Rapid Cycle Analysis of Adolescent and Adult Tetanus-Diphtheria-Acellular Pertussis (Tdap) Vaccine Safety in the Vaccine Safety Datalink Population: Preliminary Results

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Advisory Committee on Immunization Practices (ACIP)
Atlanta, GA
June 26, 2008

Vaccine Safety Datalink

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 shortcomings of VAERS
  - Responded to needs identified by two Institute of Medicine reports
- VSD tests hypotheses suggested by the Vaccine Adverse Event Reporting System (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 for Tdap: Study Design

- Identify associations between Tdap vaccine in adolescents and adults and a prespecified list of adverse outcomes
- Cohort
  - Exposed cohort - received Tdap
  - Unexposed cohort - historic subjects receiving Td
    - Incidences adjusted for age and HMO

Analysis

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

Determining Outcomes

- Reviewed literature, pre-licensure data, VAERS data
  - Tdap
  - Whole cell and acellular pediatric pertussis (DTP, DTaP)
    - Out of age range previous pertussis vaccination
  - Td and TT
- Outcomes of interest
  - Facial paralysis
  - Encephalopathy

Outcome Criteria

1) Clinically well-defined
2) Serious
3) Already observed in studies or passive surveillance
4) Biologically plausible as a consequence of vaccination

Definition of Outcomes

Adverse event category	ICD9 codes	Post-vaccination observation window (days)	Medical Setting
Encephalopathy, encephalitis, meningitis	047.8, 047.9, 049.9, 321.2, 322, 323, 348.3, 348.5	1-42	Outpatient, inpatient, Emergency department (ED)
Paralytic syndromes	342, 344, 781.4	1-42	Outpatient, inpatient, ED
Seizure	345, 780.3	0-7	Inpatient, ED
Cranial nerve disorders, including Bell's palsy	350, 351, 352	1-42	Outpatient, inpatient, ED
Guillain-Barré Syndrome (GBS)	357	1-42	Outpatient, inpatient, ED

Background Incidences for Comparison

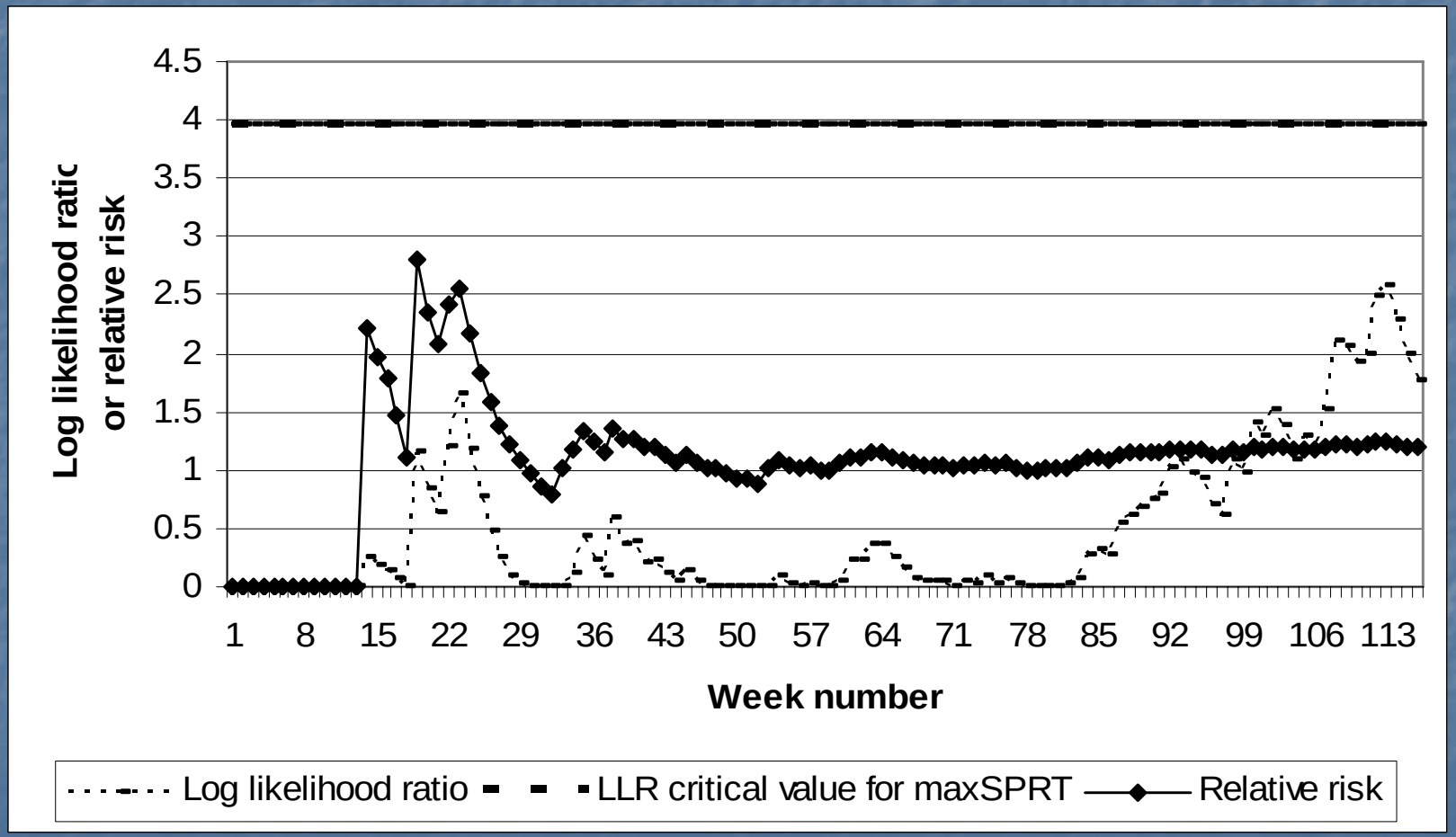
- GBS: age-specific rates from Healthcare Cost and Utilization Project (HCUP) hospital discharge data for all GBS (not only as primary diagnosis) during 2000-2004
- Seizure: age-specific rates on Days 1-7 after Td increased by 1/7 (14%) in VSD historical data for 2000-2004. Done because of day 0 problems
- All other outcomes: age- and VSD site-specific rates on Days 1-42 after Td in VSD historical data for 2000-2004.

Incidences, Inputs, and Statistical Power of MaxSPRT Analysis, by Outcome

				Statistical power	
Outcome	Range of age-specific background incidences per 100,000 in observation window*	Pre- specified upper limit of Expected events under H_0	Critical value of log-likelihood ratio corresponding to upper limit for alpha of 0.05	To detect RR of 1.5	To detect RR of 2
Encephalopathy, encephalitis, meningitis	4.0-8.9	30	3.72	60%	98%
Paralytic syndromes	7.2-21.9	80	3.92	94%	>99.99 %
Seizure	3.9-9.4	40	3.78	72%	>99.99 %
Cranial nerve disorders	6.5-34.9	100	3.96	98%	>99.99 %
Guillain-Barré Syndrome (GBS)	1.2-8.3	2.5	3.12	14%	29%

*For GBS the annual incidence from HCUP data was scaled to the 42-day observation window; for seizure the observation window is 0-7 days post-vaccination; for all other outcomes the window is 1-42 days post-vaccination.

MaxSPRT Output Example: Cranial Nerve Disorders



Results:
No Signals Observed after ~660,000 Tdap Doses

Outcome	Events observed	Events expected	RR	Log likelihood ratio (LLR)	Critical value of LLR
Encephalopathy, Encephalitis, Meningitis	18	30.53	0.59	0*	3.72
Paralytic syndromes	84	80.39	1.04	0.08	3.92
Seizure	34	40.24	0.84	0*	3.78
Cranial nerve disorders	122	101.3	1.2	1.99	3.96
Guillain-Barré syndrome (GBS)**	4	2.51	1.6	0.38	3.12

*The log likelihood ratio is set to 0 when the relative risk is <1
** Continued monitoring

Conclusions

- Adequate power to determine 1.5 or 2 relative risk over background for
  - Encephalopathy, encephalitis, meningitis
  - Paralytic syndromes
  - Seizure
  - Cranial Nerve Disorder
- Inadequate power for GBS for relative risk of <5

Conclusions

- ~660,000 doses of Tdap administered over 145 weeks
- No evidence of increased risk of predetermined adverse events
  - Encephalopathy, encephalitis, meningitis
  - Paralytic syndromes
  - Seizure
  - Cranial Nerve Disorder
  - GBS

Acknowledgements

We thank the principal investigators of participating VSD sites, members of the VSD Rapid Cycle Analysis working group, and members of the VSD project for their contributions to this study.

*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.

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