LYME DISEASE SURVEILLANCE SUMMARY

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CENTERS FOR DISEASE CONTROL

VOLUME 2 - : NO. 5
DATE: JULY 1991

FUTURE DIRECTIONS FOR DIAGNOSTIC TESTS FOR *BORRELIA burgdorferi* INFECTIONS

Laboratory tests for Lyme disease (Ld) have been disappointing. Several studies have compared various serological kits or test formats in a number of laboratories. Most of these studies show poor agreement and reproducibility. An over-reliance on serology may lead to misdiagnoses of Lyme disease. Since a large proportion of reported cases depend on positive serology to meet the CDC surveillance case definition, approximations of the incidence of Lyme disease may be incorrect. A large effort to develop better diagnostic tests is underway in government, academic, and industry laboratories.

Three methods have been proposed to improve diagnostic tests: the ELISA using recombinant antigens, PCR, and immunoblotting. Each of these, with its inherent advantages and disadvantages, has a potential role in Lyme disease laboratory testing. Predictably no single test will be appropriate for diagnosis of infection for every stage and syndrome associated with Lyme disease. It is possible that no test will be sensitive enough to be accurate in very early stage disease, which may be an inherent feature of this disease due to low spirochete numbers, sequestration of the spirochetes, characteristics of the immune recognition of spirochetes, other factors, or combinations of the above.

Recombinant antigens for diagnostic testing are being investigated by several groups. Most of these antigens have not been extensively characterized and tested. Developing recombinant antigens is expensive and time consuming. The use of recombinant antigens usually increases the specificity of the test but often reduces its sensitivity. Therefore, it may be necessary to use combinations of several recombinant antigens to provide sufficient sensitivity. Once acceptable recombinant antigens have been identified and characterized, they can generally be used in ELISA or other common testing modalities.

PCR may be the most sensitive test we can develop. But the sensitivity may also be the biggest problem in its use. Extreme care must be used to prevent cross contamination of specimens. A single positive PCR may not be sufficient to conclude that *B. burgdorferi* is present. Although methods to control contamination are being developed, PCR will probably need to be done in

highly specialized laboratories. One of the potential uses of PCR may be to validate other more extensively used tests.

Opinions about the utility of immunoblotting are widely split. A western blot does provide more information than ELISA by the number and position of reactive bands or their relative intensities. Western blots are expensive, time consuming and difficult to quantify or compare. Immunoblots are specific but lack the sensitivity needed to be useful except for late-stage disease. Recombinant antigens may also be applied to blotting.

The isolation and cultivation of *B. burgdorferi* from a specimen is the only direct method to demonstrate that viable spirochetes are present. Culture methodology is not widely used in the U.S. because the yield is thought to be low. In Europe, some studies report successful cultures for nearly 80% of patients with EM. Although there may be differences between the strains in Europe and the U.S., many other factors probably affect the rate of *B. burgdorferi* isolation in the U.S. Isolation rates from ear tissue of experimentally infected mice have approached 100% in some studies at CDC, DVBID. These data, plus the success rate in Europe, suggest that the basic culture methodology for the isolation of *B. burgdorferi* is sound. The use of culture and particularly culture of EM lesions needs to be re-evaluated as a routine diagnostic test for patients suspected to have Lyme disease.

Another factor extremely important in diagnostic test development, test standardization, and proficiency testing, is the use of a highly specific clinical case definition. We currently have only a surveillance case definition for epidemiologic purposes that is widely used. A clinical case definition without clear definition of terms, based on physicians' individual criteria, is no longer acceptable. Until an adequate case definition is universally used the confusion about laboratory diagnosis of Ld will continue.

LYME DISEASE RESEARCH PROJECTS ON DIAGNOSIS, IMMUNOLOGY AND PATHOGENSIS

Six research projects on improvement of Ld diagnosis and our understanding of the immunology and pathogenesis of infection with *B. burgdorferi* have been funded by CDC for FY 1991. Project oversight for these studies is being provided by the Molecular Biology Branch of the Division of Vector-Borne Infectious Diseases at Fort Collins.

Projects Funded through May 1992

- Antigenic Composition of *Borrelia burgdorferi* Organisms Related to Specific Clinical Manifestations. Mark S. Klempner, M.D. New England Medical Center Hospitals. Cooperative Agreement.

- Utility of *Borrelia burgdorferi* Specific Immune Complexes in Diagnosis and Treatment of Lyme Disease. Steven E. Schutzer, M.D. New Jersey Medical School. Cooperative Agreement with University of Medicine and Dentistry of New Jersey.

- Development of Improved Serologist Tests and Antigen Detection Systems for Lyme Disease. Doris Bucher, Ph.D. New York Medical College. Cooperative Agreement.

- Rapid and Specific Diagnosis of Lyme Disease. Raymond J. Dattwyler, M.D. and Benjamin J. Luft, M.D. SUNY-Stony Brook. Cooperative Agreement with the Research Foundation of the State of New York.

- A Primate Model for the Improvement of Clinical, Immunological and Molecular Diagnosis of Lyme Disease. E. Donald Roberts, D.V.M., Ph.D. and Mario T. Philipp, Ph.D. Cooperative Agreement to Tulane Regional Primate Research Center.

- Serologic Diagnosis of Lyme Disease Using Recombinant *Borrelia burgdorferi* Antigens. Daniel W. Rahn, M.D. and Richard Flavell, Ph.D. Yale University School of Medicine. Cooperative Agreement to Yale University.

LYME DISEASE AWARENESS WEEK

Congressman George Hochbruechner, 1st District, New York, introduced H.J. Resolution 138 to make the week of July 21-27 National Lyme Disease Awareness Week. The Senate version is sponsored by Senator Joseph Lieberman of Connecticut. Passage of the resolution will mark the fourth occasion upon which there has been federal recognition of the importance of Lyme disease. A number of educational and informational events will be held in Washington, DC during Lyme Awareness Week and participants from across the nation are expected to attend.

Congressman Hockbruechner has been the leading advocate of increased federal funding for research and education for Lyme disease at the Centers for Disease Control and the National Institutes of Health. Beginning fiscal year 1990, the Congressman's efforts, and those of others, have yielded over $22 million in funds distributed to these two agencies for Lyme disease efforts and he is presently working toward increased funding for fiscal year 1992.

GUIDELINES FOR ESTABLISHING THE ENDEMICITY OF LYME DISEASE

Lyme disease often presents with symptoms that are easily confused with other diseases. Even **erythema migrans** has limitations in its diagnostic utility. **EM** lesions may be absent in up to 40% of acute cases, and less experienced observers may misidentify a lesion as **EM**, particularly allergic local responses to tick bites. Serologic test results, as noted in this and previous issues, can be misleading also. Thus, attempts to establish the presence of Lyme disease in a new geographic area should not be based solely on clinical observations and serologic results.

The only reliable, currently available means to confirm a case of Lyme disease is culture of *B. burgdorferi* from blood, cerebrospinal fluid or material obtained from aspiration or biopsy of an **EM** lesion. Clinicians who suspect that Lyme disease cases may be occurring for the first time in their geographic area should make a concerted effort to document this by obtaining appropriate cultures.

The emergence of risk for Lyme disease in an area can be evaluated by determining the presence of suitable vectors and hosts. In the United States, the only competent vectors for transmission of Lyme disease identified to date are the ticks *Ixodes dammini*, *I. pacificus*, and *I. scapularis*. The absence of these vectors is important evidence against the likelihood of an endemic Lyme disease problem in an area. The status of *I. dammini* in an area can be considered to "established" (endemic) when all three stages--larva, nymph, adult--are present in a locality, on resident animals

or in the environment for at least two consecutive years (Consensus Conference on Lyme Disease, University of Guelph, Canada, 15-16 January 1991). Their presence suggests that Lyme disease transmission to humans is possible. If *Ixodes spp.* vectors are found, they or their usual hosts must be demonstrated to be infected with *B. burgdorferi* in order to confirm risk of tranmission to humans. A suggested scheme to search for *B.burgdorferi* is presented below.

SAMPLING FOR *BORRELIA burgdorferi* IN TICK VECTORS AND WILDLIFE

One hundred individual adult or nymphal *Ixodes spp* ticks collected from a defined area should be examined by darkfield or immunofluorescent antibody staining techniques. If spirochetes are recognized, then an additional 100 adults or nymphs, or the ears and bladders of 30 suspected mammalian reservoirs of infection should be cultured to attempt isolation and identification of *B. burgdorferi*. Serologic results are not adequate to declare an area either endemic or non-endemic. In those areas where *I. pacificus* is likely to be the potential vector, attention should be focused on obtaining isolates from ticks since the prevalence of infection in small mammals is usually quite low.

Biological evidence for the presence or absence of *B. burgdorferi* in a geographic area is quite useful to clinicians confronted with patients' symptoms which may or may not be the result of infection with this spirochete. These data are also important for disease surveillance and public health decisions on control strategies.

The Bacterial Zoonoses Branch and the Medical Entomology and Ecology Branch personnel at CDC in Fort Collins are happy to assist with technical advice on clinical culture techniques and on specific aspects of biologic sampling and laboratory methodology. For assistance, call 303-221-6400 and advise the receptionist on the nature of your inquiry. Your call will then be routed to the appropriate staff member.

REPORTING OF LYME DISEASE CASE IN 1991 BY NETSS

The number of Lyme disease cases reported through NETSS in the period January through June are shown in Figure 1. Of the total 2,542 cases reported through Week 25, 1,854 (73%) were reported from the mid-Atlantic region. Upstate New York reported 1,219 cases (48%) of the 1991 national total.

LYME DISEASE SURVEILLANCE (Reprinted from Morbidity and Mortality Weekly Report)

One of the more frequent sources of inquiry and comment we receive is in regard to the National Lyme Disease Surveillance Case Definition and its effect on the reported numbers of cases. This epidemiologic case definition was not adopted for official reporting use until 1 January 1991. The effect of this case definition cannot be accurately evaluated until it has been in use for some period of time. A large number of factors influence surveillance for LD cases and some of these were discussed in the June 28, 1991 edition of **Morbidity and Mortality Weekly Report**. We are reprinting that discussion here for our readers who may not have had access to that edition of **MMWR**.

Erratum. In LDSS Vol. 2. No. 3, on page 5, *Dermacentor andersoni* was incorrectly identified as the dog tick. Readers are aware that the *Dermacentor andersoni*, the main vector of Colorado tick fever, is known as the Rocky Mountain wood tick, and that *Dermacenter variabilis*, the main vector of RMSF in the U.S., is called the American dog tick.

Lyme Disease Surveillance Summary (LDSS) is edited by Drs. Robert Craven and David Dennis. If you have information to contribute or wish to receive a LDSS, please contact them at:

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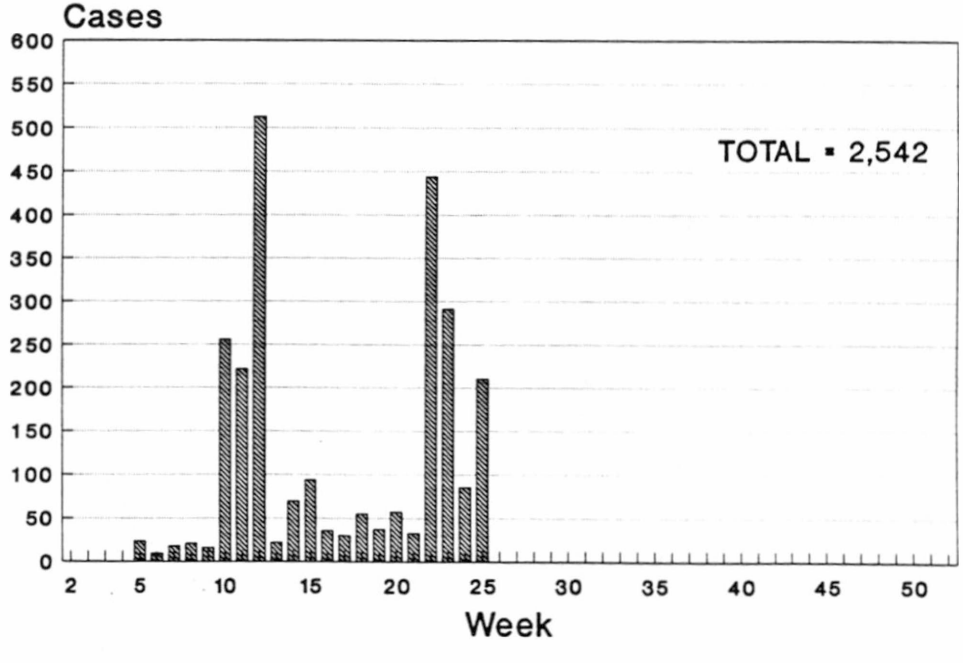
FIGURE 1
REPORTED LYME DISEASE CASES, U.S., 1991



CDC

June 28, 1991 / Vol. 40 / No. 25

MMWR

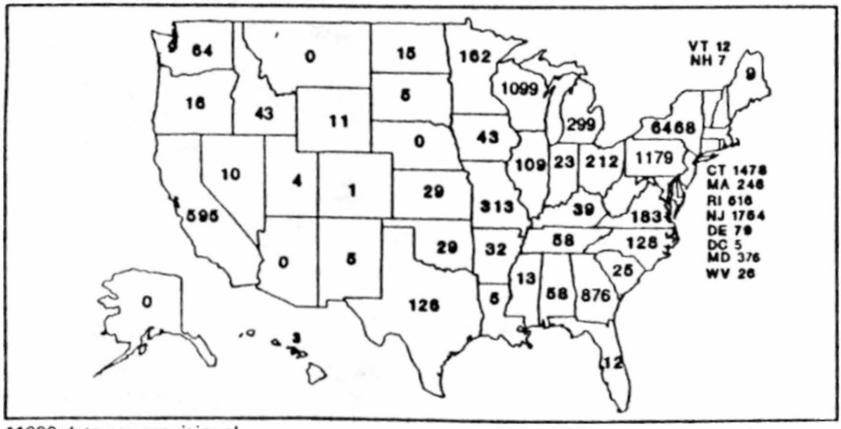
MORBIDITY AND MORTALITY WEEKLY REPORT

Current Trends

Lyme Disease Surveillance – United States, 1989–1990

Surveillance for Lyme disease (LD) was initiated by CDC in 1982 (*1*), and in January 1991, LD became nationally reportable (*2*). Forty-six states reported cases in 1989 and 1990 (Figure 1), but the occurrence in nature of the causative bacterium, *Borrelia burgdorferi*, has not been documented in all of these states. From 1982 through 1989, the annual reported number of cases of LD increased 18-fold (from 497 to 8803, respectively) and from 1986 through 1989, nearly doubled each year (Figure 2). The provisional total of 7997 cases for 1990 suggests a plateau in this trend of rapid annual increase. This report summarizes surveillance of LD during 1990 in Connecticut, Georgia, Michigan, Missouri, New Jersey, and Wisconsin.

FIGURE 1. Reported Lyme disease cases – United States, 1989–1990*



*1990 data are provisional.

Lyme Disease — Continued

Connecticut

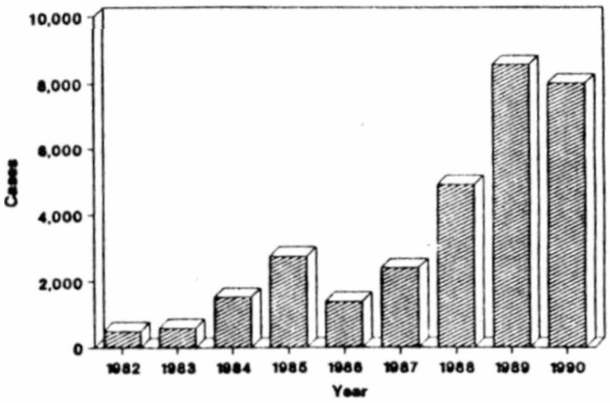
In 1990, the Connecticut Department of Health Services (CDHS) reported 704 cases (22 per 100,000 population) of LD based on the new national surveillance case definition adopted by the Council of State and Territorial Epidemiologists (CSTE) in 1990 (see box) (*2*). This total represented a 9% decrease from the 1989 total of 774 cases, but that total was based on the previous CDC case definition in use in 1989 (*3*). The total number of case reports received by CDHS (i.e., including those reports that did not meet the case definition in use), however, increased slightly (4%) from 1269 in 1989 to 1318 in 1990.

One criterion of the new national surveillance case definition is that the characteristic skin lesion of LD, erythema migrans (EM), must be ≥5 cm in diameter. In 1990, CDHS assessed the impact of this criterion on LD reporting in Connecticut by requesting physicians to record the EM diameter on the CDHS case report form (telephone follow-up was done when information was not provided). Of the 1318 LD total case reports received by CDHS in 1990, 597 (45%) were based on reports of EM alone. Of these 597 reports, the EM diameter was ≥5 cm for 388 (65%), <5 cm for 35 (6%), and unspecified for 174 (29%). Telephone follow-up for the 174 unspecified reports indicated the EM diameter was ≥5 cm for 82 (47%), <5 cm for 35 (20%), and remained unspecified for 57 (33%). If information on EM diameter had not been collected, the surveillance total for 1990 based on the official case definition would have been 831, including the 597 cases with EM alone and 234 cases with late manifestations and a supporting positive serologic test; instead, the CDHS assessment resulted in a 15% (127/831) reduction in cases.

Georgia

The Georgia Department of Human Resources (GDHR) recorded a total of 62 cases of LD from 1982 through 1988, compared with 715 cases in 1989 (*4*). In 1990, however, the total number of reported cases declined to 161. Potential explanations for these shifts are that 1) free serologic testing was offered through the state public health laboratory in 1989 but was discontinued in July 1990; 2) the cut-off for

FIGURE 2. Reported Lyme disease cases — United States, 1982–1990*



serologic positivity used by the state public health laboratory (1:128 by immunofluorescent assay) was lower than that used by many laboratories in the country (1:256); 3) in 1989 GDHR and other institutions sponsored a series of state-wide educational seminars on LD, including two programs for physicians; and 4) the new national surveillance case definition was implemented in 1990 (*5*).

Michigan

In Michigan, the number of reported LD cases with onset in 1990 (134) declined 19% when compared with 1989 (165), although the same case definition was used in both years.

Missouri

During 1990, the Missouri Department of Health (MDOH) reported 205 cases of LD, a 90% increase from 1989 (108 cases). MDOH implemented the new national surveillance case definition (*2*) in 1990, but had used the previous CDC case definition in 1989 (*3*).

New Jersey

In 1990, the New Jersey State Department of Health (NJDOH) recorded a 58% increase in the number of confirmed cases of LD compared with 1989 (1074 cases and 680 cases, respectively), although the number of cases with EM increased modestly (680 and 716 cases, respectively). Potential explanations for these increases include: 1) use of a new generic case report form for communicable diseases that had been implemented by NJDOH in June 1990 to facilitate reporting by physicians; and 2) broadening of the case definition from only cases with documented EM to the new national surveillance case definition that includes persons with EM as well as persons with a positive serologic test result and rheumatologic, neurologic, or cardiac signs of LD.

LYME DISEASE*

Clinical Description
A systemic, tick-borne disease with protean manifestations, including dermatologic, rheumatologic, neurologic, and cardiac abnormalities. The best clinical marker for the disease is the initial skin lesion, erythema migrans, that occurs among 60%–80% of patients.

Clinical Case Definition
- Erythema migrans (≥5 cm in diameter), or
- At least one late manifestation (i.e., musculoskeletal, nervous, or cardiovascular system involvement) and laboratory confirmation of infection.

Laboratory Criteria for Diagnosis
- Isolation of *Borrelia burgdorferi* from clinical specimen, or
- Demonstration of diagnostic levels of IgM and IgG antibodies to the spirochete in serum or cerebrospinal fluid, or
- Significant change in IgM or IgG antibody response to *B. burgdorferi* in paired acute- and convalescent-phase serum samples.

Case Classification
Confirmed: a case that meets one of the clinical case definitions above.

*Adapted from the 1990 Council of State and Territorial Epidemiologists surveillance case definition (*2*).

Wisconsin

In 1990, the Wisconsin Division of Health (WDOH) noted a 54% decrease in total LD case reports when compared with 1989 (909 and 1996, respectively), although the same case definition was used in both years. The number of confirmed cases also declined from 1989 to 1990 (762 and 337 cases, respectively). This is the first decrease in reported LD cases in Wisconsin since 1985. Potential explanations that may account for some of this change include: 1) a decrease in media coverage of LD; 2) a decreased prevalence of *Ixodes dammini*, the tick vector of *B. burgdorferi* in that region, based on anecdotal reports from entomologists to WDOH; and 3) success of educational efforts to prevent tick bites (*6*). In addition, from 1989 through 1990, use of commercial and reference laboratories for LD serology declined (*6*): in 1990, the Wisconsin State Laboratory of Hygiene tested 8309 specimens compared with 17,222 specimens in 1989. This decrease in laboratory use may reflect a true decrease in incidence, changing medical practices, or other factors; the effect on case reporting is unknown.

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Editorial Note: Different surveillance case definitions for LD have been used throughout the United States since 1982; each definition has incorporated a combination of elements of early and late manifestations of illness, a history of endemic exposure, and a positive serologic test result (*7,8*). On January 1, 1991, LD became nationally reportable in the United States. However, the new standardized surveillance case definition, which had been approved by CSTE (*2*), was used by some states in 1990.

The findings in this report suggest that the factors affecting trends in LD reporting are multiple and complex, and require further definition. For example, in Connecticut, a 1-year assessment that focused on reporting of EM resulted in a 15% decrease in cases that otherwise would have been included in the annual total. The findings in Georgia highlight how heightened physician awareness and laboratory-based surveillance for LD may affect reporting. In Missouri, case reports continued to increase despite the use of the new case definition, possibly reflecting increased awareness and reporting compliance and/or a true increase in incidence. Of note, however, is that *B. burgdorferi*, the etiologic agent of LD, has not been isolated from ticks, vertebrate hosts, or human case-patients in Georgia or Missouri. In New Jersey, use of the new case definition appeared to identify cases with late manifestations of illness. In Michigan and Wisconsin, case reports may have declined as a result of ecologic or other factors unrelated to a change in case criteria.

The new national surveillance case definition was developed to achieve greater specificity in case identification. This effort to exclude non-cases may have also excluded true cases from national totals. The impact of the new case definition can be further assessed after this definition has been implemented uniformly by all states and in use for at least 1 full year.