

## AN EPIDEMIOLOGIC STUDY OF LYME DISEASE IN SOUTHERN SWEDEN

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**Abstract Background.** Lyme disease is the most common vector-borne infection in some temperate regions of the Northern Hemisphere. However, for most areas of endemic disease reliable epidemiologic data are sparse.

**Methods.** Over a one-year period, we conducted a prospective, population-based survey of cases of Lyme disease in southern Sweden. The diagnosis was made on the basis of the presence of erythema migrans at least 5 cm in diameter or characteristic clinical manifestations such as arthritis, neuroborreliosis, and carditis.

**Results.** We identified 1471 patients with Lyme disease, for an overall annual incidence of 69 cases per 100,000 inhabitants. The incidence varied markedly according to geographic region, and there were several areas where disease was widely prevalent. The incidence

varied according to age, with the highest rates among people 5 to 9 and 60 to 74 years of age, but not according to sex. The most frequent clinical manifestation was erythema migrans (seen in 77 percent of all cases), followed by neuroborreliosis (16 percent) and arthritis (7 percent). Carditis was rare. A preceding tick bite was reported by 79 percent of the patients. Bites in the head and neck region were more common among children than among adults and were associated with an increased risk of neuroborreliosis.

**Conclusions.** Lyme disease is very common in southern Sweden, with a relatively high frequency of neurologic complications and arthritis. With the exception of the low incidence of carditis, the pattern of disease we found in Sweden was similar to that reported in the United States. (N Engl J Med 1995;333:1319-24.)

LYME disease, which is transmitted by ticks and caused by the spirochete *Borrelia burgdorferi* (now properly described as *B. burgdorferi sensu lato*, including the subspecies *B. burgdorferi sensu strictu*, *B. afzelii*, and *B. garinii*), is the most common vector-borne infection in temperate areas of the Northern Hemisphere. Our knowledge of the epidemiologic features of borreliosis is limited, and surveys conducted in several countries have been retrospective or limited to selected groups of patients, patients seen by physicians in certain medical specialties, or small geographic areas.<sup>1-17</sup> In Europe, unlike the United States, borreliosis is not a notifiable disease,<sup>18</sup> a fact that may explain the differences in clinical manifestations reported in Europe and in the United States.<sup>19,20</sup>

We conducted prospective, population-based active surveillance of Lyme disease in southern Sweden in order to determine the incidence of the infection and its clinical manifestations and to permit comparison with other areas in Europe and the United States.

## METHODS

### Study Area and Population

The study area, which covered 49,000 km<sup>2</sup> (11 percent of the area of Sweden), consisted of the seven southern counties and had 2,133,068 inhabitants (24 percent of the population) (Fig. 1). Agricultural areas dominate in the southern and western parts of the region, and forests in the northern and eastern parts. An extensive archipelago lies off the east coast. Borreliosis is endemic in the study area; the rates of infection in *Ixodes ricinus* ticks from different sites vary between 10 and 30 percent.<sup>5</sup> The climate during the study period did not

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differ markedly from average values for the past 30 years. The mean temperatures were below 6°C from November through April.

### Study Design

The study was an active, population-based, prospective survey conducted between May 1, 1992, and April 30, 1993. During this period borreliosis was temporarily made a notifiable disease. All general practitioners as well as specialists, residents, and fellows in dermatology, infectious diseases, internal medicine, otorhinolaryngology, pediatrics, rheumatology, and neurology were informed about the study and received educational material about the disease, as well as notification forms. All physicians, the vast majority of whom are employed by the government, were identified through central registers. Reminders about the study and informational leaflets were distributed repeatedly, and the study was widely covered by the media. In addition, all laboratory reports of serologic tests for borrelia (including reports of negative tests) contained a reminder of the study.

The notification form included the patient's unique personal identification number, age, and sex, the date of the tick bite, a checklist of symptoms and signs, the date of onset of symptoms, the date of diagnosis, details of any treatment given, laboratory-test results, and the anatomical and geographic location of the tick bite. In cases with skin manifestations, the anatomical location and the diameter of the lesion were reported. For patients with manifestations of borreliosis other than erythema migrans, physicians were asked to send a copy of the medical records. Laboratory tests, all done in government-run laboratories, were performed when judged necessary on the basis of the clinical assessment. If antibody tests were performed, testing of paired serum samples obtained at least four weeks apart was recommended. All reports were reviewed, and if necessary, additional information was obtained by means of interviews with the reporting physicians.

The study was approved by the research ethics committees of the universities of Lund, Gothenburg, and Linköping.

### Case Definition

Only patients with active disease were included in our analysis. Physicians were therefore requested to report information on all patients who received antibiotic treatment for suspected borreliosis. Diagnosis was based on case definitions that generally corresponded to those used by the Centers for Disease Control and Prevention (CDC) for surveillance purposes.<sup>21</sup> The diagnosis of Lyme disease required clinically diagnosed erythema migrans or one or more clinical manifestations of disease plus serologic confirmation. Erythema migrans was defined as a skin lesion typically beginning as a red macule or

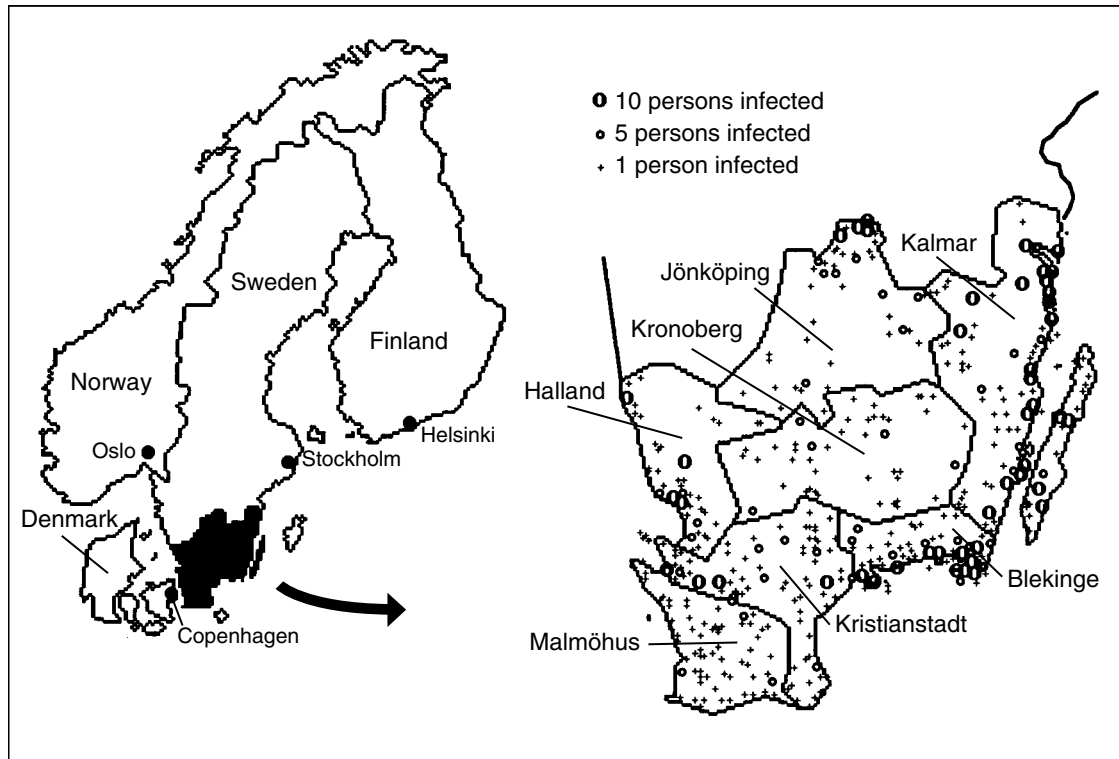


Figure 1. Scandinavia and the Study Area in Southern Sweden.  
The symbols in the right-hand map indicate where patients were probably infected with Lyme disease.

papule and expanding over a period of days or weeks to form a large, round lesion, often with central clearing. To meet the criterion for diagnosis, a solitary lesion had to reach a diameter of at least 5 cm. Annular erythematous lesions occurring within hours of a tick bite did not qualify.

Other clinical manifestations were assessed by one of the investigators. Lyme arthritis was defined as recurrent, brief attacks of visible swelling in one or a few joints, possibly followed by chronic arthritis. Manifestations that were not considered diagnostic included progressive arthritis that was not preceded by brief attacks and chronic, symmetric polyarthritis. Patients with arthralgia, myalgia, and the fibromyalgia syndrome alone were excluded.

Neuroborreliosis was diagnosed in patients presenting with lymphocytic meningitis, cranial neuritis, radiculoneuropathy, or encephalomyelitis. Encephalomyelitis had to be confirmed by the demonstration of higher titers of antibodies against *B. burgdorferi* in cerebrospinal fluid than in serum. Headache, fatigue, paresthesia, or mild neck stiffness alone was not accepted as evidence of neurologic involvement.

Lyme carditis was defined as high-grade (second- or third-degree) atrioventricular conduction defects of acute onset that resolved in days or weeks, sometimes associated with myocarditis. Palpitations, bradycardia, bundle-branch block, and myocarditis as single symptoms were not accepted.

Other skin manifestations, not included in the CDC criteria, included acrodermatitis chronica atrophicans and borrelial lymphocytoma. The criterion for acrodermatitis was the characteristic bluish-red discoloration, often with a doughy infiltration and sometimes progressing to atrophy or sclerodermic changes. Borrelial lymphocytoma was clinically defined by the typical bluish-red tumorlike skin infiltrate and, if a biopsy was performed, by the presence of lymphocytic proliferation in the dermis, subcutis, or both.

#### Serologic Testing

Routine laboratory tests to detect IgG or IgM antibodies against *B. burgdorferi* as a basis for clinical decision making were performed locally with commercially available enzyme-linked immunoassay

(ELISA) kits (kit K416, Dako; antigen, *B. afzelii*; strain DK-1; or test kit 192, Cambridge Biotech; antigen, *B. burgdorferi sensu strictu*; strain B31).<sup>22,23</sup> According to the manufacturers, these kits have a specificity of 98 percent; the sensitivity depends on the duration of the disease.

In this study we required not only a positive result on a routine ELISA, but also verification with a second ELISA before a case was included as Lyme disease. All samples were stored frozen at  $-70^{\circ}\text{C}$  until reanalyzed in duplicate at the Department of Medical Microbiology of the University of Lund with an in-house ELISA. Acute-phase and convalescent-phase serum samples were analyzed simultaneously on the same plate. Titers higher than the 97.5th percentile for normal subjects without a history of borreliosis were considered positive. When the results of the local and central serologic tests were discordant, Western blotting was performed. A preparation from an isolate from a Swedish human-skin biopsy (*B. afzelii*, strain ACA1) was used as the antigen in the ELISA and Western blot tests.<sup>23-25</sup> Western blots were evaluated with the criteria proposed by Dressler et al.<sup>26</sup> Cases with negative Western blots were excluded.

#### Missing Data

To reduce the number of cases that went unreported, all orders for serologic tests for borrelia that were received at the eight local laboratories were reviewed retrospectively. Cases that met the study criteria were included. In addition, all records of cases assigned a code indicating Lyme disease in the *International Classification of Diseases, 9th Revision* during the study period were reviewed at two health centers in the study area.

#### Statistical Analysis

A chi-square test was used to test the significance of differences between groups. To test whether the anatomical location of tick bites influenced the clinical presentation, we used the Mantel-Haenszel method, with control for age group. All P values were two-tailed, and those below 0.05 were considered to indicate statistical significance.

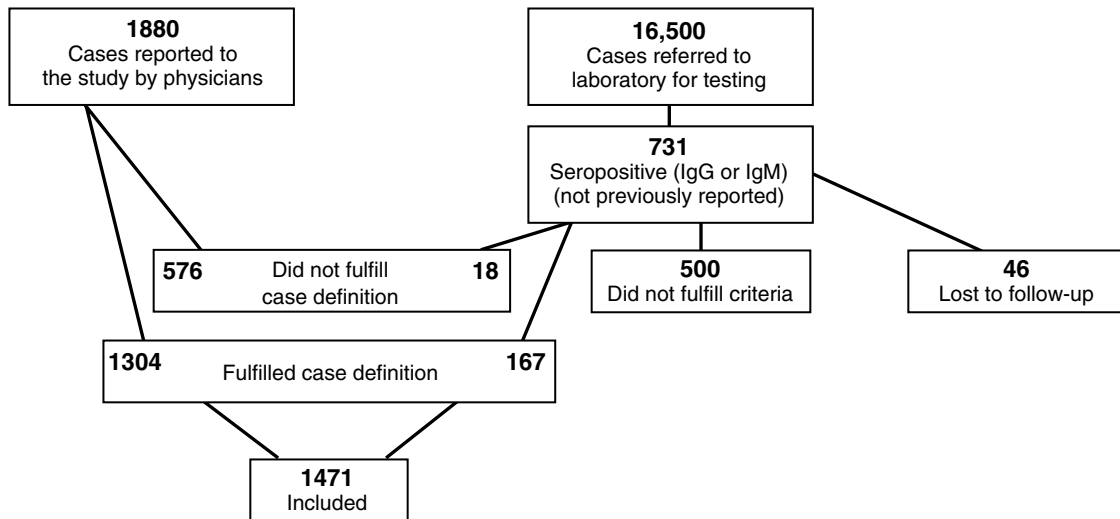


Figure 2. Cases Included in and Excluded from a Survey of Lyme Disease in Southern Sweden.

Calculation of the 95 percent confidence intervals for incidence rates was based on the Poisson distribution.

## RESULTS

A total of 1880 cases of Lyme disease were reported, of which 1304 fulfilled the case definition, and 167 additional cases were found by reviewing the records of 16,500 patients who were referred to a laboratory for serologic testing for borrelia. A total of 1471 patients fulfilled the case definitions (Fig. 2). The main reason for exclusion was that the erythematous lesions did not reach 5 cm in diameter (310 of 576 reported cases excluded, or 54 percent). Of 731 seropositive cases found through laboratory referrals, 500 were excluded because antibiotics were not prescribed. The reason for this was, in most cases, either that the patients had no symptoms or that serologic testing was performed as part of the follow-up of a previously treated patient.

The overall incidence of borreliosis was 69 cases per 100,000 inhabitants per year (95 percent confidence interval, 65 per 100,000 to 72 per 100,000), with considerable variation among the seven counties (range, 26 per 100,000 to 160 per 100,000). The incidence of borreliosis was highest in the eastern parts of the study area. In addition, 48 percent of the patients with borreliosis in the county with the lowest incidence (Malmöhus) reported that they had probably been bitten by a tick while visiting areas with high incidence (Fig. 1). The distribution of cases according to age and sex is shown in Figure 3.

### Clinical Manifestations

The most common manifestation of borreliosis was erythema migrans,

reported in 1139 of the 1471 cases (77 percent); in 26 cases there were multiple erythema lesions. Single manifestations of borreliosis were seen in 1381 cases (94 percent), and 90 patients (6 percent) had more than one manifestation (Table 1).

There were no significant differences in the frequency of the various manifestations among the seven counties or between the sexes. However, there was a difference between children and adults. Children more often had lymphocytoma and neuroborreliosis. Of 232 children ( $\leq 15$  years of age), 66 (28 percent) had neuroborreliosis, and 16 (7 percent) had lymphocytoma, as compared with 169 (14 percent) and 25 (2 percent), respectively, of 1239 adults ( $P < 0.001$  for both comparisons).

Neuroborreliosis, confirmed in 235 cases, was the second most common manifestation of disease. The most frequent neurologic symptom was cranial neuritis, which was reported in 116 cases. A lumbar puncture was performed in 74 of the patients with cranial neuritis, 42 of whom had meningitis (defined as an increased

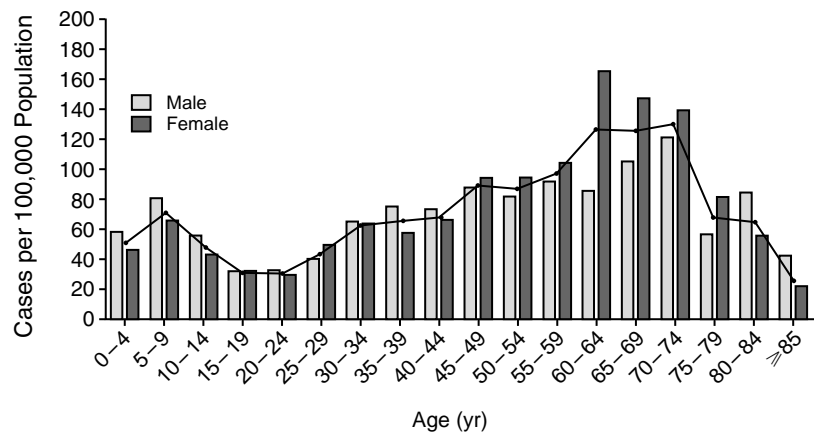


Figure 3. Incidence of Lyme Disease in Southern Sweden According to Age and Sex. The bars show cases in females and males; the line shows incidence according to age.

number of lymphocytes). Meningitis without cranial neuritis was reported in 53 additional cases. Radiculoneuropathy was diagnosed in 40 cases, and encephalomyelitis in 5. Among the 116 patients with cranial neuritis, the facial nerve was affected in 97, and more than one cranial nerve was affected in 9.

#### Tick Bites

Of the 1471 patients with Lyme disease, 1157 (79 percent) were aware of a tick bite preceding the onset of symptoms. The geographic area where the tick bites had occurred could be specified by 1091 of the patients, and the anatomical location by 1122. The geographic distribution of probably infective tick bites is plotted in Figure 1. Sixteen patients received tick bites in other countries, and 72 received bites in counties in Sweden outside the study area.

The anatomical distribution of the tick bites differed significantly between adults and children ( $P < 0.001$ ) (Fig. 4). The most common site in children was the ears, where 20 percent of their bites occurred. Altogether, 49 percent of the bites in children were located in the head and neck region, as compared with 2 percent among the adults. Adults were most commonly bitten in the popliteal fossa (10 percent of the bites). The lower limbs were the site of 62 percent of tick bites in adults and 18 percent in children. Only minor differences between the sexes were found: women were more commonly bitten on the breasts, and men in the genital region.

Of 91 people who were aware of a tick bite in the area of the head and neck, 18 (20 percent) had neurologic manifestations of Lyme disease, whereas only 68 of 1031 (7 percent) who had bites at other locations had neurologic manifestations ( $P = 0.005$ ).

#### Seasonal Distribution of Cases

Lyme disease was diagnosed during the whole year, but few cases were found from January through April. Tick bites were most frequent in July. The highest number of cases with erythema migrans occurred in August, whereas other manifestations peaked in September.

#### Laboratory Results

Blood samples for serologic testing were obtained in 649 of 1139 cases characterized by erythema migrans when the patients were first seen by the physicians. Of these, 241 (37 percent) were positive. Among the 408 patients with negative or borderline values in the acute-phase sample, convalescent-phase samples were obtained at least four weeks later from 202. Seroconversion was documented in 62 (31 percent).

Of 754 patients with reported manifestations other

Table 1. Distribution of Manifestations of Lyme Disease in 1471 Patients in Southern Sweden.\*

| MANIFESTATION     | MANIFESTATION       |                       |           |                |              |          |
|-------------------|---------------------|-----------------------|-----------|----------------|--------------|----------|
|                   | ERYTHEMA<br>MIGRANS | NEUROBOR-<br>RELIOSIS | ARTHRITIS | ACRODERMATITIS | LYMPHOCYTOMA | CARDITIS |
| Erythema migrans  | <b>1075</b>         | 40                    | 10        | 1              | 9            | 1        |
| Neuroborreliosis  | 40                  | <b>176</b>            | 8         | 2              | 3            | 1        |
| Arthritis         | 10                  | 8                     | <b>65</b> | 8              | 1            | 0        |
| Acrodermatitis    | 1                   | 2                     | 8         | <b>34</b>      | 0            | 0        |
| Lymphocytoma      | 9                   | 3                     | 1         | 0              | <b>26</b>    | 0        |
| Carditis          | 1                   | 1                     | 0         | 0              | 0            | <b>5</b> |
| ≥3 Manifestations | 3                   | 5                     | 6         | 2              | 2            | 0        |
| Total no. (%)     | 1139 (77)           | 235 (16)              | 98 (7)    | 47 (3)         | 41 (3)       | 7 (<1)   |

\*The numbers of cases with only one manifestation of disease are indicated in boldface type. Six patients had three or more manifestations, and their data are presented on a separate line.

than erythema migrans, 553 had positive serologic tests for borrelia; 85 of these had discordant results on tests at the local and central laboratories. Twenty-seven of these 85 patients had negative Western blot tests and were therefore classified as not having Lyme disease.

A lumbar puncture was performed in 284 of 369 patients with neurologic symptoms. Increased numbers of lymphocytes were found in cerebrospinal fluid from 116 of these patients, and intrathecal production of antibodies against *B. burgdorferi* was increased in samples from 69 patients. Twenty-one of the patients with increased numbers of lymphocytes had no detectable antibodies to *B. burgdorferi* in cerebrospinal fluid or in serum and were therefore classified as not having Lyme disease.

#### DISCUSSION

In this prospective, population-based study of Lyme disease in southern Sweden, we found an annual incidence of 69 cases per 100,000 inhabitants (range among counties with low and high levels of endemic disease, 26 per 100,000 to 160 per 100,000). In studies of selected population groups, the reported incidence of borreliosis has generally been lower than that in our study. In a study in Lower Saxony, Germany, the estimated annual incidence was 22 per 100,000 inhabitants.<sup>27</sup> In Connecticut, the incidence was 41 per 100,000 in 1993.<sup>28</sup>

Lyme borreliosis is endemic in areas throughout North America, Europe, and northern Asia.<sup>19,29-31</sup> The geographic distribution of the disease and the regions of endemic disease have often been defined indirectly, on the basis of seroepidemiologic studies in small geographic areas or studies of the vector.<sup>1-6</sup> Borreliosis is not a notifiable disease in any European country. In the United States, surveillance was initiated in 1982 and was fully implemented after the adoption of a uniform national case definition in 1991.<sup>21</sup> In 1993, there were 8185 reported cases of Lyme disease in the United States, corresponding to an overall incidence of 3.3 per 100,000 inhabitants<sup>28</sup>; the incidence varies markedly among states, counties, and areas within counties — as it did in our study. The highest reported incidence was 1198 per 100,000 in Nantucket, Massachusetts, in 1994.<sup>32</sup> We found similar, or even higher, rates

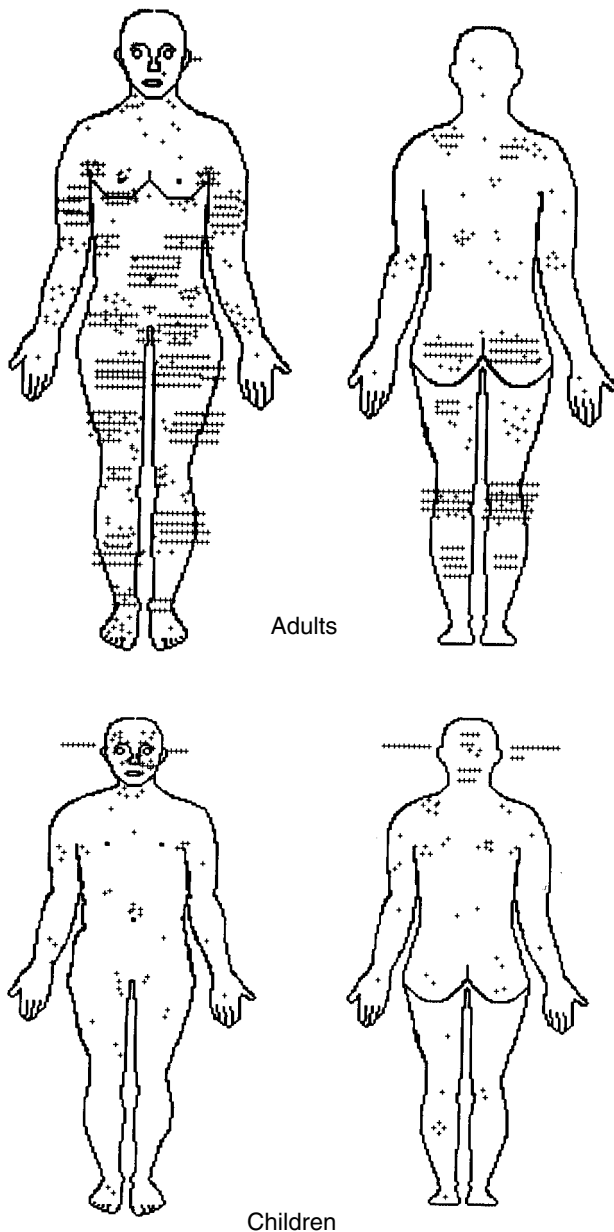


Figure 4. Anatomical Location of Tick Bites in 1122 Patients with Lyme Disease.

In these schematic drawings, each cross indicates a tick bite. Those outside the figures show the level of bites on the body.

in areas with high levels of endemic disease. As compared with the overall incidence in the United States, the figures in our study are high, and Sweden is probably one of the countries with the highest incidence of borreliosis.

The 1471 cases we identified probably represent an underestimate of the true incidence, since our case definitions were stricter than those published by the CDC. Active surveillance increases the number of reported cases, but some are nevertheless likely to remain unidentified. A review of the records of two health centers in the region showed that 10 to 15 percent of suspected

cases of borreliosis in patients who received antibiotics were not reported. In addition, borreliosis is a self-limiting infection in most patients. The degree of awareness of the disease among the population was high, as indicated by the fact that 79 percent of the patients could remember a tick bite. This high degree of awareness among patients may also have influenced others to see a doctor before the erythema had reached a diameter of 5 cm; as a result, these patients would have been classified for purposes of the study as having Lyme disease. Some of the excluded patients with known exposure to ticks, neurologic symptoms, and increased numbers of lymphocytes in cerebrospinal fluid but with no detectable antibody to *B. burgdorferi* may have had neuroborreliosis, representing "early invasion."<sup>33,34</sup>

Previous clinical studies have focused mainly on groups at high risk for tick bites, such as forest workers, participants in orienteering, and military recruits, or were restricted to medical specialties such as dermatology, rheumatology, and neurology, with patients possibly selected for specific symptoms.<sup>7-17</sup> These and other studies have led to discussions of the different clinical presentations of borreliosis in various geographic regions and of differences in pathogenicity among the strains of *B. burgdorferi* (*B. burgdorferi sensu lato*).

We found a higher proportion of erythema migrans as the only symptom of borreliosis than has previously been reported. This was probably due both to the fact that 73 percent of the patients were identified by general practitioners and to the high degree of awareness in the general population. Except for acrodermatitis, lymphocytoma, and Lyme carditis, there were no major differences in the frequency of manifestations observed in our study and in surveillance data from the United States.<sup>35</sup> Information on acrodermatitis and lymphocytoma is not included in the data collected by the CDC, so comparisons are not possible. Carditis seems less frequent in this study than in the United States, perhaps because electrocardiograms are not routinely obtained in patients with borreliosis in Sweden.<sup>36,37</sup> Arthritis occurred with a frequency similar to that in the United States. This contradicts the findings of others, whose results have suggested that the strains of *B. burgdorferi* in Europe are less likely to produce arthritis than those in the United States, but is in agreement with more recent European reports.<sup>24,38,39</sup> So far, only strains of *B. afzelii* have been identified in the study area (unpublished data).

We found that the anatomical location of the tick bite was related to the clinical manifestation of the disease and that this location varied with age. Significantly more neurologic manifestations were seen among patients bitten in the head and neck area than among those with tick bites in other parts of the body. This difference may explain the higher frequency of neuroborreliosis among children than among adults. It remains unclear whether this association is causal or not. If it is causal, neurologic manifestations may be caused by a

direct invasion of the nervous tissues through blood vessels or neurogenic spread.

The predictive value of serologic testing in patients with erythema migrans as a single manifestation is low.<sup>29</sup> In this study, only 37 percent of clinically diagnosed cases with erythema migrans were positive on ELISA when tested before treatment. The rate of seropositivity increased with the duration of symptoms before diagnosis, and even after treatment the proportion of positive cases increased to 57 percent when convalescent-phase serum samples were tested. Similar figures have been reported by others.<sup>40,41</sup>

In conclusion, we found a very high incidence of borreliosis in southern Sweden. Most of the patients had benign symptoms, of which erythema migrans was the most frequent. In contrast to previous reports from Europe, the clinical presentation of borreliosis in this study was similar to that reported in the United States.

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