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The Rise and Fall of the Lyme Disease Vaccines: A Cautionary Tale for Risk Interventions in American Medicine and Public Health

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Context: Two vaccines to prevent Lyme disease (LD) were developed and tested in the 1990s. Despite evidence of their safety and efficacy in clinical trials and initial postmarketing surveillance, one vaccine was withdrawn before the regulatory review and the other after only three years on the market. An investigation of their history can illuminate (1) the challenges faced by many new risk-reducing products and practices and (2) the important role played by their social and psychological, as distinct from their biomedical or scientific, efficacy in how they are used, and their ultimate market success or failure.

Methods: This article reviewed medical and popular literature on LD vaccines, analyzed the regulatory hearings, and conducted interviews with key participants.

Findings: Even if proved safe and effective, LD vaccines faced regulatory and market challenges because the disease was geographically limited, treatable, and preventable by other means. Pharmaceutical companies nevertheless hoped to appeal to consumers' desire for protection and control and to their widespread fear of the disease. The LD advocacy community initially supported the vaccines but soon became critical opponents. The vaccines' success was seen as threatening their central position that LD was chronic, protean, and difficult to treat. The activists' opposition flipped the vaccines' social and psychological efficacy. Instead of the vaccines restoring control and reducing fear, demand was undermined by beliefs that the vaccines *caused* an LD-like syndrome.

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Conclusions: The social and psychological efficacy of many risk-reducing practices and products, such as new "personalized vaccines," is to provide insurance and reduce fear. Yet the actions of self-interested actors can easily undermine this appeal. In addition to evaluating the scientific efficacy and safety of these practices and products, policymakers and others need to understand, anticipate, and perhaps shape the potential social and psychological work they might do.

Keywords: Lyme disease, Lyme disease vaccines, history of medicine, history of public health, vaccines, health policy.

In George Bernard Shaw's play *The Philanderer* (1893), Dr. Paramour reads with dismay a report in the *British Medical Journal* that proves that the disease bearing his name is nonexistent. His patient with the hitherto-real Paramour's disease, sitting nearby, feels liberated and is annoyed by Paramour's despondency. Shaw's caricature of late nineteenth-century medical pretensions elicited laughs when I saw the play in 1982, but I wonder if it would today, when patients often cling more tightly to controversial medical diagnoses than to their doctors.

One such prominent contemporary controversy is over the diagnosis and treatment of Lyme disease (LD). In many ways, LD is an unlikely battleground. It is an old-fashioned "new" disease. In the late 1970s and early 1980s, entomologists and clinical researchers rapidly identified the tick vector and causative bacteria, the spirochete *Borrelia burgdorferi* (named after its discoverer, Willy Burgdorfer). Diagnostic tests were developed, and antibiotics were believed to be effective. These rapid developments might have led to a reassuring narrative about scientific ingenuity and medical efficacy. But events turned out differently. Nearly every aspect of the diagnosis, treatment, and prevention of LD has been fiercely contested.

What is Lyme disease? Who gets to decide? The major issue since LD was named and "discovered" has been the legitimacy and reality of *chronic* Lyme disease (Aronowitz 1991). For many people in the LD lay advocacy community, LD is protean in its manifestations, often misdiagnosed and underdiagnosed and capable of causing months and years of debilitating pain, fatigue, and anguish. From this heterodox perspective, which has become a formidable opposition to LD orthodoxy, the

chronic form of Lyme disease requires long-term, often repeated, courses of antibiotics. In contrast, the orthodox position held by most scientific experts is that LD is typically a straightforward acute infectious disease, readily diagnosed on the basis of rash and other clinical findings, with a supporting role played by laboratory tests, and treated by short courses of oral antibiotics. Late symptoms and syndromes can occur (rarely), but there is no need for a repeated course of intravenous antibiotics. Stricker, Lautin, and Burrascano called the controversies over the definition, diagnostic criteria, and treatment of LD the *Lyme wars* and noted that "suffering patients seek out 'Lyme-literate' providers because the 'academic' researchers have failed them" (2005, 5).

The stakes in these controversies are high. The question of whether a protean condition called chronic Lyme disease with many different subjective and objective manifestations exists and should be treated with one or more courses of intravenous antibiotics remains the central issue. In a prominent consensus statement endorsed by the Infectious Disease Society of America (IDSA) in 2006, orthodox physicians stated that the evidence supported only three, narrowly defined, late manifestations of LD (Lyme arthritis, late neurological LD, and a rare skin condition called acrodermatitis chronica atrophicans), each characterized by objective diagnostic criteria in addition to subjective complaints and for which there were only limited indications for a single course of intravenous antibiotics (Wormser et al. 2006). Not only was this interpretation of the evidence contested by the heterodox community, but the IDSA was subsequently subjected to antitrust action by the Connecticut attorney general (for a discussion of what appears to be at stake in these long-lasting controversies, see Aronowitz 1991).

The heterodox position on Lyme disease could be said to have started with its first patient, Polly Murray, who believed that investigators and doctors, with whom she collaborated and whom she respected, were "playing down the severity of the illness" (Murray 1996, 121), as well as focusing too narrowly on arthritis and other objective complaints. Local support groups were started in the 1980s to provide patient and physician education, practical support for patients, and fund-raising (Murray was involved in each of these activities), often in tandem with the Arthritis Foundation, but were shortly superseded by national and local groups that positioned themselves in opposition to the leading Lyme disease physicians and scientists and their view of the disease. The most prominent among these opposition groups are the Lyme

Disease Foundation, the Lyme Disease Association, and, more recently, the International Lyme and Associated Diseases Society. But the networks of heterodox patients and their families and fellow-traveling physicians are close-knit, largely independent of organizations, held together by informal meetings and collaborations, and aided by the introduction of the Internet. (For an insightful overview of these individuals and groups and the personal journey many LD patients follow, prompted by the limitations of existing knowledge and medical care, which lead them and their families to find other members—patients and doctors—of the heterodox community, see Weintraub 2009).

Twenty years after LD made its appearance in the United States, controversy erupted over the efficacy and safety of the new LD vaccines. At first glance, these vaccines, like LD itself, might have followed an uncontroversial script. Two pharmaceutical companies, in concert with leading scientists and clinicians, developed similar vaccines based on a *B. burgdorferi* outer surface protein (OspA). Developing an effective vaccine faced steep challenges. In general, we do not have effective vaccines for infectious diseases such as malaria, which do not reliably produce immunity against subsequent disease. People can get LD multiple times. Ingeniously, the LD vaccines work by blocking the transmission of *B. burgdorferi* from the tick vector to the human host. Vaccine-induced OspA antibodies in the tick's human blood meal neutralize *B. burgdorferi* within the tick itself before it is transmitted to humans.

After animal and laboratory studies, two different vaccines based on the OspA antigen were tested in human populations and found to be effective and safe in premarketing clinical trials. Yet one of these vaccines was never submitted for FDA approval, and the other was withdrawn from the market by the manufacturer after only a few years of use. Why did these promising vaccines fail? What does their failure tell us about risk and efficacy in modern U.S. medicine and society?

What Happened?

In the 1990s, SmithKline Beecham (SKB) and Connaught Laboratories independently conducted extensive laboratory and animal studies of OspA vaccines and then launched highly publicized phase III clinical trials involving large numbers of volunteers and clinical sites (Sigal et al. 1998; Steere et al. 1998). The main difference between the two

vaccines was that SKB's LYMErix contained an aluminum adjuvant (often used to boost immunity), while Connaught's ImuLyme did not (which theoretically might lead to fewer side effects). In order to maximize the signal-to-noise ratio in a disease whose diagnostic criteria and boundaries had long been subject to intense controversy, both trials used narrow, objective criteria for what would constitute a Lyme disease case in the study population. "Definite" Lyme disease was defined as the presence of erythema migrans (EM, the characteristic LD rash) or objective neurologic, musculoskeletal, or cardiovascular manifestations of LD, plus laboratory and/or biopsy confirmation (of rash) of infection. Such criteria maximized the specificity of the diagnosis and minimized the possibility of mistakenly seeing no preventive effect of a vaccine when one existed, which might result if many wrong or questionable cases were counted as LD.

The results from the two trials suggested that both vaccines were safe and effective. Numbers of nontrivial adverse reactions were similar in controls and subjects. Subjects who received the full three doses had at least a 75 percent reduction in definite LD compared with the controls, and in the second year of the LYMErix trial (the only one to study this question), there were no cases of asymptomatic infection (defined by laboratory evidence of infection without symptoms) in the treated group. The absence of asymptomatic seropositives among the vaccinated could be understood as powerful evidence of vaccine efficacy because asymptomatic seropositive cases are ascertained only by objective measures, unlike clinical diagnoses, which might be counted mistakenly on the basis of how trial subjects perceived and reported symptoms and sought medical care and of differences in physicians' diagnostic practices.

The trials also produced a disturbing picture of the inaccuracy of clinical diagnosis. In both trials, only a small fraction of initially suspected cases were confirmed as definite Lyme disease (in the 10% to 20% range), suggesting widespread overdiagnosis (or, alternatively, that the diagnostic criteria were too narrow). Because these data were from the carefully observed conditions of a well-funded clinical trial, a much larger problem certainly existed in everyday clinical practice. At the same time, a high percentage (30%) of cases confirmed by biopsies of skin rashes in the LYMErix trial were not accompanied by positive serology, suggesting that underdiagnosis was also present in the world outside trials, especially when clinicians depended on serology, for example, in cases presenting without the characteristic rash or after the rash was gone.

The FDA licensed LYMErix in 1998 after a hedged recommendation for approval by its Vaccines and Related Biological Products Advisory Committee (VRBPAC). The committee's chair, Patricia Ferrieri, noted that "it's rare that a vaccine be voted on with such ambivalence and a stack of provisos" (Altman 1998, A1). After the FDA's approval, recommendations for use in clinical practice were taken up by the highly influential Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC). Some ACIP members considered LYMErix to be a "yuppie vaccine," its "manufacturer-driven and consumer-driven" market limited to worried suburbanites who "will pay a lot of money for their Nikes and their Esprit and shop at L.L. Bean's will have no consideration for cost-effectiveness when they want a vaccine because they're going to travel to Cape Cod" (Dr. Chinh Le, testimony, ACIP meeting 1998).

ACIP members concerned with this "yuppie vaccine" steered the committee to a lukewarm "should consider" recommendation for people at high risk and a "may be considered" for others "exposed to tick-infested habitat but whose exposure is neither frequent nor prolonged" (ACIP 1998). ACIP member Paul Offit (personal communication, 2011) noted that it was highly unusual for such a lukewarm recommendation to be given to a vaccine approved by the FDA. In addition to the small numbers of people who would unambiguously benefit, support for LYMErix among regulators and advisory boards was hedged because (1) the trials had excluded children, limiting the vaccine's use until the efficacy and safety for children were established; (2) boosters would probably be needed to keep a high enough concentration of antibodies in the tick meal to kill spirochetes; and (3) concern that vaccine's side effects might appear with a longer follow-up (especially concerns about vaccine-induced arthritis, discussed later).

The Connaught vaccine was withdrawn even before licensing. Connaught's anticipated market edge for ImuLyme may have evaporated when the vaccine was not proved to be any safer than the SKB product in the efficacy trials.[1] Leonard Sigal (personal communication, July 6, 2011), the lead investigator on the Connaught vaccine trial, believed that the manufacturer concluded that marketing and other costs would be greater than the low revenues expected from the sales. Connaught's competition, SKB, also had superior resources and experience to market its vaccine in the United States. Stanley Plotkin (personal communication, July 18, 2011), a prominent vaccine researcher and consultant

to the pharmaceutical industry, believed that there were record-keeping problems in the Connaught trial that would have made regulatory approval difficult. Although not privy to Connaught's decision-making process or drivers, Loren Cooper (personal communication, August 11, 2011), an SKB lawyer, offered that it was not uncommon for one vaccine company to look at the experience of others when making development decisions. In this instance, Connaught may have anticipated that the controversy surrounding LYMErix would also impact its vaccine and presciently decided to "stop the bleeding" rather than pursue a vaccine unlikely to be commercially successful.

One early warning sign of these problems was the report that volunteers in the clinical trials were suing vaccine manufacturers for the harm they experienced (Rierden 1996).

Many of the problems with low demand were predictable far in advance of the pharmaceutical companies' decisions to withdraw their products. In most parts of the United States, the disease is rare; it can be successfully treated by antibiotics and is not deadly. Most experts believe that complications like arthritis, Bell's palsy (temporary yet scary facial nerve paralysis), heart block, and back pain are infrequent, respond to treatment, and, even if untreated, eventually resolve. Infection can be prevented by individual measures such as tick checks and protective clothing. To the degree that these measures are a burden, a vaccine could never totally supplant them anyway because ticks carry other infectious diseases besides LD and vaccine efficacy is never 100 percent. Because there is no person-to-person LD transmission, even the most effective vaccine would offer no protection to the unvaccinated (i.e., no herd immunity). So it remains puzzling why Connaught invested so much in vaccine development and its successful phase III clinical trial only to withdraw the vaccine before FDA approval or, similarly, why SKB anticipated a much larger market. I return to this puzzle later.

At the time of the FDA's licensing of LYMErix, there were only limited data on the vaccine's long-term safety and the duration of immunity. Since the rationale for a vaccine against a "mild" and easily treated disease affecting small populations in specific regions remained marginal, regulators and others had an understandably cautious, wait-and-see attitude toward the vaccine's safety, mandating SKB to conduct postmarketing surveillance (SKB agreed to set up a novel, HMO-based surveillance system). At the time of licensing, regulators and others were quite concerned that the vaccine might induce an autoimmune reaction

that would result in arthritis and other complications resembling the late complications of Lyme disease (discussed in greater detail later). On the efficacy side, there was great interest in whether the vaccine might prevent the intermediate and long-term neurological, rheumatological, and other effects of the disease. But since the trials led to the prompt diagnosis and treatment of cases in both the experimental and control groups, such effects were rarely seen.

During the 1998 VRBAC meeting, Dr. Thomas Fleming pressed Allen Steere, the discoverer of LD and the chief investigator of the LYMErix trial, and others for evidence that the vaccine prevented these feared chronic manifestations. Steere told the committee that there were virtually no chronic or systemic problems, only one case of trigeminal neuropathy and one with Lyme arthritis. Since these sequelae also were rare in the placebo group, a reasonable interpretation of the very low rate of chronic or systemic problems was that the trial led to the prompt diagnosis and treatment of LD cases and that such treatment was very effective at warding off later problems.

When the VRBPAC met again in 2001 to review the safety and efficacy of LYMErix after more than two years on the market, SKB officials continued to argue that the vaccine was safe.[2] There was no evidence of a pattern of serious side effects reported from either the usual adverse event reporting or the HMO surveillance program. Despite some evidence of a link between the vaccine and musculoskeletal problems, there was no evidence of autoimmune reactions or treatment-resistant Lyme arthritis. "In all those studies the nature and the frequency of the adverse events were similar to the pre-licensure clinical trial experience," concluded SKB researcher Dr. Kahn (VRBPAC 2001).

But many Lyme disease activists and others at the advisory board meeting already had turned against the vaccine in a major way and were not buying SKB's assurances about its safety. Vaccine recipients at the meeting claimed that their health had been severely and negatively impacted by the vaccine. "I'm not as knowledgeable as this distinguished panel of experts that I speak to today," asserted one lay witness. "But I know one thing with all of my being. It was LYMErix which somehow had this devastating effect on my seventeen-year-old child" (Scharf Lurie, VRBPAC 2001).

Some advisory panel members were puzzled by the disconnect between the reassuring adverse event reporting and the surveillance data presented by the SKB officials and the passionate narratives of physical

and mental anguish following vaccination. Benjamin Luft, a prominent LD researcher, noted a failure to deliver on an earlier, if implicit, promise that in return for very quick approval of a "personal choice" vaccine, surveillance data would be collected to resolve lingering doubts about safety. SKB had been given "a gift," Luft argued. "I'm disappointed today. Because I hear some information here and I hear some information there. And I don't hear good data. We really are sitting in a situation in a sea of just what we feel. Because no one is giving us data" (VRBPAC 2001).

One reason that data were scarce was that the vaccine was being used much less often than predicted, making it difficult for either the adverse event–reporting system or the HMO surveillance program to reliably identify vaccine problems. The low uptake also signaled that the vaccine was in (market) trouble.

In February 2002, SKB, citing poor sales, voluntarily discontinued the manufacture and distribution of LYMErix. Dear Doctor/Investigator letters were sent, and refunds were given for returned vaccine vials. SKB promised to complete all clinical studies.

A related dog vaccine has been very successful.

Heterodox Opposition to Vaccine

The preexisting controversy over the definition, scope, and significance of chronic Lyme disease ultimately shaped every aspect of the controversy over the LD vaccine. In retrospect, the developers of the LD vaccine did not fully appreciate what was at stake in these controversies and how these stakes would affect the reception of the vaccine. SKB gave financial support to different LD advocacy groups in the 1990s, presumably expecting them to be allies in bringing an effective and safe vaccine to market. They indeed might have helped turn the great concern about LD in endemic areas into vaccine sales, but instead, many LD advocates and the groups representing them ultimately turned on the vaccine and vaccine makers. As Loren Cooper (personal communication, August 11, 2011), counsel to SKB for much of the ensuing LD litigation, put it in retrospect, given the discord within the medical community and among LD advocates and support groups, "We stepped into a hornet nest."

One example of SKB's early strategy was the testimony on behalf of SKB and LYMErix at the 1998 VRBPAC meeting given by

Dr. Robert Schoen, a physician and LD researcher. Schoen stressed LD's seriousness, arguing that the disease was analogous to syphilis. The etiological spirochete can "lurk or secrete itself in certain areas of the body, perhaps the central nervous system or perhaps the joint spaces, only to reappear months or maybe years later in the form of late stages of illness, which are harder to diagnosis and treat." He went on to show pictures of a patient with Bell's palsy and describe a patient with heart block, both real but rare LD complications. SKB's message was clear—the chronic complications of LD were serious and difficult to diagnose and treat. Because this message was consonant with the heterodox view of LD, it was understandable that SKB might have expected significant enthusiasm in the LD advocacy community for an effective vaccine.

Yet the vaccine's social and psychological efficacy—the work it does or might do for potential consumers besides blocking *B. burgdorferi* in the tick's midgut—turned out to be complex and contradictory. From SKB's perspective, the vaccine promised to restore a sense of control and reduce the fears of many people living in an LD-endemic area. This work was crucial to developing a market larger than the relatively small numbers of individuals at high risk for *B. burgdorferi* infection. And even those at high risk needed additional reasons to take the vaccine, given the concerns about its cost, side effects, boosters, and incomplete protection.

But there were a few too many missteps and misunderstandings. More than putting pressure on scientific authorities to be included in the investigator-initiated research, LD advocates focused on garnering support and attention for their alternative picture of the disease as chronic and protean and often requiring prolonged treatment. Everything else was secondary. As the prominent LD researcher Alan Barbour wrote in an op-ed about LD advocacy at the very onset of the LD vaccine controversy, "Most of the lobbying has focused on what Lyme disease is rather than how to prevent it" (1997, 23). Also absent from the heterodox opposition to the LD vaccine was any overt linkage to the long tradition of antivaccination campaigns in the United States in any of its guises: libertarian, religious, homeopathic, antimedicalization, and the like (see Colgrove 2006).

A contentious point about "what Lyme disease is"—whether it was easily treated with oral antibiotics—remained. Dr. Dixie Snyder, an FDA advisory panel member, recalled that the VRBPAC's earlier "rather benign" observation that most LD cases were treatable with antibiotics

resulted in "thousands of letters from the public indicating that that wasn't true" (VRBPAC 2001). Such a statement was perceived as a direct attack on a core heterodox position.

The gap between the orthodox and heterodox positions has been wide and consequential. From the orthodox vantage point, many LD advocates did not deserve a seat at the table. It was as if people who had biopsies for breast cancer and tested negative demanded a say in how breast cancer practices and policies were being developed. Some LD advocates believe their children or partners died from Lyme disease, while most experts are skeptical that LD is ever fatal. Members of both communities frequently acknowledge that they have been living in different and oppositional worlds. "Your reporting system might do well in the beltway," one patient advocate complained at the postmarketing regulatory hearings. "But out where the ticks are, out in the hinterland, nobody knows about it, or they are not telling you" (Pat Easton, testimony, VRBPAC 2001).

One lay advocacy organization that SKB initially supported was the Lyme Disease Foundation. At the 1998 VRBPAC meeting that ultimately gave approval to the vaccine, Karen Vanderhoof-Forschner, the foundation's president, offered passionate support for LYMErix. Similar in many ways to the SKB-sponsored clinician who addressed the meeting, Vanderhoof-Forschner argued that LD was a geographically widespread, underdiagnosed, chronic, devastating, and costly disease—and thus worthy of prevention by vaccination. But in 2001 she told the same advisory board that the vaccine "represents an imminent and substantial hazard to the public health and needs to be immediately recalled." Why did she change her mind so quickly? LD advocates were not, of course, against preventing the disease per se but were against the way the vaccine might reinforce the idea that LD was an acute, unproblematic, and clinical entity. For many in the heterodox community, the vaccine, the vaccine's scientific efficacy, and the narrow disease definition had become mutually reinforcing concepts. Once the vaccine's efficacy was established, there was a collateral implication that the narrow diagnostic criteria used to establish this efficacy "worked" as well. This type of stabilization of both the technology and its target is sometimes understood as "co-production" in science and technology studies (Jasanoff 2006). The heterodox antipathy to the vaccine also might have followed from the potential impact of widespread vaccination to reduce the ability of people to claim they had LD. Although there was never any evidence of this motivation, it was clearly in the minds of LD vaccine

supporters. David Weld, executive director of the American LD Foundation (perhaps the sole advocacy group that supported the orthodox position), in testimony at the 1998 ACIP meeting, had wondered out loud if the vaccine "may be very beneficial in that it's going to reduce the incidence of a lot of people claiming to have Lyme disease when they don't."

While the efficacy trials, adverse event reports, and the HMO surveillance system had not found evidence of the vaccine's dangers, the 2001 VRBPAC meetings heard a lot of testimony from individuals claiming serious harm. "What disturbs me is that in the SmithKline presentation there were 950 adverse events," chair Robert Daum noted.

> There was a nice presentation of that. And this afternoon we heard testimony from twenty individuals of twenty, of approximately twenty people who had very significant adverse events. And the disconnect for me is I'm hearing that and I'm seeing that data, and I don't see any reflection of one to the other as if we were in two different universes.

Not only were different types of evidence (statistics comparing the vaccinated and controls with the personal narratives) marshaled, but some heterodox advocates offered radically different interpretations of the same evidence. Rather than understanding the absence of asymptomatic seroconversion among the vaccinated as evidence of vaccine efficacy, some detractors offered a diametrically opposed interpretation: the vaccine caused people with prior or latent infection to become symptomatic with an LD-like disease, resulting in no one left to be asymptomatic. As one vaccine skeptic put it, the vaccine "is turning asymptomatic Lyme disease into symptomatic cases" (Kathleen Dixon, testimony, VRBPAC 2001). Kay Lyon, another vaccine skeptic, argued that asymptomatic infection was better understood as a "smoldering" infection and that the vaccine "might be a trigger that turns this smoldering infection on, converting it almost instantly into late-stage disseminated Lyme disease." In support of the view that asymptomatic infection could later turn into serious disease, she noted that asymptomatic seroconverters, whom the research was designed to detect, had been treated with antibiotics by study investigators. Lyon continued: "This was, of course, the humane way to treat study participants. But it is absolutely not reflective of medical practice in the real world our children live in" (VRBPAC 2001). Again, LD advocates proved adept at using insiders' knowledge of how research was conducted to score points for the heterodox position.

Some heterodox objections to the vaccine echoed a standard observation made by historians of technology and science: scientific practices and technologies often have built into them the choices, values, and interests of specific groups. Critics observed that the values and interests of LD experts and pharmaceutical companies shaped the design of vaccine and drug clinical trials, which in turn shaped beliefs about what was true about LD and everyday clinical practices. There was, in effect, great path dependency on some initial decisions and commitments made by scientists, clinicians, and regulators who shared the orthodox view.

Exhibit number one for this line of criticism was the relationship between the vaccine and the diagnostic criteria for LD, long a battlefield in the "Lyme wars." Many people in the heterodox community were incensed when in 1994, years before the launch of OspA vaccines, experts at a consensus group meeting in Dearborn, Michigan, sponsored by the CDC, removed from the diagnostic criteria a Western Blot band associated with an antigen likely to be part of the LD vaccine. This band was removed so that the immunological tests would not be "fooled" by vaccination, that is, falsely diagnosing LD among the merely vaccinated. Some LD advocates objected that some infected people would be excluded from their "rightful" LD diagnosis because of these changed criteria. In effect, these would-be LD patients, now ineligible for the diagnosis, were sacrificed by the CDC experts in order to accommodate a vaccine of dubious value. One LD advocate observed that the changed laboratory criteria meant that it was now

> impossible for us to know which of our children are infected and which are not. It is therefore impossible to gauge the true safety or efficiency of this vaccine, efficacy of this vaccine in this population. . . . On the other hand, in the world of SmithKline Beecham data, we do find LYMErix; we have an experiment whose success is based, in part, on a set of criteria created to enable the success of the experiment. (Kay Lyon, VRBPAC 2001)

From the orthodox perspective, arguing that different bands on Western blots should be used to define LD was an intrusion into matters best left to the experts. And observing that diagnostic criteria were changed to minimize the chance that vaccinated people might later be falsely diagnosed with Lyme disease was sensible and unexceptional clinical policy.

Heterodox critics pointed out that the surveillance systems used to identify vaccine complications were imperfect and rigged to underreport problems. Reports of adverse reactions depend entirely on the willingness, energy, and competence of the physicians in practice. Side effects would not be reported if physicians believed they were not related to vaccine exposure. So recognizing adverse reactions was, in effect, a closed, circular system in which preexisting biases shaped reporting, which in turn reinforced these biases. No wonder there was underreporting of the vaccine's side effects. "When asked if they had reported this to the administering doctor and if the doctor had reported the adverse event," lay advocate Pat Smith observed, "the usual response was that the doctor did not take the complaint seriously or did not think that these symptoms were related" (VRBPAC 2001).

SKB had promised to make adverse event reporting more sensitive and objective by establishing a surveillance system based on the electronic medical records of a large managed care system in New England. But the vaccine was used much less often than expected, making surveillance difficult. At the postmarketing regulatory hearings, some LD advocates heavily criticized this program, even though the low uptake that made this surveillance system a failure was partly caused by the activists' opposition to the vaccine. They argued that postmarketing surveillance had made guinea pigs out of the vaccine users. "We had no idea that there were unresolved safety issues requiring further study," one advocate observed about the licensed vaccine, "and that by taking this vaccine our family would unwittingly become subjects of an ongoing drug trial" (Lori Gerlbert, testimony, VRBPAC 2001).

The Vaccine's Immune Danger

The case against the LD vaccine was different from what had inspired the opposition to other vaccines in recent decades. Higher than expected levels of Guillame-Barre syndrome had ended the 1976 swine flu immunization program (Neustadt and Fineberg 1978); increased numbers of intussusceptions had led to the recall of an early rotavirus vaccine just around the time LYMErix was first being marketed; and the alleged link between MMR vaccine and autism has been a simmering controversy since the time of the LD vaccine controversy. The main case against the vaccine was that it *caused* LD-like complications.

This concern about the vaccine has its origin in the belief that some late-stage complications of LD were caused by immune mechanisms rather than by direct effects of the infection. In particular, LD experts have speculated that some LD-associated arthritis, particularly cases that are not responsive to antibiotics, is due to the body's immune attack on joints triggered by spirochete infection. Evidence for an autoimmune explanation of "treatment-resistant" LD-associated arthritis has included clinical similarities with rheumatoid arthritis, long understood as an autoimmune process, and the failure to find spirochetes in the affected joints.

It is a small step from belief in an autoimmune mechanism for LD-related arthritis to concerns that the LD vaccine could induce autoimmunity. What if the antigens used in the vaccine were the same spirochete bits that caused autoimmunity following natural infection? Moreover, the heterodox community frequently cited autoimmunity as the mediating mechanism for the chronic fatigue, pain, and other signs and symptoms that were prominent—and most contested and feared—in the alternative LD construction. If the vaccine itself caused a syndrome that was the same or similar to chronic Lyme disease, then these "side effects" constituted evidence in support of the alternative disease definition. And if the vaccine did not cause these symptoms, then the heterodox position, to which putative autoimmune mechanisms were central, could be undermined.

These uncertain and contested beliefs about autoimmunity were the fertile soil from which opposition to the vaccine arose. Central to the case against the vaccine was the considerable scientific speculation in the years just before the vaccine's introduction that OspA itself was the culprit antigen that triggered treatment-resistant LD-arthritis via molecular mimicry. Allen Steere, who is credited with discovering LD in the 1970s, did much of this research. He had suggested a possible connection between individuals who express HLA DR4 antigen (HLA antigens play crucial roles in distinguishing self from nonself and are frequently evoked to explain who develops autoimmunity), exposure to OspA, and subsequent treatment-resistant arthritis. There was some evidence that the OspA protein was similar to a human protein named LFA-1, which may play a role in autoimmune arthritis (Kalish, Leong, and Steere 1993).

To some observers, Steere's role in advancing and legitimating these concerns was paradoxical. After all, he helped develop the vaccine and

also led the LYMErix clinical trial while simultaneously championing a theory that suggested that the vaccine might be dangerous. Why would you develop and study a vaccine against Lyme disease that you had serious reason to believe might cause some of its late manifestations (Sigal personal communication, July 6, 2011)? According to a *New York Times* profile, Steere "has his doubts about the safety of the vaccine" (France 1999, F7). But a less contradictory interpretation of Steere's actions was that he believed that OspA's role in autoimmunity was still an unproven hypothesis and that the potential benefits of the vaccine were likely to trump any harm done by treatment-resistant arthritis. Pursuing the mechanism of LD-related arthritis and the efficacy and safety of the vaccine were both valid and important scientific efforts. In any event, the OspA molecular mimicry hypothesis subsequently fell out of favor, and neither clinical trial produced evidence of vaccine-induced arthritis.

Yet the theoretical concern about the vaccine causing LD-like damage persisted as the basis for opposition to the vaccine. A well-publicized suit against the vaccine, settled by SKB in 2003, was based on the manufacturer's liability and responsibility to the class of people *at risk for* an autoimmune reaction (Shea 2003). Promises were made about the language of a future package insert if the vaccine were ever reintroduced, and attorneys' fees (but no patient damages) were paid.[3]

Because the LYMErix trial did not result in greater numbers of arthritis cases, treatment sensitive or resistant, SKB did not include any warnings about autoimmunity in the LYMErix package insert. What seemed logical to the orthodox camp was evidence of a cover-up or hubris by the other side. At the 2001 VRBPAC meeting, advocate Jenny Marra testified that

> SmithKline was so concerned with this issue [possible autoimmunity] that they had study participants sign a paper indicating the theoretical possibility existed that vaccine might cause arthritis in certain genetically susceptible individuals. Yet SmithKline did not include this information in the product labeling or inform the health care providers of this concern. Had I known this, I personally would not have taken the vaccine.

Autoimmunity has long been a fertile imagined space for etiological thinking about chronic diseases whose etiologies are unclear and

that are characterized by exacerbations and remissions. Many of the psychosomatic diseases of midcentury (asthma, hay fever, and ulcerative colitis) were, in subsequent decades, reframed as autoimmune diseases (Aronowitz 1998). While much of this reframing was built on real and important new understandings of immunity, it was also the case that one appealing, intuitive, and flexible overriding causal scheme—psychosomatics—was replaced by another, autoimmunity. (For a general argument about the nexus of lay and scientific ideas about immunity in etiological thinking, see Martin 1994.)

The immune concerns about the LD vaccine have some parallels with concerns about drugs such as Tamoxifen and Finasteride, which have been marketed to prevent breast and prostate cancer, respectively. Despite some evidence of their scientific efficacy for prevention and their regulatory approval, these drugs—when used as preventives—have been market failures. In contrast, the screening tests for these cancers, mammography and PSA tests, are widely used despite controversy over their efficacy, overdiagnosis, and iatrogenic harm. One explanation is that these drugs, unlike the screening tests, evoke different fears because of their direct effects on the body. Tamoxifen, for example, can cause uterine cancer and immediately produces menopausal-like symptoms in many women.

The LD vaccines, like Tamoxifen and Finasteride, may be feared because of their putative direct effects on the body. In the case of the cancer preventives, the comparison with the enthusiasm for screening is telling because the indirect effects of screening—overtreatment resulting from overdiagnosis—may be as consequential but, I surmise, are feared less because their negative impact on health is less direct (Welch, Schwartz, and Woloshin 2011). In addition, the risk of radiation from screening mammography has sometimes played a large role in these controversies (Aronowitz 2007). The point is that social and psychological effects of practices and products, as much as or more than their scientific efficacy, often play a determinant role in their actual use or rejection. Consumers worry that these preventives directly impact the body in unknown and uncertain ways, in one case toward cancer itself and in the other toward murky immune problems. In each case, a preventive drug was marketed as reducing risk and controlling uncertainty/fear and yet has the potential to add risk and raise fears. As a result, many risk-reducing drugs and vaccines are unstable consumer products.

A Personalized Product?

At the postmarketing regulatory hearings (VRBPAC 2001), Dr. Richard Platt referred to LYMErix as a "personal choice vaccine." At these same hearings, consumer activist Dr. Sidney Wolfe recalled an earlier IOM report that

> placed this whole idea in what they call their less favorable category, the lowest ranking in priorities of vaccine development, just because of the fact that (a) the vaccine is not extraordinarily effective; (b) it is not preventing a life-threatening disease; and (c) for most people, a successful antibacterial intervention can occur not when you have a tick but when you have some clinical symptoms that are suggestive of actually beginning to have Lyme disease.

Not everyone agreed that these characteristics of the vaccine and LD meant that the vaccine was optional and should receive less support or tighter regulation than most other vaccines. At the initial ACIP review in 1998, committee member Stanley Plotkin argued that a safe and effective vaccine with a limited market should nevertheless get a strong recommendation from policymakers. The issue of whether to actually use a highly recommended vaccine should remain with the individual. The LD vaccine, Plotkin argued, was

> the first of many. . . . One is going to have to permit the individual to make some choices about whether a reduction from two in one thousand to one in one thousand is significant for that person. So I would urge the committee to distinguish in this type of vaccine between public health issues and individual issues. (ACIP 1998)

In this new world of personal choice, vaccine manufacturers were motivated to persuade potential consumers. In the case of LD vaccines, consumers could be sold freedom from LD fears and the moral satisfaction following proper self-care for themselves and their family. So to succeed in the marketplace, vaccine makers would need to raise awareness of the risk of LD and also of the benefits of the vaccine.

After the FDA approved LYMErix, SKB launched one of the very first large direct-to-consumer advertising (DTCA) campaigns. "I never thought I was a target for Lyme disease . . . until I found out you can get it

in your local park, in your own back yard, or even mowing the lawn," was the voice-over in one television advertisement (Goetzl 2000). A print ad from the same period pictured a woman, with her dog, standing on her lawn who offered the following advice: "I got Lyme disease last spring and I'm being treated for serious health problems. I couldn't prevent it then, but now you could."[4] The campaign aimed to increase awareness of the risk of Lyme disease and to communicate a sense of urgency about taking the vaccine.[5]

The DTCA campaign resembled the aggressive one that Merck used a decade later to promote its human papillomavirus (HPV) vaccine, Gardasil (Aronowitz 2010). In both cases, the vaccine manufacturers promoted their vaccines as consumer choices, raising awareness and fear of the target disease and promising relief from not only the target condition (a benefit that would accrue to only a small segment of the population) but also the anxiety, loss of control, and fear associated with being at risk for the disease. In both cases, vaccine manufacturers attempted to win over consumers by initially funding lay groups they believed could influence the vaccine's market success. In the case of Gardasil, Merck also took aim at state legislators who might vote to include Gardasil among the vaccines mandated for school entry.

Given the great degree of concern already present in some communities about LD, SKB had reason to believe that it had developed an economically successful vaccine. A prominent LD investigator speculated in 1999 that "one group who will demand it are people who fear Lyme disease with no real cause" (Revkin 1999, CT1). The vaccine's efficacy and safety in clinical trials only reinforced this promise. But the vaccine's social and psychological efficacy was quickly undermined by individual stories of harm related to the vaccine's putative immune dangers.[6]

Conclusions

Many informed observers of LD vaccine developments have offered explanations for why the LD vaccines failed. Allen Steere stated that "the withdrawal of the SKB vaccine . . . represents the most painful event in our Lyme disease history" and concluded that "the vaccine was really withdrawn because of fear and lawsuits, not because of scientific findings" (2006, 629). While there is a consensus among vaccine

supporters that "scientific findings" had little to do with the vaccines' downfall, there is little agreement about which nonscientific factors were at work.

Many people have observed that there turned out to be not enough demand for the vaccine to be commercially viable. But almost all the factors related to either LD (e.g., it was treatable, nondeadly, and preventable by other means) or the vaccines (potential for inducing autoimmunity, need for boosters) that might have led to low demand were known before extensive investments in clinical trials, regulatory review, and initial marketing. So these disease and vaccine characteristics are better understood as supporting players, while the more fundamental causes are the more contingent and unanticipated actions that occurred in the brief period after clinical trials were finished and before LYMErix was withdrawn from the market. These actions tipped the balance toward the vaccines' demise. Specifically, we need to understand (1) the origins of the intense heterodox opposition to the LD vaccine and the weak orthodox support for the vaccines once they were challenged and (2) why the efficacy of a "personalized vaccine" was inherently vulnerable to this opposition.

Contingent events external to the LD controversy also influenced the market failure of LD vaccines—especially the controversies surrounding the RotaShield and MMR vaccines mentioned earlier—but I want to focus my analysis on the actors and actions within the developments concerning LD. Other ancillary influences include the theory offered by Sigal (personal communication, July 6, 2011) that the advocacy community turned against the vaccine when SKB withdrew its financial support and also the claim made by both Offit (personal communication, June 28, 2011) and Plotkin (personal communication, July 18, 2011) that the weak recommendations of the FDA and CDC/ACIP led to physicians' lack of enthusiasm for the vaccine. The vaccine's supporters have blamed LD advocates for undermining the vaccine with nonscientific claims of its dangers, and SKB's vigorous DTCA promotion of LYMErix may have led to backlash and distrust.[7]

Heterodox groups came to believe that the vaccines' efficacy supported the orthodox definition of LD and did what they could to undermine the vaccines. These beliefs and actions were neither inevitable nor strictly determined by the clinical and biological characteristics of the disease or the vaccines. Early on in the vaccine story, major LD advocacy groups supported the vaccine. There was a great deal of enthusiasm in affected

communities, as reflected in the easy recruitment for vaccine trials and the early lay criticism of the lack of medical interest in preventing LD. Speaking at the 2001 VRBPAC meeting, Dr. Dixie Snider recalled the very different atmosphere at the 1998 meeting, during which lay advocates told clinicians and scientists that they were insensitive to the needs of the communities that wanted the vaccine. But shortly after the launch of LYMErix, many people in the LD activist community began to understand that the vaccine's scientific efficacy stabilized the vaccine's target: the orthodox view of LD that they so bitterly opposed. Reinforcing these connections were lay activists' opposition to the LD experts and drug companies' promotion of the vaccine (my enemy's friend is my enemy), the narrow case definition used in the trials (if the vaccine worked, then so did the case definition), and the construction of the vaccine's immune dangers in ways that reinforced the heterodox position (severe side effects attributed to the vaccine proved the protean, immune consequences of "natural" LD).

From the orthodox perspective, an effective prevention tool—the product of determined and creative laboratory and clinical science—was withdrawn because LD activists contaminated its potential market by spreading fear and confusion. But why was this lay opposition so effective at weakening the demand for these products? Labels like "yuppie vaccine" and "personalized vaccine," cited by medical experts in regulatory hearings, point to why the LD vaccines were extremely sensitive to efforts to paint them as dangerous. The social and psychological efficacy of risk-reducing products and practices is to provide safety, reassurance, fear reduction, and control of uncertainty. This efficacy was easily unraveled by the LD advocates' promotion of the vaccines' putative immune dangers.

The LD vaccine controversy resembles the recent HPV vaccine controversy in which societal wariness regarding another marginally effective, highly profitable, risk-reducing product played a large part (Aronowitz 2010). The HPV vaccines have been resisted by groups suspicious of big pharmaceutical companies, "abstinence only" supporters, and others. Unlike the LD controversy, there has not been a concerted attempt to link the HPV vaccine to a specific, if theoretical, safety risk. My analysis implies that such a risk might be the nidus in which a lot of other oppositional positions might form. In this sense, the LD vaccine controversy has more parallels with the recent Vioxx controversy, a product whose market niche was to reduce risk (of gastrointestinal complications

associated with other nonsteroidal anti-inflammatory drugs) but that was undone by evidence that the same product imposed a small but real risk of increased cardiovascular disease.

Risk-reducing products are especially vulnerable to actions that raise fear and damage trust and thus undermine the social efficacy of the product. LD activists were able to pollute the positive social and psychological efficacy with a small dose of personal anecdotes and theoretical concerns. This class of practices and products necessarily lives and dies by an "easy come, easy go" rule, that is, things that are easily and successfully promoted as relieving fear and reducing uncertainty can be just as readily undermined if they are shown—or believed—to be dangerous and risky.

The relatively weak and hedged support for the vaccine by members of both the VRBPAC and the ACIP also followed from the vaccines' identity as a risk-reducing product. While reducing fear, providing reassurance, and controlling uncertainty are valid consumer needs, medical experts were skeptical that they balanced out even a small health risk. Moreover, policymakers were concerned that even if safe, "yuppie" or "personalized" vaccines might dilute trust in the entire vaccine enterprise through their marginal health impacts (see Sidney Wolfe's testimony).

LD activists asked whether scientific and clinical developments were "good or bad for the heterodox position" usually answered "bad" and acted accordingly. Some clinicians and scientists lived in a complementary universe in which the vaccine might have contributed to a favorable end to the LD controversies by reducing the number of people who had, or could claim to have, LD.

These fixed positions reflect a very long controversy that is ultimately about who gets to decide how LD is defined and, as a result, who ultimately gets the diagnosis (Aronowitz 1991). Policymakers, clinicians, and vaccine companies failed to understand the central heterodox position that *patients* get to decide the diagnostic criteria. SKB initially funded advocacy organizations and its DTCA campaign bypassed doctors, but the support these advocates craved was for the heterodox definition of LD, not an awareness of LD or a vaccine that stabilized the orthodox viewpoint and was created by the experts they loathed. With the benefit of hindsight, it might have made more market sense for SKB to have enlisted the support of more physicians and to have avoided any involvement with LD advocacy organizations.

This well-established controversy over chronic LD has not gone away. Not long after the LD vaccines were withdrawn, the next major battle in the Lyme wars was over attempts by the Connecticut attorney general to sue a major infectious disease organization for monopolistic practices related to its consensus criteria for diagnosing and treating LD. This mobilization of antitrust laws against the typical ways that expert physicians make and communicate consensus recommendations dismayed most medical observers but was seen by many in the heterodox community as a counterbalance to the power of the medical establishment to set the entry criteria for a much-coveted diagnosis and to discipline "Lyme-literate" practitioners.

More biomedical acceptance of the legitimacy of patients' suffering, whether or not it fits an accepted diagnostic scheme, and clinical management strategies that focus on symptoms rather than specific diagnoses might go some way in lessening the heat of this thirty-five-year-old controversy (Aronowitz 1998). But because this controversy is so entrenched, these patient-centered approaches run against more dominant reductionist tendencies in clinical care and are unlikely to have much impact.

The LD vaccine controversy is unlike the controversies surrounding AIDS and other diseases that also have had a very determined and often oppositional lay advocacy (Epstein 1996). These controversies often center on the inclusion of patients, minority groups, and other stakeholders in the planning and execution of clinical trials and policymaking (Epstein 2007). But Lyme disease is not AIDS. Advocates and experts have often lived in entirely different universes, in which basic assumptions and motivations are built on the negation of the other. There has often been almost a totally incommensurate view of the opposing group's actions. Arguably, inclusion should not be valorized in itself but for what it brings: fairness, accurate research sampling, different perspectives, and so forth. The attempt to include the orthodox and heterodox perspectives in consensus conferences and other research and policymaking venues has, by any standard, failed. Perhaps it is time to name and act as if Lyme disease and chronic Lyme disease were separate entities that have very little to do with each other.

Even if there are no ready solutions to the LD controversies, it remains important to understand what was at stake in the rise and fall of the LD vaccines because American medical practice is increasingly constituted by many similar, risk-oriented interventions (Aronowitz 2009).

The LD vaccine narrative reconfirms that the success or failure of risk-reducing practices and products depends heavily on different sorts of trust. Biomedical interventions that promise risk reduction are different from others that relieve pain, take away symptoms, or reduce suffering. The consumer of a risk-reducing product or practice has to place much more trust in aggregate probabilities of benefit and harm because these practices or products have no felt impact. At the same time, consumers do generally expect a more immediate effect from risk-reducing interventions. These interventions are often designed and promoted as practices or products that promise to restore control, combat fears, and lessen uncertainty. But if these same interventions are later linked to even small probabilities of risk or harm, this social and psychological efficacy can be easily undermined, and the trust shattered. The rise and fall of the LD vaccines shows just how hard it is for this trust to be maintained and how easily it can dissipate. And a lack of trust can easily be generalized to other interventions. At the postmarketing hearings (VRBPAC 2001), consumer activist Sidney Wolfe testified that the problem with the LD vaccines was that they reduced the public's faith in other public health measures. He compared the situation with the "the tragic lesson of the swine flu vaccine . . . when one sees a very questionable immunization campaign such as this going on, about the implication and the negative effect on public health generally and on vaccinations in specific."

Knowledge of the social and historical context in which the LD vaccines became market failures may be useful to policymakers, especially as the number of health risk–reducing interventions—preventive measures, screening tests, and treatments aimed at reducing the probability of recurrence or new manifestations—is growing (Aronowitz 2009). This history suggests that the evaluation of benefit and safety of risk-reducing practices and products, which increasingly dominate medical care, should proceed with more nuanced attention to the challenges posed by their social and psychological and not only by their scientific efficacy.

In many cases, evidence-based, quantitative evaluations of objective health benefits and risks of interventions will profit from the simultaneous identification and examination of the expected and actual social and psychological work done by interventions sold as consumer products. Currently, the consideration of such factors is marginal and not explicit and is carried out in an ad hoc fashion. In the formation of LD vaccine policy, regulators and expert clinical opinion clearly had misgivings

about what was sometimes referred to as the "yuppie vaccine." These misgivings were partly a matter of the limited objective health impact of any putatively effective vaccine, but they also were about diluting the moral and political consensus that has stood behind vaccines as public health measures, and the danger to medical credibility of blurring appeals to public and individual health benefits with consumerist benefits. Policymakers were, and remain, at a loss for dealing with the kind of oppositional lay advocacy manifested in LD. Even the pharmaceutical companies acting as market actors seemed to have misunderstood, at least initially, what might be at stake in their new product. Responding to these challenges necessarily involves simultaneous critical appraisal of extant data about the objective dangers and benefits of interventions along with their anticipated social, political, and economic impacts.

Endnotes

1. Not unlike other pharmaceutical companies in the 1980s and 1990s, Connaught underwent rapid-fire changes in ownership and administration. The company's acquisition in 1990 by the Mérieux Institute (which had recently acquired Pasteur Production) for almost a billion dollars was widely reported as a sign that the hitherto moribund (in terms of profits) vaccine industry was entering a new era. The promise of a financially successful LD vaccine, which was already in the works at Connaught, was presumably part of this attraction. One article reported that Mérieux expected to increase its vaccine sales from $547 million in 1988 to $2.5 billion in 2000 (Andrews 1990, D7).
2. Although SKB merged with GlaxoWellcome in 2000 to form GlaxoSmithKline, I will continue to refer to SKB in this period to preserve continuity.
3. There also were claims of actual harm, some of which were settled by the company out of court to avoid the expense and uncertainty of litigation, according to SKB lawyers (Cooper, personal communication, August 11, 2011).
4. Available at http://www.newspaperarchive.com/SiteMap/FreePdfPreview.aspx?img=149837946.
5. Len Sigal (personal communication, July 6, 2011) did not think the DTCA campaign was a major cause of LD fear. Instead, he blamed infusion companies that sponsored billboards encouraging fears of Lyme disease and including telephone numbers to operators who referred people to "Lyme-literate" practitioners.
6. Both enthusiasm and apprehension could have been read into what had transpired earlier in the decade with dog LD vaccines. A *New York Times* article reported that "with the aid of aggressive marketing, the [dog] vaccine found a ready public. Since last July nearly two million doses have been sold" (Eckholm 1991, 48). But there was a backlash to the successful, aggressive marketing. Organized veterinarians and the U.S. Department of Agriculture urged that the vaccine be limited to dogs at high risk. They also voiced concerns that the dog vaccine might cause Lyme disease–like symptoms. Another account of dog vaccine backlash reported that Alan Barbour, a co-discoverer of *B. burgdorferi*, had seen a billboard in Houston, where there was no LD risk, that queried, "Has your dog been vaccinated for Lyme?" (Weiss 1994, F7).

7. Backlash and distrust of pharmaceutical promotion were present throughout the brief history of these vaccines. When SKB announced at the end of the premarketing trial that it was giving the vaccine to the five thousand participants who had been in the placebo arm, there was an immediate backlash (Revkin 1997) by critics arguing that this was an empty marketing gesture designed to excite the investment community, not improve anyone's health.

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