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Adverse event reports following vaccination for Lyme disease: December 1998–July 2000

Sarah L. Lathrop [a], Robert Ball [d], Penina Haber [c], Gina T. Mootrey [c], M. Miles Braun [d], Sean V. Shadomy [d], Susan S. Ellenberg [d], Robert T. Chen [c], Edward B. Hayes [b,*]

[a] *Centers for Disease Control and Prevention, Epidemic Intelligence Service, Atlanta, GA 30333, USA*
[b] *Centers for Disease Control and Prevention, Division of Vector-Borne Infectious Diseases, Fort Collins, CO 80522, USA*
[c] *Centers for Disease Control and Prevention, National Immunization Program, Atlanta, GA 30333, USA*
[d] *Food and Drug Administration, Center for Biologics Evaluation and Research, Rockville, MD 20852, USA*

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Abstract

Context: The vaccine adverse event reporting system (VAERS) monitors vaccine safety post-licensure. Although events reported to VAERS are not necessarily causally associated with vaccination, VAERS reports can be used to identify possible safety concerns that occur at too low a rate to have been identified prior to licensure.

Objective: To evaluate adverse events following Lyme disease vaccination reported to VAERS during the first 19 months of the vaccine's licensure.

Design, setting, and participants: Analysis of all VAERS reports of adverse events following vaccination for Lyme disease in the US from 28 December 1998 to 31 July 2000.

Main outcome measure: We evaluated reported adverse events for unexpected patterns in age, gender, time to onset, dose number, and clinical characteristics and compared them to adverse events observed in clinical trials of this vaccine.

Results: Over 1,400,000 doses were distributed and 905 adverse events were reported to VAERS, 440 in men and 404 in women, with ages ranging from 10 to 82 years. The majority (56%) of adverse events occurred after administration of the first dose. The most frequently reported adverse events were arthralgia (250), myalgia (195), and pain (157). There were 59 reports coded as arthritis, 34 as arthrosis, 9 as rheumatoid arthritis, and 12 as facial paralysis. Sixty-six (7.4%) events were classified as serious, involving life-threatening illness, hospitalization, prolongation of hospitalization, persistent or significant disability/incapacity, or death. Twenty-two hypersensitivity reactions were reported.

Conclusions: Based on reporting to VAERS, we did not detect unexpected or unusual patterns of reported adverse events following Lyme disease vaccine administration, other than hypersensitivity reactions, compared with adverse events observed in clinical trials. Published by Elsevier Science Ltd.

Keywords: Lyme disease; Vaccine adverse event reporting system; Major histocompatibility complex; Lyme vaccine; Adverse events; Safety

1. Introduction

In December of 1998 the US Food and Drug Administration (FDA) licensed the first vaccine to prevent Lyme disease. Manufactured by GlaxoSmithKline, LYMErix™ consists of recombinant *Borrelia burgdorferi* outer surface lipoprotein A (rOspA) adsorbed onto aluminum hydroxide [1]. The vaccine stimulates production of antibodies that are believed to destroy or inactivate the spirochetes in the midgut of the infected tick, preventing their transmission to the tick's host [2,3]. Following a randomized, controlled Phase III clinical trial in 5469 vaccine recipients and 5467 placebo recipients [4], the vaccine was licensed for use in people aged 15–70 years. The Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) stated that the vaccine should be considered for individuals in Lyme disease endemic areas who have frequent or prolonged exposure to tick-infested habitats [1].

During the clinical trial, pain at the injection site was the most commonly reported adverse event, with 24.1% of vaccine recipients and 7.6% of placebo recipients reporting soreness [4]. Significantly more vaccine recipients than placebo recipients reported transient fever, chills, myalgia, and influenza-like illness, but these problems were seen in 3.2% or fewer subjects [4]. Unsolicited reports of

* Corresponding author. Tel.: +1-970-221-6474; fax: +1-970-221-6476.
E-mail address: ebh2@cdc.gov (E.B. Hayes).

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arthralgia or myalgia were more commonly seen in vaccine recipients than placebo recipients during the first 30 days post-vaccination, but no significant differences between vaccine and placebo recipients in this group were found after 30 days [5]. There was no statistically significant difference in the occurrence of arthritis between vaccine and placebo recipients during the clinical trial, and no immediate hypersensitivity reactions to the vaccine were noted [4].

A small percentage of patients with naturally acquired Lyme disease develop treatment-resistant arthritis [6], which appears to be associated with an increased frequency of certain HLA-DR4 class II major histocompatibility complex (MHC) subtypes (0401 and 0404) and with elevated levels of antibody to rOspA [7]. There is also a possible association with several of the 15 other alleles which share a common third hypervariable region with these subtypes, but which are not in the DR4 phenotype [7]. There is theoretical concern that rOspA vaccination could exacerbate treatment-resistant Lyme arthritis, but the clinical trial found no evidence that immunization caused arthritis [4].

Even large-scale clinical trials, such as the one for LYMErix™, collect data on far fewer individuals than will receive the vaccine after it is licensed [8]. Additionally, the study protocol attempted to exclude people with active Lyme disease, Lyme disease treated in the previous 3 months, people with chronic joint or neurologic illness related to Lyme disease, as well as people with immunodeficiency, joint swelling, musculoskeletal pain, second or third degree atrioventricular block, and pregnant women [4]. Thus, the results from the clinical trial may not be completely generalizable to a more heterogeneous population, in which individuals with any of these conditions might receive the vaccine.

As with any drug or biologic product, previously unrecognized adverse events may occur during post-licensure use [8]. To evaluate the number and type of adverse events following vaccination with Lyme disease vaccine, we analyzed reports of adverse events following Lyme disease vaccination submitted to the federal Vaccine Adverse Event Reporting System (VAERS) through 31 July 2000.

2. Methods

VAERS was established in 1990 and is operated collaboratively by the CDC and the FDA [9,10]. Reports of adverse events are submitted to VAERS either directly or through the vaccine manufacturer, by vaccine providers, recipients, or others [11]. A “serious event” reported to VAERS is defined as one which resulted in life-threatening illness, hospitalization, prolongation of hospitalization, persistent or significant disability/incapacity, or death, or required an intervention to prevent any of these events [8]. The determination of seriousness is based on the reporter’s indication that at least one of the conditions has been met. Reports of serious events submitted to the manufacturer are forwarded to VAERS within 15 days, and reports of non-serious events from the manufacturer are submitted to VAERS quarterly for the first 3 years post-licensure. After the third year, non-serious event reports are submitted in batch by the manufacturer once a year, unless more frequent reporting is requested by the FDA. Reports are coded, using coding symbols for thesaurus of adverse reaction terms (COSTART) to describe the adverse event in a computerized data bank [11]. The data sets are updated daily and provided weekly to the CDC and FDA [11].

From December 1998 to 15 August 2000, 1,449,203 doses of Lyme disease vaccine were distributed (Dr. Paula Goldberg, GlaxoSmithKline, 17 January 2001, personal communication). We analyzed all reports of adverse events following administration of LYMErix™ received by VAERS from time of licensure in December 1998 to 31 July 2000. Epi-Info 6.0 and SAS software were used to analyze the data. We looked for any unusual patterns of adverse events by age, gender, time to onset, dose number, and clinical characteristics. Special attention was paid to reports of serious events, as well as reports of arthritis (and related conditions) and facial paralysis, because of concern about autoimmune pathogenesis of these conditions in naturally acquired Lyme borreliosis. Vaccine recipients reporting facial paralysis were contacted by telephone to determine recovery status. We also examined reports of adverse events in people who reported the HLA-DR4 MHC phenotype, a history of Lyme disease, or pregnancy to determine the patterns of adverse events in these populations.

3. Results

Nine hundred five adverse events following Lyme disease vaccine administration were reported to VAERS from 1 December 1998 to 31 July 2000. Most (889/905, 98.2%) of these events occurred after administration of Lyme disease vaccine alone, while 16 reports were received from people who had been given one, two, or three additional vaccines at the time of Lyme disease vaccine administration. One of these 16 reported events was classified as serious, as it resulted in hospitalization. The following results are from the 889 events occurring after Lyme disease vaccine alone, in order to better determine patterns of adverse events following Lyme disease vaccination. The 10 most commonly reported adverse events are listed in Table 1. Of the 889 reported adverse events, 181 (20.4%) required a single adverse event coding term, and 708 (79.6%) required 2 or more adverse event coding terms.

The distribution of all vaccine recipients who experienced an adverse event by age and gender is presented in the Fig. 1. Four (0.04%) adverse events were reported in people under the age of 15, and 29 (3.3%) adverse events were reported in people over the age of 70, the age bounds for recommended use of the vaccine [1]. Of the 749 events for which an onset date was reported, 453 (60.5%) occurred

Table 1
Most commonly reported adverse events following administration of LYMErix™ vaccine. Reports may include more than one coding term

Coding term	No. of reports
Arthralgia	250
Myalgia	195
Pain	157
Asthenia	129
Headache	121
Flu-like syndrome	105
Fever	103
Injection site pain	103
Rash	77
Injection site hypersensitivity	70

within 48 h of vaccination. Adverse events with onsets up to 305 days following vaccination were reported.

Most (823/889, 92.6%) of the reported adverse events following Lyme disease vaccine administration were not classified as serious, according to the definition given earlier. Sixty-six (7.4%) reported adverse events were classified as serious. These included 4 deaths, 14 reports of life-threatening illnesses, 21 of permanent disability, 35 of hospitalization, and 1 of extension of hospitalization. These categories were not mutually exclusive.

The 4 fatalities that were reported after administration of the Lyme disease vaccine were reviewed in detail. A 62-year-old man died 1 day after receiving his first dose of Lyme disease vaccine. The cause of his death, based on an autopsy, was found to be hypertensive cardiovascular disease. A second fatality was reported in a 54-year-old man, who died 3 days after receiving his second dose of Lyme disease vaccine. The autopsy report attributed the death to cardiovascular disease and hypertension. The third fatality reported to VAERS was a 43-year-old man, who committed suicide 7 months after receiving his second dose of the vaccine. One month after the second dose he developed abdominal pain and tightness in the lower back. His symptoms worsened, but an MRI and EMG were non-diagnostic.

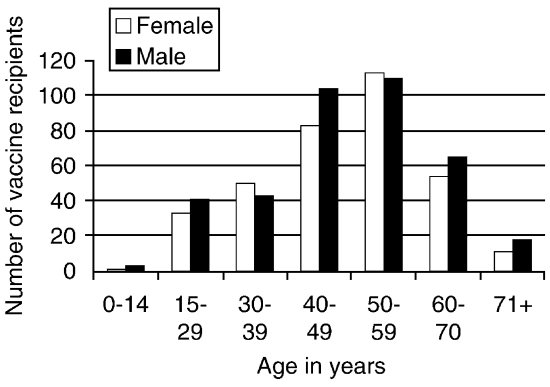

Fig. 1. Age and gender distributions of people who experienced an adverse event following vaccination for Lyme disease from December 1998 to July 2000.

The autopsy revealed no pathologic explanation for the reported symptoms; however, the reporter indicated that the suicide was related to the described symptoms. The fourth reported fatality was a 69-year-old woman who developed anemia and thrombocytopenia 7 months after the first dose of vaccine. She died 6 months later, an unknown time after receiving the third dose. The cause of death was reported as myelofibrosis, but no autopsy was performed.

Non-fatal events classified as serious included 26 reports of musculoskeletal events, including 6 reports of arthritis or arthrosis and 3 of rheumatoid arthritis; 21 reports of neurological events, including 5 reports of cerebral ischemia and 5 of demyelinating disease; and 3 reports of hypersensitivity. Other events classified as serious included 5 cases of systemic illness, 2 cases of chest pain, 2 of syncope, 2 of recurrent sinusitis, and 1 case of aseptic meningitis. The events classified as serious tended to occur later after vaccination than those classified as non-serious, with a median days to onset of 3, versus 0 for non-serious events. Seventy-nine percent of non-serious events were reported as occurring during the first week after vaccination, compared to 52% of serious events. None of the adverse events reported in vaccine recipients under the age of 15 years were classified as serious. Three of the 29 reported adverse events in vaccine recipients over the age of 70 were classified as serious; 2 hospitalizations and 1 disability.

The characteristics of adverse events for four categories of events and three types of vaccine recipients are presented in Table 2. The median age was approximately 50 years for all categories except vaccine recipients who were pregnant. Median days from vaccination to onset of the adverse event were longer for reports of facial paralysis and events in pregnant women than for all events combined. Two of the five adverse events in pregnancy were miscarriages, while the other three were non-specific disorders of pregnancy, including anorexia, anemia, and arthralgia.

The majority of non-serious adverse events were reported as occurring after the first dose. This was also true for events reported as resulting in facial paralysis and those in people with a history of Lyme disease or the HLA-DR4 subtype. The majority of serious adverse events and most events involving arthritis or arthrosis, as well as most events in pregnant women, were reported as occurring after the second or third dose. Fifty percent of adverse events in people with reported HLA-DR4 MHC subtype were classified as serious, compared with 7.4% of all events.

Follow-up information was obtained by telephone survey on 7 of the 12 patients who reported facial paralysis after vaccination. Five patients had completely recovered, and two reported mild residual facial paralysis. Four of the 7 patients contacted, including one with residual paralysis, had other potential risk factors or contributing conditions for facial paralysis, such as metabolic disease [12].

Because of theoretical concern that rOspA vaccination might exacerbate or cause autoimmune arthritis, we evaluated in detail the adverse events for three coding terms that

Table 2
Characteristics of adverse event reports by type of outcome and pre-existing conditions, in patients who received the Lyme disease vaccine only

	All reports	Non-serious events	Serious events	Arthritis and Arthrosis	Facial paralysis	HLA-DR4	History of Lyme disease	Pregnancy
No. of reports	889	823	66	102	12	10	67	5
Males, females	440, 404	407, 374	35, 31	45, 51	10, 2	5, 5	24, 43	–
Age range (years), (median)	10–82 (50)	10–82 (50)	17–78 (52.8)	15–79 (50)	18–73 (53)	41–71 (47)	20–77 (50.6)	35–38 (36)
Days to onset range (median)	0–305 (1)	0–287 (0)	0–305 (3)	0–270 (4.5)	0–51 (12)	0–63 (1.5)	0–129 (1)	0–47 (42)
No. of serious events	66 (7.4%)	–	66 (100%)	14 (13.7%)	2 (16.7%)	5 (50.0%)	8 (11.9%)	1 (20%)
Event after first dose	479/861 (55.6%)	457/800 (57.1%)	22/62 (35.5%)	37/95 (38.9%)	10/12 (83.3%)	4/8 (50%)	40/67 (59.7%)	1/5 (20%)
Event after second dose	303 (35.2%)	273 (34.1%)	31 (50.0%)	47 (49.5%)	2 (16.7%)	3 (37.5%)	25 (37.3%)	4/5 (80%)
Event after third dose	78 (9.1%)	69 (8.6%)	9 (14.5%)	11 (11.6%)	0	1 (12.5%)	2 (3.0%)	0

Table 3
Signs and symptoms reported by Lyme disease vaccine recipients who developed arthritis or arthritis-related conditions following vaccination[a]

Clinical signs and symptoms reported	Categories		
	Rheumatoid arthritis ($n = 9$)	Arthritis ($n = 59$)	Arthrosis ($n = 34$)
Painful joints	6 (66.7%)	33 (55.9%)	18 (52.9%)
Limited motion/stiffness	2 (22.2%)	8 (13.6%)	10 (29.4%)
Tenderness	0	2 (3.4%)	2 (5.9%)
Warmth/heat	2 (22.2%)	3 (5.1%)	4 (11.8%)
Swelling/joint effusion	4 (44.4%)	10 (16.9%)	30 (88.2%)

[a] $n = 102$.

captured inflammatory joint pathology: arthritis, rheumatoid arthritis and arthrosis. The symptoms recorded for these coding terms are presented in Table 3. Joint pain was noted in over half of all arthritis, rheumatoid arthritis and arthrosis reports. Joint effusion was noted in 88.2% of reports coded as arthrosis, but in only 16.9% of events coded as arthritis and 44.4% of events coded as rheumatoid arthritis. Limited motion or stiffness was noted in less than 30% of events in the three coding categories. Tenderness and warmth were rarely noted. Overall, less than half of all the events in these three arthritis-related coding categories had recorded swelling or effusion.

The reporting characteristics of events coded as arthritis, rheumatoid arthritis, and arthrosis are compared with characteristics of all events in Table 4. Reports of arthrosis and rheumatoid arthritis differ in their gender distribution from all reports combined, but the median ages for the three categories of arthritis-related events are similar to that for all events. A somewhat higher proportion (61% of those reports with a known dose number) of arthritis-related events occurred after the second or third dose of vaccine compared to all events combined (44.3%). The time between vaccination and onset of arthritis-related events varied widely and there was no evidence of a consistent temporal pattern that might support an etiologic relationship between vaccination and the events (data not shown). A higher proportion of arthritis-related events were classified as serious compared to all events combined.

Twenty-two reports of hypersensitivity following LYMErix™ administration were received by VAERS.

Table 4
Arthritis-related reported adverse events. The categories arthritis, rheumatoid arthritis, and arthrosis are mutually exclusive, with a precedence of rheumatoid arthritis, arthritis, and then arthrosis. For example, a report coded as all three would only be included in the rheumatoid arthritis group

	Condition			
	All reports	Arthritis	Rheumatoid arthritis	Arthrosis
No. of reports	889	59	9	34
Males, females	440, 404	27, 31	3, 6	21, 8
Age range (years), (median)	10–82 (50)	16–78 (49)	37–59 (49)	15–79 (50.5)
Days to onset range (median)	0–305 (1)	0–270 (4)	0–267 (25.5)	0–262 (5)
No. of serious events	66 (7.4%)	8 (13.5%)	4 (44.4%)	2 (5.9%)
Event occurred after first dose	479/861 (55.6%)	21/55 (38.2%)	1/7 (14.3%)	15/33 (45.5%)
Event occurred after second dose	303 (35.2%)	29 (52.7%)	6 (85.7%)	12 (36.4%)
Event occurred after third dose	78 (9.1%)	5 (9.1%)	0	6 (18.2%)

Twenty patients (nine female, nine male, two of unknown gender) reported urticaria, and two women reported dyspnea and urticaria. Fourteen cases of urticaria occurred after the first dose, and six after the second dose. Seven episodes of urticaria were reported to occur within 24 h of vaccination. One report of respiratory symptoms and urticaria occurred 9 h after the patient received the first dose of vaccine, and one report occurred 1 h after the second dose. In both cases, the symptoms were reported to have been relieved by treatment with epinephrine, antihistamines and steroids.

4. Comment

A total of 905 reports of adverse events was received by VAERS during the first 19 months of the vaccine's licensure, representing 0.06% of approximately 1,400,000 doses distributed, or 64 adverse events reported per 100,000 doses of vaccine. During the Phase III clinical trial of LYMErix^{TM}, soreness at the injection site was the most commonly occurring adverse event. The most common post-licensure reports to VAERS were arthralgia and myalgia, which also occurred commonly in the clinical trial with greater frequency in the vaccine than the placebo group. It is likely that injection site soreness continues to occur at a rate similar to that seen during the clinical trial (24.1%), but fewer people may report it, as it is known to be an adverse effect of the vaccine and is generally not serious. As the majority of adverse event reports (80%) required two or more coding terms, it appears that most vaccine recipients reporting adverse events experienced several symptoms simultaneously.

Passive surveillance systems such as VAERS are subject to many limitations. Adverse events with a true association with the vaccine might be underreported, and inadequate data on the number of doses administered preclude the calculation of the true incidence of adverse events. The reporting sensitivity of VAERS is unknown, but has been shown to vary with the clinical seriousness of the specific adverse event, its temporal association with the vaccination, and other factors [13]. The incidence of adverse events among people similar to the vaccinees but who have not been vaccinated is often unavailable to compare with the rates of such events reported to VAERS. Reporting of unconfirmed diagnoses is common, and initially reported diagnoses may be found to be inaccurate upon follow-up. Report coding depends on the reporters' use of certain words or phrases, resulting in the same coding term being used for reports with different degrees of diagnostic precision.

Because of these limitations, it is usually not possible to determine causal associations between vaccines and adverse events reported to VAERS. Signals of possible causally linked adverse events are identified by finding unexpected patterns in age, gender, dose number, time to onset, and clinical characteristics. Additional criteria such as biological plausibility, the presence of pre-existing conditions, medication usage, or other exposures need to be examined to further determine the plausibility of an association between a vaccine and an adverse event, and this information is often not included in VAERS reports. A controlled study is almost always needed to confirm a possible causal relationship between a reported adverse event and a vaccine.

Each year, approximately 15% of the 10,000 VAERS reports for all vaccines are classified as serious [9]. This percentage varies by vaccine, and can be affected by the newness of a vaccine, the age group receiving the vaccine, and simultaneous administration of other vaccines [9]. Seven percent of the LYMErix^{TM}-associated adverse events were classified as serious. Serious events following vaccination are typically more likely to be reported than less serious events, but rarely can be proven to have been caused by the vaccine based on VAERS data alone. When large numbers of individuals receive a medical intervention, as is the case with vaccines, even uncommon adverse events will occur coincidentally in a small number of people. Nevertheless, the reported adverse event may be a true reaction that will be seen in future vaccine recipients.

It is difficult to evaluate a causal relationship between Lyme vaccine and the cases of arthritis and facial paralysis reported to VAERS. Because of the inherent limitations of assigning coding terms, it is possible that some of the adverse events coded as arthritis represented arthralgia rather than true arthritis, as suggested by the relatively low frequency of recorded joint swelling or effusion. The lack of mention of a symptom, however, does not necessarily mean the symptom was absent. Although population-based incidence rates for arthritis are not available, an estimated 15% of the US population suffers from arthritis and arthritis-like conditions [14]. The relatively high prevalence of arthritis makes reports of vaccine-associated arthritis difficult to distinguish from background occurrence unrelated to vaccination.

During the clinical trial, 53 vaccine recipients reported the occurrence of arthritis within 30 days of receiving the vaccine, as did 49 placebo recipients [15], yielding a reported cumulative incidence of 333 per 100,000 doses in vaccine recipients and 308 per 100,000 doses in placebo recipients. If only half of 1,400,000 vaccine doses distributed were administered, we would expect to see 2156 cases of arthritis following vaccination if the incidence were the same as that in placebo recipients during the clinical trial. Thus, the number of cases of arthritis reported to VAERS (59) was far below what might be expected as background incidence unrelated to vaccination. At least some of this difference was presumably due to underreporting, but it does not appear that the numbers of arthritis reports to VAERS are unexpectedly high.

A higher proportion of arthritis-related events were reported after the second or third dose compared to all events combined. Such a pattern would be expected if an autoimmune process were triggered by repeated vaccinations. However, an autoimmune process might also be expected to occur within a particular time period following vaccination, and we found no evidence of such a temporal pattern for the

arthritis-related adverse events. As there is only 1 month between the first and second doses, but 11 months between the second and third doses, the increased number of arthritis and rheumatoid arthritis cases reported after the second dose may be due at least in part to the increased amount of time available for a vaccine recipient to report an adverse event.

During the clinical trial, facial paralysis was reported by 9 vaccine recipients and 12 placebo recipients [15], yielding an incidence of 57 per 100,000 doses and 75 per 100,000 doses, respectively. Following the assumptions stated above, one would expect 525 cases among vaccine recipients. Again, it is not possible to determine if the cases reported to VAERS were attributable to the vaccine, or part of the expected background incidence of facial paralysis, or caused by Lyme disease. It is unusual that there were 10 reports of facial paralysis in men and only 2 in women, as naturally acquired facial paralysis occurs with equal frequency in men and women [12]. This could be influenced by the gender distribution of vaccine recipients, although there is no reason to believe that more men than women received the vaccine.

The patterns of age, gender, time to onset, and relationship to dose in people with a reported history of Lyme disease or HLA-DR4 MHC subtype did not seem to differ from patterns seen in reports of adverse events in people without these characteristics. Although a larger percentage of adverse events in people with HLA-DR4 MHC subtype was classified as serious compared to all reports, we were unable to determine from these data whether people reporting HLA-DR4 subtypes were more likely to experience serious events, or if people experiencing serious events were more likely to be tested for HLA subtype and report the event to VAERS.

Hypersensitivity reactions were not observed during the clinical trial. No clear patterns in age or gender could be seen in the 22 episodes of hypersensitivity reported during the first 19 months of licensure, but some could be plausibly linked to the vaccine because of the specificity of the symptoms, close temporal proximity to vaccination, and the known association of such reactions with other vaccines.

Only five adverse events in pregnant women were reported, and causality between the events and vaccination cannot be established from these data. We were not able to discern any single pattern of adverse events in pregnancy that would suggest a causal relationship with the vaccine. Since pregnant women were excluded from the clinical trial, and the safety of the vaccine during pregnancy is unknown, it seems prudent to avoid vaccination of women who are known to be pregnant.

In conclusion, except for the 22 hypersensitivity reactions, the adverse events reported to VAERS appeared to be consistent with adverse events noted during the Phase III clinical trial. A study to further evaluate the nature and outcome of reports of arthritis is underway. Reports of facial paralysis will continue to be assessed, due to biologic plausibility and the unusual gender pattern observed so far. VAERS reports will continue to be monitored for any trends in adverse event occurrence associated with LYMErix^{TM} administration.

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