Guidance for Flea-Borne Typhus Surveillance and Reporting

September 2019

The California Department of Public Health (CDPH), in collaboration with local public health and vector control agencies, has developed this guidance to assist local health jurisdictions in the investigation, management, and reporting of flea-borne typhus cases in California.

Disease and Epidemiology

Overview

Flea-borne typhus, a.k.a. murine or endemic typhus, is a bacterial disease caused by *Rickettsia typhi* and possibly *Rickettsia felis*. Human cases of flea-borne typhus are reported worldwide, primarily in tropical and coastal areas. In the United States, most cases occur in Texas, California, and Hawaii with an average of 300 cases every year. In recent years, the annual number of reported cases has increased in Texas and California (*1,2,3*). The Texas state health department reported over 500 cases in 2017, the highest number in the United States since the 1940s when typhus was widespread (*4*).

Flea-borne Typhus in California

California averaged 70 reported flea-borne typhus cases annually between 2009 and 2014, 98 between 2015 and 2017, and a record 174 cases in 2018 (*3*). Four local health jurisdictions in southern California cover areas that are considered endemic for flea-borne typhus: Los Angeles County, City of Pasadena, City of Long Beach, and Orange County. Isolated cases also have been reported from San Diego and San Bernardino counties.

Symptoms

Flea-borne typhus symptoms range from mild to severe, with death occurring in less than 1% of clinical cases receiving treatment. Eighty-one percent of case-patients in California have required hospitalization. Symptoms usually begin within two weeks post-exposure with the most common symptoms being headache, muscle ache, and rash. Common laboratory findings may include anemia, thrombocytopenia, leukopenia, hyponatremia, and elevated liver enzymes.

Transmission

Flea-borne typhus is transmitted to people through contact with *R. typhi*-infected fleas, typically when infectious flea feces are rubbed into cuts or scrapes in the skin or mucus membranes. *Rickettsia typhi* may also be transmitted through flea bites (*5*).

Incubation Period

The incubation period, or time between exposure and onset of symptoms, for flea-borne typhus typically ranges from 6 to 14 days.

Reinfection

While there is limited documented research on the persistence of immunity to *R. typhi* once infected, the literature suggests immunity is short-lived. Studies on scrub typhus, a disease caused by a closely related bacterium, suggest that reinfection may occur 1 to 3 years after initial infection (*6*).

Clinical Management

Clinical management decisions should be made by the case-patient's primary care provider or infectious disease specialist. Due to the non-specific presentation of flea-borne typhus and the unreliability of early diagnostic tests, treatment decisions should be made based on clinical presentation and epidemiologic settings. Treatment should never be withheld pending diagnostic tests. Doxycycline is an effective treatment for flea-borne typhus and other rickettsial infections. While some people recover without treatment, case-patients may experience severe disease. When left untreated, severe illness can cause damage to one or more organs including the liver, kidneys, heart, lungs, and brain.

Diagnosis

Commercial tests to diagnose flea-borne typhus include serologic assays to detect immunoglobulin M (IgM) or immunoglobulin G (IgG) antibodies in serum. IgG antibodies are considered more accurate than IgM, which can often be cross-reactive and bind non-specifically. IgG antibody is generally detected 7 to 10 days after the onset of illness (*7*). *Testing of paired acute and convalescent serum samples is recommended to demonstrate an increase in titers*. Polymerase chain reaction (PCR) testing of whole blood or serum (prior to antibiotic treatment) is also confirmatory.

Prevention

The key to preventing flea-borne typhus is to avoid direct contact with fleas and their feces. Use flea control products on pet dogs or cats, and keep cats indoors. Discourage rats, opossums, feral cats, skunks, raccoons, and other wild animals from visiting or living around homes by bringing pet food indoors, keeping garbage containers tightly covered, trimming and removing plants around buildings, animal-proofing attics, crawl spaces, and storage sheds, and not feeding wildlife (*8*).

Typhus and other Rickettsial Disease Testing at VRDL

Antibodies to rickettsial pathogens can be cross-reactive among related species, thus serum specimens are tested against both *R. rickettsii* and *R. typhi* to help differentiate between spotted fever group (SFG) and non-SFG *Rickettsia* disease agents.

- IgG titers are determined using an indirect immunofluorescence assay. A single elevated IgG titer of $\geq$1:128 is considered supportive evidence of a rickettsial infection. A four-fold or greater rise in IgG titers in paired acute/convalescent samples is required to confirm a recent infection.

- Collection of both acute (within 1-2 weeks of illness onset) and convalescent (>2-3 weeks after illness onset) sera is ideal to test for a significant rise in IgG titer. Collect 5-10 ml of blood in a red top or serum separator tube.
- Although IgM is considered supportive evidence of a recent infection (per the CDPH case definition), IgM testing is no longer routinely performed at VRDL or the U.S. Centers for Disease Control and Prevention (CDC) due to cross-reactivity and non-specificity (*7*).

All serum specimens collected within 14 days of illness onset and submitted for flea-borne typhus serology will also be routed for PCR testing, which is currently only available for surveillance purposes and not for clinical diagnosis.

CDPH Surveillance Case Definition

Typhus and Other Non-Spotted Fever Rickettsioses (CDPH working definition, 2011)

CLINICAL EVIDENCE

Acute onset of fever (≥ 100.4 °F) and at least one of the following signs/symptoms: headache, myalgia, or rash; and at least one of the following lab parameters: leukopenia, thrombocytopenia, or elevation of hepatic transaminases, in the absence of any other known cause.

LABORATORY CRITERIA FOR DIAGNOSIS

Because serology for rickettsial diseases can be cross-reactive, specimens should be tested against a panel of *Rickettsia* antigens, including, at minimum, *R. rickettsii* and *R. typhi*, to differentiate between disease due to spotted fever group (SFG) and non-SFG *Rickettsia* spp. Specimens should be submitted to CDPH-VRDL or another public health laboratory for confirmation whenever possible.

For surveillance purposes:

Laboratory confirmed

- 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* species antigen by indirect immunofluorescence assay (IFA). Convalescent titers must be ≥ 1:128; OR
- Serologic evidence in a single serum specimen of elevated IgM and IgG antibody reactive to *R. typhi* or other *Rickettsia* species antigen by IFA. Titers must be ≥ 1:128; OR
- Detection of *R. typhi* or other *Rickettsia* species* DNA in a clinical specimen via amplification of a specific target by PCR assay; OR
- Detection of *R. typhi* or other *Rickettsia* species antigen in tissue or skin lesion biopsy or autopsy specimen by immunohistochemistry (IHC); OR
- Isolation of *R. typhi* or other *Rickettsia species** from a clinical specimen in cell culture.

*Cases with 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.

Laboratory supportive

- Serologic evidence in a single serum specimen of elevated IgM or IgG antibody reactive to *R. typhi* or other *Rickettsia* species antigen by IFA with a titer of ≥ 1:128.

EXPOSURE

Rickettsioses are typically transmitted by biting arthropods such as fleas and ticks; however, recognized arthropod bite is not required.

CASE CLASSIFICATION

Confirmed: a) a clinically compatible case (meets clinical evidence criteria) that is laboratory confirmed, or b) a clinically compatible case that has supportive laboratory results and an epi-link to a confirmed case (e.g., same household/same suspect defined exposure as a confirmed case within the past 14 days before onset of symptoms).

Probable: A clinically compatible case (meets clinical evidence criteria) that has supportive laboratory results.

Suspected: a) a clinically compatible case with epi-link to a confirmed case (e.g., same household/same suspect defined exposure as a confirmed case within the past 14 days before onset of symptoms) but no laboratory testing, or b) a case with laboratory evidence of past or present infection but no clinical information available (e.g., a laboratory report).

Limitations of Current Surveillance Case definition

The current case definition was developed in 2011. At the time, the primary concern was ensuring flea-borne typhus case-patients who had only acute but not convalescent testing would be reported, since few case-patients had convalescent samples submitted. The current case definition relies heavily upon IgM serologic testing, and was developed prior to the current scientific literature which demonstrates IgM testing for rickettsial diseases is very non-specific (*9,10,11*), resulting in a large number of false-positive test results. The CDC does not recommend IgM for diagnostic testing of rickettsial diseases including flea-borne typhus (*7*). For this reason, CDPH along with health departments from other endemic states, are working with CDC to develop an updated case definition, which is scheduled to be implemented in January 2020.

Case Investigation and Reporting

Flea-borne typhus is not nationally notifiable but is reportable in California under Title 17 of the California Code of Regulations.

Purpose of Reporting and Surveillance

- To characterize the epidemiology of flea-borne typhus in California and to use this information to develop and implement targeted interventions to decrease rates of infection
- To identify outbreaks and potential epicenters of ongoing transmission
- To educate people on how to reduce their risk of infection

Local Health Jurisdiction Reporting

Flea-borne typhus is reportable in California by clinicians and laboratories. Flea-borne typhus cases that meet the laboratory criteria of the CDPH case definition should be reported to CDPH.

Instructions for CalREDIE-participating jurisdictions:

- Enter the case-patient information into CalREDIE upon notification by the clinical laboratory or health care provider. Select "Typhus and Other Non-Spotted Fever Rickettsioses" as "Disease Being Reported."
- Flea-borne typhus is a Case Report Form (CRF)-required condition. Therefore, please complete the Clinical, Laboratory, and Epidemiological Information sections. Please also note any epidemiological links to other cases or outbreaks in the notes section.

Non-participating jurisdictions should complete the CRF and submit to CDPH by fax or secure email as soon as the investigation is complete.

VRDL Resources

Viral and Rickettsia Disease Laboratory

https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/VRDL.aspx

Case Management and Public Health Control Measures

CDC Typhus Information for Health Care Providers

https://www.cdc.gov/typhus/healthcare-providers/index.html

Flea-Borne Typhus Environmental Surveillance and Risk Reduction Measures

Vector Control Authority and Flea-borne Typhus Programs

The legal authority for government agencies to control vectors and vector-borne diseases is found in the California Health and Safety Code Chapter 1, Division 3, Sections 2000-2093. Pertaining to flea-borne typhus, any property artificially altered from its natural condition that

supports the development, attraction, or harborage of flea vectors may be declared a public nuisance and abated. In addition, any developed property onto which rats, opossums, skunks, raccoons, and feral cats are fed or congregate, and those animals are found to be harboring fleas, can be declared a public nuisance and abated.

Collaboration between Local Public Health and Vector Control Agencies

Local health jurisdictions reporting human cases of flea-borne typhus are encouraged to establish a Memorandum of Understanding (MOU) with their local vector control agency (VCA) to ensure timely notification and response to suspect, probable, and confirmed human cases. The MOU should include the sharing of any suspected case-patient exposure site(s), such as the residential and employment addresses, and additional information about animal or flea exposure. In response to reported human cases, the VCA may conduct surveillance for fleas and/or host animals around the suspected exposure site(s) as appropriate. The VCA should notify the local health jurisdiction if fleas or host animals are present at the suspected exposure site(s), indicating a potential risk for on-going flea-borne typhus transmission, and if additional response is necessary.

Human Case Flea-borne Typhus Exposure Site Environmental Assessment and Response

A comprehensive flea-borne typhus program includes both public education and management of fleas and vertebrate hosts. If fleas or host animals are present during a site assessment, a response involving multiple local agencies may be necessary. If these conditions are present in the neighborhood over a wide area (affecting many property owners), an escalated response may be indicated to reduce the presence of fleas and host animals. When necessary, referrals should be made to the appropriate agencies responsible for enforcing local health and safety codes. These agencies may include city code enforcement, local animal control jurisdictions, and local public health agencies.

Property owners should be educated that fleas found on rodents, cats and dogs, and urban wildlife such as opossums, raccoons, and skunks can carry the bacteria that cause flea-borne typhus in humans. Risk reduction measures on private properties should emphasize flea control and host animal management, including application of flea control products to pets and the environment, removal or reduction of animal harborage, food, and water sources and/or the removal of animals from the property.

PERSONAL PROTECTION FOR INVESTIGATORS

Investigators should wear appropriate personal protective equipment (PPE) to prevent exposure to fleas, specifically long sleeves and long pants (or coveralls), closed toed shoes, and disposable gloves. An EPA-registered insect repellent should be applied to the lower extremities prior to assessments. If large numbers of host-seeking fleas are found on the property of a suspected exposure site, the assessment of the property should cease until flea control is conducted at the site.

FLEA COLLECTION AND TESTING

Fleas can be collected and sent to CDPH VRDL to detect *R. typhi* and *R. felis*. Samples should be preserved in 70% ethanol and labeled with collection site data and flea species. Species identification of the most common fleas found on pets and backyard wildlife can be made using a free photographic key (www.ocvector.org/fk) or line drawn key (https://www.cdc.gov/nceh/ehs/docs/pictorial_keys/fleas.pdf). Assistance on flea identification can also be provided by CDPH.

Adult fleas can be collected by a variety of methods including removal from host animals and collection from the environment. Fleas can be removed from the bodies of host animals using a flea comb. If sampling from wild or feral animals, trapping and anesthesia/euthanasia must follow local, state, and federal regulations. When sampling host animals for fleas, the average number of fleas per animal, referred to as the flea index, can be used to assess the need and effectiveness of control measures. Host-seeking fleas can be collected from the environment using a variety of methods including cotton flannel "flags," lighted lures, and sticky boards (https://www.ocvector.org/flea-borne-typhus).

Applicable State Statutes and Regulations

California Code of Regulations, Title 17, Public Health, Sections 2500, 2505 (http://ccr.oal.ca.gov/linkedslice/default.asp?SP=CCR-1000&Action=Welcome)

2500: Health care providers shall submit reports for flea-borne typhus to the local health officer for the jurisdiction where the patient resides by mailing a written report, telephoning, or electronically transmitting a report within 7 calendar days of the time of identification.

2505: Flea-borne typhus shall be reported by laboratories within one working day after the health care provider or other person authorized to receive the report has been notified. Laboratories shall transmit these reports to the local health officer by courier, mail, electronic facsimile, or electronic mail.

California State Health and Safety Code (Chapter 1, Division 3, Sections 2000-2093)

Additional Resources

General Information/Patient Education

CDPH Flea-borne Typhus webpage (https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/Typhus.aspx)

CDC Murine Typhus webpage (https://www.cdc.gov/typhus/murine/index.html)

References

1. Murray KO, Evert N, Mayes B, Fonken E, Erickson T, Garcia MN, Sidwa T. Typhus group rickettsiosis, Texas, USA, 2003–2013. Emerging Infectious Diseases. 2017;23(4):645.
2. Blanton LS, Vohra RF, Bouyer DH, Walker DH. Reemergence of murine typhus in Galveston, Texas, USA, 2013. Emerging Infectious Diseases. 2015;21(3):484.
3. California Department of Public Health. Human flea-borne typhus cases in California. https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/Flea-borneTyphusCaseCounts.pdf.
4. Texas Department of State Health Services. Flea-borne typhus statistics. https://www.dshs.state.tx.us/IDCU/disease/murine_typhus/Statistics.aspx.
5. Azad A and Traub R. Experimental transmission of murine typhus by *Xenopsylla cheopis* fela bites. Medical and Veterinary Entomology. 1989;3:429-433.
6. Koralur MC, Singh R, Varma M, Stenos J, Bairy I. Scrub typhus reinfection. Tropical Doctor. 2018;48(1):69-72.
7. Centers for Disease Control and Prevention. Spotted fever rickettsiosis (*Rickettsia* spp.) 2010 case definition [cited 2018 Dec 28]. https://wwwn.cdc.gov/nndss/conditions/spotted-fever-rickettsiosis/case-definition/2010/.
8. University of California, San Francisco. Integrated pest management checklist. https://cchp.ucsf.edu/sites/g/files/tkssra181/f/ipm_checklist.pdf.
9. Abdad MY, Abdallah RA, Fournier PE, Stenos J, Vasoo S. A Concise Review of the Epidemiology and Diagnostics of Rickettsioses: *Rickettsia* and *Orientia* spp. Journal of Clinical Microbiology. 2018:JCM-01728.
10. Paris DH, Dumler JS. State of the art of diagnosis of rickettsial diseases: the use of blood specimens for diagnosis of scrub typhus, spotted fever group rickettsiosis, and murine typhus. Current Opinion in Infectious Diseases. 2016;29(5):433.
11. McQuiston JH, Wiedeman C, Singleton J, Carpenter LR, McElroy K, Mosites E, Chung I, Kato C, Morris K, Moncayo AC, Porter S. Inadequacy of IgM antibody tests for diagnosis of Rocky Mountain spotted fever. The American Journal of Tropical Medicine and Hygiene. 2014;91(4):767-70.

Additional Publications

Blanton LS, Walker DH. Flea-borne rickettsioses and *Rickettsiae*. The American Journal of Tropical Medicine and Hygiene. 2017;96(1):53-6.

Blanton LS, Idowu BM, Tatsch TN, Henderson JM, Bouyer DH, Walker DH. Opossums and cat fleas: new insights in the ecology of murine typhus in Galveston, Texas. The American Journal of Tropical Medicine and Hygiene. 2016;95(2):457-61.

Billeter SA, Diniz PP, Jett LA, Wournell AL, Kjemtrup AM, Padgett KA, Yoshimizu MH, Metzger ME, Barr MC. Detection of *Rickettsia* species in fleas collected from cats in regions endemic and

nonendemic for flea-borne rickettsioses in California. Vector-Borne and Zoonotic Diseases. 2016;16(3):151-6.

Eremeeva ME, Karpathy SE, Krueger L, Hayes EK, Williams AM, Zaldivar Y, Bennett S, Cummings R, Tilzer A, Velten RK, Kerr N. Two pathogens and one disease: detection and identification of flea-borne *Rickettsiae* in areas endemic for murine typhus in California. Journal of Medical Entomology. 2014;49(6):1485-94.

Civen R, Ngo V. Murine typhus: an unrecognized suburban vectorborne disease. Clinical Infectious Diseases. 2008;46(6):913-8.

Abramowicz KF, Rood MP, Krueger L, Eremeeva ME. Urban focus of *Rickettsia typhi* and *Rickettsia felis* in Los Angeles, California. Vector-Borne and Zoonotic Diseases. 2011;11(7):979-84.

Newhouse VF, Shepard CC, Redus MD, Tzianabos T, McDade JE. A comparison of the complement fixation, indirect fluorescent antibody, and microagglutination tests for the serological diagnosis of rickettsial diseases. The American Journal of Tropical Medicine and Hygiene. 1979;28(2):387-95.

Wekesa JJ. Use of abatement to reduce intensity of a flea-borne typhus outbreak in the San Gabriel Valley, Los Angeles County, California. Proceedings and Papers of the Mosquito and Vector Control Association of California. 2016;84:104-106.

Wekesa JW, Nelson K, Brisco A, Fujioka K. Vector control has a role to play in mitigating the high incidence of flea-borne typhus in Los Angeles County, California. In Proceedings of the Vertebrate Pest Conference 2016;27(27):288-292.