SYSTEMATIC REVIEW

A systematic review and meta-analysis for the adverse effects, immunogenicity and efficacy of Lyme disease vaccines: Guiding novel vaccine development

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ABSTRACT

BACKGROUND: Lyme borreliosis (LB) is the most prevalent arthropod-borne infectious disease in North America. Currently, no vaccine is available to prevent LB in humans, although monovalent and multivalent vaccines have been developed in the past.

OBJECTIVE: The aim of the current study is to conduct a systematic review and meta-analysis to evaluate and compare the findings from these two classes of vaccines for their reactogenicity, immunogenicity and efficacy, in the hope this may assist in the development of future vaccines.

METHODS: A search strategy was developed for online databases (PubMed, Ovid MEDLINE, and Embase). Search terms used were "vaccine/vaccination", "Lyme disease/Borreliosis", "clinical trial(s)" and "efficacy". Only seven clinical trials were included to compare the results of the monovalent vaccines to those of the multivalent one. Meta-analyses were conducted to evaluate the reactogenicity and immunogenicity of the two vaccine classes. Odds ratio (OR) for LB (and 95% confidence intervals; 95% CI) were calculated for the efficacy of the monovalent vaccine from three different clinical trials at different dose schedules.

RESULTS: Incidence of redness (local adverse effect) and fever (systemic side effect) were, respectively, 6.8- and 2.9-fold significantly lower ($p < 0.05$) in individuals who received multivalent vaccines compared to those receiving the monovalent one. Incidences of all other local and systemic adverse effects were non-significantly lower in the multivalent vaccine compared to the monovalent vaccines. Seroprotection was comparable among individuals who received the two vaccine classes at the 30 μg dose level. Efficacy in the prevention of LB was only evaluated for the monovalent vaccines. OR of LB ranged from 0.49 (95% CI: 0.14–0.70; $p < 0.005$, vs. placebo) to 0.31 (95% CI: 0.26–0.63; $p < 0.005$) for the initial and final doses respectively, with an overall OR of 0.4 (95% CI: 0.26–0.63, $p < 0.001$).

CONCLUSION: The current study further validates that the monovalent and multivalent LB vaccines result in mild local side effects and self-limiting systemic adverse effects, with the multivalent vaccine slightly more tolerable than the monovalent one. Both vaccine classes were similarly highly immunogenic. A new vaccine with high safety standards, better efficacy, low cost, and public acceptance is yet to be developed. Meanwhile, personal protection limiting exposure to ticks is recommended.

KEY WORDS: Lyme disease; vaccine; clinical trial; efficacy; systematic review

La traduction du résumé se trouve à la fin de l'article.

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Lyme disease or Lyme borreliosis (LB) is the most prevalent arthropod-borne disease in North America.[1] It is caused by *Borrelia burgdorferi* sensu stricto (*B. burgdorferi*) in North America, which is transmitted by *Ixodes scapularis* and *Ixodes pacificus* blacklegged ticks.[2] Currently, LB is becoming a major health problem in Canada due to northward expansion of the tick population driven by introduction of *B. burgdorferi* and its vectors by migratory birds,[2] and facilitated by a warming climate which shortens ticks' lifecycles and increases the species' survival.[3,4] The expanding geographical distribution of ticks has been associated with an approximately sixfold increase in LB incidence (from 128 to 707 cases) from 2009 to 2015.[5] The true number of cases is expected, however, to be higher, as it is unlikely that all cases are captured by surveillance. As of 2014, LB was endemic in 22 locations across New Brunswick, Nova Scotia, Quebec, Ontario and Manitoba, in comparison to only one location in Ontario in the 1970s.[6]

The expansion of tick populations and the subsequent increased incidence of LB cases underscore the demand for developing effective and safe approaches for disease prevention and control. Currently, however, there is no human vaccine available.[7] Two recombinant monovalent vaccines were simultaneously developed by SmithKline Beecham (LYMErix) and Pasteur Merieux Connaught (ImmuLyme) in the 1990s. Both were based on outer surface protein A (OspA) lipoprotein expressed in *E. coli*, adsorbed to aluminum hydroxide in phosphate-buffered saline.[8–10] The purpose was to develop circulating bactericidal antibodies against *B. burgdorferi* that would be sufficient to prevent the bacterial transmission from the tick gut to the host following a tick bite.[11]

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Both vaccines underwent large Phase III clinical trials with over 10 000 subjects each and produced promising outcomes.[8,9] Both ImmuLyme and LYMErix exhibited moderate efficacy (49%–68%) in the first year with high efficacy (83%–92%) following a booster dose.[8,9] However, FDA approval in 1998 was sought only for LYMErix.[8,12]

Following the introduction of LYMErix, it was suspected that molecular mimicry between the human lymphocyte function-associated antigen-1 (hLFA-1) adhesion molecules and *B. burgdorferi*-OspA was contributing to the development of antibody-mediated arthritogenesis.[13] The sequence similarities between OspA and hLFA-1, particularly in patients with HLA-DR4, was thought to be the underlying mechanism of progression to the persistent form of LB observed in a small percent of patients.[13–15] Indeed, HLA-DR4 and HLA-DR2 alleles were previously linked to chronic Lyme arthritis in LB cases.[16] This led to questioning the safety of using LYMErix in patients with HLA-DR4 allele being based on OspA antigen. Further investigation led to two reports suggesting the development of chronic arthritis in a hamster model and four human cases.[17,18] These indications – although not corroborated against the safety of LYMErix by the FDA – together with its slow acceptance due to high cost, the extensive anti-vaccination campaigns, the complicated administration schedules and the failure to identify populations at risk of infection, all resulted in its voluntary withdrawal from the market in 2002 together with its licence.[7–11]

More recently, Baxter BioScience developed a second-generation multivalent vaccine against LB with a purpose of global application.[7,19] Although *B. burgdorferi* sensu stricto causes Lyme disease in North America, several other pathogenic strains are found across Europe and worldwide. The new trial-vaccine, therefore, was comprised of three chimeric OspA protective epitopes of *B. burgdorferi*, *B. afzelii, B. garinii* and *B. bavariensis* which are intended to prevent the possibility of molecular mimicry and induce potent antibody responses against all major *Borrelia* species.[19] Safety and immunogenicity evaluation of that vaccine were recently conducted through Phase I/II dose-finding studies in adult populations.[19,20]

Despite the increasing prevalence of LB in North America, Europe and Asia, there is currently no vaccine available to prevent the transmission of *B. burgdorferi* from the tick to humans. Future development of a safe, potent, well-tolerated and cost-effective vaccine would entail evaluating the past vaccine approaches, strategies and effectiveness.[7,21] The current study quantitatively and qualitatively assesses the safety, immunogenicity and efficacy profiles of the monovalent and multivalent LB vaccines from the available clinical trials, in the hope this may assist in the development of future vaccines for the human disease. The outcome of this study may permit establishing a benchmark relationship between immunogenicity of the older vaccines and their clinical efficacy. This will allow for inferring the expected utility of immunogenicity of newer vaccines as a surrogate endpoint for their efficacy.

METHODS

Search strategy and selection criteria

A search was conducted in PubMed, Ovid MEDLINE, and Embase databases to the last week of January 2016 using the search terms (MeSH) "vaccine", "vaccination", "Lyme disease/Borreliosis", "clinical trial(s)" and "efficacy". When we limited the search to English language (since no clinical trials were published in other languages) and studies in human subjects, the search resulted in 72 articles that were selected for title and abstract review. After removing duplicates and excluding reports published as review articles, letters, case studies, editorials, conference abstracts, and animal studies, only 11 articles were considered for full text review. Full article review resulted in the further exclusion of four reports that were only in children (as we focused on adult population because initial licensure of most vaccines was for use in adults), assessed the effect of booster vaccine doses, or evaluated the effect of vaccine on disease serological testing (see Figure 1). A total of seven peer-reviewed articles on the monovalent LYMErix[9,22,23] and ImmuLyme vaccines[8,24] and the multivalent novel vaccine[19,20] were identified for the current study.

Inter-reviewer agreement

The abstracts of the identified studies were independently reviewed by two readers (SH and MS). Differences were resolved through discussions so that a consensus could be reached. Percentage agreement and Cohen's Kappa (κ) statistic[25] were calculated and interpreted in accordance with Landis and Koch's benchmarks[26] for assessing the agreement between reviewers as poor (<0), slight (0.0–0.20), fair (0.21–0.40), moderate (0.41–0.60), substantial (0.61–0.80), and excellent (0.81–1.0). The agreement on the inclusion between the two reviewers was 97%, with $\kappa = 0.89$ (95% CI: 0.74–0.99).

Data extraction

Data extracted from the selected studies included the first author's name, publication date, trial type, recruitment dates, vaccine type, dose schedule, dose level in μg, number of subjects, sex ratio (M:F), age, and the study outcome (Table 1). Moreover, the percentage of solicited and unsolicited, local and systemic adverse effects were extracted for both monovalent and multivalent vaccines (Table 2) together with information on the seropositivity rates of IgG anti-OspA levels (in enzyme-linked immunosorbent assay (ELISA) units; ELU/mL) in vaccinated subjects (Table 3). To determine the rates of immunogenicity (%) in the vaccinated subjects, meta-analysis of percentage of subjects positive for the IgG anti-OspA (and 95% CIs) were calculated from the identified studies for the initial and final dose schedules. Percentage of subjects with 1400 and 5000 ELU/mL for the monovalent and multivalent vaccines, respectively, was used as a cut-off point for IgG as these levels were proposed to ensure a protection for one tick season.[19,20,22,23] Since no Phase III clinical trials were conducted for the multivalent vaccine, data on the vaccine initial, final and overall efficacy were only available for the monovalent vaccines[8,9,24] (Figure 2).

Data analysis

The primary outcome measure was to compare the reactogenicity and immunogenicity between the monovalent and multivalent vaccines from the results of the available clinical trials. Meta-analyses were carried out for the local and systemic side effects as well as the percent seropositivities of the two vaccine classes. We used a binary random-effects model since we assumed that the vaccination for LB can vary across populations. Odds ratio (OR) and 95% confidence intervals (95% CI) were also evaluated for the

LB risk in vaccinated people at the initial and final dose schedules as well as the overall protection following vaccination with the monovalent vaccine (Figure 2). Meta-analysis tests were conducted using the OpenMeta Analyst version 10.10, a free, cross-platform, open-source program.[27] Weighted average of efficacy was calculated at each vaccination stage from the reported efficacy results of the individual studies. To assess whether there is true heterogeneity among the three selected studies,[8,9,24] we used the Q test.[28] Q test only informs about the presence versus the absence of heterogeneity and does not report on the extent of such heterogeneity. Therefore, we calculated the I^2 index to complement the Q test and quantify the degree of heterogeneity among studies.[29] Given the poor power of Q test to detect true heterogeneity among this small number of studies, we also quantified the true heterogeneity by estimating the between-study variance in the random-effects model (τ^2) as previously described.[30] A p-value < 0.05 was considered to be statistically significant. Forest plots were used to illustrate the OR of LB following vaccination from the selected studies and to inspect the heterogeneity of the individual findings (Figure 2).

RESULTS

The monovalent adjuvant vaccines LYMErix and ImmuLyme and the multivalent vaccine were evaluated in several studies, as shown in Table 1. The clinical trials were Phase III double-blind, placebo-controlled or open-label, randomized trials for the monovalent vaccines to assess their efficacy, safety and immunogenicity. On the other hand, the multivalent vaccine was evaluated only through double-blind, randomized, Phase I/II trials that also included a dose-escalation schedule and were limited to assess the vaccine reactogenicity and immunogenicity. The number of the examined subjects varied from 300 to 10 936 in the seven identified studies. Given the nature of the clinical studies, i.e.,

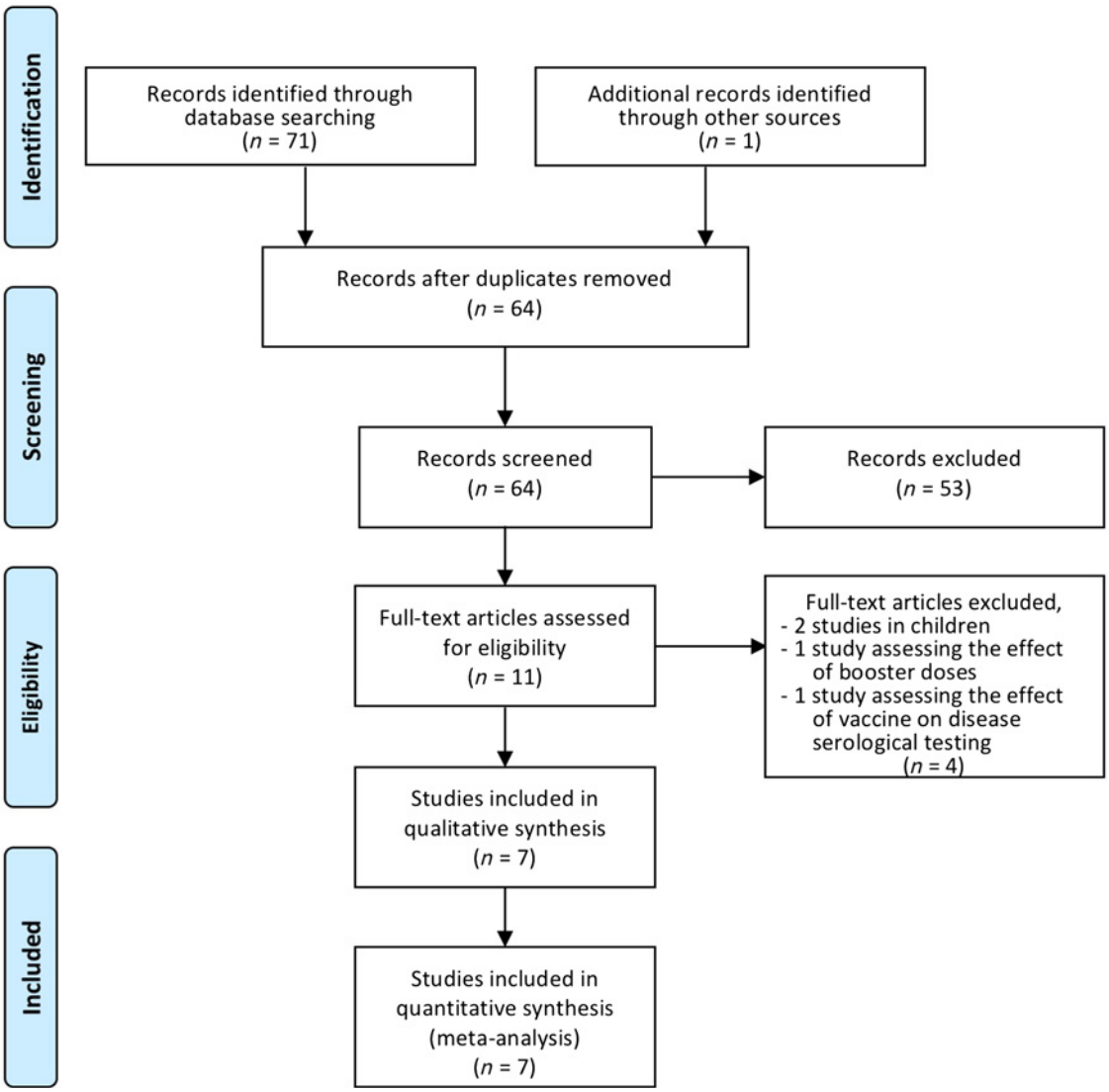


Figure 1. Systematic literature review process. The flow diagram describes the systematic review of literature on the adverse effects, immunogenicity and efficacy of Lyme borreliosis monovalent and multivalent vaccines. The additional record was identified from an initial pre-study literature search. A total of seven unique clinical trials were identified from the total of 64 examined titles.

Table 1. Characteristics of the identified studies

Study ID	Trial type	Recruitment dates (mm.yy–mm.yy)	Vaccine	Dose schedule (months)	Dose(s) (μg)*	Number of subjects	Sex ratio (M:F)	Age range (years)	Average age (years)	Study outcome
Steere et al., 1998[9]	Double-blind, placebo-controlled randomized trial	01.95–04.96	Monovalent (LYMErix)	0, 1 and 12	30	10 936	1.38	15–70	46	Efficacy and safety
Van Hoecke et al., 1999[22]	Open-label, randomized trial	ns	Monovalent (LYMErix)	0, 1 and 6 0, 1 and 12	30	800	0.98	15–50	31.5	Safety and immunogenicity
Schoen et al., 2000[23]	Open-label, randomized trial	01.95–04.96	Monovalent (LYMErix)	0, 1 and 12 0, 1, 2 and 12	30	956	1.11	17–72	51	Safety and immunogenicity
Sigal et al., 1998[8]	Double-blind, placebo-controlled randomized trial	03.94–04.95	Monovalent (ImmuLyme)	0, 1 and 12	30	10 305	1.43	21–79	48.7	Efficacy and safety
Wormser et al., 1998[24]	Double-blind, placebo-controlled randomized trial	Spring 94–Early 96	Monovalent (ImmuLyme)	0, 1 and 12	30	1634	1.63	18–94	50	Efficacy and safety
Wressnigg et al., 2013[19]	Double-blind, randomized, dose-escalation Phase I/II trial	03.11–05.12	Multivalent	0, 1, 2 and 12	30, 60 and 90	300	0.88	18–70	37.4	Safety and immunogenicity
Wressnigg et al., 2014[20]	Double-blind, randomized, Phase I/II study	03.11–03.13	Multivalent	0, 1, 2 and 6 0, 1, 2 and 9–12	30 and 60	350	1.23	18–70	40.5	Safety and immunogenicity

Note: ns = not stated.
* Only the 30 μg dose level was included in the meta-analysis.

Phase I/II vs. Phase III trials, the number of participants in the monovalent vaccines trials (n = 12 292 for LYMErix and 11 939 for ImmuLyme, total n = 24 231) was significantly higher than that in the multivalent vaccine trials (n = 650). The sex ratio of the participants in all clinical trials was 1.23 (M:F). The average age of the participants in the individual trials ranged from 31 to 51 years with an overall age range of 15 to 79 years.

Dose levels and schedules

A common vaccine administration schedule from the identified trials to provide an effective protection for one tick season was 0, 1 and 12 months.[8,9,22–24] However, to evaluate a different dosage schedule that may lead to a better protection, a few studies compared the safety and immunogenicity profiles for LYMErix[22,23] and the multivalent vaccine[20] at either shorter (<6 months) dose schedule[20,22] or with more than three doses within a 12-month period.[19,20,23] The identified studies primarily evaluated the effect of a dose level of 30 μg for both the monovalent and multivalent vaccines (Table 1). Phase I/II trials for the multivalent vaccine also explored the effect of higher dose levels of 60 and 90 μg.[19,20] Increasing the dose from 30 to 60 or 90 μg did not result in higher rates of reactogenicity or significant improvement in seropositivity (data not shown). Therefore, only the 30 μg dose level was included in the meta-analysis to compare the monovalent and multivalent vaccines for the percentages of incidence of local and systemic, solicited and unsolicited adverse effects (Table 2) and their immunogenicity depicted by the seropositivity rates of IgG anti-OspA levels (Table 3).

Safety and reactogenicity

The percentage incidence of adverse effects in the study subjects who received 30 μg monovalent and multivalent vaccines is shown in Table 2. Among the local adverse effects, incidence of redness in individuals who received multivalent vaccines was 6.8-fold significantly lower than in those administered the monovalent LYMErix or ImmuLyme (2.6%, 95% CI: 0.0%–5.1% vs. 17.7%, 95% CI: 5.4%–30.1%; $p < 0.05$). Similarly, individuals who received the multivalent vaccine exhibited 2.9-fold lower incidence of fever compared to those administered the monovalent ones (0.7%, 95% CI: −0.6% to 1.8% vs. 2.0%, 95% CI: 1.6%–2.3%; $p < 0.05$). The incidences of other local and systemic adverse effects, such as site pain, swelling, tenderness, arthralgia, fatigue, headache, malaise and myalgia, were lower in the multivalent vaccinated subjects compared to in those who received the monovalent vaccines, although these differences were not statistically significant, probably due to the small number of evaluated studies and the large difference in effect size between the two vaccines. For example, swelling occurred in 0.6%–16% of the cases in response to monovalent vaccines compared to 0%–3% in response to the multivalent vaccine. Similarly, site pain was observed in 15%–70% of the subjects who received the monovalent vaccines compared to incidences of 6%–42% in those who received the multivalent vaccine.

Immunogenicity

Subjects vaccinated with the monovalent or multivalent vaccines and who developed anti-OspA IgG antibody titers of ≥1400[22,23] or ≥5000 ELU/mL,[19,20] respectively, were considered seroprotected for

Table 2. Percentage of solicited and unsolicited, local and systemic adverse effects of monovalent and multivalent Lyme disease vaccines*

Adverse effect		Monovalent vaccine[8,9,22,23]			Multivalent vaccine[19,20]			$p^{\ddagger}$
		Incidence (%)	95% CI	$p^{\dagger}$	Incidence (%)	95% CI	$p^{\dagger}$	
Local	Redness	17.7	5.4–30.1	0.005	2.6	0.0–5.1	0.046	<0.05
	Site pain	47.6	−7.5–102.7		28.8	3.8–53.9	0.024	
	Swelling	9.8	7.6–12.1	<0.001	1.8	−0.3 to 3.9		
	Tenderness	2.3[§]	1.8–2.8		33.8	3.0–64.7	0.032	
Systemic	Arthralgia	5.3	3.0–7.6	<0.001	1.5	−0.4 to 3.4		
	Fatigue	14.5	−0.2 to 29.2		4.7	−1.1 to 10.5		
	Fever	2.0	1.6–2.3	<0.001	0.7	−0.6 to 1.8		<0.05
	Headache	11.4	5.2–17.6	<0.001	9.0	3.3–14.8	0.002	
	Malaise	10.5	9.0–12.0	<0.001	2.6	−1.2 to 6.4		
	Myalgia	3.2[§]	2.7–3.7		9.0	3.3–14.8	0.002	

* Only data from the 30 μg dose were used.
† Statistically non-significant values are not shown.
‡ Significantly different between monovalent and multivalent vaccines (*t*-test).
§ Based on the findings from one study population.

Table 3. Seropositivity rates of IgG anti-OspA levels that ensure protection for one tick season in vaccinated subjects at initial and final receipt of the vaccines*

Vaccine	IgG anti-OspA (ELU/mL)	Dose timing	Percent positive (%)	95% CI†
Monovalent[22,23]	≥1400	Initial	60.7	53.0–68.4
		Final	91.4	89.8–93.0
Multivalent[19,20]	≥5000	Initial	55.7	47.7–63.6
		Final	88.4	70.8–103.1

* Only data from the 30 μg dose were used.
† $p < 0.001$.

one tick season. Following the initial dose of the monovalent vaccine LYMErix, 60.7% (95% CI: 53.0%–68.4%) of the study population was seropositive (Table 3). The seroprotection was improved to 91.4% (95% CI: 89.8%–93.0%) following the 12-month final dose schedule. Similarly, at 30 μg dose of the multivalent vaccine, the average percentages of seropositivity following the initial and final doses increased, respectively, from 55.7% (95% CI: 47.7%–63.6%) to 88.4% (95% CI: 70.8%–103.1%). Overall, the seropositivity rates of IgG anti-OspA levels that ensured protection for one tick season were comparable between the monovalent and multivalent vaccines at both the initial and final dose schedules.

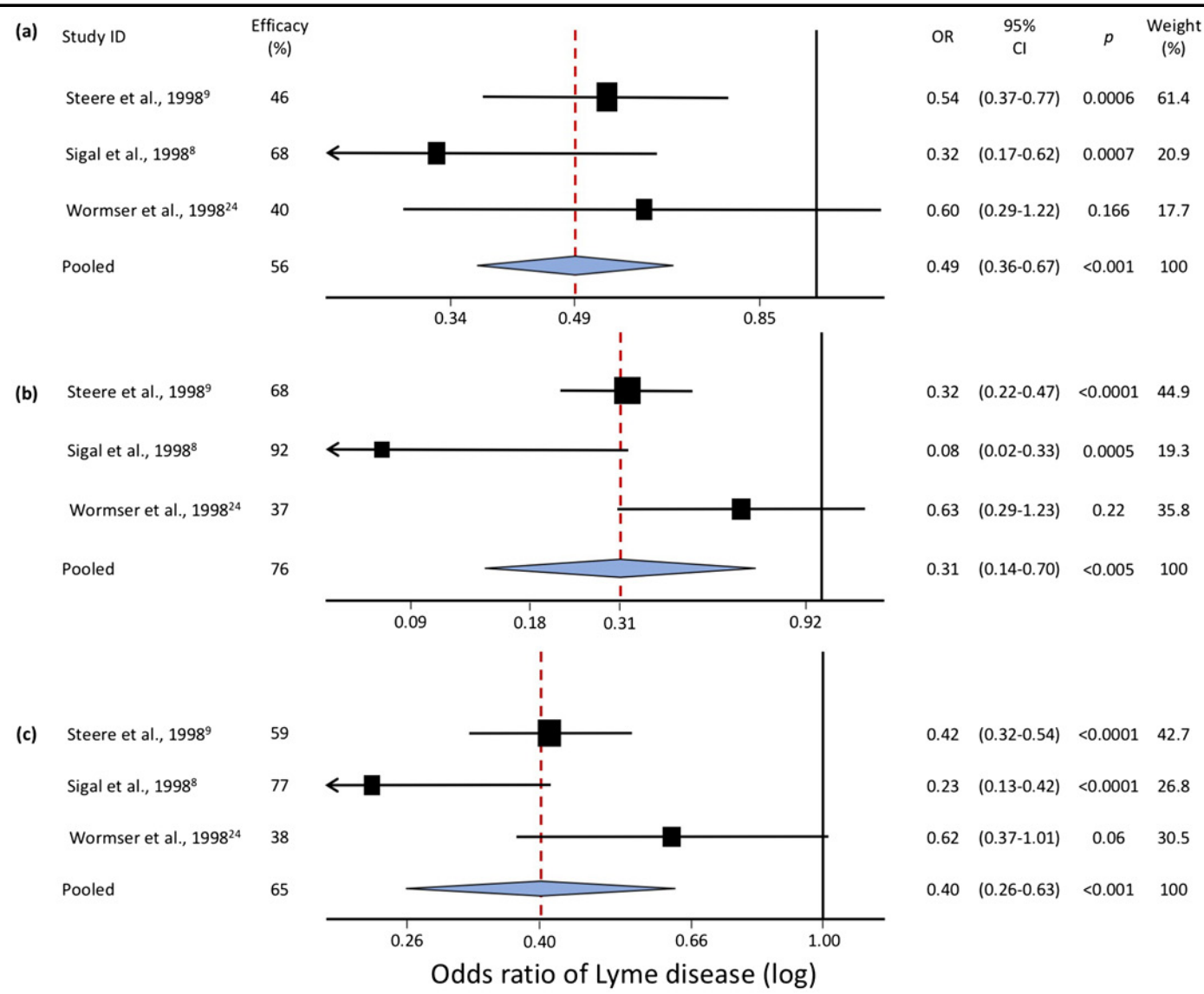
Efficacy

Vaccine efficacy in the prevention of human LB was evaluated for the monovalent LYMErix and ImmuLyme vaccines from three Phase III clinical studies[8,9,24] but not for the multivalent vaccine (Figure 2). During the first year, the disease OR was 0.49 (95% CI: 0.14–0.70; $p < 0.005$ vs. placebo). Following the 12-month final dose, the LB OR improved to 0.31 (95% CI: 0.26–0.63; $p < 0.005$). The overall disease OR from the three identified clinical trials was 0.4 (95% CI: 0.26–0.63, $p < 0.001$). The weighted average efficacy of the monovalent vaccines ranged from 56% to 76% for the initial and 12-month final doses, respectively, with an overall weighted average of 65% (Figure 2). The overall vaccination effects displayed a heterogeneity between the effect sizes (χ^2 test, $Q = 6.13$, $p = 0.047$, df = 2). This was also confirmed by an I^2 value of 67.4%, which represent a moderate level of inconsistency between the studies.[31] The source of this effect heterogeneity is primarily due to the large inter-study variation in sample size and the small number of trials being evaluated for two different monovalent vaccines (LYMErix and ImmuLyme).

DISCUSSION

The goals of LB prevention and control are primarily to reduce the number of new cases of the disease and the number of patients experiencing late-stage or persistent conditions, such as post-treatment syndrome. These measures include the reduction of tick host populations, control of tick vectors (ecological and/or chemical), and promoting personal protection of at-risk individuals.[21] Personal protection practices vary from avoidance of tick habitat to using tick or insect repellents and vaccination. Currently, no vaccine is available to prevent LB in humans. The findings from the first (monovalent) and second (multivalent) generation vaccines were promising and can guide the development of novel strategies for future vaccine design.

In the late 1990s, the two monovalent LB vaccines LYMErix and ImmuLyme underwent extensive Phase III clinical trials and demonstrated 76% to 92%[8,9] efficacy after three doses with mild-to-moderate local and systemic reactions (Table 2). The success of LYMErix was compromised by non-substantiated claims that it may be associated with autoimmune arthritis (see above).[13–15] A retrospective study of joint complaints following vaccination demonstrated the lack of increased frequency of this adverse event and association between vaccine administration and the onset of symptoms.[32] However, animal studies in dogs did show a causal relationship between vaccination using monovalent preparations and autoimmune destructive arthritis.[33] The current study further validates that monovalent vaccines resulted in mild local solicited and unsolicited side effects in humans with incidence rates ranging from 2.3% to 17.7%[8,9,22,23] with a self-limiting site pain occurrence in 47.6% of the cases (Table 2). The incidence of systemic adverse



Insert	Vaccination stage	Odds Ratio	Heterogeneity Analysis		
			τ^2	Q (p)	I^2
a	Initial	0.49	0.004	2.11 (0.349)	5.0
b	Final	0.31	0.342	6.99 (0.031)	71.4
c	Overall	0.40	0.102	6.13 (0.047)	67.4

Figure 2. Meta-analysis for the efficacy of the monovalent vaccines and their effect on the risk of Lyme borreliosis. Weights are calculated from binary random-effects model analysis. Values represent OR (95% CI) of LB in response to vaccination. Weighted averages (pooled) were calculated for the vaccine efficacy. Heterogeneity analysis was carried out using Q test, the among-studies variation (I^2 index) and between-study variance in the random-effects model (τ^2) at the initial, final and overall dosing schedules.

effects ranged only from 2% to 14.5% of the cases. Compared to 15% average of serious side effects for all vaccines monitored by the Vaccine Adverse Event Reporting System,[32] these results further corroborate the lack of elevated frequency of unusual effects from the monovalent vaccines. In 2002, and despite the emergence of various findings[11,32] indicating the safety of the vaccine, LYMErix was voluntarily withdrawn from the market.[12] However, the increasing health burden of LB and its high incidence, together with the reported safety and efficacy of the vaccine, support the need for studies to design and develop another human LB vaccine.[7,34]

A novel approach was considered in a preclinical setting using a single recombinant OspA containing two OspA serotypes (1 and 2), which was shown to induce antibody responses that protected

mice against infection with both *B. burgdorferi* (OspA-1) and *Borrelia afzelii* (OspA-2).[35] The new vaccine was designed to provide protection against almost all *B. burgdorferi* strains linked to human LB worldwide. The vaccine contained protective epitopes from the six OspA serotypes 1–6 where the risk of T-cell cross-reactivity is eliminated by replacing the putative cross-reactive OspA-1 epitope with the corresponding OspA-2 sequence.[19] As mentioned above, this vaccine offered protection in immunized mice against infection with *B. burgdorferi*, *B. afzelii*, *B. bavariensis* and *B. garinii*.[12] Efficient antibodies were also stimulated against other *Borrelia* species such as *B. spielmani*, *B. valaisiania*, *B. lusitaniae* and *B. japonica*.[7,12] Most of these other species are minimally pathogenic or non-pathogenic for human. Since *B. mayonii* is established to be endemic in parts of North America as a cause of human infections, we are not aware of any data about cross protection for this species. A similar method was also presented to allow for the generation of a hexavalent OspA-based vaccine that potentially protects against a wide range of globally distributed Borrelia species causing LB.[36] Phase I/II dose finding studies for the multivalent vaccine were initiated to examine its safety and immunogenicity in a healthy adult population.[19] These clinical trials were extended to investigate the tolerability and immunogenicity of the vaccine in individuals who have been previously infected with *B. burgdorferi* (seropositive) and in seronegative adults and evaluated the longevity of the antibody response maintained through the tick season. It also evaluated the requirement for additional booster immunizations.[20]

The monovalent vaccines suffered from poor durability of protection. This outcome cannot be concluded for the multivalent vaccines since Phase III clinical trials are yet to be undertaken. Indeed, it might be difficult to compare safety and immunogenicity data reported for different studies. However, based on the results of the current study and others,[12] it is reasonable to suggest that the multivalent vaccine is as well tolerated and highly immunogenic as the earlier monovalent ones (Table 2). In the Phase I/II study of the multivalent vaccine,[19,20] some solicited and unsolicited local and systemic reactions occurred at a lower rate by alum-adjuvanted formulations than reported for the Phase III study of the monovalent vaccine.[8,9,24] For example, the incidences of local adverse effects such as redness and systemic side effects such as fever were, respectively, 6.8- and 2.9-fold significantly lower in subjects who received the multivalent vaccine compared to their counterparts who were administered the monovalent vaccines. Although not statistically significant, the incidences of other local and systemic adverse effects reported for the two vaccine types were lower in the multivalent vaccinated subjects than in those who received the monovalent vaccines. The slight improvement in the reactogenicity of the multivalent vaccine compared to the monovalent ones may be related to the absence of the molecular mimicry between hLFA-1 and OspA that was present in the the first generation monovalent vaccines – and compromised their success – when cross-reactive OspA-1 epitope was replaced by the corresponding OspA-2 sequence in the second generation multivalent vaccines.[19] Furthermore, the percentage of vaccinated subjects who were seropositive for IgG anti-OspA at levels that ensure protection for one tick season was comparable between the two vaccine types at both the initial and final vaccination stages (Table 3). It should be highlighted, however, that the smaller sample size in the Phase I/II study compared to Phase III trials may preclude definitive conclusion as to whether this lower reactogenicity and similar immunogenicity of the multivalent vaccine compared to the monovalent vaccines represent a statistically significant better tolerability or merely reflect a sampling bias.[12,37]

The efficacy of the monovalent vaccines in the prevention of LB was evaluated in three clinical trials.[8,9,24] During the first year, the disease OR was 0.49 (95% CI: 0.14–0.70; $p < 0.005$) and improved to 0.31 (95% CI: 0.26–0.63; $p < 0.005$) following the 12-month booster dose with an overall disease OR of 0.4 (95% CI: 0.26–0.63, $p < 0.001$). The weighted average efficacy of the monovalent vaccines was 56% and 76% for the initial and 12-month final dose schedules, respectively, with an overall efficacy of 65% (Figure 2). Based on the comparable tolerability and immunogenicity between the monovalent and multivalent vaccines, it can be expected that the latter will result in a similar, if not an improved, efficacy against human LB. Based on the promising findings of the Phase I/II trials,[19,20] Phase III efficacy trials of the multivalent vaccine were expected from Baxter BioScience.[12,23] However, these studies are stalled and yet to be launched[38] following the acquisition of Baxter's marketed vaccines and Vaccine Division by Pfizer in December 2014.

Although successfully constituting the first systematic review on the efficacy and reactogenicity of the monovalent and multivalent Lyme disease vaccines, the current study has a number of limitations. The limited number of trials for each vaccine, together with the large between-studies variation in the effect size both for local and systemic adverse effects, rendered a thorough comparison between the two vaccine types inconclusive. Furthermore, the lack of Phase III trials for the multivalent vaccines did not permit for evaluating the comparative efficacies between the monovalent and multivalent vaccines.

The multivalence nature of the new vaccine, the absence of the molecular mimicry between hLFA-1 and OspA, and the reduced overall reactogenicity compared to the monovalent vaccines, all suggest a promising turnover for the multivalent vaccine if further developed. However, it was argued that a minimum of safety data about the new vaccine were presented and that a simple replacement of a vaccine with another that has the same problems and approach may not be the proper course for a new vaccine development.[39] New strategies for the development of an effective LB vaccine are currently under extensive evaluation[7,21,34,36,40] and they are based primarily on the fact that *B. burgdorferi* spirochetes when transmitted by ticks utilizes a tick protein to stabilize the host infection.[40] These approaches included immunization with a cocktail of several *B. burgdorferi* Osps (e.g., OspB, OspC, OspF and DbpA); employment of tick salivary proteins to modulate host immune responses (e.g., Th-1 response); use of tick proteins to induce an immune response at the site of tick bite or interfere with other host defense responses (e.g., coagulation system); or immunization with a combination of tick protein and *B. burgdorferi* Osps.[7,35] In general, future development of an effective vaccine against *Borrelia* was proposed to be based on a combination of vaccinogenic factors consisting of multiple *Borrelia* antigens, antigens of ticks, or a combination of both to elicit a synergistic immune response against the bacteria and the tick.[21] This promising direction might not only be applicable for the prevention of transmission of *B. burgdorferi* from the tick to the

host but could also prove instrumental in the prevention of transmission of other vector-borne pathogens. Whether this approach is considered, or further development of the multivalent vaccine is undertaken, the new vaccine must be characterized by higher safety standards, improved efficacy, lower cost and enhanced public acceptance compared to the previous generation of the monovalent vaccines. In addition to incorporating all major *Borrelia* species, the new vaccine should also take into consideration the recent identification of the novel pathogenic species causing LB with high spirochaetaemia (*B. mayonii*).[41] Last, data on cost-effectiveness of monovalent vaccine suggest that the vaccine was not cost effective outside high incidence areas.[42] If the new vaccines do not have better efficacy and cost-effectiveness profiles, they can be recommended only for persons who live in endemic areas and are in frequent or prolonged exposure to ticks.[43,44] Under these circumstances, it can be challenging for the pharmaceutical industry to gain governmental approval for the new vaccines. Until this new vaccine makes it into the marketplace, personal protective strategies that limit exposure to ticks should continue to be recommended.

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RÉSUMÉ

CONTEXTE : La borréliose de Lyme (BL) est la plus prévalente des maladies infectieuses transmises par les arthropodes en Amérique du Nord. Il n'existe actuellement aucun vaccin pour prévenir la BL chez les humains, mais deux vaccins monovalents et un vaccin multivalent ont été mis au point par le passé.

OBJECTIF : Notre étude vise à mener une revue systématique et des méta-analyses pour évaluer et comparer les constatations sur la réactogénicité, l'immunogénicité et l'efficacité potentielle de ces deux classes de vaccins, dans l'espoir que cela aidera à mettre au point de futurs vaccins.

MÉTHODE : Nous avons élaboré une stratégie de consultation de bases de données en ligne (PubMed, Ovid MEDLINE et Embase). Les termes de recherche utilisés ont été « vaccine/vaccination » (vaccin/vaccination), « Lyme disease/Borreliosis » (maladie de Lyme/borréliose), « clinical trial (s) » (essai(s) clinique(s)) et « efficacy » (efficacité potentielle). Nous n'avons inclus que sept essais cliniques pour comparer les résultats des vaccins monovalents à ceux du vaccin multivalent. Nous avons mené des méta-analyses pour évaluer la réactogénicité et l'immunogénicité des deux classes de vaccins. Des rapports de cotes (RC) pour la BL (et des intervalles de confiance de 95 %; IC de 95 %) ont été calculés pour déterminer l'efficacité potentielle des vaccins monovalents administrés durant trois essais cliniques menés selon des schémas posologiques différents.

RÉSULTATS : L'incidence de rougeurs (un effet indésirable local) et de fièvre (un effet indésirable général) a été, respectivement, de 6,8 et de 2,9 fois significativement inférieure ($p < 0,05$) chez les sujets ayant reçu le vaccin multivalent que chez ceux ayant reçu les vaccins monovalents. Les incidences de tous les autres effets indésirables locaux et généraux ont été non significativement inférieures pour le vaccin multivalent que pour les vaccins monovalents. La séroprotection était comparable chez les sujets ayant reçu les deux classes de vaccins en doses de 30 µg. L'efficacité potentielle des vaccins pour prévenir la BL n'a été évaluée que pour les vaccins monovalents. Le RC de la BL variait entre 0,49 (IC de 95 % : 0,14–0,70; $p < 0,005$, contre un placebo) et 0,31 (IC de 95 % : 0,26–0,63; $p < 0,005$) pour les doses initiale et finale, respectivement, avec un RC global de 0,4 (IC de 95 % : 0,26–0,63, $p < 0,001$).

CONCLUSION : L'étude actuelle confirme que les vaccins monovalents et multivalent contre la BL entraînent de légers effets secondaires locaux et des effets indésirables généraux spontanément résolutifs, et que le vaccin multivalent est légèrement mieux toléré que les vaccins monovalents. Les deux classes de vaccins ont la même immunogénicité élevée. Un nouveau vaccin avec des normes de sécurité élevées, une efficacité potentielle accrue, un prix abordable et une bonne acceptation par le public n'est pas encore au point. Entre-temps, il est recommandé de prendre des mesures de protection individuelles pour limiter l'exposition aux tiques.

MOTS CLÉS : maladie de Lyme; vaccin; essai clinique; efficacité potentielle; revue systématique