LYMEnrix® Safety Data Reported to the Vaccine Adverse Event Reporting System (VAERS)

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What is the Vaccine Adverse Event Reporting System (VAERS)?

- National system for surveillance of adverse events after vaccination
- Jointly managed by FDA and CDC
- Reports received from health professionals, vaccine manufacturers, and the public
- All death and serious (hospitalization, prolongation of hospitalization, life-threatening illness, or permanent disability) reports receive follow-up
- Death and serious reports are reviewed by FDA medical officers
Uses of VAERS

– Detecting unrecognized adverse events
– Monitoring known reactions
– Identifying possible risk factors
– Vaccine lot surveillance
Limitations of VAERS

- Reported diagnoses are not verified
- Lack of consistent diagnostic criteria
- Wide range in data quality
- Underreporting
- Inadequate denominator data
- No unvaccinated control group
- Usually not possible to assess whether a vaccine caused the reported adverse event
Analysis of VAERS Data

• Describe characteristics and look for patterns to detect signals of adverse events plausibly linked to a vaccine
  – Age, gender, time to onset, dose, “positive rechallenge” reports, symptom codes, and clinical characteristics
  – Biological plausibility, pre-existing conditions, and concomitant illness and medication usage

• Signals detected through analysis of VAERS data almost always require confirmation through a traditional epidemiological or other (e.g. laboratory) study
Coding of VAERS Reports

- No standardized case definitions
- Processed by non-physician nosologists
- Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART)
  - Report coding depends on the use of certain words or phrases
    - rheumatoid arthritis if report mentions “rheumatoid arthritis”
    - arthritis if report mentions “arthritis” or “arthritic”
    - arthrosis if report mentions “joint swelling”
- Reports with different degrees of diagnostic precision may have the same coding term
- Coding terms must be interpreted very cautiously
LYMЕrix® Safety Surveillance Through VAERS

• Purpose: describe characteristics and look for patterns to detect adverse events plausibly linked to LYMЕrix®

• Review from licensure (12/21/98) to 10/31/00

• Selected adverse events
  – Death and Serious
  – Hypersensitivity
  – Facial paralysis, arthritis, arthrosis, and rheumatoid arthritis
  – Lyme disease

• Selected potential risk factors
  – Self-reported HLA DR4
  – Self-reported history of Lyme disease
LYMErix® Safety Surveillance Through VAERS

Results Overview

• 1,048 reports and ~1.44 million doses distributed
• 1,026 (98%) reports after Lyme vaccine alone
• 4 (0.4%) deaths
• 85 (8%) serious
• Selected adverse events
  – Hypersensitivity (22)
  – Arthritis (74), arthrosis (46), rheumatoid arthritis (13)
  – Facial Paralysis (13)
  – Lyme Disease (16)
• Selected potential risk factors
  – HLA DR4 (19)
  – History of Lyme disease (76)

Interpretation of VAERS data is subject to important limitations - see methods for details.
Number of VAERS LYMErix® Reports by State
December 21, 1998 to October 31, 2000

Interpretation of VAERS data is subject to important limitations - see methods for details

State not available for 55 reports
Frequency Distribution of All VAERS LYMErix® Reports (n=878) by Calendar Quarter

- Date Vaccinated
- Date Reported

Number

Date vaccinated not available for 165 of 1,048 reports (16%). 105 reports prior to 1999.
Frequency Distribution of All VAERS LYMErix® Reports (n=877) by *Age at Onset* of Adverse Event

Age not available for 171 of 1,048 (16%) reports

Interpretation of VAERS data is subject to important limitations - see methods for details
Frequency Distribution of All VAERS LYMErix® Reports (n=739) by Time to Onset of Adverse Event

Time to onset not available for 309 of 1,048 (29%) reports

Interpretation of VAERS data is subject to important limitations - see methods for details
Frequency Distribution of All VAERS LYMErix® Reports (n=1,007) by Dose

Dose not available for 41 of 1,048 (3.9%) reports

Interpretation of VAERS data is subject to important limitations - see methods for details
Ten Most Common VAERS LYMErix® Adverse Event Coding Terms

- *Arthralgia* (322)
- *Myalgia* (227)
- Pain (196)
- Asthenia (167)
- Headache (151)
- Fever (126)
- *Flu syndrome* (124)
- *Injection site pain* (117)
- Rash (85)

*Italicized* = event associated with vaccine in pre-licensure trial

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Summary of Deaths (n=4) after LYMErix® Reported to VAERS

• Deaths
  - 54 y/o man died of autopsy proven “hypertensive cardiovascular disease” 1 day after 2nd dose
  - 63 y/o man died of autopsy proven “hypertensive and arteriosclerotic cardiovascular disease” 3 days after 1st dose
  - 43 y/o man developed arthritic and neurologic symptoms attributed by the reporter to LYMErix® and committed suicide 7 months after 2nd dose
  - 69 y/o woman developed illness, including anemia and thrombocytopenia, 7 months after 1st dose and died 6 months later an unknown time after 3rd dose with diagnosis of myelofibrosis

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Summary of Serious Reports (n=85) Following LYMErix® Reported to VAERS

- 44 reports of musculoskeletal events
  - 12 arthritis or arthrosis
  - 6 rheumatoid arthritis
- 24 reports of a variety of neurological events
  - 5 reports of cerebral ischemia
  - 5 reports of demyelinating disease
- 3 reports of hypersensitivity events

Interpretation of VAERS data is subject to important limitations - see methods for details
Summary of Serious Reports Following LYMErix® (n=85) Reported to VAERS (cont)

- 13 miscellaneous events
  - 5 multiple systemic complaints including dizziness, nausea, fever, photophobia, headache, fatigue, sore throat
  - 2 chest pain (1 pericarditis)
  - 2 syncope
  - 2 chronic or recurrent sinusitis (1 with depression)
  - 1 aseptic meningitis
  - 1 Lyme disease

Interpretation of VAERS data is subject to important limitations - see methods for details
Frequency Distribution of VAERS LYMErix® Reports (n=21) of Hypersensitivity by *Time to Onset*

Time to onset not available for 3 of 24 (13%) reports

Interpretation of VAERS data is subject to important limitations - see methods for details
Frequency Distribution of Reports of Arthritis, Arthrosis, and Rheumatoid Arthritis (n=132) by Calendar Quarter

Vaccination date not available for 1 of 133 reports (1%)
Interpretation of VAERS data is subject to important limitations - see methods for details
Reports of *Arthritis* (n=74), *Arthrosis* (n=46), and *Rheumatoid Arthritis (RA)* (n=13) Following LYMErix®

- **Gender**
  - Arthritis: 39 women, 34 men
  - Arthrosis: 15 women, 24 men
  - RA: 9 women, 4 men
  - Total: 63 women, 62 men

- **Dose (1st, 2nd, 3rd, 4th)**
  - Arthritis (25, 32, 12, 0)
  - Arthrosis (19, 15, 8, 1)
  - RA (3, 8, 0, 0)
  - Total (47, 55, 20, 1)

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Frequency Distribution of VAERS LYM Er ix® Rheumatoid Arthritis Reports (n=8) by *Time to Onset and Dose*

- **Time to Onset (weeks)**
  - 1st Dose
  - 2nd Dose

Time to onset or dose not available for 5 of 13 (38%) reports

Interpretation of VAERS data is subject to important limitations - see methods for details
Frequency Distribution of VAERS LYMErix® Arthritis Reports (n=40) by *Time to Onset and Dose*

Time to onset or dose not available for 34 of 74 (46%) reports

Interpretation of adverse event reports is subject to limitations - see methods for details
**Clinical Characteristics of VAERS LYMErix® Reports Coded Arthritis, Arthrosis, and Rheumatoid Arthritis (RA)**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Arthritis (n=74)</th>
<th>Arthrosis (n=46)</th>
<th>RA (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint Pain</td>
<td>41</td>
<td>29</td>
<td>10</td>
</tr>
<tr>
<td>Limited Motion</td>
<td>9</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Joint Tenderness</td>
<td>3</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Joint Warmth</td>
<td>3</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Joint Swelling</td>
<td>12</td>
<td>40</td>
<td>6</td>
</tr>
</tbody>
</table>

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Frequency Distribution of VAERS LYMErix®
“Arthritis” Reports Indicating Joint Swelling (n=30)
by Time to Onset and Dose

Time to Onset or dose not available for 28 of 58 reports (48%) of joint swelling
Interpretation of VAERS data is subject to important limitations - see methods for details
Reports of *Facial Paralysis* Following LYMErix®

- 13 reports (2 serious)
  - Median age 53 years (range: 18 - 73)
  - 10 men, 2 women
  - Dose: 9 after 1st, 4 after 2nd

- Follow-up survey (October 2000)
  - 7/12 contacted
    - 4/7 had concomitant illness
    - 5/7 completely recovered

Interpretation of VAERS data is subject to important limitations - see methods for details
Frequency Distribution of VAERS LYMErix® Reports of Facial Paralysis (n=11) by Time to Onset

Time to onset not available for 2 of 13 (15%) reports

Interpretation of VAERS data is subject to important limitations - see methods for details
Reports of Adverse Events Following LYMErix® for People with a Self-Reported HLA Type

• 19 reports of HLA DR4 and 17 reports of other HLA types
• Coding terms “arthritis” and “arthrosis” were more common in people who reported any HLA type than for all reports following LYMErix®
• Clinical characteristics and coding terms similar in both groups
  – no predominance of arthritic conditions in DR4 group
• More reports after second dose for both groups
• Time to onset reported to occur over a wide range

Interpretation of VAERS data is subject to important limitations - see methods for details
Ten Most Common VAERS Coding Terms Following LYMErix® for People with a Self-Reported History of Lyme Disease (n=76)

<table>
<thead>
<tr>
<th>Term</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthralgia</td>
<td>25</td>
</tr>
<tr>
<td>Asthenia</td>
<td>19</td>
</tr>
<tr>
<td>Myalgia</td>
<td>19</td>
</tr>
<tr>
<td>Headache</td>
<td>18</td>
</tr>
<tr>
<td>Pain</td>
<td>16</td>
</tr>
<tr>
<td>Injection Site Pain</td>
<td>12</td>
</tr>
<tr>
<td>Fever</td>
<td>10</td>
</tr>
<tr>
<td>Injection Site Hypersensitivity</td>
<td>8</td>
</tr>
<tr>
<td>Chills</td>
<td>7</td>
</tr>
<tr>
<td>Rash</td>
<td>7</td>
</tr>
</tbody>
</table>

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### Ten Most Common VAERS Coding Terms Following LYMErix® for People with a Self-Reported History of Lyme Disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>Self-Reported History of Lyme Disease (n=76)</th>
<th>All Reports (n=1,048)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthralgia</td>
<td>25 (33%)</td>
<td>322 (31%)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>19 (25%)</td>
<td>167 (16%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>19 (25%)</td>
<td>227 (22%)</td>
</tr>
<tr>
<td>Headache</td>
<td>18 (24%)</td>
<td>151 (14%)</td>
</tr>
<tr>
<td>Pain</td>
<td>16 (21%)</td>
<td>196 (19%)</td>
</tr>
<tr>
<td>Injection Site Pain</td>
<td>12 (16%)</td>
<td>117 (11%)</td>
</tr>
<tr>
<td>Fever</td>
<td>10 (13%)</td>
<td>126 (12%)</td>
</tr>
<tr>
<td>Injection Site Hypersensitivity</td>
<td>8 (11%)</td>
<td>76 ( 7%)</td>
</tr>
<tr>
<td>Chills</td>
<td>7 ( 9%)</td>
<td>78 ( 7%)</td>
</tr>
<tr>
<td>Rash</td>
<td>7 ( 9%)</td>
<td>85 ( 8%)</td>
</tr>
</tbody>
</table>

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Self-Reported Lyme Disease Following LYMErix®

- 16 reports
  - Clinical characteristics and coding terms consistent with Lyme Disease
  - 14 after first or second dose before completion of series
    - may not have achieved adequate immune response
  - A few reports of “reactivation” of Lyme disease

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Summary of VAERS Analysis

- VAERS has limited ability to assess the causal relationship of adverse events and vaccines
- Hypersensitivity reactions reported to VAERS are uncommon, but can be plausibly linked to LYMErix® because of their specific timing and clinical features
- Question of the association of arthritis with LYMErix® cannot be resolved with VAERS data alone, although reports of arthritic events reported to date do not provide clear evidence of a causal association
Follow-up Study

• Telephone survey to evaluate joint problems reported following LYMErix®
  – events coded arthritis, arthrosis, rheumatoid arthritis, joint disease, or arthralgia

• Purpose:
  – obtain detailed information about the events including medical records
  – look for patterns of unusual disease or laboratory values
  – confirm diagnoses of arthritis for case-control study

• 35 of ~200 planned interviews completed as of 1/25/01
Planned Follow-up Study

• Case-control study planned to examine the hypothesis that LYMErix® is associated with arthritis
  – arthritis cases confirmed by survey
  – two control groups identified from VAERS
    • arthritis cases reported following other vaccines
    • events other than arthritis reported following LYMErix®
  – conduct high resolution HLA typing and test for T-cell reactivity to OspA and LFA-1
  – probably only a very strong risk will be detectable
Plans for Continued Safety Evaluation of LYMErix®

• We continue to monitor VAERS reports of adverse events following LYMErix®

• We are conducting a VAERS-based telephone survey and a case-control study is planned to further evaluate joint problems following LYMErix®

• Results of LYMErix® manufacturer sponsored phase IV study will be important to help evaluate safety concerns
Collaborators in Analysis of VAERS Data

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