VACCINATION AGAINST LYME DISEASE WITH RECOMBINANT *BORRELIA BURGDORFERI* OUTER-SURFACE LIPOPROTEIN A WITH ADJUVANT

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ABSTRACT

Background   The risk of acquiring Lyme disease is high in areas in which the disease is endemic, and the development of a safe and effective vaccine is therefore important.

Methods   We conducted a multicenter, double-blind, randomized trial involving 10,936 subjects who lived in areas of the United States in which Lyme disease is endemic. Participants received an injection of either recombinant *Borrelia burgdorferi* outer-surface lipoprotein A (OspA) with adjuvant or placebo at enrollment and 1 and 12 months later. In cases of suspected Lyme disease, culture of skin lesions, polymerase-chain-reaction testing, or serologic testing was done. Serologic testing was performed 12 and 20 months after study entry to detect asymptomatic infections.

Results   In the first year, after two injections, 22 subjects in the vaccine group and 43 in the placebo group contracted definite Lyme disease (P=0.009); vaccine efficacy was 49 percent (95 percent confidence interval, 15 to 69 percent). In the second year, after the third injection, 16 vaccine recipients and 66 placebo recipients contracted definite Lyme disease (P<0.001); vaccine efficacy was 76 percent (95 percent confidence interval, 58 to 86 percent). The efficacy of the vaccine in preventing asymptomatic infection was 83 percent in the first year and 100 percent in the second year. Injection of the vaccine was associated with mild-to-moderate local or systemic reactions lasting a median of three days.

Conclusions   Three injections of vaccine prevented most definite cases of Lyme disease or asymptomatic *B. burgdorferi* infection. (N Engl J Med 1998; 339:209-15.)

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LYME disease, which is caused by the tick-borne spirochete *Borrelia burgdorferi,* is now the most common vector-borne disease in the United States.[1] Since the initial descriptions of Lyme disease in 1977,[2,3] the number of cases has increased dramatically, and in recent years, more than 10,000 new cases have been reported each year to the Centers for Disease Control and Prevention (CDC).[1] Most cases have been clustered in the northeastern United States from Massachusetts to Maryland, in the Midwest in Wisconsin and Minnesota, and to a lesser degree, in the West in northern California.[1] Currently, there are no practical methods to control enzootic *B. burgdorferi* infection or prevent its spread.

Because of the increasing risk of Lyme disease, the development of a safe and effective vaccine for this infection has been a high priority.[4] In 1990, Fikrig and coworkers in the United States[5] and Schaible and his colleagues in Germany[6] demonstrated that high titers of antibody to outer-surface protein A (OspA) of the spirochete prevented *B. burgdorferi* infection in mice. Vaccination with OspA was subsequently shown to be effective in preventing the infection in hamsters, dogs, and monkeys.[7-9] With the success of OspA immunization in animals, studies were begun in human subjects.[10] We report the results of a multicenter, double-blind, randomized, phase 3

study involving nearly 11,000 subjects that was designed to determine the efficacy, safety, and immunogenicity of this vaccine.

METHODS

Study Sample

During an eight-week period in the winter of 1995, a total of 10,936 subjects (age, 15 to 70 years) were enrolled in the study by investigators at 31 sites in 10 states in which Lyme disease is endemic (see the Appendix). The study was approved by the human investigations committees at all centers. Determinations of sample size were based on the conservative estimate of a seasonal incidence of Lyme disease of 0.5 percent in the locations studied.[11-14] Assuming an attack rate of definite Lyme disease of 0.5 percent and a vaccine efficacy of 80 percent, we calculated that 8000 subjects — 4000 in each group — would be needed to provide the study with a power of 90 percent to detect a significant difference between the groups at the 0.05 level with a two-tailed test.[15] The enrollment goal was exceeded because of investigators' commitments to those already scheduled for participation in the study.

Vaccine and Placebo Preparations

Full-length OspA to which the lipid moiety had been added after translation (L-OspA) was expressed in *Escherichia coli* strain AR58, which had been transformed with plasmid pOA15 containing the *ospA* plasmid gene of *B. burgdorferi* strain ZS7. The vaccine contained 30 μg of purified L-OspA adsorbed to aluminum hydroxide in phosphate-buffered saline (L-OspA with adjuvant, SmithKline Beecham, Collegeville, Pa.). The placebo preparation was identical to the vaccine, except that it did not contain L-OspA.

Vaccination and Study Design

At the initial visit, the subjects provided their medical histories and underwent a brief physical examination. Subjects were excluded if they had active Lyme disease or had been treated for Lyme disease with antibiotics within three months before the study began, but those with a more remote history of Lyme disease were not excluded. Subjects were also excluded if they had other illnesses that might interfere with the assessment of Lyme disease, including those associated with swelling of the joints, musculoskeletal pain, and second-degree or third-degree atrioventricular block; if they were receiving treatments, such as long-term antibiotic therapy, that might hinder the evaluation of Lyme disease; if they had immunodeficiency, a history of alcohol or drug abuse, or hypersensitivity to any previous vaccine; if they had received an investigational drug or another type of vaccine in the four weeks before the initial visit; if they were to receive immune globulin or blood products during the study; or if they were pregnant or lactating.

After providing written informed consent, the study participants were randomly assigned with use of a computer-generated randomization table to receive three injections of either L-OspA with adjuvant or placebo. The second injection was given approximately 1 month after the first, and the third was given at 12 months. The first round of injections was given from January 23, 1995, through late March 1995, and in almost every case the second injection was administered by mid-May of that year; the third injection was administered to almost all participants between January 28, 1996, and April 30, 1996. Blood samples were drawn from all subjects at the time of the first injection and 2, 12, and 20 months later (the final visit took place at 20 months). A subgroup consisting of the 938 subjects enrolled at the Yale University School of Medicine also had blood samples drawn at 13 months to determine the levels of vaccine-induced antibodies to OspA.

Safety Assessment

Participants were asked to report all adverse events that occurred during the study, especially serious adverse events such as those requiring hospitalization. In addition, the 938 subjects enrolled at the Yale site completed diary cards specifying signs and symptoms that occurred on the day of vaccination and for the first three days after each injection.

Efficacy Assessment

All study participants were asked to call the investigator if they had symptoms of Lyme disease. In addition, the subjects received postcards during the two summer and fall seasons, the periods of disease transmission, asking whether they had symptoms of Lyme disease or had had any adverse events related to vaccination. Subjects with suspected cases of Lyme disease were asked to come to the clinic for evaluation. The evaluation included history taking, physical examination, serologic tests performed during the acute and convalescent stages of the illness, culture and polymerase-chain-reaction (PCR) tests of erythema migrans lesions, PCR tests of joint fluid or cerebrospinal fluid, and photographic documentation of erythema migrans or facial palsy. To detect asymptomatic infection, serum samples obtained from all study participants 12 and 20 months after study entry were tested for IgG antibody to *B. burgdorferi*. Antibiotic treatment was recommended according to published guidelines.[16]

Case Definitions and Data and Safety Monitoring Board

The case definitions for Lyme disease are given in Table 1. Patients who met the criteria for Lyme disease were classified as having definite, asymptomatic, or possible Lyme disease. A data and safety monitoring board, which was independent of the investigators, oversaw the study. The board monitored reports of possible adverse effects of the vaccine and confirmed, before unblinding, the categorization of all cases.

Laboratory Methods

Serologic testing was done exclusively by Western blotting (Mardex, San Diego, Calif.), since the standard enzyme-linked immunosorbent assay would be expected to give positive results in patients who had been vaccinated with OspA. The blots were read by experienced technicians according to the CDC criteria[17]; reactivity with the vaccine-induced 31-kd band was not reported, so that all investigators remained unaware of the subjects' treatment assignments. Serologic support for the diagnosis of Lyme disease was provided by the demonstration of seroconversion between base line and the acute phase of the illness or between the acute phase of the illness and convalescence. As proof of asymptomatic infection, documentation of IgG seroconversion between 2 months and 12 months or between 12 months and 20 months was required. Paired samples from the same subject were always tested in the same assay.

Skin-biopsy specimens from erythema migrans lesions were obtained with a 2-mm punch. Half of each sample was cultured in a 15-ml sterile tube containing modified Barbour–Stoenner–Kelly medium (Sigma, St. Louis) plus ciprofloxacin (0.4 μg per milliliter) and rifampin (40 μg per milliliter),[18] and the other half was tested for *B. burgdorferi* DNA by PCR. As soon as the culture tubes arrived in the laboratory, half the medium was replaced with fresh medium without antibiotics. The tubes were incubated at 33°C and examined weekly for one month by darkfield microscopy for motile spirochetes. PCR assays of skin-biopsy samples and joint fluid or cerebrospinal fluid samples were done as previously described.[19,20] The primer–probe set used targeted oligonucleotide base pairs 788 to 943 of the 50-kb plasmid encoding *ospA* and was followed by hybridization with an internal oligonucleotide probe labeled with phosphorus-32 on the 5′ end.

In the subjects at the Yale site, antibody responses to the protective epitope of OspA (a conformational epitope in the C-terminal half of the protein[21]) were determined with a murine monoclonal antibody (called LA-2) to that epitope in a competitive-inhibition enzyme immunoassay, as previously described.[6,22] The levels of LA-2–equivalent antibodies have been shown to

TABLE 1. CASE DEFINITIONS FOR LYME DISEASE.

Definite Lyme disease

Any of the following clinical manifestations observed by the investigator and at least one confirmatory laboratory test. In subjects with erythema migrans, a photograph of the lesion was also required.

Clinical manifestations
  Erythema migrans (an expanding red skin lesion, often with partial central clearing)
  Neurologic manifestations (meningitis, cranial neuritis)
  Musculoskeletal manifestations (with objective evidence of joint swelling in one or a few joints)
  Cardiovascular manifestations (atrioventricular block)
Laboratory confirmation
  Positive culture for *B. burgdorferi* from skin-biopsy sample
  Positive PCR result for *B. burgdorferi* DNA from skin-biopsy sample, cerebrospinal fluid, or joint fluid
  Seroconversion on Western blotting (defined as a negative result followed by a positive result)
    Positive IgM blot — at least 2 of the following 3 IgM bands: 23 kd (outer-surface protein C), 39 kd, and 41 kd
    Positive IgG blot — at least 5 of the following 10 IgG bands: 18, 23, 28, 30, 39, 41, 45, 58, 66, and 93 kd

Laboratory-confirmed asymptomatic *B. burgdorferi* infection

No symptoms
IgG seroconversion on Western blotting between month 2 and month 12 in the first year or between month 12 and month 20 in the second year

Possible Lyme disease

Influenza-like illness — fever, fatigue, headache, chills, muscle aches, mild stiff neck, or backache without cough, coryza, diarrhea, or vomiting — with IgM or IgG seroconversion on Western blotting
Physician-diagnosed erythema migrans lesions ≥5 cm without laboratory confirmation

Unconfirmed Lyme disease

All suspected cases that could not be confirmed

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correlate with the level of bactericidal activity against the spirochete.[22] A positive result was defined as a level of at least 100 ng of LA-2–equivalent antibodies per milliliter.

Statistical Analysis

The attack rates for all three categories of Lyme disease as well as the frequency of adverse events were compared between the vaccine and placebo groups with chi-square tests or, when appropriate, Fisher's exact tests. For attack rates of 0 percent, the confidence interval was calculated as described by Miettinen and Nurminen.[23] Vaccine efficacy, defined as the difference in the frequency of Lyme disease in vaccinated subjects as compared with that in the placebo group, was calculated according to the following formula: $1-$ (the attack rate in vaccine recipients/the attack rate in placebo recipients)×100; two-tailed 95 percent confidence intervals were also computed. The influence of age, sex, and geographic location on vaccine efficacy was analyzed in subjects with definite cases of Lyme disease with Cox proportional-hazards analysis, with the time of onset as the outcome variable. The assumption of proportional hazards was tested by correlating the Shoenfeld residuals and the time of onset.[24] Reverse cumulative curves of LA-2–equivalent antibody titers were compared among groups by the Wilcoxon rank-sum test.

RESULTS

Characteristics of the Subjects

The mean age of the 10,936 study subjects was 46 years (range, 15 to 70); 58 percent were male, and 98 percent were white. At study entry, 11 percent of the subjects reported a history of Lyme disease, and 2.3 percent had serologic evidence of previous *B. burgdorferi* infection, as shown by a positive IgG Western blot. Approximately 1 month after study entry, 99 percent of the subjects received the second injection (72 vaccine recipients did not receive it, as compared with 50 placebo recipients, P=0.045); and 12 months after study entry, 92 percent, with similar proportions in the vaccine and placebo groups, were given the third injection. No significant differences were observed between the vaccine and placebo groups regarding age, sex, race, or withdrawal from the study; the only significant difference between the groups was in the number receiving the second injection.

Vaccine Efficacy

During the first year, 1109 of the 10,936 subjects (10 percent) were evaluated for suspected cases of Lyme disease (Table 2). In 89 percent of these subjects, other diagnoses were made. During the second year, 808 subjects (7 percent) were evaluated for this infection, and other diagnoses were made in 82 percent. During both years, the patients in whom other diagnoses were made were almost evenly divided between the vaccine and placebo groups. The remaining subjects met the criteria for definite, asymptomatic, or possible Lyme disease.

In the first year, after two injections, 22 subjects in the vaccine group and 43 in the placebo group had definite Lyme disease, usually manifested by erythema migrans (P=0.009); vaccine efficacy, analyzed according to the intention to treat, was 49 percent (95 percent confidence interval, 15 to 69 percent) (Table 2). In the second year, after the third injection, 16 vaccine recipients and 66 placebo recipients had definite Lyme disease (P<0.001); vaccine efficacy was 76 percent (95 percent confidence interval, 58 to 86 percent). Among the subjects with definite cases, no significant variation was found in vaccine efficacy in either year according to age, sex, time of onset, or geographic location.

By definition, each subject with a definite case of Lyme disease had a characteristic clinical picture and evidence of *B. burgdorferi* infection on the basis of culture, PCR assay, or Western blotting. When the results for both years were added together, *B. burgdorferi* was cultured from erythema migrans skin lesions in 105 of 134 subjects with definite cases (78 percent) in whom skin biopsies were done, spirochetal DNA was detected in 85 of 132 skin-biopsy samples (64 percent) on PCR testing, and IgM or IgG seroconversion to *B. burgdorferi* or both were found in 94 of 146 subjects (64 percent). When the subjects were grouped according to the method of laboratory confirmation, the rates of vaccine efficacy were similar with each method.

TABLE 2. ATTACK RATES OF LYME DISEASE AND VACCINE EFFICACY IN THE STUDY POPULATION.*

LYME DISEASE	YEAR 1						YEAR 2					
	VACCINE (N=5469)		PLACEBO (N=5467)		P VALUE	VACCINE EFFICACY (95% CI)		VACCINE (N=5469)		PLACEBO (N=5467)		P VALUE	VACCINE EFFICACY (95% CI)
	No. of Cases	Attack Rate	No. of Cases	Attack Rate			No. of Cases	Attack Rate	No. of Cases	Attack Rate		
		%		%		%		%		%		%
Definite												
Erythema migrans	21	0.38	41	0.75	0.01	49 (14 to 70)	15	0.27	65	1.19	<0.001	77 (60 to 87)
Neurologic involvement	0	0	1	0.02			0	0	1	0.02		
Arthritis	1	0.02	1	0.02			1	0.02	0	0		
Carditis	0	0	0	0			0	0	0	0		
Total definite cases	22	0.40	43	0.79	0.009	49 (15 to 69)	16	0.29	66	1.21	<0.001	76 (58 to 86)
Asymptomatic												
Asymptomatic infection	2	0.04	13	0.24	0.004	83 (32 to 97)	0	0	15	0.27	0.001	100 (26 to 100)
Total definite and asymptomatic cases	24	0.44	56	1.02	<0.001	57 (31 to 73)	16	0.29	81	1.48	<0.001	80 (66 to 88)
Possible												
Influenza-like illness with seroconversion	13	0.24	17	0.31	0.46	24 (−57 to 63)	12	0.22	21	0.38	0.12	43 (−16 to 72)
Physician-diagnosed erythema migrans	7	0.13	9	0.16	0.61	22 (−109 to 71)	7	0.13	6	0.11	0.78	−17 (−247 to 61)
Total definite, asymptomatic, and possible cases	44	0.80	82	1.50	0.001	46 (23 to 63)	35	0.64	108	1.98	<0.001	68 (53 to 78)
Unconfirmed	515	9.42	468	8.56	0.12		339	6.20	326	5.96	0.61	

*CI denotes 95 percent confidence interval.

Serum samples were obtained from study subjects 12 and 20 months after study entry, and positive samples were retested with base-line samples. During the first year, 2 subjects in the vaccine group and 13 in the placebo group had asymptomatic IgG seroconversion (P=0.004) (Table 2). In the second year, all 15 subjects with asymptomatic seroconversion were in the placebo group (P=0.001). Thus, vaccine efficacy in this group was 83 percent in the first year and 100 percent in the second year.

Thirty subjects in the first year and 33 in the second year had influenza-like symptoms accompanied by IgM or IgG seroconversion, or both, that were classified as possible Lyme disease (Table 2). For this category, vaccine efficacy was 24 percent during the first year (P=0.46) and 43 percent during the second year (P=0.12). For physician-diagnosed erythema migrans without laboratory confirmation, the vaccine efficacy was low during both years of the study.

Antibody Responses to the Protective Epitope of OspA

At study entry, levels of antibody to the protective epitope of OspA (LA-2–equivalent antibody) were undetectable in 932 of the 938 participants at the Yale site; 6 seropositive subjects had low titers of antibodies as a result of a previous natural infection. At month 2, one month after the second injection, 95 percent of the vaccine recipients had positive test results for LA-2–equivalent antibody (levels of 100 ng per milliliter or higher), and at month 13, one month after the third injection, 99 percent had positive results associated with a marked anamnestic response to OspA (Fig. 1). The titers did not differ significantly according to age. Antibody levels in placebo recipients were undetectable at each time point.

In an effort to determine the role of LA-2–equivalent antibody in vaccine failure, antibody levels were measured in samples obtained at month 2 from 20 subjects in the vaccine group who had breakthrough cases of definite Lyme disease, 512 subjects in the vaccine group in whom the diagnosis of Lyme disease was not confirmed, and 395 vaccinated subjects from the Yale site. The titers were significantly lower in the vaccinated subjects with breakthrough cases of Lyme disease than in the other two groups of subjects (P≤0.01 for each comparison) (Fig. 2).

Adverse Effects

When the groups were analyzed according to the intention to treat, significantly more subjects in the vaccine group noted soreness, redness, or swelling at the injection site than did those in the placebo group (Table 3). In addition, significantly more vaccine than placebo recipients reported systemic symptoms of myalgias, achiness, fever, or chills that were thought to be related or possibly related to vaccination. At the Yale site, where information about adverse events
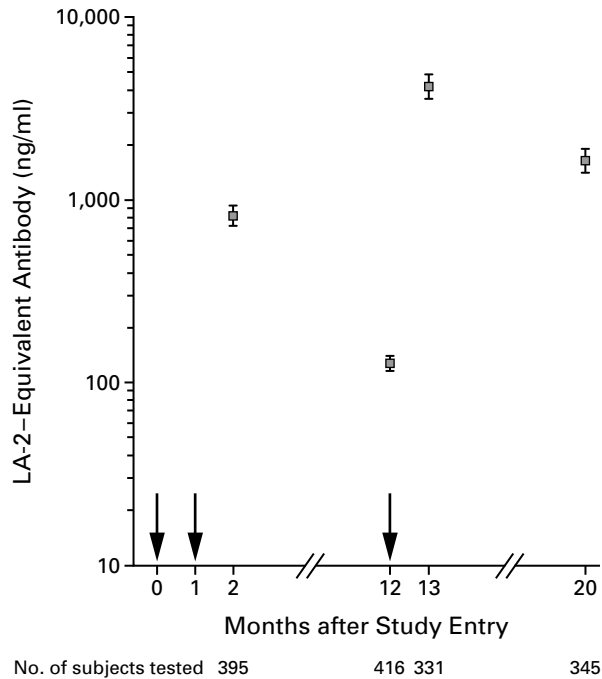
Figure 1. Levels of Antibody to the Protective Epitope of OspA (LA-2–Equivalent Antibody) in Vaccine Recipients at the Yale Site.

At month 2, one month after the second injection, the geometric mean antibody titer was 816 ng per milliliter. Ten months later, the mean titer had declined. At month 13, one month after the third injection, a marked anamnestic response was seen and the mean value 4127 ng per milliliter. At month 20, the mean response was still twice as high as at month 2. The I bars indicate 95 percent confidence intervals. Arrows indicate injections.

Figure 2. Reverse Cumulative Curve of LA-2–Equivalent Antibody Levels at Month 2 in 20 Vaccinated Subjects with Breakthrough Cases of Definite Lyme Disease, 512 Vaccinated Subjects Evaluated for Lyme Disease during Year 1 in Whom the Diagnosis Was Not Confirmed, and 395 Vaccinated Subjects from the Yale Site.

At month 2, one month after the second injection, the titers were significantly lower in vaccinated subjects with breakthrough cases of Lyme disease than in the other two groups of subjects (P≤0.01 for each comparison).

during the first three days after injections was solicited by diary cards, 63 percent of vaccine recipients recorded related or possibly related early systemic symptoms, as compared with 53 percent of placebo recipients (P=0.004). At the other sites, 19.4 percent of those in the vaccine group reported such early systemic symptoms, as compared with 15.1 percent of those in the placebo group (P<0.001). These reactions usually occurred within 48 hours after vaccination and lasted a median of 3 days. They were usually mild or moderate in severity, and the severity usually did not increase with subsequent injections. At the Yale site, where information was solicited about fever, no patient reported a temperature above 39°C. No hypersensitivity reactions were noted.

Thirty days or more after the injections, there were no significant differences between vaccine and placebo recipients in the type or frequency of symptoms (Table 3). Moreover, no unusual patterns of symptoms were observed, in the group as a whole or in the 2.3 percent of subjects who were seropositive at study entry. Similarly, the 11 percent who reported a history of Lyme disease were not different
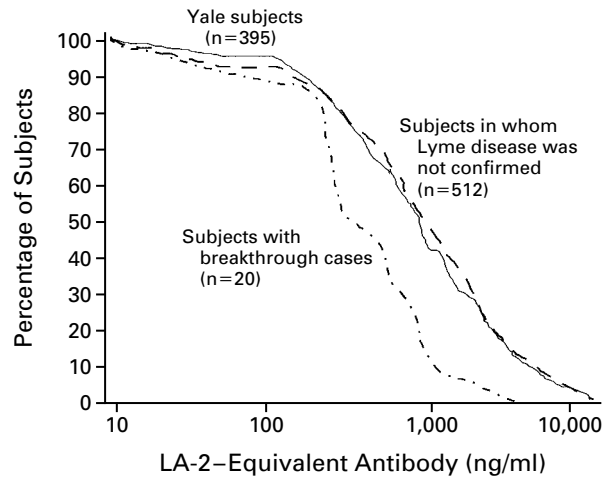
from the rest of the subjects with respect to the safety profile of the vaccine.

DISCUSSION

This study showed that a high level of protection from *B. burgdorferi* infection can be achieved with three injections of L-OspA with adjuvant. After two injections, vaccine efficacy with respect to definite cases of Lyme disease was 49 percent, and after three injections, it was 76 percent. Since *B. burgdorferi* may establish a latent infection, subjects with asymptomatic seroconversion were also identified, and the vaccine was found to be highly effective in preventing this type of infection. If the serologic status of these subjects had not been known and if they had not been treated with antibiotic therapy, arthritis or chronic neuroborreliosis might have developed in some. In such subjects, the vaccine would prevent these serious, late manifestations of Lyme disease.

Since the mechanism of this vaccine is thought to be antibody-mediated killing of the spirochete in the tick,[25] OspA antibody titers are likely to be the critical factor in determining the vaccine's efficacy. In support of this hypothesis, levels of antibody to the protective epitope of OspA were significantly lower one month after the second injection in vaccinated subjects with breakthrough cases of definite Lyme disease than in vaccinated subjects in whom Lyme disease was not confirmed or in vaccinated subjects followed at the Yale site. Moreover, the reason that

TABLE 3. Percentage of Subjects with Symptoms with an Overall Incidence of at Least 1 Percent That Were Classified as Related or Possibly Related to Vaccination or Unrelated to Vaccination.

Symptom	Vaccine Group	Placebo Group	P Value
	percent		
Related or possibly related to vaccination*			
Local at injection site			
Soreness	24.1	7.6	<0.001
Redness	1.8	0.5	<0.001
Swelling	0.9	0.2	<0.001
Systemic			
Early (≤30 days)			
Arthralgia	3.9	3.5	0.34
Headache	3.0	2.5	0.14
Myalgias	3.2	1.8	<0.001
Fatigue	2.3	2.0	0.37
Achiness	2.0	1.4	0.01
Influenza-like illness	2.0	1.1	<0.001
Fever	2.0	0.8	<0.001
Chills	1.8	0.5	<0.001
Upper respiratory tract infection	1.0	1.1	0.69
Total†	19.4	15.1	<0.001
Late (>30 days)			
Arthralgia	1.3	1.2	0.54
Total†	4.1	3.4	0.06
Unrelated to vaccination			
Early (≤30 days)	27.1	27.9	0.37
Late (>30 days)	53.3	52.6	0.48

*Data from the Yale site about related or possibly related early local or systemic symptoms were collected by a different method (diary cards) and are reported separately. In this table, the data on these events are based on the remaining 4999 subjects in each of the groups. Data on late systemic symptoms or unrelated events were collected in the same way in all patients, and thus, the data on these events are based on all 5469 subjects in the vaccine group and all 5467 subjects in the placebo group.

†Totals include all early or late related or possibly related systemic events, not just those with a frequency of at least 1 percent.

vaccine efficacy is higher in the second year than in the first year is undoubtedly that an anamnestic antibody response follows the third injection of vaccine. Among subjects at the Yale site, the geometric mean titer of LA-2–equivalent antibody one month after the third injection was five times as high as the titer measured one month after the second injection. It will be important to learn whether there is an antibody correlate of protection. Moreover, it will be critical to determine the duration of protection afforded by three injections of vaccine and whether or when additional booster injections will be necessary.

Subjects who had an influenza-like illness with *B. burgdorferi* seroconversion or erythema migrans without laboratory confirmation of infection were classified as having possible Lyme disease because of the potential for misdiagnosis. Erythema migrans often has a characteristic appearance, but it may be mistaken for other dermatologic entities.[26] Although some subjects with physician-diagnosed erythema migrans may have had *B. burgdorferi* infection, misdiagnosis is presumably the reason that vaccine efficacy was not demonstrated in subjects who were thought to have erythema migrans without laboratory documentation of the infection. In addition, infection with other tick-borne agents (babesia or ehrlichia), which are carried by the same tick that transmits *B. burgdorferi,* may cause influenza-like symptoms,[27,28] and ehrlichia may cause false positive results on Western blotting for Lyme disease.[28] It is likely that some patients with an influenza-like illness and seroconversion had these infections in addition to or instead of *B. burgdorferi* infection.

The L-OspA vaccine with adjuvant was associated with soreness, redness, or swelling at the site of vaccination and systemic reactions, including fever, chills, myalgia, and achiness, that lasted for a median of three days. However, vaccination with OspA was not associated with a significantly higher incidence of late events or clinical syndromes (more than 30 days after vaccination). In the natural infection, the cellular and humoral immune responses to OspA correlate with the occurrence of prolonged and severe Lyme arthritis, and in genetically susceptible persons, particularly those with HLA-DR4, this response is associated with persistent arthritis despite treatment with antibiotics.[29,30] Recently, it has been proposed that autoimmunity develops within the proinflammatory milieu of the joints of such patients because of molecular mimicry between the dominant T-cell epitope of OspA and human-leukocyte-function–associated antigen 1 (hLFA-1).[31] Although inflammatory polyarthritis developed in several subjects during the study, these subjects were found in both the vaccine and placebo groups. As with any vaccine trial, rare side effects may not be recognized in comparisons of vaccine and placebo groups, even in studies of nearly 11,000 subjects.

In summary, three injections of L-OspA with adjuvant prevented most definite cases of Lyme disease or asymptomatic *B. burgdorferi* infection and had an acceptable rate of local or systemic side effects. Thus, this vaccine provides an important new public health approach to the prevention of Lyme disease.

APPENDIX

In addition to the authors, members of the Lyme Disease Vaccine Study Group were as follows: *New England sites:* Connecticut — S. Cohen, J. Boyer, K. Hanrahan, Clinical Research Consultants, Trumbull; P. Dalgin, J. Dalgin, A. Garrett, M. Petelaba, Fairfield County Lyme Vaccine Study, Stamford; H. Feder, S. Good, University of Connecticut Health Center, Farmington; J. Green, K. Miller, M. Spiegel, G. Daniel, R. Jacob, Arthritis Associates of Connecticut–New York, Danbury; E. Maderazo, M. Maiorano, Norwich; A. Seidner, L. Bruno, Middlesex Hospital, Middletown; P. Si-

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