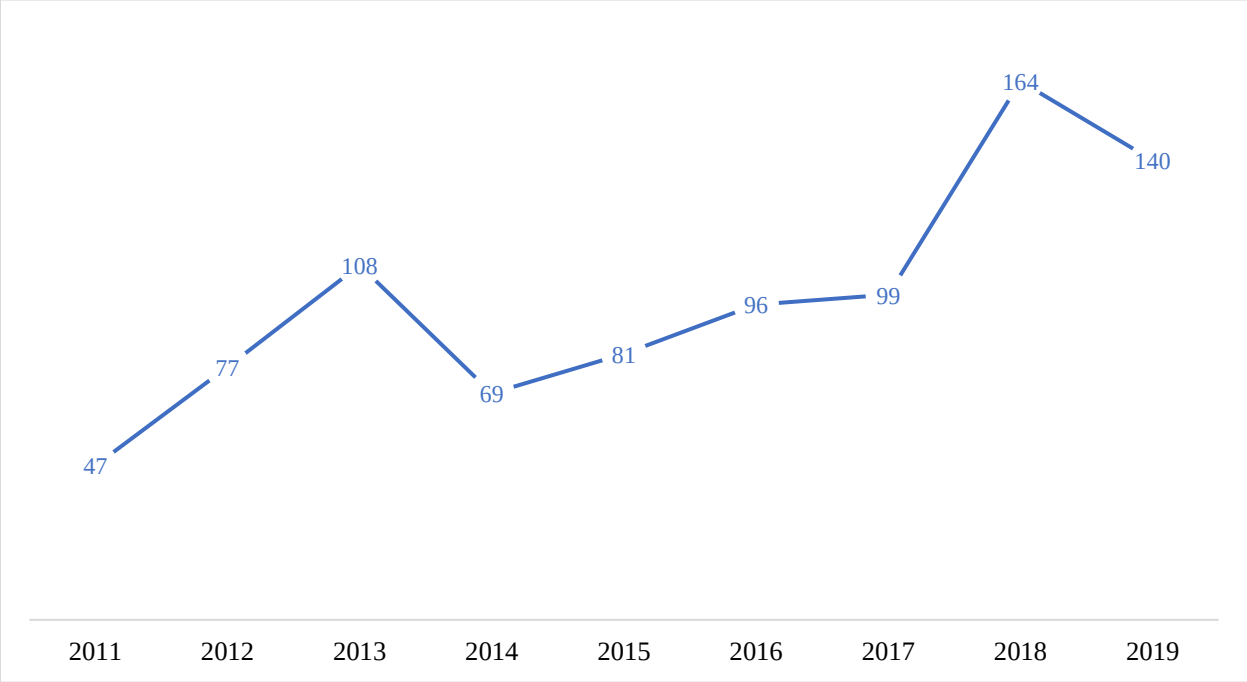

Figure 2: Reported flea-borne typhus (FBT) cases by month, California, 2011-2019.

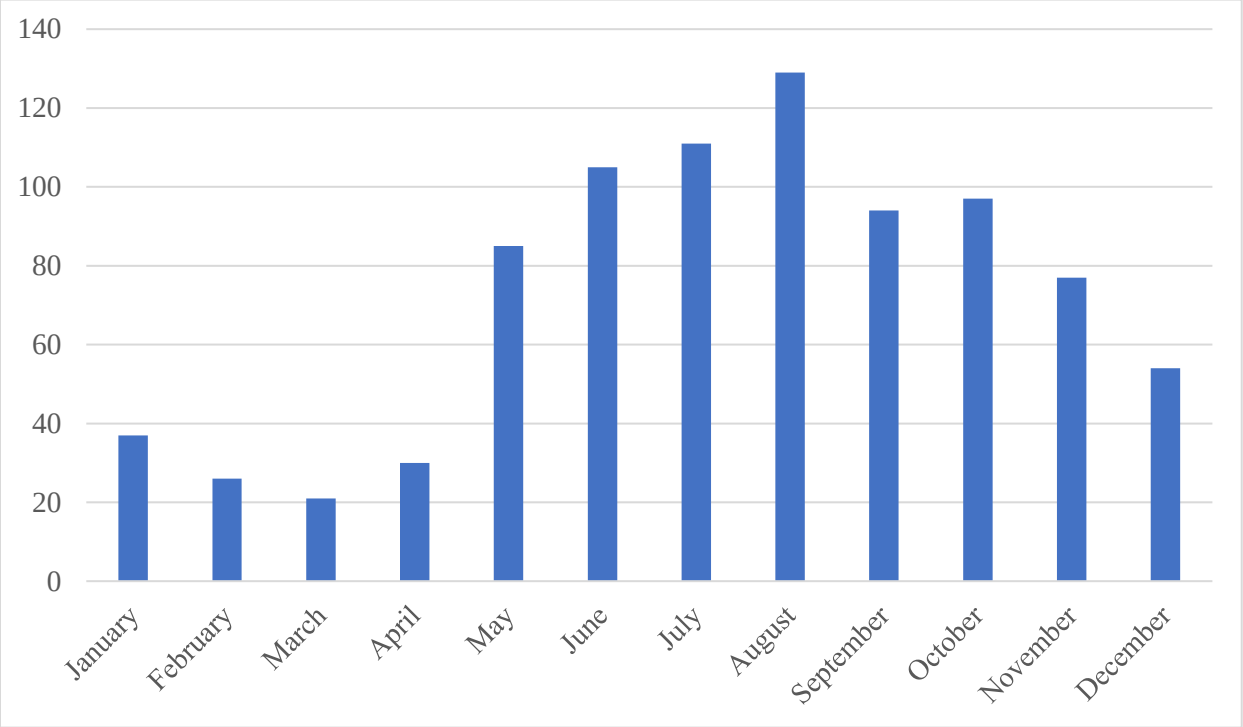

Figure 3: *Human FBT spatiotemporal clusters detected, Los Angeles Basin, California, 2011-2019.*

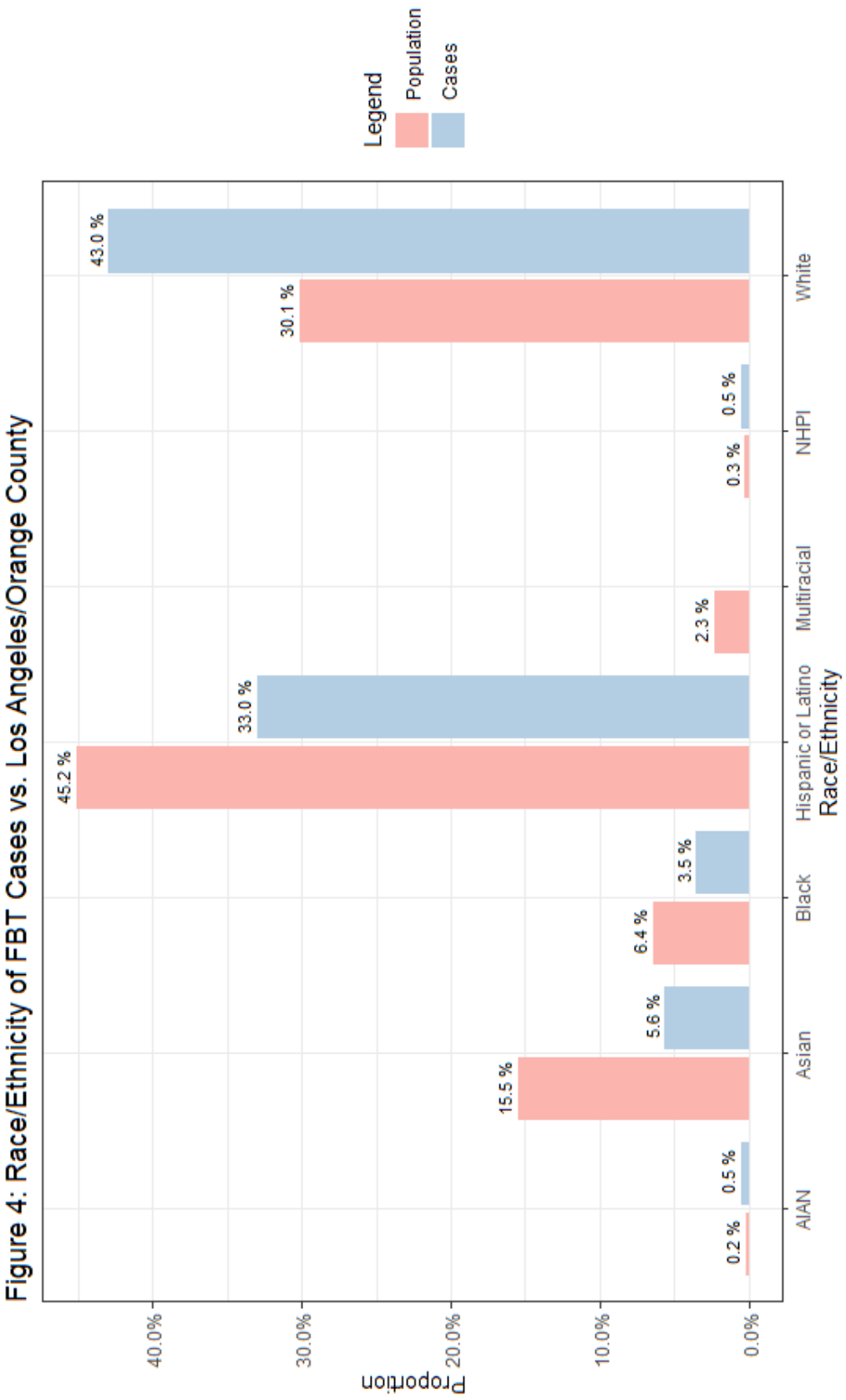
Figure 4: Race/Ethnicity of FBT Cases vs. Los Angeles/Orange County
Legend
Population
Cases
Proportion
40.0%
30.0%
20.0%
10.0%
0.0%
0.2 %
0.5 %
15.5 %
5.6 %
6.4 %
3.5 %
45.2 %
33.0 %
2.3 %
0.3 %
0.5 %
30.1 %
43.0 %
AIAN
Asian
Black
Hispanic or Latino
Multiracial
NHPI
White
Race/Ethnicity

Table 1: Sex and age of reported flea-borne typhus case-patients, California, 2011-2019.

Demographics	Case-patients (N = 881)
Sex	
Female	375 (42.6%)
Male	504 (57.2%)
Unknown	2 (0.2%)
Age Group	
0-9	43 (4.9%)
10-19	96 (10.9%)
20-29	108 (12.3%)
30-39	123 (14.0%)
40-49	169 (19.2%)
50-59	169 (19.2%)
60-69	105 (11.9%)
70-79	55 (6.2%)
80+	7 (0.8%)
Unknown	6 (0.7%)
Race/Ethnicity	
American Indian or Alaska Native (AIAN)	4 (0.5%)
Asian	49 (5.6%)
Black or African American	30 (3.4%)
Hispanic or Latino	291 (33.0%)
Native Hawaiian or other Pacific Islander (NHPI)	5 (0.6%)
White	374 (42.5%)
Unknown or Unspecified	128 (14.5%)

Table 2: Clinical and laboratory findings among case-patients with clinically compatible symptoms to FBT, California, 2011-2019

	Total Reported (%) (N = 881)
Clinically Compatible Signs and Symptoms	
Fever	865 (98.2)
Headache	651 (73.9)
Myalgia	494 (56.1)
Rash	379 (43.0)
Other Signs and Symptoms	
Nausea or vomiting	453 (51.4)
Cough	314 (35.6)
Abdominal pain	278 (31.6)
Diarrhea	259 (29.4)
Non-specific arthralgias	214 (24.3)
Eye pain	125 (14.2)
Hypotension	157 (17.8)
Serology Results*	
Thrombocytopenia	194 (22.0)
Leukopenia	227 (25.8)
Elevated ALT or AST	169 (19.2)

*A high proportion of cases were missing data for thrombocytopenia (22.2%), leukopenia (21.8%), and elevated ALT or AST (66.9%)

Table 3: Self-reported animal exposures around household or employment location among FBT case-patients, California, 2011-2019

Reported Exposure	Total Reported (N = 881)
Cats	466 (52.9%)
Dogs	436 (49.5%)
Opossums	333 (37.8%)
Rodents	230 (26.1%)
Fleas	188 (21.3%)

Table 4: *Human FBT spatiotemporal clusters* detected, Los Angeles and Orange Counties, California, 2011-2019.*

Cluster	Location	RR (cases)	p-value	Period
1	Willowbrook	102.9 (n = 11)	< 0.0001	9/1/2018 – 11/30/2019
2	Long Beach	7.54 (n = 29)	< 0.0001	7/1/2015 – 10/31/2019
3	Pasadena	21.76 (n = 16)	< 0.0001	6/1/2016 – 2/28/2019
4	San Gabriel Valley	232.37 (n = 5)	0.0009	3/1/2015 – 8/31/2015
5	Silver Lake	8.76 (n = 16)	0.0042	7/1/2016 – 11/30/2019
6	Cypress Park	10.71 (n = 14)	0.0042	12/1/2016 – 11/30/2019
7	Alhambra	14.42 (n = 11)	0.013	9/1/2014 – 12/31/2018
8	Downtown Los Angeles	14.94 (n = 10)	0.039	7/1/2017 – 11/30/2019

**Cluster locations are generalized to major cities or prominent neighborhoods and may also include neighboring areas. Clusters are ordered by increasing p-value. For this study, exact p-values were not indicated if < 0.0001.*

2. Bayesian population-based assessment of ascertainment bias in flea-borne typhus surveillance in California, 2011-2019

Abstract

Passive surveillance systems often introduce a great deal of uncertainty to any analysis. Prevalence estimates are likely inaccurate if derived without consideration for how data were ascertained. In California, public health disease surveillance data for flea-borne typhus (FBT) is generated by healthcare providers and laboratories who are responsible for notifying local health jurisdictions when the disease is detected. When accounting for the associations between socioeconomic factors, *R. typhi* reservoir host presence (e.g., rats), and healthcare-seeking behaviors, it is reasonable to consider whether these factors also lead to under-ascertainment of FBT surveillance and distorted estimations of incidence.

This study aimed to explore population-level associations between SES factors and FBT surveillance reporting using a Bayesian hierarchical model including a spatially autocorrelated random effect. Census tract-level covariates were sourced from the American Community Survey and Healthy Places Index (HPI). Specifying a zero-inflated Poisson distribution to FBT surveillance report counts, we estimated spatially smoothed, census tract-level estimates of FBT surveillance report rates and attributed variability in report rates to census tract characteristics.

Socioeconomic advantage, as measured by the HPI, had the largest effect (IRR = 1.34 [1.07, 1.69], corresponding to a 34% increase in FBT surveillance reporting in more advantaged census tracts. The results herein suggest that FBT surveillance may be biased in its ascertainment

of surveillance data, which may be helpful to contextualizing and interpreting current trends in FBT epidemiology.

Introduction

Nationwide, public health agencies systematically collect, analyze, and publish data regarding morbidity and mortality in their respective communities. Public health infectious disease surveillance is an essential element in the assessment of infectious disease epidemiology and often stimulates public health action and interventions. California is one of three states (Texas and Hawai'i) that captures cases of flea-borne typhus as part of its public health disease surveillance efforts. In California, public health disease surveillance data is generated by healthcare providers and laboratories who are responsible for notifying local health jurisdictions when any of the 90 reportable diseases and conditions are detected. In turn, epidemiological measurements (e.g., incidence, prevalence) heavily rely on reporting for infections of public health significance by health care providers or testing laboratories.

Flea-borne typhus (FBT) is a vector-borne febrile disease caused by the bacteria *Rickettsia typhi*. Symptoms of FBT are non-specific, often characterized by fever and headache. Severe disease and complications occur, but most infections tend to be clinically mild to moderate and may self-resolve.[1–4] *R. typhi* is primarily transmitted through infected flea feces and may cause infection when the mucous membranes of a vertebrate host are exposed of his bacteria.[1,5,6] In the United States, rats, opossums, and cats are implicated as primary hosts of *R. typhi* and competent flea vectors.[7,8] FBT can be detected in humans through serological testing for antibody response or DNA. Both are surveilled through electronic laboratory reporting (ELR) in California whenever an individual tests positive for *R. typhi*. Between 2011 and 2019, 881 cases of FBT were reported in California, the majority of which were reported among residents in Los Angeles and Orange Counties.[9,10] Almost all of these were reported among residents in Los Angeles and Orange Counties

Various factors may make an environment more suitable for flea-burdened peridomestic hosts. Rats, cats, and opossums will settle in or near households if conditions are suitable and may raise the chance of exposure.[8] This has been described for rats, where environmental deprivation and economic disadvantage have downstream effects promoting urban rat populations.[11–13] Historically, flea-borne typhus cases are associated with suboptimal living conditions due to a greater chance of coming in contact with peridomestic hosts, primarily rats and their flea ectoparasites. This has also been underscored in the context of persons experiencing homelessness more recently.[14] Transient persons may be at a higher risk than the housed population, but it is not exclusive.

Likewise, disparities in social and economic factors contribute to the under-ascertainment of infectious disease surveillance data. Following the definitions outlined by Gibbons et al., under-ascertainment is a feature of infectious disease surveillance underestimation, the number of infections in a population that have not been captured by disease surveillance systems, that may occur at the community-level when individuals do not seek healthcare and subsequently not captured in disease surveillance systems.[15] In other words, under-ascertainment may occur because not all who contract a given disease will seek healthcare. Existing financial barriers may deter individuals from seeking healthcare. Another potential reason for under-ascertainment is that asymptomatic, mild, or self-limiting symptoms may not sufficiently raise the urgency for an individual to seek healthcare.[16] Knowledge, attitudes, and perceptions related to health behaviors and intentions to seek healthcare also vary when considering age, sex, race and ethnicity. For example, a population-based study in France noted that children aged less than 15 years are more likely to seek healthcare for symptoms of gastroenteritis compared to adults.[17]

Understanding that socioeconomic factors are associated with host presence (consequently, exposure to *R. typh*i) and healthcare-seeking behaviors, it is reasonable to consider whether these factors also lead to under-ascertainment of FBT surveillance and distorted estimations of incidence. As such, this study aimed to assess population-level associations between SES factors and FBT surveillance reporting. Our guiding hypothesis is that lower socioeconomic status (SES) may be associated with higher risk of FBT, but lower likelihood of being measured through passive surveillance. We utilized a population-based Bayesian framework with spatially dependent random effects to measure associations. Additionally, we analyzed the relationship between census tract FBT reporting and the Healthy Places Index (HPI), a commonly used metric that characterizes census tract advantage by measuring factors pertaining to the social determinants of health (SDOH) in census tracts. This information may be useful to contextualize and improve FBT surveillance efforts in endemic regions in California.

Methods

Flea-borne typhus surveillance data, California

The California Department of Public Health (CDPH) tracks surveillance data pertaining to notifiable diseases and conditions through the California Reportable Disease Information Exchange (CalREDIE). For FBT, diagnostic laboratories typically report results to CalREDIE through ELR after sample tests positive. Local health jurisdictions (i.e., county or city health departments) may also directly record disease incidences in the surveillance system after notification or receipt of a case report form from a health care provider. FBT diagnostic testing results reported through ELR are assigned a status corresponding to the FBT case definition summarized in Supplemental Table 1. Briefly, if an initial test meets the criteria for a probable or

confirmed FBT, then the local health jurisdiction will follow up with the provider and patient to collect more information regarding exposure history and clinical signs and symptoms. Laboratory reports that do not initially meet the laboratory requirements of the case definition are classified as non-cases and often do not receive additional investigation.

Most FBT non-case reports do not contain basic demographic information or clinical information (e.g., symptom onset date, reason for testing). Fortunately, non-case reports contain residential addresses for individuals, enabling the use of a population-based approach to assess socioeconomic factor relationships with FBT reporting. Residence locations of individual FBT reports, whether they were classified as a case or non-case, were mapped and aggregated to census tracts. The total report count aggregated by census tract was established as the dependent variable in this analysis.

Census tract selection

More than 95% of FBT cases reported between 2011 and 2019 were among residents of Los Angeles County and Orange County. Consequently, we only included census tracts within these two counties for analysis. Five census tracts pertaining to the coastline (i.e., beaches and no population) were excluded. County and census tract TIGER/Line shapefiles were retrieved from the U.S. Census Bureau, Department of Commerce. Shapefiles were reduced to the desired census tracts using ArcGIS Pro 2.7.0.

Census tract variables

Census tract population and SDOH data were retrieved from the 2017 ACS 5-year Estimates.[18] To select ACS variables, we adapted an approach outlined by Zhang et al. where the investigators selected variables representing three SDOH domains: "socioeconomic stability,

demographic characteristics of disadvantaged groups, housing and transportation".[19] In total, sixteen ACS variables were retrieved and standardized for their respective census tracts using the *tidycensus* package in R.[20]

The U.S. National Land Cover Database (NLCD) measures 20 classifications of land-use types. Data are made available by the Multi-Resolution Land Characteristics Consortium. NLCD data are presented in 30-meter pixels, representing 900 square meters of a given land-use type per pixel. Census tract area by land-use type was extracted if a pixel's center was within the census tract boundaries using ArcGIS Pro. Specific land-use type area was divided by the total land-use area extracted to give the proportion of area by land-use type in each census tract. In the study region, only the four levels of developed land were found in most census tracts, which are exclusively urban. Furthermore, we combined the middle two developed land types (i.e., low intensity and high intensity) since both are characteristic of standalone single-family homes (Supplemental Table 2). The resulting land-use variables were then standardized prior to analyzing.

The Healthy Places Index (HPI), developed by the Public Health Alliance of Southern California, is a well-known and widely used metric of SDOH in the state. Many local health departments, including those in Los Angeles and Orange Counties, use the HPI as a tool to conduct needs assessments, prioritize funding and attention, and assess health equity. Briefly, the HPI is a standardized value summarizing eight domains related to SDOH: education, healthcare access, housing, neighborhood conditions, clean environment, social environment, and transportation. These domains source data from ACS, NLCD, U.S. Department of Agriculture, California Environmental Protection Agency, and U.S. Environmental Protection Agency. Higher HPI scored indicates greater census tract advantage. The HPI 2.0 iteration was selected as

its indicator data was sourced from 2011 to 2015 and best represents the surveillance period under study (2011-2019).

Multivariable spatial model selection

Multivariable models were specified using queen's adjacency to address spatial autocorrelation. Covariate selection was conducted by performing a backward stepwise elimination algorithm based on maximum likelihood function and a penalty that includes the least absolute shrinkage and selection operator (LASSO), minimax concave penalty (MCP) and smoothly clipped absolute deviation (SCAD). The algorithm is available in the *mpath* package in R.[21,22]

Univariable and multivariable Bayesian spatial analysis

Census tract shapefiles form non-overlapping spatial areal units in the form of a lattice. In most cases, data often exhibit similar values in areal units close together, a pattern known as spatial autocorrelation. The presence of spatial autocorrelation in observed FBT surveillance reports was assessed by the Moran I test in the R package *spdep*.[23] To remedy spatial autocorrelation, a localized conditional autoregressive (CAR) prior was included as a spatially autocorrelated random effect in univariable Bayesian hierarchical models. The CAR priors were obtained using spatial adjacency and given the Besag-York-Mollié (BYM) random effect specification. The BYM model includes both spatial and independently structured error terms and determines the extent of spatial smoothing used. Spatial random effects require a spatial zero-one weight matrix of dimension *J* by *J*, where *J* is the number of census tracts in the study population. The *spdep* package was used to construct the weight matrix based on queen's adjacency (i.e., any neighboring census tract with a shared edge or vertex). The resulting weight

matrix gives element [*i*, *j*] a value of one if census tract *i* and census tract *j* are adjacent to each other and zero if otherwise. Census tract FBT surveillance report counts were modeled using a zero-inflated Poisson distribution with the log-transformed census tract population size as the offset. The model structures (Equation 1) were used to estimate spatially smoothed, census tract-level estimates of FBT surveillance report rates and attributed variability in report rates to census tract characteristics.

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[1] $$ZIP(\mu_i,\ \omega_i)\begin{cases}\ln(\mu_i) = \beta X_i + \ln(population_i) + \varphi_i, \\ \ln\left(\frac{\omega_i}{1-\omega_i}\right) = \delta X_i + \ln(population_i)\end{cases}$$

Equation 1: For each census tract *i*, X_i represents the ACS, land-use, or HPI variable. β represents the corresponding regression coefficient in the Poisson process (i.e., mean) for variable X_i, while δ represents the coefficient for zero-inflation. In implementing the model, a binary random variable Z_i (not shown) is sampled for each census tract *i*, where $Z_i = 1$ if the census tract has 0 reports, and $Z_i = 0$ if the census tract has 1 or more reports.[24]

Model inference for the regression coefficients was based on credible intervals obtained from 30,000 Markov Chain Monte Carlo samples with 10,000 burn-in samples and thinned by every 10th sample. The CARBayes package in R was used for all model analyses.

Ethics statement

This study was considered Exempt; approval was obtained from the Los Angeles County Ambulatory Care Network and Health Services Administration Institutional Review Board (Project No.: 2021-11-967) and the California Department of Health and Human Services, Office of Human Research Protections Committee for the Protection of Human Subjects (Project No.: 2021-174).

Results

Between January 1, 2011 and December 31, 2019, a total of 1,805 FBT surveillance reports were generated by 2,923 census tracts in Orange County and Los Angeles County. When aggregated by census tract, the frequency of reports ranged from 0 to 11 per census tract (Figure 1). Approximately 30.6% (n = 893) census tracts had any history of a FBT surveillance report (Table 1). The Moran I statistic was 0.261 ($p < 0.001$), indicating that the residuals contain substantial spatial autocorrelation for FBT surveillance reporting.

Posterior estimates of FBT surveillance reporting rate ratios and 95% credible intervals from the univariable CAR models are presented in Table 2. The relationships between the covariates and FBT surveillance reporting are shown for the zero-inflation model (i.e., probability of observing a zero count) and the count model (i.e., log-linear model of report counts). Census tracts with a greater proportion of the population being 65 years or older (OR = 0.47 [0.18, 0.89]) or with more health insurance coverage (OR = 0.63 [0.43, 0.94] were inversely associated with FBT surveillance reporting for the zero-inflation probability (i.e., lower probability of observing a zero count in a given census tract). However, in the count (i.e., Poisson) probability, health insurance coverage had a positive effect (IRR = 1.14 [1.01, 1.25]). Non-white race and ethnicity had a large positive effect (OR = 12.49 [1.31, 71.37]) for the zero-inflation probability, albeit with a large credibility interval. Apartment density (IRR = 0.86 [0.77,

0.96]), overcrowding (IRR = 0.79 [0.70, 0.88]), and highly developed land use (IRR = 0.88 [0.79, 0.99]) were negatively associated with FBT surveillance reporting in the count model. Conversely, higher proportions of single-family homes (IRR = 1.16 [1.03, 1.31]) were positively associated with reporting.

The Healthy Places Index and a few of its components were positively associated with FBT surveillance reporting in the count model. Overall, the HPI had the largest effect (IRR = 1.34 [1.07, 1.69], corresponding to a 34% increase in FBT surveillance reporting in more advantaged census tracts. Sub-analysis of the HPI component scores resulted in similar positive associations for greater economic advantage (IRR = 1.24 [1.08, 1.44]), healthcare access (IRR = 1.11 [1.00, 1.24]), and housing (IRR = 1.18 [1.03, 1.36]).

The final zero-inflated Poisson multivariable model was fitted with seven covariates in the zero-inflation (i.e., logit) component and six in the count (i.e., Poisson) component (Table 3). The zero-inflation component of the model addresses the likelihood of having zero flea-borne typhus reports and the count component accounts for the populations (i.e., census tracts) with one or more FBT surveillance reports. Higher odds in the zero-inflation component coefficients are a positive association with a census tract not having any FBT surveillance reports. Therefore, at the census tract level, insurance coverage (OR = 0.40 [0.16, 0.72]) and highly developed land use (OR = 0.43 [0.13, 0.86]) were associated with history of FBT surveillance reporting. Conversely, more new housing (e.g., housing built after 2000) in a census tract was associated with no FBT reporting history (OR = 1.70 [0.13, 0.86)]. In the count component of the multivariable model, low (IRR = 1.07 [1.00, 1.16]) and moderate (IRR = 1.09 [1.01, 1.20]) development land-use were positively associated with higher frequency of FBT reporting. New

housing was associated with lower frequency of FBT reporting at the census tract level (IRR = 0.86 [0.79, 0.94]).

The resulting fitted values from the spatial Bayesian multivariable zero-inflated Poisson model, being the posterior mean count of reports predicted or each census tract while adjusting for the given covariates, were compared to the observed number of reports in Los Angeles and Orange Counties from 2011 to 2019. Census tracts in these two counties that may have under-ascertainment (teal color) or over-ascertainment (dark blue color) of FBT surveillance reports when compared to the predicted values (Figure 2).

Discussion

This study identifies population-level variables related to FBT surveillance reporting in FBT-endemic local health jurisdictions in California. Directly assessing individual-level associations between socioeconomic status and FBT is difficult due to the heterogeneity in data availability between cases and non-cases of FBT. Furthermore, such a comparison may not be appropriate considering both cases and non-cases were likely tested due to exposure history, clinical course, or differential diagnoses noted by a healthcare provider. Therefore, non-cases may be more similar to cases, biasing estimates of risk factors towards the null.

Interpreting the negative relationship between apartment density, overcrowding, and highly developed land use and FBT surveillance reporting in the model's count component requires some considerations. These variables are typical for highly urbanized, metropolitan areas, associated with lower socioeconomic status and, consequently, potential barriers to health care access. The opposite trend in single-family homes also follows the same relationship. On the other hand, if we consider the ecology of FBT, these areas may provide differential habitat suitability for reservoirs of *R. typhi* resulting in varying risks of exposure. For example, densely

populated metropolitan areas may not feature large opossum populations, a highly implicated reservoir of disease, compared to less urban areas.[25,26] Instead, urban communities may support large and dense rat populations. A rat parasitized with an *R. typhi*-infected flea may contaminate its burrow and create an endemic locus exponentially larger than that of opossums or cats within urban environments when considering the life cycles of rats (e.g., lifespan, habitat, reproduction). Improvements in animal surveillance locally would greatly supplement human surveillance. Furthermore, those data could determine whether the associations presented in this paper are artifacts of ascertainment bias or truly representative of exposure risk.

We utilize the HPI to assess the relationship between social determinants of health and FBT surveillance reporting. This approach may be more accessible to local health jurisdictions interested in assessing other disease surveillance reporting. Recently, similar approaches using the HPI have been used to assess population-level risk factors for syphilis,[27] tuberculosis,[28] and preterm births among Black women.[29] Here, we observed a positive association between the HPI and FBT surveillance reporting counts indicating that higher counts of FBT surveillance reports were associated with greater socioeconomic advantage. This finding supports our hypothesis that lower SES status may indeed result in fewer case reports.

The conflicting direction of association between the two parts (zeros and count) of the zero-inflated Poisson model for health insurance coverage require further attention. It is interesting that the odds of no reports being observed (i.e., zero-inflation component) in a census tract is lower with greater health insurance coverage in the univariable and the adjusted multivariable models. Indeed, this relationship is likely driven by confounding factors at the population-level; particularly when considering the unmeasured confounding in the univariable

models. Future studies should consider multi-level models if individual-level demographics are available for all FBT surveillance reports to explore this relationship further.

Social determinants of health and disease have been at the core of public health for decades. The conditions of the environments in which individuals live, work, and socialize play a crucial role in morbidity and mortality for a wide range of conditions. Differences in socioeconomic conditions among individuals and communities have been related to disparities in health status.[30] Often, investigations characterize the relationship between socioeconomic status, chronic conditions (e.g., Type-2 diabetes, cancer), and differences in health outcomes (e.g., morbidity or mortality rate).[31–33] These relationships have also been explored in the context of infectious disease outcomes such as COVID-19 or influenza.[34,35] Such assessments should also be extended to the systems public health entities use to measure infectious diseases. Some efforts to do so have been applied to COVID-19 responses with the aim of ensuring equitable access to testing,[36] assessing disproportionate reporting of disease,[37] or highlighting inequalities in access to non-pharmaceutical interventions.[38] Similar attention is warranted for other reportable diseases or conditions that public health agencies measure.

This assessment is not without limitations. The most important of which is that the data presented here are aggregated and analyzed on a population scale (i.e., census tracts) and may not be representative of an individual's demographics. For example, an individual may have greater income than the median income of the census tract in which they reside. Additionally, an individual's health-seeking behaviors may be driven by their knowledge, attitudes, or perceptions of febrile disease or FBT-related exposures. While individual perceptions of health-related issues are often associated with socioeconomic factors, these subjective aspects driving health behaviors were only explored through population-level factors. Vector or animal

population distributions may be correlated with measured variables such as land use, potentially allowing unmeasured confounding in the analysis. Lastly, interpretation of under-ascertainment or over-ascertainment of FBT surveillance in census tracts displayed in Figure 2 are contingent on the degree to which FBT reporting represents the true pattern of *R. typhi*-tested samples in Los Angeles and Orange Counties. Surveillance data sourced through CalREDIE are the best available data to estimate under-ascertainment, but data on all *R. typhi*-tested samples from healthcare providers or laboratories would be a substantial improvement.

Conclusions and Significance

It is generally understood that passive surveillance systems tend to under-ascertain the true burden of a given disease.[15] The guiding hypothesis of this study was that lower socioeconomic status may be associated with lower likelihood of being measured through passive surveillance for FBT. The population-level associations observed here suggest that FBT surveillance may be biased in its ascertainment of FBT surveillance data, particularly when considering health insurance coverage. As such, it is not appropriate to consider the current ascertainment of FBT cases as a comprehensive measurement of incidence or prevalence of FBT. Fortunately, differential ascertainment or under-ascertainment of disease reporting can be modeled to approximate prevalence of disease and provide risk estimates. Such models have been demonstrated for various infectious diseases, including COVID-19.[39,40] The data and analysis presented here may be used to inform similar applications in FBT surveillance and provide context for determining risk factors for FBT. Two sources of information would greatly improve flea-borne typhus surveillance and lead to more accurate prevalence estimates; 1) inclusion of geographical animal surveillance data to characterize the populations at risk of

disease exposure, and 2) inclusion of all *R. typhi*-tested samples in the region to verify under-ascertainment as characterized in this study and quantify underestimation of FBT surveillance.

Tables and Figures

Figure 5: FBT surveillance report counts by census tract, 2011-2019

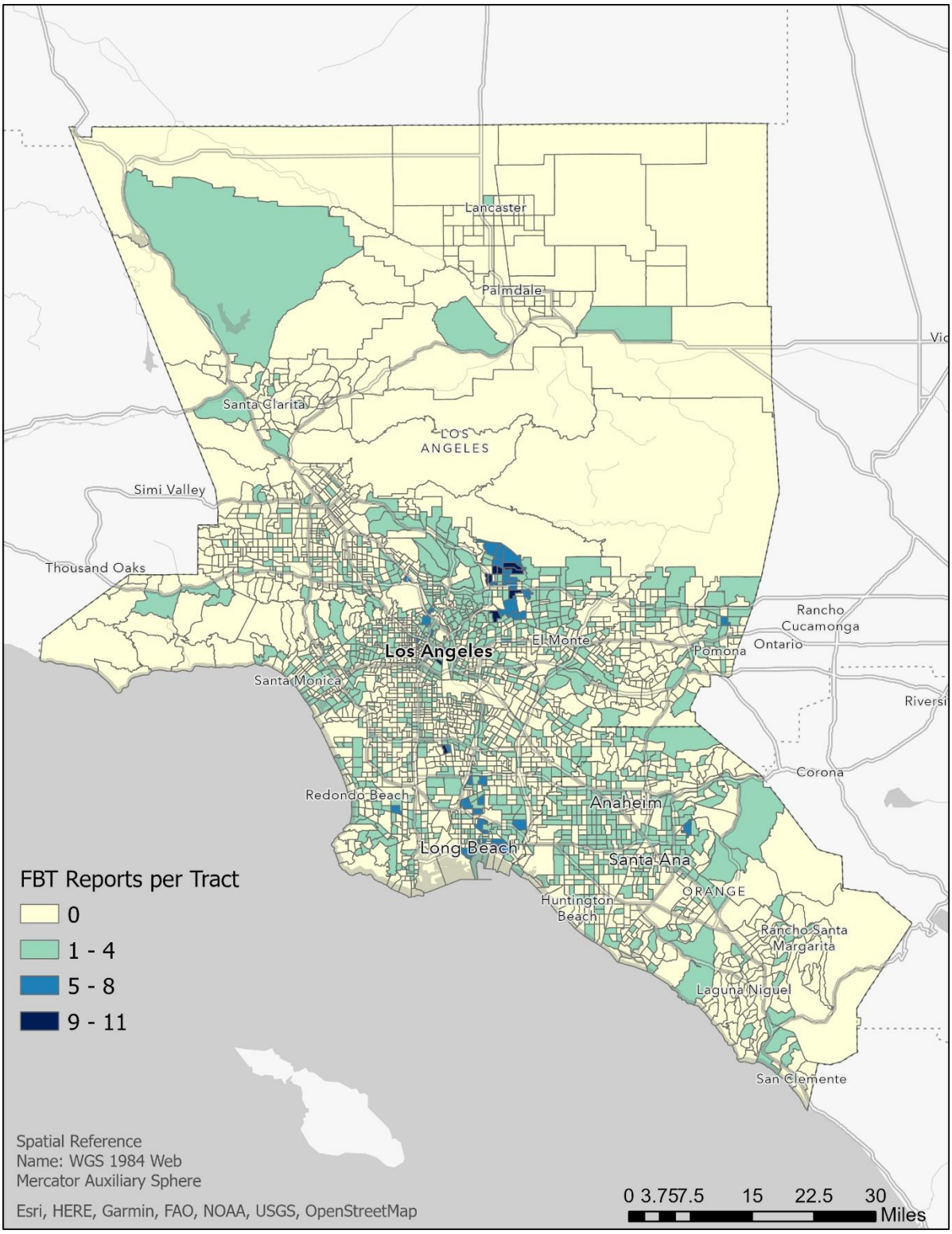


Figure 6: Comparison of predicted and observed flea-borne typhus reports in Los Angeles and Orange Counties, CA, 2011-2019.

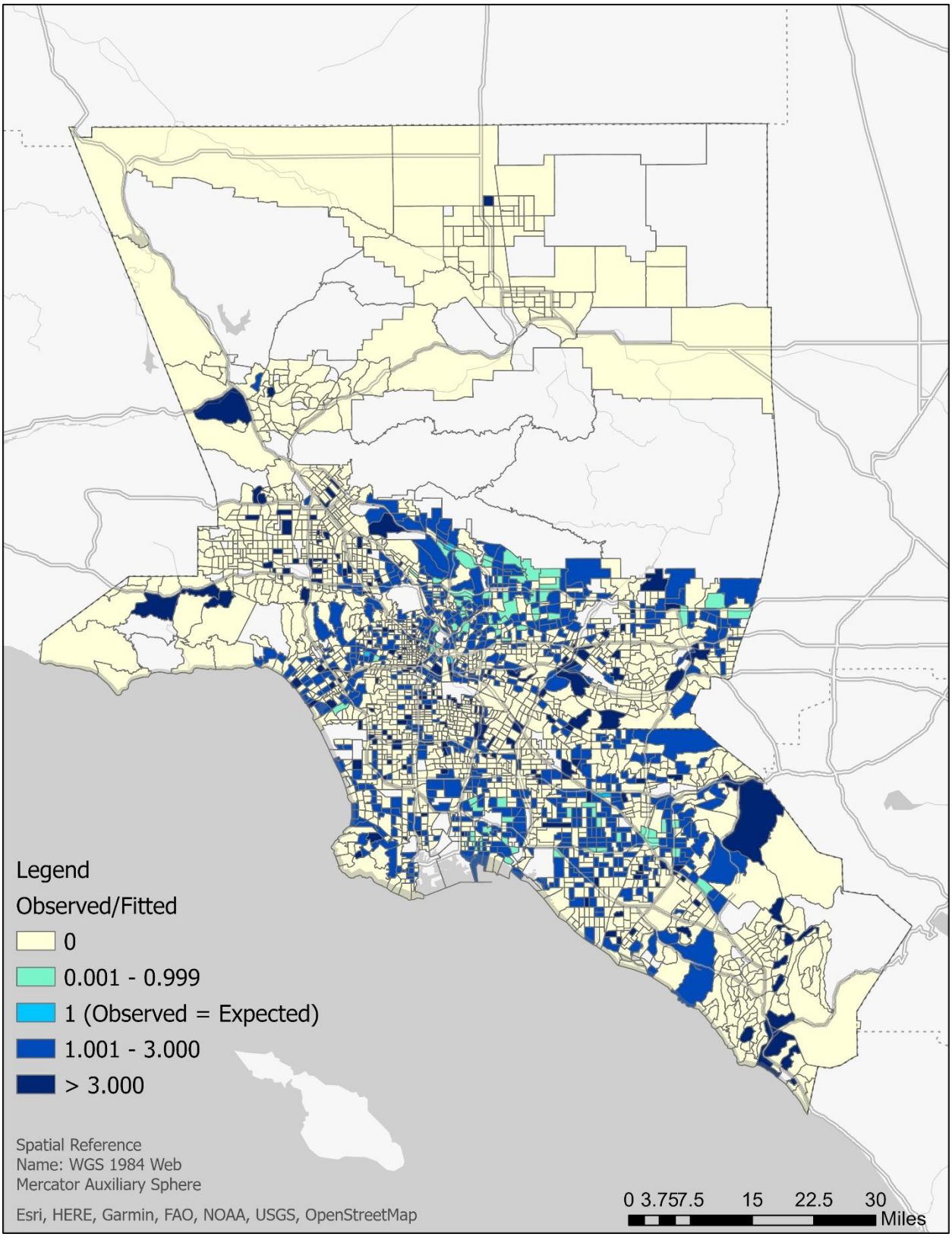


Table 5: Characteristics of census tract surveillance counts and ACS, land-use, and HPI variables; Los Angeles and Orange Counties, CA. (N = 2,923)

Variable	Mean (SD)	Median [Min., Max.]
Hx any report	n = 893	
Report frequency	0.55 (1.15)	0.00 [0.00, 11.00]
Total population‡	4.59 (1.75)	4.40 [0.06, 24.04]
Median household income†, $		6.33 [0.57, 25.00]
Median age		36.50 [19.20, 76.20]
Age: 0-14 years, %	0.13 (0.04)	0.13 [0.00, 0.29]
Age: 65+ years, %	0.14 (0.07)	0.13 [0.00, 0.85]
Racial minority, %	0.62 (0.31)	0.68 [0.02, 1.00]
Living poverty, %	0.17 (0.13)	0.15 [0.00, 1.00]
Insured, %	0.87 (0.08)	0.88 [0.45, 1.00]
Disability, %	0.10 (0.04)	0.10 [0.00, 0.42]
Unemployed, %	0.07 (0.03)	0.07 [0.00, 0.32]
Rent burdened, %	0.58 (0.13)	0.07 [0.00, 0.32]
Overcrowded housing, %	0.13 (0.12)	0.09 [0.00, 0.65]
Housing units±	1.50 (0.65)	1.39 [0.02, 7.63]
Apartments, %	0.37 (0.29)	0.32 [0.00, 1.00]
Single-family homes, %	0.61 (0.29)	0.66 [0.00, 1.00]
Mobile homes, %	0.02 (0.06)	0.00 [0.00, 0.87]
Residences built before 2000, %	0.81 (0.18)	0.86 [0.03, 1.00]
Open development, %	0.04 (0.07)	0.02 [0.00, 0.50]
Moderately development, %	0.64 (0.23)	0.70 [0.00, 1.00]
High development, %	0.24 (0.22)	0.18 [0.00, 0.99]

‡In 1,000 person increments
†In $10,000 increments
±In increments of 1,000

Table 6: Posterior summary of zero-inflated Poisson univariable models of population-based Bayesian hierarchical spatial analysis

	Zero-inflation posteriors OR (95% CrI)	*Count posteriors* IRR (95% CrI
Demographics		
Age, 0-14 years	1.17 (0.66, 1.90)	0.95 (0.86, 1.05)
Age, 65 years or older	0.47 (0.18, 0.89)*	1.08 (0.99, 1.18)
Race and ethnicity		
Non-Hispanic white	0.14 (0.01, 0.97)*	1.23 (1.08, 1.47)*
Racial minority	12.49 (1.31, 71.37)*	0.83 (0.73, 0.93)*
Black or African American	1.50 (1.10, 1.93)*	0.99 (0.85, 1.17)
Asian	0.39 (0.07, 1.01)	0.87 (0.79, 0.97)*
Hispanic or Latino	1.08 (0.60, 1.78)	0.88 (0.78, 1.00)*
Native American or Indigenous	0.82 (0.47, 1.27)	1.02 (0.94, 1.12)
Native Hawaiian or Pacific Islander	0.86 (0.27, 1.29)	0.96 (0.87, 1.06)
Multiple Race	0.86 (0.47, 1.60)	1.12 (1.00, 1.26)
Economic Status		
Median income	0.63 (0.24, 1.60)	1.18 (1.07, 1.28)
Poverty	0.70 (0.24, 1.40)	0.90 (0.81, 1.00)
Health insurance coverage	0.63 (0.43, 0.94)*	1.14 (1.01, 1.25)*
Disability status	0.68 (0.40, 1.07)	0.97 (0.89, 1.06)
Unemployment	1.58 (0.97, 2.30)	1.02 (0.92, 1.13)
Rent burden	0.82 (0.57, 1.18)	0.90 (0.82, 0.98)
Housing Characteristics		
Total housing units	0.81 (0.47, 1.15)	0.99 (0.93, 1.07)
Apartments	2.01 (0.72, 27.32)	0.86 (0.77, 0.96)*
Single-family homes	0.31 (0.01, 5.19)	1.16 (1.03, 1.31)*
Mobile homes	0.16 (0.00, 1.20)	0.99 (0.92, 1.08)
Houses built pre-2000	0.91 (0.61, 1.39)	0.82 (0.75, 0.91)
Overcrowding	0.96 (0.48, 1.52)	0.79 (0.70, 0.88)*
Land Use		
Open developed space	0.00 (0.00, 0.00)	1.05 (0.96, 1.15)
Moderately developed space	1.12 (0.66, 3.02)	1.05 (0.96, 1.15)
Highly developed space	1.01 (0.46, 1.66)	0.88 (0.79, 0.99)*
Healthy Places Index		
HPI	0.68 (0.24, 6.28)	1.34 (1.07, 1.69)*
Economic	0.92 (0.50, 2.17)	1.24 (1.08, 1.44)*
Education	0.82 (0.52, 1.53)	1.12 (0.99, 1.27)
Healthcare access	0.73 (0.46, 1.51)	1.11 (1.00, 1.24)*
Housing	1.03 (0.59, 2.02)	1.18 (1.03, 1.36)*
Neighborhoods	0.69 (0.23, 1.82)	1.03 (0.81, 1.30)
Environmental pollution	0.79 (0.33, 3.27)	0.86 (0.64, 1.16)
Social	0.64 (0.36, 1.14)	1.07 (0.94, 1.22)
Transportation	0.76 (0.16, 5.64)	0.88 (0.64, 1.22)

Table 7: Posterior summaries of zero-inflated Poisson multivariable models for population-based Bayesian hierarchical spatial analysis**.**

Zero-inflation model coefficients	
Variable	**OR (95% CrI)**
Total population	0.57 (0.23, 1.39)
Insurance coverage %	0.40 (0.16, 0.72)*
Unemployment %	1.49 (0.99, 2.44)
Age, 0-17 years %	1.35 (0.79, 2.48)
Housing units	0.98 (0.20, 2.48)
New housing %	1.70 (1.01, 3.46)*
Land use – high %	0.43 (0.13, 0.86)*
Count model coefficients (Poisson)	
Variable	**IRR (95% CrI)**
Median income	1.05 (0.94, 1.16)
Rent burden %	0.97 (0.89, 1.16)
Housing units	0.96 (0.89, 1.03)
New housing %	0.86 (0.79, 0.94)*
Land use – low %	1.07 (1.00, 1.16)*
Land use – mod. %	1.09 (1.01, 1.20)*

3. Determining influential parameters in flea-borne typhus transmission dynamics in California: parameter sensitivity and qualitative analysis

Abstract

Flea-borne typhus (FBT), also known as endemic or murine typhus, is a vector-borne disease caused by the bacterium *Rickettsia typhi.* This disease has resurged in the past two decades in the United States associated with changing reservoir host ecologies. We elected to explore the nuanced ecology of FBT using compartmental mathematical models, which are often employed to express complex disease systems and refine epidemiological questions. This study proposes a novel stochastic, continuous time model using ordinary differential equations (ODEs) based on the known ecology of FBT in the United States. Using literature specific to California, sensitivity analyses were performed using Latin hypercube sampling and partial ranked correlation coefficients to highlight parameters' quantitative and qualitative influence on FBT infections in humans. The two parameters with the greatest influence on FBT in humans were *Ctenocephalides felis-Didelphis virginiana* contact rates and opossum-human contact rates. These results may be used to inform control and intervention campaigns for FBT. Additionally, this model provides a framework for future research that would greatly improve understanding of FBT ecology.

Introduction

Flea-borne typhus (FBT) is a vector-borne human febrile disease caused by *Rickettsia typhi*. Although FBT transmission is typically associated with the rat flea (*Xenopsylla cheopis*), the cat flea (*Ctenocephalides felis*) also serves as a competent vector. Fleas can become infected with *R. typhi* after feeding on infected reservoirs such as rats *(Rattus* spp.), opossums *(Didelphis virginianus*), and cats (*Felis catus*).[22] *R. typhi* multiplies in the epithelial cells of an infected flea's midgut and is shed in the flea's feces while feeding.[18,89,90] *R. typhi* is primarily maintained through horizontal transmission from fleas to hosts via inoculation of infected flea feces to an open bite wound or mucosal membranes. Transovarial transmission has been demonstrated among *X. cheopis* as *R. typhi* may also infect reproductive organs and foregut tissues of the flea[91]. Flea longevity is not affected by *R. typhi* infection and a flea can therefore sustain the infection for the duration of its life.[18,23] Similar to other vertebrate hosts, humans become infected when open wounds or mucosal surfaces are exposed to contaminated flea feces.

Sylvatic cycles of FBT in the continental United States (i.e., Texas and California) feature complicated transmission dynamics with two vectors and three hosts. Currently most public health interventions are reactive to new FBT outbreaks, but there is great interest among local health jurisdictions for a proactive, preventative approach. Mathematical models have increasingly been used in epidemiologic literature to inform public health decision making.[92] The complex ecology of FBT has historically been a hurdle to modeling FBT, however, even simple models could represent an improvement over the diagrammatic presentations of host-vector relationships that currently exist. Modeling can be a cheap and quick way for us to evaluate the dynamic ecology and transmission dynamics of FBT.

The present study aimed to develop a novel mathematical model for FBT using a system of ODEs and identify key parameters using sensitivity analysis to target for intervention strategies and allocation of resources. Scenario analyses are also provided as example applications for the proposed FBT mathematical model and may prove useful to vector control agencies in FBT endemic regions.

Methods

We propose a stochastic continuous-time model consisting of 22 compartments with consideration for humans, reservoir host species (rats, cats, opossums), and two primary flea vector species in the United States (*rat flea, cat flea; Figure 7)*. Humans are incidental dead-end hosts in the model, meaning that infected humans are unable to infect fleas, reservoir hosts, or other humans. Because the ecologies of fleas, their hosts, and FBT differ among environments, we prioritized literature regarding FBT ecology in California. Each of the ODEs below follow notation and parameter inputs as outlined in Table 8. The resulting model represents the reported FBT ecology in the United States using parameters specific to California.[18,93]

Modeling flea species

The cat flea (*C. felis*) maintains *R. typhi* the entirety of its life without reproductive or other vital consequences[12] and parasitizes all hosts included in this model. As such, the ODEs corresponding to *C. felis* are as follows:

$$\frac{dS_{cf}(t)}{dt} = \mu_{cf} - S_{cf}\varphi_{hc}\left(a_{cr}I_{rat} + a_{co}I_{opo} + a_{cc}I_{cat}\right) - \mu_{cf}S_{cf}$$

$$\frac{dE_{cf}(t)}{dt} = S_{cf}\varphi_{hc}\left(a_{cr}I_{rat} + a_{co}I_{opo} + a_{cc}I_{cat}\right) - \lambda_{cf}E_{cf} - \mu_{cf}E_{cf}$$

$$\frac{dI_{cf}(t)}{dt} = \lambda_{cf}E_{cf} - \mu_{cf}I_{cf}$$

The rat flea (*X. cheopis*) is considered the primary vector of FBT and typically parasitizes rat species. This flea also maintains *R. typhi* for the entirety of its lifespan. Unlike other competent vectors, it has limited transovarial transmission of *R. typhi* its progeny[91]. The ODEs for *X. cheopis* are as follows:

$$\frac{dS_{xc}(t)}{dt} = (1-\tau_{xc})\mu_{xc} - S_{xc}\varphi_{hx}\left(a_{xr}I_{rat} + a_{xo}I_{opo} + a_{xc}I_{cat}\right) - \mu_{xc}S_{xc}$$

$$\frac{dE_{xc}(t)}{dt} = S_{xc}\varphi_{hx}\left(a_{xr}I_{rat} + a_{xo}I_{opo} + a_{xc}I_{cat}\right) + (\tau_{xc})\mu_{xc} - \lambda_{xc}E_{xc} - \mu_{xc}E_{xc}$$

$$\frac{dI_{xc}(t)}{dt} = \lambda_{xc}E_{xc} - \mu_f I_{xc}$$

The ODEs for both flea species allow flexibility for fleas to feed on various hosts (rats, opossums, or cats) despite flea-specific host preferences. This allows the model to be malleable to different contexts where fleas may parasitize hosts at varying rates in various habitats [See further explanation in *Parameter Input Selection*]. The key difference between the two flea ODE systems is the allowance for vertical transmission among rat fleas, modeled as $(\tau_{xc})\mu_{xc}$, where the probability of vertical transmission is multiplied by the birth rate. In turn, the proportion of *X. cheopis* births not resulting in transovarial transmission is given as $(1-\tau_{xc})\mu_{xc}$.

Modeling host species

Rats, especially black rats (R. Rattus), are the primary hosts of FBT worldwide. In the U.S., the brown rat (*R. norvegicus)* may also serve as a reservoir for *R. typhi*[6,8]. For this model, both species were assumed to play an equal role in FBT transmission and combine both into a single system of ODEs. We also assume that the brown rat is similar to the black rat in that they are only rickettsemic and can transmit to fleas for a limited period of time[11].

$$\frac{dS_{rat}(t)}{dt} = \mu_r - (\varphi_{rx}a_{xr}S_{rat}I_{xc} + \varphi_{rc}a_{cr}S_{rat}I_{cf}) - \mu_r S_{rat}$$

$$\frac{dE_{rat}(t)}{dt} = (\varphi_{rx}a_{xr}S_{rat}I_{xc} + \varphi_{rc}a_{cr}S_{rat}I_{cf}) - \mu_r E_{rat} - \lambda_r E_{rat}$$

$$\frac{dI_{rat}(t)}{dt} = \lambda_r E_{rat} - \mu_r I_{rat} - \gamma_r I_r$$

$$\frac{dR_{rat}(t)}{dt} = \gamma_r I_r - \mu_r R_{rat}$$

Molecular assays have demonstrated *R. typhi* DNA in opossums for up to four weeks[94] but this may represent detection of non-viable nucleic acids of rickettsiae, and these hosts may not be able to infect a naïve flea for the entirety of that period.[94] For this paper, it was conservatively assumed that the upper limit of infectivity for an opossum is 21 days. It is unknown how long cats remain rickettsemic after becoming infected with *R. typhi*. Cats were assumed to follow the same maximum recovery period as opossums (21 days, permitting the ODEs for cats and opossums to be structurally the same and represented as:

$$\frac{dS_{cat}(t)}{dt} = \mu_c - (\varphi_{cx} a_{xc} S_{cat} I_{xc} + \varphi_{cc} a_{cc} S_{cat} I_{cf}) - \mu_c S_{cat}$$

$$\frac{dE_{cat}(t)}{dt} = \left(\varphi_{cx} a_{xc} S_{cat} I_{xc} + \varphi_{cc} a_{cc} S_{cat} I_{cf}\right) - \mu_c E_{cat} - \lambda_c E_{cat}$$

$$\frac{dI_{cat}(t)}{dt} = \lambda_c E_{cat} - \mu_c I_{cat} - \gamma_c I_c$$

$$\frac{dR_{cat}(t)}{dt} = \gamma_c I_c - \mu_c R_{cat}$$

$$\frac{dS_{opo}(t)}{dt} = \mu_o - (\varphi_{ox} a_{xo} S_{opo} I_{xc} + \varphi_{oc} a_{co} S_{opo} I_{cf}) - \mu_o S_{opo}$$

$$\frac{dE_{opo}(t)}{dt} = (\varphi_{ox} a_{xo} S_{opo} I_{xc} + \varphi_{oc} a_{co} S_{opo} I_{cf}) - \mu_o E_{opo} - \lambda_o E_{opo}$$

$$\frac{dI_{opo}(t)}{dt} = \lambda_o E_{opo} - \mu_o I_{opo} - \gamma_o I_o$$

$$\frac{dR_{opo}(t)}{dt} = \gamma_o I_o - \mu_o R_{opo}$$

Modeling humans as dead-end hosts

Humans enter the FBT transmission cycle as dead-end, incidental hosts of *R. typhi*. While the two flea species in the model can feed on humans, *X. cheopis* and *C. felis* are commonly

found attached or in the nests of hosts.[95] Therefore, human infections are modeled as 1) infrequent, but direct contact between fleas and humans, and 2) contact with fleas through direct human contact with a rickettsemic rat, cat, or opossum that is carrying infectious fleas of either species. Humans cannot transmit *R. typhi* back to fleas and therefore are not included in the previously mentioned ODEs for hosts and fleas.

$$\frac{dS_h(t)}{dt} = \mu_h - \{\varphi_h a_{fh} S_h\left(I_{xc} + I_{cf}\right) + \varphi_h S_h\left[a_{rh} I_{rat}\left(a_{xr} I_{xc} + a_{cr} I_{cf}\right) + a_{ch} I_{cat}\left(a_{xc} I_{xc} + a_{cc} I_{cf}\right) + a_{oh} I_{opo}\left(a_{xo} I_{xc} + a_{co} I_{cf}\right)\right]\} - \mu_h S_h$$

$$\frac{dE_h(t)}{dt} = \{\varphi_h a_{fh} S_h\left(I_{xc} + I_{cf}\right) + \varphi_h S_h\left[a_{rh} I_{rat}\left(a_{xr} I_{xc} + a_{cr} I_{cf}\right) + a_{ch} I_{cat}\left(a_{xc} I_{xc} + a_{cc} I_{cf}\right) + a_{oh} I_{opo}\left(a_{xo} I_{xc} + a_{co} I_{cf}\right)\right]\} - \lambda_h E_h - \mu_h E_h$$

$$\frac{dI_h(t)}{dt} = \lambda_h E_h - \mu_h I_h - \gamma_h I_h$$

$$\frac{dR_h(t)}{dt} = \gamma_h I_h - \mu_h R_h$$

Parameter input selection

Lacking data, we assumed that the latency period, or intrinsic incubation period, of *R. typhi* in cats and opossums was equal to that of rats (7 days). To-date transmission probabilities from *C. felis* to opossums and cats have not been studied in lab settings and were assumed to be equal to those of *X. cheopis* (approximately 50%). Birth and death rates were assumed to be in equilibrium based on average lifespan for all species included in the model (Table 8).

Contact rates between hosts and fleas were determined through literature of the average flea index for each flea species on each host. While the ODEs allowed each flea to contact and potentially infect each host species, in the literature *C. felis* was commonly not found on rats, effectively producing a nil index, and therefore contact rate, between the two species. Therefore,

the term in the ODE for *C. felis* or rat infection by these two species contacting would equal 0 (i.e., if $a_{cr} = 0$, then $\varphi_{rc} a_{cr} S_{rat} I_{cf} = 0$).

Contact rates between humans and fleas or humans and FBT reservoir hosts were calculated using surveillance data collected in California from 2011-2019 by the California Department of Public Health (Table 8). These values were obtained from case investigations where people with FBT acknowledged whether they had exposure to these species during the suspected exposure window (i.e., 7-14 days prior to onset of symptoms). These exposure proportions were converted to rates by dividing by the total population in Los Angeles and Orange Counties, then scaled to the contacts per day. These counties were selected as they represent the endemic foci of FBT in California, reporting over 95% of all cases between 2011 and 2019. In other words, the contact rate between humans, fleas, and hosts was represented as the number of contacts per day divided by the sum of the human population size.

Sensitivity analysis

Although there are limited data and studies to inform certain parameter input values, we relied on stochastic sensitivity analysis to explore a broad range of possible values and outcomes. Due to lack of data, a uniform distribution was considered for all model parameters. The lower and upper bounds of the 36 model parameters were sourced from prior studies on FBT (Supplemental Table 1), some of which have only limited data. Latin Hypercube Sampling (LHS) and partial rank correlation coefficients (PRCC) were applied to the model parameters to carry out sensitivity analyses in order to measure the relative influence of parameters on variation in model outcomes. LHS is a stratified Monte Carlo sampling method that randomly draws one sample from *N* equal intervals from a given parameter's range. PRCC is then combined with LHS to evaluate the parameter space by measuring a nonlinear, but monotonic,

relationship between a parameter of interest and the model output. PRCC values fall between -1 and +1, with values close to the bounds indicating that a parameter has strong influence on the model output[96]. Therefore, a small change in highly influential parameters will likely produce a significant change in the model outcome.

Models were analyzed for parameter value sets and sensitivity of FBT infections were quantified with PRCCs. The PRCC values for the 36 parameters in the model system are presented using 1000 runs of Latin hypercube sampling and 2000 bootstrap replicates to retrieve confidence intervals. All analyses were conducted in R using the *lhs* package[97]. Code and data used can be found on GitHub or in the Supplementary Files.

Scenario analysis

Five scenarios representing possible prevention or intervention activities were evaluated to demonstrate potential applications of this model. First, we consider a hypothetical human vaccine for *R. typhi* that reduces *R. typhi* transmission probability in humans by 25% (Scenario 1). In reality, an effective vaccine against *R. typhi* is not available as of yet, as killed rickettsial vaccines offer incomplete protection and live-attenuated vaccines may revert to virulence[98]. Next, we evaluate intervention activities which local health jurisdictions may implement such as health education practices improving knowledge and awareness of FBT exposure risks or pest control in and around households. While intervention activities may have varying impacts across populations, we assume that they reduce human contact rates with fleas, opossums, rodents, and cats (Scenarios 2-5, respectively) by 25% for our scenario analyses. All scenarios were compared to the baseline model in which no parameters were changed from their initial inputs (Supplemental Table 1).

Results

The model outcome (predicted FBT-infected human population) was sensitive to all human-host interfacing parameters (i.e., cat-human contact rate, opossum-human contact rate, and rat-human contact rate) with cat-human contact and opossum-human contact exhibiting the highest recorded PRCCs (Figure 8). To a lesser degree, human FBT was also positively sensitive to the *X. cheopis*-rat contact rate. Time-to-resolution of *R. typhi* rickettsemia in opossums were most influential in the opposite direction. Parameters most influential in the model, with PRCC values in the range ±0.75 to ±0.99, are indicated with two asterisks (*). Moderately influential parameters, with PRCCs between ±0.50 to ±0.74, were assigned a single asterisk (Table 9).

Of the scenarios representing prevention and intervention activities, Scenario 1 (hypothetical vaccine with 25% reduction in transmission probability) and Scenario 3 (25% reduction in human-opossum contact) yielded an average reduction of 0.57% and 0.49%, respectively, in infected human population proportion compared to the baseline model (1.15%). Scenarios 2 (human-flea contact reduction; 0.10%), 4 (human-rodent contact reduction; 0.20%), and 5 (human-cat contact reduction; 0.07%) also reduced the infected population proportion but to a less notable degree (Figure 9).

Discussion

This model describes the transmission of FBT in the U.S within sylvatic cycles of two flea and three vertebrate host species, and spreading to humans through incidental spillover. Sensitivity analyses of the contact rates between humans, hosts, and fleas documented that contact between opossums and *C. felis* was the most significant parameter for FBT transmission, likely due to the high flea burden on opossums relative to the other hosts. Consequently, human-opossum and human-flea contact were also highly influential in the model. Unsurprisingly, *X.*

cheopis contact with rats also was an influential parameter given that this is the typical and primary epidemiological cycle of *R. typhi.*

In our first scenario (a hypothetical vaccine that reduces that transmission probability of *R. typhi* in humans by 25%), model results indicate effective reduction in the proportion of infected humans assuming absolute uptake in the vaccine. Such a vaccine does not currently exist, though historical FBT immunization campaigns were conducted in 1944 and 1946 although with little available information about the vaccine used.[99] More recently, *R. typhi* vaccine proof-of-principle studies have been reported with encouraging early results.[100] When a vaccine becomes available, Scenario 1 could be extended to account for its actual efficacy and uptake to better predict risk. Scenario 3, an intervention reducing opossum and human contact by 25%, had similarly beneficial results as Scenario 1 compared to the base model. Because opossums have particularly high flea burdens, reducing contact between humans and opossums has a strong impact on reducing the contact of humans and fleas. Scenarios 2, 4, and 5 each evaluated a 25% reduction in human contact with fleas, rodents, and cats, respectively. Each produced smaller epidemic curves compared to the base model but to a lesser degree compared to Scenarios 1 and 3. Scenarios 4 and 5 likely produced smaller effects because of relatively low flea burdens on these hosts compared to opossums. These scenarios provide simplified example applications of the FBT transmission model. Applied epidemiologists should consider local ecology and prevention and intervention activities when interpreting simulated scenarios.

There are several considerations that may influence the structure and interpretation of this model. First, other flea species may be vector-competent for *R. typhi* but have limited vectorial capacity in California, such as *Leptopsylla segnis*, the European mouse flea. Despite its colloquial name, this species preferentially infests rats. Because it is similarly if not more vector-

competent for *R. typhi* than *X. cheopis*, it may play a role in FBT ecology wherever present, although it is not implicated as a vector for FBT to humans.[39] The assumption that transmission probability from fleas to hosts was 50% was based on a study finding 50% of rats seroconverting when exposed to less than 1 plaque-forming unit in lab settings.[101] Transmission from fleas to some hosts may be much higher than 50%, as *R. typhi* may evade some immune responses. The model does not account for some intricacies of flea and host biology including non-zero probability of transmission via flea bite, host immune response to recurrent exposure to *R. typhi*, varying host preference and behavior among fleas depending on age and sex, and the potential for asymptomatic infections among humans.[12–14,39,102,103] Lastly, while improbable, the assumption that cats do not remain rickettsemic and infectious for the entirety of their lives may not hold true.

The limitations in parameter estimates from prior literature outline areas for future research that would improve the current model. The present model assumes that there is homogeneous mixing, where all host species have identical rates of disease-causing contacts. In reality, there is spatial fragmentation and high heterogeneity in FBT transmission between flea vectors, intermediate hosts, and humans that alter disease ecology and risk. For example, one study noted significant variation in flea abundance and diversity among black rats in Los Angeles County across different sampling sites.[104] Given that *X. cheopis* was not collected on any rats in this study, our model may be best utilized with species-specific initial values for hosts and vectors derived from local measurements. Likewise, while this model is useful for identifying parameters influential in FBT infections in humans, it should not be used for predicting number of FBT infections unless applied to smaller, confined geographical areas where assumptions of homogeneous mixing hold.[105] Homogeneous-mixing compartment models

can be effectively modified for a few classes of non-homogeneous networks.[105] Alternatively, an agent-based model can be adapted to capture heterogeneous attributes across individuals and their respective interaction networks in localized settings.

Conclusions and Significance

The presented model for FBT transmission dynamics highlights several parameters influencing FBT risk in humans. Most notable of these were *C. felis*-opossum contact rates and opossum-human contact rates. This model and complementing scenario analyses may be informative to applied epidemiologists interested in planning control or intervention methods for FBT and could be adapted to their location-specific needs. For example, population sizes were not specified in the models to predict the number of infections due to heterogeneous human population size geographically and unknown host population sizes. Local health jurisdictions can easily model local flea-borne typhus transmission and solve for the basic reproduction number (R_0) wherever these data are available. Additionally, this model provides a framework for future research that would greatly improve understanding of FBT ecology.

Tables and Figures

Figure 7: Conceptual model of flea-borne typhus ecology, California.

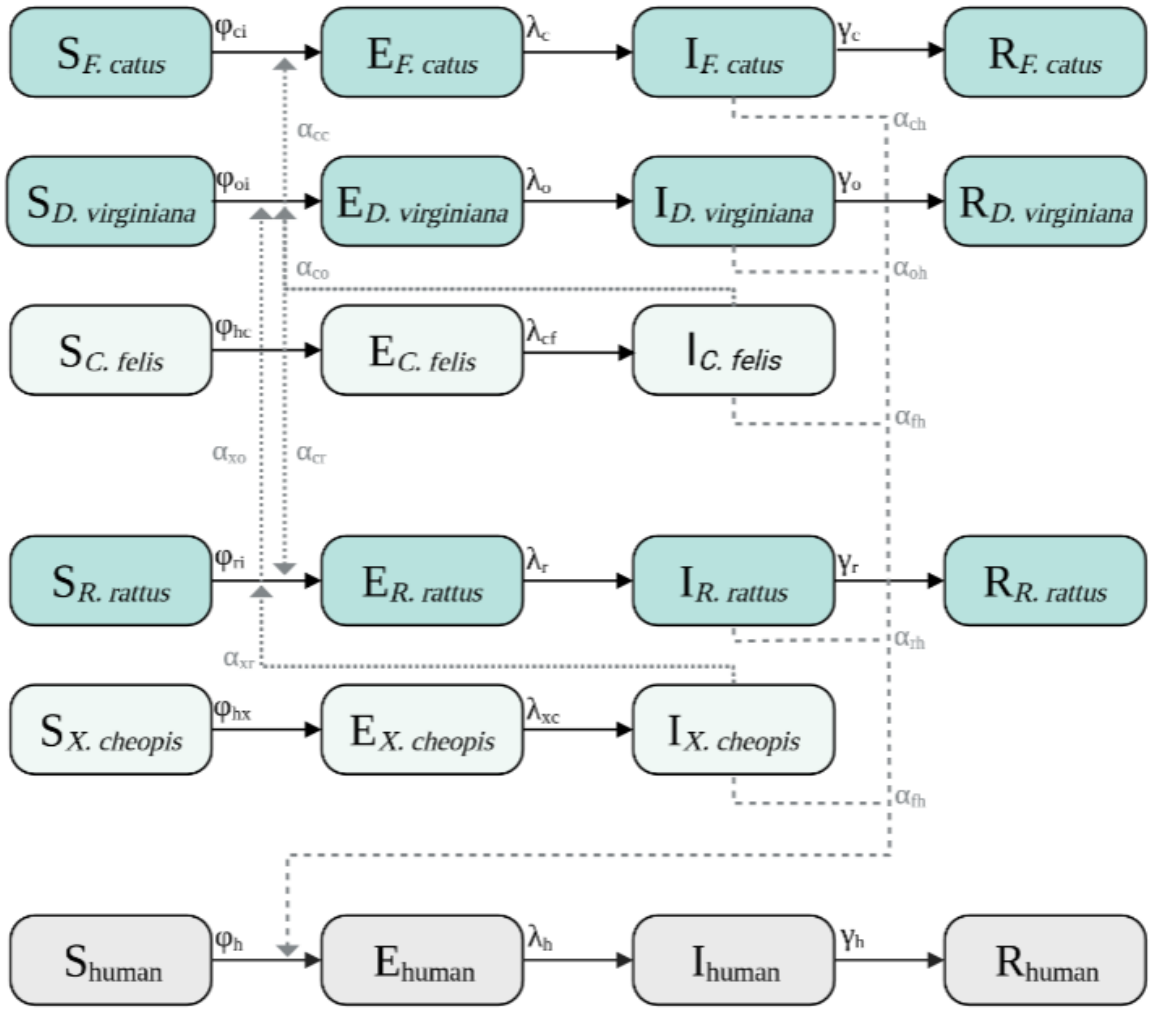


Table 8: Flea-borne typhus ordinary differential equation symbol notation, corresponding parameter notation, and descriptions.

#	Symbol	Parameter	Description	Range	Source
1	a_{cc}	a_cc	Contact rate between *C. felis* and cats.	Uni(3, 11)	[93]
2	a_{ch}	a_ch	Contact rate between cats and humans.	Uni(0, 9)	Calculated[†]
3	a_{co}	a_co	Contact rate between *C. felis* and opossums.	Uni(2, 144)	[93,106]
4	a_{cr}	a_cr	Contact rate between *C. felis* and rats.	Uni(0, 21)	[4,93,107]
5	a_{fh}	a_fh	Contact rate between fleas and humans.	Uni(0, 0.0000145)	Calculated[†]
6	a_{oh}	a_oh	Contact rate between opossums and humans.	Uni(0, 0.0000256)	Calculated[†]
7	a_{rh}	a_rh	Contact rate between rats and humans.	Uni(0, 0.0000177)	Calculated[†]
8	a_{xc}	a_xc	Contact rate between *X. cheopis* and cats.	Uni(0, 0)	[9,93]
9	a_{xo}	a_xo	Contact rate between *X. cheopis* and opossums.	Uni(0, 5)	[93]
10	a_{xr}	a_xr	Contact rate between *X. cheopis* and rats.	Uni(0, 32.5)	[93,108,109]
11	φ_{cc}	b_cc	Transmission probability from *C. felis* to cats.	Uni(0.012, 0.910)	[101]
12	φ_{cx}	b_cx	Transmission probability from *X. cheopis* to cats.	Uni(0.012, 0.910)	[101]
13	φ_{h}	b_h	Transmission probability to humans	Uni(0.012, 0.910)	Assumed[101]
14	φ_{hc}	b_hc	Transmission probability from infected host to *C. felis*.	Uni(0.5, 1)	Assumed[12,110§]
15	φ_{hx}	b_hx	Transmission probability from infected host to *X. cheopis*.	Uni(0.5, 1)	Assumed[12,110§]
16	φ_{oc}	b_oc	Transmission probability from *C. felis* to opossums.	Uni(0.012, 0.910)	Assumed[101]
17	φ_{ox}	b_ox	Transmission probability from *X. cheopis* to opossums.	Uni(0.012, 0.910)	Assumed[101]
18	φ_{rc}	b_rc	Transmission probability from *C. felis* to rats.	Uni(0.012, 0.910)	Assumed[101]
19	φ_{rx}	b_rx	Transmission probability from *X. cheopis* to rats.	Uni(0.012, 0.910)	Assumed[101]
20	λ_{c}	l_c	Latency period for cats	Uni(0.071, 0.143)	Assumed[94]
21	λ_{cf}	l_cf	Latency period for *C. felis*	Uni(0.111, 0.167)	[12]
22	λ_{h}	l_h	Latency period for humans	Uni(0.071, 0.143)	[111]
23	λ_{o}	l_o	Latency period for opossums	Uni(0.143, 0.250)	[94]
24	λ_{r}	l_r	Latency period for rats	Uni(0.071, 0.143)	[112]
25	λ_{xc}	l_xc	Latency period for *X. cheopis*	Uni(0.1, 0.143)	[91,113]
26	μ_{c}	mu_c	Birth/mortality rate for cats	Uni(0.0005, 0.0014)	
27	μ_{cf}	mu_cf	Birth/mortality rate for *C. felis*	Uni(0.01, 0.04)	[114]
28	μ_{h}	mu_h	Birth/mortality rate for humans	Uni(3.42E-05, 3.68E-05)	
29	μ_{o}	mu_o	Birth/mortality rate for opossums	Uni(9.13E-05, 2.74E-03)	[106]

30	μ_r	mu_r	Birth/mortality rate for rats	Uni(0.0014, 0.0027)	[115]
31	μ_{xc}	mu_xc	Birth/mortality rate for *X. cheopis*	Uni(0.010, 0.024)	[116]
32	γ_h	r_h	Recovery period in humans	Uni(0.1, 0.05)	[117,118]
33	γ_r	r_r	Recovery period in rats	Uni(0.025, 0.1)	[112]
34	γ_o	r_o	Recovery period in opossums	Uni(0.0476, 0.143)	[94]
35	γ_c	r_c	Recovery period in cats	Uni(0.0476, 0.143)	Assumed[94]
36	τ_{xc}	t_xc	Vertical transmission probability in *X. cheopis*	Uni(0.02, 0.04)	[14]

[†]Calculated based on surveillance data collected in California from 2011-2019 by the California Department of Public Health

[§]Transmission probability of *R. typhi* from an infected host to a naïve flea has not been quantified but are assumed to be high considering exception immune evasion among *Rickettsiae* and high infection rates among fleas in laboratory settings. Unknown parameter values were assumed to be equal to values derived from similar research (e.g., latency period for cats is assumed to be equal to that of opossums).

Table 9: Partial rank correlation coefficient (PRCC) between predicted proportion of population infected and each model parameter.

#	Symbol	Parameter	PRCC	CI
1	a_{cc}	a_cc	0.116	(0.009, 0.220)
2	a_{ch}	a_ch	0.213	(0.120, 0.323)
3	a_{co}	a_co	0.768**	(0.721, 0.821)
4	a_{cr}	a_cr	0.210	(0.097, 0.326)
5	a_{fh}	a_fh	0.449	(0.342, 0.539)
6	a_{oh}	a_oh	0.798**	(0.758, 0.845)
7	a_{rh}	a_rh	0.513*	(0.439, 0.596)
8	a_{xc}	a_xc	0.003	(-0.148, 0.119)
9	a_{xo}	a_xo	0.077	(-0.031, 0.184)
10	a_{xr}	a_xr	0.354	(0.252, 0.453)
11	φ_{cc}	b_cc	0.032	(-0.084, 0.149)
12	φ_{cx}	b_cx	0.023	(-0.089, 0.146)
13	φ_{h}	b_h	0.603*	(0.535, 0.671)
14	φ_{hc}	b_hc	0.028	(-0.079, 0.138)
15	φ_{hx}	b_hx	-0.036	(-0.158, 0.074)
16	φ_{oc}	b_oc	-0.006	(-0.110, 0.123)
17	φ_{ox}	b_ox	0.027	(-0.086, 0.120)
18	φ_{rc}	b_rc	-0.005	(-0.115, 0.114)
19	φ_{rx}	b_rx	-0.022	(-0.131, 0.096)
20	λ_{c}	l_c	0.000	(-0.104, 0.106)
21	λ_{cf}	l_cf	0.016	(-0.095, 0.128)
22	λ_{h}	l_h	-0.006	(-0.116, 0.102)
23	λ_{o}	l_o	0.008	(-0.112, 0.108)
24	λ_{r}	l_r	0.034	(-0.074, 0.147)
25	λ_{xc}	l_xc	0.012	(-0.102, 0.116)
26	μ_{c}	mu_c	-0.022	(-0.135, 0.084)
27	μ_{cf}	mu_cf	-0.173	(-0.285, -0.066)
28	μ_{h}	mu_h	-0.010	(-0.131, 0.114)
29	μ_{o}	mu_o	0.203	(0.081, 0.318)
30	μ_{r}	mu_r	0.112	(0.000, 0.205)
31	μ_{xc}	mu_xc	-0.025	(-0.125, 0.089)
32	γ_{h}	r_h	0.002	(-0.101, 0.123)
33	γ_{r}	r_r	-0.375	(-0.476, -0.283)
34	γ_{o}	r_o	-0.522*	(-0.619, -0.447)
35	γ_{c}	r_c	-0.158	(-0.289, -0.050)
36	τ_{xc}	t_xc	-0.052	(-0.155, 0.063)

**Highly influential parameter to infected humans (±0.75 to ±0.99)
*Moderately influential parameter (±0.50 to ±0.74)

Figure 8: Partial rank correlation coefficients of model parameters.

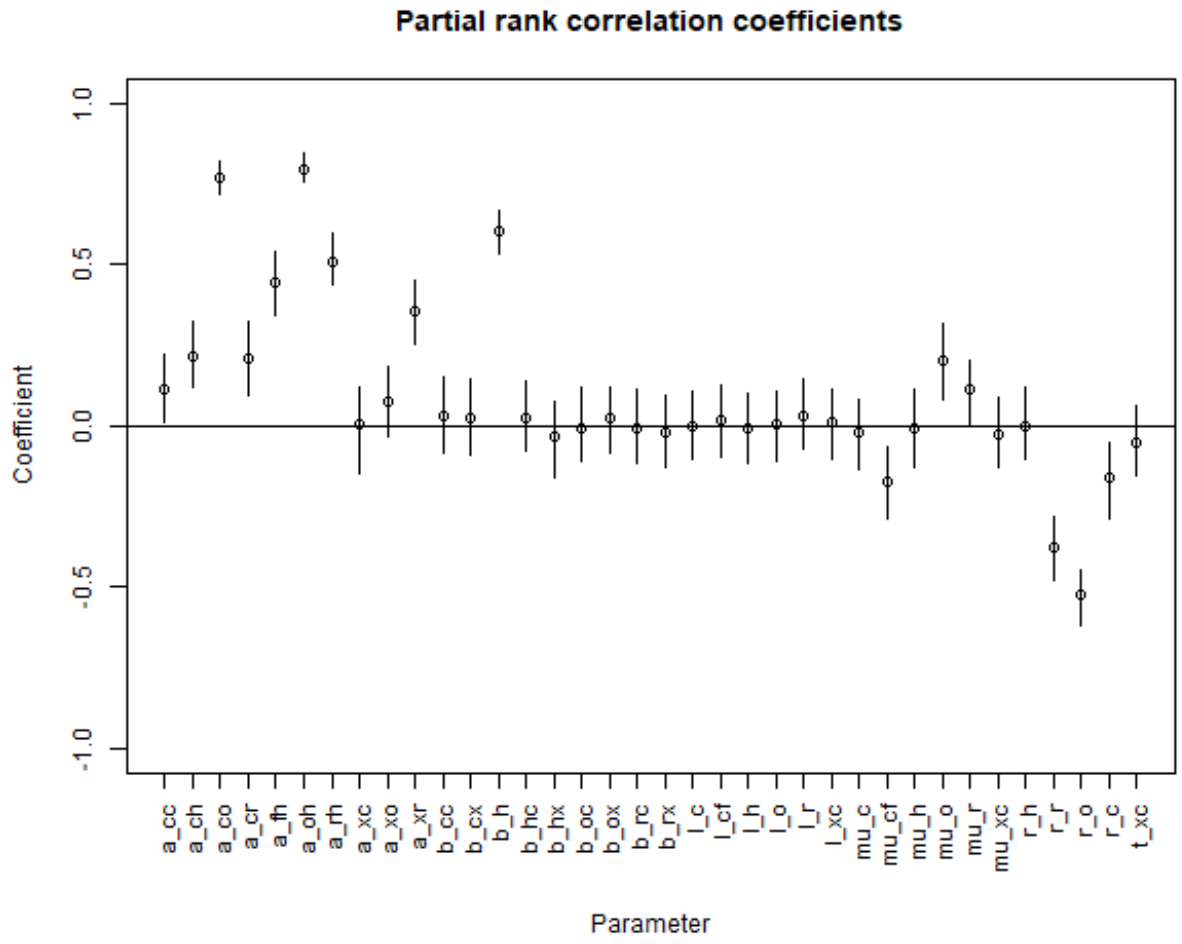
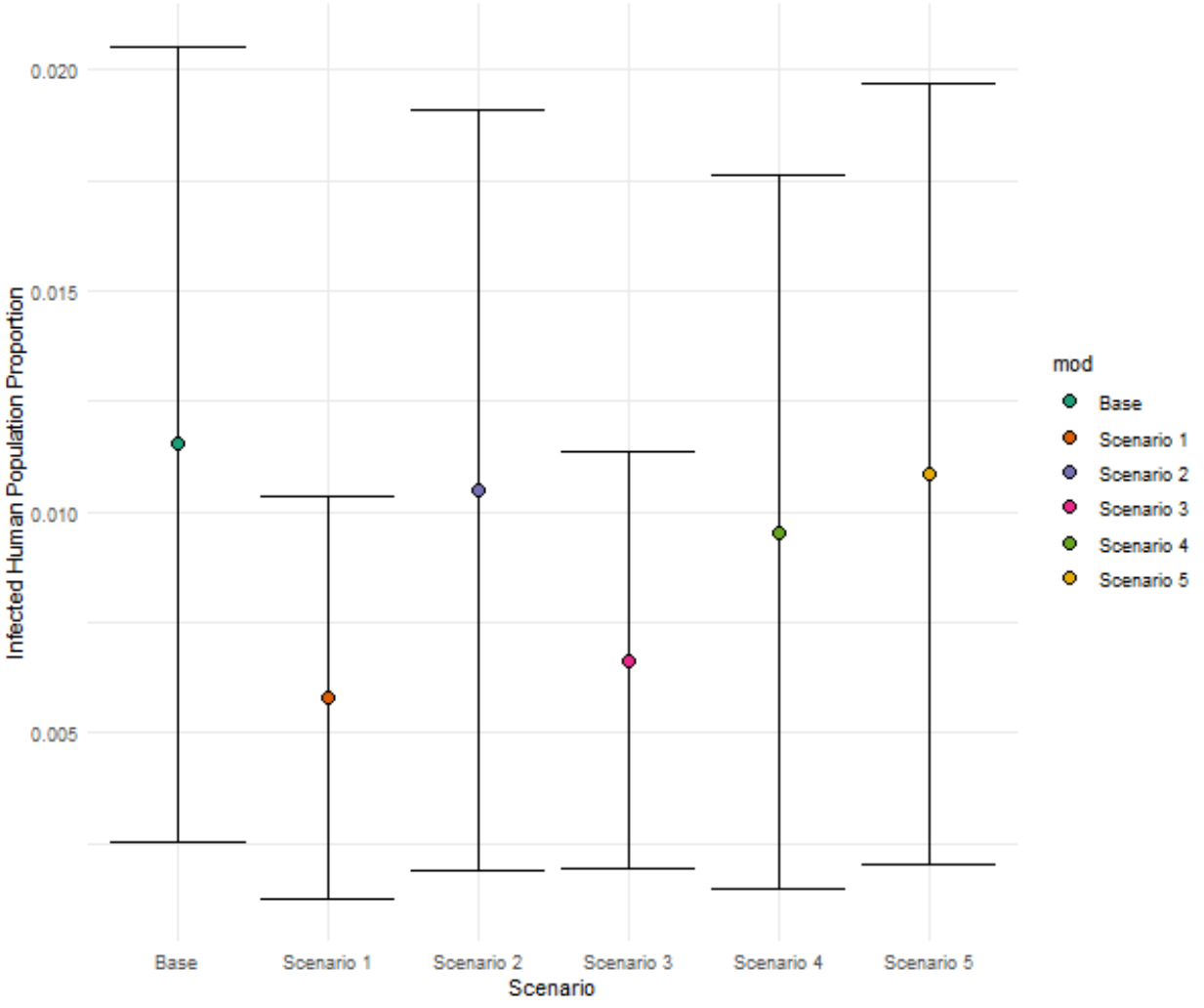


Figure 9: Results of five stochastic scenario analyses compared to the original (base) model with no parameter changes.



Closing Remarks

The chapters proposed attempt to incrementally improve our understanding of FBT epidemiology with approaches that have not been used for this disease. In Chapter 1, we characterized more recent trends in flea-borne typhus in California and pointed to areas with concerning trends in flea-borne typhus reporting. In noticing that our surveillance could be biased in its data ascertainment, we then evaluated the potential factors to which that ascertainment may be related in Chapter 2. Altogether, we highlighted some potentially high transmission or persistent reporting areas in Southern California while also noting communities that may be underrepresented or missed in surveillance data ascertainment. Lastly, in Chapter 3, we developed a mathematical model and evaluated the variables most influential to causing human infections in flea-borne typhus ecology while also testing some practical scenarios that may reduce the number of cases showing that limiting exposure to opossums, generally, may be the most effective route for preventing FBT cases.

This data may inform and guide active surveillance approaches in the future. For example, cases or reports from these areas may be given higher priority in investigations to not miss additional cases. The mathematical model may also be applied in these areas using locally generated data to prioritize active surveillance efforts, predict risk, and tailor prevention or intervention efforts.

Future flea-borne typhus and *R. typhi* research should consider further characterizations of *Rickettsia typhi* prevalence in reservoirs and vectors in different areas of southern California. Some semblances of host or sentinel surveillance would be useful in generating these data and complementing human typhus surveillance data. Such efforts should also consider sampling and testing for other competent flea vectors such as *Leptopsylla segnis*. Although *L. segnis* is not considered a primary vector for *R. typhi*, the species has demonstrated a higher rate of

transmission than *X. cheopis* in laboratory settings. *L. segnis* has often been disregarded as a vector of concern due to its sessile behavior (e.g., fewer hosts and mostly fixed position) and lower likelihood to bite humans relative to *C. felis* and *X. cheopis*.[110] However, the same behavior among *L. segnis* could theoretically promote dense viable patches of infected flea feces on hosts after significant period of time leading to hyperendemic loci of *R. typhi* among densely populated host populations or nests, such as rats.[110,119] Such a phenomenon may partly explain persistence of *R. typhi* in sylvatic cycles. Nonetheless, steps to characterize fleas and host ecology in natural settings would surely improve our understanding of transmission dynamics.

It is also worth considering future findings in flea-borne rickettsioses, specifically *Rickettsia felis. R. felis* was first identified in colonized *C. felis* fleas in 1990 but not officially recognized until 2001. *Rickettsia felis* is the causative agent of flea-borne spotted fever, a disease clinical and ecologically similar to flea-borne typhus. The bacteria are commonly found in opossums, cats, and cat fleas. The significance of *Rickettsia felis* in flea-borne rickettsia epidemiology and ecology is indeterminate due to the paradox of *R. felis* and *C. felis* ubiquity on every continent excluding Antarctica, despite low case incidence.[120–126] One study compared *R. felis* positivity in flea pools between endemic and non-endemic regions in California and concluded that risk of FBT between endemic and non-endemic areas may not be due to differential exposure to *R. felis*.[127] This is further confounded due to cross-reactivity of serological antibody tests and timing of sample collection for isolation and sequencing. Similarly, due to indiscriminate testing of the bacteria, *R. felis* may represent a cluster of *R. felis*-like variants with widely ranging pathogenicity to fleas, hosts, and humans.[128] Furthermore, there is limited evidence that interspecific competition between *R. felis* and *R. typhi* exists due to absence of coinfection of both rickettsia in individual fleas.[129] However, *C. felis* has demonstrated the ability to be coinfected in laboratory settings at lower rates than being solely

infected with *R. felis*.[130] The relationship between *R. felis* and *R. typhi* warrants further investigation to understand flea-borne rickettsioses and flea-borne diseases, broadly. Assessments of flea-borne typhus risk factors and *R. typhi* ecology would drastically change if *R. felis* and RFLOs prove to have varying, or even limited, pathogenicity to humans and interspecific competition with *R. typhi*.

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Supplemental Table 1: California Flea-borne Typhus Case Classification (2011)

		Clinical Criteria*	
		Yes	No
Laboratory Criteria	Serological evidence in paired acute and convalescent serum specimens of a four-fold or greater change in IgG-specific antibody titer reactive with *Rickettsia typhi* or other *Rickettsia*ǂ species antigen by indirect immunofluorescence assay (IFA).	Confirmed	Suspected
	Serologic evidence in a single serum specimen of elevated IgM or IgG antibody reactive to *R. typhi* or other *Rickettsia*ǂ species antigen by IFA. Titers must be ≥ 1:128	Probable+	Suspected
	Detection of *R. typhi* or other *Rickettsia* species DNA in a clinical specimen via amplification of a specific target by PCR assay	Confirmed	Suspected
	Detection of *R. typhi* or other *Rickettsia*ǂ species antigen in tissue or skin lesion biopsy or autopsy specimen by immunohistochemistry (IHC)	Confirmed	Suspected
	Isolation of *R. typhi* or other *Rickettsia species*ǂ from a clinical specimen in cell culture.	Confirmed	Suspected

*fever ≥ 100.4 °F and at least one of the following: headache, myalgia, or rash.

ǂ Cases with the recovery of *R. rickettsii* DNA by PCR, detection of *R. rickettsii* antigen by IHC, or isolation of *R. rickettsii* by culture should be reported as spotted fever rickettsiosis

+Can be considered confirmed if epi-linked to an existing confirmed case.

Supplemental Table 2: National Land Cover Database developed space classification descriptions.

Supplemental Table 2	
Variable	**NLCD Description**
Developed, Open Space	Areas most commonly include large-lot single-family housing units, parks, golf courses, and vegetation planted in developed settings for recreation, erosion control, or aesthetic purposes.
Developed, Low Intensity	Areas most commonly include single-family housing units. Impervious surfaces account for 20% to 49% percent of total cover.
Developed, Medium Intensity	Areas most commonly include single-family housing units. Impervious surfaces account for 50% to 79% of the total cover.
Developed High Intensity	Examples include apartment complexes, row houses and commercial/industrial. Impervious surfaces account for 80% to 100% of the total cover.