LYME disease

ANTIBIOTIC PROPHYLAXIS OF LYME DISEASE FOLLOWING RECOGNIZED TICK BITE

One of the most frequently asked questions concerning the prevention of Lyme disease is what to do about persons in endemic areas who have had a recognized tick bite. Although the prophylactic use of antibiotics for a tick bite may be a common, albeit controversial, medical practice in some areas,[1-3] a definitive risk- or cost-benefit analysis of the practice does not exist. The recent NIH workshop on the "state of the art" of diagnosis and therapy of Lyme disease held in Washington, DC, March 25-26, 1991, stated that "The use of antibiotics, as with all medicines, is associated with some risk of adverse reactions and untoward side effects. Thus, prophylactic use of antibiotics could be very costly in terms of potential side effects as compared to case prevention. At this time, antibiotic prophylaxis for prevention of Lyme disease among the general population is not indicated. . . . At the present time it does not appear necessary to prescribe antibiotics solely on the basis of a tick bite, although this is being investigated." In conclusion, it was stated that "The decision as to whether prophylactic treatment of a patient with a tick bite is warranted is ultimately up to the attending physician and should be made on a case by case basis."[4] To help health care workers and others make rational decisions on prophylaxis, we provide a summary of the available epidemiologic evidence on this subject, including the results of five clinical trials and two observational studies, some of which are unpublished or have been published in abstract form only:

AGRE F, SCHWARTZ RM, 1991. The value of early treatment for the prevention of Lyme disease. *Am J Dis Child 145:* 391 [Abstract 175].

> CLINICAL TRIAL: These researchers reported the results of a randomized placebo-controlled double-blinded prospective study of patients between 3 and 19 years of age presenting with *Ixodes dammini* tick bites over a 3 year period in New York. Subjects were randomized to receive oral antibiotics (penicillin or tetracycline) for 10 days or placebo and were followed for 2.5 years for development of clinical evidence of Lyme disease. Tests for antibodies to *Borrelia burgdorferi* (IFA) were performed on paired serum specimens taken at times 0 and 6 weeks. Ticks were not examined for infection

rates with *B. burgdorferi*. Of the 89 patients in the treatment group, none developed clinical evidence of Lyme disease and none seroconverted. Four (4.4%) of the 90 patients in the placebo group had a "weakly positive" rise in antibody titer, and one of these (1.1%) developed erythema migrans. Of the remaining 3 patients with titer rises, 1 had a nonspecific ("flu-like") illness and 2 had no symptoms. In the 2.5 year follow-up period, no patient developed later stage Lyme disease. NOTE: The authors recently provided CDC with the following additional information. The study area was northern Westchester County. The 4 seroconversions by IFA were conversions from <1:8 to 1:32.

COSTELLO CM, STEERE AC, PINKERTON RE, FEDER HM JR, 1989. A prospective study of tick bites in an endemic area for Lyme disease. *J Infect Dis 159:* 136-9.

CLINICAL TRIAL: These researchers reported the results of a randomized placebo-controlled double-blinded prospective study of patients presenting with *I. dammini* tick bites in Connecticut during 1986. The treatment group received oral penicillin for 10 days. Tests for antibodies to *B. burgdorferi* (EIA) were performed serially for 6 months. Ticks were examined for spirochetes using fluorescence microscopy. Patients who developed illness during the study were examined by their physician. Six to 12 months following their *I. dammini* bite, patients were questioned by mail regarding symptoms of illness. Of 68 patients initially enrolled in the study, 56 (82%) completed the study protocol. No seroconversions were observed. None of the 27 patients in the treatment group developed Lyme disease. One treated subject developed an allergic dermatitis after 5 days of penicillin, but subsequently completed the 10-day treatment. One (3.4%) of the 29 patients in the placebo group developed erythema migrans and constitutional symptoms 14 days following the tick bite (this tick was not suitable for study, so it was not known whether it was infected). The patient responded completely to 10 days of oral doxycycline and had no recurrence of the illness. She remained seronegative. Twenty-one of the 48 *I. dammini* found on patients could be tested for infection (the rest were too desiccated for study), and 6 (29%) of these were positive for spirochetes compatible with *B. burgdorferi*. These 6 infected ticks included 3 each from patients in the treatment and placebo groups. None of these 6 patients developed Lyme disease. None of the 12 patients who dropped out of the study developed symptoms of Lyme disease.

FALCO RC, FISH D, 1988. Ticks parasitizing humans in a Lyme disease endemic area of southern New York State. *Am J Epidemiol 128:* 1146-52.

OBSERVATIONAL STUDY (RETROSPECTIVE): These researchers identified 126 ticks submitted by bite victims in Westchester County, New York, during 1985. Ninety-six (76.2%) of these were identified as *I. dammini*, either larvae, nymphs, or adults; the remainder were *Dermacentor variabilis* or *Amblyomma americanum*. Infection rates of ticks with *B. burgdorferi* were not determined. Bite victims were contacted for follow-up information 7-22 months after the tick bite. Retrospectively, 31 (44%) of 71 *I. dammini* bite victims from whom information was obtained had received prophylactic antibiotics following their bite. None of these 31 persons reported illness following their tick bite. Of the 40 *I. dammini* bite victims from whom information was obtained and who had not received prophylactic antibiotics, 2 (5%) had been diagnosed with Lyme disease. Both

of these reported having been diagnosed with erythema migrans at the site of the tick attachment, from several days to 2 weeks following removal of nymphal *I. dammini*. No illnesses were attributed to *Dermacentor* or *Amblyomma* bites.

GERBER MA, SHAPIRO ED, PERSING DH, FEDER HM, LUGER SW, 1990. Risk of developing Lyme disease after a deer tick bite. IV International Conference on Lyme Borreliosis. Stockholm. Book "A", p. 175 [Abstract M/TU-P-131].

OBSERVATIONAL STUDY (PROSPECTIVE): These researchers reported the results of a study of victims of *I. dammini* bites in southeastern Connecticut. Subjects were questioned serially for the presence of signs or symptoms of Lyme disease for 3 months following their tick bite. Tests for antibodies to *B. burgdorferi* (EIA) were performed serially for 3 months. None of the 39 enrolled subjects received antibiotic therapy during the 3 month evaluation period and none developed Lyme disease or seroconverted. Ticks were tested for evidence of infection with *B. burgdorferi* using PCR. Eight (32%) of 25 ticks examined were infected with *B. burgdorferi*. NOTE: This was a preliminary study to Shapiro *et al.* (1991), described below.

NADELMAN R, FORSETER G, HOROWITZ H, FISH D, WELCH P, MARCUS R, BITTKER S, PAVIA C, WORMSER G, 1990. Single dose doxycycline as prophylaxis for Lyme borreliosis after *Ixodes dammini* bites in a Lyme endemic area. IV International Conference on Lyme Borreliosis. Stockholm. Book "B", p. 34 [Abstract TH-L-12].

CLINICAL TRIAL: These researchers reported the results of a randomized placebo-controlled double-blinded prospective study of patients presenting with *I. dammini* tick bites in Westchester County, New York. Subjects were randomized to receive a single dose of either 200 mg doxycycline or placebo. Tests for antibodies to *B. burgdorferi* (IFA), blood cultures for *B. burgdorferi*, and evaluations for clinical evidence of Lyme disease were performed serially for 6 weeks. A total of 161 subjects had been enrolled at the time of this publication but the results had not been decoded. Of these, 132 were evaluable. Of these 132 subjects, 72 (55%) removed nymphal *I. dammini* and 60 (45%) removed adult *I. dammini*. Fifty-seven (43%) of these 132 subjects removed engorged *I. dammini* (35 nymphs, 22 adults). Two (1.5%) of the 132 evaluable patients developed erythema migrans. A third subject had an "influenza-like" illness with atypical rash and seroconversion. Thus a total of 3 (2.3%) of 132 evaluable patients developed clinical evidence of Lyme disease. Another 16 (12%) of these 132 subjects developed "influenza-like" illness without seroconversion. No asymptomatic subjects seroconverted. One unevaluable subject (due to multiple tick bites) developed a nonspecific ("influenza-like") illness with a positive blood culture for *B. burgdorferi*. Ten percent of subjects experienced possible adverse drug effects, including nausea, vomiting, or diarrhea. NOTE: The authors recently provided CDC with the following additional information: this study is ongoing and the results have not been decoded.

SHAPIRO ED, GERBER MA, PERSING DH, LUGER SW, FEDER HM, 1991. Risk of developing Lyme disease after a deer tick bite in an endemic area. *Pediatr Res 29:* 185A [Abstract 1091].

CLINICAL TRIAL: These researchers reported the results of a randomized placebo-controlled double-blinded prospective study of patients presenting with *I. dammini* tick bites in southeastern Connecticut during 1989 and 1990. Subjects were randomized to receive either oral amoxicillin for 10 days or placebo. Tests for antibodies to *B. burgdorferi* (EIA) were performed serially for 3 months. Ticks were tested for evidence of infection with *B. burgdorferi* using PCR. Antibiotic compliance was measured with a urine bioassay. Subjects were observed for 1 year for clinical evidence of Lyme disease. No seroconversions were observed. None of the 120 treated subjects developed clinical evidence of Lyme disease. One (0.9%) of the 110 subjects in the placebo group developed clinical evidence of Lyme disease (erythema migrans). Nobody in the placebo group and 56% in the treatment group had antimicrobial activity in their urine on day 7. Twenty percent of *I. dammini* removed from each group (treatment and placebo) were positive for infection with *B. burgdorferi*. NOTE: This was a follow-up study to Gerber *et al.* (1990), described above. The authors recently provided CDC with the following additional information: of the 204 identifiable ticks, 141 (69%) were nymphs, 43 (21%) were adults, and 20 (10%) were larvae. Thirteen percent of nymphs, 35% of adults, and no larvae were positive for infection with *B. burgdorferi*.

In addition, CDC is aware of at least one other ongoing epidemiologic study of this issue, a randomized double-blinded placebo-controlled clinical trial by Dr. Tom Sell and colleagues at the Marshfield Clinic in Marshfield, Wisconsin. Subjects who present with attached ticks are randomized to receive either 3 days of oral minocycline or placebo. Ticks are examined for the presence of spirochetes using an indirect immunofluorescence assay. The following are preliminary results as of August, 1991: enrollment of 173 subjects, 85.7% of the ticks submitted were *I. dammini*, similar rates of infection (about 18%) were found in *I. dammini* removed from each of the 2 groups (treatment and placebo), and no development of clinical evidence of Lyme disease in any subject.

COMMENT: These studies highlight the relatively low risk of infection and disease arising from a recognized tick bite in an endemic area. The principal factor that would seem to explain the low apparent risk of infection is that transmission is probably inefficient in the first 36-48 hours of tick attachment.[5-6] Attached ticks which are removed are less likely to have transmitted infection than are ticks that are not noticed. Only about 30% of persons with early Lyme disease remember having been bitten by ticks in a four-week period prior to onset of symptoms.[7] Engorged infected ticks have the highest probability of transmission of *B. burgdorferi* to humans, and yet a substantial majority of these apparently have not produced infection at the time of removal (Nadelman *et al.* 1990, above). The incidence of transmission of *B. burgdorferi* by a recognized *I. dammini* bite in an endemic area may be no higher than the incidence of adverse effects from a standard course of antibiotics.[2] If it can be shown to be effective and safe, single dose prophylaxis may be a reasonable alternative to no prophylaxis at all.

All of the above epidemiologic studies were done in the northeastern or north central United States where *I. dammini* is the vector of Lyme disease. The risk of transmission from a recognized bite by *Ixodes pacificus*, the vector on the West coast, is unknown. If prophylactic antibiotics are not routinely indicated in areas where *I. dammini* occurs (and where typically 20-80% of nymphs or adults of this species are infected with *B. burgdorferi*), their use is probably even less warranted in the West, where typically only 1-3% of nymphal or adult *I. pacificus* are infected.

When consulted by health care providers, CDC/DVBID staff do not currently recommend the routine administration of antibiotics to prevent Lyme disease following a known tick bite. The CDC does promote primary prevention with the following approach:

- persons should be aware of and, if possible, avoid areas likely to be infested with disease-bearing ticks,

- persons in tick-infested areas should take personal protective measures, such as wearing of proper clothing, use of repellents and contact acaricides, and frequent inspection for ticks on clothing and body surfaces so that ticks can be detected and removed promptly.

Secondary prevention can be achieved by educating care providers and the public to quickly recognize the signs and symptoms of Lyme disease, and on the need to promptly diagnose and treat the disease should it occur.

References:

1. Falco RC, Fish D. Ticks parasitizing humans in a Lyme disease endemic area of southern New York State. *Am J Epidemiol*. 1988;128:1146-52.

2. Costello CM, Steere AC, Pinkerton RE, Reder HM, Jr. A prospective study of tick bites in an endemic area for Lyme disease. *J Infect Dis*. 1989;159:136-9.

3. Leigner KB. Lyme disease. Letter to the Editor. *N Eng J Med*. 1990;322:474-75.

4. NIH State-of-the-Art Conference: Diagnosis and treatment of Lyme disease. *Clinical Courier*. 1991;9:1-8. ISSN0264-6684.

5. Piesman J, Mather TN, Sinsky RJ, Spielman A. Duration of tick attachment and *Borrelia burgdorferi* transmission. *J Clin Microbiol*. 1987;25:557-8.

6. Piesman J, Maupin GO, Campos EG, Happ CM. Duration of adult female *Ixodes dammini* attachment and transmission of *Borrelia burgdorferi*, with description of a needle aspiration isolation method. *J Infect Dis*. 1991;163:895-7.

7. Steere AC, Bartenhogen NH, Craft JE, et al. The early clinical manifestations of Lyme disease. *Ann Intern Med*. 1983;99:76-82.
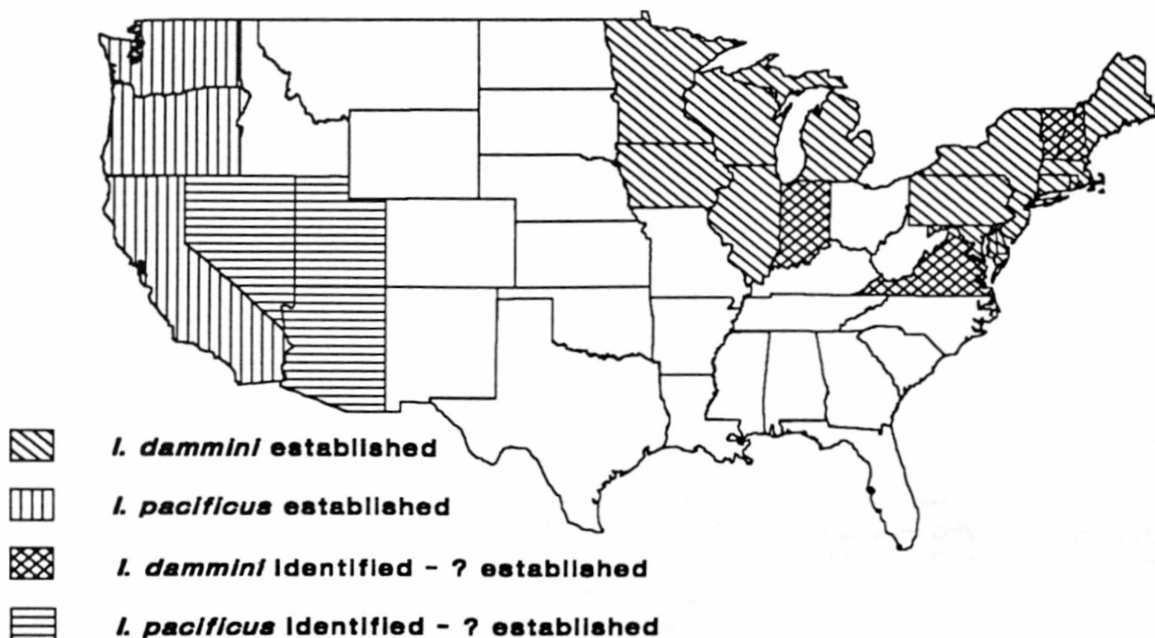
DISTRIBUTION OF PROVEN TICK VECTORS FOR LYME DISEASE - UNITED STATES

A number of ticks and other hematophagous arthropods have been proposed as possible vectors of Lyme disease in the United States. Vector studies to date, however, have failed to identify any vectors other than *I. dammini* and *I. pacificus* as being of any major importance in the transmission cycle. General guidelines for establishing the endemicity of Lyme disease vectors in an area were presented in the last issue of **LDSS** (Vol 2 No. 5). To assess the importance of finding *I. dammini* or *I. pacificus* in an area, it should be determined whether the presence of the ticks is

adventitious or established. If a population is established, what is its geographic range and is it infected with *B. burgdorferi*? Proof of infection of vector ticks requires that *B. burgdorferi* organisms are cultured from the vector and identified by appropriate microbiologic techniques. Microscopic identification of spirochetes in a tick does not establish the tick as a vector of Lyme disease.

The distribution of *I. dammini* and *I. pacificus* in the continental United States by state of report is presented in Figure 1. Neither of these ticks has been reported to be present in Alaska or Hawaii. Data presented to us by county are now being collated and will be sent to State Epidemiologists and other key personnel in the near future for a final evaluation of accuracy and completeness. Although Figure 1 distinguishes adventitious and established populations, it does not show whether these populations are infected with *B. burgdorferi*, or are present in limited foci only. Even in states with long-established populations, the distribution is usually very focal, and large areas of the state may be uninfested. Additional data clarifying these issues are being collected. *I. dammini* collections have recently been made in Virginia, Indiana, New Hampshire and Vermont. In the West, *I. pacificus* has been identified in Nevada, Utah and Arizona. None of the tick populations in these states has yet been shown to be established. In Ohio, three *I. dammini* (1 nymph, 2 adult females) have been collected; single adult specimens of *I. dammini* have been collected in West Virginia and Idaho. The extent to which new geographic records reflect recent territorial expansion of these vectors as opposed to discovery of previously existing established or adventitious populations cannot be determined from data presently available. Negative data (attempted collections which have yielded neither *I. dammini* or *I. pacificus*) are obviously important to the national vector distribution database.
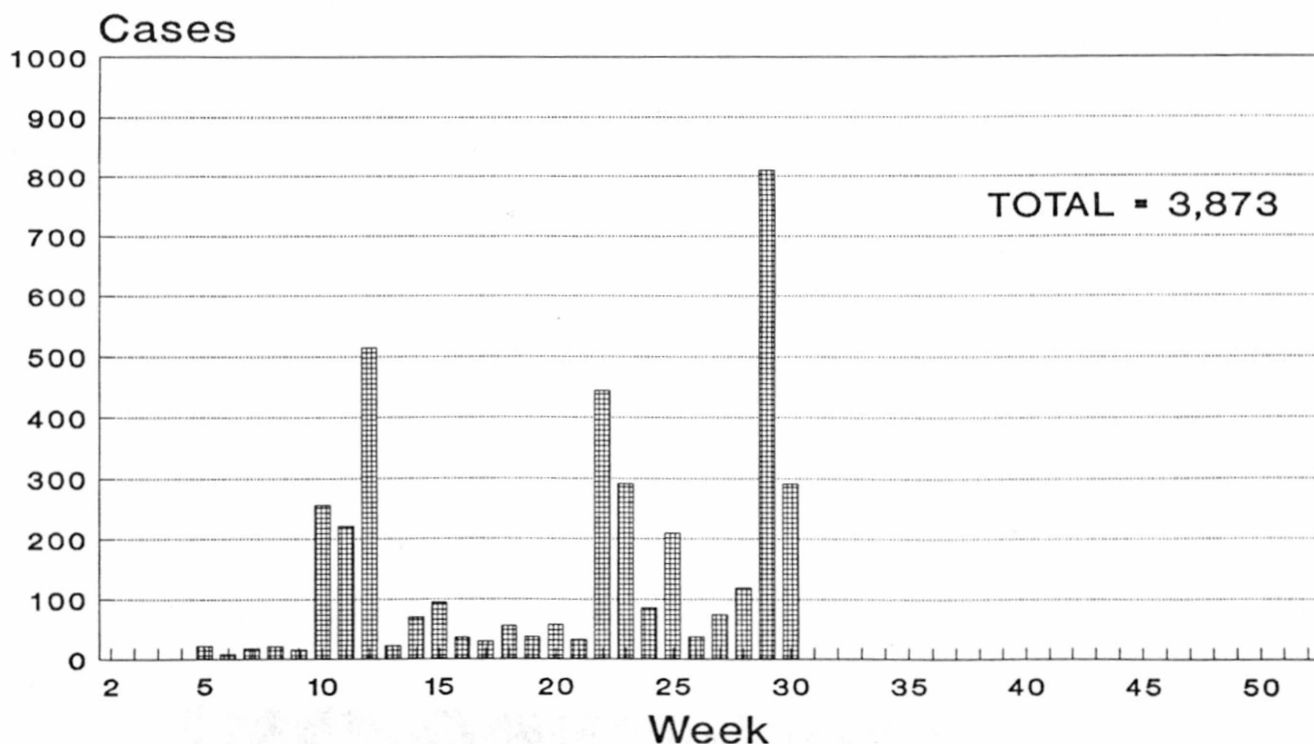
Figure 1.
Distribution of <u>*Ixodes dammini*</u> and <u>*Ixodes pacificus*</u>
by State of record, United States

▨	*I. dammini* established
⦀	*I. pacificus* established
▩	*I. dammini* identified – ? established
▤	*I. pacificus* identified – ? established

REPORTING OF LYME DISEASE CASES IN 1991 BY NETSS

The numbers of Lyme disease cases reported through NETSS in the period January through July are shown in Figure 2. Of the total 3,873 cases reported through Week 30, 2,311 (60%) were reported from the mid-Atlantic region. Upstate New York reported 1,462 cases (38%) of the 1991 national total. In attempting to evaluate temporal trends from these data, it should be noted that numbers cited are by week of report to CDC and not by week of disease onset. Technical electronic transmission problems from at least one state with a high number of cases was delayed until recently, thus inflating the figures from the past month with cases which actually occurred earlier in the summer. At the end of this calendar year we will analyze data presented via NETSS and provide the correct temporal distribution of cases by month of onset as well as other demographic and epidemiologic data.

FIGURE 2
REPORTED LYME DISEASE CASES, U.S., 1991