LYMErix® 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

LYMErix® Safety Surveillance Through VAERS

- Purpose: describe characteristics and look for patterns to detect adverse events plausibly linked to **LYMErix®**
- 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

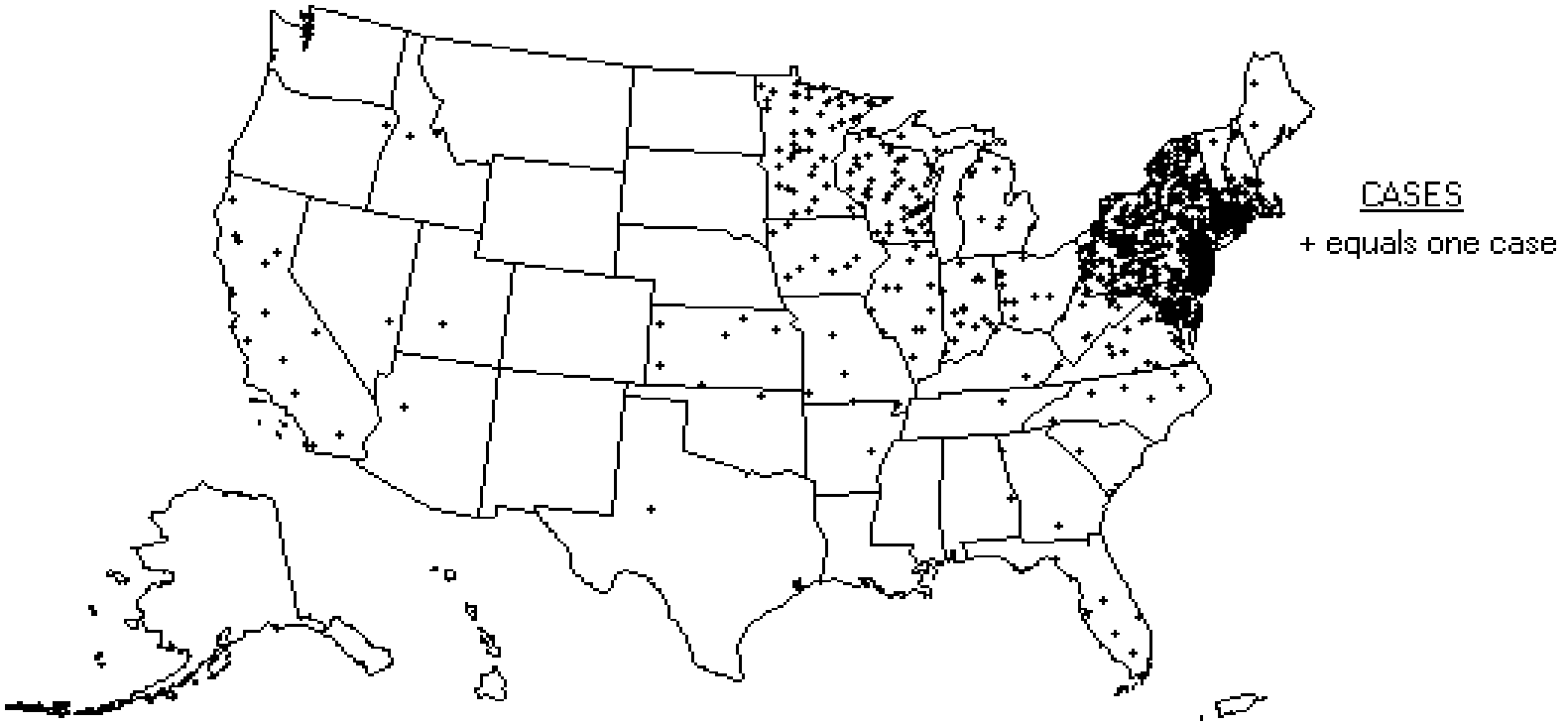
- 1,048 reports and ~ 1.44 million doses distributed
- 1,026 (98%) reports after Lyme vaccine alone
- 4 (0.4%) deaths
- 85 (8%) serious
- Selected adverse events
  - Hypersensitivity (22)
  - Arthritis (74), arthrosis (46), rheumatoid arthritis (13)
  - Facial Paralysis (13)
  - Lyme Disease (16)
- Selected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

FDA CBER

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

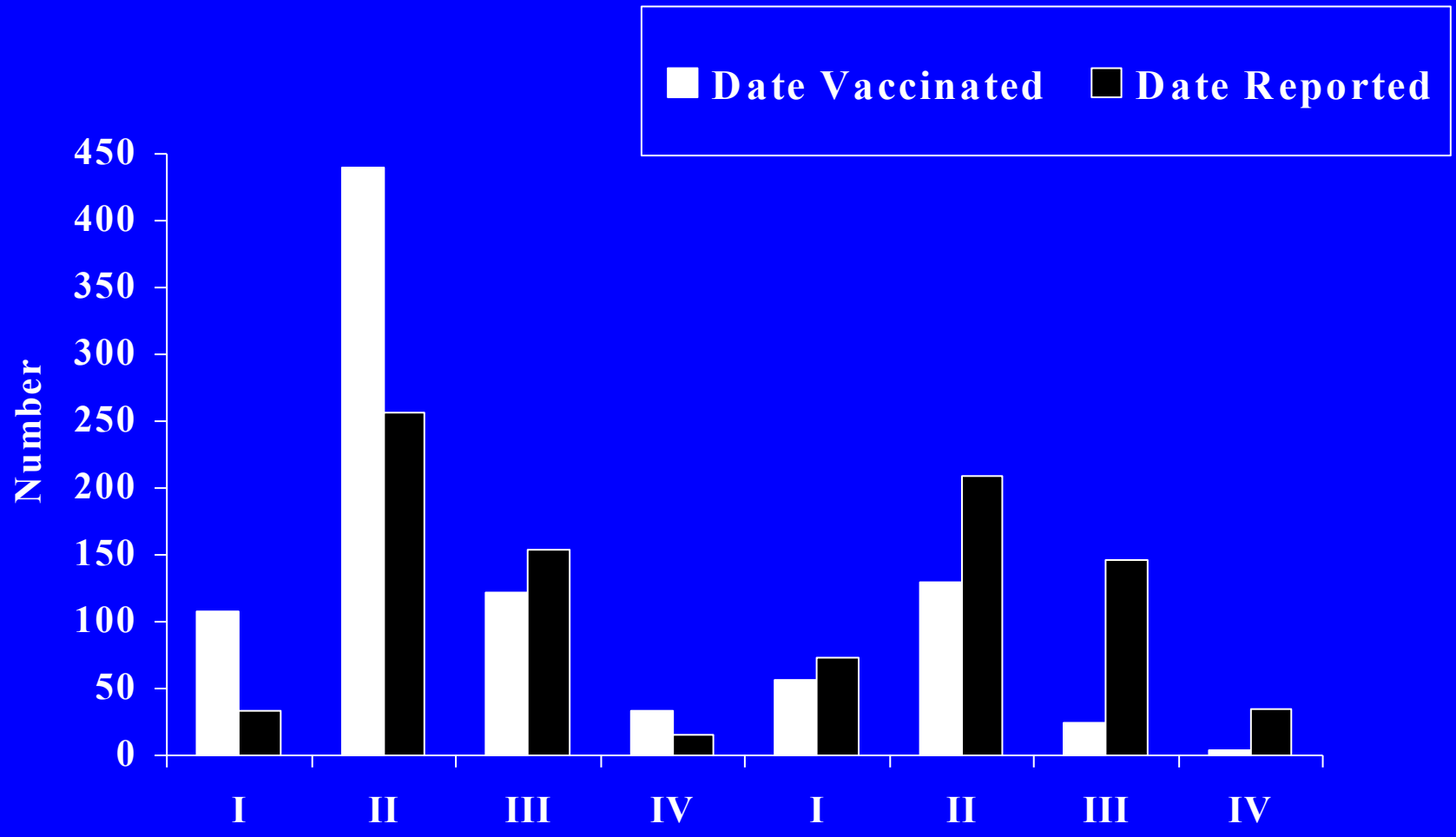
Number of VAERS LYMErix® Reports by State

December 21, 1998 to October 31, 2000



State not available for 55 reports

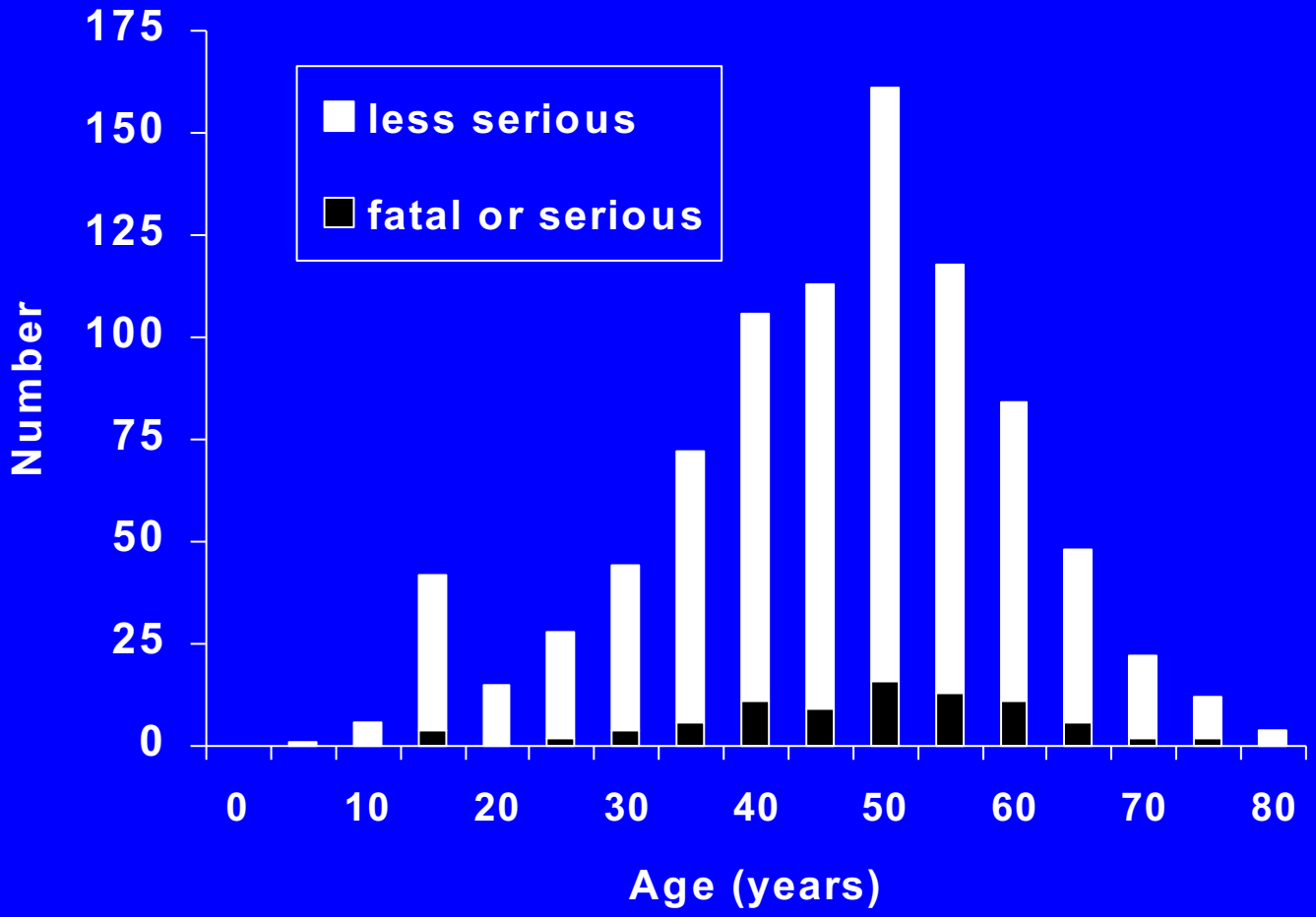
Frequency Distribution of All VAERS **LYMErix®** Reports (n=878) by *Calendar Quarter*



Date vaccinated not available for 165 of 1,048 reports (16%), 10 5 reports prior to 1999

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

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

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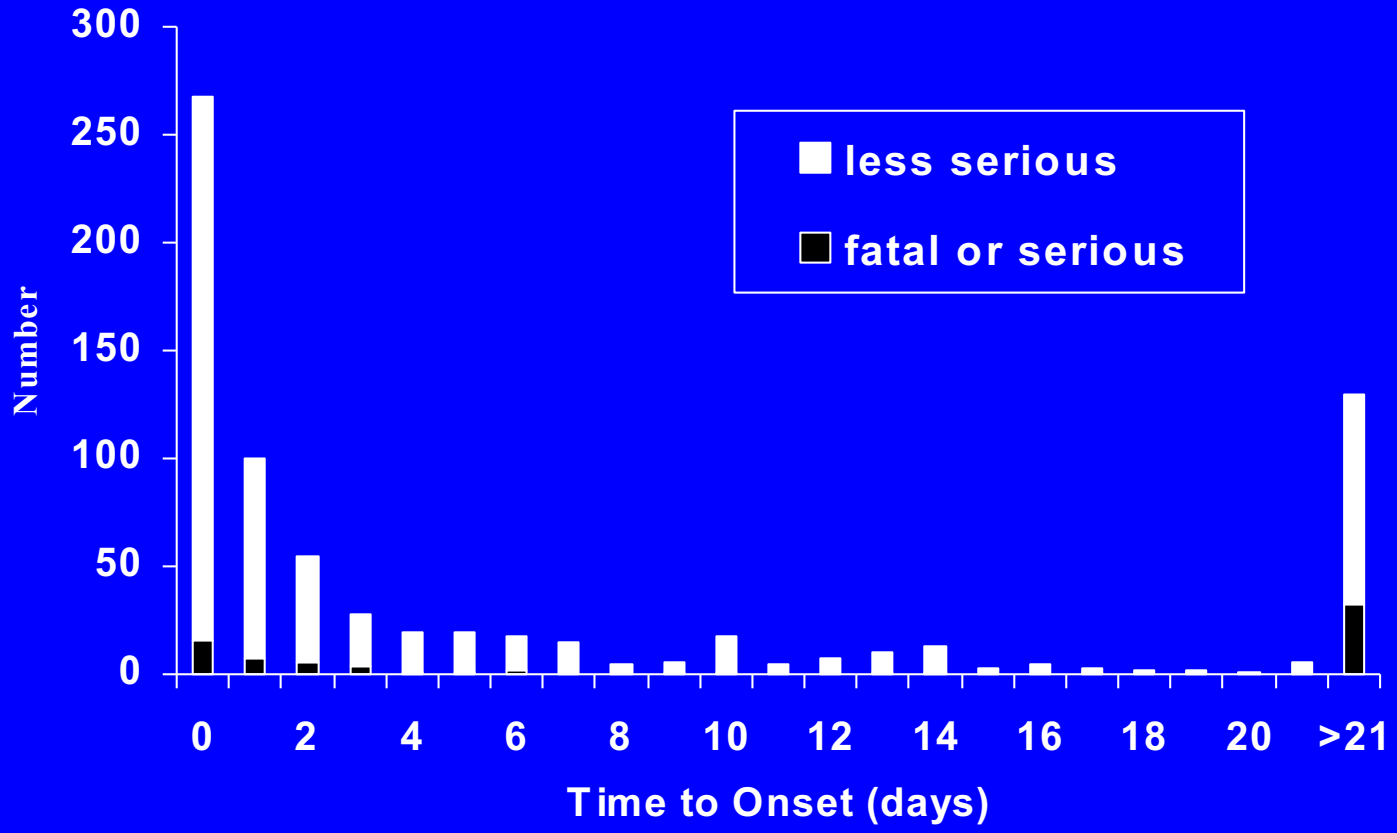
Frequency Distribution of All VAERS LYMErix® Reports (n=739) by *Time to Onset* of Adverse Event



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

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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**

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

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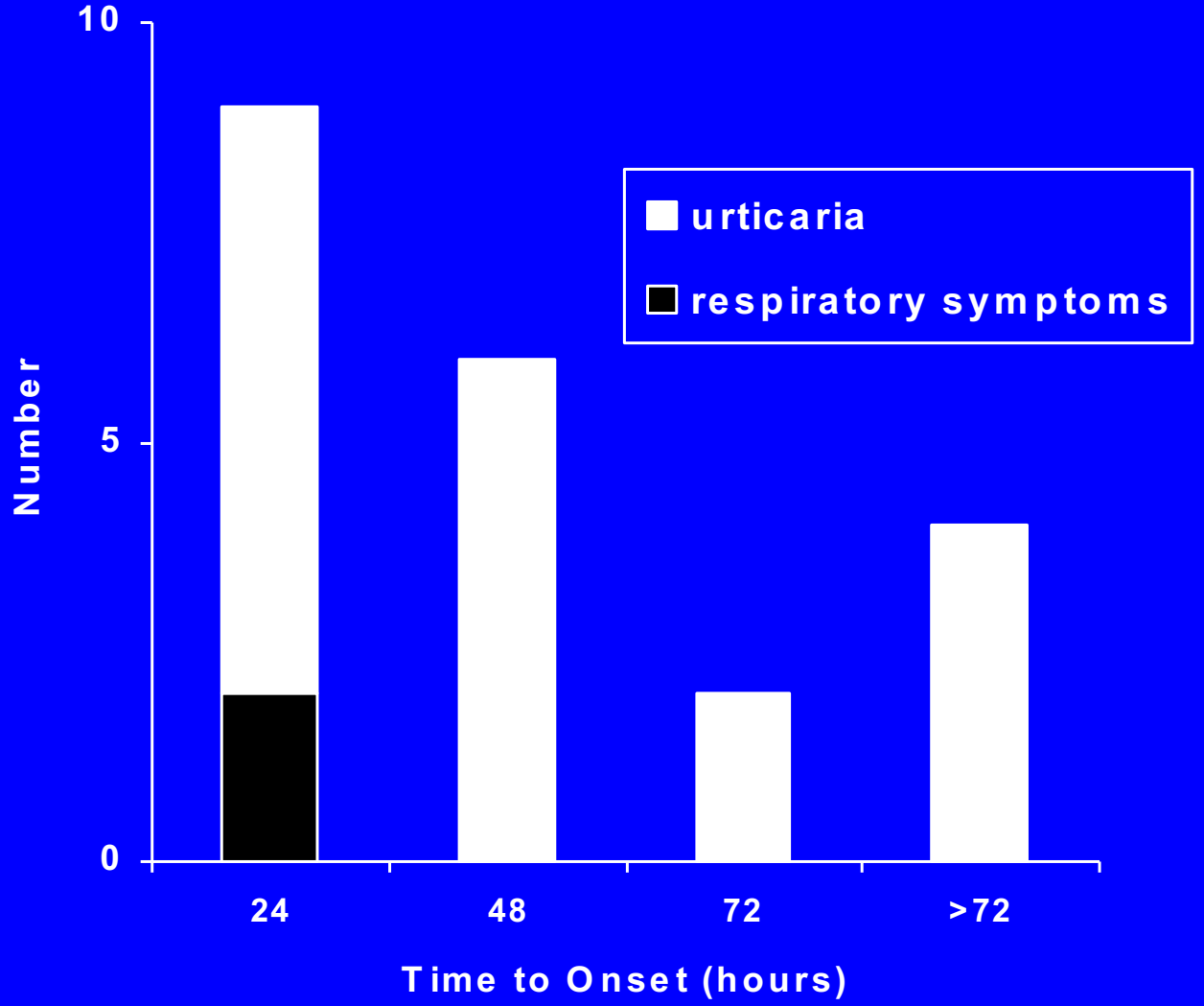
Summary of Serious Reports Following LYMErix® (n=85) Reported to VAERS (cont)

- 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

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

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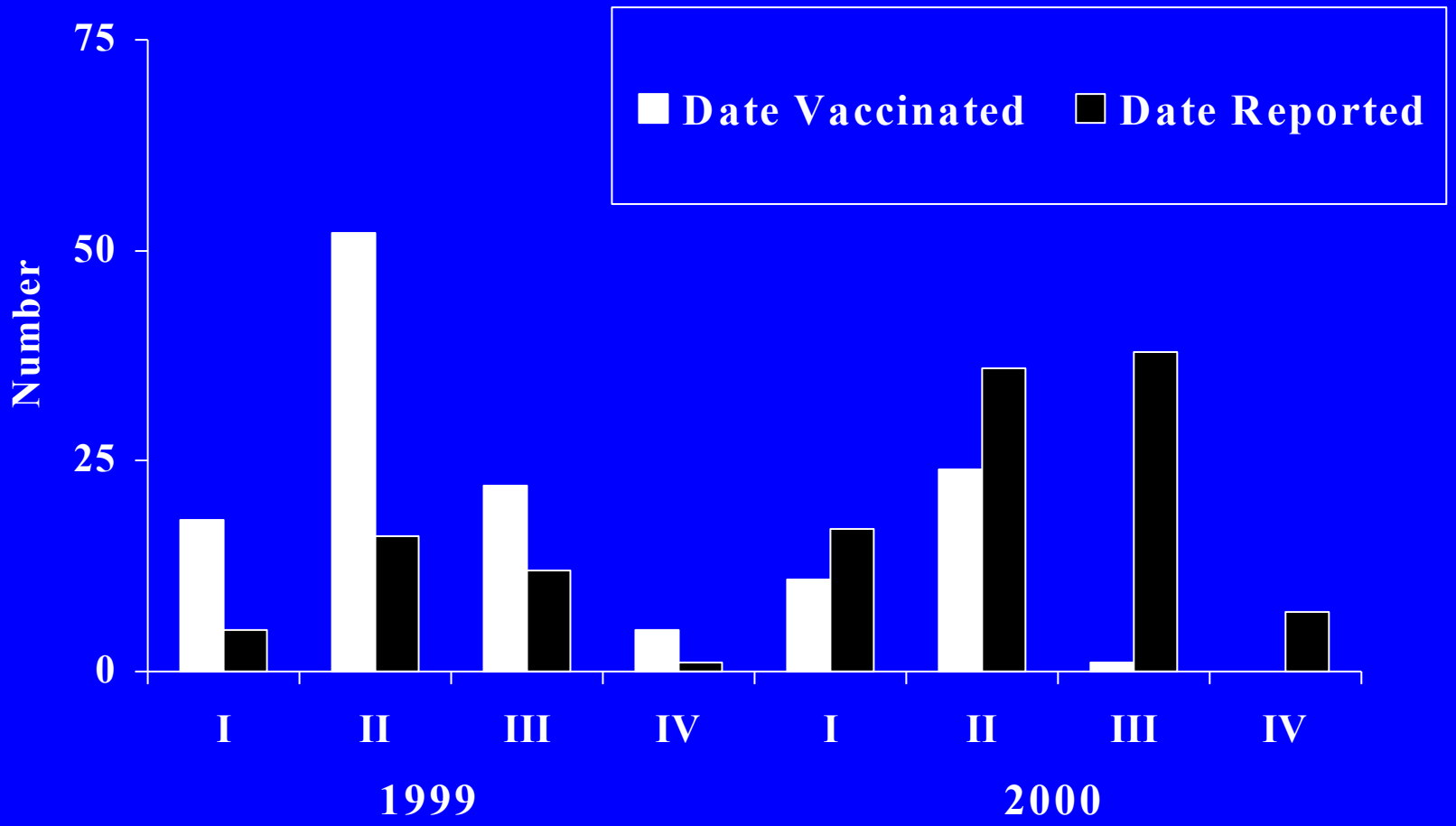
Frequency Distribution of Reports of Arthritis, Arthrosis, and Rheumatoid Arthritis (n=132) by *Calendar Quarter*



Vaccination date not available for 1 of 133 reports (1%)

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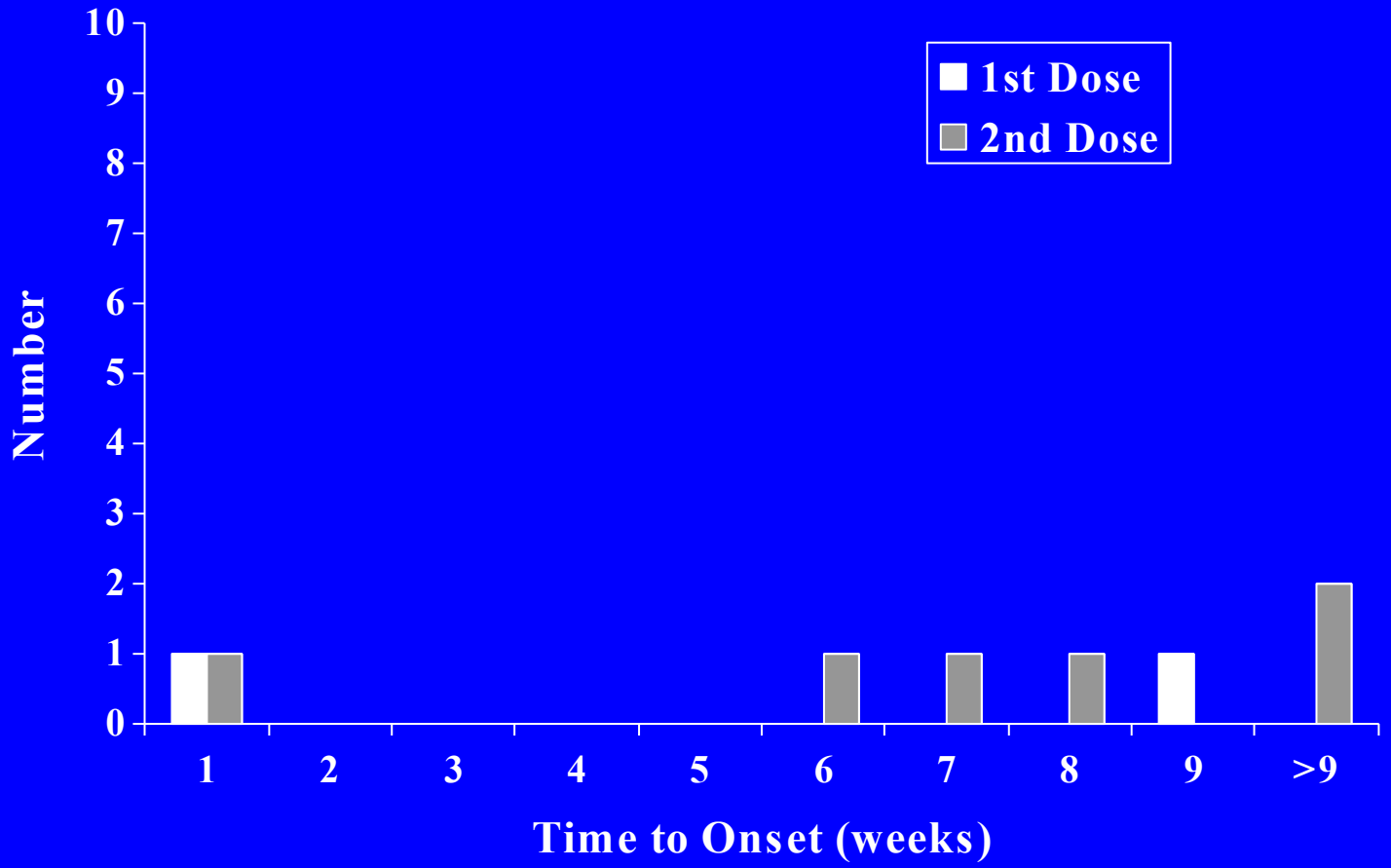
Reports of *Arthritis (n=74), Arthrosis (n=46), and Rheumatoid Arthritis (RA)* (n=13) Following LYMErix®

- 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)**

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



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

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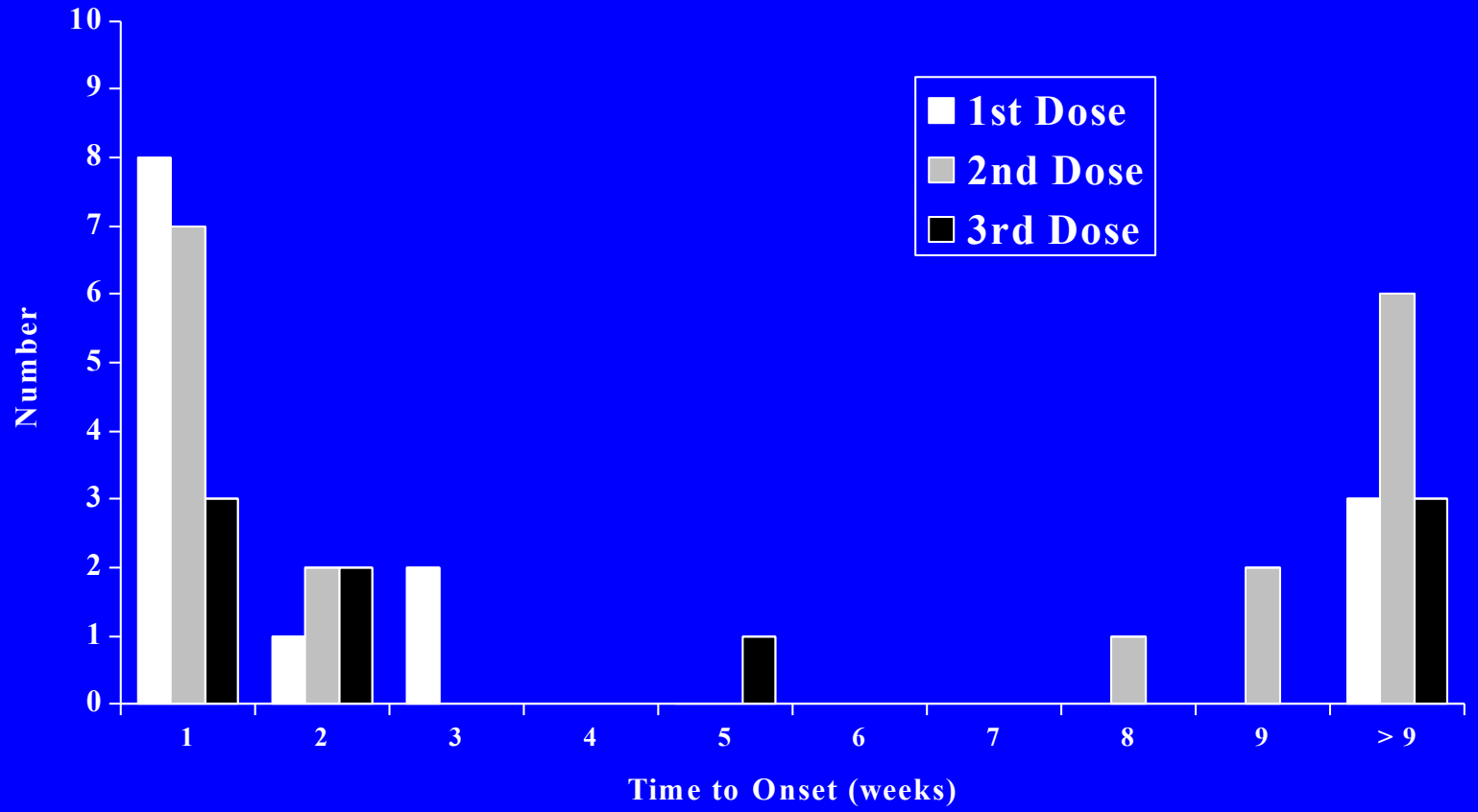
Frequency Distribution of VAERS LYMErix® Arthritis Reports (n=40) by *Time to Onset* and *Dose*



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)*

	Arthritis (n=74)	Arthrosis (n=46)	RA (n=13)
Joint Pain	41	29	10
Limited Motion	9	12	5
Joint Tenderness	3	2	-
Joint Warmth	3	4	2
Joint Swelling	**12**	**40**	**6**

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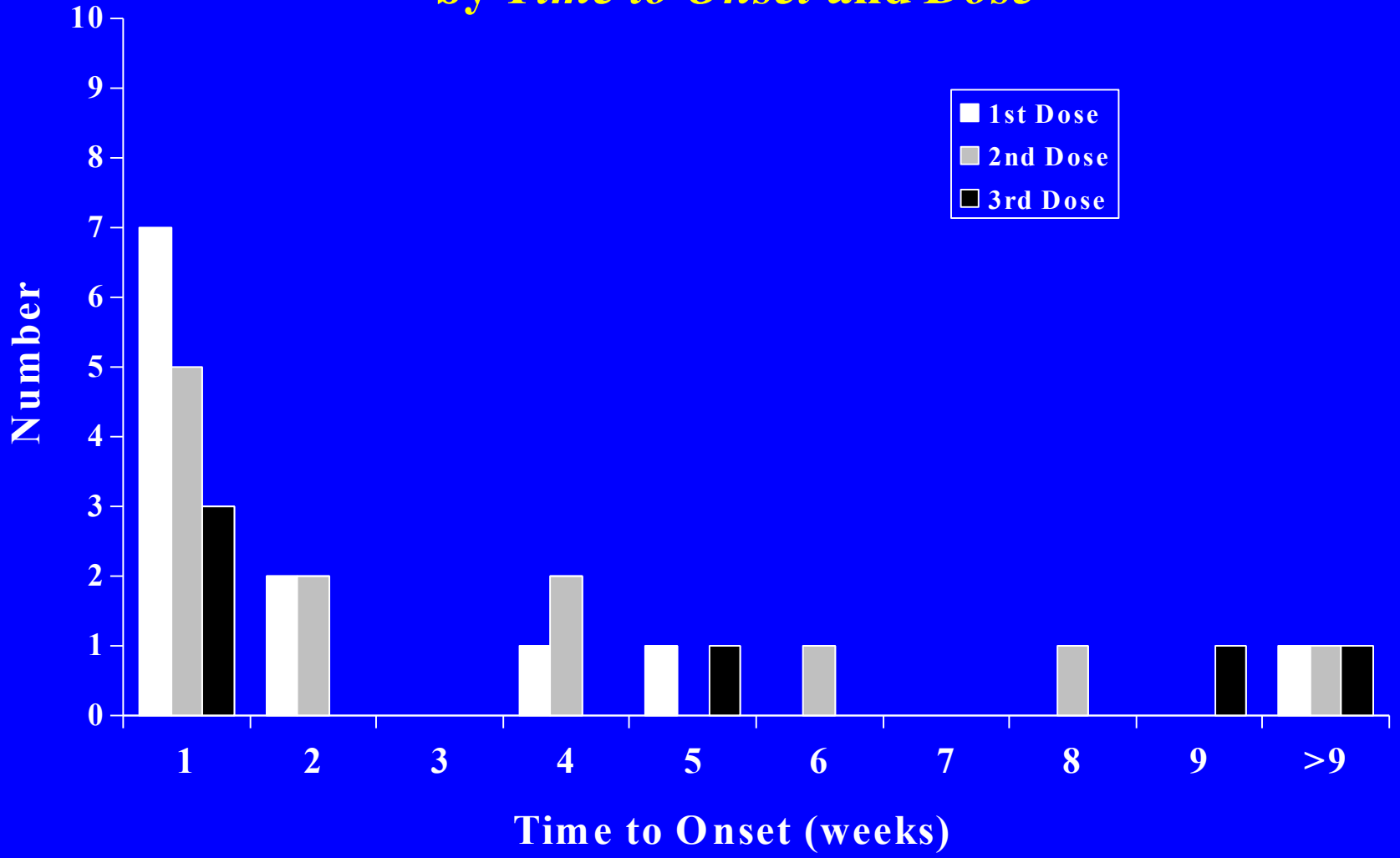
Frequency Distribution of VAERS LYMErix® "Arthritis" Reports Indicating Joint Swelling (n=30) by *Time to Onset* and *Dose*



Time to onset or dose not available for 28 of 58 reports (48%) of joint swelling

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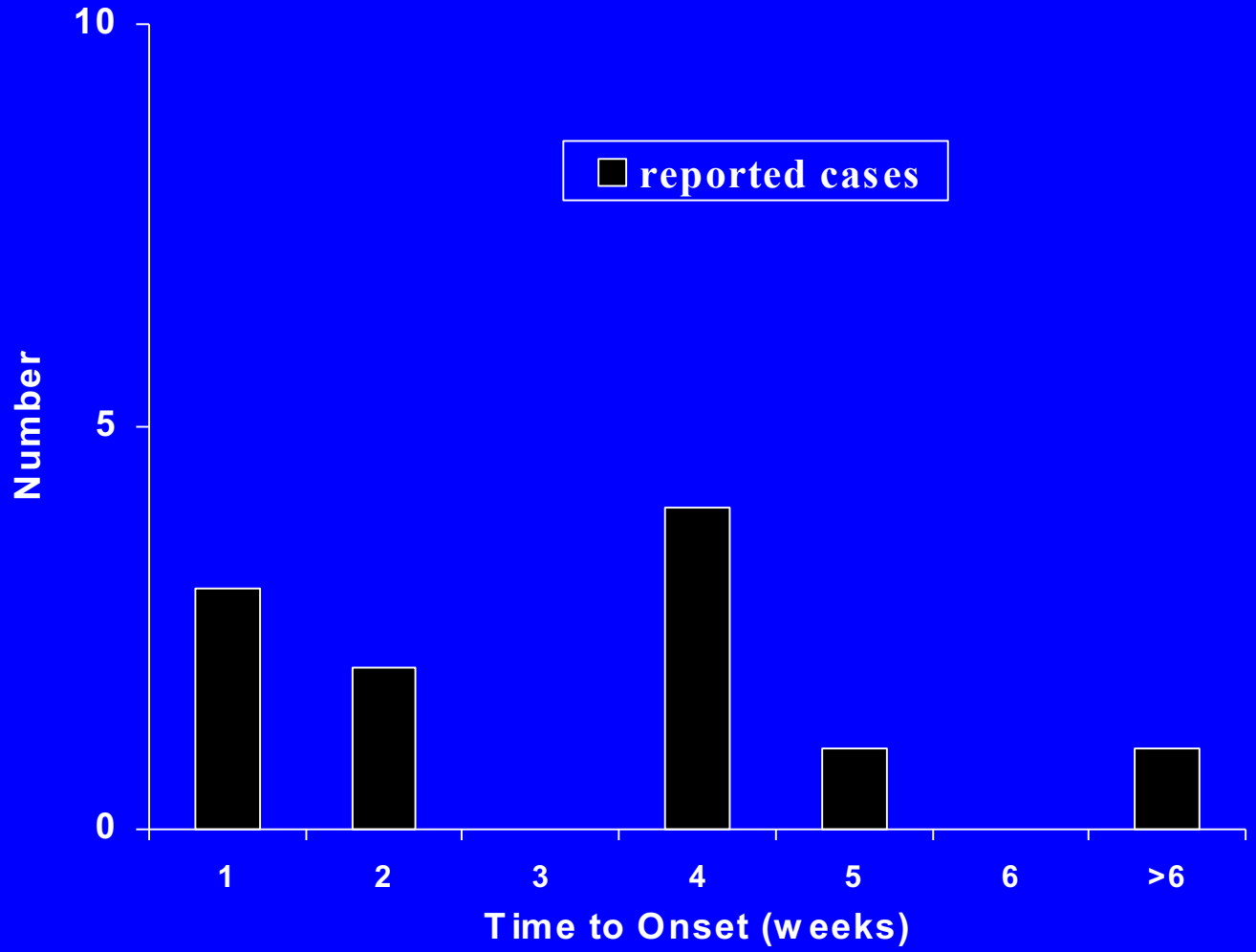
Reports of *Facial Paralysis* Following LYMErix®

- 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

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

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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

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Ten Most Common VAERS Coding Terms Following LYMErix® for People with a Self-Reported History of Lyme Disease (n=76)

• Arthralgia	25
• Asthenia	19
• Myalgia	19
• Headache	18
• Pain	16
• Injection Site Pain	12
• Fever	10
• Injection Site Hypersensitivity	8
• Chills	7
• Rash	7

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

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

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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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