Correcting a Public Health Fiasco: The Need for a New Vaccine against Lyme Disease

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A vaccine against Lyme disease was licensed in the United States in 1998 but was subsequently removed from the market because of lack of sales. I believe that the poor acceptance of the vaccine was based on tepid recommendations by the Centers for Disease Control and Prevention (CDC), undocumented and probably nonexistent safety issues, and insufficient education of physicians. A new vaccine is feasible but will not be developed unless there is a demand by infectious diseases specialists, epidemiologists, authorities in affected states and the public that is evident to manufacturers. The fact that there is no vaccine for an infection causing ~20,000 annual cases is an egregious failure of public health.

In 1998, a vaccine against Lyme disease was licensed in the United States that consisted of the outer surface protein A (OspA) of *Borrelia burgdorferi* sensu stricto. Antibody against OspA neutralizes the borrelia in the midgut of the tick and, thus, prevents transmission to humans [1]. The vaccine was withdrawn by the manufacturer in 2002 for reasons that will be described in this article.

I have previously argued [2] and will argue here that the loss of a Lyme disease vaccine was a public health fiasco.

**Case History**

A 39-year-old man was walking his dog near his home in West Chester, Pennsylvania, in August 2005, when he suddenly lost consciousness and collapsed. Fortunately, a neighbor saw him and called 911. When the man arrived at the emergency department of a local hospital, his heart rate was 30 beats/min, and he had a complete atrioventricular block. The patient was revived by urgent insertion of a transvenous cardiac pacemaker, which increased his heart rate but did not eliminate the block.

An experienced cardiologist visited the patient in the emergency department and asked him about recent rashes. The patient reported that 3 weeks previously he had consulted a physician for a retropopliteal rash, which was diagnosed as cellulitis for which local treatment was advised, and the rash resolved spontaneously. The cardiologist then requested an enzyme-linked immunosorbent assay (ELISA) for IgM antibodies to Lyme borrelia; the result was reported to be strongly positive and was later confirmed by Western blot. Intravenous ceftriaxone was initiated 24 h after admission. After 1 week in the intensive care unit, the cardiac block was reduced from complete to first degree, and the patient was discharged from the hospital with intravenous ceftriaxone therapy.

**DISCUSSION**

The patient, who had 1 of the ~20,000 cases of Lyme disease reported annually in the United States, was my son. Current reporting is based on the CDC case definition, which is physician diagnosis of erythema migrans or another objective clinical manifestation, with laboratory confirmation of *B. burgdorferi* infection. The extent of underreporting is unknown. The case history also illustrates failure of patients to be aware of tick bites.
and failure of diagnosis by a primary physician even in an area of endemicity [3, 4]. Table 1 lists the counties with reported Lyme disease rates of >200 cases per 100,000 population [5]. If one corrects for unreported cases, the incidence would likely be higher. In Connecticut, 4000 confirmed and probable cases were reported in 2008, yielding an annual incidence of >100 cases per 100,000 population, which over 10 years would involve at least 1% of the population [6].

Lyme disease due to *B. burgdorferi* sensu lato is also important in Europe. A recent publication reported that "the data presented here, and also the results of some other studies, indicate that the incidence of Lyme borreliosis may be increasing in certain European countries. Nine of 16 European countries with time-series data available show evidence of increasing incidence of Lyme borreliosis. Increases have been seen in Poland, eastern Germany, Slovenia, Bulgaria, Norway, Finland, Belgium, Britain, and the Netherlands" [7, E060622.1].

To respond to the need for a prophylactic vaccine against Lyme disease, 2 companies expended considerable human and financial resources to develop a vaccine for the United States, and one achieved licensure, only to find that a demand for the vaccine did not materialize [8, 9]. Why?

The most important reason was that the CDC and its Advisory Committee on Immunization Practices (ACIP) damned the vaccine with faint praise.

The actual ACIP recommendations read as follows [10]:

Decisions regarding the use of vaccine should be based on individual assessment of the risk for exposure to infected ticks and on careful consideration of the relative risks and benefits of vaccination compared with other protective measures, including early diagnosis and treatment of Lyme disease. Lyme disease vaccination should be considered for persons 15–70 years who engage in activities (eg, recreational, property maintenance, occupational, or leisure) that result in frequent or prolonged exposure to tick-infested habitat.

"Lyme disease vaccination may be considered for persons aged 15–70 years who are exposed to tick-infested habitat but whose exposure is neither frequent nor prolonged. The benefit of vaccination beyond that provided by basic personal protection and early diagnosis and treatment of infection is uncertain."

Note that even for what they thought was a group at high risk, the recommendation was only that vaccination "should be considered." Thus, in the recommendations, emphasis was placed on wearing protective clothing, using tick repellents, and receiving an early diagnosis and treatment with antibiotics, despite the paucity of data showing that those measures work and even fewer data showing that individuals actually use them. According to a case-control study in Connecticut [11], the efficacy of protective clothing is 40%, the efficacy of tick repellents is 20%, and the efficacy of tick inspection is 0%, although another study attributed protection of 45% to tick inspection [12]. However, surveys have shown that only a minority of Connecticut residents and <20% of visitors to Martha’s Vineyard take preventive measures against tick bites [13].

A second reason for the nonacceptance of vaccination was reports of putative reactions to the vaccine that were mainly rheumatic. Because the vaccine was licensed initially only for adults, it is not surprising that joint complaints were common. In fact, in the phase 3 licensing study, transient arthralgia occurred more frequently in vaccinees than in placebo recipients, but arthritis did not.[1]

A third factor in the demise of the vaccine was the unenthusiastic response of opinion leaders. At the US Food and Drug Administration committee meeting that recommended a license for the vaccine, 2 participants qualified their approval by saying, "it remains a concern whether the vaccine could be eliciting or inducing chronic sequelae over an interval of time that would not have been detected within the period of follow-up," and "we have a vaccine that I’m comfortable with, but it’s not something I would push tomorrow" [14, 1938]. In addition, at the ACIP meeting where these recommendations were adopted, a noted infectious diseases physician said “this is a vaccine for yuppies.”

Lastly, in my opinion, the manufacturer erred in attempting to promote the vaccine directly to the lay public, rather than attempting to educate physicians concerning the advantages of vaccination. Nevertheless, there were some real issues about the licensed Lyme disease vaccine that are common to new vaccines: occurrence of rare adverse reactions, duration of protection, the absence of a license for vaccination of children, and cost-effectiveness.

Safety of the Lyme disease vaccine became a particularly contentious issue. A relationship between Lyme vaccine and joint reactions was hypothesized because of partial homology of
OspA protein in the vaccine with LFA-1 antigen and increased susceptibility of persons with HLA-DRB1 class II HLA group to joint reactions after borrelial infection [15–17]. However, in humans, no evidence was adduced that the LFA-1 homology resulted in auto-immunity. Although evidence for a relationship between joint manifestations and the HLA DRB1 group after infection with *B. burgdorferi* is reasonably good [8,18–21], there is no evidence that a similar phenomenon occurred after vaccination. A retrospective study of joint complaints after vaccination reported to the Vaccine Adverse Event Reporting System showed no correlation between complaints and HLA group or, for that matter, no unusual number of such complaints considering the age group vaccinated [22, 23]. In the phase 3 study of the vaccine, the incidence of transient arthralgia was nonsignificantly increased in vaccinees, but the incidence of arthritis was not increased. Remarkably, 3.5% of placebo recipients had joint complaints [1].

Nevertheless, a class action lawsuit against the manufacturer claimed that "Lymerix effectively introduces high levels of OspA into the blood stream and places HLA-DR4–positive recipients at risk of developing the autoimmune reaction of treatment-resistant Lyme arthritis" [24, A181]. Presumably, HLA DR-4 was cited because of its association with autoimmune diseases. As McSweegan [25] has remarked, little effort was made by public health officials, researchers, or vaccine manufacturers to counter the online denouncements of the Lyme vaccine by patient groups or lawyers.

Fortunately, there was good evidence for efficacy and, moreover, solid data on the serological correlate of protection, which is antibody against the LA-2 epitope of OspA [26]. A level of 1400 ELISA antibody units after vaccination, or 400 enzyme immunoassay units at the time of exposure, is protective [27]. Three doses of OspA vaccine were at least 76% effective against symptomatic Lyme disease and 100% effective against asymptomatic infection [9]. As shown in Table 2, although there are no efficacy data after a fourth dose, >90% of vaccinees developed a level of antibodies correlating with protection, and the decrease in antibodies was slower than after the third dose [28]. We do not know whether yearly boosters would have been necessary, but if so, there is a precedent for yearly boosters in influenza vaccination.

### Table 2. Lymerix Efficacy in the Phase III Trial

<table>
<thead>
<tr>
<th>Disease type</th>
<th>Year 1 (2 doses)</th>
<th>Year 2 (3 doses)</th>
<th>Efficacy, %</th>
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<tbody>
<tr>
<td>Symptomatic</td>
<td>49</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>83</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>57</td>
<td>80</td>
<td></td>
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</tbody>
</table>

**NOTE.** Data are from [9].

The incidence of Lyme disease is high in children; thus a license for vaccination of children was badly needed. The manufacturer was accumulating data from studies in children at the time that the vaccine was withdrawn. To no surprise, as shown in Table 3, children developed even higher antibody levels than did adults and almost certainly would have been protected by vaccination [29–31].

Cost-effectiveness studies are now routine for all vaccines, although many of the newer ones are not cost-saving. Three published studies on Lyme disease vaccine agree that, at an annual incidence of 1%, the cost per case averted would be $3400–$10,000 [32–34]. If one takes into account underreporting, much of the northeastern and parts of the Midwest United States may have such an incidence. However, it was not suggested that Lyme disease vaccine would be federally mandated. Instead, the decision to buy the vaccine could have been the choice of patients and their physicians. Estimation of risk and risk avoidance is a private decision in our society, and many individuals might have wanted to lower their risk.

I do not argue that the first Lyme OspA vaccine was ideal, and the theoretical safety issues are not to be dismissed lightly. Nevertheless, potential problems exist with many other new vaccines, and that is not considered to be a reason to abandon them, but rather to improve them. Many academic groups and pharmaceutical manufacturers have been developing Lyme disease vaccines, and there are a variety of potential antigens for a vaccine—notably, OspC and OspA with a deletion in the region homologous for LFA-1. [21,35–41] Table 4 lists some of the antigens [38]. However, what company will invest in the improvement of Lyme vaccine and in clinical studies leading to

### Table 3. Immunogenicity of OspA in Children Aged 4–14 Years

<table>
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<tr>
<th></th>
<th>Geometric mean titer</th>
<th>Percentage &gt;1400 EU</th>
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<tbody>
<tr>
<td>After dose 2</td>
<td>5383</td>
<td>91</td>
</tr>
<tr>
<td>Before dose 3</td>
<td>1371</td>
<td>58</td>
</tr>
<tr>
<td>After dose 3</td>
<td>29,650</td>
<td>100</td>
</tr>
</tbody>
</table>

**NOTE.** Data are from [29].

### Table 4. Vaccine Candidates for Lyme Disease for Which Protection Demonstrated in Animals

<table>
<thead>
<tr>
<th>Major Protection</th>
<th>Minor Protection</th>
</tr>
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<tbody>
<tr>
<td>OspA</td>
<td>OspF</td>
</tr>
<tr>
<td>Osp B</td>
<td>p.110</td>
</tr>
<tr>
<td>OspC</td>
<td>PG</td>
</tr>
<tr>
<td>Decorin-binding proteins</td>
<td>p35, p37</td>
</tr>
</tbody>
</table>

licensure if it is uncertain that the medical and public health communities consider protection worthwhile? To add to the poignancy, there are effective OspA Lyme vaccines for dogs that have brisk sales [42, 43].

This situation strikes at the development of vaccines for other diseases for which there are nonvaccine approaches or limited geographical distribution. Should vaccine development cease against West Nile virus, which is causing fewer cases than Lyme disease? Or should we only advise mosquito repellents? Should we eschew development of vaccines for coccidiomycosis or cholera because there are alternative ways of avoiding infection? The Healthy People 2020 goals contain no objective of reduction in the incidence of Lyme disease [44], possibly because that goal will never be reached without a vaccine.

To rectify the situation, I propose that the Lyme working group of the Infectious Diseases Society of America write a formal statement to the effect that a new vaccine is desirable and would be recommended to its members. I also propose that the National Vaccine Advisory Committee analyze the situation and make recommendations to manufacturers on how to advance Lyme vaccine development. These steps could reawaken commercial interest in a new vaccine against Lyme disease.

At the beginning of this article, I qualified the history of Lyme disease vaccine as a public health fiasco. I define that as a situation in which prevention is unused or undeveloped owing to a failure of the public health community to support efforts to control a serious endemic or epidemic disease. Surely, the absence of a Lyme disease vaccine fits that definition.

Acknowledgments

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References

27. Van HC, Lebacq E, Beran J, Parenti D. Alternative vaccination schedules (0, 1, and 6 months versus 0, 1, and 12 months) for a recombinant OspA Lyme disease vaccine. Clin Infect Dis 1999; 28:1260–4.


