Vaccine Safety Datalink Project: Monitoring the Safety Of Quadrivalent Human Papillomavirus Vaccine (HPV4)

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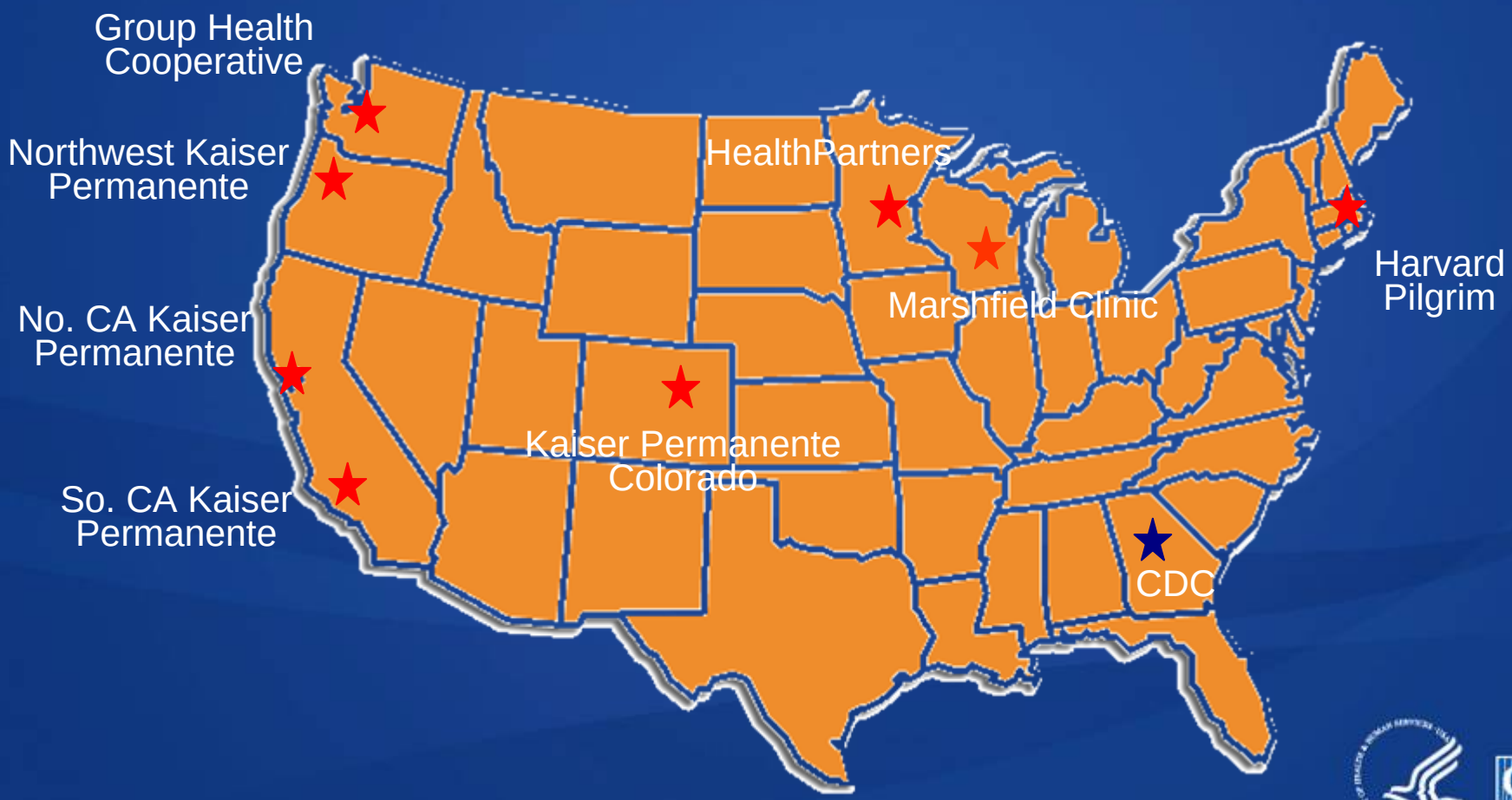
Vaccine Safety Datalink (VSD)

Collaboration between CDC and 8 managed care organizations

Data from 8.8 million members captured annually (3% of US population)



Vaccine Safety Datalink (VSD)

- Established in 1990 to improve the evaluation of vaccine safety through use of active surveillance and epidemiological studies
  - Addressed limitations of the Vaccine Adverse Event Reporting System (VAERS)
  - Responded to needs identified by two Institute of Medicine reports
- VSD tests hypotheses suggested by VAERS reports and pre-licensure trials

Rapid Cycle Analysis (RCA)

- Alternative to traditional post-licensure vaccine safety study methods, which generally take years to complete
- RCA Studies:
  - Tests specific hypotheses with well-defined outcomes
  - Each week, evaluate the number of events in vaccinated persons
  - Compare it to the expected number of events based on a comparison group
    - Historical or concurrent
  - Weekly analyses with statistical adjustment for multiple looks

Lieu TA, et al. Real-time vaccine safety surveillance for the early detection of adverse events. Med Care. 2007 Oct;45:S89-95.

HPV4 RCA Study

- Objective: Identify associations between HPV4 and a pre-specified list of adverse outcomes in females age 9-26 years
- 7 participating VSD sites
- Females 9-26 yrs
  - Youth: 9-17 yrs
  - Adults: 18-26 yrs
- Data from August 20, 2006-July 20, 2008
  - Allow for late arriving data
- Monitor until:
  - Youth: 350,000 doses
  - Adults: 150,000 doses

HPV RCA Outcomes

Outcome	Exposure window (days)	Medical Setting	First in what period?
Guillain Barré Syndrome (GBS)	1 to 42	All	42 days
Seizures	0 to 42	Inpatient, ED	42 days
Syncope	0	All	2 days
Appendicitis	0 to 42	Inpatient, ED	42 days
Stroke	0 to 42	Inpatient, ED	42 days
Venous Thromboembolism (VTE)	1 to 42	All	1 year
Anaphylaxis	0 to 2	All	2 days
Other Allergic rxns	0 to 2*	All	42 days

*exclude day 0 if clinic setting

HPV4 RCA: Cohort

- Exposed cohort: Females 9-26 years receiving HPV4
- Historical comparison group (Poisson Max SPRT*):
  - Background rates of select outcomes for females 9-26 yr of age:
    - Enrolled in a participating VSD site
    - Other data sources (Health Care Utilization Project)
  - Outcomes: GBS, Appendicitis, Stroke, VTE
- Concurrent comparison group (Flex Exact Sequential Analysis)
  - Females in the same age range who had a preventative or vaccination visit during the same time period as the exposed group
  - Outcomes: Seizures, Syncope, Allergic Reactions
- No formal comparison being performed for anaphylaxis

* Poisson Maximum Sequential Probability Ratio Test

Poisson MaxSPRT Analysis

- Observed number of events compared to expected number from historical group
- Association (“signal”) detected if critical value of log likelihood ratio (LLR) exceeded

Kulldorff M, et al. A Maximized Sequential Probability Ratio Test for Drug and Vaccine Safety Surveillance. *Submitted for Publication.*

Flexible Exact Sequential Analysis

- Threshold p-value is established that accounts for continuous monitoring
- Observed number of events compared to expected number from concurrent group
  - matched by the variables of interest
- Association (“signal”) detected if weekly p-value is less than the threshold p-value

Preliminary Results: HPV4 Doses Administered

- Total HPV4 doses administered (through week July 20, 2008): 377,960
  - Youth: 259,986
  - Adults: 117,974
- Total utilization by dose:
  - Dose 1: 50.4%
  - Dose 2: 31.5 %
  - Dose 3: 18.1%

Preliminary Results: Historical Comparison - Adults

Outcome	Events Observed	Events Expected	RR	Log Likelihood Ratio (LRR)	Critical Value of LRR	Signal ?
GBS	0	0.31	0.00	0.00*	2.86	No
Appendicitis	21	21.12	0.99	0.00*	3.68	No
Stroke	3	1.58	1.91	0.51	2.97	No
VTE	7	10.11	0.69	0.00*	3.57	No

* LRR is automatically set to zero when RR < 1

Preliminary Results: Concurrent Comparison- Adult

Outcome	Exposed Cases	Unexposed Cases	Comparison visit	RR	Binomial Test P-Value	Threshold P-Value	Signal ?
Seizure	18	26	PC	1.18	0.39	0.02	No
Syncope	129	57	Vac	0.54	0.99	0.03	No
Other Allergic reactions	32	7	Vac	1.45	0.26	0.02	No

Total preventative care (PC) comparison visits: 211,878
Total vaccination (Vac) comparison visits: 34,917

Preliminary Results: Historical Comparison-Youth

Outcome	Events Observed	Events Expected	RR	Log Likelihood Ratio (LRR)	Critical Value of LRR	Signal ?
GBS	0	0.50	0.00	0.00*	2.86	No
Appendicitis	33	41.99	0.79	0.00*	3.86	No
Stroke	0	0.84	0.00	0.00*	2.97	No
VTE	7	3.57	1.96	1.28	3.25	No

* LRR is automatically set to zero when RR < 1

Preliminary Results: Concurrent Comparison- Youth

Outcome	Exposed Cases	Unexposed Cases	Comparison Visit	RR	Binomial Test P-Value	Threshold P-Value	Signal ?
Seizure	34	14	PC	1.13	0.45	0.02	No
Syncope	452	120	Vac	0.99	0.56	0.04	No
Other allergic reactions	44	24	Vac	0.75	0.85	0.02	No

Total comparison preventative care (PC) visits: 141,329
Total comparison vaccination (Vac) visits: 106,252

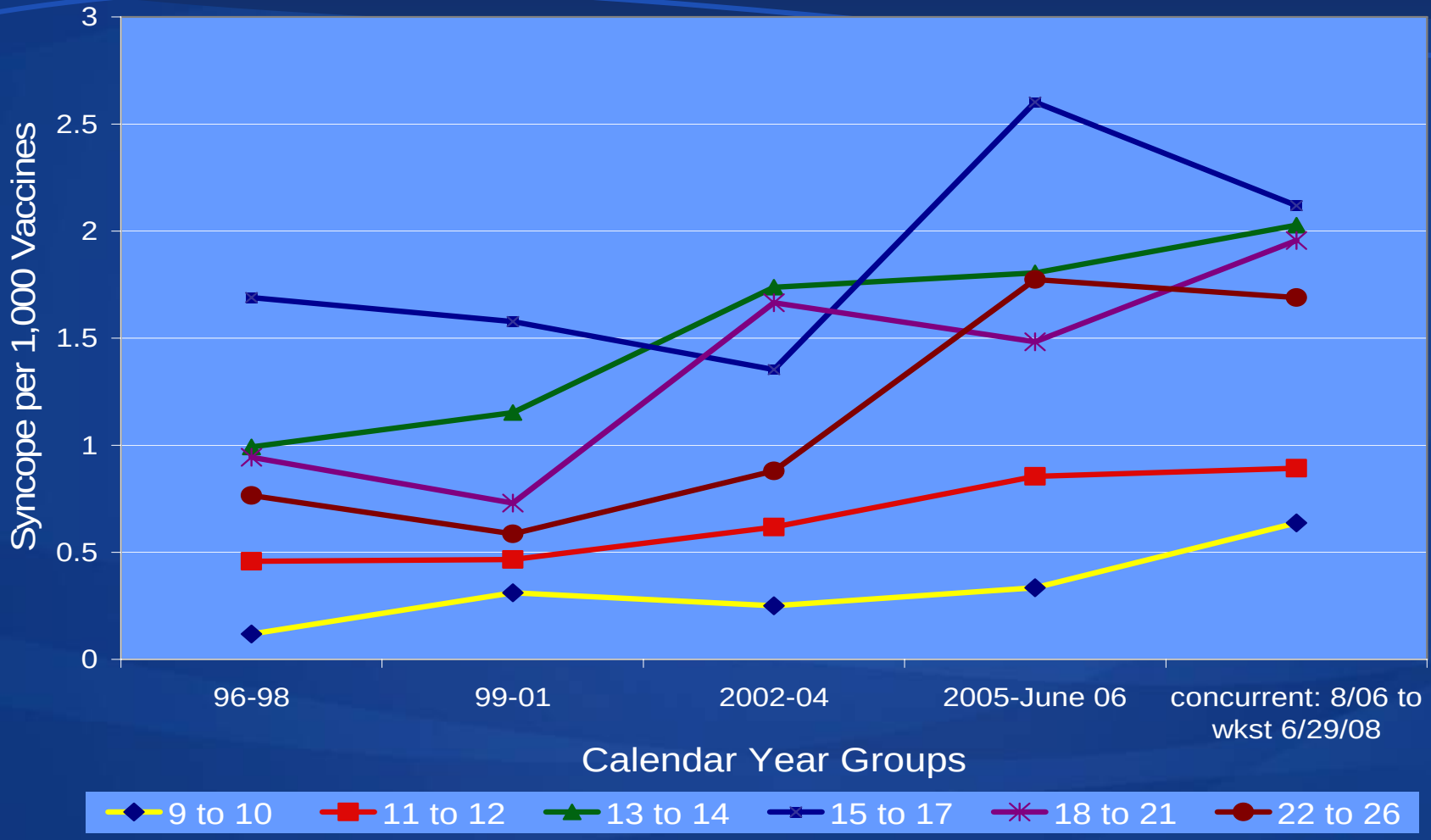
Syncope Logistic Regression Results: Concurrent Comparison Group

	Age and Secular Trend Adjustment *		
	RR	95% CI	p-value
Youth	0.99	0.80, 1.22	0.93
Adult	0.66	0.48, 0.91	0.01
Combined	0.88	0.74, 1.05	0.16

*Age adjusted by 2-3 year groups: 9-10, 11-12, 13-14, 15-17, 18-19, 20-21, 22-23, 24-26

Years of analysis: 8/20/06-6/29/08

Syncope per 1000 Vaccines Visits
Following Td, Tdap, Menactra, and Varicella



Anaphylaxis

- # of events youth in automated data:
  - Exposed: 8
  - Comparison group: 9
- # of events among adults in automated data:
  - Exposed: 7
  - Comparison group: 2
- Chart confirmed number of vaccine-related cases:
  - Youth: 0
  - Adult: 0
- Rate:
  - 0 cases/million doses (95% CI: 0.0 -9.76)
- Background rate:
  - 1.53 cases/million doses (95% CI: 0.04-8.52) *

* Bohlke K, et al. Risk of Anaphylaxis after Vaccination of Children. Pediatrics 112(4); 2003

Additional monitoring

- Weekly monitoring ongoing since July 20, 2008
- Highlighted findings:
  - 1 GBS case identified
    - Preliminary chart review conducted
      - Not a confirmed exposed case
  - Limited power at this time to rule out a true risk of GBS following HPV4
    - Based on a probability of observing 0 cases per 420,000 doses, we are unable to rule out a RR of less than 5

Major Findings and Next Steps

- With >375,000 doses administered, VSD active surveillance did not find statistically significant risk for any of the pre-specified adverse events after vaccination for either age group
- No major increase in rate of anaphylaxis following HPV4 as compared to previous studies
- Continue to monitor outcomes until reach upper limits for adverse events or until reach dose limit
- Continue to monitor rare adverse events
  - GBS, VTE, stroke

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Disclosure

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