Rapid Cycle Analysis of Pentavalent Rotavirus (RotaTeq®) Vaccine Safety in the Vaccine Safety Datalink Population: Preliminary Results

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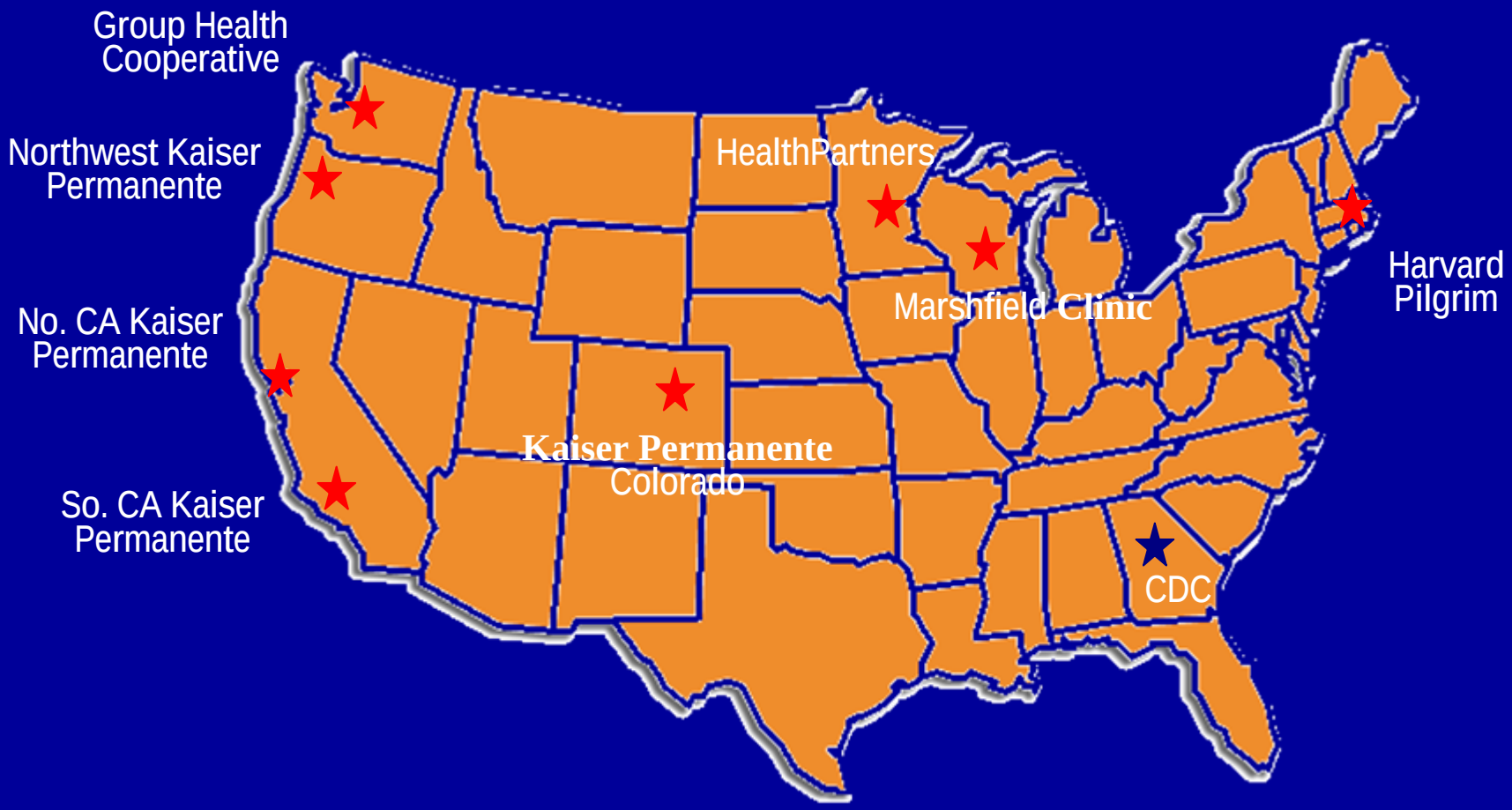
Vaccine Safety Datalink (VSD)

Collaboration between CDC and 8 managed care organizations

Data from 8.8 million members captured annually (2.9% of US population)



Vaccine Safety Datalink

- 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

- Alternative to traditional post-licensure vaccine safety study methods, which generally take years to complete
- Can identify pre-specified vaccine adverse events in near real-time
  - Tests specific hypotheses with well-defined outcomes
  - Number of events in vaccinated persons compared to expected number of events
  - Data available within weeks of vaccination
  - Weekly analyses with adjustment for repeated hypothesis testing

Rapid Cycle Analysis of RotaTeq® Vaccine

Study Objectives

- Monitor for increased risk of intussusception (IS) during a 30 day window after receipt of RotaTeq®
- Monitor for increased risk of other pre-specified adverse events following receipt of RotaTeq®

Study Population

- 7 of 8 VSD sites participated
- **Exposed population**: children who received any dose of RotaTeq® (with or without other vaccines) from age 4 through 48 weeks
- **Historical comparison group**: children 4 through 52 weeks of age with a VSD enrollment record from 1991 through 2004
  - Baseline IS incidence calculated by week of age with adjustment for secular trend

Outcome Ascertainment

Adverse Event	ICD-9 Codes	Data Source
Intussusception	543.9, 560.0	ED**, Inpatient, Outpatient
Meningitis and Encephalitis	047.8, 047.9, 049.9, 321.2, 322*, 323.5, 323.9	Inpatient
Seizures	780.3, 779.0, 333.2, 345*	ED, Inpatient, Outpatient
Myocarditis	429.0, 422*	Inpatient
Gram negative sepsis	038.4, 038.9	Inpatient
Kawasaki syndrome	446.1	ED, Inpatient, Outpatient

* 322.0-9; 345.0-9; 422.0-9

** ED = Emergency department

Validation of Intussusception Cases

- All cases validated by medical record review
- Brighton Collaboration criteria used to validate cases*
  - Level 1 diagnostic certainty (surgical criteria and/or radiologic criteria, and/or autopsy criteria) required to define cases

* Available at http://www.brightoncollaboration.org/internet/en/index/definition___guidelines.html

Poisson maxSPRT* Analyses

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

* maximized sequential probability ratio test

RotaTeq® Utilization in VSD*

Vaccine Dose	# Administered
1	77,162
2	67,977
3	50,651
Total doses **	205,179

* Through 05/24/2008

** Total includes 9,389 doses administered outside of recommended age range for dose 1, 2, or 3

Poisson maxSPRT Results: Intussusception (IS)

Dose	IS Events observed	IS Events expected	RR	Log likelihood ratio (LLR)	Critical value of LLR	Signal?
All doses	5	6.65	0.75	0.00	3.30	NO
Dose 1	2	1.39	1.44	0.12	2.86	NO
Dose 2	2	2.27	0.73	0.00	3.05	NO
Dose 3	1	2.19	0.46	0.00	3.05	NO

Medical Record Validation Results

Sex	Age (wks)	Dose (#) preceding IS diagnosis	Days between vaccination and IS diagnosis	Met IS case criteria	Narrative diagnosis	ICD-9 data source
M	28	3	16	YES	Intussusception	ED
F	17	2	12	YES	Intussusception	Outpatient
M	9	1	19	No	Normal air enema; no intussusception	Outpatient
M	8	1	11	No	Viral, acute gastroenteritis	Outpatient
M	22	2	10	No	Breath-holding spells	Outpatient

Poisson maxSPRT Results: Additional Adverse Events

Adverse Event	Events observed	Events expected	RR	Signal?
Meningitis and Encephalitis	8	12.91	0.62	NO
Seizures	37	55.71	0.66	NO
Myocarditis	0	0.41	0	NO
Gram negative sepsis	3	5.57	0.54	NO

Kawasaki Syndrome (KS) Results*

KS Diagnoses in RotaTeq Recipients	KS Diagnoses in Comparison Group	RR	Signal?
2	8	0.205	NO

* Kawasaki syndrome analyzed using a concurrent comparison group

Concurrent comparison group:

Children in the same age range who received any licensed vaccine (and not RotaTeq®) during the post-licensure period.

Major Findings

- Five cases of IS within 30 days after RotaTeq® in the computerized data
  - Not more than expected
  - No cases within 7 days of vaccination
- Only 2 cases validated after medical record review
  - Neither case occurred following dose 1
- Results provide no evidence that RotaTeq® receipt is associated with an increased risk for IS or other pre-specified adverse events

Intussusception Risk 1-7 Days after RotaTeq®

- Concern about increased risk identified from VAERS reports
- No events in days 1-7 following any dose in VSD population

1st Dose Probability Calculations: *7 of 8 VSD Sites*

Hypothetical risk of IS in RotaTeq® recipients (case/1st doses)	Rate Ratio	Expected cases to date*	Probability of observing zero cases given the expected
1 / 5,000	58	15.4	10^{-8}
1 / 10,000	29	7.7	0.00045
1 / 25,000	12	3.1	0.046
1 / 50,000	6	1.5	0.214
1 / 77,162	4	1.0	0.368

* Based on cases occurring within 1-7 days after 77,162 first doses administered, assuming hypothetical risk were true risk.

1st Dose Probability Calculations: All *VSD Sites and Clinical Trial**

Hypothetical risk of IS in RotaTeq® recipients (case/1st doses)	Rate Ratio	Probability of observing zero cases given the expected – All VSD Sites**	Probability of observing zero cases given the expected – All VSD Sites + Clinical Trial**
1 / 5,000	58	10^{-11}	10^{-14}
1 / 10,000	29	0.0000022	10^{-9}
1 / 25,000	12	0.0055	0.0014
1 / 50,000	6	0.074	0.038

* Vesikari T, et al. Safety and Efficacy of a Pentavalent Human-Bovine (WC3) Reassortant Rotavirus Vaccine. NEJM 2006;354:23-33.

**Based on cases occurring with 1-7 days.

1st Dose Probability Calculations: *Key Points for RotaTeq® RCA*

- Virtually no possibility of observing zero cases given a level of risk comparable to that of RotaShield® vaccine* (~1 case per 10,000 first doses).
- Unable to rule out a small probability of observing zero cases given a true risk smaller than 1-2 cases/50,000 first doses.
- Estimated 10 years needed to detect RR=3 in VSD (852K 1st doses)
  - 31 years to detect RR=2 (2.7 million first doses)

*RotaShield® was withdrawn from the US market in 1999

Next Steps in VSD

- Continue surveillance for intussusception occurring 1-7 days after RotaTeq® vaccination
- Begin rapid cycle analysis of Rotarix®
  - Monitor for same adverse events as for RotaTeq®
  - Additional outcome: hospitalized pneumonia
  - VSD can distinguish between Rotarix® and RotaTeq® vaccinations

Acknowledgements

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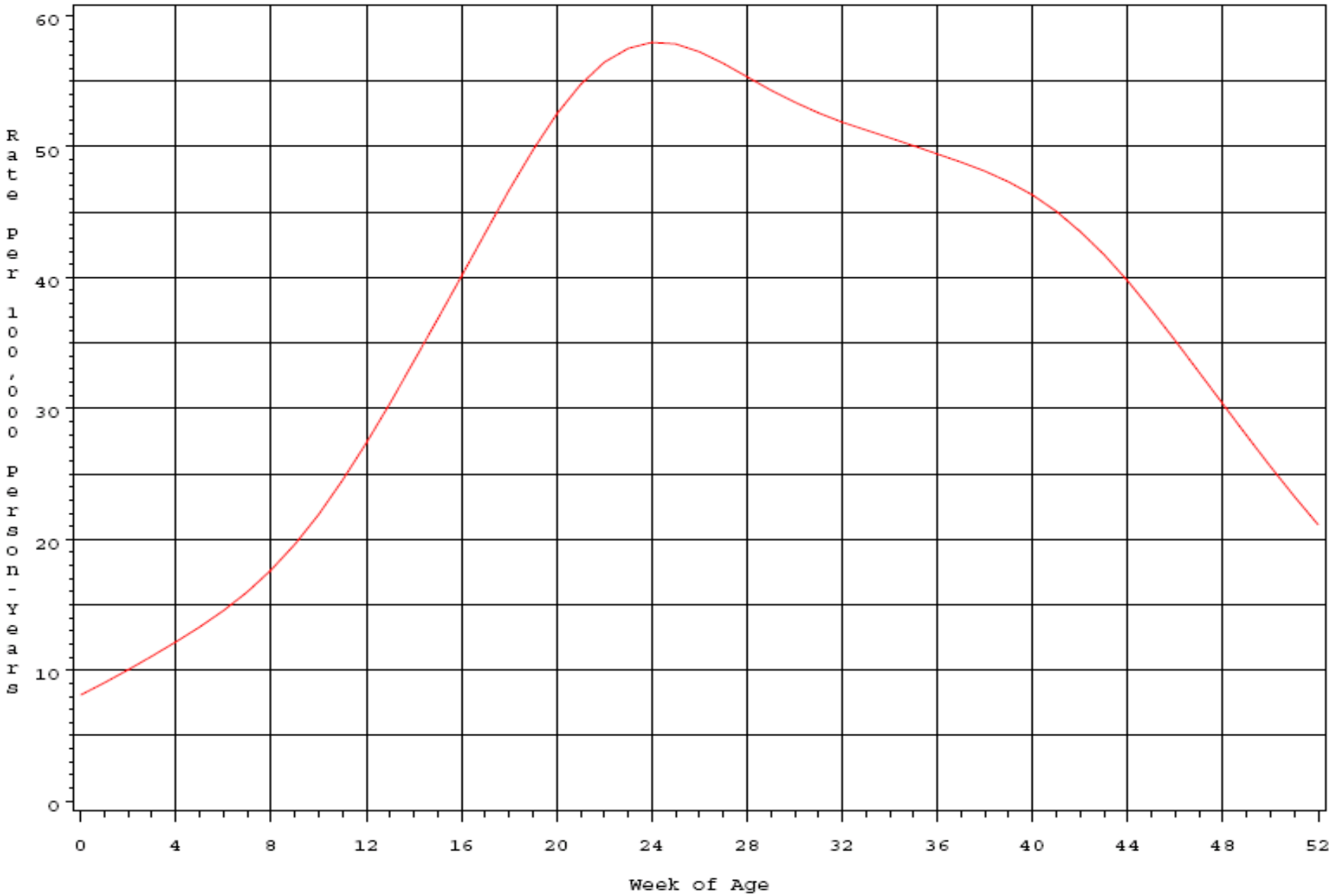
*The findings and conclusions in this presentation are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

CDC Immunization Safety Office Summary: RotaTeq® VAERS and VSD Postlicensure Safety Monitoring

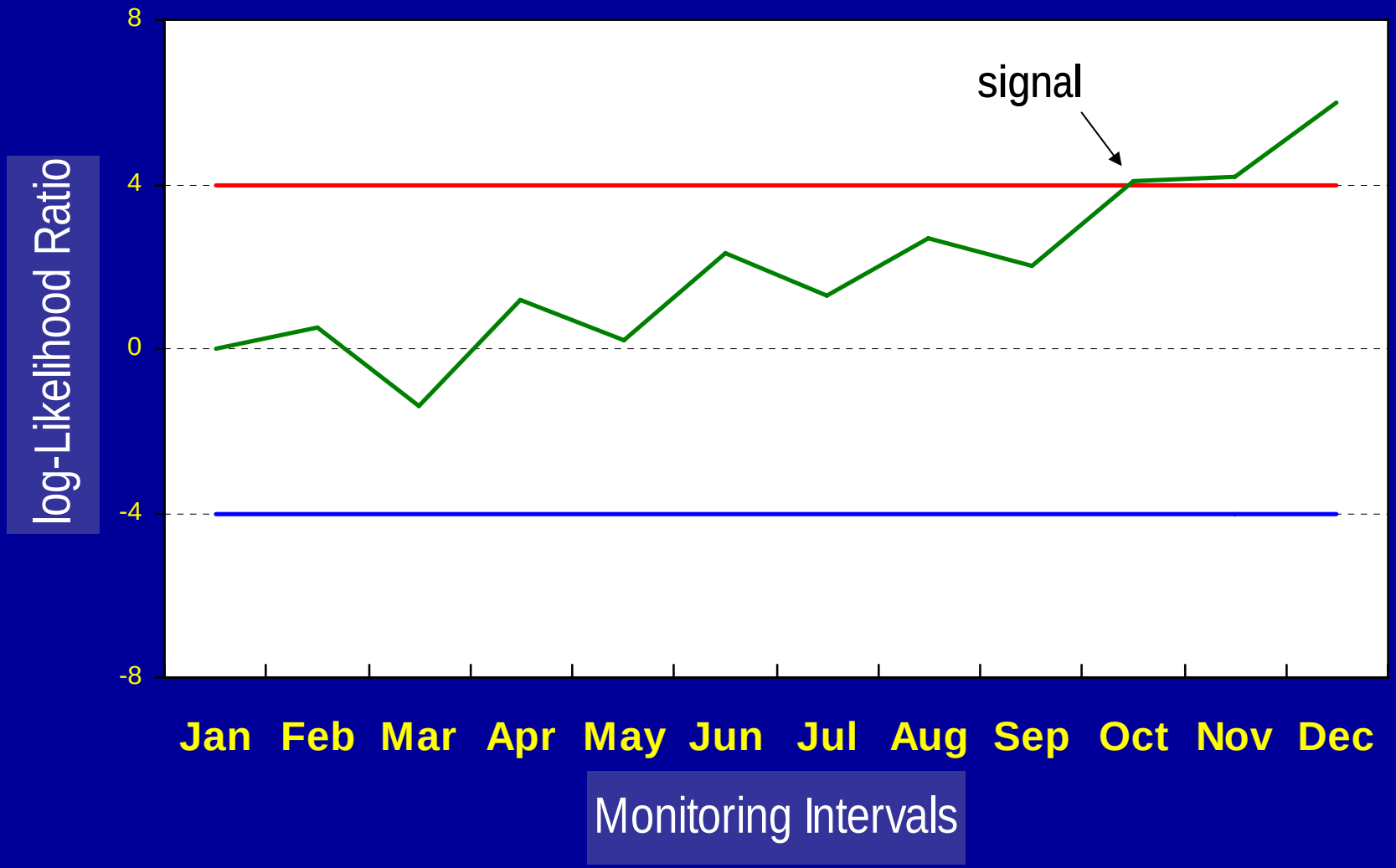
- With >14 million doses distributed since 2006, VAERS passive surveillance did not identify a specific safety concern for intussusception (IS) during 1-21 days after any dose
  - Apparent cluster observed 1-7 days after first RotaTeq® dose
- With >200,000 doses administered, VSD active surveillance did not identify an increased risk for IS or other pre-specified adverse events during 30 days after vaccination
- With >160,000 first doses administered in VSD and the prelicensure trial, no cases of IS identified during 1-7 days after vaccination
  - Available data suggest risk for IS after first RotaTeq® dose not greater than 1-2 cases per 50,000 first doses administered

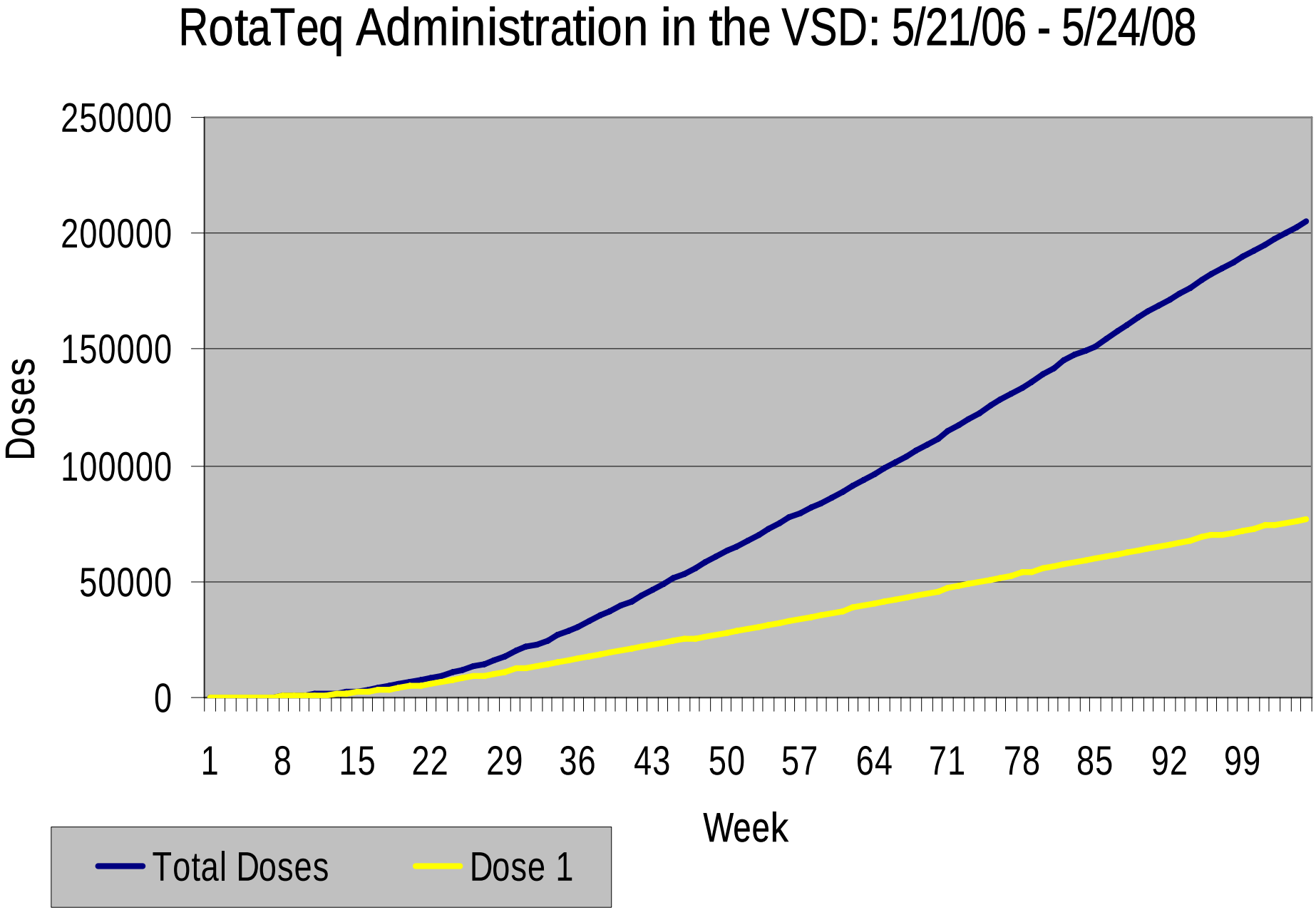
Additional Slides

Intussusception Incidence by Week of Age in VSD



Sequential Probability Ratio Test (SPRT): Graphical Model




RotaTeq Administration in the VSD: 5/21/06 - 5/24/08
250000
200000
150000
100000
50000
0
Doses
1
8
15
22
29
36
43
50
57
64
71
78
85
92
99
Week
Total Doses
Dose 1