Standardized Surveillance for Soft Tick-borne Relapsing Fever (including *B. hermsii*, *B. parkeri*, and *B. turicatae*)

Statement of the Problem

Tick-borne Relapsing Fever (TBRF) is an illness caused by infection with some members of the genus *Borrelia,* including *Borrelia hermsii, Borrelia parkeri,* and *Borrelia turicatae* (1-4). *Borrelia* spirochetes that cause TBRF are transmitted to humans through the bite of infected soft ticks of the genus *Ornithodoros* (2-4). Each relapsing fever-group *Borrelia* species is usually associated with a specific tick species: *B. hermsii* is transmitted by *O. hermsi*, *B, parkeri* is transmitted by *O. parkeri*, and *B. turicatae* by *O. turicata* ticks (1-4). These bacteria are maintained in enzootic cycles involving small rodent hosts and the tick vectors (5,6). Disease incubation averages one week following a tick bite. Illness is characterized by periods of fever, often exceeding 38.8ºC (102°F), lasting 2-7 days alternating with afebrile periods of 4-14 days (2,3,6). Febrile periods are often accompanied by shaking chills, sweats, headache, muscle and joint pain, arthralgia, or nausea/vomiting (2). TBRF may be fatal in 5-10% of untreated cases. TBRF contracted during pregnancy can cause spontaneous abortion, premature birth, and neonatal death (4,7,8).

TBRF is among the most common tick-borne diseases in the western United States, and several states conduct surveillance for human cases to understand geographic distribution, to conduct remediation measures, and to target preventative educational efforts (4). Surveillance for human cases is needed because public health intervention can prevent further cases, raise awareness in non-endemic states, and improve prevention messaging. Human surveillance may become increasingly important as changing climate leads to changing distributions of vectors and reservoirs. However, no national standardized case definition exists for TBRF in the United States, limiting data comparisons across state lines.

Background and Justification

In the United States (US), soft tick transmitted TBRF occurs most commonly in 14 western states: Arizona, California, Colorado, Idaho, Kansas, Montana, Nevada, New Mexico, Oklahoma, Oregon, Texas, Utah, Washington, and Wyoming (4). Reporting practices vary across the states and there is not a unifying case definition. As a result, there are likely ascertainment and reporting biases that limit comparison of case numbers between the states where TBRF is endemic (4). Many exposures may occur among travelers who seek medical care in their home states where TBRF is not endemic. Disease recognition may not occur in non-endemic states or may be attributed to Lyme disease or other clinically similar diseases such as Colorado tick fever. The emergence of the *Ixodes* spp. (hard tick) transmitted *Borrelia miyamotoi* may confound the diagnosis. The proposed standardized case definition is designed to focus on soft-tick transmitted TBRF in order to improve its surveillance, differentiate it from other relapsing fever agents, and better focus public health response.

TBRF presents as a single case or sometimes in small case clusters through common exposure to tick infested buildings or caves. Currently, the ability to identify and report cases is variable in endemic states due to the different reporting requirements. One intent of the proposed standardized case definition is to expand reporting of clusters which can help prioritize follow up interventions if necessary.

Diagnostic approaches for soft tick-transmitted TBRF have been changing. As it has been for more than a century, the most common diagnostic test for confirmation of relapsing fever is the stained blood smear taken just before or at the height of a febrile episode. The stained blood smear cannot differentiate relapsing fever *Borrelia* species. Moreover, with the increase in the use of automated examination of blood smears in hospitals and clinics, there are fewer opportunities for the diagnosis to be serendipitously made by an alert technician in the clinical laboratory. There is a PCR-based assay currently available at the CDC only that can differentiate soft-tick transmitted TBRF from other relapsing fever spirochetes (e.g. the louse-borne relapsing fever agent *Borrelia recurrentis* and the hard-tick relapsing fever agent, *Borrelia*

miyamotoi) as well as other PCR-based assays at commercial laboratories that can detect the relapsing fever *Borrelia* species more generally. Cultivation of the organism is possible and confirmatory, but this time-consuming diagnostic procedure is performed in few diagnostic laboratories. Serologic detection of antibodies to the GlpQ protein, which is produced by relapsing fever *Borrelia* species, including *B. miyamotoi* but not by the agents of Lyme disease, is available in some commercial laboratories. Assays for antibodies to the GlpQ protein of *B. miyamotoi* yield positive results with sera from patients with other forms of relapsing fever and other pathogens on the basis of cross-reactivity between GlpQ proteins of different species. In the proposed case definition, both confirmatory and presumptive laboratory support are expanded to better define confirmed, probable, and suspect cases.

Goals of Surveillance

The goals of surveillance are threefold:

1. To identify endemic geographic areas in the United States, including areas with emerging disease, and to describe the epidemiology of cases.
2. To perform public health follow-up of reported cases, possibly including remediation measures when a tick-infested property is identified, identification of persons with a shared exposure history to facilitate early diagnosis and treatment, and prophylaxis for exposed pregnant women.
3. To prevent disease through targeted educational efforts.

Case Definition for Case Classification

A. Narrative: Description of criteria to determine how a case should be classified.

Tick-borne Relapsing Fever (TBRF) is an illness caused by infection with some members of the genus *Borrelia,* including *Borrelia hermsii, Borrelia parkeri,* and *Borrelia turicatae. Borrelia* spirochetes that cause TBRF are transmitted to humans through the bite of infected soft ticks of the genus *Ornithodoros*. Each relapsing fever group *Borrelia* species is usually associated with a specific tick species: *B. hermsii* is transmitted by *O. hermsi*, *B, parkeri* is transmitted by *O. parkeri*, and *B. turicatae* by *O. turicata* ticks. Disease incubation averages one week following a tick bite. Illness is characterized by periods of fever, often exceeding 38.8ºC (102°F), lasting 2-7 days alternating with afebrile periods of 4-14 days. Febrile periods are often accompanied by shaking chills, sweats, headache, muscle and joint pain, arthralgia, or nausea/vomiting. TBRF may be fatal in 5-10% of untreated cases. TBRF contracted during pregnancy can cause spontaneous abortion, premature birth, and neonatal death.

A1. Clinical Criteria

An acute febrile illness, with:

- Measured fever $\geq$ 38.8ºC (102ºF) OR
- One or more episodes of lower measured or subjective fever AND two or more of the following: headache, myalgia, nausea/vomiting, or arthralgia.

A2. Laboratory Criteria

Serology can be useful for surveillance, however, antibody response may not be detectable in acute samples. A negative test result may be repeated if early in disease. Antibodies stimulated by other *Borrelia* sp. infections (e.g., *B. miyamotoi*) are expected to cross-react on TBRF serologic assays. Likewise, tests for other spirochetal infections (e.g., Lyme disease) may be false-positive in a patient infected with relapsing fever *Borrelia* spp. Epidemiological information including exposure history is crucial to differentiate positive serology results.

Confirmatory laboratory evidence:

1. Isolation of *Borrelia hermsii, B. parkeri,* or *B. turicatae* from blood using a *Borrelia*-specific medium such as Barbour-Stoenner-Kelly (BSK) broth medium.

2. *Borrelia hermsii, B. parkeri,* or *B. turicatae* detection through nucleic acid testing, such as PCR**,** which differentiates soft-tick relapsing fever *Borrelia* spp. from other relapsing fever *Borrelia* sp.[1]

Presumptive laboratory evidence:

1. Identification of *Borrelia* spirochetes in peripheral blood, bone marrow, or cerebrospinal fluid (CSF).
2. Serologic evidence of *Borrelia hermsii, B. parkeri,* or *B. turicatae* infection by EIA, immunofluorescence assay (IFA), IgM or IgG western immunoblot (WB), or another method specific for relapsing fever *Borrelia* species.
3. *Borrelia hermsii, B. parkeri,* or *B. turicatae* detection through nucleic acid testing, such as PCR, which does not differentiate soft-tick relapsing fever *Borrelia* spp. from other relapsing fever *Borrelia* sp.[2]

[1]This includes only PCR tests that can differentiate soft-tick relapsing fever *Borrelia* spp. from hard-tick and louse-borne relapsing fever *Borrelia* spp. At the time of writing, this type of test is only available from CDC.
[2]This includes PCR tests that are specific to relapsing fever *Borrelia* sp. but that cannot differentiate soft-tick relapsing fever *Borrelia* spp. from hard-tick and louse-borne relapsing fever *Borrelia* spp. This does not include pan-*Borrelia* PCR tests.

A3. Epidemiologic Linkage

The habitats where relapsing fever *Borrelia* spp. are present are sympatric with that of their *Ornithodoros* spp. tick vectors. *Ornithodoros hermsi*, the vector for *B. hermsii*, is typically found in rodent nests in mountainous areas above 450 m (1,500 ft) elevation where chipmunks or squirrels are present. The vector for *B. parkeri*, *O. parkeri*, is found at lower elevations in the Southwest and inhabits burrows of prairie dogs, ground squirrels and burrowing owls. *Ornithodoros turicata*, the vector for *B. turicatae*, occurs in caves, and nests and burrows of prairie dogs and ground squirrels in the plains regions of the Southwest.

Exposure is defined as living in, working in, or visiting a county in which *Ornithodoros* soft ticks are present or where a confirmed autochthonous case of TBRF has been previously reported. Exposure activities include entering, sleeping, or working in cabins, caves, around firewood, or other possible soft tick habitat within 2-18 days of symptom onset.

Epidemiologic link: Onset of clinically compatible illness in a person who had a shared exposure location as a confirmed case with symptom onset 2-18 days after exposure.

A4. Case Classifications

Confirmed: A clinically compatible illness in a person with confirmatory laboratory evidence,
OR
A clinically compatible illness in a person with presumptive laboratory evidence and meets the above criteria for exposure or epidemiologic linkage.

Probable: A clinically compatible illness in a person with presumptive laboratory evidence of infection,
OR
A clinically compatible case who meets the epidemiologic link criteria,

Suspect: A clinically compatible case who meets the exposure criteria above, with no laboratory testing performed,
OR

A case with laboratory evidence of infection but no clinical, exposure, or epidemiologic linkage information available.

B. Criteria to distinguish a new case of this disease or condition from reports or notifications which should not be enumerated as a new case for surveillance

Case not previously reported to public health authorities and with epi linkage within one month of disease onset or laboratory support (date of collection) within four months of disease onset.

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