Vaccines against Lyme Disease: What Happened and What Lessons Can We Learn?

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This article reviews events that led to the withdrawal of the only vaccine to prevent Lyme disease licensed in the United States. The primary issues that led to the vaccine's withdrawal appear to be a combination of vaccine safety concerns, sparked by a molecular mimicry hypothesis that suggested that the vaccine antigen, outer surface protein A, serves as an autoantigen and hence was arthritogenic; concerns raised by anti-vaccine groups regarding vaccine safety; vaccine cost; a difficult vaccination schedule and the potential need for boosters; class action lawsuits; uncertainty regarding risk of disease; and low public demand. This article reviews lessons learned from these events and proposes that future candidate Lyme disease vaccines are unlikely to be developed, tested, and used within the United States in the near future, thus leaving at-risk populations unprotected.

In this article, I endeavor to review the US experience with vaccines against Lyme disease and the eventual withdrawal of the only licensed vaccine from the market. In the United States, a vaccine against Lyme disease was licensed by the US Food and Drug Administration (FDA) and was used in the population for ~4 years. A phase III clinical trial in support of an application for licensure was completed for a second vaccine candidate that was never submitted to the FDA for licensure. A number of events conspired to diminish public support for a Lyme disease vaccine, and this, in combination with class action lawsuits, led the manufacturer to decide to voluntarily withdraw the product from the market, citing insufficient sales volume. This brief article explores what those issues were and how this experience has impacted the field of Lyme disease vaccine development.

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Clinical Infectious Diseases 2011;52(S3):S253–S258

1058-4838/2011/52S3-0001$37.00
DOI: 10.1093/cid/ciq116

BACKGROUND

Lyme disease is now recognized as the most common vector-borne disease in the United States and Europe. Approximately 20,000 new cases are reported in the United States each year, but estimates are that the true incidence is 3–5-fold higher. The highest number of cases in the United States occurs in the Midwest, the Northeast, and the Pacific coast regions, although cases have now been reported from every state. Two age groups in particular experience the highest incidence of Lyme disease: children 2–15 years of age, and adults 30–55 years of age. Because of the public health importance of this disease and its consequences, a US Healthy People 2010 objective was devised to provide impetus to reduce the incidence of Lyme disease to no more then 6.5 cases per 100,000 in states where the disease was endemic. At the time that the objective was written, the baseline population rate was 17.4 cases per 100,000 population in high-incidence states. Of note is that this was the first time that Lyme disease reduction was included as a defined public health objective. It is perhaps self-obvious that, absent a prophylactic vaccine for prevention, there are no practical means to reach this objective.

LYME VACCINES

The strategy behind the development of a vaccine against Lyme disease was based on identifying and using an immunogenic recombinant *Borellia burgdorferi* outer surface protein (OspA) [1, 2]. From this strategy, 2 vaccine candidates proceeded through phase III clinical trials—a vaccine that was registered and licensed as LYMErix by SmithKline Beecham, and a vaccine registered as ImuLyme by Pasteur Mérieux Connaught [3–6]. In both vaccines, the mechanism of action for protection against Lyme disease involved vaccinating humans against OspA with the subsequent development of circulating bactericidal antibodies that would be ingested by the tick during a blood meal. In turn, these antibodies were sufficient to bind and neutralize viable *Borellia* spirochetes present in the tick gut, such that, during a blood meal, infectious spirochetes could not be regurgitated through the dermis, effectively preventing infection.

With the support of advocacy groups and the subsequent research funding provided in response to concerns about Lyme disease, 3 different candidate vaccines were developed [7]. Following this, 2 companies pursued additional development and clinical trials of vaccine candidates. LYMErix, manufactured by SmithKline Beecham (now called GlaxoSmithKline), was released in December 1998 and was voluntarily withdrawn from the market in February 2002. The vaccine was manufactured using 30 μg of recombinant lipoprotein OspA expressed in *Escherichia coli* with 0.5 mg of aluminum hydroxide as an adjuvant. The specific OspA strain used for the vaccine was *B. burgdorferi* sensu stricto strain ZS7. The vaccine was administered as a 0.5-mL dose intramuscularly as a 3-dose series at 0, 1, and 12 months, in a pivotal phase III clinical trial involving 10,906 individuals 15–70 years of age [3]. The trial was a randomized placebo-controlled study in areas where Lyme disease was endemic of a 3-dose vaccine series. Subjects were observed for 1 year, and no significant adverse effects were reported. The prevalence of local reactions was greater among vaccine recipients than among placebo recipients (27% vs 8%), systemic reactions were more common among vaccinated recipients than among placebo recipients (19% vs 15%), and vaccine subjects reported a greater number of transient arthralgias then did placebo subjects. End points of disease were defined as definite cases (clinical symptoms plus laboratory confirmation), asymptomatic cases (no compatible clinical symptoms but positive Western blot results), or possible cases (influenza-like illness and positive Western blot results). Vaccine efficacy was 76% (95% confidence interval [CI], 58%–86%) after 3 doses of vaccine against symptomatic disease and was 49% (95% CI, 15%–69%) after 2 doses. Efficacy against asymptomatic disease was 100% (95% CI, 26%–100%) after 3 doses and 83% (95% CI, 32%–97%) after 2 doses (Table 1).

On the basis of these data, including the safety profile of the vaccine, the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) gave a permissive recommendation for the use of LYMErix vaccine in persons 15–70 years of age who lived or worked in *B. burgdorferi*–infected woody and grassy areas [8]. In addition, the ACIP noted that persons who had previously had Lyme disease were not necessarily protected against future infections and could also be considered as vaccine candidates. In particular, the ACIP recommended that persons who reside, work, or recreate in high- or moderate-risk areas should be considered for vaccination if they engaged in activities that resulted in frequent or prolonged exposure to tick-infested habitats. Vaccine could also be considered for persons exposed to tick-infested habitats but whose exposure was neither frequent nor prolonged. Lastly, vaccine was not recommended for persons who had minimal or no exposure to tick-infested habitats.

It is worth noting that these recommendations were problematic for both patients and health care providers. Neither group was likely to be able to effectively or precisely estimate an individual or personal risk for tick exposure. Geographic data on tick populations and density in a given area were practically nonexistent, precluding determination of whether a given neighborhood was at low, moderate, or high risk.

The ACIP also noted limitations of the LYMErix vaccine [8]. These included the fact that vaccine efficacy was noted to be only ~80% against definite disease outcome; that 3 doses were required over a 12-month period, effectively meaning that individuals could not be fully protected in the first year of vaccination; that no safety or efficacy data were available for persons <15 years of age, who were among those at highest risk for infection; and that the vaccine was only effective against the North American strain of *Borellia* and hence was unlikely to be protective against Lyme disease acquired in other regions of the world. Other concerns included the unknown but possible need for booster doses and continued advocacy for reducing tick exposure by personal protective measures, rather than by relying on vaccine alone.

The second vaccine developed in the United States was produced by Pasteur Mérieux Connaught as a nonadjuvanted vaccine (ImuLyme). A double-blind, placebo-controlled multicenter pivotal trial involving 10,305 adults 18–92 years of age was performed among subjects in areas where Lyme disease was endemic, such that 5,149 subjects received placebo and 5,156 subjects received 2 or 3 doses of recombinant OspA [4]. Subjects were observed over 2 tick seasons, and end points of disease included the CDC definition of Lyme disease, erythema migrans or later manifestations, and laboratory confirmation of infection. Recombinant OspA *B. burgdorferi* sensu stricto strain B31 was used in the manufacture of the vaccine, without adjuvant. Efficacy was measured at 68% after 2 doses and at 92% after 3 doses. There was no difference in the rate or severity of adverse events in vaccine recipients versus placebo recipients. An

Table 1. Immunogenicity and Safety Results of the SmithKline Beecham Phase III Clinical Trial [3]

Variable	Vaccine group	Placebo group	Efficacy	*P*
Definite Lyme disease, no. of cases				
Year 1	22	41	49%	<.001
Year 2	16	66	76%	<.001
Asymptomatic Lyme disease, no of cases				
Year 1	2	13	83%	.001
Year 2	0	15	100%	.001
Adverse events after vaccine, % of subjects				
Arthralgia	3.9	3.5		.34
Myalgias	3.2	1.8		<.001
Achiness	2.0	1.4		.01
Late arthralgia (>30 days after receipt of dose)	1.3	1.2		.54

NOTE. Adapted from [3].

interesting observation was that subjects >60 years of age appeared to be less well protected then others (Table 2).

The manufacturer of this vaccine did not pursue licensure because of several issues. These included technical issues with case reports in the phase III trial and issues related to royalties and patents with GlaxoSmithKline, as well as a decision that the market size was likely to be too small to make the vaccine profitable.(Stanley Plotkin, personal communication).

FDA REVIEW

Based on concerns raised about the potential safety of the vaccine, in May 1998, an FDA panel met to review the proposed Lyme disease vaccine (LYMErix). The conclusions of the panel were that the vaccine did not protect against Lyme disease due to other *B. burgdorferi* subspecies outside of the United States and that individuals who were vaccinated would not be fully protected until the year after the start of the series, and concerns were raised with regard to the cost effectiveness of the vaccine. In addition the panel noted there were no long-term safety data, that persons who received vaccine would be positive by enzyme-linked immunosorbent assay for antibody to Lyme disease (which could be confusing to clinicians), data were not available to determine whether booster doses might be necessary, the vaccine could not be used in young children (who were at the highest risk), and, perhaps of greatest importance, the panel raised the question of a possible relationship to autoimmune arthritis. Although theoretical, the idea that the vaccine could result in an inflammatory arthritis, at least in genetically susceptible individuals, raised considerable alarm. After discussion of these concerns, the FDA panel gave unanimous support for licensure of this vaccine.

Table 2. Immunogenicity and Safety Results of the Pasteur Mérieux Connaught Phase III Clinical Trial

Variable	Vaccine Group	Placebo Group	Efficacy, %
Lyme disease, no of cases			
Year 1	12	37	68%
Year 2			
2 doses	5	2	0%
3 doses	2	26	92%
Adverse effect after vaccination, % of subjects			
Any			
Dose 1	9.8	4.1	
Dose 2	6.1	3.1	
Dose 3	11.2	5.5	
Myalgia			
Dose 1	5.5	0.6	
Dose 2	2.5	0.4	
Musculoskeletal			
Dose 1	6.4	1.3	
Dose 2	3.3	1.1	

NOTE. Adapted from [4].

THE LYME ARTHRITIS HYPOTHESIS

Previous clinical and research observations noted that, in the disease state, Lyme arthritis was influenced by host immunogenetic factors. In particular, it was reported that patients with chronic Lyme arthritis had an increased frequency of HLA-DR4 and HLA-DR2 alleles and that this led to host immune responses that, in turn, led to chronic arthritis [9]. This engendered the hypothesis that the vaccine itself could cause arthritis in vaccine recipients who carried these same HLA alleles. Starting in 2001, Steere and colleagues published a series of articles demonstrating that, in subjects with HLA-DR4 who developed Lyme disease, marked antibody- and cell-mediated immune responses to OspA occurred. Furthermore, they proposed a molecular mimicry model between OspA and human lymphocyte function associated antigen-1 (hLFA-1) as responsible for this finding, stating that ''sequence homology between bacterial and self-antigenic epitopes may be the basis for the molecular mimicry

between host and bacteria and may play an important role in the etiology of treatment-resistant Lyme arthritis'' [10p. 1] [11, 12]. Steere et al [13] further refined this model in a 2003 article, in which they identified OspA as the critical epitope triggering treatment-resistant Lyme arthritis. Others also proposed a molecular mimicry autoimmune hypothesis for chronic Lyme disease in articles published in 1998 [14], 2001 [15], and 2003 [13], when the question arose as to whether OspA vaccination itself could induce an autoimmune arthritis in HLA-DR4–positive subjects. Indeed, in one article, the authors reported 4 HLA-DR4–positive subjects who reportedly developed ''autoimmune arthritis'' after receipt of LYMErix [15]. However, the authors note in the body of the article that the ''autoimmune arthritis'' outcome was transient and inconsequential. Finally, an article published in 2000 reported the occurrence of a destructive arthritis in a hamster model whereby animals received repeated OspA vaccine and then were challenged with *B. burgdorferi* [16].

The above articles raised the scientific question as to whether OspA vaccination itself was arthritogenic. This led to significant media coverage, sensationalism, the development of anti–Lyme vaccine groups, such as the Lyme Disease Network, who urged withdrawal of the vaccine from the market, and eventually a number of class action lawsuits. Extensive internet coverage highlighting high-profile cases of ''vaccine victims,'' allegations of a multitude of adverse effects that were primarily musculoskeletal in nature, and a large class action lawsuit alleging that the vaccine caused harm and that the manufacturer concealed evidence of this harm ensued.

As a result, an FDA panel was convened in January 2001 to further review alleged safety concerns. This FDA panel concluded that there was no evidence of an association between vaccine and arthritis and that the benefits of vaccination outweighed the theoretical risks. Nonetheless, the panel called for enhanced enrollment in a phase IV safety study (fda.gov/ohrms/dockets/ac/98/transcpt/3422t1.pdf) that had been planned for a 4-year period but ended after 2 years because of the voluntary withdrawal of the vaccine from the market. Still, 2,568 vaccinated subjects and 7,497 control subjects were enrolled. Importantly, there were no differences in any significant adverse reactions noted between control subjects and vaccinated persons.

In addition, the vaccine adverse events reporting system (VAERS) database was used in a retrospective study that examined the time period from the time of vaccine licensure through 31 July 2000 [17]. By then, 1.4 million doses of the vaccine had been distributed and 905 reports of adverse events had occurred. These reports revealed an equal male/female distribution, and 56% of the reports occurred after the first dose was administered. In terms of relevant outcomes, 250 cases of arthralgia, 195 cases of myalgia, 157 cases of pain, 59 cases of arthritis, 34 cases of arthrosis, 9 cases of rheumatoid arthritis, and 12 cases of facial paralysis were reported. The investigators concluded that the arthritis incidence was not different than the background rate among unvaccinated persons, that there was no evidence of a dose-response relationship (ie, there was no spike in reports of adverse events after administration of a second or third dose), and the authors noted that the FDA had found no suggestion of concern. In addition, the authors noted that less then half of the ''arthritis'' reports mentioned the swelling or effusion that would be expected with a diagnosis of ''arthritis.'' There was no evidence of a consistent temporal pattern supporting an etiologic relationship between vaccination and subsequent events. The investigators noted that, in the clinical trial supporting licensure, 53 subjects developed arthritis within 30 days after vaccine receipt, versus 49 placebo recipients who developed cases in the same period. Investigators noted that, if only half of the 1.4 million doses distributed had actually been administered and the incidence of arthritis was the same as in the placebo arm of the study, then 2,156 reports of arthritis should have occurred. Thus, VAERS reports of arthritis were significantly less than the expected background rate of cases.

FURTHER CONCERNS REGARDING THE MOLECULAR MIMICRY HYPOTHESIS

The companion article in this issue by Steere et al describes the scientific evidence for a relationship between OspA and antibiotic-resistant Lyme arthritis, as well as, the paucity of evidence that vaccine doses of OspA could evoke a persistent arthritis.

QUESTIONS ABOUT THE ARTHRITOGENIC OspA HYPOTHESIS

Importantly, no difference was found between early or late onset arthritis when comparing vaccine recipients with placebo recipients—including among those with preexisting musculoskeletal disorders. In addition, the FDA had found no statistical evidence of elevated rates of arthritis in vaccine recipients, compared with background rates or rates in placebo recipients.

Thus, the overall conclusion was that no compelling scientific evidence or biologic plausibility existed supporting the idea that the administration of recombinant OspA to an individual with a given HLA haplotype would increase the risk of an autoimmune arthritis. This conclusion was justified by the lack of direct evidence, the theoretical rather then scientific basis for the hypothesis, and the lack of evidence for such a sequence of events in phase III trials. Still, one could argue that, at least in genetically susceptible individuals, such an adverse effect might occur at a level of magnitude below what studies to date have been powered to detect. Unfortunately, it is impossible to know. As is the case in all such questions, it is impossible to completely disprove a safety concern. However, as shown by Livey et al in

their companion article in this issue, it is possible to remove the OspA epitope that prompted concern in the first place and still immunize against Lyme borreliosis.

WITHDRAWAL OF THE LYME DISEASE VACCINE

Because of the hypothesis of molecular mimicry and autoimmune responses to the vaccine, anti-vaccine sentiment and class action lawsuits, a complicated vaccine administration schedule, diminishing physician support for the vaccine, and low public demand for the vaccine; the manufacturer voluntarily terminated vaccine production and marketing of the vaccine in 2002. In one review of these events, it was noted that, by 2001, sales of LYMERix had decreased to $5 million annually with the purchase of only 93,000 doses of vaccine. In the first 2 months of 2002, sales had dwindled to 10,000 doses (Angela K. Shen, personal communication).

In addition, Pasteur Mérieux Connaught, noting the above events, decided not to go forward with a biologic license application for its own Lyme disease vaccine candidate, despite efficacy in their phase III clinical trial. Since 2002, there has been no active, sustained interest in developing or licensing a Lyme disease vaccine in the United States.

LESSONS LEARNED

Lessons important to the field of vaccinology should be extracted from the above sequence of events. Notable is the fact that this was the first time in the modern era that an FDA-licensed vaccine in the United States was withdrawn because of low public demand and class action lawsuits, despite the context of a high background rate of disease and a continuing, if not increasing, significant public health burden of morbidity. This effectively precludes achievement of the Healthy People 2010 Lyme disease reduction goal, because dependence upon personal protective measures is unlikely to be efficacious at the population level. Such measures are difficult to perform, unreliable, and of variable efficacy [6]. For example, in a recent report from the Department of Defense, the incidence of new cases of Lyme disease from 2001 through 2008 was reviewed. Despite the use of personal protective measures, 3,222 documented cases of Lyme disease occurred at >100 locations worldwide [18].

Thus, public concern, further induced by anti-vaccine groups and class action lawsuits, resulted in increasingly low demand for the vaccine and its eventual withdrawal from the market. These events have effectively dampened further interest in the development of other Lyme disease vaccine candidates within the United States by vaccine manufacturers. The consequence of this is that continuing significant morbidity and cost due to Lyme disease, both at the public health level and the individual level, continues to occur. Unfortunately, no solution to this state of affairs is immediately obvious.

In a comprehensive review of Lyme disease vaccine, the National Vaccine Program Office noted several other key lessons learned. These included the following: (1) communication and education are critical components to a successful vaccine strategy, (2) public confidence and trust in vaccines is important to vaccine uptake, and (3) companies must understand the risk-benefit profile of a vaccine and the commercial market to optimize financial success(Angela K. Shen, personal communication). In turn, the author of this review argued that strategic national vaccine plans can and should reinforce and support commercial vaccine success by the following key objectives: (1) coordinate activities in the public and private sectors to drive development (of vaccines) on public health objectives; (2) support key components of the vaccine and immunization delivery system (including disease surveillance, post-marketing surveillance, public engagement, communication, and education), in addition to research and development; and (3) educate stakeholders that key components in the US vaccine and immunization delivery system are interrelated (Angela K. Shen, personal communication). The apparent validity of these suggestions is such that it can be accepted that these lessons would have been valuable in the development, use, recommendations, public and provider education, and post-licensure safety surveillance of these highly novel vaccines.

The intent of this article is not to claim that the only licensed vaccine developed in the United States was ideal or even sufficient. Rather, it is important to note that few, if any, scientists believe the evidence points to any substantive safety concerns. Although multiple factors played a role, it appears that the anti-vaccine sentiment and class action lawsuits that resulted, will, in and of themselves, effectively hamper development of any further Lyme disease vaccine candidate in the United States. One microbiologist involved with Lyme disease published a letter in which he quotes an anti-vaccine activist who wrote: "I would encourage all Lyme patients to consider writing letters, emphasizing the lack of demand for the last vaccine, and also the fact that any future vaccines can expect a lack of cooperation, protests, legal quagmires, etc."[19 p. 278]. As another example, the Lyme disease association published, among other contentions, material speculating on manufacturer mal-intent in regards to safety concerns with the LYMERix vaccine (http://www.lymediseaseassociation.org/index.php?ption=com_content&view=article&id=261:lymerix-meeting&catid=80:controversy&Itemid=76). A recent Google search for "Lymerix and attorneys" yielded hits for 2,200 web sites for attorneys advertising class action and injury lawsuits against LYMErix.

Such sentiments co-occurring with a generally innumerate public are unfortunate, because the need for a Lyme disease vaccine is acute, clear, and compelling. It will, however, be very difficult, if not impossible, to develop such a vaccine in the United

States in the near- to mid-term. The factors mentioned above conspire to create an unfavorable scientific, cultural, legal, and economic environment for the future development of a vaccine against Lyme disease. Although there has been variable and sporadic interest among manufacturers outside of the United States in developing such a vaccine, this interest has not been sustained and has not led to additional significant research to the point of developing a vaccine candidate ready for large-scale clinical trials.

Importantly, other segments of the public recognize the real and potential risks for harm from Lyme disease. The author is aware of anecdotal reports from patients who, in desperate attempts to protect themselves from Lyme disease, have been administered canine Lyme disease vaccines. Such reports reveal the need and desire to have a protective vaccine among individuals who are at continued risk for this disease.

From a public health point of view, more research into Lyme disease vaccine development is needed. Considerable morbidity results from the disease, first-generation vaccines demonstrated safety and efficacy, and no other viable options are available. It is unlikely that any viable vaccine candidates will be developed, at least within the United States, in the near future. That is unfortunate and likely means that such vaccine candidates will have to be developed outside the litigious, anti–Lyme disease vaccine, US environment. As articulated by other investigators, among the lessons learned by the withdrawal of Lyme disease vaccines is the illustration that "…media focus and swings of public opinion can pre-empt the scientific weighing of risks and benefits in determining success or failure" [20 p. 6]. In turn, this may inform the need for more-sophisticated methods of informing and educating the public as to the benefits of vaccines, with use of enhanced social media and other tools.

Acknowledgments

Supplement sponsorship. This article was published as part of a supplement entitled "The Need for a New Lyme Disease Vaccine Sponsor" sponsored by Baxter Laboratories and Centers for Disease Control, Fort Collins, CO, and Stanley Plotkin.

Potential conflicts of interest. All authors: no conflicts.

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