DISEASE SURVEILLANCE AND CASE DEFINITIONS
IN TICK-BORNE DISEASES

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Prepared for the IOM Committee on Lyme Disease and Other Tick-borne Diseases - The State of the Science
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This briefing on case definitions and surveillance for tickborne disease is presented in three main sections: Background on surveillance and methods, particularly as they relate to tickborne diseases and nationally notifiable diseases; Lyme disease surveillance and case definitions; and Public Health Surveillance for other tickborne diseases in the United States.

BACKGROUND

Public health surveillance is the ongoing, systematic collection, analysis, interpretation, and dissemination of data regarding a health-related event for use in public health action to reduce morbidity and mortality and to improve health (CDC, 2001). For any given public health surveillance activity, it is critical to define the purpose of surveillance, use surveillance methods that are efficient and appropriate to achieving that purpose, and subsequently evaluate whether surveillance efforts are meeting the surveillance objectives (CDC, 2001; Meriwether 1996).

Depending on the objectives, a variety of methods can be used to conduct vector-borne public health surveillance (Hadler and Petersen, 2007). For example, to evaluate potential and emerging tickborne diseases, ongoing systematic efforts can be done to capture vector ticks, monitor their population size and determine infection rates. In addition, if appropriate serologic tests are available, serosurveys can be done to monitor the percentage of the population that has been infected with the disease agent. To determine the annual burden of human illness and its epidemiology, surveillance for human illness using provider and/or laboratory reporting to public health authorities, analysis of hospital discharge and death data, and, for high incidence diseases, population surveys can be done. To determine and monitor the prevalence of risk factors for tickborne disease (e.g., spending time outdoors, tick bites) and prevention practices (e.g., daily tick checks, wearing long light-colored pants tucked into socks, use of insect repellants), regular telephone and/or community surveys can be done.

Each method of surveillance has its particular limitations, however. Surveillance for ticks and tick infection rates is limited in part by the need to sample, the uneven distribution of vectors and infection rates geographically, and the need to confirm human risk by obtaining human infection data. Human disease reporting is limited by the need for laboratory and/or explicit symptom confirmation of disease for diseases such as Lyme disease in which many other diseases may present with similar symptoms, and underreporting by healthcare providers who do not take the time needed to report. Reporting of laboratory findings alone, while less subject to underreporting than clinician reporting, is limited in part by the fact that positive tests may indicate infection long in the past or be falsely positive, necessitating the need to get clinical
information to back up the laboratory report. In addition, they can take weeks to turn positive, so that persons in the early stages of infection may not have positive laboratory tests. Telephone and community surveys may have limited and non-representative response rates, and community surveys are only clearly applicable to the communities in which they are done. In addition, each of these methods of surveillance has substantial costs to conduct and maintain.

**Human Disease Surveillance and Nationally Notifiable Diseases**

Constitutionally, local public health is a responsibility of state rather than federal government (Moulton et al, 2007). Correspondingly, surveillance for human disease using mandatory reporting of cases and laboratory findings to public health authorities is generally a state and local health department function rather than a federal one. State and local health departments have the legal authority, spelled out in statute in each state, to collect personally identifiable data on persons with selected diseases from laboratories and clinicians. Each state conducts surveillance for human disease according to its needs and resources. There is no standard list of diseases for which all states have reporting and each has its own legislatively specified means for adding diseases to its state-specific list. The federal Centers for Disease Control and Prevention (CDC) conducts national surveillance for diseases reportable at the state level through collaboration with states via the Council of State and Territorial Epidemiologists (CSTE). Through resolutions passed by the majority of state representatives attending the annual CSTE meeting each June (a quorum is required, one vote per state present), a list of nationally notifiable diseases reportable to the CDC has been established, known as the National Notifiable Disease Surveillance System (NNDSS). For a disease to be included in the NNDSS, the purpose of national surveillance and a case definition to be used to count cases for national purposes must be agreed upon. Placement of a disease in the NNDSS does not obligate each state to conduct surveillance for it or to conduct surveillance in a standardized manner. The NNDSS is simply an agreement that states that conduct surveillance will de-identify and share their information with CDC using a standard case definition. Placement of a disease in the NNDSS also does not guarantee that resources are or will be available to each state to conduct surveillance. However, to the extent that CDC provides funding through cooperative agreements with states, CDC can require recipients to conduct surveillance for a specific disease and specify surveillance methods within the limits of funding provided.

**Principles of Surveillance Based on Case Reporting - Case Definitions**

There are at least four important principles of public health surveillance for human illness through disease reporting. First, surveillance for human disease based on clinician or laboratory reporting generally requires that a suspected case be confirmed. Cause-specific diagnoses based on a physician’s best guess may be wrong, especially for persons with symptoms that can be caused by a number of different microbial agents or mechanisms other than infection (e.g., fever, malaise, skin rash, arthritis, headache, cough, diarrhea). Positive laboratory tests alone may reflect past disease (e.g., serologic tests for antibodies) or a carrier state without disease (e.g., bacterial colonization of the intestinal tract). Thus, case definitions are needed to define relevant symptoms in combination with relevant laboratory results that make it highly likely that a “case” really has the disease under surveillance, or, when laboratory confirmation is not possible, to define symptoms and findings that are characteristic of only of the disease under surveillance (e.g., erythema migrans for Lyme disease).
Second, because of the need for laboratory confirmation to make sure that only real cases of disease due to any given microbe are being counted, surveillance based on reporting is likely to underestimate the true magnitude of a disease. Cases for which it is technically difficult or too costly to confirm will not be counted, nor will cases that go unreported. Despite the legal requirements for reporting, some clinicians never get around to reporting patients they suspect of having a disease. To determine the true number of people with a given disease (e.g., Lyme disease), it may be necessary to conduct population and/or provider surveys.

Third, it is not critical for most surveillance purposes to count every possible case of a disease. For purposes of monitoring a disease over time to determine whether its epidemiology (which groups are most affected) is changing and its occurrence is stable, increasing or decreasing, it is only necessary to count cases in the same way and to invest the same effort over time. If one monitors a consistent part of the “iceberg” of disease, then changes in it will reflect what is happening to the whole iceberg.

Finally, consistency of the means of surveillance is important. It can be expected that there will be under-reporting and/or inability to follow-up every reported clinical case and laboratory finding because of resource restraints. If no funding is appropriated for surveillance, it may be impossible for a health department to follow-up on thousands of laboratory reports to find out if a person had symptoms consistent with recent disease.

LYME DISEASE SURVEILLANCE AND CASE DEFINITIONS

Of the five tickborne diseases under national surveillance in the U.S., Lyme disease is by far the most common and has had the most public interest and dynamic surveillance history. Lyme disease was first recognized as a distinct entity in 1975 by epidemiologists investigating an apparent cluster of juvenile arthritis cases in Lyme, Connecticut. Informal national surveillance for human illness via annual surveys of states conducted by the CDC began in 1980 (CDC, 1981), and Lyme disease was formally added to the National Notifiable Disease Surveillance System in 1991 (CSTE, 1990). The causative infectious agent, *Borrelia burgdorferi*, was recognized in 1982 after which time laboratory tests were developed and gradually over several years began to be available for surveillance and clinical purposes.

Features of Lyme Disease Relevant to Surveillance

Lyme disease has a number of clinical, laboratory and epidemiologic features that make conducting surveillance for human illness a challenge. These include: 1) erythema migrans (EM), an early stage disease manifestation and the most common one, a spreading skin lesion that begins as a papule or macule and over the course of days to weeks becomes a red, expanding lesion that must be diagnosed clinically because supportive laboratory tests are often negative, and only begins to be readily distinguishable from insect bite reactions or local skin infections when it gets to a substantial size and has a characteristic “target” pattern; 2) later clinical manifestations such as arthritis, neurologic involvement (lymphocytic meningitis, Bells’ palsy, radiculoneuropathy) and cardiac complications (transient, high grade atrioventricular conduction defects sometimes accompanied by myocarditis) that are not unique to Lyme disease and need laboratory confirmation of *B. burgdorferi* infection; 3) confirmatory laboratory test methods which produce results that can be falsely positive and result in mistaken diagnosis of Lyme
disease, especially in geographic areas where neither a competent tick vector (*Ixodes* ticks) nor *B. burgdorferi* are present; 4) positive serologic tests occurring after true infection that can remain positive indefinitely, making it essential that there be corroborating clinical data to back up laboratory findings (i.e., laboratory findings alone cannot be used for surveillance); 5) transmission from a tick that is small enough that attachment and feeding (i.e., “bites”) often go unnoticed, making a history of having an antecedent tick bite an insensitive way to conduct surveillance; and 6) limited geographic areas in which infected, competent tick vectors are present, making it important for epidemiologic and public health purposes to distinguish between human disease in “endemic” areas and disease diagnosed in residents of geographic areas without a previous history of Lyme disease.

**Case Definitions of Lyme Disease for Public Health Surveillance**

The objectives of formal national public health surveillance for human Lyme disease were agreed upon at the CSTE meeting in 1990 and have not changed since: (1) define the demographic, geographic, and seasonal distribution; (2) consistently monitor disease trends; (3) identify risk factors for transmission in areas where Lyme disease is newly emerging; and (4) develop strategies of prevention and control and evaluate the impact of prevention and control measures (CSTE, 1990 and 2007). The recommended methods of surveillance for disease have also not changed: a combination of clinician and laboratory reporting of suspected cases with public health follow-up as needed to obtain detailed clinical information to confirm cases. The above clinical, laboratory and epidemiologic features of Lyme disease have been taken into consideration in the consensus case definitions that have been crafted over time by CSTE and CDC for surveillance to meet these public health surveillance objectives (CDC, 1990 and 1997; CSTE, 2007). Importantly, as noted in the publication of each case definition, the surveillance definition for Lyme disease (and for other diseases under public health surveillance) was developed for national reporting of Lyme disease; it is NOT appropriate for clinical diagnosis, including reimbursement by insurers.

To enable comparability between states and over time, public health epidemiologists have favored restriction of clinical manifestations that can be counted to those that are most likely to be Lyme disease rather than counting all possible cases. Thus, measurement of geographic distribution, the descriptive epidemiology and trends in Lyme occurrence within geographic areas have been emphasized over measuring the full magnitude of the problem.

To overcome the lack of specificity of small, evolving erythema migrans (EM) lesions, a lesion must be at least 5 centimeters in diameter to be counted. Annular erythematous lesions occurring within several hours of a tick bite represent hypersensitivity reactions and do not qualify as EM. For later musculoskeletal (joint), neurologic and cardiac manifestations to be counted, there must be laboratory confirmation. In addition, to count arthritis as being due to Lyme disease, the arthritis must be adequately characterized. Recurrent, brief attacks (weeks or months) of objective joint swelling in one or a few joints, sometimes followed by chronic arthritis in one or a few joints is typical of Lyme arthritis. However, manifestations not considered as criteria for diagnosis include chronic progressive arthritis not preceded by brief attacks and chronic symmetrical polyarthritis. Additionally, arthralgia, myalgia, or fibromyalgia syndromes alone are not criteria for musculoskeletal involvement. To count neurologic manifestations, any of the following, alone or in combination qualify in the absence of another explanation: lymphocytic meningitis; cranial neuritis, particularly facial palsy (may be bilateral);
radiculoneuropathy; or, rarely, encephalomyelitis. Encephalomyelitis must be confirmed by
demonstration of antibody production against *B. burgdorferi* in the cerebrospinal fluid (CSF),
evidenced by a higher titer of antibody in CSF than in serum. Headache, fatigue, paresthesia, or
mildly stiff neck alone are not criteria for neurologic involvement. Similar restrictions apply for
cardiovascular manifestations. Acute onset of high-grade (2nd-degree or 3rd-degree)
atrioventricular conduction defects that resolve in days to weeks and are sometimes associated
with myocarditis can be counted. However, palpitations, bradycardia, bundle branch block, or
myocarditis alone are not criteria for cardiovascular involvement.

To increase the probability that a case reported from a county in which Lyme disease has
not previously been recognized is truly a case of Lyme disease, persons with suspected EM
either should have been in a county in which Lyme disease is known to be endemic some time in
the preceding 30 days or have laboratory confirmation. Endemic counties are those in which at
least two laboratory confirmed cases meeting the clinical criteria defined above have been
acquired and/or in which a known tick vector has been shown to be infected with *B. burgdorferi.*
Of note, having a tick bite is not required for a case to be counted, as only about 20% of cases
will report noticing a tick bite in the 3-30 days prior to the onset of EM (CDC, 1982).

There is also a definition for laboratory confirmation to assure the same standards for
considering a test positive are used across states and, to the extent possible, over time.

**Modification of the Case Definition Over Time**

The purpose of public health surveillance for Lyme disease has not changed over time.
Thus with one exception (2007), there has not been a particular need to radically change the case
definition. The focus has continued to be on specificity (counting only true cases) and on
consistency in who is counted in order to monitor trends in geographic distribution and incidence
within geographic areas over time.

The original case definition for national public health surveillance published in 1990 and
used beginning in 1991 has been modified twice, in 1996 and in 2007 for use beginning the year
modifications have been to the laboratory criteria for confirming a diagnosis to incorporate new
laboratory testing methods and to standardize methods for counting tests as positive for
surveillance purposes. The latter has become particularly important as test methods for Lyme
disease have proliferated and testing has become more common, and as states have been using
laboratory reporting to supplement provider reporting to conduct surveillance for Lyme disease.
In the 1990 definition, the laboratory criteria for a positive test were: 1) isolation of *Borrelia*
burgdorferi from a clinical specimen, or 2) demonstration of diagnostic levels of IgM and IgG
antibodies to the spirochete in serum or CSF, or 3) a significant change in IgM or IgG antibody
response to *B. burgdorferi* in paired acute- and convalescent-phase serum samples. States were
authorized to determine their own criteria for laboratory confirmation and diagnostic levels of
antibody (CDC, 1990).

The main change in the case definition in 1996 was a new recommendation to use a two-
test approach for laboratory confirmation, using a sensitive enzyme immunoassay or
immunofluorescence antibody test followed by immunoblot confirmation (CDC, 1997; CSTE,
1996). In 2007, the laboratory criteria were modified slightly. The criterion: “demonstration of
diagnostic levels of IgM and IgG antibodies in serum or CSF” was removed and *arequirement*
made for “single-tier IgG immunoblot seropositivity interpreted using established criteria.” (CSTE, 2007) This completed a shift from dependence on serologic tests using IFA or ELISA methods to only relying on immunoblot methods for confirmation, a positive immunoblot test providing firmer evidence of *B. burgdorferi* infection than positive tests using the other two methods.

There was another important revision contained in the 2007 case definition. In addition to having a category of “confirmed” cases, two new categories with less stringent criteria were added, “probable” and “suspect” cases. “Probable” cases were defined as “any other case of physician-diagnosed Lyme disease that has laboratory evidence of infection” (as defined above). This means that cases with laboratory criteria for infection who do not meet the strict clinical criteria specified in the confirmed case definition could be counted – for example, persons whose EM diameter is less than 5 centimeters and persons with any disease manifestation that a clinician diagnosed as Lyme disease. “Suspected” cases were defined as “a case of EM where there is no known exposure (i.e., not having been in an endemic county in the 30 days before EM onset) and no laboratory evidence of infection, or “a case with laboratory evidence of infection but no clinical information available” (i.e., a person with only a positive laboratory report [as defined above]) (CSTE, 2007). The purpose of this change is to enable states to count more cases if they so chose and to better account for the surveillance burden of the huge number of laboratory reports, a burden that some states have been unable to meet (i.e., make efforts to obtain clinical information), resulting in potentially decreased confirmed case counts. Both confirmed and probable cases are designated as under national as well as state surveillance. The suspect case category is a category designed for optional use by states only. With these changes, it is expected that the national case counts will increase.

**Findings from National Surveillance**

Taking the national surveillance findings at face value, national public health surveillance for Lyme disease has largely met the major public health surveillance objectives. The demographic, geographic and seasonal distribution of Lyme disease have been defined and trends from 1992 to 2006 have been measured (CDC 2008). By age, the pattern is similar from year to year with all age groups being affected but incidence being bimodal with 5-9 year olds and 45-49 year olds providing the most cases. The sex distribution has been slowly changing over time, with the percentage of cases that are male gradually increasing, especially among 5-19 year olds and in the 10 states with the highest incidence. Clinically, EM has been present in nearly 70% of reported cases overall and over time, with a fairly wide variation by state, ranging from 87% in Minnesota to 51% in Delaware. Seasonally, new diagnoses of Lyme disease occur throughout the year, with peak occurrence of both early (EM) and later stage (arthritis, neurologic and cardiac) diagnoses during June through August when vector ticks most actively seek mammalian hosts and people spend the most time outdoors. Most importantly, national surveillance has documented the slowly expanding geographic distribution of Lyme disease and its initial intensification in areas as they become endemic, followed by reaching a fluctuating plateau in many endemic areas as, presumably, the ecologic dynamics of the tick, mice, deer and *B. burgdorferi* populations stabilize.

Figure 1 shows the annual number of reported cases to CDC from 1982 to 2008, including the period of informal national surveillance from 1982 to 1990.
FIGURE 1 Annual Number of Reported Cases to CDC 1982 to 2008

There has been a steady upward trend in number of reported confirmed cases. Underlying this trend is an increasing number of states identifying and reporting Lyme disease (from 11 in 1982 to 21 in 1984 to all 50 by 1987) and increasing rates in most states and counties. Figure 2 shows maps of Lyme disease incidence by county in the US in 1999 (the first time a county-level map was published by the CDC) and 2007. These illustrate the continually expanding geographic distribution and intensification in counties bordering well-established areas. In addition, using data from human surveillance, risk factor studies have been done (Ley et al, 1995; Orlosky et al, 1998; Cromley et al, 1998), a map of risk of acquiring Lyme disease was produced to guide vaccination recommendations when a vaccine was transiently available (CDC, 1999), and prevention and control demonstration projects have been conducted in high Lyme disease incidence areas (Vazquez et al, 2008; Connally et al, 2009; Gould et al, 2008).

Impact of Case Definition and Other Factors Affecting Number of Reported Cases

As previously mentioned, counting every single diagnosed case of human Lyme disease has not been the purpose of ongoing national public health surveillance. However, it is important to be able to define the extent to which current surveillance methods may underestimate the magnitude of the problem. With data from special studies conducted by states, often with CDC support, it is possible to crudely estimate the extent of undercounting of Lyme disease cases – or at least those with disease manifestations that are widely accepted as being due to *B. burgdorferi* infection. Studies done in Connecticut and Maryland in the early 1990s examined underreporting by physicians, and estimated that only 6-12% of EM cases were actually reported (Meek et al, 1996; Coyle et al, 1996). Laboratory reporting, which is particularly important for the 30% of reported cases that do not have EM, tends to be much more complete, but each report needs follow-up to obtain clinical data. States that attempt to follow up on positive laboratory reports to obtain clinical information that could make a person with a positive laboratory test countable as a case, find that they have success in getting case information back from physicians on only about 40-50% of positive laboratory reports (Connecticut Department of Public Health and New York State Department of Health, personal communication). Assuming these findings apply to all
states and are still pertinent, and that EM accounts for 70% of all reported cases, one can estimate that for every counted, reportable case, another 6-12 countable cases occur.

To the extent that the above factors, underreporting of EM and unsuccessful follow-up of positive laboratory reports are stable, changes in numbers of cases reported and counted should be meaningful. However, to the extent that they are unstable, artifactual increases or decreases could occur. In recent years, several important and interrelated sources of instability of surveillance efforts have been identified, resulting in challenges to interpretation of trends within some states and nationally. Instability of effort has occurred when funding for surveillance has changed and as the work of surveillance has increased with increasing use of laboratory tests for Lyme disease. For example, between 1998 and 2002, Connecticut used CDC funding given to
evaluate vaccine impact to support two full time positions to initiate full scale laboratory-result based surveillance with multiple attempts at follow up of positive laboratory test results to obtain clinical information. This was done in part to be able to evaluate vaccine impact on laboratory test result defined disease as well as on EM. As a result, the number of reported cases more than doubled (Ertel et al, 2006). After the vaccine was withdrawn and CDC switched emphasis from supporting enhanced surveillance to evaluate vaccine impact to other prevention efforts, Connecticut could no longer sustain nor needed such a labor-intensive level of surveillance and ceased laboratory surveillance beginning in 2003 in favor of Lyme disease prevention efforts. The result was a 70% decrease in cases from 4,631 in 2002 to 1,403 in 2003, although physician-reported cases were stable (Ertel et al, 2006). When reporting from laboratories that could submit data electronically was restarted in 2007 with some but lesser efforts at follow-up, the reported case count rose 71% from 1,788 in 2006 to 3,058 in 2007 (Ertel et al, 2008). In 2007, the Connecticut Department of Public Health had 16,799 positive laboratory reports. In New York State (excluding New York City), the number of unique persons with positive laboratory reports needing follow-up increased from 18,420 in 2005 to 38,503 in 2008 (New York State Health Department, personal communication).

These issues need to be taken into account when interpreting trends in national as well as state data. Thus, interpretation of national trends has balanced issues of changes in intensity of surveillance with data from states with stable surveillance. For example, from 2001 to 2002, there was a 40% increase in the number of reported cases of Lyme disease nationally. The interpretation was “Factors potentially contributing to the increase in reported cases include growing populations of deer that support the *Ixodes* tick vector, increased residential development of wooded areas, tick dispersal to new areas, improved disease recognition in areas where LD is endemic, and enhanced reporting.” (CDC, 2004). When there was no substantial change in incidence from 2003-2005, in part because Connecticut dropped laboratory reporting and other states were also adjusting surveillance methods to resources, the interpretation was more measured: “Since Lyme disease became nationally notifiable in 1991, the annual number of reported cases has more than doubled. This increase likely is the result of several factors, including a true increase in disease incidence and enhanced case detection resulting from implementation of laboratory-based surveillance in several states….To address this surveillance burden (laboratory reporting) and create more sustainable Lyme disease surveillance systems, some states (e.g., Connecticut) have modified components of their systems, leading to acute reductions in reported cases. However, no evidence exists to suggest a true decrease in Lyme disease incidence in these states.” (CDC, 2007).

**Other Lyme disease surveillance activities**

Although this report focuses on national public health surveillance for human Lyme disease, it should be noted that many states also conduct surveillance for vector tick density and percentage of *Ixodes* ticks infected with *B. burgdorferi*. This form of surveillance is used to complement human surveillance, to help define whether a county with reported cases for the first time is becoming endemic, and to help interpret fluctuating incidence in highly endemic areas. It has been well established that infected tick density can vary from year to year and that variations in infected tick density within a county or state correlate well with variation in human incidence (Stafford et al, 1998; Mather et al, 1996).
Current Issues in Human Lyme disease Surveillance: Questions and Answers

There are a number of Lyme disease human surveillance issues that have been raised recently by various persons and groups including state and local health departments conducting surveillance for Lyme disease. The following is a list of some of the issues with discussion in Issue and Response format.

**Issue:** Should we be making more of an effort through public health surveillance to fully measure the full magnitude of the Lyme disease problem annually, in part to call more attention to it and possibly more funding devoted to it?

**Response:** This would require a change in the objectives of public health surveillance and a change in the Lyme disease surveillance case definition to make it inclusive of any clinician-reported case of EM and any clinician-diagnosed case who has a positive laboratory test for *B. burgdorferi* infection. Such a change would require the consensus of the majority of the official state representatives (usually State Epidemiologist) at the annual CSTE meeting. While CSTE decided not to change the objectives of surveillance the last time this was considered in 2007, they did partially address the issue of measuring more of the Lyme disease problem by creating new categories of Lyme disease case reports (CSTE, 2007). Beginning in 2008, any person with a positive laboratory test meeting the laboratory criteria who had a physician diagnosis of disease regardless of symptoms could be called a “probable” case. Thus, persons with non-classical manifestations of Lyme disease potentially could be counted as cases. In addition, persons with clinician-diagnosed EM that was less than 5 cm in diameter could be counted if they had a positive laboratory test. Further, persons with a qualifying positive laboratory test but no clinical information could be counted as a “suspect” case. Thus, all persons with qualifying positive laboratory reports can be counted in state-level surveillance. For national surveillance, however, only those with confirmed and probable status will be counted. It will take some years using this system before any additional changes are likely to be considered. Data from 2008 illustrates that it will take time for this system to become fully established. In 2008, there were a total of 28,921 confirmed and 6,277 probable cases reported nationally, a ratio of 0.22 probable cases per confirmed case (CDC, 2010). While 49 states (including Washington, DC) reported at least one confirmed case, only 36 states reported at least one probable case. Neither Pennsylvania nor Delaware, together accounting for 4,590 confirmed cases, reported any probable cases, although at least 1000 probable cases might have been expected. Given inadequate staffing to follow up or successfully follow up on laboratory reports, suspect cases are likely to provide many more additional reports than probable cases. In 2008, Connecticut reported 2,738 confirmed and 1,158 probable cases, but identified an additional 3106 suspect cases in state surveillance (Connecticut Department of Public Health, personal communication).

**Issue:** How can we accurately determine the full magnitude of the human Lyme disease problem in the US?

**Response:** A definition of what should be included in the full magnitude of the Lyme disease problem is needed. It potentially includes the following: 1) persons truly infected with *B. burgdorferi* who have widely agreed upon (“classic”) symptoms and disease (currently being partially captured through confirmed case surveillance); 2) persons truly infected with *B.*
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*B. burgdorferi* who have non-classical Lyme disease symptoms that some would attribute to *B. burgdorferi* (e.g., persons with “chronic” Lyme disease, being partially addressed through “probable” case surveillance); 3) persons with a non-qualifying positive laboratory test who have been diagnosed as having Lyme disease (not all laboratories rely on immunoblot testing or a standard interpretation of the pattern found), and 4) persons without documented *B. burgdorferi* infection by any test or classic EM who are being treated for Lyme disease (includes persons with “seronegative Lyme disease”). In other words, the full impact of Lyme disease on the U.S. healthcare system potentially includes all persons who truly have Lyme disease and all persons getting treated for Lyme disease without standard laboratory confirmation, whether they have Lyme disease or not. There is no easy method to get at this. Given the limitations and challenges of public health surveillance in general and for Lyme disease in particular, conventional reporting of cases to public health departments will not give a complete answer no matter what the case definition, and it is unlikely that there will ever be a surveillance case definition for Lyme disease that is so inclusive. One could conduct a large population-based survey and ask respondents whether or not they have been treated for Lyme disease in the past year and the nature of that disease. However, this is not as easy as it sounds: the sample frame would have to be large, given that it is likely that the expected rate would be somewhere between 1 in a hundred and 1 in a thousand, given that the measured rate through national surveillance is most recently approximately 1.2 per 10,000 population (CDC, 2010). It might also need to be conducted in all states to determine state-specific rates and, subsequently, trends. Thus, a substantial financial investment would be needed to do this.

**Issue:** Can public health surveillance for human Lyme disease be used to determine whether there is chronic Lyme disease and the magnitude of the problem with it?

**Response:** Public health surveillance based on case reporting is dependent on having a case definition that can be applied to determine if a suspected case meets the criteria for being counted as a case. Clinically, many diseases can have similar symptoms. Clinicians faced with making a diagnosis of a patient with a given set of symptoms typically make a list of the possibilities (differential diagnoses) and then methodically do testing to determine what disease the patient likely has. It is similar with public health surveillance. At present, there is no standard case definition that could be used, as there is a lack of consensus even for whether there is “chronic Lyme disease.” Until those involved in clinical research establish that there is such an entity and what a standard set of symptoms are, public health surveillance with all its limitations cannot be conducted.

**Issue:** Given current surveillance objectives and methods, how can we improve physician reporting and the percentage of laboratory reports on which we get clinical information?

**Response:** There is a hidden question in this issue. Given that clinician reporting of Lyme disease has been well established for a long time and that maintaining a constant level of surveillance is needed to accurately determine trends (a major public health objective of Lyme disease surveillance), do we want to improve physician reporting? Generally, we want to do whatever is necessary to keep it at more or less the same level. In order to maintain a constant level of surveillance, some states have established sentinel provider networks in which more active surveillance is done. Physicians in these networks are actively asked weekly to provide a list of all the persons they have seen with a new Lyme disease diagnosis. In some states, an
epidemiologist will visit the practice to extract the necessary clinical information, limiting the work a physician has to do to report. The trends in the numbers of reports from these practices are compared to those from outside the network. As long as both show similar trend results, a state can reasonably assume that reporting levels are constant.

The laboratory question is a newer one. It is only recently that the number of positive laboratory reports in some high incidence states has overwhelmed the scarce public health resources to follow-up on them, threatening the ability to sustain laboratory surveillance for Lyme disease. One proposed solution that has worked well in New York State to address the problem created by the number of laboratory reports on unique individuals increasing from 18,420 in 2005 to 38,503 in 2008, has been to follow up on a random sample of reports (in New York, 1 in 5), then estimate the total number of cases based on the results of follow-up of the sample. In an unpublished validation, the sampling method has been shown to accurately predict what would have been obtained by following up all laboratory reports (New York State Health Department, personal communication). While sampling has not improved the percentage of laboratory reports successfully followed up (40-50% statewide, the percentage usually gotten by a single attempt by mail to contact the provider to complete a case report form), it takes a lot less work and may be a means that could be used by many states to achieve a sustainable, consistent level of Lyme disease laboratory based surveillance in the future. For sampling to be used for national surveillance purposes, it will ultimately be necessary for CSTE to endorse states reporting an estimated case count as a substitute for an exact one when reporting through the National Notifiable Disease Surveillance System.

**Issue**: Given the challenges of public health surveillance, can one fairly compare rates of reported Lyme disease between states? Within a single state over time?

**Response**: One cannot reliably compare rates of reported Lyme disease between states unless one knows whether or not they are making the same level of surveillance effort and what the density and infection rates of tick vectors are. Further, most states with high levels of endemic Lyme disease have very different rates from one part of the state to another. Thus, even the overall state incidence of Lyme disease does not reflect the different risk in different parts of the state (see Figure 2). The same principles apply to comparison of rates of Lyme disease within a state over time (Ertel, 2006 and 2008). If surveillance methods are stable, then data should accurately reflect changes in Lyme disease risk over time. However, overall state numbers and trends may not reflect risk and trends throughout the state. Some parts of the state may have plateaued and have some years when human disease incidence (and number of infected ticks) decrease while tick populations in other parts of the state and human illness are increasing.

**Issue**: A number of states and counties report cases of Lyme disease annually but are not known to have a competent tick vector or the presence of *B. burgdorferi* in tick populations. Do they really have Lyme disease? Are these really cases of Lyme disease?

**Response**: For purposes of national public health surveillance, a laboratory confirmed case meeting the clinical case definition will be counted from any state that chooses to count it, even if infection cannot be readily attributed to exposure where *B. burgdorferi* and competent tick vectors are known to be well established (i.e., travel to an endemic area, as defined in the case definition). However, such a “case” in a state or county with no known competent tick vector or infected ticks could be a false case. Other diseases can cause similar symptoms and even immunoblot tests are not perfect. When such disease is diagnosed, it is incumbent on the state or
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Public Health Surveillance for Other Tickborne Diseases in the US

There are at least 6 other recognized tickborne diseases in the United States: Rocky Mountain Spotted Fever, Ehrlichiosis/anaplasmosis, babesiosis, Powassan virus meningoencephalitis, tickborne relapsing fever and STARI. Of these, four, Rocky Mountain Spotted Fever, Ehrlichiosis/anaplasmosis, Powassan virus encephalitis and babesiosis are included in the National Notifiable Disease Surveillance System. A presentation of the public health surveillance objectives for each and their past and current case definitions and history of public health surveillance are discussed below. None has had the public interest that has been generated by Lyme disease nor as complicated a clinical picture with different stages of illness. Thus far, there has been less concern about what surveillance efforts and case definitions for these diseases can and cannot do.

Rocky Mountain Spotted Fever

Rocky Mountain Spotted Fever (RMSF) is an acute, severe and sometimes fatal tickborne illness transmitted in most parts of the country by the bite of Dermacentor species but in Arizona by Rhipicephalus sanguineus (the brown dog tick). It has been under public health surveillance since at least 1944 (CDC, 1994). The main objective of public health surveillance is to provide information on the temporal, geographic, and demographic occurrence of Rocky Mountain Spotted Fever (and other spotted fever rickettsioses) to facilitate its prevention and control (CSTE, 2009). Recommended surveillance methods are both provider and laboratory reporting. Although under national public health surveillance for a long time, the case definition for national surveillance was first published in 1990 (CDC, 1990). At that time, a case was defined as follows:

“Clinical description - An illness most commonly characterized by acute onset and fever, usually accompanied by myalgia, headache, and petechial rash (on the palms and soles in two-thirds of the cases). To be counted as confirmed, a case needs to be laboratory confirmed. Four different laboratory criteria can independently be used to confirm a diagnosis: a) fourfold or greater rise in antibody titer to the spotted fever group antigen by immunofluorescent antibody (IFA), complement fixation (CF), latex agglutination (LA), microagglutination (MA), or indirect hemagglutination (IHA) test, or a single titer greater than or equal to 64 by IFA or greater than or equal to 16 by CF; or b) demonstration of positive immunofluorescence of skin lesion (biopsy) or organ tissue (autopsy); or c) Isolation of Rickettsia rickettsii from a clinical specimen.” In addition to confirmed cases, a “probable” case is: “a clinically compatible case with supportive
serology (fourfold rise in titer or a single titer greater than or equal to 320 by Proteus OX-19 or OX-2, or a single titer greater than or equal to 128 by LA, IHA, or MA test).”

Since 1990, the case definition has been revised several times, each time to make modifications based on newer laboratory test methods. In 1996, the laboratory confirmation criteria changed to include having a positive polymerase chain reaction assay to \( R. rickettsii \) as another independent confirmation criterion (CDC, 1997). In 2003, the 4 main confirmatory laboratory test results were reframed in an effort to make them clearer (CSTE, 2003).

In 2007, another revision was made to “clarify misleading or poorly defined laboratory statements, and to improve case classification for reporting” including adding a “suspected” case category (CSTE, 2007) The clinical description of disease was simplified to “any reported fever and one or more of the following: rash, headache, myalgia, anemia, thromobocytopenia, or any hepatic transaminase elevation,” and the description of confirmatory laboratory tests was further clarified. A positive laboratory test became one of the following: a) serological evidence of a fourfold change in immunoglobulin G (IgG)-specific antibody titer reactive with \( Rickettsia rickettsii \) antigen by indirect immunofluorescence assay (IFA) between paired serum specimens (one taken in the first week of illness and a second 2-4 weeks later); b) detection of \( R. rickettsii \) DNA in a clinical specimen via amplification of a specific target by PCR assay; c) demonstration of spotted fever group antigen in a biopsy/autopsy specimen by IHC; or d) isolation of \( R. rickettsii \) from a clinical specimen in cell culture. Laboratory supportive evidence was defined as: has serologic evidence of elevated IgG or IgM antibody reactive with \( R. rickettsii \) antigen by IFA, enzyme-linked immunosorbent assay (ELISA), dot-ELISA, or latex agglutination. A confirmed case needed to have both clinical and laboratory confirmation, a probable case needed clinical confirmation in combination with laboratory supportive evidence, while a suspect case only needed laboratory evidence or recent or past infection (no clinical information needed).

The various iterations of surveillance definitions have been used to describe the geographic distribution within the U.S. and trends in occurrence over time. Most recently, without a substantial change in geographic distribution (mostly southeastern and south central U.S. with scattered cases throughout the country), the number of reported cases has increased 300% in the past decade with a trend toward stabilization in the 4 years since 2005 (CDC, 2010). In 2008, a total of 190 confirmed and 2,367 probable cases were reported.

**Ehrlichiosis/Anaplasmosis**

Human ehrlichiosis was recognized as a distinct acute disease entity caused by an intracellular parasitic organism in the Rickettsiae family in the late 1980s, when human monocytic ehrlichiosis (HME) was described (CDC, 1988). Since then, three different species with their own ecology have been identified as causing ehrlichiosis and one has been reclassified as *Anaplasma*. Despite there being at least three known causes of ehrlichiosis, they have been grouped together for public health surveillance purposes. After recognition of a second type of ehrlichiosis that resulted in severe, acute disease with a predilection to affect granulocytes (human granulocytic ehrlichiosis, HGE) and which had an apparently different epidemiology than the previously described HME (Bakken et al, 1994; CDC, 1995), CSTE approved a standard case definition for voluntary reporting to CDC, recognizing that this was an emerging infection. However, it did not initially vote to include it in the Nationally Notifiable Disease Surveillance System, in part because it was reportable in only a minority of states (CSTE, 1996). At that time
there were two known causes: *E. chaffeensis* causing HME, apparently transmitted by Lone Star (*Amblyomma americanum*) ticks, mainly affecting persons in the southeastern and south central US, and an *E. equi*-like agent causing HGE, suspected of being transmitted by *Ixodes* ticks and mainly affecting persons in the northeastern and north central states.

The provisional case definition included a clinical description of illness and laboratory criteria for diagnosis, a confirmed case being a person with a clinically compatible illness who met the laboratory criteria (CSTE, 1996). The clinical description was “A febrile illness most commonly characterized by acute onset, accompanied by headache, myalgia, rigors and/or malaise; clinical laboratory findings may include: intracytoplasmic microcolonies (morulae) in leukocytes of peripheral smear, cerebrospinal fluid or bone marrow aspirate or biopsy, cytopenias (especially thrombocytopenia and leukopenia), and elevated liver enzymes (especially alanine aminotransferase or aspartate aminotransferase).” Laboratory criteria included any of the following: “a) fourfold or greater change in antibody titer to *Ehrlichia* spp. antigen by immunofluorescence antibody (IFA) test in acute and convalescent specimens ideally taken four weeks or more apart. HME diagnosis requires *E. chaffeensis* antigen and HGE diagnosis currently requires *E. equi* or HGE-agent antigen; b) positive polymerase chain reaction (PCR) assay. Distinct primers are used for the diagnosis of HGE and HME; or c) intracytoplasmic morulae identified in blood, bone marrow or CSF leukocytes and an IFA antibody titer >=1:64.” Probable cases were defined as persons with a compatible illness with a single IFA serologic titer >=1:64 or intracytoplasmic morulae identified in blood, bone marrow or CSF leukocytes.

In 1998, CSTE voted to formally add ehrlichiosis to the NNDSS effective January 1999 (CSTE, 1998). The purpose of public health surveillance was severalfold: 1) to define the epidemiology of ehrlichia infections in the United States; 2) to monitor incidence trends and changes in the geographic distribution of these infections over time; and 3) to identify risk factors for ehrlichia infections. The earlier recommended case definition was approved for national public health surveillance. In 2000, the case definition was revised to account for the recognition that *E. phagocytophilum* was the cause of HGE, to add a new human disease-causing species, *E. ewingii*, and to incorporate newer laboratory test methods (CSTE, 2000). In addition, the reporting classification was modified, “Three categories of confirmed or probable ehrlichiosis should be reported: 1) human ehrlichiosis caused by *E. chaffeensis* (HME), 2) human ehrlichiosis caused by *E. phagocytophilum* (HGE), and 3) human ehrlichiosis (other or unspecified agent), which includes cases that cannot be easily classified by available laboratory techniques, and cases caused by novel *Ehrlichia* species such as *E. ewingii.*” In addition, the laboratory criteria became ehrlichia category-specific.

Additional changes to the case definition were made in 2007 in part to update taxonomic changes in the pathogens causing ehrlichiosis (CSTE, 2007). *E. phagocytophilum* was reclassified to *Anaplasma phagocytophilum*, the specific disease name changed from HGE to human granulocytic anaplasmosis (HGA) and the overall ehrlichiosis reporting classification was further expanded to 4 categories: 1) human ehrlichiosis caused by *Ehrlichia chaffeensis*, 2) human ehrlichiosis caused by *E. ewingii*, 3) human anaplasmosis caused by *Anaplasma phagocytophilum*, and 4) human ehrlichiosis/anaplasmosis - undetermined. Cases reported in the fourth sub-category can only be reported as “probable” because the cases are only weakly supported by ambiguous laboratory test results. Laboratory confirmatory and supportive (probable) criteria were modified to include *E. ewingii* and “undetermined” categories as follows: *E. ewingii:* “Because the organism has never been cultured, antigens are not available.
Thus, *Ehrlichia ewingii* infections may only be diagnosed by molecular detection methods. *E. ewingii* DNA detected in a clinical specimen via amplification of a specific target by polymerase chain reaction (PCR) assay.” “Undetermined” infections “can only be reported as “probable” because the cases are only weakly supported by ambiguous laboratory test results.”.

In 2008, a total of 2107 confirmed cases of human ehrlichiosis were reported, with disease caused by *A. phagocytophilum* (1009 cases) and by *E. chaffeensis* (957 cases) accounting for 93% of all cases (CDC, 2010). The incidence of both major forms of ehrlichiosis (HGA, HME) has been steadily increasing since 1999, with a 4-5-fold increase since 2001. Surveillance has also confirmed the early findings on geographic distribution of HME and HGA and demonstrated that ehrlichiosis caused by *E. ewingii* has a similar geographic distribution as HME.

**Powassan Virus Encephalitis/Meningitis**

Powassan virus encephalitis/meningitis results from central nervous system infection with Powassan virus, a tickborne virus that causes rare cases of arboviral encephalitis in the upper Midwest and northeastern U.S. It was placed under national public health surveillance in 2002 to be included at the same time West Nile virus was added to the list of other domestic arboviral encephalitis viruses which had been under national public health surveillance since 1995, including California serogroup virus, equine encephalitis, St. Louis encephalitis, and western equine encephalitis (CSTE, 2001). At the time it was described as “an under-recognized tickborne disease.” It was noted that laboratory testing was not widely available, but that 2 cases were diagnosed in New England during evaluation for West Nile virus infection and that there was a case-fatality rate of approximately 10%. The goals of surveillance were multiple: 1) assess the national public health impact of Powassan viral and other arboviral diseases of the CNS and monitor national trends, 2) identify high-risk population groups or geographic areas to target interventions and guide analytic studies, and 3) develop hypotheses leading to analytic studies about risk factors for infection and disease.

The original case definition was the same for all the arboviruses causing central nervous system infection and recognized that infection may result in clinical disease of variable severity and variable CNS involvement. There was no specific definition for Powassan virus infection. However, cases could be classified as “neuroinvasive” or “nonneuroinvasive” depending on symptoms and demonstration of CNS involvement and required laboratory confirmation in one of 4 ways: a) fourfold or greater change in virus-specific serum antibody titer; b) isolation of virus from or demonstration of specific viral antigen or genomic sequences in tissue, blood, cerebrospinal fluid (CSF), or other body fluid; c) virus-specific immunoglobulin M (IgM) antibodies demonstrated in CSF by antibody-capture enzyme immunoassay (EIA); or d) virus-specific IgM antibodies demonstrated in serum by antibody-capture EIA and confirmed by demonstration of virus-specific serum immunoglobulin G (IgG) antibodies in the same or a later specimen by another serologic assay (e.g., neutralization or hemagglutination inhibition).

From 2002-2008, a total of 13 cases of Powassan virus infection were reported with a peak of 7 cases in 2007. All were neuroinvasive, most from upstate New York with several from Maine, Minnesota and Wisconsin (CDC, 2010). In 2009, CSTE voted to continue surveillance for Powassan virus infection with the same objectives (CSTE, 2009). The one change to the case definition was to add a “probable” category. Confirmed cases continue to need clinical criteria
for neuroinvasive (any of a variety of central nervous system symptoms plus pleocytosis on lumbar puncture) or non-neuroinvasive (at least fever) and laboratory confirmation. Probable cases need to have a compatible clinical illness plus a lesser degree of laboratory confirmation, either a) stable (less than or equal to a two-fold change) but elevated titer of virus-specific serum antibodies, or b) virus-specific serum IgM antibodies detected by antibody-capture EIA but with no available results of a confirmatory test for virus-specific serum IgG antibodies in the same or a later specimen.

**Babesiosis**

Babesiosis is a tickborne disease caused by several different species of malaria-like red blood cell infecting parasites of the genus *Babesia*. *B. microti* is the most common cause of babesiosis in the U.S., particularly in New England, East coast and Midwestern states, with *B. duncani* causing disease in California and Washington. Infection ranges from asymptomatic to a life-threatening illness resembling malaria, being most severe in immunosuppressed, asplenic and/or elderly persons. Prior to the 1980s, documented human illness was rare and largely acquired in islands off the coast of New England and New York. In addition to causing disease following tick bites, *Babesia* can be transmitted by blood transfusion from asymptotically infected persons, with transfusion-associated disease first described in the U.S. in 1979.

During the 1980s, it was recognized that in some states, babesiosis was a growing problem. In some of those states, babesiosis was made reportable and increases in incidence and geographic range were documented. For example, New York made babesiosis reportable in 1986 following apparent increases in incidence on Long Island. In 1986, 18 cases were reported, all from Long Island. In 2008, 261 cases were reported: 96 from Long Island, 126 from 12 additional counties in New York state and 39 from New York City (New York State Department of Health, 1994 and 2008). In Connecticut, a cluster of 6 cases occurred in 1989 in New London County, near where Lyme disease was first recognized (CDC, 1989). Babesiosis was made reportable in 1991. In 2007, 156 cases were reported from all 8 counties (Connecticut Department of Public Health, 2007).

With the increasing incidence and spread of babesiosis, the incidence of blood transfusion-associated disease increased (Stramer et al, 2009). Correspondingly, in 2010, CSTE voted to add babesiosis to the list of notifiable diseases under national public health surveillance (CSTE, 2010). The purpose of surveillance is to provide information on the temporal, geographic, and demographic occurrence of babesiosis, including transfusion-associated babesiosis, to facilitate its prevention and control. It is recommended that states conduct both healthcare provider and laboratory surveillance. The case definition has three categories of disease: confirmed, probable and suspect, with confirmed and probable being under national public health surveillance. The probable definition includes blood donors and recipients without symptoms associated with a transfusion case or a known infected donor, as long as the probable case has either supportive or confirmatory laboratory evidence of infection.

**Other Tickborne Illnesses, Coinfection**

There are several other tickborne infections known to occur in the US that currently are not under national public health surveillance: STARI and tickborne relapsing fever. Neither disease is known to be common nor widespread enough for CSTE to seriously consider voting it to be
part of the National Notifiable Disease Surveillance System. However, individual states in which they are present can choose to make them locally reportable. Given that *Ixodes* ticks, especially in the northeast and north-central states, are vectors for Lyme disease, ehrlichiosis/anaplasmosis and babesiosis, it is possible for ticks to carry and transmit more than one agent. In fact, coinfections are not unusual and can result in more severe illness than infection with a single agent (Swanson et al, 2006). At present, there is no systematic effort at national surveillance for coinfection. However, the potential exists in any state to match persons reported with one infection to reports of those with either of the other infections. Thus far, no results of such matching to determine population levels of coinfection have been reported.

References*


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* All with Internet URLs accessed September 1-10, 2010.