CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

June 4, 1999 / Vol. 48 / No. RR-7

MMWR™
MORBIDITY AND MORTALITY
WEEKLY REPORT

Recommendations and Reports

Inside: Continuing Education Examination

Recommendations for the Use of Lyme Disease Vaccine

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention (CDC)
Atlanta, Georgia 30333

The *MMWR* series of publications is published by the Epidemiology Program Office, Centers for Disease Control and Prevention (CDC), U.S. Department of Health and Human Services, Atlanta, GA 30333.

SUGGESTED CITATION

Centers for Disease Control and Prevention. Recommendations for the use of Lyme disease vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1999;48(No. RR-7):[inclusive page numbers].

Copies can be purchased from Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402-9325. Telephone: (202) 512-1800.

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Recommendations for the Use of Lyme Disease Vaccine

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

Summary

This report provides recommendations for use of a newly developed recombinant outer-surface protein A (rOspA) Lyme disease vaccine (LYMErix,™ SmithKline Beecham Pharmaceuticals) for persons aged 15–70 years in the United States. The purpose of these recommendations is to provide health-care providers, public health authorities, and the public with guidance regarding the risk for acquiring Lyme disease and the role of vaccination as an adjunct to preventing Lyme disease. The Advisory Committee on Immunization Practices recommends that decisions regarding vaccine use be made on the basis of assessment of individual risk, taking into account both geographic risk and a person's activities and behaviors relating to tick exposure.

INTRODUCTION

Lyme disease is a tickborne zoonosis caused by infection with the spirochete *Borrelia burgdorferi*. The number of annually reported cases of Lyme disease in the United States has increased approximately 25-fold since national surveillance began in 1982; during 1993–1997, a mean of 12,451 cases annually were reported by states to CDC (*1,2,* CDC, unpublished data, 1998). In the United States, the disease is primarily localized to states in the northeastern, mid-Atlantic, and upper north-central regions, and to several areas in northwestern California (*1*).

Lyme disease is a multisystem, multistage, inflammatory illness. In its early stages, Lyme disease can be treated successfully with oral antibiotics; however, untreated or inadequately treated infection can progress to late-stage complications requiring more intensive therapy. The first line of defense against Lyme disease and other tickborne illnesses is avoidance of tick-infested habitats, use of personal protective measures (e.g., repellents and protective clothing), and checking for and removing attached ticks. Early diagnosis and treatment are effective in preventing late-stage complications.

Recently, two Lyme disease vaccines have been developed that use recombinant *B. burgdorferi* lipidated outer-surface protein A (rOspA) as immunogen — LYMErix,™ SmithKline Beecham Pharmaceuticals, and ImuLyme,™ Pasteur Mérieux Connaught. As of publication of this report, only LYMErix has been licensed by the U.S. Food and Drug Administration for use in the United States; therefore, these recommendations apply only to the use of that vaccine. Additional statements will be provided as other Lyme disease vaccines are licensed.

Results of a large-scale, randomized, controlled (Phase III) trial of safety and efficacy of LYMErix in persons aged 15–70 years residing in disease-endemic areas of

the northeastern and north-central United States indicate that the vaccine is safe and efficacious when administered on a three-dose schedule of 0, 1, and 12 months (*3,4*). Information regarding vaccine safety and efficacy beyond the transmission season immediately after the third dose is not available. Thus, the duration of protective immunity and need for booster doses beyond the third dose are unknown.

CLINICAL FEATURES OF LYME DISEASE

Clinical Description

Most often, Lyme disease is evidenced by a characteristic rash (erythema migrans) accompanied by nonspecific symptoms (e.g., fever, malaise, fatigue, headache, myalgia, and arthralgia) (*5–7*). The incubation period from infection to onset of erythema migrans is typically 7–14 days but can be as short as 3 days or as long as 30 days. Some infected persons have no recognized illness (i.e., asymptomatic infection determined by serologic testing), or they manifest only nonspecific symptoms (e.g., fever, headache, fatigue, and myalgia).

Lyme disease spirochetes disseminate from the site of inoculation by cutaneous, lymphatic, and bloodborne routes. The signs of early disseminated infection usually occur from days to weeks after the appearance of a solitary erythema migrans lesion. In addition to multiple or secondary erythema migrans lesions, early disseminated infection can be manifested as disease of the nervous system, the musculoskeletal system, or the heart (*5–7*). Early neurologic manifestations include lymphocytic meningitis; cranial neuropathy, especially facial nerve palsy; and radiculoneuritis. Musculoskeletal manifestations can include migratory joint and muscle pains with or without objective signs of joint swelling. Cardiac manifestations are rare but can include myocarditis and transient atrioventricular block of varying degree.

B. burgdorferi infection in the untreated or inadequately treated patient can progress to late-disseminated disease from weeks to months after infection (*5–7*). The most common objective manifestation of late-disseminated Lyme disease is intermittent swelling and pain of one or some joints, usually large, weight-bearing joints (e.g., the knee). Some patients experience chronic axonal polyneuropathy, or encephalopathy, the latter usually manifested by cognitive disorders, sleep disturbance, fatigue, and personality changes. Infrequently, Lyme disease morbidity can be severe, chronic, and disabling (*8,9*). An ill-defined post-Lyme disease syndrome occurs in some persons after treatment for Lyme disease (*10–12*). Lyme disease is rarely, if ever, fatal.

Diagnosis

The diagnosis of Lyme disease is based primarily on clinical findings, and treating patients with early disease solely on the basis of objective signs and a known exposure is often appropriate (*13*). Serologic testing can, however, provide valuable supportive diagnostic information in patients with endemic exposure and objective clinical findings that indicate later-stage disseminated Lyme disease (*13*).

When serologic testing is indicated, CDC recommends testing initially with a sensitive first test, either an enzyme-linked immunosorbent assay (ELISA) or an indirect

fluorescent antibody test, followed by testing with the more specific Western immunoblot (WB) test to corroborate equivocal or positive results obtained with the first test (*14*). Although antibiotic treatment in early localized disease can blunt or abrogate the antibody response, patients with early disseminated or late-stage disease usually have strong serologic reactivity and demonstrate expanded WB immunoglobulin G (IgG) banding patterns to diagnostic *B. burgdorferi* antigens (*15,16*).

Antibodies often persist for months or years after successfully treated or untreated infection. Thus, seroreactivity alone cannot be used as a marker of active disease. Neither positive serologic test results nor a history of previous Lyme disease ensures that a person has protective immunity. Repeated infection with *B. burgdorferi* has been reported (*17*).

B. burgdorferi can be cultured from 80% or more of biopsy specimens taken from early erythema migrans lesions (*18*). However, the diagnostic usefulness of this procedure is limited because of the need for a special bacteriologic medium (i.e., modified Barbour-Stoenner-Kelly medium) and protracted observation of cultures. Polymerase chain reaction (PCR) has been used to amplify genomic DNA of *B. burgdorferi* in skin, blood, cerebrospinal fluid, and synovial fluid (*19,20*), but PCR has not been standardized for routine diagnosis of Lyme disease.

Treatment

Lyme disease can usually be treated successfully with standard antibiotic regimens (*5,6*). Early and uncomplicated infection, including infection with isolated cranial nerve palsy, usually responds satisfactorily to treatment with orally administered antibiotics (*21*). Parenteral antibiotics are generally recommended for treating meningitis, carditis, later-stage neurologic Lyme disease, and complicated Lyme disease arthritis. Late, complicated Lyme disease might respond slowly or incompletely, and more than one antibiotic treatment course can be required to eliminate active infection (*8,9*). Refractory Lyme disease arthritis is associated with expression of certain Class II major histocompatibility complex (MHC II) molecules (*22*), and can require anti-inflammatory agents and surgical synovectomy for relief of symptoms (*8*). In a limited number of patients, persistent or recurrent symptoms after appropriate antibiotic therapy often can be attributed to causes other than persistent infection (*22,23*).

EPIDEMIOLOGY OF LYME DISEASE

Antigenic Variation of *B. burgdorferi* Sensu Lato*

In the United States, a number of genospecies of *B. burgdorferi* sensu lato have been isolated from animals and ticks, but only OspA expressing *B. burgdorferi* sensu stricto† has been isolated from humans (*24*). Existing evidence also demonstrates that rOspA vaccines will be protective against most if not all human infections in the United States (*25*). *B. burgdorferi* sensu stricto also occurs in Europe, but the

*sensu lato: including all subordinate taxa of a taxon that would otherwise be considered separately.
†sensu stricto: excluding similar taxa that otherwise would be considered together.

dominant European and Asian genospecies are *B. garinii* and *B. afzelii*, both of which are antigenically distinct from *B. burgdorferi* sensu stricto (*26*) and vary in their expression of OspA. Vaccines using combinations of immunogenic proteins might be necessary to provide protection against multiple genospecies (*27*).

Routes of Transmission

Humans acquire *B. burgdorferi* infection from infected ticks at the time the tick takes a blood meal (*28*); Lyme disease is not spread by person-to-person contact or by direct contact with infected animals. Transplacental transmission of *B. burgdorferi* has been reported (*29,30*), but the effects of such transmission on the fetus remain unclear. The results of two epidemiologic studies document that congenital Lyme disease must be rare, if it occurs at all (*31,32*). Transmission in breast milk has not been described. *B. burgdorferi* can be cultured from the blood in some patients with early acute infection, and it is able to survive for several weeks in stored blood. However, at least one study has found that the risk for transfusion-acquired infection is minimal (*33*).

Tick Vectors of Lyme Disease

B. burgdorferi is transmitted to humans by ticks of the *Ixodes ricinus* complex (*34*). *I. scapularis*, the black-legged or deer tick, is the vector in the eastern United States; *I. pacificus*, the western black-legged tick, transmits *B. burgdorferi* in the western United States (*35,36*). *I. scapularis* is also a vector for human granulocytic ehrlichiosis and babesiosis *(34,37)*. In their nymphal stage, these ticks feed predominantly in the late spring and early summer. The majority of Lyme disease cases result from bites by infected nymphs. In highly enzootic areas of the United States, approximately 15%–30% of questing *I. scapularis* nymphs and up to 14% of *I. pacificus* nymphs are infected with *B. burgdorferi* (*38–41*). However, in the southern United States, the prevalence of infection in *I. scapularis* ticks is generally 0%–3% (*36*). The risk for acquiring Lyme disease in the United States varies with the distribution, density, and prevalence of infection in vector ticks (Appendix).

During the past several decades, the distribution of *I. scapularis* has spread slowly in the northeastern and upper north-central regions of the United States (*42*). Although deer are not competent reservoirs of *B. burgdorferi*, they are the principal maintenance hosts for adult black-legged ticks, and the presence of deer appears to be a prerequisite for the establishment of *I. scapularis* in any area (*43*). The explosive repopulation in the eastern United States by white-tailed deer during recent decades has been linked to the spread of *I. scapularis* ticks and of Lyme disease in this region. The future limits of this spread are not known (*42*).

Distribution of Human Cases of Lyme Disease

Lyme disease is endemic in several regions in the United States, Canada, and temperate Eurasia (*1,44*). The disease accounts for more than 95% of all reported cases of vectorborne illness in the United States. Using a national surveillance case definition (*45*), state health officials reported >62,000 cases to CDC during 1993–1997, and the national mean annual rate during this 5-year period was 5.5 cases/100,000

population (*1,2*, CDC, unpublished data, 1998). Persons of all ages are equally susceptible to infection, although the highest reported rates of Lyme disease occur in children aged <15 years and in adults aged 30–59 years (*1*). Both underreporting and overdiagnosis are common (*46–48*). Approximately 90% of cases are reported by approximately 140 counties located along the northeastern and mid-Atlantic seaboard and in the upper north-central region of the United States (Appendix).

A rash similar to erythema migrans of Lyme disease, but not caused by *B. burgdorferi* infection, has been described in patients who have been bitten by ticks in the southern United States (*49,50*). This rash is suspected of being associated with the bite of *Amblyomma americanum* ticks (*51*).

Populations at Risk for Lyme Disease

Most *B. burgdorferi* infections result from periresidential exposure to infected ticks (*38,52–55*) during property maintenance, recreation, and leisure activities. Thus, persons who live or work in residential areas surrrounded by woods or overgrown brush infested by vector ticks are at risk for acquiring Lyme disease. In addition, persons who participate in recreational activities away from home (e.g., hiking, camping, fishing, and hunting) in tick habitat and persons who engage in outdoor occupations (e.g., landscaping, brush clearing, forestry, and wildlife and parks management) in endemic areas might also be at elevated risk for acquiring Lyme disease (*56–58*).

PREVENTION AND CONTROL OF LYME DISEASE

Avoidance of Tick Habitat

Whenever possible, persons should avoid entering areas that are likely to be infested with ticks, particularly in spring and summer when nymphal ticks feed. Ticks favor a moist, shaded environment, especially that provided by leaf litter and low-lying vegetation in wooded, brushy, or overgrown grassy habitat. Both deer and rodent hosts must be abundant to maintain the enzootic cycle of *B. burgdorferi*. Sources of information regarding the distribution of ticks in an area include state and local health departments, park personnel, and agricultural extension services.

Personal Protection

Persons who are exposed to tick-infested areas should wear light-colored clothing so that ticks can be spotted more easily and removed before becoming attached. Wearing long-sleeved shirts and tucking pants into socks or boot tops can help keep ticks from reaching the skin. Ticks are usually located close to the ground, so wearing high rubber boots can provide additional protection. Applying insect repellents containing DEET (n,n-diethyl-m-toluamide) to clothes and exposed skin and applying permethrin, which kills ticks on contact, to clothes, should also help reduce the risk of tick attachment. DEET can be used safely on children and adults but should be applied according to the U.S. Environmental Protection Agency guidelines to reduce the possibility of toxicity (*59*). Because transmission of *B. burgdorferi* from an infected tick is

unlikely to occur before 36 hours of tick attachment (*28,60*), daily checks for ticks and their prompt removal will help prevent infection.

Strategies for Reducing Tick Abundance

The number of ticks in endemic residential areas can be reduced by removing leaf litter, brush, and woodpiles around houses and at the edges of yards and by clearing trees and brush to admit more sunlight, thus reducing deer, rodent, and tick habitat (*61*). Tick populations have also been effectively suppressed by applying pesticides to residential properties (*62,63*). Community-based interventions to reduce deer populations or to kill ticks on deer and rodents have not been extensively implemented, but might be effective in reducing communitywide risk for Lyme disease (*64*). The effectiveness of deer feeding stations equipped with pesticide applicators to kill ticks on deer and other baited devices to kill ticks on rodents is currently under evaluation.

Prophylaxis After Tick Bite

The relative cost-effectiveness of postexposure treatment of tick bites to avoid Lyme disease in endemic areas is dependent on the probability of *B. burgdorferi* infection after a tick bite (*65*). In most circumstances, treating persons for tick bite alone is not recommended (*6,66*). Persons who are bitten by a deer tick should remove the tick and seek medical attention if any signs and symptoms of early Lyme disease, ehrlichiosis, or babesiosis develop during the ensuing days or weeks.

Early Diagnosis and Treatment

Lyme disease is readily treatable in its early stages (*5,6*). The early diagnosis and proper antibiotic treatment of Lyme disease are important strategies for avoiding the morbidity and costs of complicated and late-stage illness.

LYME DISEASE VACCINE

Description

LYMErix is made from lipidated rOspA of *B. burgdorferi* sensu stricto. The rOspA protein is expressed in *Escherichia coli* and purified. Each 0.5-mL dose of LYMErix contains 30 μg of purified rOspA lipidated protein adsorbed onto aluminum hydroxide adjuvant.

Mechanism of Action

Several studies in animals have provided evidence that *B. burgdorferi* in a vector tick undergoes substantial antigenic change between the time of tick attachment on a mammalian host and subsequent transmission of the bacterium to the host. The spirochetes residing in the tick gut at the initiation of tick feeding express primarily OspA. As tick feeding begins, the expression of outer-surface protein C (OspC) is increased and the expression of OspA is decreased, so that spirochetes that reach the mammalian host after passing through the tick salivary glands express primarily OspC (*67*).

Thus, the rOspA vaccine might exert its principal protective effect by eliciting antibodies that kill Lyme disease spirochetes within the tick gut (*68,69*).

Route of Administration, Vaccination Schedule, and Dosage

LYMErix is administered by intramuscular injection, 0.5 mL (30 μg), into the deltoid muscle. Three doses are required for optimal protection. The first dose is followed by a second dose 1 month later and a third dose administered 12 months after the first dose. Vaccine administration should be timed so that the second dose of the vaccine (year 1) and the third dose (year 2) are administered several weeks before the beginning of the *B. burgdorferi* transmission season, which usually begins in April. The safety and immunogenicity of alternate dosing schedules are currently being evaluated.

VACCINE PERFORMANCE

Safety

Randomized, Controlled Clinical (Phase III) Trial of LYMErix

A total of 10,936 subjects aged 15–70 years living in Lyme disease-endemic areas were recruited at 31 sites and randomized to receive three doses of vaccine or placebo (*3*); 5,469 subjects received at least one 30-μg dose of rOspA vaccine, and 5,467 subjects received at least one injection of placebo. The subjects were then followed for 20 months. Information regarding adverse events that were believed to be related or possibly related to injection were available from 4,999 subjects in each group. Soreness at the injection site was the most frequently reported adverse event, which was reported without solicitation by 24.1% of vaccine recipients and 7.6% of placebo recipients ($p < 0.001$). Redness and swelling at the injection site were reported by <2% of either group but were reported more frequently among vaccine recipients than among those who received placebo ($p < 0.001$). Myalgia, influenza-like illness, fever, and chills were more common among vaccine recipients than placebo recipients ($p < 0.001$), but none of these was reported by more than 3.2% of subjects (*3*). Reports of arthritis were not significantly different between vaccine and placebo recipients, but vaccine recipients were significantly ($p < 0.05$) more likely to report arthralgia or myalgia within 30 days after each dose (*70*). No statistically significant differences existed between vaccine and placebo groups in the incidence of adverse events more than 30 days after receiving a dose, and no episodes of immediate hypersensitivity among vaccine recipients were noted (*3*).

Safety in Patients with Previously Diagnosed Lyme Disease

The safety of three different dosage strengths of rOspA vaccine with adjuvant in 30 adults with previous Lyme disease was evaluated in an uncontrolled safety and immunogenicity trial (*71*). Doses were administered at 0, 1, and 2 months. Follow-up of subjects was conducted 1 month after the third dose. No serious adverse events were recorded during the study period.

In the randomized controlled Phase III trial of LYMErix, the incidence of adverse events among vaccinees who were seropositive at baseline was similar to the incidence among those who were seronegative (*70*). The incidence of musculoskeletal symptoms within the first 30 days after vaccination was higher among vaccinees with a self-reported previous history of Lyme disease compared with vaccinees with no such history. This difference was not statistically significant at the p = 0.05 level in the placebo group. No statistically significant difference existed in the incidence of late musculoskeletal adverse events between vaccine and placebo recipients with a self-reported previous history of Lyme disease (*70*).

Risk for Possible Immunopathogenicity of rOspA Vaccine

After infection with *B. burgdorferi*, persons who express certain MHC II molecules are more likely than others to develop chronic, poorly responsive Lyme arthritis associated with high levels of antibody to OspA in serum and synovial fluid (*22*). In chronic Lyme arthritis patients, the levels of antibody to OspA, and especially to the C-terminal epitope of OspA, have been found to correlate directly with the severity and duration of the arthritis (*72*). Researchers have proposed that an autoimmune reaction might develop within the joints of some Lyme arthritis patients as a result of molecular mimicry between the dominant T-cell epitope of OspA and human leukocyte function associated antigen 1 (hLFA-1) (*73*). The Phase III trial did not detect differences in the incidence of neurologic or rheumatologic disorders between vaccine recipients and their placebo controls during the 20 months after the initial dose (*3*). However, because the association between immune reactivity to OspA and treatment-resistant Lyme arthritis is poorly understood, the vaccine should not be administered to persons with a history of treatment-resistant Lyme arthritis.

Efficacy

Randomized, Controlled Trial (Phase III) of LYMErix

Using an intention-to-treat analysis, the vaccine efficacy in protecting against "definite" Lyme disease after two doses was 49% (95% confidence interval [CI] = 15%–69%) and after three doses was 76% (95% CI = 58%–86%) (*3*). (In this study, "definite" Lyme disease was defined as the presence of erythema migrans or objective neurologic, musculoskeletal, or cardiovascular manifestations of Lyme disease, plus laboratory confirmation of infection by cultural isolation, PCR positivity, or WB seroconversion.) Efficacy in protecting against asymptomatic infection (no recognized symptoms, but with WB seroconversions recorded in year 1 or year 2) was 83% (95% CI = 32%–97%) in year 1 and 100% (95% CI = 26%–100%) in year 2.

Immunogenicity

A subset of adult subjects enrolled in the Phase III clinical trial of LYMErix was studied for the development of OspA antibodies at months 2, 12, 13, and 20 (*3*). At month 2, one month after the second injection, the geometric mean antibody titer (GMT) of IgG anti-OspA antibodies was 1,227 ELISA units/mL. Ten months later, the GMT had declined to 116 ELISA units/mL. At month 13, one month after the third injection, a marked anamnestic response resulted in a GMT of 6,006 ELISA units/mL. At month 20,

the mean response had decreased to 1,991 ELISA units/mL (*70*). An analysis of antibody titers and the risk for developing Lyme disease for a subset of subjects enrolled in the Phase III clinical trial concluded that a titer >1,200 ELISA units/mL correlated with protection (SmithKline Beecham poster at Infectious Disease Society of America Conference, Denver, Colorado, November 1998).

Effect of Vaccination on the Serologic Diagnosis of Lyme Disease

Care providers and laboratorians should be advised that vaccine-induced anti-rOspA antibodies routinely cause false-positive ELISA results for Lyme disease (*74*). Experienced laboratory workers, through careful interpretation of the results of WB, can usually discriminate between *B. burgdorferi* infection and previous rOspA immunization, because anti-OspA antibodies do not develop after natural infection.

COST-EFFECTIVENESS OF LYME DISEASE VACCINATION

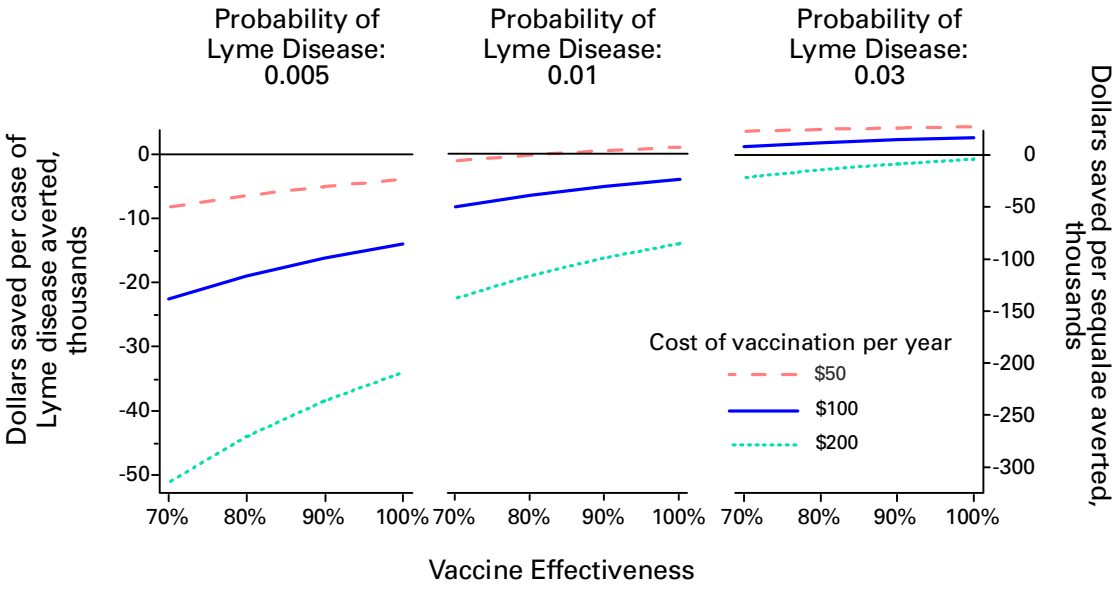
The cost of Lyme disease has been evaluated from both a societal and a third-party–payer perspective (*75*). The cost-effectiveness of vaccinating against Lyme disease has also been analyzed from a societal perspective (*76*). At an assumed cost of vaccination of $100/person/year, a vaccine effectiveness of 0.85, a probability of 0.85 of correctly identifying and treating early Lyme disease, and an assumed incidence of Lyme disease of 1,000/100,000 persons/year, the net cost of vaccination to society was $5,692/case averted and $35,375/complicated neurologic or arthritic case avoided (Figure 1). Using these same baseline assumptions, the societal cost of vaccination exceeds the cost of not vaccinating, unless the incidence of Lyme disease is >1,973/100,000 persons/year. Of the variables examined, the incidence of Lyme disease had the greatest impact on cost-effectiveness of vaccination. The likelihood of early diagnosis and treatment also has a substantial impact on vaccine cost-effectiveness because of the reduced incidence of sequelae when Lyme disease is diagnosed and patients are treated early in the disease.

Most disease-endemic states and counties report Lyme disease incidence that are substantially below 1,000/100,000 persons/year. For example, in 1997, the highest reported state incidence was 70/100,000 persons in Connecticut, and the highest reported county incidence was 600/100,000 population in Nantucket County, Massachusetts. However, some studies document that approximately 10%–15% of physician-diagnosed cases of Lyme disease are reported to state authorities in highly endemic areas (*46,47*). Epidemiologic studies of populations at high risk in the northeastern United States have estimated annual incidence of >1,000/100,000 persons/year in several communities (*77–80*).

ASSESSING THE RISK FOR LYME DISEASE

The decision to administer Lyme disease vaccine should be made on the basis of an assessment of individual risk, which depends on a person's likelihood of being bitten by tick vectors infected with *B. burgdorferi*. This likelihood is primarily determined by the following:

FIGURE 1. Cost-effectiveness of Lyme disease vaccination



Note: This graph documents the effect of variations in cost of vaccination, vaccine effectiveness, and the probability of contracting Lyme disease on the cost-effectiveness of vaccination. The left-hand y-axis measures cost per case of Lyme disease averted. The right-hand y-axis measures the cost per long-term sequelae (e.g., cardiac, neurologic, and musculoskeletal sequelae) averted. Underlying assumptions are as follows: probability of identifying and treating early Lyme disease, 85%; cost of treating cardiac sequelae, $6,845; cost of treating neurologic sequelae, $61,193; cost of arthritis $34,304; cost of treating early Lyme disease without sequelae $161).

- density of vector ticks in the environment, which varies by place and season;
- the prevalence of *B. burgdorferi* infection in vector ticks; and
- the extent of person-tick contact, which is related to the type, frequency, and duration of a person's activities in a tick-infested environment.

Assessing risk should include considering the geographic distribution of Lyme disease. The areas of highest Lyme disease risk in the United States are concentrated within some northeastern and north-central states. The risk for Lyme disease differs not only between regions and states and counties within states (Appendix), but even within counties and townships. Detailed information regarding the distribution of Lyme disease risk within specific areas is best obtained from state and local public health authorities.

The second step in determining Lyme disease risk is to assess a person's activities. Activities that place persons at high risk are those that involve frequent or prolonged exposure to the habitat of infected ticks at times of the year when the nymphal stages of these ticks are actively seeking hosts, which in most endemic areas is April–July. Typical habitat of *Ixodes* ticks are wooded, brushy, or overgrown grassy areas that are favorable for deer and the ticks' rodent hosts. Several recreational, property

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MORBIDITY AND MORTALITY WEEKLY REPORT

June 4, 1999 / Vol. 48 / No. RR-7

Recommendations and Reports

Continuing Education Activity Sponsored by CDC

Recommendations for the Use of Lyme Disease Vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP)

OBJECTIVE

This *MMWR* provides recommendations regarding prevention and control of Lyme disease. These recommendations were developed by CDC staff members and the ACIP members. This report is intended to guide clinical practice and policy development related to administration of the Lyme disease vaccine. Upon completion of this educational activity, the reader should be able to describe the epidemiology of Lyme disease in the United States; list effective methods of Lyme disease prevention; describe the characteristics and use of the currently licensed Lyme disease vaccine; and recognize the most common adverse reactions following administration of Lyme disease vaccine.

ACCREDITATION

Continuing Medical Education (CME) Credit: This activity has been planned and implemented in accordance with the Essentials and Standards of the Accreditation Council for Continuing Medical Education (ACCME) through CDC. CDC is accredited by the ACCME to provide continuing medical education for physicians. CDC awards 1.0 hour of category 1 credit toward the AMA Physician's Recognition Award for this activity. Each physician should claim only those hours he/she actually spent in the educational activity.

Continuing Education Unit (CEU) Credit: CDC awards 0.1 hour of CEUs. This activity has been structured following the International Association for Continuing Education and Training (IACET) Criteria and Guidelines and therefore is awarding CEUs. The CEU is a nationally recognized unit designed to provide a record of an individual's continuing education accomplishments.

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EXPIRATION — June 4, 2000

The response form must be completed and returned electronically, by fax, or by mail, **postmarked no later than 1 year from the publication date of this report**, for eligibility to receive continuing education credit.

INSTRUCTIONS

1. Read this *MMWR* (Vol. 48, RR-7), which contains the correct answers to the questions beginning on the next page.
2. Complete all registration information on the response form, including your name, mailing address, phone number, and e-mail address, if available.
3. Indicate whether you are registering for Continuing Medical Education (CME) credit, Continuing Education Unit (CEU) credit, or Continuing Nursing Education (CNE) credit.
4. Select your answers to the questions, and mark the corresponding letters on the response form. To receive continuing education credit, you must answer *all* of the questions. Questions with more than one correct answer will instruct you to "indicate all that are true."
5. Sign and date the response form.
6. Return the response form, or a photocopy of the form, no later than **June 4, 2000**, to CDC by one of the following methods:

   Internet: <http://www2.cdc.gov/cep>
   Fax: 404-639-4198

   Mail: MMWR CE Credit
   Office of Scientific and Health Communications
   Epidemiology Program Office — MS C08
   Centers for Disease Control and Prevention
   1600 Clifton Road, N.E.
   Atlanta, GA 30333

   If you answer all of the questions, you will receive an award letter for 1.0 hour of CME credit, 0.1 hour of CEU credit, or 1.2 hours of CNE credit within 90 days. No fees are charged for participating in this continuing education activity.

U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES

To receive continuing education credit, please answer all of the following questions.

1. Which of the following best describes *Borrelia burgdorferi*, the causative agent of Lyme disease?

A. Virus.

B. Rickettsia.

C. Protozoa.

D. Spirochete.

E. Fungi.

2. Which of the following statements is NOT true concerning the epidemiology of Lyme disease in the United States?

A. *B. burgdorferi* is acquired from an infected tick.

B. The majority of cases of Lyme disease are reported from the southeastern United States.

C. The risk of acquiring Lyme disease depends on the density and infection prevalence of vector ticks.

D. Children aged less than 15 years are among the age groups at highest risk for acquiring Lyme disease.

E. Most Lyme disease is thought to be acquired from periresidential exposure to infected ticks.

3. Which of the following factors should be considered when assessing whether a person should consider Lyme disease vaccination?

A. The geographic area where the exposure to ticks will occur.

B. The frequency or length of exposure to tick habitat.

C. The time of year when exposure to tick habitat will occur.

D. The age of the person who will be exposed to ticks.

E. All the above factors should be considered when assessing a person's need for Lyme disease vaccination.

4. Which of the following best describes the currently licensed Lyme disease vaccine?

A. Live attenuated bacteria.

B. Inactivated whole bacteria.

C. Recombinant outer-surface protein A.

D. Toxoid.

E. Plasmid DNA.

5. What is the youngest age at which the currently licensed Lyme disease vaccine should be administered?

A. 2 months.

B. 6 months.

C. 12 months.

D. 5 years.

E. 15 years.

6. What is the recommended schedule for administering Lyme disease vaccine?

A. Two doses separated by 1 month, followed by a third dose 12 months after the first dose.

B. Three doses, each separated from the preceding dose by at least 6 months.

C. Two doses separated by at least 6 months.

D. Two doses separated by 1 month.

E. One dose.

7. Which of the following are effective methods for preventing Lyme disease?

A. Avoidance of tick habitat.

B. Protective clothing.

C. Application of insect repellent.

D. Prompt removal of attached ticks.

E. All the above are effective methods for the prevention of Lyme disease.

8. What is the most common adverse reaction following Lyme disease vaccination?

A. An illness resembling a mild case of Lyme disease.

B. Fever.

C. Soreness at the injection site.

D. Joint pain.

E. Serum sickness.

9. Which of the following statements is true regarding the currently licensed Lyme disease vaccine?

A. The vaccine is more than 90% effective in preventing symptomatic Lyme disease after two doses.

B. The vaccine is not recommended for women who are known to be pregnant.

C. Booster doses of Lyme disease vaccine are recommended every 5 years after the primary series.

D. Persons with a previous history of Lyme disease should never be vaccinated.

E. Lyme disease vaccine is administered by subcutaneous injection.

10. Indicate your work setting.

A. State/local health department.

B. Other public health setting.

C. Hospital clinic/private practice.

D. Managed care organization.

E. Academic institution.

F. Other.

11. Which best describes your professional activities?

A. Patient care — emergency/urgent care department.

B. Patient care — inpatient.

C. Patient care — primary-care clinic.

D. Laboratory/pharmacy.

E. Administration.

F. Public health.

12. I plan to use these guidelines as the basis for . . . (*Indicate all that apply.*)

A. health education materials.

B. insurance reimbursement policies.

C. local practice guidelines.

D. public policy.

E. other.

13. Each month, approximately how many patients with Lyme disease do you treat or provide counseling for?

A. None.

B. 1–5.

C. 6–15.

D. 16–25.

E. 26 or more.

14. How much time did you spend reading this report and completing the exam?

A. 1–1½ hours.

B. More than 1½ hours but fewer than 2 hours.

C. 2 hours or more.

15. Overall, this report met the stated objectives.

A. Strongly agree.

B. Agree.

C. Neither agree nor disagree.

D. Disagree.

E. Strongly disagree.

16. The figures are useful.

A. Strongly agree.

B. Agree.

C. Neither agree nor disagree.

D. Disagree.

E. Strongly disagree.

17. Overall, the presentation of the report enhanced my ability to understand the material.

A. Strongly agree.

B. Agree.

C. Neither agree nor disagree.

D. Disagree.

E. Strongly disagree.

18. These recommendations will affect my practice.

A. Strongly agree.

B. Agree.

C. Neither agree nor disagree.

D. Disagree.

E. Strongly disagree.

Correct answers for questions 1–9

1. D; 2. B; 3. E; 4. C; 5. E; 6. A; 7. E; 8. C; 9. B.

MMWR Response Form for Continuing Education Credit
June 4, 1999 / Vol. 48 / No. RR-7

Recommendations for the Use of Lyme Disease Vaccine
Recommendations of the Advisory Committee on Immunization Practices (ACIP)

Fill in the appropriate block(s) to indicate your answer(s).
To receive continuing education credit, you must answer all of the questions.

Detach or photocopy.

1.	[ ] A	[ ] B	[ ] C	[ ] D	[ ] E	
2.	[ ] A	[ ] B	[ ] C	[ ] D	[ ] E	
3.	[ ] A	[ ] B	[ ] C	[ ] D	[ ] E	
4.	[ ] A	[ ] B	[ ] C	[ ] D	[ ] E	
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10.	[ ] A	[ ] B	[ ] C	[ ] D	[ ] E	[ ] F
11.	[ ] A	[ ] B	[ ] C	[ ] D	[ ] E	[ ] F
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17.	[ ] A	[ ] B	[ ] C	[ ] D	[ ] E	
18.	[ ] A	[ ] B	[ ] C	[ ] D	[ ] E	

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I completed this exam on

_____
(Date)

maintenance, occupational, or leisure pursuits that are carried out in tick habitat can be risky activities.

When in highly endemic areas, persons can reduce their risk for Lyme disease and other tickborne illnesses by avoiding tick-infested habitats. If exposure to a tick-infested habitat cannot be avoided, persons should use repellents, wear protective clothing, and regularly check themselves for ticks.

Persons who are unlikely to seek medical care for early manifestations of Lyme disease can be at increased risk for Lyme disease complications. Morbidity from Lyme disease can be substantially reduced by detecting and treating the infection in its early stages, because early and correct treatment usually results in a prompt and uncomplicated cure.

RECOMMENDATIONS FOR USE OF LYME DISEASE VACCINE

Lyme disease vaccine does not protect all recipients against infection with *B. burgdorferi* and offers no protection against other tickborne diseases. Vaccinated persons should continue to practice personal protective measures against ticks and should seek early diagnosis and treatment of suspected tickborne infections. Because Lyme disease is not transmitted person-to-person, use of the vaccine will not reduce risk among unvaccinated persons. Decisions regarding the use of vaccine should be based on individual assessment of the risk for exposure to infected ticks and on careful consideration of the relative risks and benefits of vaccination compared with other protective measures, including early diagnosis and treatment of Lyme disease. The risk for Lyme disease is focally distributed in the United States (Appendix). Detailed information regarding the distribution of Lyme disease risk within specific areas is best obtained from state and local public health authorities.

The following recommendations are made regarding use of Lyme disease vaccine:

- **Persons Who Reside, Work, or Recreate in Areas of High or Moderate Risk**
  - — Lyme disease vaccination should be considered for persons aged 15–70 years who engage in activities (e.g., recreational, property maintenance, occupational, or leisure) that result in frequent or prolonged exposure to tick-infested habitat.
  - — Lyme disease vaccination may be considered for persons aged 15–70 years who are exposed to tick-infested habitat but whose exposure is neither frequent nor prolonged. The benefit of vaccination beyond that provided by basic personal protection and early diagnosis and treatment of infection is uncertain.
  - — Lyme disease vaccination is not recommended for persons who have minimal or no exposure to tick-infested habitat.
- **Persons Who Reside, Work, or Recreate in Areas of Low or No Risk**
  - — Lyme disease vaccination is not recommended for persons who reside, work, or recreate in areas of low or no risk.

- **Travelers to Areas of High or Moderate Risk**

  — Because of the limited time of exposure, travelers to Lyme disease-endemic areas within the United States are generally expected to be at lower risk for Lyme disease than those who permanently reside in endemic areas. Vaccination should be considered for travelers to areas of high risk if frequent or prolonged exposure to tick habitat is anticipated.

Travelers can obtain some protection from two doses of vaccine but will not achieve optimal protection until the full series of three doses has been administered. All travelers to high- or moderate-risk areas during Lyme disease transmission season should practice personal protection measures as described earlier and seek prompt diagnosis and treatment if signs or symptoms of Lyme disease develop. Lyme disease is endemic in some temperate areas of Europe and Asia; however, considerable heterogeneity of expression exists in the Eurasian strains of *B. burgdorferi* sensu lato that infect humans, and whether the rOspA vaccine licensed for use in the United States would protect against infection with Eurasian strains is uncertain.

- **Children Aged <15 Years**

  — Until the safety and immunogenicity of rOspA vaccines in children have been established, this vaccine is not recommended for children aged <15 years. Currently, LYMErix is licensed for use in persons aged 15–70 years only.

- P**ersons Aged >70 Years**

  — The safety and efficacy of LYMErix have not been established for persons aged >70 years. LYMErix is licensed for use in persons aged 15–70 years only.

- **Pregnant Women**

  — Because the safety of rOspA vaccines administered during pregnancy has not been established, vaccination of women who are known to be pregnant is not recommended.

No evidence exists that pregnancy increases the risk for Lyme disease or its severity. Acute Lyme disease during pregnancy responds well to antibiotic therapy, and adverse fetal outcomes have not been reported in pregnant women receiving standard courses of treatment. A vaccine pregnancy registry has been established by SmithKline Beecham Pharmaceuticals. In the event that a pregnant women is vaccinated, health-care providers are encouraged to register this vaccination by calling, toll-free, (800) 366-8900, ext. 5231.

- **Persons with Immunodeficiency**

  — Persons with immunodeficiency were excluded from the Phase III safety and efficacy trial, and no data are available regarding Lyme disease vaccine use in this group.

- **Persons with Musculoskeletal Disease**
  - Persons with diseases associated with joint swelling (including rheumatoid arthritis) or diffuse musculoskeletal pain were excluded from the Phase III safety and efficacy trial, and only limited data are available regarding Lyme disease vaccine use in such patients.
- **Persons with a Previous History of Lyme Disease**
  - Vaccination should be considered for persons with a history of previous uncomplicated Lyme disease who are at continued high risk.
  - Persons who have treatment-resistant Lyme arthritis should not be vaccinated because of the association between this condition and immune reactivity to OspA.
  - Persons with chronic joint or neurologic illness related to Lyme disease, as well as second- or third-degree atrioventricular block, were excluded from the Phase III safety and efficacy trial, and thus, the safety and efficacy of Lyme disease vaccine in such persons are unknown.
- **Vaccine Schedule, Including Spacing and Timing of Administration**
  - Three doses of the vaccine should be administered by intramuscular injection. The initial dose should be followed by a second dose 1 month later and a third dose 12 months after the first dose. Vaccine administration should be timed so that the second dose of the vaccine (year 1) and the third dose (year 2) are administered several weeks before the beginning of the *B. burgdorferi* transmission season, which usually begins in April.
- **Boosters**
  - Whether protective immunity will last longer than 1 year beyond the month-12 dose is unknown. Data regarding antibody levels during a 20-month period after the first injection of LYMErix indicate that boosters beyond the month-12 booster might be necessary (see Immunogenicity). Additional data are needed before recommendations regarding vaccination with more than three doses of rOspA vaccine can be made.
- **Simultaneous Administration with Other Vaccines**
  - The safety and efficacy of the simultaneous administration of rOspA vaccine with other vaccines have not been established. If LYMErix must be administered concurrently with other vaccines, each vaccine should be administered in a separate syringe at a separate injection site.

FUTURE CONSIDERATIONS

Recommendations for Surveillance, Research, Education, and Program Evaluation Activities

- Determine safety, immunogenicity, and efficacy of Lyme disease vaccine in children.
- Determine optimal vaccine dosage schedules and timing of administration.
- Determine the need for and spacing of booster doses.
- Determine safety and efficacy of the vaccine in persons aged >70 years.
- Develop additional serodiagnostic tests that discriminate between infection and vaccine-induced antibody production.
- Develop a program of Lyme disease vaccine education for care providers and prospective vaccine clients.
- Develop an information sheet to be distributed to prospective vaccine recipients or to persons at the time of vaccine administration.
- Conduct surveillance for rare or late-developing adverse effects of vaccination.
- Establish postlicensure epidemiologic studies of safety, efficacy, prevention effectiveness, cost-effectiveness, and patterns of use.
- Develop a program to monitor vaccine use at the local, state, and national levels and to measure its public health and economic impact.
- Develop population-based studies to assess the impact of vaccine use on incidence of Lyme disease in communities.
- Continue to develop maps of geographic distribution of Lyme disease with improved accuracy and predictive power.

References

1. Dennis DT. Epidemiology, ecology, and prevention of Lyme disease. In: Rahn DW, Evans J, eds. Lyme disease. Philadelphia, PA: American College of Physicians, 1998;7–34.
2. CDC. Lyme disease—United States, 1996. MMWR 1997;46:531–5.
3. Steere AC, Sikand VK, Meurice F, et al. Vaccination against Lyme disease with recombinant *Borrelia burgdorferi* outer-surface lipoprotein A with adjuvant. N Engl J Med 1998;339:209–15.
4. Sigal LH, Zahradnik JM, Levin P, et al. Vaccine consisting of recombinant *Borrelia burgdorferi* outer-surface protein A to prevent Lyme disease. N Engl J Med 1998;339:216–22.
5. Steere AC. Lyme disease. N Engl J Med 1989;321:586–96.
6. Nadelman RB, Wormser GP. Lyme borreliosis. Lancet 1998;352:557–65.
7. Rahn DW. Natural history of Lyme disease. In: Rahn DW, Evans J, eds. Lyme disease. Philadelphia, PA: American College of Physicians, 1998;35–48.
8. Steere AC, Levin RE, Molloy PJ, et al. Treatment of Lyme arthritis. Arthritis Rheum 1994;37: 878–88.
9. Logigian EL, Kaplan RF, Steere AC. Chronic neurologic manifestations of Lyme disease. N Engl J Med 1990;323:1438–44.
10. Shadick NA, Phillips CB, Logigian EL, et al. Long-term clinical outcomes of Lyme disease. Ann Intern Med 1994;121:560–7.

11. Bujak DI, Weinstein A, Dornbush RL. Clinical and neurocognitive features of the post Lyme syndrome. J Rheumatol 1996;23:1392–7.
12. Gaudino EA, Coyle PK, Krupp LB. Post-Lyme syndrome and chronic fatigue syndrome. Neuropsychiatric similarities and differences. Arch Neurol 1997;54:1372–6.
13. Tugwell P, Dennis DT, Weinstein A, et al. Clinical guideline, part 2: laboratory evaluation in the diagnosis of Lyme disease. Ann Intern Med 1997;127:1109–23.
14. CDC. Recommendations for test performance and interpretation from the Second National Conference on Serologic Diagnosis of Lyme Disease. MMWR 1995;44:590–1.
15. Dressler F, Whalen JA, Reinhart BN, Steere AC. Western blotting in the serodiagnosis of Lyme disease. J Infect Dis 1993;167:392–400.
16. Johnson BJB, Robbins KE, Bailey RE, et al. Serodiagnosis of Lyme disease: accuracy of a two-step approach using a flagella-based ELISA and immunoblotting. J Infect Dis 1996; 174:346–53.
17. Nowakowski J, Schwartz I, Nadelman RB, Liveris D, Aguero-Rosenfeld M, Wormser GP. Culture-confirmed infection and reinfection with *Borrelia burgdorferi*. Ann Intern Med 1997; 127:130–2.
18. Berger BW, Johnson RC, Kodner C, Coleman L. Cultivation of *Borrelia burgdorferi* from erythema migrans lesions and perilesional skin. J Clin Microbiol 1992;30:359–61.
19. Brettschneider S, Bruckbauser H, Klugbauer N, Hofmann H. Diagnostic value of PCR for detection of *Borrelia burgdorferi* in skin biopsy and urine samples from patients with skin borreliosis. J Clin Microbiol 1998;36:2658–65.
20. Nocton JJ, Dressler F, Rutledge BJ, Rys PN, Persing DH, Steere AC. Detection of *Borrelia burgdorferi* DNA by polymerase chain reaction in synovial fluid from patients with Lyme arthritis. N Engl J Med 1994;330:229–34.
21. Dotevall L, Hagberg L. Successful oral doxycycline treatment of Lyme disease—associated facial palsy and meningitis. Clin Infect Dis 1999;28:569–74.
22. Kalish RA, Leong JM, Steere AC. Association of treatment-resistant chronic Lyme arthritis with HLA-DR4 and antibody reactivity to OspA and OspB of *Borrelia burgdorferi*. Infect Immun 1993;61:2774–9.
23. Sigal LH. Persisting complaints attributed to chronic Lyme disease: possible mechanisms and implications for management. Am J Med 1994;96:365–74.
24. Mathiesen DA, Oliver JH, Kolbert CP, et al. Genetic heterogeneity of *Borrelia burgdorferi* in the United States. J Infect Dis 1997;175:98–107.
25. Fikrig E, Telford SR, Wallich R, et al. Vaccination against Lyme disease caused by diverse *Borrelia burgdorferi*. J Exp Med 1995;181:215–21.
26. Baronton G, Postic D, Saint Girons I, et al. Delineation of *Borrelia burgdorferi* sensu stricto, *Borrelia garinii* sp. nov., and group VS461 associated with Lyme borreliosis. Int J Syst Bacteriol 1992;42:378–83.
27. Lovrich SD, Callister SM, Lim LCL, DuChateau BK, Sehell RF. Seroprotective groups of Lyme borreliosis spirochetes from North America and Europe. J Infect Dis 1994;170:115–21.
28. Piesman J. Dynamics of *Borrelia burgdorferi* transmission by nymphal *Ixodes dammini* ticks. J Infect Dis 1993;167:1082–5.
29. Schlesinger PA, Duray PH, Burke BA, Steere AC, Stillman MT. Maternal-fetal transmission of the Lyme disease spirochete, *Borrelia burgdorferi*. Ann Intern Med 1985;103:67–8.
30. Weber K, Bratzke H-J, Neubert U, Wilske B, Duray PH. *Borrelia burgdorferi* in a newborn despite oral penicillin for Lyme borreliosis during pregnancy. Pediatr Infect Dis J 1988;7:286–9.
31. Strobino BA, Williams CL, Abid S, Chalson R, Spierling P. Lyme disease and pregnancy outcome: a prospective study of two thousand prenatal patients. Am J Obstet Gynecol 1993;169:367–74.
32. Williams CL, Strobino B, Weinstein A, Spierling P, Medici F. Maternal Lyme disease and congenital malformations: a cord blood serosurvey in endemic and control areas. Paediatr Perinat Epidemiol 1995;9:320–30.
33. Gerber MA, Shapiro ED, Krause PJ, Cable RG, Badon SJ, Ryan RW. The risk of acquiring Lyme disease or babesiosis from a blood transfusion. J Infect Dis 1994;170:231–4.
34. Spielman A, Wilson ML, Levine JF, Piesman J. Ecology of *Ixodes dammini*-borne human babesiosis and Lyme disease. Annu Rev Entomol 1985;30:439–60.

35. Lane RS, Piesman J, Burgdorfer W. Lyme borreliosis: relation of its causative agent to its vectors and hosts in North America and Europe. Annu Rev Entomol 1991;36:587–609.
36. Dennis DT, Nekomoto TS, Victor JC, Parel WS, Piesman J. Reported distribution of *Ixodes scapularis* and *Ixodes pacificus* (Acari: Ixodidae) in the United States. J Med Entomol 1998; 35:629–38.
37. Des Vignes F, Fish D. Transmission of the agent of human granulocytic ehrlichiosis by host-seeking *Ixodus scapularis* (Acari: Ixodidae) in southern New York state. J Med Entomol 1997; 34:379–82.
38. Maupin GO, Fish D, Zultowsky J, Campos EG, Piesman J. Landscape ecology of Lyme disease in a residential area of Westchester County, New York. Am J Epidemiol 1991;133:1105–13.
39. Stafford KC III, Magnarelli LA. Spatial and temporal patterns of *Ixodes scapularis* (Acari: Ixodidae) in southeastern Connecticut. J Med Entomol 1993;30:762–71.
40. Nelson JA, Bouseman JK, Kitron U, et al. Isolation and characterization of *Borrelia burgdorferi* from Illinois *Ixodes dammini*. J Clin Microbiol 1991;29:1732–4.
41. Clover JR, Lane RS. Evidence implicating nymphal *Ixodes pacificus* (Acari: Ixodidae) in the epidemiology of Lyme disease in California. Am J Trop Med Hyg 1995;53:237–40.
42. Wilson ML. Distribution and abundance of *Ixodes scapularis* (Acari: Ixodidae) in North America: ecological processes and spatial analysis. J Med Entomol 1998;35:446–57.
43. Wilson Ml, Adler GH, Spielman A. Correlation between abundance of deer and that of the deer tick, *Ixodes dammini* (Acari: Ixodidae). Annuals of the Entomological Society of America 1985;7:172–6.
44. O'Connell S, Granström M, Gray JS, Stanek G. Epidemiology of European Lyme borreliosis. Zentralbl Bakteriol 1998;287:229–40.
45. CDC. Case definitions for infectious conditions under public health surveillance. MMWR 1997; 46(No. RR-10):12–21.
46. Coyle BS, Strickland GT, Liang YY, Peña C, McCarter R, Israel E. Public health impact of Lyme disease in Maryland. J Infect Dis 1996;173:1260–2.
47. Meek JI, Roberts CL, Smith EV Jr, Cartter ML. Underreporting of Lyme disease by Connecticut physicians, 1992. Journal of Public Health Management Practice 1996;2:61–5.
48. Steere AC, Taylor E, McHugh GL, Logigian EL. Overdiagnosis of Lyme disease. JAMA 1993; 269:1812–6.
49. Campbell GL, Paul WS, Schriefer ME, Craven RB, Robbins KE, Dennis DT. Epidemiologic and diagnostic studies of patients with suspected early Lyme disease, Missouri, 1990–1993. J Infect Dis 1995;172:470–80.
50. Kirkland KB, Klimko TB, Meriwether RA, et al. Erythema migrans-like rash illness at a camp in North Carolina. Arch Intern Med 1997;157:2635–41.
51. Barbour AG. Does Lyme disease occur in the South? A survey of emerging tick-borne infections in the region. Am J Med Sci 1996;311:34–40.
52. 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.
53. Orloski KA, Campbell GL, Genese CA, et al. Emergence of Lyme disease in Hunterdon County, New Jersey, 1993: a case-control study of risk factors and evaluation of reporting patterns. Am J Epidemiol 1998;147:391–7.
54. Cromley EK, Cartter ML, Mrozinski RD, Starr-Hope E. Residential setting as a risk factor for Lyme disease in a hyperendemic region. Am J Epidemiol 1998;147:472-7.
55. Lane RS, Manweiler SA, Stubbs HA, Lennette ET, Madigan JE, Lavoie PE. Risk factors for Lyme disease in a small rural community in northern California. Am J Epidemiol 1992;136: 1358–68.
56. Kitron U, Kazmierczak JJ. Spatial analysis of the distribution of Lyme disease in Wisconsin. Am J Epidemiol 1997;145:558–66.
57. Schwartz BS, Goldstein MD, Childs JE. Antibodies to *Borrelia burgdorferi* and tick salivary gland proteins in New Jersey outdoor workers. Am J Public Health 1993;83:1746–8.
58. Smith PF, Benach JL, White DJ, Stroup DF, Morse DL. Occupational risk of Lyme disease in endemic areas of New York State. Ann N Y Acad Sci 1988;539:289–301.
59. Brown M, Hebert AA. Insect repellents: an overview. J Am Acad Dermatol 1997;36:243–9.
60. Piesman J, Mather TN, Sinsky RJ, Spielman A. Duration of tick attachment and *Borrelia burgdorferi* transmission. J Clin Microbiol 1987;25:557–8.

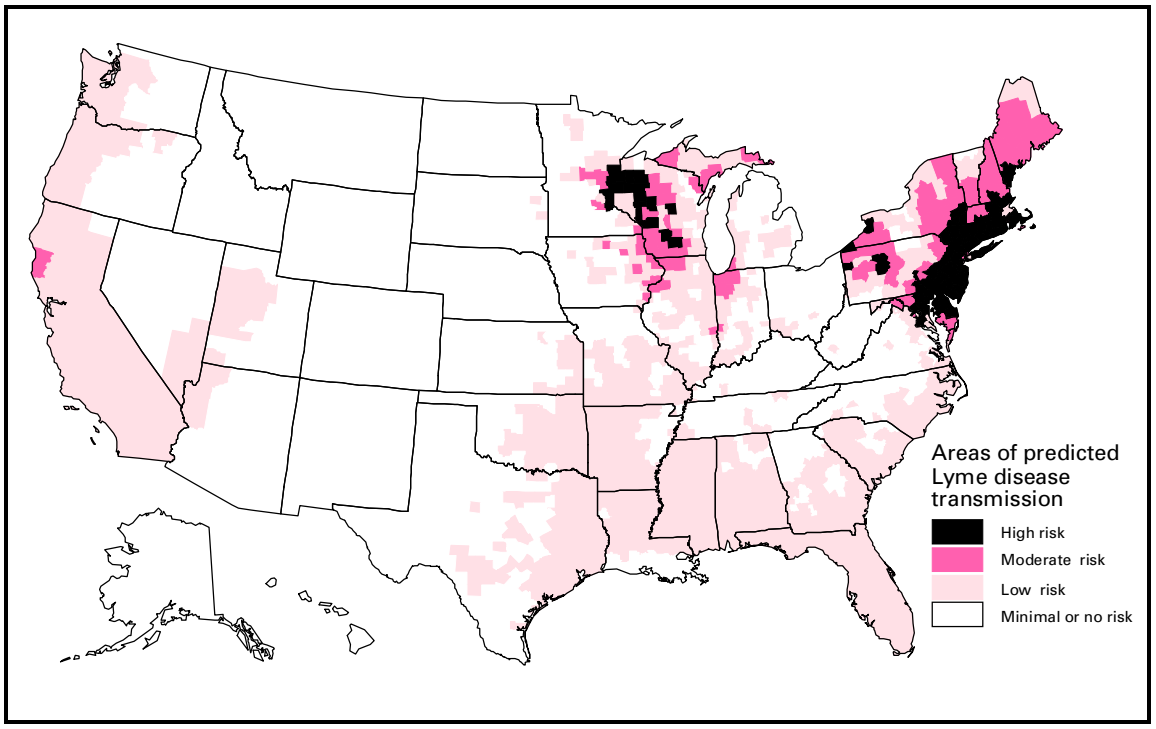
61. Schulze TL, Jordan RA, Hung RW. Suppression of subadult *Ixodes scapularis* (Acari: Ixodidae) after removal of leaf litter. J Med Entomol 1995;32:730–3.
62. Curran KL, Fish D, Piesman J. Reduction of nymphal *Ixodes dammini* (Acari: Ixodidae) in a residential suburban landscape by area application of insecticides. J Med Entomol 1993;30: 107–13.
63. Schulze TL, Jordan RA, Vasvary LM, et al. Suppression of *Ixodes scapularis* (Acari: Ixodidae) nymphs in a large residential community. J Med Entomol 1994;31:206–11.
64. Hayes EB, Maupin GO, Mount GA, Piesman J. Assessing the effectiveness of local Lyme disease control. Journal of Public Health Management and Practice 1999;5:86–94.
65. Magid D, Schwartz B, Craft J, Schwartz JS. Prevention of Lyme disease after tick bites: a cost-effectiveness analysis. N Engl J Med 1992;327:534–41.
66. Dennis DT, Meltzer MI. Antibiotic prophylaxis after tick bites. Lancet 1997;350:1191–2.
67. Schwan TG, Piesman J, Golde WT, Dolan MC, Rosa PA. Induction of an outer surface protein on *Borrelia burgdorferi* during tick feeding. Proc Natl Acad Sci U S A 1995;92:2909–13.
68. de Silva AM, Telford SR, Brunet LR, Barthold SW, Fikrig E. *Borrelia burgdorferi* OspA is an arthropod-specific transmission-blocking Lyme disease vaccine. J Exp Med 1996;183:271–5.
69. de Silva AM, Zeidner NS, Zhang Y, Dolan MC, Piesman J, Fikrig E. Influence of outer surface protein A antibody on *Borrelia burgdorferi* within feeding ticks. Infect Immun 1999;67:30–5.
70. LYMErix,™ Lyme disease vaccine [U.S. prescribing information]. Philadelphia, PA: SmithKline Beecham, 1998. Available at <http://www.sb.com/products/index.html>. Accessed April 1999.
71. Schoen RT, Meurice F, Brunet CM, et al. Safety and immunogenicity of an outer surface protein A vaccine in subjects with previous Lyme disease. J Infect Dis 1995;172:1324–9.
72. Akin E, McHugh GL, Flavell RA, Fikrig E, Steere AC. Immunoglobulin (IgG) antibody response to OspA and OspB correlates with severe and prolonged Lyme arthritis and the IgG response to P35 correlates with mild and brief arthritis. Infect Immun 1999;67:173–81.
73. Gross DM, Forsthuber T, Tary-Lehmann M, et al. Identification of LFA-1 as a candidate autoantigen in treatment-resistant Lyme arthritis. Science 1998;281:703–6.
74. Zhang Y-Q, Mathiesen D, Kolbert CP, et al. *Borrelia burgdorferi* enzyme-linked immunosorbent assay for discrimination of OspA vaccination from spirochete infection. J Clin Microbiol 1997; 35:233–8.
75. Maes E, Lecomte P, Ray N. Cost-of-illness study of Lyme disease in the United States. Clin Ther 1998;20:993–1008.
76. Meltzer MI, Dennis DT, Orloski KA. 1999 Cost-effectiveness of a vaccine against Lyme disease in humans. Emerging Infect Dis 1999;5:1–8.
77. Hanrahan JP, Benach JL, Coleman JL, et al. Incidence and cumulative frequency of Lyme disease in a community. J Infect Dis 1984;150:489–96.
78. Steere AC, Taylor E, Wilson ML, Levine JF, Spielman A. Longitudinal assessment of the clinical and epidemiologic features of Lyme disease in a defined population. J Infect Dis 1986;154: 295–300.
79. Lastavica CC, Wilson M, Berardi VP, Spielman A, Deblinger RD. Rapid emergence of a focal epidemic of Lyme disease in coastal Massachusetts. N Engl J Med 1989;320:133–7.
80. Alpert B, Esin J, Sivak SL, Wormser GP. Incidence and prevalence of Lyme disease in a suburban Westchester County community. New York State Journal of Medicine 1992;92:5–8.

Appendix
Methods Used for Creating a National Lyme Disease Risk Map

Appendix

Methods Used for Creating a National Lyme Disease Risk Map*

National Lyme disease risk map with four categories of risk



Note: This map demonstrates an approximate distribution of predicted Lyme disease risk in the United States. The true relative risk in any given county compared with other counties might differ from that shown here and might change from year to year. Risk categories are defined in the accompanying text. Information on risk distribution within states and counties is best obtained from state and local public health authorities.

INTRODUCTION

Lyme disease risk is measurable as a function of two epidemiologic parameters — entomologic risk and human exposure. Entomologic risk for Lyme disease is defined as the density per unit area of host-seeking nymphal ticks infected with *Borrelia burgdorferi* (*1*). Field studies needed for determination of entomologic risk require trained entomologists, and such studies are limited to a narrow seasonal window within the life-cycle of vector ticks. Limited resources preclude the direct measurement of entomologic risk over large geographic areas; therefore, indirect measures were used to estimate risk to develop this national Lyme disease risk map. First, data on vector distribution, abundance, *B. burgdorferi* infection prevalence, and human

*Source: Durland Fish, Ph.D. and Carrie A. Howard, M.A. Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut.

exposure were compiled on a county-unit scale for the United States. Then geographic information systems (GIS) technology was used to combine these data and categorize each of the 3,140 counties into four risk classes.

ENTOMOLOGIC RISK

Vector Distribution

Vector data were obtained from a national distribution map of *Ixodes scapularis* and *I. pacificus*, which was previously published by CDC (*2*). These data delineate three classes of tick distribution based on all published and unpublished county collection records available to CDC before 1998. The three classes are as follows:

- established populations (≥6 ticks reported or more than one life stage);
- reported occurrence (<6 ticks reported and only one life stage); and
- absence of ticks or missing data.

Although these data are currently the best source of vector distribution available, many gaps exist because of uneven sampling efforts among the counties. Therefore, a neighborhood analysis GIS procedure was used to modify the original tick distribution to smooth absent data and minimize the impact of reporting gaps. In this process, the original tick coverage map was rasterized to 1 km, and each cell was given a numeric value corresponding to the county tick class (0 = absent; 1 = reported; and 2 = established). A neighborhood analysis was performed using ERDAS IMAGINE* image-processing software. This function employed a moving filter (25 by 25 km), which summed the values of the area surrounding each 1-km pixel and created a new focally smoothed image. An outline of counties was overlaid to define boundaries on the smoothed map, and new values were summed from the total pixel values for each county. The three original vector classes were maintained with the new classification. The revised map employed a threshold reclassification based on mean summary statistics generated from the neighborhood analysis. This procedure resulted in a weighted value for each county that was determined by the classes of surrounding counties, thus smoothing the map to minimize rough edges and isolated holes in the data. The modified vector distribution increased the number of counties containing *I. scapularis* and *I. pacificus* from 1,058 counties (34% of total counties) in the original data set to 1,404 (45% of total) in the modified version. This modification resulted in greater continuity among adjacent counties, as well as a less-conservative description of vector distribution.

Infection Prevalence in Vectors

The prevalence of infection with *B. burgdorferi* is low throughout the distribution of *I. pacificus* (*3*) with the exception of one California county (*4*). Within the entire southern distribution of *I. scapularis*, prevalence of infection with *B. burgdorferi* is low compared with the Northeast and upper Midwest (*3*). One possible reason for these

*ERDAS IMAGINE map production computer software, a product of ERDAS, Inc., 2801 Buford Highway, Atlanta, GA 30329-2137, (404) 248-9000, <http://www.erdas.com>.

differences is the geographic variations in abundance of hosts that are competent reservoirs of infection for immature ticks. The white-footed mouse (*Peromyscus leucopus*) is the principal host for ticks in the Northeast and upper Midwest and is a competent reservoir for the spirochete. But in the Southeast and West Coast regions, reptiles appear to serve as major hosts for immature ticks, and reptiles are either inefficient or incompetent reservoir hosts for spirochetes. This pattern of tick-host association might result from the greater population density of lizards relative to rodents (*5*), resulting in reduced transmission rates in regions where lizards dominate. An index was created to map the effect of host-species composition on infection prevalence in *I. scapularis* ticks.

A literature survey was conducted to identify a complete list of hosts for *I. scapularis* (*6*). A total of 38 nondomestic host species was identified, including 32 mammal species and 6 reptile species. Birds were excluded because of their migratory nature and their uncertain role as natural reservoir hosts. Species range maps were obtained from the literature (*7,8*), then digitized by county into ArcView GIS* software for presence or absence of reservoir hosts. The county data were then summed to determine the total host species composition available for *I. scapularis*.

A ratio of total reptiles divided by the total hosts multiplied by 100 was calculated for each county and mapped. The reptile ratio index delineates those areas having a high reptile-to-total-hosts ratio (>10) and forms a linear boundary, below which reptiles are more likely to serve as hosts for ticks. The geographic boundary runs roughly on the 38° north latitude from Virginia to Missouri. This reptile ratio illustrates that although total hosts in the northern states can be equal to those of the southern states, reptiles dilute the force of transmission, thus lowering the prevalence of infection in ticks and creating less of a risk to humans in the South.

HUMAN EXPOSURE TO RISK

CDC case reports were used as a measure of human exposure to entomologic risk. County-specific data were compiled for the years 1994–1997. Counties comprising the ninetieth percentile of all human cases reported during this 4-year period were selected to represent counties with high human exposure. These 137 counties reported a minimum total of 23 cases. Heuristic, or procedure-based decision rule, was employed to construct the national Lyme disease risk map. Expert decision rule was applied to construct the risk classification as follows:

Risk Classes

- **High Risk.** Counties where *I. scapularis* or *I. pacificus* populations are established and where prevalence of infection is predicted to be high, and which are in the top tenth percentile of counties reporting human cases during the 4-year period, 1994–1997.
- **Moderate Risk.** Counties where *I. scapularis* or *I. pacificus* populations are established and where the prevalence of infection is predicted to be high.

*ARCView GIS computer software, a product of Environmental Systems Research Institute, Inc., 380 New York Street, Redlands, CA 92373-8100, <http://www.esri.com>.

- **Low Risk.** Counties where *I. scapularis* populations are established, but infection prevalence is predicted to be low, or where *I. scapularis* populations are reported but not established, or where *I. pacificus* populations are either established or reported.
- **Minimal or No Risk.** Counties where neither *I. scapularis* nor *I. pacificus* are established or reported.

The national map illustrates a clear focal pattern of Lyme disease risk with the greatest risk occurring in the Northeast and upper Midwest regions. Overall, 115 (4%) counties were classified as high risk, followed by 146 (5%) moderate risk, 1,143 (36%) low risk, and 1,736 (55%) as minimal or no-risk counties.

Appendix References

1. Mather TN. Dynamics of spirochete transmission between ticks and vertebrates. In: Ecology and Environmental management of Lyme Disease. H Ginsberg, ed. New Brunswick, NJ: Rutgers University Press 1993;43–62.
2. Dennis DT, Nekomoto TS, Victor JC, William SP, Piesman J. Reported distribution of *Ixodes scapularis* and *Ixodes pacificus* ticks (Acari: Ixodidae) in the United States. J Med Entomol 1998;35:629–38.
3. Lane RS, Piesman J, Burgdorfer W. Lyme borreliosis: relation of its causative agent to its vectors and hosts in North America and Europe. Annu Rev Entomol 1991;36:587–609.
4. Clover JR, Lane RS. Evidence implicating nymphal *Ixodes pacificus* (Acari: Ixodidae) in the epidemiology of Lyme disease in California. Am J Trop Med Hyg 1995;53:237–40.
5. Apperson CS, Levine JF, Evans TL, Braswell A, Heller J. Relative utilization of reptiles and rodents as hosts by immature *Ixodes scapularis* (Acari: Ixodidae) in the coastal plain of North Carolina, USA. Exp Appl Acarol 1993;17:719–31.
6. Anderson JF, Magnarelli LA. Enzootiology of *Borrelia burgdorferi* in the Northeast and North Central United States. In: Proceedings of the IX International Congress of Acarology, Columbus, OH 1994 (in press).
7. Hall ER. Mammals of North America. Vol II, 2nd ed. New York, NY: John Wiley & Sons, 1981.
8. Society for the Study of Amphibians and Reptiles. Catalogue of American Amphibians and Reptiles. [published irregularly as loose-leaf pages] New York, NY; 1963–Present. Subscription information available at <http://www.bio.cornell.edu/neurobio/adler/ssar.html>. Accessed April 1999.

Summary Table

Recommendations for Use of Recombinant Outer-Surface Protein A Vaccine for the Prevention of Lyme Disease

Advisory Committee on Immunization Practices, 1999

	Vaccination Recommendation
Persons who reside, work, or recreate in areas of high or moderate risk	
Persons aged 15–70 years whose exposure to tick-infested habitat is frequent or prolonged	Should be considered
Persons aged 15–70 years who are exposed to tick-infested habitat, but whose exposure is not frequent or prolonged	May be considered
Persons whose exposure to tick-infested habitat is minimal or none	Not recommended
Persons who reside, work, or recreate in areas of low or no risk	Not recommended
Travelers to areas of high or moderate risk	
Travelers aged 15–70 years whose exposure to tick-infested habitat is frequent or prolonged	Should be considered
Children aged <15 years	Not recommended
Pregnant women	
Health-care providers are encouraged to register vaccinations of pregnant women by calling SmithKline Beecham, toll free, at (800) 366-8900, ext. 5231	Not recommended
Persons with immunodeficiency	No available data
Persons with musculoskeletal disease	Limited data available
Persons with previous history of Lyme disease	
Persons aged 15–70 years with previous uncomplicated Lyme disease who are at continued high risk	Should be considered
Persons with treatment-resistant Lyme arthritis	Not recommended
Persons with chronic joint or neurologic illness related to Lyme disease and persons with second- or third-degree atrioventricular block	No available data
Other Recommendations	
Vaccine schedule	
Three doses administered by intramuscular injection as follows: Initial dose, followed by a second dose 1 month later, followed by a third dose 12 months after the first dose	
Second dose (year 1) and third dose (year 2) administered several weeks before the beginning of the disease-transmission season, which is usually April	
Boosters	
Existing data indicate that boosters might be needed, but additonal data are required before recommendations can be made regarding booster schedules	
Simultaneous administration with other vaccines	
Additional data needed	
If simultaneous administration is necessary, use separate syringes and separate injection sites	

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