Rapid Cycle Analysis for Early Detection of Vaccine Adverse Events

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for the
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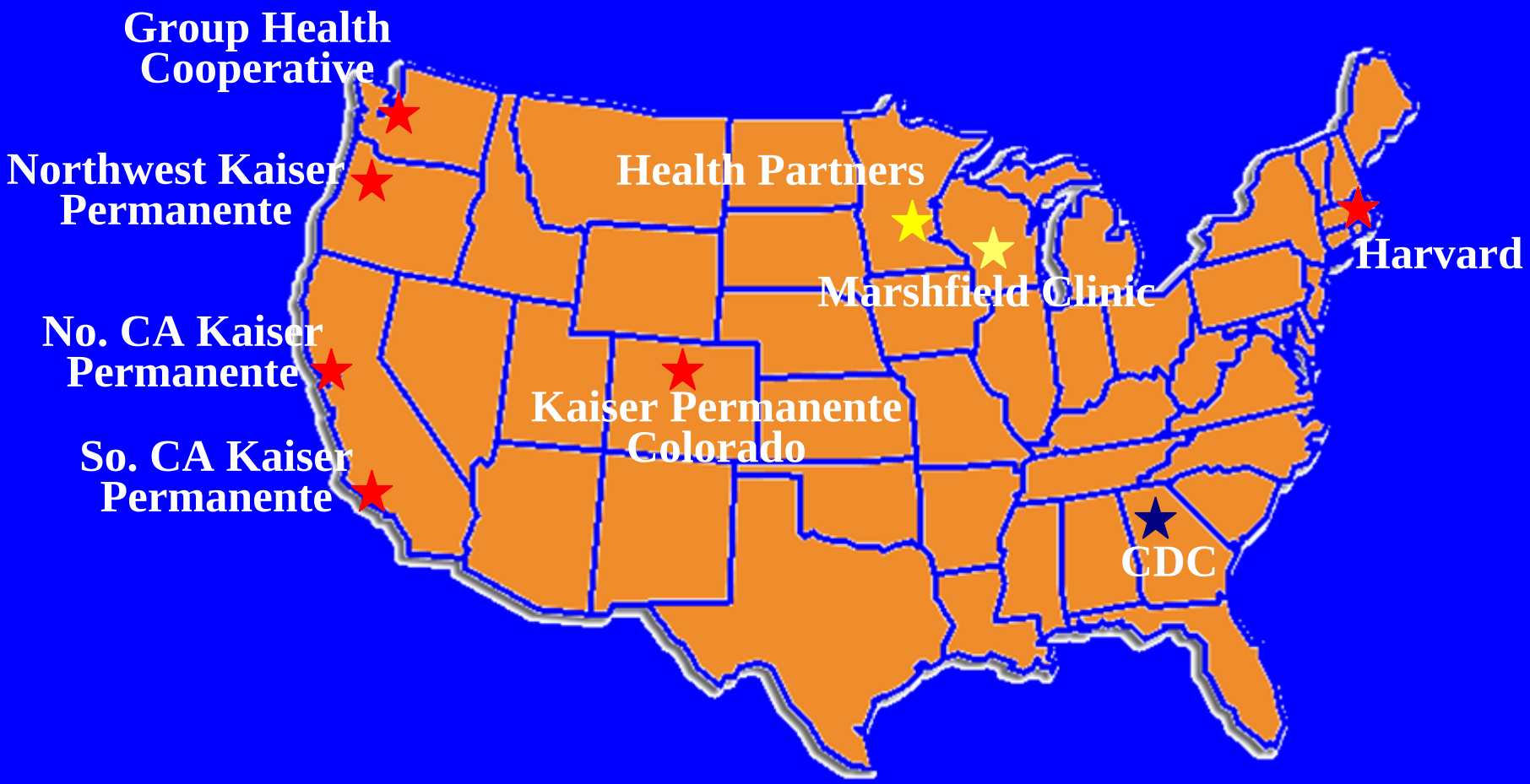
Why We Need Early Detection Systems in Vaccine Safety

- Rare adverse events may be impossible to detect in pre-licensure studies
- Reports to passive surveillance systems (e.g., the Vaccine Adverse Event Reporting System) often need rapid follow-up
- Follow-up studies can take months to years using traditional approaches

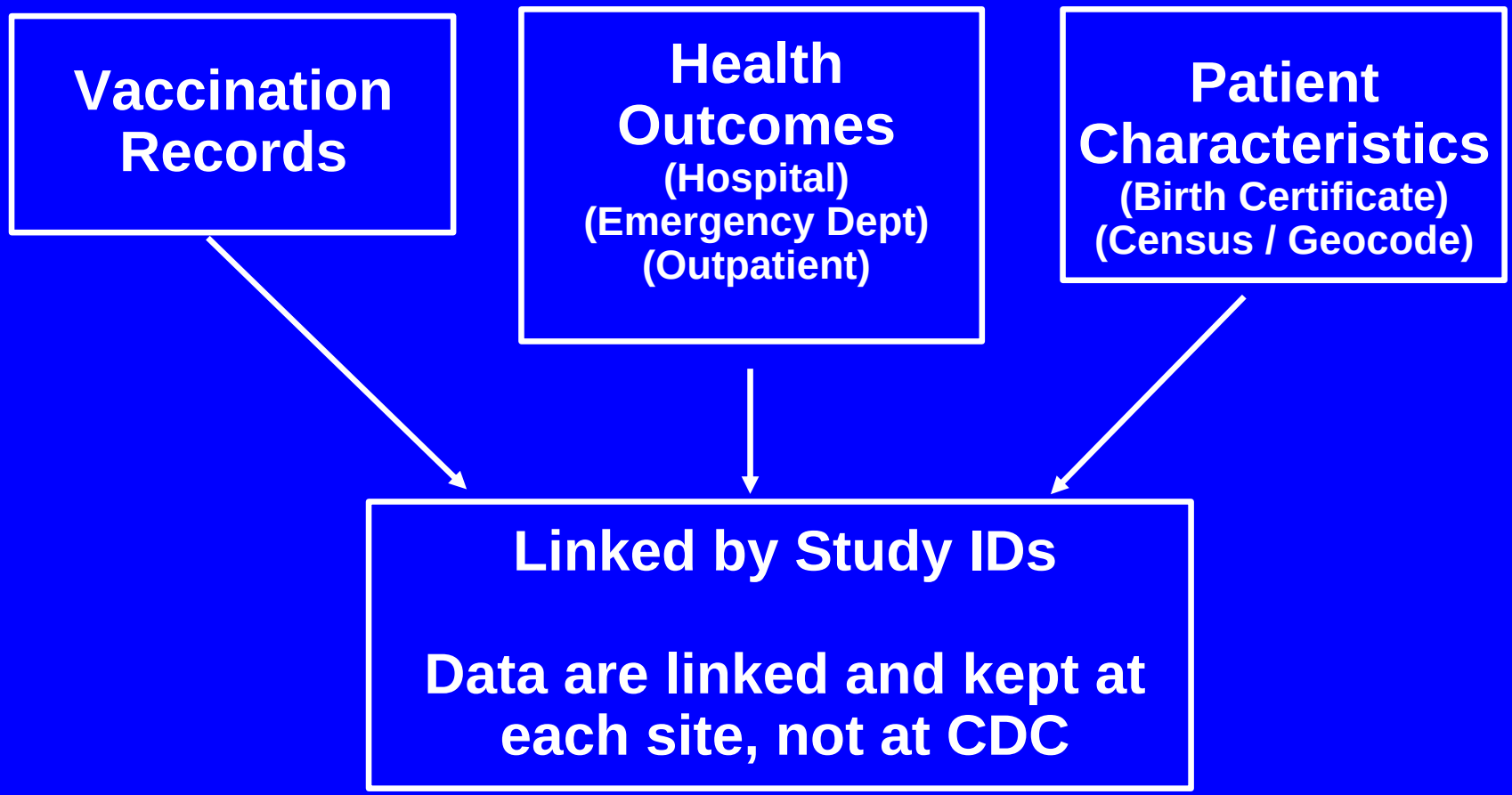
Vaccine Safety Datalink Project

- 8 health plans
- Data on >5.5 million persons annually
  ~ 1.9% of U.S. population
- At the end of 2005:
  - 2.3 million children
  - 3.2 million adults
  - Birth cohort = 94,000

Vaccine Safety Datalink Sites



VSD Data


Vaccination Records
Health Outcomes
(Hospital)
(Emergency Dept)
(Outpatient)
Patient Characteristics
(Birth Certificate)
(Census / Geocode)
Linked by Study IDs
Data are linked and kept at each site, not at CDC

Rapid Cycle Analysis

- A new approach to surveillance that takes advantage of VSD's strengths
- VSD now updates data on all vaccines and all outcomes every week
- We conduct updated analyses every week

Ongoing Surveillance via Rapid Cycle Analysis of VSD Data

- **Menactra – for Guillain-Barre syndrome**
- **Rotateq – for intussusception, gastrointestinal bleeding, other outcomes**
- **MMRV and Tdap – for seizures and other outcomes**
- **HPV and influenza – being implemented**

Collaborators – partial list

- James Baggs, CDC
- Roger Baxter, NCK
- Bob Davis, CDC
- Bruce Fireman, NCK
- Rich Fox, HAR
- Paul Gargiullo, CDC
- Julianne Gee, CDC
- Jason Glanz, CDC
- Sharon Greene, HAR
- Nicky Klein, NCK
- Margarette Kolczak, CDC
- Martin Kulldorff, HAR
- Ned Lewis, Kaiser
- Renny Li, HAR
- Dave McClure, KPC
- Jennifer Nelson, GHC
- Rich Platt, HAR
- Irene Shui, HAR
- Eric Weintraub, CDC
- Katherine Yih, HAR
- Ruihua Yin, HAR

GHC, Group Health Cooperative; HAR, Harvard; KPC, Kaiser Permanente Colorado; NCK, Northern California Kaiser

Basics of Rapid Cycle Analysis

- For each vaccine, choose specific outcomes to monitor
- Hypothesis testing, not data mining
- Each week, evaluate the number of outcomes in vaccinated persons
- Compare it to the expected number of outcomes based on a comparison group

Sequential Analysis Methods

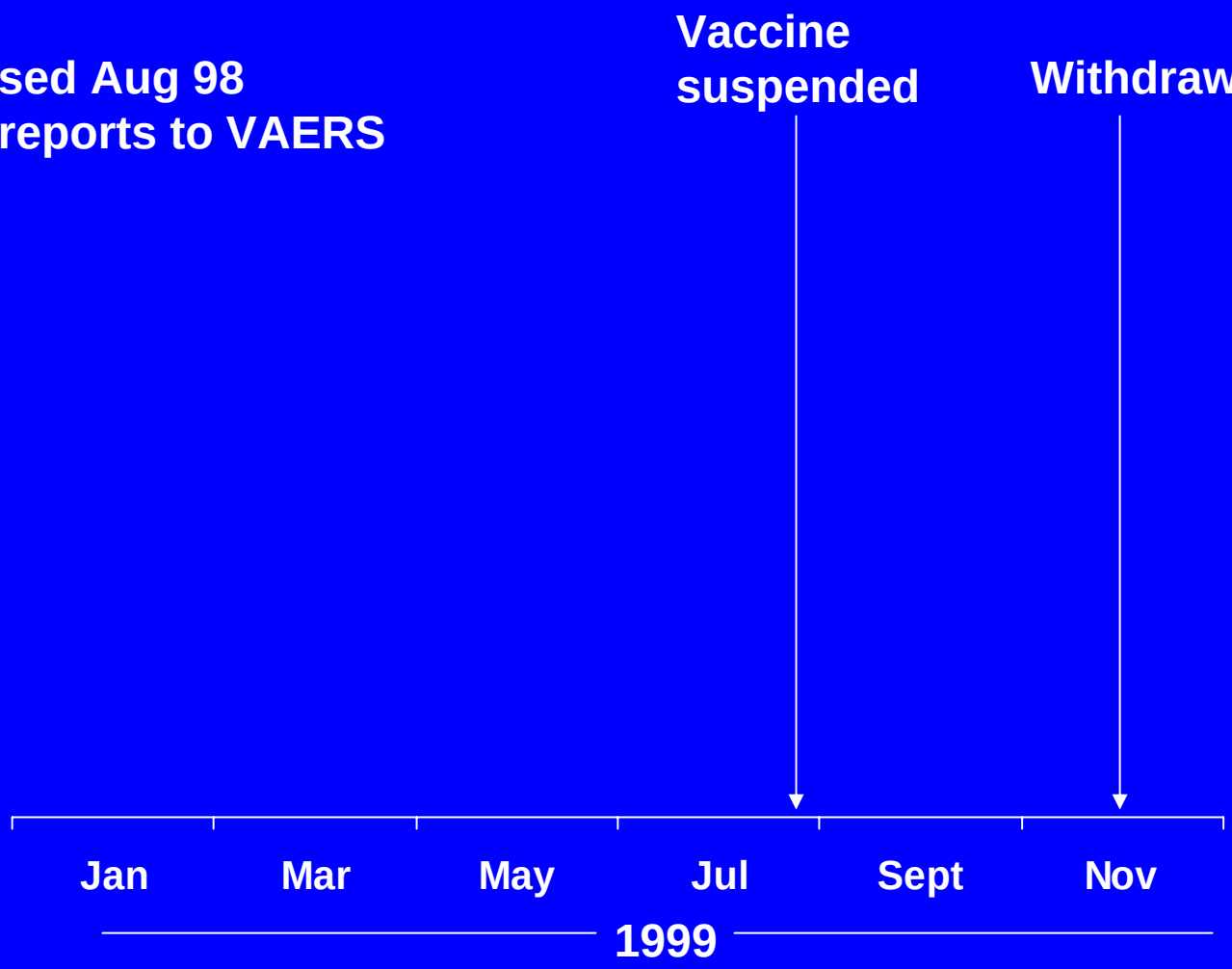
- Each week, our analysis includes data from all previous weeks
- Problem: Repeated testing of the same data increases the chance of false-positive results
- Need to adjust for this statistically
- Solution: Maximized sequential probability ratio testing

Maximized Sequential Probability Ratio Testing (maxSPRT)
(Kulldorff et al., 2004)

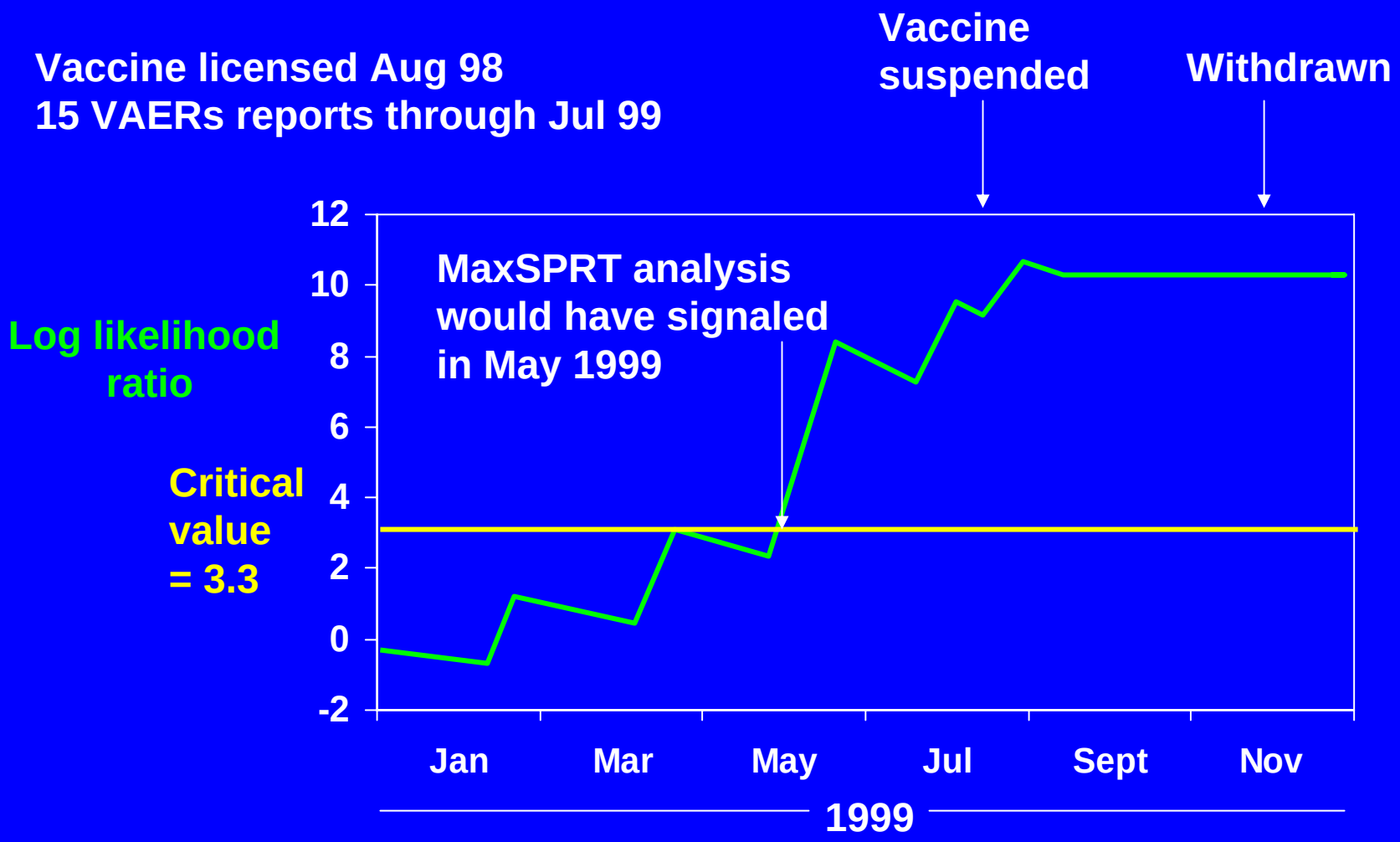
- A refinement of a classical statistical method (Wald, 1945)
- Null hypothesis – No excess risk
- Alternative hypothesis – Increase in risk
- The test statistic is the log likelihood ratio -- depends on the observed vs. expected number of events

Example: Rotashield® vaccine and intussusception (historical analysis)

Vaccine licensed Aug 98
By Jul 99, 15 reports to VAERS



Example: Rotashield® vaccine and intussusception (historical analysis)



Setting Up A Rapid Cycle Analysis

- Choose outcomes to monitor
- Choose comparison method(s) – e.g., historical, concurrent
- Set the upper limit for when to stop

Choosing Outcomes

- RCA is hypothesis testing, not data mining

1. Select outcomes based on:
   a. Pre-licensure data
   b. Known biologic properties of the vaccine
   c. Early analyses from VAERS

Choosing Outcomes for Hypothesis Testing

2. Additional criteria
   - Clearly defined
     - e.g., Guillain-Barre syndrome rather than “neurologic problems”
   - Acute-onset
   - Plausible
   - Relatively uncommon
3. Do extensive preliminary testing of the sets of ICD9 codes

Historical Comparison Method

- **Uses incidence rates from historical data**
  - **Advantage: Knowing the historical rate of rare events allows earlier recognition that a small number of cases is unusual**
  - **Example: 4 cases of Guillain-Barre syndrome in vaccinees, 0 expected**
  - **Limitation: Background rates may vary over time (secular trends)**

Concurrent Comparison Method

- Uses matched controls, e.g., patients making preventive visits
  - Advantage: Avoids false signaling or missed signals due to secular trends
  - Limitations:
    - Need to define an appropriate control group – not simple!
    - Vaccines may be adopted rapidly, leaving few controls

Comparison Groups

Menactra®	Teens making preventive visits
Rotateq®	Infants who received any other vaccine
MMRV	Toddlers who received MMR or MMR+V
Tdap	Teens who received Td
HPV	Female teens and 18-26 yr old females with preventive visits

What Happens When a Signal Occurs?

- Rapid cycle analysis methods detect signals – values above specified statistical thresholds
- Not all signals represent a true increase in risk
- When a signal occurs, we conduct a series of evaluations using traditional epidemiologic methods

How We Evaluate Signals – 1

1. Check data quality
2. Check whether comparison groups are defined appropriately
3. Conduct the analysis using a different control group (e.g., concurrent vs. historical) or different vaccine

How We Evaluate Signals – 2

4. Conduct a temporal scan to see if outcomes cluster during a post-vaccination time window

5. Conduct a definitive study using logistic regression analysis

6. Review charts to confirm or exclude cases as true cases

Example of Signal Evaluation: Rotateq® and GI bleeding

- Nov 2006 – 6 GI bleeding diagnoses had occurred among 3,400 vaccine recipients, vs. 1.3 expected from the historical incidence rate
- RR 4.7, LLR 4.6 → Signal
- Problem – Historical incidence rate hadn't been adjusted for age and secular trend
- Resolution – signal disappeared

Example of Signal Evaluation: Rotateq® and GI bleeding

- Feb 2007 – 36 GI bleeding diagnoses had occurred among 27,000 vaccine recipients, vs. 18 expected from the historical incidence rate
- RR 2.0, LLR 6.7 → Signal

Example of Signal Evaluation: Rotateq® and GI bleeding

1. A maxSPRT analysis was run comparing recipients of other vaccines (who hadn't received Rotateq) with the historical incidence rates – still signaled

2. A maxSPRT analysis was run comparing Rotateq recipients with a concurrent comparison group (children with other vaccines) – no signal

Example of Signal Evaluation: Rotateq® and GI bleeding

3. Definitive analysis – logistic regression comparing Rotateq® recipients with the concurrent comparison group – no signal
   - Age, seasonality, and VSD site were associated with GI bleeding
   - Rotateq® exposure was not
- Conclusion – No true increase in risk

Context

- Rapid cycle analysis is relatively new
- The outcomes to be studied need to be chosen thoughtfully
- Signals do not always represent true increases in risk
- When a signal occurs, we conduct traditional epidemiologic studies

Rapid Cycle Analysis – Next Steps

- VSD plans to implement surveillance whenever a new vaccine is introduced
- Statistical methods have been described in publications
- Protocol for evaluating signals is in use
- Findings will be communicated on a routine basis

References

Davis RL, Kolczak M, Lewis E, et al. Active surveillance of vaccine safety: a system to detect early signs of adverse events. Epidemiology 2005;16:336-41

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

Kulldorff M, Davis RL, Kolczak M, et al. A maximized sequential probability ratio test for drug and vaccine safety surveillance. Unpublished data being submitted for publication.

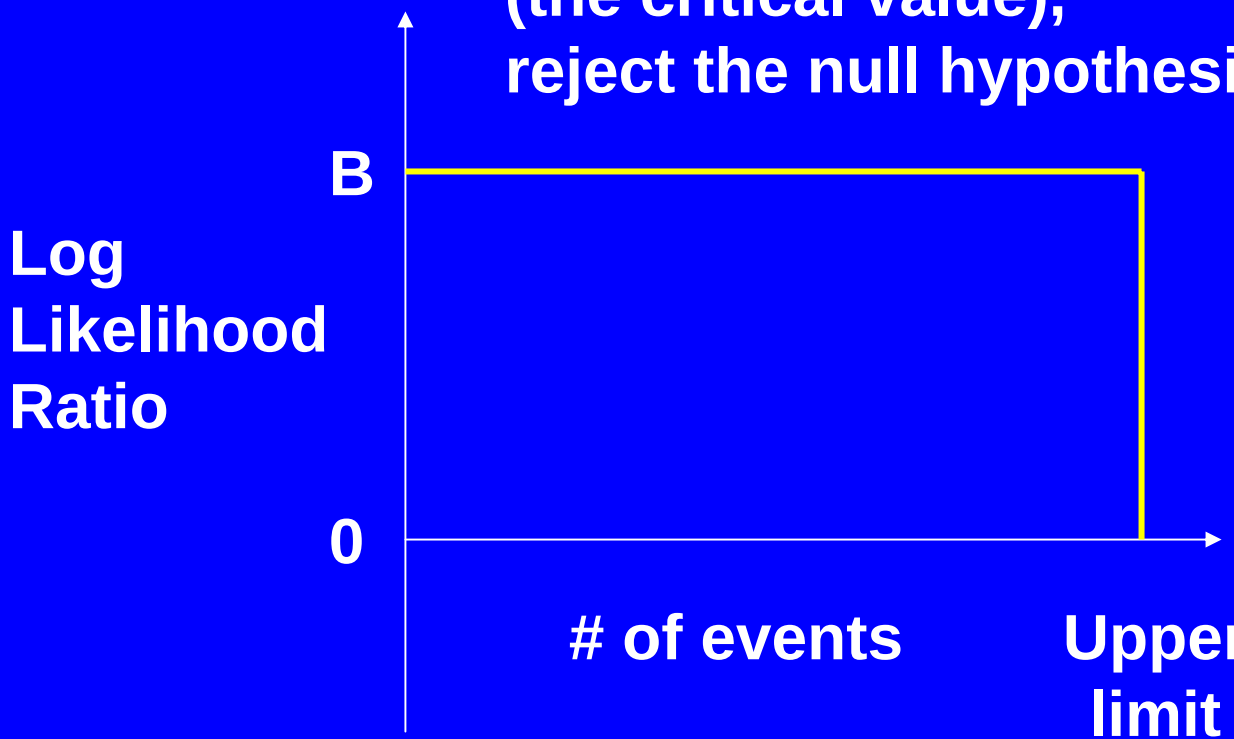
Extra Slides Follow

Why Do We Need to Set an Upper Limit in Advance?

- Using maxSPRT, the criterion for signaling depends on how many observed or expected events you want to accrue before you stop
- The upper limit is defined as this number of events

When the Analysis Should End

1. If the LLR exceeds B (the critical value), reject the null hypothesis



2. When the # of events exceeds the upper limit, reject the alternative hypothesis

RCA Uses VSD's Distributed Data Model

1. CDC or VSD sites use centrally created programs that run at the sites to create the files of interest
2. These files contain only aggregated data, not individual-level data (and NO PHI)
3. When needed, the VSD sites can access individuals' electronic and paper medical records

Aggregated Data Files of Exposures and Outcomes

1. Vaccine visits
2. Comparison visits
3. Outcomes within defined time windows after the exposures

- Each file is created separately for each site
- Each line represents a different combination of week, age, and sex

Maximized SPRT

Log likelihood ratio test statistic at time t:

$$\mathrm{LLR(t)} = \max_{\mathrm{RR}>1} \ln\left(\prod_{\mathrm{i}=1}^{t} \frac{\mathrm{P}(\mathrm{c_i} \mid H_A(RR))}{\mathrm{P}(\mathrm{c_i} \mid H_0)} \right)$$

where c_i = the observed number of events at time i

Reject H0 when LLR(t) > B, the critical bound
Reject HA when t > T

Specify alpha and T in advance, calculate B.