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## EDITORIAL REVIEW

### The Lyme vaccine: a cautionary tale

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#### SUMMARY

People living in endemic areas acquire Lyme disease from the bite of an infected tick. This infection, when diagnosed and treated early in its course, usually responds well to antibiotic therapy. A minority of patients develops more serious disease, particularly after a delay in diagnosis or therapy, and sometimes chronic neurological, cardiac, or rheumatological manifestations. In 1998, the FDA approved a new recombinant Lyme vaccine, LYMERix™, which reduced new infections in vaccinated adults by nearly 80%. Just 3 years later, the manufacturer voluntarily withdrew its product from the market amidst media coverage, fears of vaccine side-effects, and declining sales. This paper reviews these events in detail and focuses on the public communication of risks and benefits of the Lyme vaccine and important lessons learned.

#### BACKGROUND

##### Lyme disease

Clinicians first recognized Lyme disease in the United States in 1977 when a cluster of juvenile 'rheumatoid arthritis' cases occurred in Lyme, Connecticut. Researchers identified the source of the cluster of cases as a tick-borne infection rather than an auto-immune disease. By 1983, investigators identified the causative agent, a previously unrecognized spirochetal bacteria called *Borrelia burgdorferi* [1, 2]. Lyme disease is the most common vector-borne human disease in the United States, with 23 763 cases reported to the Centers for Disease Control and Prevention (CDC) in 2002 with cases concentrated in the north-east [3]. In Europe and Asia, Lyme disease is caused

by two other *Borrelia* genospecies, *B. afzelii* and *B. garinii*, which results in regional variations in disease manifestations [4].

*B. burgdorferi* causes a multi-system, multi-stage inflammatory process in infected individuals. Lyme disease typically begins with an expanding skin lesion, erythema migrans, often accompanied by non-specific symptoms including fever, myalgias, and fatigue. If untreated, patients may develop neurological, cardiac, or musculoskeletal complaints. In the chronic phase, large-joint arthritis predominates. Rarely, *B. burgdorferi* infection may be asymptomatic [5]. Some patients complain of chronic musculoskeletal pain, neurocognitive difficulties or fatigue, referred to as 'post-Lyme disease syndrome', which may last for many years after appropriate treatment [6]. Lyme disease rarely, if ever, leads to mortality.

Lyme disease, when diagnosed and treated early in its course, responds to oral antibiotics. Patients with complicated courses, particularly those with central nervous system involvement, require several

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weeks of intravenous antibiotic therapy to adequately treat the infection. Patients that require prolonged intravenous antibiotics may incur other risks, including drug reactions, treatment-resistant disease, intravenous catheter complications, and medical errors during hospitalization. However, with appropriate therapy, almost all patients fully resolve their symptoms [7, 8].

### Prevention strategies

Although effective therapies for Lyme disease exist, primary prevention of infection remains the best approach. Preventive measures include the following strategies: exposure reduction, post-tick bite prophylaxis, and vaccination [9].

Individuals can limit their exposure by avoidance of tick-infested areas, using protective clothing, and applying insect repellents containing DEET (*N,N*-diethyl-*m*-toluamide). Removing underbrush and applying pesticides can reduce tick populations in residential wooded areas. Because infection with *B. burgdorferi* requires a prolonged exposure to the infected *Ixodes* tick (typically >36 h), careful inspection after a potential exposure and removal of any ticks reduces infections [10]. The efficacy of these strategies depends on individual behaviour.

A single dose of doxycycline administered within 72 h of a tick bite reduces the risk of *B. burgdorferi* disease by 87% [11]. However, this requires recognizing the tick bite and identifying the type of tick. Nearly three-quarters of people with erythema migrans indicate they were unaware of a previous tick bite [12]. In addition, people often mistake the more common and larger wood or dog ticks for the small *Ixodes* tick. An individual exposed to a tick must weigh the risk of developing Lyme disease against the cost and risks from potentially unnecessary antibiotic administration. Doxycycline is not approved for use in children <8 years of age due to the potential for teeth staining [13, 14], although recent studies have suggested that short courses may be safely given [15].

### Vaccination

Vaccines stimulate an immune response to prevent future infections with the same microbe. In the early 1990s, two different Lyme vaccines emerged that both used the recombinant *B. burgdorferi* surface protein called outer-surface protein A (OspA) as the

immunogen: LYMERix™ (SmithKlineBeecham, Pittsburgh, PA, USA) and ImuLyme™ (PasteurMérieux-Connaught, Swiftwater, PA, USA). Although researchers recognized the known genetic variability in the OspA within the *B. burgdorferi* strains [16, 17], they chose the most common OspA protein as a target. The OspA vaccines proved effective in animal models and safe in human volunteers [18]. Both manufacturers conducted clinical trials in a race to gain the first license for their vaccine [19, 20]. In the LYMERix™ phase III safety and efficacy trial, researchers enrolled 10906 subjects between 15 and 70 years old who lived in endemic areas and randomized them to receive either the three-dose Lyme vaccine regimen or placebo injections. Vaccinated individuals showed a 76% reduction in Lyme disease in the year following vaccination [20], with no significant side-effects noted. Based on these promising findings, the U.S. Food and Drug Administration (FDA) approved LYMERix™ on 21 December 1998. Although ImuLyme™ underwent a similar phase III study, the manufacturer, for unpublicized reasons, did not apply to the FDA for licensure [21].

The available Lyme vaccine came with several immediately apparent limitations. First, the vaccine efficacy of <80% meant that 20% of fully vaccinated individuals could still get Lyme disease [20]. Second, achieving full protection required three vaccine doses given at the time of the initial dose and 1 month and 12 months after the initial dose. Third, the vaccine safety and efficacy database lacked tests in young children, a population at high risk of developing Lyme disease [3]. Also the vaccine was effective only against the predominant North American *Borrelia* strain without necessarily conferring protection against international subspecies [16, 22]. Finally, uncertainty about the length of vaccine-induced immunity implied that recipients might need booster vaccine doses as often as every year to prevent waning immunity.

The effects of vaccination on human behaviour presented yet another important uncertainty. Lyme vaccination, although it provides incomplete protection, may make individuals less likely to limit their exposure to ticks, which might actually increase their risk of Lyme and other tick-borne diseases (e.g. ehrlichiosis, babesiosis and Rocky Mountain spotted fever).

Despite these limitations, the vaccine offered an effective prevention strategy for those at high risk for Lyme disease. In a 1999 cost-effectiveness analysis

the vaccine appeared cost-effective (\$4466 per case averted), and even cost-saving in high-risk situations [23]. In 1999, after reviewing the available information, the Advisory Committee on Immunization Practices (ACIP) suggested the LYMERix™ vaccine for persons who live in an endemic area and who engage in activities that result in frequent or prolonged exposure to ticks [24]. The ACIP did not recommend Lyme vaccination for patients in non-endemic areas, or for those with low exposure risk or at the extremes of age (i.e. <15 years or >70 years).

### Media coverage

Lyme disease entered the high-profile public spotlight with the first descriptions of the infection. The licensure of the LYMERix™ vaccine also received extensive prime-time coverage, with the reports emphasizing the vaccine benefits with little mention of potential risks. The media encouraged people living in endemic areas to speak to their health-care providers about vaccination.

However, LYMERix™ experienced only a short time of popularity. Within a year of licensure, reports of adverse reactions occurring after vaccination started to appear. Although individuals claimed a wide variety of vaccine side-effects, musculoskeletal complaints such as arthritis dominated. The media put a human face on this suffering by carrying the stories of these 'vaccine victims'. The Lyme Disease Network, a non-profit citizen action group, devoted extensive website coverage to this growing controversy.

Spawned by the growing concern over vaccine safety, the Philadelphia law firm of Sheller, Ludwig & Bailey filed a class action lawsuit against the LYMERix™ manufacturer, SmithKlineBeecham, on 14 December 1999. The law firm represented 121 individuals who claimed they experienced significant adverse reactions to the licensed Lyme vaccine. The suit claimed that the vaccine caused harm and that the manufacturer concealed evidence about its potential risks.

### Adverse events

Growing public concerns about vaccine safety forced the FDA to re-examine the adverse reactions reported after Lyme vaccine. The FDA re-examined the published phase III trial that allowed licensing of the vaccine [20]. Significantly more vaccine recipients

than controls (i.e. 26.8% vs. 8.3%) experienced local reactions, including soreness, redness, or swelling at the injection site as well as systemic symptoms such as myalgias, fever, or chills (i.e. 19.4% vs. 15.1%). These symptoms, seen with virtually all immunizations, occurred within 48 h of injection and lasted a median of 3 days. All symptoms resolved without treatment and no difference appeared in the frequency of long-term joint symptoms between the vaccine and the placebo groups (i.e. 1.3% vs. 1.2%). However, the trial followed the patients for only 1 year after LYMERix™ vaccination. This reassuring side-effect profile allowed vaccine licensure, but left open key questions about long-term effects.

To monitor ongoing safety, physicians report all adverse events temporally related to vaccine administration to the Vaccine Adverse Events Reporting System (VAERS). Established in 1990, this cooperative programme of the CDC and FDA provides post-marketing safety surveillance for all U.S.-licensed vaccines. Although successful vaccine licensing requires demonstration of safety, rare health effects appear only post-licensure. For example, the VAERS network identified an association between intussusception and rotavirus vaccination (RotaShield™; Wyeth Lederle Vaccines, Philadelphia, PA, USA) [25, 26], which was later confirmed by subsequent studies [26–28]. This surveillance network allows for nationwide monitoring for side-effect patterns, although further studies are needed to demonstrate a causal relationship. For example, to detect with confidence a side-effect that occurs in 1/10 000 patients, a licensing study would need to include ~250 000 patients. To keep vaccine licensure financially viable, post-marketing surveillance is necessary to identify these rare side associations.

By 2001, with over 1.4 million Lyme vaccine doses distributed in the United States the VAERS database included 905 reports of mild self-limited reactions and 59 reports of arthritis associated with vaccination [29]. The arthritis incidence in the patients receiving Lyme vaccine occurred at the same rate as the background in unvaccinated individuals. In addition, the data did not show a temporal spike in arthritis diagnoses after the second and third vaccine dose expected for an immune-mediated phenomenon. The FDA found no suggestion that the Lyme vaccine caused harm to its recipients.

SmithKlineBeecham researchers also looked carefully for adverse reactions to the Lyme vaccine. A

post-licensure vaccine safety and efficacy case-control study planned to enrol 25 000 LYMERix™ vaccine recipients and 75 000 matched controls within a large New England health maintenance organization [30]. The researchers planned to follow patients for 4 years for the following outcomes: Lyme disease (particularly treatment-resistant types), arthritis, neurological diseases, allergic events, hospitalizations, and death. However, 2 years after licensure, only 10% of the study target patients had been enrolled due to lower than expected vaccine utilization (i.e. 2568 vaccine recipients and 7497 matched unvaccinated individuals). In this small sample, however, the LYMERix™ recipients did not have a higher rate of adverse reactions.

At the same time, laboratory investigators started to gain a better molecular understanding of Lyme arthritis. Following infection with *B. burgdorferi*, people with the human leukocyte associated antigen (HLA) type DR4+ genotype (*HLA-DRB1\*0401*) might experience increased risk of developing chronic treatment-resistant arthritis. These patients produce high levels of autoantibody to OspA in their synovial fluid [31]. Laboratory experiments found a striking resemblance between the immunodominant epitope of OspA, in the context of DR4+, to peptides within the leukocyte integrin LFA-1. Indeed, patients with treatment-resistant Lyme arthritis, but not other forms of chronic arthritis, demonstrated autoreactivity against LFA-1 [32]. Although more recent studies suggest that LFA-1 does not represent the relevant autoantigen [33], OspA antibodies might react against other, as yet unidentified, autoimmune targets.

These findings suggested that, in patients with the DR4+ genotype, an immune response against OspA could translate into a cross-reactive autoimmune response. By implication, an OspA Lyme vaccine might result in autoimmunity in these genetically predisposed individuals. Although causality proved difficult to demonstrate, one study reported four male patients with the DR4+ genotype who developed autoimmune arthritis after receiving LYMERix™ vaccine [34].

Differential genetic susceptibility applied to immunization risk represents a new concept. Although the clinical importance of the DR4+ genotype to a person receiving an OspA Lyme vaccine remains incompletely understood, some suggest screening recipients for HLA type DR4+ and vaccinating only non-carriers. However, genetic screening would add

significantly to the costs of a vaccination programme, shifting the cost-benefit ratio towards only the patients at the highest risks of acquiring Lyme disease. However, this approach might limit the potential risks from a vaccine with demonstrated ability to provide more good than harm for the majority of the population.

### The gathering storm: the FDA meets

With lawsuits pending and questions from the public and the media, and facing an increasingly complex and explosive situation, the FDA reconvened its advisory panel on 31 January 2001 to discuss the future of the Lyme vaccine. The participants included the FDA scientific advisors, the LYMERix™ manufacturer, independent experts, practising physicians, the ‘vaccine victims’ and their lawyers.

This panel, described by one participant as raucous and riotous [35], provided a forum for all of the stakeholders [36]. In support of the vaccine, the FDA summarized the VAERS data and concluded that the evidence did not support a causative association. The vaccine manufacturer, now GlaxoSmithKline following a corporate merger, assured the assembled parties that the LYMERix™ vaccine did not cause harm to its recipients. They reviewed the status of their phase IV post-marketing surveillance. Practising physicians spoke of vaccine efficacy by describing the dramatic reduction in Lyme disease cases in their own practices.

Others raised concerns about the vaccine’s safety. Scientists argued a potential role for genetic susceptibility and OspA-related autoimmunity in vaccine complications. Poignant presentations by several ‘vaccine victims’ described in detail their suffering. The prosecuting lawyers for the largest class action suit claimed that manufacturers suppressed reports of adverse events from the licensing trial and provided inadequate warnings to genetically susceptible individuals.

After hearing compelling testimonies from all the interested parties, the panel concluded the benefits of LYMERix™ continued to outweigh its risks. The panel made no changes to the product’s labelling or indications. However, the FDA required the manufacturer to provide more vaccine safety and efficacy data by increasing the enrolment in their ongoing phase IV trial. The LYMERix™ vaccine remained available for public use.

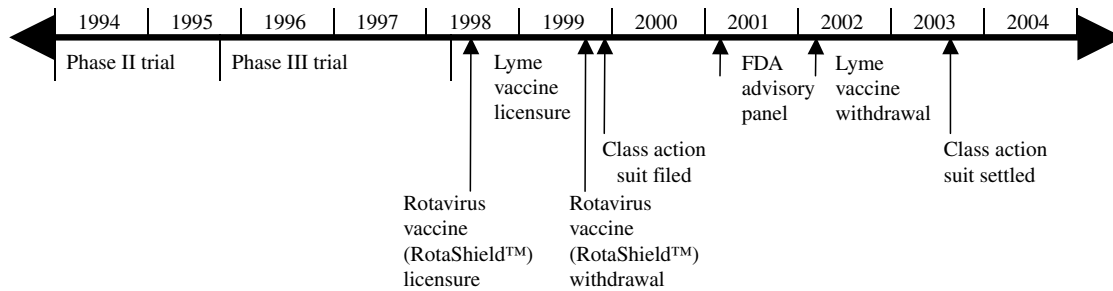


Fig. Time line showing the key events for Lyme vaccine and rotavirus vaccine.

### Market withdrawal

Spawned by the press coverage of vaccine risks and the ongoing litigation, vaccine sales fell off dramatically in 2001. On 26 February 2002 GlaxoSmithKline decided to withdraw LYMERix™ from the market citing poor market performance [37].

On 9 July 2003 the pharmaceutical giant settled the class action suits with Sheller, Ludwig & Bailey as well as several other smaller law firms. The final agreement included over 1 million dollars in legal fees for the prosecuting lawyers, but provided no financial compensation to the ‘vaccine victims’. The plaintiffs’ attorneys stated that the voluntary removal of LYMERix™ from the market accomplished the main goal of the suit. Despite the settlement, the manufacturer continued to deny that LYMERix™ caused harm and indicated that the decision to settle represented a choice based on economic concerns (i.e. the desire to avoid the costs of lengthy litigation) for a product showing relatively poor performance in the market.

## DISCUSSION

### Risk communication and policy implications

Risk communication represents the process of informing individual and collective decision-making by describing benefits as well as risks. As illustrated by the case of Lyme vaccine, the issues involved often become very complex and require an in-depth understanding to accurately assess risk. However, the public attention span is typically short. The media often serve as the only channel through which the general public obtains its health information.

In the aftermath of the LYMERix™ market withdrawal, we must look for lessons learned. The vaccine developers believed they developed a safe and effective vaccine to prevent the most common tick-borne

infection in the United States. Even available post-market surveillance failed to demonstrate convincing harm from the LYMERix™ vaccine. After review of available data, the FDA found insufficient evidence to support a causal relationship between the reported adverse effects and the vaccine and continued to permit use of the vaccine. However, the public’s perception of potential risks, heavily influenced by the negative press coverage and limited awareness of the benefits of the vaccine, decreased consumer demand for the vaccine.

Vaccines represent unique pharmaceutical products because we administer them to healthy people to prevent future disease. This contrasts with most other pharmaceutical products where physicians prescribe the product to treat a condition and patients must weigh the potential side-effects of the medication compared to the symptoms of their disease. In this sense, vaccines require that we may need to take a small risk of potential side-effects in order to avoid the potential of more serious health outcomes associated with the disease. Given this up-front risk, vaccines generally must present exceptionally high safety profiles. As concerns for adverse effects rise, public evaluation of the risk-benefit ratio changes dramatically. The moving anecdotal stories of the ‘vaccine victims’ swung public opinion against the Lyme vaccine, particularly in the absence of stories from people helped by the vaccine [38, 39]. In the media, and hence in the minds of the public, temporal association became equated with causation. In contrast, the benefits of the vaccine from avoiding the effects of Lyme disease did not get the same kind of coverage. This suggests that physicians may need to play a more active role in communicating the benefits of vaccines to patients and the mainstream media, in particular by providing important contexts that will help put the anecdotal stories in perspective and by offering examples of

stories of people whose lives were saved or improved due to the vaccine.

LYMERix™ vaccine was released just as the manufacturer of the oral rotavirus vaccine, RotaShield™, was pulled from the market (Fig.). After nearly a decade in clinical trials, RotaShield™ entered the market in August 1998 with the promise of dramatically reducing the burden of disease from rotavirus, the most important cause of childhood infectious diarrhoea worldwide. Several months later both the American Academy of Pediatrics (AAP) and ACIP added the RotaShield™ vaccine to the routine immunization schedule for all infants [40, 41]. With the increase in use, VAERS quickly began receiving rare reports of intussusception, a potentially life-threatening intestinal blockage [26], and subsequent large case-control and population studies confirmed the association [27, 28]. Epidemiological studies suggested that intussusception occurred in 1–2/10 000 vaccinees, and most experts agreed that this potentially life-threatening risk outweighed the protection against childhood diarrhoea. Consequently in October 1999, 14 months after licensure, the manufacturer withdrew the vaccine [25].

The rotavirus vaccine experience along with ongoing attacks against other childhood vaccines such as the measles–mumps–rubella vaccine (MMR) significantly eroded public trust in all vaccination programmes. Driven by extensive media coverage, the RotaShield™ vaccine underwent an ‘early idealization–sudden condemnation’ sequence where adverse events initially went ignored and later vaccine benefits received inappropriate discounting [42]. This contributed to erosion in public appreciation of the benefits of vaccines and the associated tolerance for vaccine risk. Although studies never adequately substantiated the safety concerns associated with LYMERix™, the decline in public tolerance for risk and uncertainty combined with the relatively low morbidity of Lyme disease contributed to the inability of the vaccine to find a market niche.

## CONCLUSIONS

The complicated history of LYMERix™ provides important lessons. Although the FDA did not revoke the licence, the manufacturer withdrew the product amidst falling sales, extensive media coverage, and ongoing litigation, even though studies indicated the vaccine represented a cost-effective public health intervention for people at high risk of acquiring

Lyme disease [23]. Although preliminary evidence supported LYMERix™ safety, product withdrawal precluded completion of more definitive studies. In the wake of the scientifically justified withdrawal of the rotavirus vaccine, LYMERix™ entered the market at a time of extremely low public tolerance for vaccine risk. Nonetheless, in the absence of a Lyme vaccine, the incidence of *B. burgdorferi* infection continues to be ~20 000 case per year in the United States [3] with thousands of additional cases occurring globally. Physicians effectively treat the majority of these cases with antibiotics, although some cases have complicated courses. Low demand for the vaccine and its subsequent withdrawal from the market represent a loss of a powerful tool for Lyme disease prevention. Although the European vaccine manufacturer Baxter Vaccines has developed a new Lyme vaccine, which they are considering studying in clinical trials, the new vaccine must overcome considerable public aversion for this product to gain widespread global acceptance [38, 39]. As we ask how to weigh public health benefits of interventions against potential risks (notably incurred by identifiable individuals), the LYMERix™ case illustrates that media focus and swings of public opinion can pre-empt the scientific weighing of risks and benefits in determining success or failure.

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## DECLARATION OF INTEREST

None.

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