

A VACCINE CONSISTING OF RECOMBINANT *BORRELIA BURGdorFERI* OUTER-SURFACE PROTEIN A TO PREVENT LYME DISEASE

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ABSTRACT

Background Lyme disease is a multisystem inflammatory disease caused by infection with the tick-borne spirochete *Borrelia burgdorferi* and is the most common vector-borne infection in the United States. We assessed the efficacy of a recombinant vaccine consisting of outer-surface protein A (OspA) without adjuvant in subjects at risk for Lyme disease.

Methods For this double-blind trial, 10,305 subjects 18 years of age or older were recruited at 14 sites in areas of the United States where Lyme disease was endemic; the subjects were randomly assigned to receive either placebo (5149 subjects) or 30 μg of OspA vaccine (5156 subjects). The first two injections were administered 1 month apart, and 7515 subjects also received a booster dose at 12 months. The subjects were observed for two seasons during which the risk of transmission of Lyme disease was high. The primary end point was the number of new clinically and serologically confirmed cases of Lyme disease.

Results The efficacy of the vaccine was 68 percent in the first year of the study in the entire population and 92 percent in the second year among the 3745 subjects who received the third injection. The vaccine was well tolerated. There was a higher incidence of mild, self-limited local and systemic reactions in the vaccine group, but only during the seven days after vaccination. There was no significant increase in the frequency of arthritis or neurologic events in vaccine recipients.

Conclusions In this study, OspA vaccine was safe and effective in the prevention of Lyme disease. (N Engl J Med 1998;339:216-22.)

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LYME disease is a multisystem inflammatory disease caused by *Borrelia burgdorferi*, transmitted by the bite of infected ixodes ticks. *B. burgdorferi* elicits an antibody response to a repertoire of borrelial proteins, including outer-surface protein C (OspC) and flagellin. In the early stage of the disease, free antibodies to OspC and flagellin are measurable, whereas only later are responses to outer-surface protein A (OspA) — a surface lipoprotein — demonstrable in standard assays.¹ The protective role of antibodies to *B. burgdorferi* has been explored in animal models of Lyme disease.² Findings indicated that antibodies against OspA

were protective,³⁻⁸ making this antigen a likely candidate for a vaccine.⁹⁻¹³

Early clinical trials demonstrated that recombinant OspA was immunogenic and well tolerated,^{14,15} even in subjects with a history of Lyme disease.¹⁶ A dose-ranging study showed that as compared with doses of 1, 5, and 10 μg , a dose of 30 μg of the OspA vaccine elicited an optimal antibody response without causing an increased rate of symptomatic reactions. We conducted a multicenter, randomized, double-blind, placebo-controlled study in areas of the United States in which Lyme disease is endemic to evaluate the protective efficacy of a 30- μg dose of vaccine in adults at risk for *B. burgdorferi* infection.

METHODS

Vaccine Preparation

The vaccine consists of purified OspA lipoprotein produced as described previously.^{14,17} The lipoprotein was expressed in *Escherichia coli* and purified from the Triton X-114 detergent phase of chromatography with two ion-exchange resins: diethylaminoethyl-Sephacel and S-Sepharose. Sodium dodecyl sulfate-polyacrylamide-gel electrophoresis of the material purified with use of S-Sepharose indicated that OspA constitutes approximately 92 to 95 percent of the total protein. The material contained less than 0.05 endotoxin unit per microgram of OspA on testing with the limulus amoebocyte lysate assay¹⁸ and was nonpyrogenic in rabbits at a dose of 0.17 μg per kilogram of body weight (equivalent on the basis of weight to a 10- μg dose in a 60-kg human).

For the preparation of the final vaccine, the purified OspA was sterilized by passage through a 0.2- μm filter and diluted to vaccine strength in phosphate-buffered saline, with a final detergent concentration of less than 0.02 percent. The protective epitopes of the protein appear to be conserved after recombinant expression and purification: serum from vaccinated mice inhibited the growth of the spirochete in vitro.¹⁹ The vaccine contained 30 μg of purified recombinant protein and was supplied in single-use vi-

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als. The identical-appearing placebo preparation consisted of phosphate-buffered saline without OspA and was also provided in single-use vials. Vaccine was administered under double-blind conditions.

Study Sample and Design

The study subjects were healthy men and women, 18 years of age or older, who were at risk for Lyme disease because they lived, worked, or spent their leisure time in areas in which Lyme disease was endemic as defined by the Centers for Disease Control and Prevention (CDC) and county and state health departments in Connecticut, Massachusetts, New Jersey, New York, and Wisconsin. Subjects were excluded from the study if they were receiving long-term antibiotic therapy, had received any vaccine for Lyme disease within the 18 months before the study began, or had a history consistent with the occurrence of Lyme disease within the two months preceding the study.

A total of 10,305 subjects (age range, 18 to 92 years of age) were enrolled at 14 study sites in areas of the United States in which Lyme disease was endemic and were randomly assigned to receive two doses of either 30 μ g of OspA vaccine or placebo, given one month apart, according to a preset randomization schedule. Randomization was balanced at each study center in treatment blocks of 10. The first injection was given between March 1, 1994, and April 30, 1994, and the second injection was given approximately one month later, between April 1, 1994, and May 31, 1994. At the request of the Food and Drug Administration, we obtained data on a third dose of vaccine given 12 months after the first injection. A total of 7515 subjects received a third (booster) injection of placebo or vaccine between March 1, 1995, and April 30, 1995. The subjects were observed during the two seasons in which the risk of disease transmission was greatest, irrespective of whether they had received the booster dose.

The sample size was selected to test the null hypothesis of 60 percent efficacy of the vaccine against the alternative hypothesis of superior efficacy. Assuming an attack rate of 0.8 percent (67 cases in the control group and 13 cases in the vaccine group), we calculated that a sample size of 10,000 (5000 in each group) was sufficient to provide the study with a power of 81 percent to reject the null hypothesis according to a one-sided hypothesis test with a type I error of 5 percent. The study design was based on a one-sided alternative, but two-sided results are given to conform with the standard practice of the *Journal*.

Vaccination Protocol

Before receiving the first injection, all subjects provided written informed consent by signing a document approved by the institutional review board at each participating site and were counseled on Lyme disease and its prevention. A single dose (0.5 ml) of vaccine or placebo was injected intramuscularly into the deltoid. A second dose was administered 30 days after the first dose. The timing of entry into the study was such that both inoculations occurred before the end of May 1994 — before the start of the “Lyme disease season” in the areas included in the study. Subjects who enrolled in the extension study received a single booster dose of vaccine or placebo approximately 12 months after the first dose. All these subjects received the booster dose before the end of May 1995.

Follow-up Procedures

Identification of Cases of Lyme Disease

Subjects were instructed to contact the study center immediately if they had any symptoms suggestive of Lyme disease. In addition, the subjects were also monitored monthly by mail (postcards), telephone, or both for adverse events during the first nine months after vaccination and then every three months for a total of two years (covering two Lyme disease seasons), the follow-up period of this study. Subjects who did not respond to any single

postcard or who replied positively to any question on a postcard were contacted by study personnel.

Serologic Assessment

Subjects in whom Lyme disease was suspected returned to the study center, where a clinical evaluation was performed by the investigator and serum samples were obtained during the acute and convalescent phases of the illness. Western blot analyses (MarDx Western blot kit, MarDx Diagnostics, Carlsbad, Calif.) to determine whether IgG or IgM antibodies to *B. burgdorferi* were present were performed for all subjects with suspected cases of Lyme disease by the central laboratory (Division of Infectious Diseases, New York Medical College, Valhalla), according to the manufacturer's instructions. Results were considered positive if the serum sample contained IgM antibodies that reacted with at least 2 of the following 3 bands: 25 kd (corresponding to band 23, which indicates OspC), 39 kd, and 41 kd within the first 60 days after the onset of erythema migrans, symptoms, or both or with IgG to at least 5 of the following 10 bands: 21, 25 (23), 28, 30, 39, 41, 45, 58, 66, and 83 (corresponding to band 93) kd at any time after the onset of symptoms. The reports of the results of these tests were sent to the investigators and did not include specific information on reactivity to OspA bands.

Safety Assessment

Subjects reported any adverse effects that occurred within seven days after each vaccination. They were also asked to report any unexpected visits to physicians other than the investigators that took place in the first 30 days after each injection. Serious or unexpected adverse events were followed up throughout the study.

Case Definitions

Data on all subjects with symptoms that the local investigator decided were consistent with the presence of Lyme disease were reviewed by an independent data and safety monitoring board whose members were unaware of subjects' treatment assignments. The diagnosis was confirmed only if it met the strict CDC case definition,²⁰ which requires the presence of erythema migrans or later manifestations of Lyme disease, with laboratory confirmation in either case. Erythema migrans had to be documented by a photograph or a definitive descriptive clinical note clearly stating the size of the lesion. Laboratory confirmation consisted of proof of seroconversion (from seronegative results at base line to seropositive results at a subsequent analysis). In the absence of laboratory confirmation, the presence of erythema migrans, regardless of the size of the lesion, or of late manifestations of Lyme disease was insufficient for a diagnosis of Lyme disease.

Efficacy Analysis

According to criteria established before the study began, for a case of Lyme disease to be included in the efficacy analysis, the signs and symptoms must have begun to appear at least one month after the second injection and the Western blotting criteria described above must have been met. The primary efficacy end point was based on the number of definite cases of Lyme disease, as determined by the data and safety monitoring board. The risk of Lyme disease in vaccine recipients as compared with placebo recipients was calculated by dividing the number of cases in each group by the number of subjects in each group. The relative risk is the ratio of the two risks. Vaccine efficacy and the associated 95 percent confidence interval were derived from the relative risk and its confidence interval with the following equation: vaccine efficacy = 1 – relative risk. We computed exact 95 percent confidence intervals according to the assumption that the number of cases in the vaccine group followed a binomial distribution (whereas the total number of cases was fixed), correcting the estimates of the upper and lower bounds for the number of subjects in each treatment group. The study had insufficient power to compare treatments within subgroups.

The data were analyzed in the following categories: all cases occurring during the first year per protocol, all cases occurring during the second year, all cases occurring in both years, cases occurring in the second year among subjects who did not receive the booster dose, cases occurring in the second year among subjects who did receive the booster dose, and cases occurring in both years among subjects who received three injections. No interim efficacy analyses were planned or performed. We used SAS software (version 6.12, SAS Institute, Cary, N.C.) for all analyses.

Statistical Analysis

Adverse events were classified according to the Medical Dictionary for Drug Regulatory Affairs.²¹ The rates of adverse events in the vaccine and placebo groups were compared with Fisher's exact test among subjects who received only one injection during the original study phase, subjects who received two injections during the original study phase, and subjects who received two injections as well as the booster dose. All P values are two-sided.

RESULTS

Characteristics of the Subjects

A total of 5149 subjects were randomly assigned to receive placebo, and 5156 were assigned to receive OspA vaccine. The proportion of subjects enrolled at each of the 14 study sites ranged from 1.4 to 15.8 percent of the total population. There were no significant differences with respect to age, sex, race, or history of Lyme disease between groups; the predominance of whites in the study populations reflects the makeup of the communities from which subjects were recruited (Table 1).

In the first year of the study, 211 subjects in the vaccine group and 187 subjects in the placebo group withdrew or were withdrawn from the study or died. The respective numbers for the second year of the study (booster phase) were 43 and 17. Reasons for not completing the study are given in Figure 1.

All subjects received at least one dose of vaccine or placebo; 5050 (98.1 percent) subjects in the placebo group and 5034 (97.6 percent) subjects in the vaccine group received the first two inoculations. A total of 3770 (73.2 percent) subjects in the placebo group and 3745 (72.6 percent) in the vaccine group received two immunizations and a booster dose. Thus, 1280 (24.9 percent) subjects in the placebo group and 1289 (25.0 percent) subjects in the vaccine group received only the first two doses, but not the booster.

Confirmed Cases of Lyme Disease

During the two-year observation period, 1734 subjects reported clinical symptoms that were considered by the investigators to be consistent with a diagnosis of Lyme disease and required Western blot testing. These potential cases were reviewed to determine whether the clinical and laboratory results warranted further review by the data and safety monitoring board. A total of 499 were reviewed in depth by the board, and 86 cases of Lyme disease in 84 subjects were confirmed. Five subjects (6.0 per-

TABLE 1. BASE-LINE CHARACTERISTICS OF THE SUBJECTS.

CHARACTERISTIC	INITIAL PHASE		BOOSTER PHASE	
	PLACEBO GROUP (N=5149)	VACCINE GROUP (N=5156)	PLACEBO GROUP (N=3770)	VACCINE GROUP (N=3745)
Age (yr)				
Mean	46.2	46.1	48.7	48.7
Range	18–88	18–92	19–86	19–94
Male sex (%)	59.4	59.4	59.2	59.6
Range at the 14 study centers	42.3–67.0	45.8–68.4	40.3–69.1	46.7–71.8
White race (%)	98.7	98.8	98.8	98.8
History of Lyme disease (%)	12.7	13.2	12.8	13.3
Range at the 14 study centers	1.4–32.4	5.6–30.7	1.6–34.3	6.7–32.9

cent) did not have erythema migrans as the presenting feature. In the first year of the study, there was one case of Lyme arthritis in a placebo recipient and one case of radiculoneuritis in a placebo recipient. In the second year of the study, there was one case of Lyme arthritis in a placebo recipient; one case of isolated facial-nerve palsy in a vaccine recipient, which occurred 11 days after the booster injection; and one case of arthritis in a placebo recipient that was followed, 6 months later, by tertiary neuroborreliosis, with a cerebrospinal fluid analysis revealing antibodies to *B. burgdorferi*.

Vaccine Efficacy

During the Lyme disease season in the first year of the study, all subjects were monitored for evidence of Lyme disease and there were only 49 with confirmed cases of disease: 37 in the placebo group and 12 in the vaccine group. The overall vaccine efficacy was 68 percent (95 percent confidence interval, 36 to 85 percent) (Table 2). In the second year of the study, 35 cases of confirmed Lyme disease were reported: 28 in the placebo group and 7 in the vaccine group. Vaccine efficacy among subjects who received the booster dose was 92 percent (95 percent confidence interval, 69 to 97 percent). In the absence of the booster dose, there was little demonstrable effect of vaccination during the Lyme disease season in the second year of the study; however, because there was such a wide confidence interval, these results do not rule out the possibility of a significant protective effect in this population.

The efficacy of the vaccine did not differ significantly between subjects who reported prior exposure to Lyme disease and those with no history of exposure (86.3 percent [95 percent confidence interval, 0 to 96.9 percent] vs. 68.1 percent [95 percent confidence interval, 27.0 to 84.9 percent] in the first year; 100 percent [95 percent confidence interval, 43.3 to

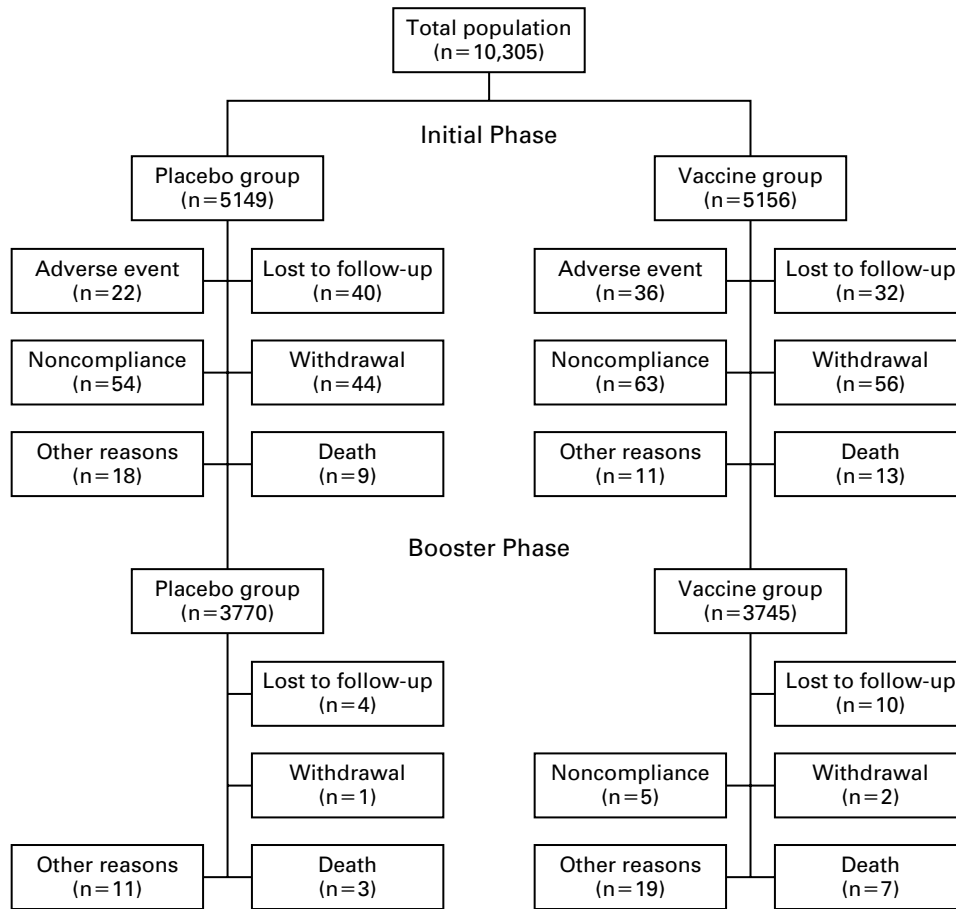


Figure 1. Reasons for Not Completing the Study. Subjects were followed irrespective of the number of immunizations they received.

100 percent] vs. 86.6 percent [95 percent confidence interval, 42.2 to 95.6 percent] in the second year among subjects who received the booster dose).

In the first year of the study, the efficacy rate was highest among subjects less than 60 years old. In the second year of the study, among subjects who received the booster dose, the rate was 100 percent in all women and in all men less than 60 years old.

Overall, cases of Lyme disease were confirmed at 11 of the 14 study sites. The percentage of subjects with definite Lyme disease was significantly higher in the placebo group than in the vaccine group (1.3 percent vs. 0.4 percent, $P<0.001$). In addition, the percentage reporting symptoms of Lyme disease was significantly higher in the placebo group than in the vaccine group (5.5 percent vs. 4.2 percent, $P=0.002$), as was the percentage with seroconversion (1.5 percent vs. 0.6 percent, $P<0.001$).

Vaccine Safety

As expected, adverse effects were more common in the subjects who received the vaccine than in

those who received placebo. In the first year of the study, 2857 events were reported by 1661 of the 5156 subjects in the vaccine group (32 percent), whereas 2313 events were reported by 1431 of the 5149 placebo recipients (28 percent). In the second year of the study, among those who received the booster dose, 2818 events were reported by 1361 of 3745 vaccine recipients (36 percent) and 2370 events were reported by 1211 of 3770 placebo recipients (32 percent). The difference in the incidence of adverse effects between groups was significant only during the first seven days after vaccination (Table 3). The most frequently reported vaccine-related effects were pain or tenderness at the injection site and local muscle pain. The effects were typically mild and self-limited.

There was no significant difference between groups in the overall incidence of adverse effects reported as having occurred more than seven days after the first or second vaccination ($P=0.10$), although the differences in some of the individual effects were significant (data not shown). After the first and second

TABLE 2. VACCINE EFFICACY.

GROUP	PLACEBO GROUP		VACCINE GROUP		VACCINE EFFICACY (95% CI)*
	NO. OF SUBJECTS	NO. OF CASES	NO. OF SUBJECTS	NO. OF CASES	
%					
First year of study					
Two injections, per protocol	5149	37	5156	12	68 (36-85)
Second year of study					
Two injections and booster	3770	26	3745	2	92 (69-97)
Two injections, no booster	1379	2	1411	5	0 (0-60)
Both years of study					
Three injections, per protocol	5050	60	5034	14	77 (58-88)

*CI denotes confidence interval.

TABLE 3. INCIDENCE OF ADVERSE EFFECTS WITHIN SEVEN DAYS AFTER INJECTION.

VARIABLE	VACCINE GROUP	PLACEBO GROUP
First injection		
No. of subjects	5156	5149
Adverse effect (%)		
Any	9.8	4.1
Musculoskeletal	6.4	1.3
Myalgia	5.5	0.6
General	1.8	0.9
Pain at injection site	0.3	0.04
Second injection		
No. of subjects	5050	5034
Adverse effect (%)		
Any	6.1	3.1
Musculoskeletal	3.3	1.1
Myalgia	2.5	0.4
General	1.7	0.8
Pain at injection site	0.8	0.1
Third injection		
No. of subjects	3745	3770
Adverse effect (%)		
Any	11.2	5.5
General	7.3	2.6
Tenderness	2.3	0.2
Pain at injection site	1.5	0.2
Unspecified pain	1.0	0.1
Reaction at injection site	0.8	0.2
Swelling	0.6	0.1
Pain in limb	0.5	0.02
Edema at injection site	0.5	0
Rigors	0.2	0
Skin or subcutaneous tissue	2.1	0.2
Erythematous rash	1.9	0.1

immunizations, the placebo group had a higher incidence of viral infection (25 subjects, as compared with 9 subjects in the vaccine group; $P=0.01$) and hypoesthesia (9 subjects, as compared with 2 subjects; $P=0.04$). After the booster dose, more subjects in the placebo group than in the vaccine group reported pneumonia (27 subjects vs. 13 subjects, $P=0.04$), colonic polyps (8 vs. 1, $P=0.04$), and coronary artery disease (12 vs. 3, $P=0.04$). The vaccine group had a higher incidence of otitis externa (7 subjects vs. 1 subject, $P=0.04$), pain in the injected arm (21 vs. 10, $P=0.05$), and headache (40 vs. 23, $P=0.02$). There was no significant difference ($P=0.94$) in the occurrence of neurologic events between the vaccine group (77 subjects) and the placebo group (76 subjects).

Despite the higher overall incidence of adverse effects in the vaccine group, there were no significant differences between the groups in the frequency of severe effects or serious or unexpected effects. During the two years of observation, severe effects were reported by 2 to 3 percent of vaccine recipients and 4 percent of placebo recipients and serious or unexpected effects were reported by 4 to 5 percent in each group. There was no significant difference between the groups in the number of deaths (20 in the vaccine group and 12 in the placebo group, $P=0.21$ by Fisher's exact test). All deaths were reviewed by the data and safety monitoring board, and none were considered to have been related to vaccination.

There were only three cases of Lyme arthritis in the study population during the clinical follow-up. There was no evidence that the vaccine predisposed subjects with prior self-reported Lyme arthritis to an exacerbation of arthritis. There was no increase in the frequency of erythema migrans in subjects with a history of Lyme disease or Lyme arthritis in either group. There was no evidence of a vaccine-associated

exacerbation of neurologic events or conditions among the few subjects with a history of such conditions. Early in the first year, there were two cases of transverse myelitis in each study group, with no additional events occurring in the remainder of the study. In all cases, the data and safety monitoring board determined that the transverse myelitis represented neither a case of Lyme disease nor an adverse effect related to vaccination.

DISCUSSION

We evaluated the efficacy and safety of an OspA vaccine without adjuvant, which contained 30 μg of purified recombinant protein, in more than 10,000 adults. Although the total number of confirmed cases of Lyme disease reported during the two-year surveillance period was somewhat lower than anticipated, largely because of the very stringent case definition used, vaccine efficacy was high.

Two doses of vaccine administered one month apart reduced the incidence of confirmed Lyme disease during the first year of the study, with an efficacy of 68 percent for all enrolled subjects. However, the vaccine was more effective when a booster dose was administered 12 months after the first immunization, achieving an efficacy of 92 percent among the group of subjects who received the booster dose. Subjects who did not receive the booster dose appeared to be minimally protected against disease during the second year of observation.

Although there has been some concern about the efficacy of a vaccine that includes only a single OspA protein against different strains of *B. burgdorferi*,^{22,23} in our study, such a vaccine prevented Lyme disease at locations in five different states in the United States, suggesting that it provides coverage against a wide range of strains. Nevertheless, it may be necessary to use different OspA proteins in the development of vaccines intended for use in Europe and North America.²⁴ No inference can be drawn regarding the ability of this vaccine to protect against the two other genospecies implicated in so-called European Lyme disease, *B. garinii* and *B. afzelii*.

The OspA vaccine was well tolerated. Not unexpectedly, there was a higher incidence of acute vaccine-related side effects in the vaccine group within 7 days after injection and, frequently, within 24 hours. These side effects consisted mostly of pain or tenderness at the injection site, were mild and self-limited, and were similar to those seen after the administration of other vaccines.²⁵

Previous studies have suggested that there is an autoimmune component to Lyme disease,²⁶⁻³⁰ although the specific molecule underlying the presumed molecular mimicry implicit in the proposed OspA-based autoimmune model has not been identified.³¹ Nonetheless, analysis of the safety data from our trial revealed no evidence that the vaccine exac-

erbated prior Lyme arthritis, or caused arthritis in either subjects with a history of Lyme disease or those without such a history. Similarly, the vaccine did not cause neurologic disease in recipients.

Finally, there has been some concern that an OspA vaccine might alter the natural course of infection, rather than preventing the infection,^{2,9} a possibility for which there may be a precedent in other infectious diseases.³² If vaccination prevented erythema migrans or other early (and more easily treated) manifestations of Lyme disease, then vaccine recipients would probably have no signs or symptoms related to early infection³³ (latent Lyme disease) and would seek medical attention only after the onset of later-stage manifestations of *B. burgdorferi* infection. Approximately 60 percent of our subjects have now been followed up for four years, and no cases of late Lyme disease have been recognized, indicating that there has been no progression of subclinical infection to clinical disease.

Further studies will be needed to evaluate the vaccine in children and adolescents. In addition, although the booster dose clearly increased the efficacy of the vaccine in the second year of the study, the optimal regimen remains to be determined. Whether booster doses are required beyond the second year is as yet unresolved. Nevertheless, our results indicate that OspA vaccine is a successful and safe antispirochetal vaccine.

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APPENDIX

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REFERENCES

1. Fikrig E, Barthold SW, Sun W, Feng W, Telford SR III, Flavell RA. *Borrelia burgdorferi* P35 and P37 proteins, expressed *in vivo*, elicit protective immunity. *Immunity* 1997;6:531-9.
2. Wormser GP. Prospects for a vaccine to prevent Lyme disease in humans. *Clin Infect Dis* 1995;21:1267-74.
3. Barthold SW, Bockenstedt LK. Passive immunizing activity of sera from mice infected with *Borrelia burgdorferi*. *Infect Immun* 1993;61:4696-702.
4. Barthold SW, DeSouza M, Feng S. Serum-mediated resolution of Lyme arthritis in mice. *Lab Invest* 1996;74:57-67.
5. Fikrig E, Bockenstedt LK, Barthold SW, et al. Sera from patients with chronic Lyme disease protect mice from Lyme borreliosis. *J Infect Dis* 1994;169:568-74.
6. Simon MM, Schaible UE, Kramer MD, et al. Recombinant outer surface protein A from *Borrelia burgdorferi* induces antibodies protective against spirochetal infection in mice. *J Infect Dis* 1991;164:123-32.
7. Schaible UE, Kramer MD, Eichmann K, Modolell M, Museteanu C, Simon MM. Monoclonal antibodies specific for the outer surface protein A (OspA) of *Borrelia burgdorferi* prevent Lyme borreliosis in severe combined immunodeficiency (*scid*) mice. *Proc Natl Acad Sci U S A* 1990;87:3768-72.
8. Fikrig E, Telford SR III, Wallich R, et al. Vaccination against Lyme disease caused by diverse *Borrelia burgdorferi*. *J Exp Med* 1995;181:215-21.
9. Telford SI, Fikrig E. Progress towards a vaccine for Lyme disease. *Clin Immunother* 1995;4:49-60.
10. Fikrig E, Barthold SW, Kantor FS, Flavell RA. Protection of mice against the Lyme disease agent by immunizing with recombinant OspA. *Science* 1990;250:553-6.
11. Fikrig E, Barthold SW, Marcantonio N, Deponce K, Kantor FS, Flavell RA. Roles of OspA, OspB, and flagellin in protective immunity to Lyme borreliosis in laboratory mice. *Infect Immun* 1992;60:657-61.
12. Fikrig E, Barthold SW, Kantor FS, Flavell RA. Long-term protection of mice from Lyme disease by vaccination with OspA. *Infect Immun* 1992;60:773-7.
13. Probert WS, LeFebvre RB. Protection of C3H/HeN mice from challenge with *Borrelia burgdorferi* through active immunization with OspA, OspB, or OspC, but not with OspD or the 83-kilodalton antigen. *Infect Immun* 1994;62:1920-6.
14. Keller D, Koster FT, Marks DH, Hosbach P, Erdile LF, Mays JP. Safety and immunogenicity of a recombinant outer surface protein A Lyme vaccine. *JAMA* 1994;271:1764-8.
15. Van Hoesche C, Comberbach M, De Grave D, et al. Evaluation of the safety, reactogenicity and immunogenicity of three recombinant outer surface protein (OspA) Lyme vaccines in healthy adults. *Vaccine* 1996;14:1620-6.
16. Schoen R, 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.
17. Erdile LF, Brandt MA, Warakowski DJ, et al. Role of attached lipid in immunogenicity of *Borrelia burgdorferi* OspA. *Infect Immun* 1993;61:81-90.
18. Bacterial endotoxins test. In: The United States pharmacopeia: the national formulary. USP 23, NF 18. Rockville, Md.: United States Pharmacopeial Convention, 1994:1696-7.
19. Sadziene A, Thompson PA, Barbour AG. In vitro inhibition of *Borrelia burgdorferi* growth by antibodies. *J Infect Dis* 1993;167:165-72.
20. Lyme disease. *MMWR Morb Mortal Wkly Rep* 1990;39(RR-13):19-21.
21. Medical dictionary for drug regulatory affairs. Version 1.5. Yokohama, Japan: International Conference on Harmonization (ICH) Medical Terminology (M1) Expert Working Group, November 1996.
22. Schaible UE, Wallich R, Kramer MD, et al. Immune sera to individual *Borrelia burgdorferi* isolates or recombinant OspA thereof protect SCID mice against infection with homologous strains but only partially or not at all against those of different OspA/OspB genotype. *Vaccine* 1993;11:1049-54.
23. Lovrich SD, Callister SM, DuChateau BK, et al. Abilities of OspA proteins from different seroprotective groups of *Borrelia burgdorferi* to protect hamsters from infection. *Infect Immun* 1995;63:2113-9.
24. Gern L, Hu CM, Voet P, Hauser P, Lobet Y. Immunization with a polyvalent OspA vaccine protects mice against *Ixodes ricinus* tick bites infected by *Borrelia burgdorferi* ss, *Borrelia garinii* and *Borrelia afzelii*. *Vaccine* 1997;15:1551-7.
25. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 1997;46(RR-9):1-12.
26. Kalish R, 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.
27. *Idem*. Early and late antibody responses to full-length and truncated constructs of outer surface protein A of *Borrelia burgdorferi* in Lyme disease. *Infect Immun* 1995;63:2228-35.
28. Kamradt T, Krause A, Burmester G-R. A role for T cells in the pathogenesis of treatment-resistant Lyme arthritis. *Mol Med* 1995;1:486-90.
29. Kamradt T, Lengel-Janssen B, Strauss AF, Bansal G, Steere AC. Dominant recognition of a *Borrelia burgdorferi* outer surface protein A peptide by T helper cells in patients with treatment-resistant Lyme arthritis. *Infect Immun* 1996;64:1284-9.
30. Lengel-Janssen B, Strauss AF, Steere AC, Kamradt T. The T helper cell response in Lyme arthritis: differential recognition of *Borrelia burgdorferi* outer surface protein A in patients with treatment-resistant or treatment-responsive Lyme arthritis. *J Exp Med* 1994;180:2069-78.
31. Sigal LH. Lyme disease: a review of aspects of its immunology and immunopathogenesis. *Annu Rev Immunol* 1997;15:63-92.
32. Szmuness W, Stevens CE, Zang EA, Harley EJ, Kellner A. A controlled clinical trial of the efficacy of the hepatitis B vaccine (Heptavax B): a final report. *Hepatology* 1981;1:377-85.
33. Fahrer H, van der Linden SM, Sauvain MJ, Gern L, Zhioua E, Aeschlimann A. The prevalence and incidence of clinical and asymptomatic Lyme borreliosis in a population at risk. *J Infect Dis* 1991;163:305-10.

CORRECTION

Immunization against Lyme Disease

To the Editor: The studies by Steere et al.¹ and Sigal et al.² (July 23 issue) suggest that the vaccine consisting of recombinant *Borrelia burgdorferi* outer-surface protein A is well tolerated and efficacious and "provides an important new public health approach to the prevention of Lyme disease."¹ The role of this vaccine in public health efforts to prevent Lyme disease needs further consideration.

Many vaccines benefit public health by providing widespread immunity against potentially severe or fatal, and often untreatable, diseases. Vaccine-induced herd immunity against contagious diseases reduces the risk among unvaccinated persons. Lyme disease is a noncontagious, treatable, and nonfatal disease. Because humans are dead-end hosts of *B. burgdorferi*, vaccinating some humans will not decrease the risk of acquiring Lyme disease for others. Although the incidence of Lyme disease is highest in children,³ the safety and efficacy of the vaccine in children have not been established. The need for and timing of booster doses are also unknown. Furthermore, whether vaccination is more cost effective than early diagnosis and treatment of Lyme disease has not been established. Finally, should vaccination against Lyme disease result in a complacent decrease in personal efforts to avoid tick bites, then vaccinated persons in areas in which the disease is endemic may be at increased risk for other tick-borne diseases, such as ehrlichiosis, babesiosis, Rocky Mountain spotted fever, and tularemia.

In the United States, Lyme disease is primarily transmitted in certain counties in northeastern, north central, and Pacific states.³ Vaccination of persons with frequent or prolonged exposure to tick habitats in areas where the disease is endemic is likely to be an important preventive strategy. For those who have only brief or intermittent exposure to tick habitats in such areas, the public health benefits of vaccination, as compared with those of early recognition and treatment of Lyme disease, are not clear. For persons who live in areas in which the disease is not endemic and for those who travel to areas in which the disease is endemic but who are not exposed to tick habitats, vaccination would not seem to be beneficial.

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References

1. 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;339:209-215.
2. Sigal LH, Zahradnik JM, Lavin P, et al. A vaccine consisting of recombinant *Borrelia burgdorferi* outer-surface protein A to prevent

Lyme disease. *N Engl J Med* 1998;339:216-222.

3. Lyme disease – United States, 1996. *MMWR Morb Mortal Wkly Rep* 1997;46:531-535.

To the Editor: In the report by Steere et al., what were the clinical outcomes for the patients in the group with laboratory-confirmed asymptomatic *B. burgdorferi* infection? Did symptoms develop? Did the results of Western blotting for IgG indicate a possible progressive latent infection? This group did not have asymptomatic infection (no living organisms were demonstrated), it had asymptomatic seroconversion. Seroconversion could be caused by the transfer of dead or nonviable spirochetes to the host from the feeding tick. It is more likely that the results in this group reflect either the success of the body's immune defense against the invading organism or the occurrence of a latent infection, in which case, clinical symptoms may develop at a future time. If in fact these patients were infected, were they treated? If they had asymptomatic seroconversion, I see no reason to treat them.

From a cost standpoint, it seems very expensive to treat 11,000 patients with three doses of a vaccine (at a total cost of probably well over \$1 million) to prevent 70 cases of erythema migrans, which could be treated with oral antibiotics at a cost of \$15 per patient. The importance of a Lyme disease vaccine is not its ability to prevent erythema migrans or asymptomatic seroconversion but its ability to prevent the later (and more difficult to treat) complications of Lyme disease. This difference may become clear if the later complications of Lyme disease develop in the patients with asymptomatic seroconversion.

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To the Editor: The conduct of the studies by Steere et al. and Sigal et al. raises serious ethical issues. Both Steere et al. and Sigal et al. recruited their subjects during an eight-week period and demonstrated the efficacy of the two injections of vaccine given in the first year (estimated efficacy, 49 percent [$P=0.009$] and 68 percent [$P<0.001$], respectively). Therefore, at the time of the third injection, 12 months after the first, both groups should have had evidence of the vaccine's effectiveness. Nevertheless, they chose to give the subjects in the placebo group a placebo injection at 12 months and to monitor them without additional intervention for an additional 12 months. Had the subjects in the placebo group been given vaccine injections at months 12 and 13, many of the 94 cases of Lyme disease reported during the second year of follow-up in this group could have been prevented.

It is particularly troubling that both studies had data and safety monitoring committees, but neither committee apparently insisted on any interim analyses of the outcome. Clinical trials are only ethical when there is no compelling reason to suggest that one intervention is to be preferred over another.¹ Most randomized trials now require interim analyses to allow early termination should there be compelling evidence of differences in outcome between treatment groups. Such

information should then be made available to subjects.² The ethical duty to act is not conditional on the seriousness of the outcome being studied. Definitive information on the effectiveness of these vaccines should have been available to the researchers before the scheduled 12-month visit, and subjects who were randomly assigned to the placebo group should have been informed of the vaccine's effectiveness at the time of the 12-month visit and offered the opportunity to receive vaccine injections at months 12 and 13.

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References

1. Freedman B. Equipoise and the ethics of clinical research. *N Engl J Med* 1987;317:141-145.
2. Food and Drug Administration. Rules and regulations, 21 CFR part 50: protection of human subjects, §50.25: elements of informed consent. *Fed Regist* 1981;46:8942-8942.

The authors reply:

To the Editor: We reported that vaccination with outer-surface protein A with adjuvant was safe and effective in preventing most cases of definite Lyme disease or asymptomatic *B. burgdorferi* infection. As pointed out by Drs. Hayes and Dennis, there are still unanswered questions. One concerns the efficacy and safety of the vaccine in children. A large clinical trial is currently in progress to evaluate the safety of the vaccine in children. Additional studies are under way to assess the need for booster injections. Official recommendations from the Advisory Committee for Immunization Practices regarding vaccine use should be available after the vaccine is licensed.

We agree with Dr. Luger that an important reason for vaccination is to prevent the later and more serious complications of Lyme disease. The vaccine was highly effective in preventing asymptomatic seroconversion, which in some cases might have been followed by late manifestations of the disorder. In our study, it was not possible to determine the frequency of late disease after asymptomatic seroconversion, since most patients with asymptomatic seroconversion, after discussion with their physician, were treated with antibiotic therapy. However, Lyme arthritis subsequently developed in one such patient who decided against antibiotic treatment. This finding shows that Lyme arthritis after asymptomatic seroconversion may be the presenting manifestation of the illness. Thus, at least in some cases, asymptomatic seroconversion does indicate infection.

It is always difficult to decide how long a double-blind, placebo-controlled trial should be continued before the code is broken. The design of our study was conceived after a meeting of the Vaccine Advisory Committee of the Food and Drug Administration in 1994.

At that meeting, two years of follow-up data were requested to assess the safety of the vaccine, which required a comparison of the vaccine and placebo groups. In addition, the members of the data and safety monitoring board thought that a clearer picture of the vaccine's efficacy could be obtained with the use of three injections of vaccine over a two-year period, rather than two injections over a one-year period. The study investigators, the members of the data and safety monitoring board, and the study sponsor decided that this design was justified, without interim analysis, since all study participants were followed carefully and antibiotic treatment was recommended for all subjects in whom evidence of *B. burgdorferi* infection developed.

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To the Editor: We agree with many of the points made by Drs. Hayes and Dennis. The cost effectiveness of a vaccine cannot be estimated until the efficacy and side effects of the vaccine have been established. The Food and Drug Administration would not allow studies of the efficacy of the vaccine in children until the completion of the studies in adults; these studies will be performed. Responsible and prudent educational programs and materials¹ stress the importance of personal precautions in avoiding Lyme disease. As suggested by Meltzer et al. at the recent International Conference on Emerging Infectious Diseases,² only targeted use of vaccination can be recommended; its use in persons with minimal risk of infection would not be beneficial to society, just as routine antibiotic prophylaxis against tick bites has no demonstrable utility.^{3,4} Since *Ixodes scapularis* ticks carry other pathogens, the use of this vaccine should not lead to a decrease in personal precautions. To achieve maximal public health benefit, the vaccine should be part of broader strategies to prevent Lyme disease and other tick-borne diseases.

Dr. Anderson contends that it was unethical for the data and safety monitoring committee to have allowed the study to proceed into the second year. Since there was prior evidence that three injections of the vaccine were needed to achieve optimal levels of specific antibodies,⁵ there was reason to believe that a third (or booster) injection at month 12 was needed to provide the increased efficacy noted in results obtained in the second year (months 13 to 24). Although the calculated efficacy of the vaccine was 68 percent after two doses, the lower bound of the 95 percent confidence interval was only 36 percent. The importance of continuing the double-blind study into the second year can be seen in the results: the overall efficacy was 77 percent, with a lower bound of the 95 percent confidence interval of 58 percent. Therefore, ending the study after 12 months or shortly thereafter would have precluded us from learning the very data needed to determine the cost effectiveness of the vaccine, as discussed by

Hayes and Dennis. Thus, we disagree with Dr. Anderson: there was no ethical issue raised by continuing the study to its completion.

The last entry in the left-most column of Table 2 of our article should have read, "Two or three injections per protocol," not "Three injections, per protocol." Also, on page 218, line 7 from the top of the left-hand column should have read, "both years among subjects who received two or three injections," not "both years among subjects who received three injections." Finally, the last seven authors were omitted from the title page of our article. The complete list of authors is as follows: L.H. Sigal, M.D., J.M. Zahradnik, M.D., P. Lavin, Ph.D., S.J. Patella, M.S.N., N.P.-C., G. Bryant, M.D., R. Haselby, D.O., E. Hilton, M.D., M. Kunkel, M.D., D. Adler-Klein, M.D., T. Doherty, M.D., J. Evans, M.D., S.E. Malawista, M.D., P. Molloy, M.D., A. Seidner, M.D., J. Sabetta, M.D., H.J. Simon, M.D., M.S. Klempner, M.D., J. Mays, Ph.D., and D. Marks, M.D.

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References

1. Sigal LH, ed. National Clinical Conference on Lyme Disease. *Am J Med* 1995;98:Suppl 4A:1S-91S.
2. Meltzer MI, Dennis DT, Orloski KA. The cost and benefits of vaccinating against Lyme disease: a decision analysis. Presented at the International Conference on Emerging Infectious Diseases, Atlanta, March 8–11, 1998.
3. Magid D, Schwartz B, Craft J, Schwartz JS. Prevention of Lyme disease after tick bites – a cost-effectiveness analysis. *N Engl J Med* 1992;327:534-541.
4. Gerber MA, Shapiro ED, Burke GS, Parcells VJ, Bell GL. Lyme disease in children in southeastern Connecticut. *N Engl J Med* 1996;335:1270-1274.
5. Keller D, Koster FT, Marks DH, Hosbach P, Erdile LF, Mays JP. Safety and immunogenicity of a recombinant outer surface protein A Lyme vaccine. *JAMA* 1994;271:1764-1768.

CORRECTION

A Vaccine Consisting of Recombinant *Borrelia burgdorferi* Outer-Surface Protein A to Prevent Lyme Disease

A Vaccine Consisting of Recombinant *Borrelia burgdorferi* Outer-Surface Protein A to Prevent Lyme Disease . The names listed in the Appendix should have appeared in a footnote on the first page of the article. The footnote on page 216 should have read as follows:

Other authors were Philip J. Molloy, M.D., Jordan Hospital, Plymouth, Mass.; Adam L. Seidner, M.D., M.P.H., Middlesex Hospital Family Practice Residency Program, Middletown, Conn.; James R. Sabetta, M.D., Greenwich Hospital, Greenwich, Conn.; Henry J. Simon, M.D., Physicians Research Center, Toms River, N.J.; Mark S. Klempner, M.D., Tufts University–New England Medical Center, Boston; and John Mays and Donald Marks, M.D., Pasteur Mérieux Connaught, Swiftwater, Pa.

In addition, the last author should have been listed as Stephen E. Malawista, M.D.

We regret the errors.