Clinical Effectiveness of Lyme Vaccine: A Matched Case-Control Study

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Abstract:

We conducted a matched case-control study to assess the effectiveness of Lyme vaccine (LYMErix™) as it was used in clinical practice. We found ≥3 doses to be 71% effective against Lyme disease. This is the first study to show that the Lyme vaccine was effective in a real-world setting.

Key words: vaccine effectiveness; Lyme vaccine; LYMErix; post-licensure.
Background

Lyme disease, caused by *Borrelia burgdorferi* (Bb) and transmitted by *Ixodes* ticks, is the most common vector-borne disease in the United States (US), with approximately 30,000 new cases reported to the Centers for Disease Control and Prevention (CDC) annually [1]. In 1998, a recombinant outer surface protein A (OspA) vaccine (LYMErix™) was approved by the US Food and Drug Administration for the prevention of Lyme disease in individuals aged 15–70 years [2]. Three doses of the Lyme vaccine had a protective efficacy of 76% against definite cases of Lyme disease in a prelicensure clinical trial [3]. However, poor sales of the vaccine led the manufacturer to voluntarily discontinue its production in February 2002 [4]. Since then, there has been an increase both in the incidence of Lyme disease and in its geographic distribution [5]. The increasing public health burden of Lyme disease has led to renewed enthusiasm for developing new Lyme vaccines, including improved vaccines based on OspA [6].

Although prelicensure clinical trials have found the Lyme vaccine to be both safe and efficacious, there are no data about how well the vaccine prevented Lyme disease in clinical practice (i.e., its effectiveness). The objective of this study was to determine how effective the Lyme vaccine was at preventing Lyme disease as it was being used in clinical practice.

Methods:

We conducted a matched case-control study of individuals 15–70 years of age in Connecticut (CT) to measure the protective effect of the Lyme vaccine. Data collection for the study ended in 2003 after the sudden withdrawal of the vaccine from the market and estimates of the vaccine’s effectiveness were never published. Given the renewed interest in Lyme vaccines, we have re-analyzed the data from the original study and estimated the real-world effectiveness of Lyme vaccine against definite cases of Lyme disease. For the original study, potential cases of Lyme disease from 2000 to 2003 were identified through both an active practice-based surveillance system (a limited number of practices in highly endemic
areas), and a passive statewide case-reporting system [7]. Subjects were eligible to be cases if they were residents of CT, were 15–70 years of age, and were reported through one of the surveillance systems as having had Lyme disease from 2000–2003. All potential cases were called and invited to participate in the study. After informed consent was obtained, trained personnel conducted a structured telephone interview within a year of diagnosis to obtain information on demographics, prior sources of medical care, risk factors, and prior utilization of personal protective measures to prevent Lyme disease. Medical records at the subject’s primary care office were manually reviewed by research assistants to record immunization status, past medical history (including prior treatment for Lyme disease) and clinical data associated with the incident diagnosis of Lyme disease. Controls were individuals who did not have any signs or symptoms of Lyme disease at focal time (defined for case/control sets as the date of onset of illness for the index case) and were identified by sequential-digit dialing. Controls were matched by age (±5 years) and geographic area (e.g., same telephone exchange) to each enrolled case-subject. Identical methods and equal efforts were used to ascertain immunization history for both cases and matched controls.

The accuracy of the diagnosis of Lyme disease was assessed by two clinical experts (EDS, MV) — who were blinded to the subject’s immunization status — using solely the clinical and laboratory information extracted from the medical records prepared by trained personnel. Cases were excluded if, after review of their medical records, they did not meet the National Notifiable Disease Surveillance System’s case definition for Lyme disease: physician-diagnosed erythema migrans measuring ≥5 cm, or a positive two-tier serologic test (interpreted using established CDC criteria) and objective evidence of an extracutaneous manifestation of Lyme disease (e.g., facial nerve palsy, meningitis, radiculopathy, carditis, or arthritis) [8]. Subjects were also excluded if, after review of their medical records, they had a history of either immunosuppression or of prior treatment for Lyme disease. For the primary
analyses, subjects were considered “fully immunized” if there was written documentation of receipt of ≥3 doses of Lyme vaccine ≥4 weeks prior to focal time in the patient’s medical record. Unadjusted and adjusted matched odds ratios (mOR) for receipt of Lyme vaccine and their associated 95% confidence intervals (95% CIs) were calculated by conditional logistic regression using Stata statistical software (StataCorp, College Station, TX). The vaccine’s effectiveness (VE) was calculated as 1 – the mOR X 100%. The mOR from these conditional logistic regression models were estimated by number of doses received (≥1, 1, 2, and ≥3 doses) and compared with no prior doses. The adjusted VE (aVE) was estimated using multivariable models that controlled for the effects of variables the distributions of which were statistically significantly different between cases and controls in matched bivariate analyses (bivariate conditional logistic regression). Statistical significance was defined as a p-values ≤0.05 (two-tailed). This study was approved by the Institutional Review Boards of Yale University, the CDC, and the CT Department of Public Health.

Results:
A total of 1,436 potentially eligible persons reported to have Lyme disease were identified from 2000–2003. Of these, 869 provided consent for investigators to review their medical records and completed the structured interview (372 could not be reached and 195 refused to participate). After review of medical records, 325 potential cases were excluded for either not having sufficient documentation that would allow for the confirmation of Lyme disease, or because no matched control had yet been enrolled for that case when the vaccine was withdrawn from the market and the study was stopped. An additional 186 cases were excluded for having documentation of treatment for Lyme disease prior to the index case. The final sample for these analyses was comprised of 358 cases, of which, 68% had early localized Lyme disease, 23% had early disseminated Lyme disease, and 9% had late Lyme disease. A total of 554 matched controls were enrolled (171 sets with 2 controls per case and 212 sets with 1 control per case).
Of the enrolled subjects, 45 (3% of the cases and 6% of the matched controls) had received at least one dose of Lyme vaccine. Cases and matched controls were similar in the distributions of age (46 and 47 years, respectively; p=0.88) and of race (97% and 98% identified as White, respectively; p=0.35). Cases and matched controls differed in the distributions of sex (53% vs. 66% females, respectively; p<0.01), level of education (70% vs. 77% with college education, respectively; p<0.01), use of tick repellents on either skin or clothes (27% and 34%, respectively; p=0.03), use of protective clothing while outdoors (44% vs. 59%, respectively; p<0.01), having pets at home (62% vs. 67%, respectively; p=0.02), and of occupational exposure to ticks (15% vs. 9%, respectively; p<0.01).

The adjusted and unadjusted effectiveness of Lyme vaccine by the number of doses received are shown in Figure 1. Adjusting for potential confounders, the effectiveness of ≥3 doses of the vaccine was 71% (mOR=0.29 p = 0.02).

* Adjusting for sex, level of education, occupational exposure, having pets, use of protective clothing while outdoors, use of tick repellents, and use of acaricides at home

mOR= Matched Odds Ratio
VE= Vaccine Effectiveness
Discussion:

The effectiveness of a vaccine differs from a vaccine’s efficacy in that effectiveness is a measure of how well the vaccine works in real-world settings, rather than in a controlled setting like a clinical trial [9]. Studies of a vaccine’s effectiveness offer a more realistic view of the benefits of a vaccine in the general population, as these observational studies do not control for many factors that could affect the vaccine’s efficacy, such as compliance with timing of doses of the vaccine. In multivariate models, adjusting for the effects of potential confounders, we found that the adjusted effectiveness of ≥3 doses of the vaccine (71%; 95%CI: 20–90%) was similar to the efficacy reported during the pre-licensure clinical trials (76%; 95%CI: 58%–86%) [3]. To our knowledge, this is the first study to quantify the effectiveness of Lyme vaccine post-licensure. Given the relative ineffectiveness of personal protective measures, such as tick repellents and protective clothing, our data highlights that an effective tool for the prevention of Lyme disease was lost when the vaccine was withdrawn from the market.

There are limitations to our study. First, cases could have been misclassified. The diagnosis of Lyme disease is based on the presence of objective and characteristic clinical findings in the context of significant exposure, and, for disseminated infection, an antibody response to Bb antigens [10]. Even though serological tests for Lyme disease have poor sensitivity during early infection, in patients with objective findings of extracutaneous disseminated disease, serology is highly sensitive and specific [8]. In clinical practice, however, misdiagnosis of Lyme disease occurs commonly [11, 12]. To minimize the risk of misclassification errors, we performed an independent review of medical records to adjudicate cases and only included individuals for whom Lyme disease could be confirmed. Second, this study could have been affected by its definition of immunization status, as immunization status was made to depend on completeness of the records (must include immunization dates) and on our ability to review records from medical providers. Third, uptake of Lyme vaccine was low (only 6% among controls), which limited the statistical
power of our study. Given that 6% of controls received the vaccine, our study, with 358 case-
control sets, was powered to detect an effectiveness of $\geq 50\%$ (with a type 1 error of $\leq 0.05$).
We found that the effectiveness of 1 or 2 doses of the vaccine was 7 and 38%, respectively,
and was not statistically significant ($p>0.05$). However, to have statistical power to detect an
effectiveness this low, we would have needed to enroll $>3,000$ subjects. We can, however,
say that it is likely that the effectiveness of $<2$ doses of the vaccine is $<50\%$. Lastly, as is the
case with most case-control studies, there might be selection bias or confounding. To
mitigate this, our controls were matched to the cases by age and geographic area.
Moreover, we collected data on known potential confounders and adjusted our estimates
accordingly.

Conclusion:

A safe and efficacious vaccine against Lyme disease was introduced in 1998. However, it
was soon withdrawn from the market. We found that receipt of $\geq 3$ doses of Lyme vaccine
was 71% effective at preventing Lyme disease. This is the first and only study to show that
the Lyme vaccine was in-fact effective in real-world settings.
Acknowledgments: This study was supported, in part, by the Patrick and Catherine Weldon Donaghue Medical Research Foundation (M.V.), by the Robert Wood Johnson Minority Medical Faculty Development Program (M.V.), by CDC, and by the following grants from the National Institutes of Health: K23-AI068280 (M.V.), K24-AI01703 (E.D.S.) K24-RR022477 (E.D.S.), M01-RR00125 (to Yale’s General Clinical Research Center), UL1TR000142 (E.D.S.), and KL2-TR001862 (E.D.S., C.R.O.), from the National Center for Advancing Translational Science (NCATS) at the National Institutes of Health and NIH Roadmap for Medical Research. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of NIH.

Conflict of Interest: Dr. Shapiro received an honorarium from Sanofi for a conference call about Lyme vaccine, he also receives royalties from UptoDate and has severed as an expert witness in cases related to Lyme disease. The remaining authors have no conflicts of interest to report.

Patient Consent Statement: Written consent was obtained for all enrolled patients in this study. This study was approved by the Institutional Review Boards of Yale University, the United States Centers for Disease Control and Prevention, and the Connecticut Department of Public Health.
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