# EPIDEMIOLOGY OF LYME BORRELIOSIS

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## SUMMARY

The epidemiological aspects of Lyme borreliosis in humans are reviewed. The up-to-date classification of *Borrelia burgdorferi* based on assessment by monoclonal antibodies and on 16SrRNA sequence analysis are reported. The route of infection as well as the mode of involvement of target organs are surveyed. Distribution in various geographical regions and prevalence are described. The problems concerning the prophylaxis are also mentioned.



KEY WORDS:

*Lyme borreliosis, epidemiology, identification of Borreliae burgdorferi, geographical distribution, prevalence*


## INTRODUCTION

The aim of an epidemiological consideration of Lyme borreliosis is the description of the frequency of the disease with respect to its causative agent. It deals with questions concerning the sources of the infection, route of infection and the target of it. All living beings wherein the causative agent exists and multiplies is designated as the infection source. The infection route concerns the possibilities of the agent to spread from the source to the next susceptible human host, which represents the target of infection. Epidemiological considerations further address the clinical characteristics of the disorder, age distribution, manifestation rate, infectivity, susceptibility, incidence, geographical and seasonal distribution, diagnostic measures, and preventive measures.

## SOURCE OF INFECTION

**Agents:** The causative agent of Lyme borreliosis, *Borrelia burgdorferi*, has been discovered in, and isolated from, the American deer tick *Ixodes dammini* in the early eighties (Burgdorfer et al. 1982). Shortly thereafter it was recovered from patients with Lyme disease. It was recognized as a new species within the genus *Borrelia* and named *Borrelia burgdorferi* (Johnson et al. 1984). European borrelia isolates show certain differences with isolates from the United

States in molecular weights of major proteins and in reactivity with monoclonal antibodies raised against the outer surface proteins of *Borrelia burgdorferi* type strain (Barbour et al. 1984). A certain amount of heterogeneity of European isolates has been described (Stanek et al. 1985; Wilske et al 1985; Wilske et al. 1988). A typing system based on the reactivity with monoclonal antibodies (H5332 and H3TS) to the outer surface protein A (OspA) has been suggested by A G Barbour (1986). It allows to differentiate between 3 main groups. Interestingly, North American isolates belong almost exclusively to group I whereas European isolates are belonging to groups I through III. Studies from Austria suggested relationship of certain types of *Borrelia burgdorferi* to certain geographic regions (Stanek et al. 1990). Serogroup I was prevalent in the western parts of Europe and groups II and III were prevalent in Central and Eastern Europe (Germany, Austria, Czechoslovakia). More recently, a serotyping system based on the reactivity of OspA with 8 monoclonal antibodies (H3TS, H5332, L32 1C8, L32 1F11, L32 1F7, L32 1G3, L32 1G3, LA26) has been proposed (Wilske et al. 1991 and 1993); and seven serotypes have been defined. Although it is unlikely that every tick or animal isolate is a pathogenic strain there is presently no technique to differentiate between pathogenic and nonpathogenic strains. However, according to the findings of Wilske et al. (1988, 1991 and 1993) serotype 2 is prevalent among European isolates from the skin, whereas European isolates from ticks and human cerebrospinal fluid are more heterogeneous. Studies on the differences between the genoms of North American and European isolates revealed significant differences and lead to the suggestion of 3 genospecies (Baranton et al. 1992), *B. burgdorferi sensu stricto, B. garinii,* and *B.VS461* (*B. afzelii*). The correlation between the OspA serotyping system with the 3 described genospecies was studied on 136 B. burgdorferi isolates based on serotyping and 16SrRNA sequence analysis. (Wilske et al. 1993). The genospecies *B. burgdorferi sensu stricto* corresponds with serotype 1, *B. afzelii* (VS461) with serotype 2, and *B. garinii* with serotypes 3-7. *B. afzelii* (serotype 2) was most prevalent among European skin isolates (79%). The *B. garinii* strains (serotypes 3-7) were isolated from a variety of sources. But serotypes 4 and 5 were only isolated from human specimens and in a high proportion from the cerebrospinal fluid of patients with neuroborreliosis. These observations suggest different pathogenic potentials and organotropisms of certain OspA serotypes.

**Reservoirs:** Feral rodents and other wildlife (Krampitz and Bark 1989) are considered reservoirs. Different to North American findings roe deer plays obviously no important role as borrelia reservoir in Europe and hares may act as reservoirs in ecosystems without rodents (Jaenson and Talleklint 1992, Talleklint and Jaenson 1993). The woodmouse *Apodemus sylvaticus* and other wild mice have been recognized as a reservoir of tick transmitted spirochetes in several European countries (DeBoer et al. 1993). The capacity of micromammals seems to vary with the season as is suggested by results of studies from Sweden (Talleklint et al. 1993). Again, results of recent findings in Sweden suggest that seabirds play an important part in the maintenance of *B. burgdorferi sensu lato* and that mammals may not be a prerequisite for its life cycle (Olsen et al. 1993).

## ROUTE OF INFECTION

**Vectors:** Hard ticks, particularly these of the "Ixodes ricinus" complex, and other hematophagous arthropodes, such as tabanides and fleas are considered vectors of *Borrelia burgdorferi.* Involvement of soft (argasid) ticks in maintaining and distributing the Lyme disease spirochete is still a matter of conjecture even though the pigeon tick *Argas persicus* in Italy (Stanek and Simeoni 1989) and *Ornithodorus coriaceus* in California were found infected with this spirochete. Although the latter were identified as vectors in single cases, there is little known about their interactions with *Borrelia burgdorferi.*

*Ixodes ricinus* is the most common species among European ixodid ticks. It occurs in an area covering Scandinavia, the British Isles, Central Europe, France, Spain, Portugal, Italy, the Balkans, the Baltic States, Bela Russia, Ukraine, the European part of Russia, northern Iran and northern Africa. Within the living ground of these ticks there are distinct geographic regions wherein ixodid ticks may additionally be infected with the tick-borne encephalitis virus. Also infection with rickettsiae or protozoon agents may be possible. To the east, another Ixodes species, *I. persulcatus*, is abundant and appears to be the principal vector of *Borrelia burgdorferi* (Korenberg et al. 1993).

Compared with the tick-borne encephalitis (TBE) virus the prevalence of ticks infected with *Borrelia burgdorferi* is very high. In areas of Europe endemic for TBE, every thousandth tick carries the virus whereas every third tick on the average is infected with borrelia. The prevalence of ticks infected with

*Borrelia burgdorferi* has been studied in many countries including Austria, Czechoslovakia, Russia, Southern Germany, Sweden and Switzerland (Aeschlimann et al. 1986, Bergstrom et al. 1990, Burgdorfer et al. 1983, Kmety et al. 1986, Korenberg et al 1993, Radda et al. 1986, Wilske et al. 1987). According to these studies the infection rate of ticks is 20.5 % on the average (range 8-55 %). Transmission of Borrelia from ticks to humans is of the cyclic type whereas tabanides or other hematophageous insects are said to transmit the spirochetes acyclically i.e. they contaminate their mouth parts through feeding on a parasitimic host and as a result of interrupted feeding may transmit the spirochete to another host.

**Contact infection:** Transmission of *Borrelia burgdorferi* by contact infection has been described in the American literature in animals (Burgess 1987) and also here in Europe where an erythema migrans was said to have developed from a scratch wound which was contaminated with manure days before (Rockstroh et al. 1989). Examination of the manure by darkfield microscopy, silver stain and use of monoclonal antibodies to the Lyme disease agent identified it. This report suggests that *Borrelia burgdorferi* can be transmitted by contact infection and can live outside of an animal host.

There is no evidence of transmission of *Borrelia burgdorferi* by sexual contact.

## TARGET OF INFECTION

**Clinical manifestations:** Lyme borreliosis of humans has initially been described as a systemic infection that could be divided in three stages (Steere et al. 1986). A recently modified concept (Steere 1989) distinguishes between localized, disseminated and chronic manifestations. The most frequent manifestation is erythema chronicum migrans (ECM). It migrates centrifugally from a red macula or papula on the site of the tick bite. It may extend over large skin areas and sometimes appear with multiple lesions on other skin areas. In untreated individuals ECM may extend or persist for many weeks. Lesions smaller than 5 cm in diameter may not be diagnostic. Lesions may be accompanied by local itching or burning, malaise, fatigue, fever, headache, myalgia, migratory arthralgia, or lymphoadenopathy. These symptoms may precede the skin lesions or be the only manifestations of early disease in a very small number of cases. Within weeks to months after the onset of infection (tick bite with or without ECM) neurologic signs and symptoms may develop, reflecting aseptic meningitis, meningo-polyradiculoneuritis, cranial nerve pareses (mostly N. facialis), encephalomyelitis, peripheral neuropathies (in about 50% associated with acrodermatitis chronica atrophicans; Kristoferitsch et al. 1988), or nodular myositis (Schmutzhard et al. 1986).

Cardiac symptoms may develop within one week after onset of ECM. They are usually of short duration and may be based on atrioventricular conduction disorders or acute myopericarditis (Van der Linde et al. 1990, Van der Linde and Ballmer 1993).

Lyme arthritis may begin weeks to years after the initial infection (mean 6 months) with swelling and pain in the large joints and may recur over several years.

Acrodermatitis chronica atrophicans is most frequently seen in Central Europe. Only single cases were reported from North America. This chronic skin disorder is characterized by atrophy of all skin layers, discoloration of skin and pseudophlebectasy (Aberer et al. 1991). Some chronic sklerotic skin disorders as circumscribed scleroderma may also be due to Borrelia infection (Aberer et al. 1991).

Chronic cardiac manifestation like chronic dilated cardiomyopathy has been discussed to be related to Lyme disease (Stanek et al. 1990, Stanek et al. 1991).

**Sex ratio:** In adults, skin manifestations are more numerous in female patients; this is especially true for acrodermatitis chronica atrophicans (Pirilä 1951, Asbrink et al. 1984). Neurological manifestations of Lyme borreliosis are slightly more frequently seen in male patients (Müller et al. 1993).

**Age distribution:** The chronic skin disease, acrodermatitis chronica atrophicans, occurs mainly in elderly women (Asbrink et al. 1984, Stanek et al. 1985, Schmidt et al. 1986, Wilske et al. 1987). All other manifestations as e.g. erythema migrans or meningopolyneuritis reveal a more or less even age distribution. In children, however, meningitis and cranial nerve palsy are more frequently observed than meningoradiculoneuritis (Pfister et al. 1986, Christen et al. 1989, Millner et al. 1989, Pleterski-Rigler 1989).

**Seasonal distribution:** A clear seasonal dependence is noticed in patients with erythema migrans in Austria and Slovenia, with a peak constantly in July (Figure 1). The same seasonal incidence of erythema migrans was also observed in Germany (Wilske et al. 1987). In Figure 2 the time interval is shown which may gap between an arthropode bite, onset

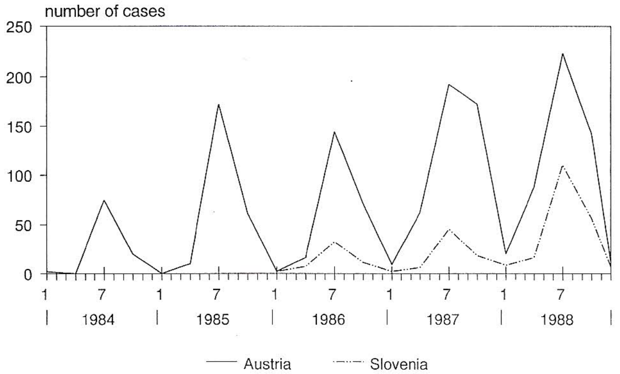


*Figure 1:*
*Seasonal distribution of erythema migrans. Cases were registered at the Hygiene Institute of the University of Vienna, Austria, during 1984 to 1988, and at the Clinic for Infectious Diseases in Ljubljana, Slovenia, during 1986 to 1988.*

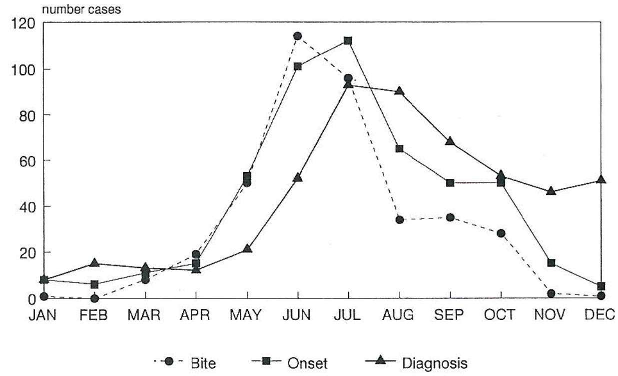


*Figure 2:*
*Time intervals between arthropode bite, real onset of erythema migrans and its exact clinical diagnosis (522 cases). Data were obtained at the Clinic for Infectious Diseases in Ljubljana, Slovenia, in 1988.*

of erythema migrans, and exact clinical diagnosis. Data were obtained in Slovenia. Thus, erythema migrans will come to diagnosis throughout the year but most frequently in early summer and autumn. These data may serve as an example for the situation throughout most of Europe. Some authors, however, have shown that the onset of erythema migrans may differ to some extent. Weber and Neubert (1986) observed a more evenly distributed onset of erythema migrans between May and October.

A peak of neurological cases was found in August in the years 1984-1986, in the southern parts of Germany, in Austria and in Denmark (Stanek et al. 1986, Hansen and Lebech 1992). For late manifestations, i.e. acrodermatitis and arthritis, no seasonal distribution has been observed.

**Incubation period:** The incubation period, a time period from the transmission of the infectious agent by an arthropode bite to the onset of clinical manifestations, was studied in 169 Lyme borreliosis cases in Bavaria (Wilske et al. 1987). In 80 % of the various manifestations, erythema migrans (n=51), neurological disorders (n=98), and arthritis (n=20) revealed an incubation period of 5-29 days, 20-59 days, and 2-8 months, respectively.

**Risk groups:** Several studies (Münchhoff et al. 1986; Pejcoch et al. 1989; Guy et al. 1989) are available on risk groups as, e.g., forestry workers who are regularly exposed to tick bites. These investigations claim that none of one of the forestry workers had ever been ill with Lyme Borreliosis. However, seropositive persons were found in 14 to 48 %. Whether such antibodies are nonspecific or represent a response to a latent infection is a matter of speculation.

To establish an index of manifestation by studying persons who are exposed to vectors of borreliae, a prospective study was conducted with Austrian army recruits who were on outside duties for three months. Recruits were instructed to show each tick bite to the military physician. A first blood sample was then taken, and a second blood sample 6 weeks later when the person was also examined clinically. An erythema migrans was diagnosed in 4% and seroconversion was observed in 22% (Schmutzhard et al. 1988). A similar study was performed in Southwest Germany in a children's holiday camp (Paul et al. 1986). The results were quite similar. A further risk group is constituated by crosscountry hikers (orienteerers) of Switzerland. A study of this subpopulation revealed that 77% gave a history of tick-bites, 20% elevated antibodies to *Borrelia burgdorferi*, and 3.8% showed a seroconversion within 2 years but only individual cases developed clinical manifestations of Lyme borreliosis (Fahrer et al.

1988).

How difficult it is to obtain information on the incidence of Lyme borreliosis by serological methods even in a relevant study group show the following examples. Smith et al. (1988) in the United States, studied outdoor workers and people who spent leisure outdoors and found that they were 2 times and 2.5 times, respectively, more likely to be seropositive than those who did not. In less than 50% of the seropositives, about 3% of all persons investigated, a history of Lyme borreliosis was recorded. Gern et al. (1989) conducted a study on about 500 persons from the Swiss plateau, an area of Switzerland which is known to be heavily infested with *Ixodes ricinus* ticks of which about 20% were found infected with *Borrelia burgdorferi*. Screening of sera from individuals aged 14 to 103 years who never had symptoms of Lyme borreliosis, revealed seropositivity in 32% by IFA and 26.6% by ELISA.

Risk groups reflect the problems that exist with seroprevalence and serodiagnosis of Lyme borreliosis. Data on seroprevalence rank between 3 to more than 40% in Europe. In Switzerland, seropositivity of the healthy population has been reported to be 10% on the average. Satz et al. (1988), however, have shown, that about 40% of the population near the city of Berne (Berner Seeland) is seropositive.

In contrast to the high prevalence of antibodies to *Borrelia burgdorferi* in the risk groups, the seroprevalence of TBE infection is comparably low. Of 242 forestry workers of Bavaria antibodies to *Borrelia burgdorferi* and the TBE virus were found in 16.5 and 2.5 %, respectively (Wilske et al. 1985).

However, it should be considered that the differences between seroprevalence values reported by different investigators may also reflect differences of cut off levels for the seropositive results.

**Incidence:** Based on data from Central Europe (personal communications) the overall incidence is about 300 cases per 100,000 inhabitants per year. About 90% of these persons suffer solely from ECM. The remaining 10% account for neurological cases and all the other manifestations.

**Geographical distribution of Lyme borreliosis:** Lyme borreliosis is an endemic disease. Early in the study of Lyme borreliosis it could be shown that it occurs everywhere where ixodid ticks are living. From Europe we have reports about the widespread distribution of today proven features of Lyme borreliosis that date back to the sixties and early seventies (Müller and Schaltenbrand 1973). Interestingly, the conditions erythema migrans, lymphocytoma, acrodermatitis chronica atrophicans (ACA) and meningoradiculoneuritis were considered as arbovirus infections. Although the etiology was unknown, researchers were aware of the widespread distribution of some of the disorders, e.g., ACA and related neuropathies (Hauser 1955, Danda 1963, Hopf 1966). Danda (1963) obtained information about the frequency of ACA from all parts of the world by means of a questionnaire. He could show, that Central and Eastern Europe are the locations where ACA is most frequently diagnosed and, interestingly, with increasing frequency during the years 1945 to 1958. The highest prevalence of ACA cases was reported from Czechoslovakia and Finland (Pirilä 1951). These data support in part what was later on described by Hopf and Stroux (1968). These authors elaborated, that there is a clustering of cases of acrodermatitis in Central Europe. The chronic skin disorder was seen frequently in Germany, Czechoslovakia, Austria and Hungary. Less frequently, cases of acrodermatitis were observed in Scandinavia, Poland, Switzerland, Yugoslavia and in certain areas of European Russia. These findings coincide with the current knowledge. ACA and associated peripheral neuropathies (Kristoferitsch 1989) are known in Europe and in Eurasia, but information about ACA from North America is rare. There is just one report of a patient with ACA from California (Lave et al. 1986).

By 1985 (Stanek et al. 1986) and 1987 (Stanek et al. 1989), it became evident that Lyme borreliosis is a health problem of the whole Northern hemisphere. Reports from Austria (Stanek et al 1986), Belgium (Bigaignon et al. 1989), Czechoslovakia (Kmety and Rehacek 1986; Strnad et al 1989), Denmark (Hansen et al. 1986), France (Dournon and Assous 1986), Germany (Schmidt et al. 1986; Wilske et al. 1987), Hungary (Lakos 1986), Italy (Trevisan et al. 1986; Cimmino et al. 1989), Luxemburg (Bigaignon et al. 1989), The Netherlands (Houwerzijl et al. 1984; van der Linde et al. 1990), Slovenia (Strle et al. 1989), Sweden (Lanner et al. 1989), Switzerland (Aeschlimann et al. 1986), displayed that Lyme borreliosis occurs in all parts of these countries. Reports on erythema migrans from Finland date back to the early fifties. The disorder has been known there since decades (Pirilä 1951; Putkonen et al. 1962, Wahlberg et al. 1993).

A Swiss study showed that the risk of becoming infested by ticks is limited by an altitude of approximately 1,000 to 1,200 m above sea level where primary tick vector *Ixodes ricinus* no longer exists (Aeschlimann et al. 1986). Single reports of

Lyme borreliosis cases have been published from Great Britain, Norway and the USSR. First British cases of erythema migrans were reported from the Southern part of England (Muhlemann and Wright 1987). Studies from Russia describe the enormous extension of infected ticks from the European parts of Russia over the Asian parts to the Pacific coast (Dekonenko et al. 1988, Korenberg et al. 1993). The disease has also been observed in Japan (Kawabata et al. 1987), and well- documented cases were also reported from the Hailin County in the area of Beijing, China (Chengxu et al. 1988). Seroprevalence studies undertaken in Africa suggest that Lyme Borreliosis may also be present in regions of central and southern Africa (Stanek et al. 1989).

In the United States, Lyme borreliosis was recognized in 41 states by 1987 (MMWR 1989). First reports of erythema migrans and neurological manifestations of Lyme borreliosis exist also from Canada (Lycka 1986; Doby et al. 1986). Thus, Lyme borreliosis is distributed over the whole Northern hemisphere.

**Prevalence of Lyme borreliosis:** Since the introduction of commercial tests in the serodiagnosis of Lyme borreliosis, it is very difficult to obtain relevant figures of cases of Lyme borreliosis in a given country. Moreover, there are no reporting systems because widely accepted case definitions are still not available.

The number of cases reported by serodiagnostic laboratories has increased constantly. Interestingly, the number of the more prominent clinical manifestations i.e. erythema migrans, neuroborreliosis, acrodermatitis chronica atrophicans and arthritis varied. In 1984, for example, 341 cases were identified in Vienna, Austria. Erythema migrans was seen most frequently. Meningopolyneuritis and arthritis cases ranked second and third; there were just a few cases of acrodermatitis. In 1985, 1,303 cases were registered. This reveals a fourfold increase. Now, *Borrelia burgdorferi* infections of the nervous system were the most frequently registered condition and erythema migrans ranked second.

There are similar observations in other laboratories of Europe as, e.g., in Munich, Budapest, Brussels, and Stockholm. Thus, the distribution frequency recorded by serodiagnostic laboratories does not reflect the true distribution of manifestations of Lyme borreliosis. It is evident from clinical observations, however, that erythema migrans is the most frequent disorder of Lyme borreliosis. It is, however, serologically not identifiable since 40% to more than 60% of cases are seronegative. Erythema migrans cases rank first when a laboratory has recently started to test samples and get response from the physicians who were informed about the typical skin lesion. Later on the clinically clearly identifiable lesion, erythema migrans, will no longer be controlled serologically. Increase of Lyme borreliosis cases e.g. was observed during the time-period of 5 years in Vienna and Ljubljana. The number of registered cases increased from two (Vienna) to about one hundredfold (Ljubljana) during these years. The exponential increase displays an artefact due to increased awareness of doctors and patients in their recognition of Lyme borreliosis.

At the Hygiene Institute of the University of Vienna, Austria, 4,000 to 5,000 cases of Lyme borreliosis have been registered every year since 1988. Based on these data, the incidence rate per 100,000 inhabitants per year from 3 different parts of Europe, averages 0.05%. This, however, does not reflect the true incidence because a large number of Lyme borreliosis cases go unrecognized. It is safe to speculate, therefore, that the incidence of Lyme borreliosis for the total population of Central Europe is about 0.1 to 0.2% per year (several thousand cases).

**Prophylaxis:** Lyme borreliosis is predominantly a self-limiting disorder. Follow-up studies on treated or untreated persons who suffered from early localized or disseminated manifestations showed that there were no chronic or progressive changes (Würzburg, Plöver et al. 1993). Comparison of the recovery based on a rating score of patients suffering from meningopolyneuritis and with and without treatment showed no differences when examined 6 months after onset of disease (Kristoferitsch et al. 1986). However, results of long-term studies undertaken on an island that is intensly infested with ticks show that there are sequelae years after initial infection which are very likely due to Lyme borreliosis (Wahlberg et al. 1993). Consideration about prompt "treatment" of tick-bites were made but withdrawn. General immunization was desired for populations in those locations.

There is ongoing intense research on vaccine development for Lyme borreliosis. Currently, preliminary data from early experiments suggest some efficacy of certain vaccine preparations. Phase one trials could demonstrate an immune response to the vaccine, which also appeared to meet the demands of safety. The protective efficacy of the vaccine candidates has not been proven yet.

## CONCLUSION

In Europa and in other parts of the world, Lyme borreliosis is recognized increasingly by physicians and serodiagnostic laboratories. However, it is currently difficult to present conclusive epidemiologic data. There are no widely accepted case definitions for the numerous clinical features due to or supposed to be linked to infection with *Borrelia burgdorferi*. Clinical diagnosis of suspected cases of Lyme borreliosis requires confirmation by the demonstration of the etiologic agent and the recognition of its causative role in the respective disorder.

The specificity of serological tests for Lyme borreliosis is impaired by several phenomena including cross-reacting antibodies (Bruckbauer et al. 1992). Interpretation of serological test results may lead to the clinical diagnosis of Lyme borreliosis and in consequence to antibiotic treatment. Complications in order to treat suspected disseminated Lyme disease may be severe, as recently reported in MMWR (1993).

No reliable data of Lyme borreliosis prevalence can be offered so far. This is partly due to incomplete reporting of Lyme borreliosis cases to specialized institutions, and partly due to the insufficiency of the diagnostic process.

The true incidence and prevalence of this disease cannot be determined and must await the development of specific and dependable methods to identify actual infection.

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