Lyme Disease Vaccine in North America

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North American Lyme disease was first described in 1977 in Lyme, Connecticut, during an arthritis epidemic in children [1]. In the early 1980s, the etiologic agent, Borrelia burgdorferi, was identified after it was isolated from the cerebrospinal fluid, blood, and skin of patients with Lyme disease and from Ixodes scapularis, the deer-tick vector of the disease [2]. Lyme disease is a multisystem disorder, with the most common manifestations being cutaneous, neurologic, rheumatologic, and cardiac. With early treatment, most patients do extremely well and have little long-term morbidity. However, unrecognized or untreated Lyme disease may go on to produce considerable disability in a small fraction of patients.

People who live, work, and travel in endemic areas are at risk for acquiring Lyme disease. In some series, 10% of people living or working in endemic areas had serologic evidence of exposure to, and presumed previous infection with, B. burgdorferi [3–7]. In areas where Lyme disease is highly prevalent, even rare sequelae pose a significant public health problem. A vaccine against Lyme disease approved in 1998 may decrease the morbidity and financial costs associated with the illness.

Epidemiology and Relationship to Vectors

The main U.S. reservoirs for B. burgdorferi are the white-footed mouse and white-tailed deer. Incidence of Lyme disease varies by location and is determined by the geographic distribution of the infected hosts and by the life cycle of B. burgdorferi. When the nymphal ixodid tick feeds on an infected mouse, it becomes infected with B. burgdorferi, which resides in the mid-gut of the tick. The infected nymph then bites and transmits B. burgdorferi to another mouse or other small animal in the course of normal feeding behavior. Nymphs feed predominantly in the late spring and early summer. Human disease is caused largely by nymphal ticks when they are questing for a blood meal and happen upon a human host. Humans become incidental hosts when the tick has been feeding for more than a day (the minimum amount of time needed to acquire B. burgdorferi from a tick bite) [8,9]. Nymphal ticks molt into adults in the fall. Adult ticks feed and mate on deer, which can carry the adult ticks over long distances. Adult ticks can transmit B. burgdorferi trans-ovarily to daughter ticks [10].

Lyme disease is seen in the United States primarily in the Northeast, from Massachusetts to Maryland; in the Midwest, from Wisconsin to Minnesota; and the West Coast, in Oregon and California [11]. In certain endemic areas, 33% to 88% of ixodid ticks are infected with B. burgdorferi [12,13]. Lyme disease also has been seen in Europe and Asia. In these regions, however, the disease is transmitted by other ticks (including I. ricinus), is caused by various different subspecies (including B. afzelii and B. garinii), and presents with different signs and symptoms than the variant seen in the United States [14,15]. Of interest, I. scapularis has also been found on other rodents, birds, and even lizards, and these animals may be part of the natural reservoir for Lyme disease in parts of the United States or elsewhere in the world [16].

Borrelial Antigens and Vaccine Candidates

The search for a vaccine began in 1986. In the initial animal studies, hamsters that were immunized with an inactivated whole-cell B. burgdorferi vaccine were successfully protected against infection with live B. burgdorferi. This led to the development and use of whole-cell vaccines for dogs [17,18]. Whole-cell vaccination was not pursued in humans because many antibodies to B. burgdorferi cross-react in vitro with human muscle, heart, and nerve tissue [19,20]. Purified subunits were tested for their ability to induce antibodies and to confer protection against Lyme disease. The outer-surface proteins—OspB, OspC, and especially OspA—seemed to be the most promising candidates in animal studies. The OspA antigen binds to plasminogen, which is converted to plasmin by the host and is involved with motility through extracellular tissue [21]. This protein is expressed primarily while the organism is in the gut of the ixodid tick.

In several animal studies, mice were given an OspA subunit preparation and after a sufficient time to produce IgG antibodies received either direct injection of live B. burgdorferi...
or exposure to infected ticks. The mice did not develop clinical signs or serologic evidence of infection [22–24]. In a later study, when ixodid ticks known to be infected with \textit{B. burgdorferi} were allowed to feed on an animal actively immunized with OspA antibodies, there was a large reduction in viable bacteria in the tick gut after feeding [25]. This suggested that the vaccine's mechanism of action is the killing of the \textit{B. burgdorferi} within the tick gut before migration to the tick's salivary gland and inoculation into the host.

### Human Vaccine

Two large trials published in 1998 looked at the effectiveness of 2 slightly different variants of an OspA vaccine in preventing Lyme disease in adults (Table 1) [26,27]. The first trial [26] randomized 10,936 patients in areas endemic for Lyme disease to receive either OspA vaccine (with adjuvant) or placebo at 0, 1, and 12 months. Patients were followed for 2 years after the initial vaccination for clinical and/or serologic evidence of infection. Clinical evidence of infection included cutaneous, neurologic, cardiac, or rheumatologic findings known to be associated with Lyme disease. Twenty-four patients in the vaccinated group and 56 patients in the placebo group developed Lyme disease in the first year, and 16 patients in the vaccinated group and 81 patients in the placebo group developed it in the second year. Thus, the efficacy of the vaccine was 57% (49% for symptomatic disease) in the first year and 80% (76% for symptomatic disease) in the second year. The second trial [27] randomized 10,305 patients to receive either OspA vaccine (without adjuvant) or placebo. The patients were followed for clinical evidence of infection (confirmed serologically) for 2 years. In the first year of the study (after 2 injections), vaccine efficacy was 68%. In the second year, it was 92%. Both studies showed considerably better results after all 3 injections were administered.

The vaccine was well-tolerated. Patients suffered mild local side effects, and some patients developed flu-like symptoms. Because the definitions of adverse events were different in the 2 studies and because adverse events tended to be mild in both vaccine and placebo recipients, it is difficult to calculate absolute risk. Adverse events were at least twice as common in vaccine recipients as in placebo recipients. The most common problems were vaccine site pain, rash, and myalgia. Serious side effects were rare in both groups. A small study done in New York State using the same vaccine schedule noted above followed 1634 volunteers and found that the efficacy of the OspA vaccine was only 40% in the first year and 37% in the second year based on clinical or serologic evidence for Lyme disease [28]. A shorter vaccination schedule (0, 1, and 6 months) appears to be as effective as the standard 0,1,12–month schedule in the development of adequate antibody titers. The clinical efficacy of the shorter schedule has not been studied [29].

The vaccine has been studied in 250 children in the Czech Republic and found to be immunogenic and safe [30]. It is difficult to interpret these data, however, as Lyme disease in Europe is caused by a different subspecies of \textit{Borrelia}. There are no trials of Lyme vaccine in children in the United States; this is unfortunate given the tendency of children to be exposed to infected ticks and to develop clinical Lyme disease at rates higher than those seen in adults.

### Limitations of Vaccine

OspA vaccine with adjuvant (LYMErix™, SmithKline Beecham) appears to be well-tolerated and moderately effective. However, there are concerns regarding its widespread use. The long-term sequelae of this vaccine are not yet known, and it is not known for how long vaccination confers immunity after the full series of 3 shots. A high antibody titer for OspA at the time of the tick bite is required to kill \textit{B. burgdorferi} within the tick gut during feeding. For this reason, there is no opportunity for an anamnestic response to work for this vaccine. It takes many people more than 1 year to develop protective titers of antibody; these people are only partially protected during the first tick season following the initiation of the vaccine. It is also not known whether the vaccine protects against early Lyme disease but leaves patients susceptible to the long-term effects of Lyme borreliosis, such as neuroborreliosis or carditis. Follow-up studies of vaccine recipients who develop actual Lyme disease will

### Table 1. Outcomes in the 2 Largest OspA Lyme Disease Vaccine Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Year 1</th>
<th>Year 2</th>
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<tbody>
<tr>
<td></td>
<td>No. Placebo Pts Infected</td>
<td>No. Vaccine Pts Infected</td>
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<tr>
<td>Steere [26] (n = 10,936)</td>
<td></td>
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<tr>
<td>Symptomatic infection</td>
<td>43</td>
<td>22</td>
</tr>
<tr>
<td>Asymptomatic infection</td>
<td>13</td>
<td>2</td>
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<tr>
<td>Sigal [27] (n = 10,305)</td>
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LYME DISEASE VACCINE

shed light on this; early data are encouraging. It is also not clear if some of the later manifestations of Lyme disease are a result of infection or immune response to infection. It has been shown that late Lyme arthritis may not be responsive to antibiotics and has an association with the HLA-DR4 haplotype, suggesting a possible immune mechanism for this form of arthritis [31]. It is not known if high titers of antibody to OspA from vaccination could predispose patients to the development of Lyme arthritis later in life. A 2-part study in hamsters showed that the OspA antigen in the vaccine caused arthritis in 50% to 100% of hamsters and that 57% of hamsters developed arthritis after vaccination and challenge with B. burgdorferi [32].

Interpretation of Serologic Testing After Vaccination

Lyme vaccination will confuse the interpretation of current serologic tests for Lyme disease. The usual serologic approach to Lyme disease consists of an enzyme-linked immunosorbent assay (ELISA) followed by a Western blot test if the ELISA is positive. The ELISA measures the amount of antibody against all of the subunits of B. burgdorferi and is the more sensitive test, especially in early disease. The Western blot test uses an electrophoretic gel to spread the antigens of B. burgdorferi by molecular size and looks for binding of the patient's antibodies to each of these components. Although the Western blot test is less sensitive, it is more specific and excludes patients with false-positive ELISA results. Successfully vaccinated but uninfected patients should have a positive ELISA test, and the Western blot will have at least 1 positive band [33]. To confirm the diagnosis of Lyme disease in vaccine recipients, clinicians would need to rely on the Western blot test. Because of the Western blot's lower sensitivity, relying only on the Western blot may diminish the value of serologic testing in vaccinated patients. Investigators are looking into an ELISA test lacking the OspA antigen to use in vaccinated patients, but these tests are still under development and have not yet been utilized in clinical practice [34,35]. There are no current guidelines regarding minimum titers of antibody to OspA that correlate with protection against Lyme disease, so routine postimmunization testing is not recommended. However, such guidelines may help to determine revaccination schedules once a longer experience with the vaccine has been established.

Cost-effectiveness

In both of the large trials, there was a relatively small number of new cases of Lyme disease. Although both studies were done in areas endemic for Lyme disease, the annual incidence of Lyme disease among placebo recipients was 10 to 15 per 1000 in one study and 6 per 1000 in the other. Based on these figures, the number of people needed to treat (NNT) with OspA vaccine to prevent 1 case of Lyme disease was roughly 75 to 108 after the full series of 3 injections in the 2 trials combined. One can extrapolate from this to estimate the cost-effectiveness of the vaccine. A population of 5000 people in an endemic area would make 15,000 doctor visits to receive the 3-shot vaccination series. Based on the NNT in the Steere study [26], this would be expected to prevent 60 cases of Lyme disease. The Red Book price of the vaccine is $69 per dose. Assuming a doctor’s visit charge of $40, no lost wages from time spent at the doctor’s office, and no cost of vaccine toxicity, the minimum cost to avert 1 case of Lyme disease would be $27,250 (15,000 × [69 + 40]/60). The amount will differ depending on the assumptions used. Using the incidence rate and vaccine efficacy from the other large trial [27] and the same cost estimates, the cost per case averted would be $51,094.

In both trials, there was a large number of unconfirmed cases: about 10% of vaccine recipients and 10% of placebo recipients in each study had suspicious clinical manifestations but did not meet clinical criteria for Lyme disease and had negative serologic tests. There are 2 issues here. First, the vaccine does not appear to prevent the common Lyme-like syndrome that many patients are convinced is sero-negative Lyme disease. Second, there will be a large fraction of vaccinees who will still suspect they have Lyme disease and will require a careful evaluation (including Western blot serologic testing).

Recommendations for Vaccine Use

The decision to administer the Lyme vaccine should be based on an assessment of an individual’s risk for exposure to infected ticks. The CDC has developed guidelines regarding the use of Lyme vaccine [36], which are summarized in Table 2. In nonendemic areas, the risk of Lyme disease is so low (sometimes less than 1% of that in highly endemic areas) that vaccination may not meet a reasonable standard of risk or cost-effectiveness.

Conclusion

For 1 year after the full vaccination cycle, the Lyme vaccine is a moderately effective prevention measure in endemic areas. The vaccine appears to be well-tolerated. A small number of people living in areas endemic for Lyme disease have significant irreversible morbidity. Data are not yet convincing that vaccinating patients will prevent these later manifestations or whether the cases prevented would have been mild or easily treated, but it is reasonable to expect that the reduction in total cases will be matched by a reduction in serious long-term Lyme-related problems. However, the threshold of safety for a vaccine given to prevent a non-life-threatening disease is very high. The recent withdrawal of the pediatric rotavirus vaccine because of a small
risk of intussusception (about 300 cases/100,000 infant years versus an expected rate of 50/100,00) illustrates that we have a low tolerance for iatrogenic problems even for an otherwise safe vaccine given to prevent a common (50,000 hospitalizations annually) and potentially serious disease (20 deaths annually). A similar rationale is used for limiting oral poliovirus vaccine, ie, polio is now so rare that a very safe and effective vaccine that causes as little as 1 case of paralytic polio per million vaccinees may not be prudent when an even safer if somewhat less convenient vaccine (killed virus) is available [37].

In areas where Lyme disease is endemic, there are frequently other tick-borne illnesses transmitted by I. scapularis (eg, babesiosis, ehrlichiosis). Therefore, efforts to control the tick population and to educate the public to routinely check for ticks are probably the most important preventive strategies even when Lyme vaccination has been undertaken. Early tick removal should be emphasized by physicians and educators in endemic areas, and information about tick removal should be provided at sites where Lyme vaccine is provided in an effort to minimize risk to all patients.

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References

LYME DISEASE VACCINE

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