Current (+ Future) Vaccine Safety Data Sources

Robert T. Chen MD, MA
Vaccine Safety and Development Activity
National Immunization Program
Outline

- Current data sources
  - Pre-licensure
  - Post-licensure
- Strengths and weaknesses
- New/potential data sources
IOM Vaccine Safety Reports: 1991 + 1993

- 50/76 (66%) VAE evaluated: "None or inadequate evidence to accept or reject"
- "Many gaps and limitations" in current knowledge + research capacity:
  - Inadequate understanding of biologic mechanisms
  - Insufficient/inconsistent info from case reports
  - Inadequate size/follow-up of many epi studies
  - Existing surveillance limited in assessing causation
  - Few experimental studies
Life Cycle of a Vaccine Safety Concern

Case report → Standard assessment → Case series
- Plausibility
  - Alternative hypothesis
    + (Communications)

Controlled studies → Communications → Risk/benefit policy
- Societal
- Individual

Pathophysiology
- Treatment
- Compensation
- Safer vaccine
- Appropriate C/I
- Screening

Risk factors
Vaccine Safety Data: Pre-licensure

- Laboratory and animal studies
- Humans
  - Phases I: gross toxicity (N: ~ 10)
  - Phase II: dosing range/ reactogenicity (N: 10-100)
  - Phase III: efficacy (+ preliminary safety) (N: 1000-10,000)
- Advantages:
  - Close, detailed follow-up
  - Randomized double blind placebo-controlled design => causality assessment easy
- Disadvantage:
  - Poorly detected rxns: rare, delayed, subpopulations
  - Lack of standard case definition for “safety”
Vaccine Safety Data: Post-licensure

- Traditional tools
  - Passive surveillance (spontaneous reporting system)
  - Ad hoc controlled epidemiologic studies

- Newer tools
  - Phase IV trials “tied” to licensure of new vaccine: large-linked database (LLDB) in HMO (N ~10,000)
  - Pre-organized LLDB's in several HMO’s
    - Ongoing safety monitoring
    - Controlled epidemiologic studies
**Vaccine Adverse Event Reporting System**

24 Hour Toll-free information line 1-800-822-7967  
P.O. Box 1100, Rockville, MD 20849-1100  
**Patient Identity Kept Confidential**

<table>
<thead>
<tr>
<th><strong>Patient Name:</strong></th>
<th><strong>Vaccine administered by (Name):</strong></th>
<th><strong>Form completed by (Name):</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Last</strong></td>
<td><strong>Responsible</strong></td>
<td><strong>Relation</strong></td>
</tr>
<tr>
<td><strong>First</strong></td>
<td><strong>Physician</strong></td>
<td><strong>Vaccine Provider</strong></td>
</tr>
<tr>
<td><strong>M.I.</strong></td>
<td><strong>Facility Name/Address</strong></td>
<td><strong>Patient/Parent to Patient</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Address</strong></td>
<td><strong>Manufacturer</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Other</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Address (if different from patient or provider)</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>City</strong></th>
<th><strong>State</strong></th>
<th><strong>Zip</strong></th>
<th><strong>City</strong></th>
<th><strong>State</strong></th>
<th><strong>Zip</strong></th>
<th><strong>City</strong></th>
<th><strong>State</strong></th>
<th><strong>Zip</strong></th>
</tr>
</thead>
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<table>
<thead>
<tr>
<th><strong>Telephone no. (___)</strong></th>
<th><strong>Telephone no. (___)</strong></th>
<th><strong>Telephone no. (___)</strong></th>
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<tbody>
<tr>
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<table>
<thead>
<tr>
<th><strong>1. State</strong></th>
<th><strong>2. County where administered</strong></th>
<th><strong>3. Date of birth (mm/dd/yy)</strong></th>
<th><strong>4. Patient age</strong></th>
<th><strong>5. Sex M/F</strong></th>
<th><strong>6. Date form completed (mm/dd/yy)</strong></th>
</tr>
</thead>
<tbody>
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<thead>
<tr>
<th><strong>7. Describe adverse event(s) (symptoms, signs, time course) and treatment, if any</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>8. Check all appropriate:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient died (date mm/dd/yy)</td>
</tr>
<tr>
<td>Life threatening illness mm/dd/yy</td>
</tr>
<tr>
<td>Required emergency room/doctor visit</td>
</tr>
<tr>
<td>Required hospitalization (days)</td>
</tr>
<tr>
<td>Resulted in prolonged hospitalization</td>
</tr>
<tr>
<td>Resulted in permanent disability</td>
</tr>
<tr>
<td>None of the above</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>9. Patient recovered</strong></th>
<th><strong>10. Date of vaccination (mm/dd/yy AM/PM)</strong></th>
<th><strong>11. Adverse event onset (mm/dd/yy AM/PM)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>12. Relevant diagnostic tests/laboratory data</strong></th>
</tr>
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<tbody>
<tr>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>13. Enter all vaccines given on date listed in no. 10</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vaccine (type)</th>
<th>Manufacturer</th>
<th>Lot number</th>
<th>Route/Site</th>
<th>No. Previous doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>a.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>14. Any other vaccinations within 4 weeks prior to the date listed in no. 10</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Vaccine (type)</th>
<th>Manufacturer</th>
<th>Lot number</th>
<th>Route/Site</th>
<th>No. Previous doses</th>
<th>Date given</th>
</tr>
</thead>
<tbody>
<tr>
<td>a.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>15. Vaccinated at:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Private doctor's office/hospital</td>
</tr>
<tr>
<td>Military clinic/hospital</td>
</tr>
<tr>
<td>Public health clinic/hospital</td>
</tr>
<tr>
<td>Other/unknown</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>16. Vaccine purchased with:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Private funds</td>
</tr>
<tr>
<td>Military funds</td>
</tr>
<tr>
<td>Public funds</td>
</tr>
<tr>
<td>Other/unknown</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>17. Other medications</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>18. Illness at time of vaccination (specify)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>19. Pre-existing physician-diagnosed allergies, birth defects, medical conditions (specify)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>20. Have you reported this adverse event previously?</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>To health department</td>
</tr>
<tr>
<td>To doctor</td>
</tr>
<tr>
<td>To manufacturer</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>21. Adverse event following prior vaccination (check all applicable, specify)</strong></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>Only for children 5 and under</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</table>

<table>
<thead>
<tr>
<th><strong>22. Birth weight lb. oz.</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>23. No. of brothers and sisters</td>
</tr>
</tbody>
</table>

| Only for reports submitted by manufacturer/immunization project |
Passive Surveillance (e.g., VAERS)

Strengths

- National in scope
- Timeliness
- Relatively inexpensive/cost-effective
- Generation of hypotheses ("signals")
Passive Surveillance (e.g., VAERS) 

Weaknesses

- Underreporting (~ severity, timing, publicity, etc.)
- Biased reporting (~ severity, timing, publicity, etc.)
- Complexity >> traditional PH surveillance
  - multiple "exposures" + "outcomes"
  - detect "new" + change "known" AE's
  - mix of causal and coincidental events
- Inadequate report quality (opposite of clinical trial)
- Lack of denominators and control group
- Generally unable to address causality (test hypothesis)
Intussusception following Rotavirus Vaccine: Report Date by Week of Cases Reported to VAERS
## VAE Passive Surveillance Reporting Efficiencies*

<table>
<thead>
<tr>
<th>Event</th>
<th>Reports</th>
<th>MSAEFI</th>
<th>VAERS (Overall)</th>
<th>VAERS (Public sector)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAPP</td>
<td>13</td>
<td>72%</td>
<td>68%</td>
<td></td>
</tr>
<tr>
<td>Seizures (DTP)</td>
<td>2,184</td>
<td>42%</td>
<td>24%</td>
<td>36%</td>
</tr>
<tr>
<td>Seizures (MMR)</td>
<td>1,267</td>
<td>23%</td>
<td>37%</td>
<td>49%</td>
</tr>
<tr>
<td>HHE</td>
<td>1,465</td>
<td>4%</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>Rash</td>
<td>2,399</td>
<td>&lt;1%</td>
<td>&lt;1</td>
<td>5%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>39</td>
<td>&lt;1%</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>SIDS</td>
<td>419</td>
<td>55%</td>
<td>43%</td>
<td>36%</td>
</tr>
</tbody>
</table>

### Risk of Seizures Within 2 Days Following DTP4 vs. 1-3 Passive & Active Surveillance

<table>
<thead>
<tr>
<th>DTP Dose No.</th>
<th>Passive Surveillance</th>
<th>Active Surveillance</th>
<th>Active/Passive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MSAEFI</td>
<td>VAERS</td>
<td>VSD</td>
</tr>
<tr>
<td>1-3</td>
<td>2.8</td>
<td>2.7</td>
<td>9.7</td>
</tr>
<tr>
<td>4</td>
<td>9.3</td>
<td>8.6</td>
<td>36.3</td>
</tr>
</tbody>
</table>

Risk Ratio DTP4 vs 1-3

- MSAEFI: 3.3 (2.9, 3.7)
- VAERS: 3.1 (2.7, 3.6)
- VSD: 3.7 (1.2, 11.1)

N = reporting rate/100,000 doses distributed
Establishing Causal Link: Adverse Event and Vaccine

- Unique lab result
- Unique clinical syndrome
- Epidemiologic study
- (VAERS = biased cell "a")

<table>
<thead>
<tr>
<th></th>
<th>Illness or Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Yes</td>
<td>a</td>
</tr>
<tr>
<td>No</td>
<td>b</td>
</tr>
</tbody>
</table>

Vaccination

<table>
<thead>
<tr>
<th></th>
<th>Rate in vaccinated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>a/(a+b)</td>
</tr>
<tr>
<td>No</td>
<td>c/(c+d)</td>
</tr>
</tbody>
</table>

Rate in unvaccinated

<table>
<thead>
<tr>
<th></th>
<th>c/(c+d)</th>
</tr>
</thead>
</table>
Vaccine Safety Datalink (VSD) Project

- Collaboration between CDC & HMOs, 1991+:
  - GHC, Seattle, WA
  - NW Kaiser, Portland, OR
  - N CA Kaiser, Oakland CA
  - S CA Kaiser, Los Angeles CA
  - Colorado Kaiser, Denver CO (new)
  - Harvard Pilgrim, Boston MA (new)

- Total over 6 million members (~2% US popul)
VACCINE SAFETY DATALINK (VSD) DATA LINKAGES

Vaccination Records

Health Outcomes
(Hospital)
(ER)
(OPD)

Patient Characteristics
(Birth Tapes)
(Census)

VSD Linked Analysis Database
Statistical Analysis

- 1st dose
- 2nd dose
- 3rd dose

Vaccinated Child

Unvaccinated Child

- Risk interval ("exposed" person-time)
- Outside risk interval ("unexposed" person-time)

\[ IRR^* = \frac{IR(\text{risk interval})}{IR(\text{background})} \]

* Crude and adjusted (Poisson regression) for age
Risk of Seizure and Persistent Seizure Disorders Following DTP & MMR*, Vaccine Safety Datalink

*Controlling for Simultaneous Vaccine Administration
Vaccine Safety Datalink

Strengths

- infrastructure for vaccine safety studies
  - large cohort with unique study IDs
  - (mostly) pre-existing computerized administrative data
  - Followup diagnosis validation possible
  - incidence rates & attributable risks available
  - More timely & efficient vs. ad hoc epidemiologic study
Vaccine Safety Datalink

Weaknesses

• Dynamic HMO membership = dynamic cohort
• Timeliness (~1 year delay data tape preparation)
• More costly than basic passive surveillance
• Not large or diverse enough to test some hypotheses (e.g., GBS, thimerosal)
• Difficulty studying AE’s with insidious or delayed onsets, especially with universal vaccinations
Enhancing Vaccine Safety System: Pre-licensure Needs

- Data Safety Monitoring Board composition:
  need “rare” (vs. infectious) disease epi skill

- Large Simple Trial?

- Brighton Collaboration to standardize case definitions for “safety” = lack many AE’s
Enhancing Vaccine Safety System: Post-licensure Needs

- Brighton Collab: standardize case definitions
- Expand Vaccine Safety Datalink (VSD)
- VAERS reporting via web
- Clinical Immunization Safety Assessment (CISA) centers
- Artificial intelligence for signal detection
- Vaccine ID standards initiative (VISI)
- Safety => computer immunization registry
Clinical Immunization Safety Assessment (CISA) Centers: The Need

- Limits of pre-licensure trials => reliance on post-licensure for safety surveillance.
- Most common post-licensure surveillance: passive “spontaneous” reporting system.
- AE’s occur rarely => each reporter likely doing so 1st time => nonstandardized data.
  - unlike clinical trial.
  - data heterogeneity => interpretation difficult.
  - source of unnecessary conflict.
Clinical Immunization Safety Assessment (CISA) Centers

- **Tasks:**
  - Intensive study: person with true reactions.
  - Standard assessment => => new “syndrome X”?
  - Monitoring next dose in patients with severe AE.
  - Consultation for clinical safety questions + followup to track compliance & outcome.

- **Goal:**
  - Increase scientific knowledge of “outliers.”
  - Maximize utility of VAERS as “disease registry”.
  - Eventual regional distribution.
  - Disseminate protocols and findings via web.
Evaluation of “Artificial Intelligence” (AI) Commercial Software for Cluster Analysis

• Current method: crosstabs + persistent caller
• Use AI to aid ID of “patterns” by humans?
• Evaluation methodology:
  – Test datasets with artificially created patterns
  – “Test drive” on real-life VAERS data to detect known associations
  – Identify most user friendly software
• Rotavirus subset of VAERS data:
  – Report receipt date before July 1, 1999
  – 227 reports, 19 with INTUSS code
GBS Reports after Influenza Vaccination, VAERS, 1990 - 1997

No. GBS Reports

<table>
<thead>
<tr>
<th>Influenza Season</th>
<th>90-91</th>
<th>91-92</th>
<th>92-93</th>
<th>93-94</th>
<th>94-95</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>34</td>
<td>22</td>
<td>39</td>
<td></td>
<td>46</td>
</tr>
</tbody>
</table>

(CDC logo)
Adverse Event Reports After Infant (< 1 y.o.) Vaccination, by Received Vaccine Combination, U.S., 1985-98*

*1985-90: MSAEFI; 1991-98: VAERS

Year

DTP Doses (Million)
DTP VAERS (1,000s)
Total VAERS (1,000s)
Importance of Accurate Vaccination Records

- Individual => appropriate immunizations
- Population/Program = "exposure" for studies of:
  - vaccine safety
  - vaccine coverage
  - vaccine effectiveness/efficacy
Vaccine Identification Standards Initiative (VISI) (www.cdc.gov/nip/visi)

- Bar-coded Peel Off Sticker
  - EAN-UCC 128 coding symbology
  - Reduced Space Symbology (RSS)
Integrating Safety => Immunization Registries

- 1º goal: maintain/improve coverage
- Co-1º goal: enhance Vaccine Safety
  - timely + accurate reporting => VAERS
  - accurate denominators for rates
  - alert providers to potential contra-indications
  - timely advice/enrollment in AE studies
  - potential linkages to other databases
  - “Immunize smarter not just more”
Vaccine Safety Monitoring: Key Components

VACCINE SAFETY MONITORING
Maintain Public Confidence in Immunization Programs

VAERS
Hypothesis Generation
Could Vaccine Cause AE?

IOM
Hypothesis Evaluation
Level of PH Concern?

CISA
Hypothesis Clarification
Clinical Syndromes?

VSD
Hypothesis Testing
Did Vaccine Cause AE?

RISK COMMUNICATIONS
Disseminating Results

VACCINE DEVELOPMENT
Ensure New Safer Vaccines
Evolution of Immunization Program and Prominence of Vaccine Safety

1. Prevaccine
2. Increasing Coverage
3. Loss of Confidence
4. Resumption of Confidence
5. Eradication

Incidence

Maturity

- Disease
- Vaccine Coverage
- Adverse Events
- Outbreak
- Vaccinations Stopped
- Eradication
How to sustain (+ advance) mature national immunization programs?

- New chapter /challenge in human history
- Computerized immunization registries
- Education on benefits in absence of VPD
- Assessing and reducing immunization risks
  - Change paradigm in program goals: Reduce all disease: vaccine-induced + preventable
  - Need for immunization safety system
    - Best scientific data possible
    - Appropriate resources and staffing
    - Appropriate structural relationships
Assessment of VAERS as a Surveillance System*

- Simplicity and Flexibility
- Acceptability
- Sensitivity (Reporting Efficiency)
- Accuracy (Misclassification)
- Representativeness (Bias)
- Timeliness
- Cost
- Causality to Vaccine

Reporting Efficiency
Surveillance for Vaccine-Preventable Diseases

- Pertussis hospitalizations: 32
- Pertussis deaths: 33
- Tetanus deaths: 40
- Congenital rubella syndrome: 22
Criteria for Establishing Causality: (Bradford Hill, Modified)

- Coherence with existing info (biologic plausibility)
- Consistency of the association
- Specificity of the association
- Time sequence
- Strength of the association
  - Quantitative strength
  - Dose-response relationship (biological gradient)
  - Study design
## Common Causality Questions:

### Data Sources

<table>
<thead>
<tr>
<th>Question</th>
<th>Source of Data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Can It?</strong></td>
<td>Hill Criteria</td>
</tr>
<tr>
<td></td>
<td>Answer to <em>Did It?</em></td>
</tr>
<tr>
<td><strong>Did It?</strong></td>
<td>Individual case report</td>
</tr>
<tr>
<td><strong>Will It?</strong></td>
<td><em>Can It</em> $\Rightarrow$ <em>Yes</em></td>
</tr>
<tr>
<td></td>
<td>Individual (Risk factors)</td>
</tr>
<tr>
<td></td>
<td>Population (Attributable risk)</td>
</tr>
</tbody>
</table>
Rotavirus Vaccine: Background I

- Most common cause severe diarrhea
- Kapikian, 1986: rhesus reassortants + tetravalent vaccine (RRV-TV)
- 1988+: >10.5K vaccinated in trials
  - Efficacy: 50-68% (all), 64-91% (severe)
  - Safety:
    - mild: fever, irritability, loss appetite.
    - serious: intussusception?
      - 5/10,054 (0.05%) vaccinees, all dose 2 or 3
      - 1/4,633 (0.022%) placebo, p=NS
Seasonal Distribution – RV vs. intussusception

- RV diarrhea (n=1,513)
- Intussusception (n=539)

Rennels et al. PIDJ 1998
Rotavirus Vaccine: Background II

- 8/31/98 Licensure: W-L Rotashield
- 3/99 ACIP recommends universal infant
- Post-licensure surveillance:
  - Phase IV @ Northern California Kaiser (NCK)
  - Vaccine Adverse Event Reporting System (VAERS)
    - Centers for Disease Control and Prevention (CDC)
    - Food and Drug Administration (FDA)
- Intussusception =>
  - package insert
  - Gina Mootrey: COSTART (VAERS code)
Results: RRV-TV Surveillance, VAERS

- 9 cases of intussusception (IS)
  - 8/9 cases after dose 1
  - 8/9 cases within 1 week of vaccination
  - Median age 4 months
  - 5 required surgical intervention
- Nov. 1990 - Nov. 1998 VAERS
  - 3 cases IS reported following receipt of any other vaccine

=> May 15, 1999
Observed vs. Expected Intussusception Cases, VAERS, 7/99

• Assumptions:
  • 1.5 million doses administered
  • Background rate: 51/100,000 infant-years*

• Expect: 14-16 cases w/i 1 week of RV vax by chance

• Observe: 12/15 VAERS reports with onset < 1 week

• Know VAERS reporting sensitivity <<100%

* New York State Hospital D/C 1991-97
Intussusception Following RV Vaccine
VAERS 9/1/98-07/14/99

* N=18
Age Distribution of Intussusception

VAERS Reports Following Rotavirus Vaccination vs. Background Rates, VSD *

![Graph showing age distribution of intussusception with VAERS and VSD reports.](image)
## Intussusception and RV Vaccine
Northern California Kaiser, 12/1/98-6/17/99

<table>
<thead>
<tr>
<th>Exposed to RV Vaccine</th>
<th>Intussusception Cases</th>
<th>Rate per 100,000 infant-years</th>
<th>RR (95%CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>6</td>
<td>45</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>3</td>
<td>125</td>
<td>1.9 (7.7-0.4)</td>
<td>0.39</td>
</tr>
<tr>
<td>Past 3 Weeks</td>
<td>2</td>
<td>219</td>
<td>3.7 (0.7-19)</td>
<td>0.12</td>
</tr>
<tr>
<td>Past Week</td>
<td>1</td>
<td>314</td>
<td>5.7 (0.7-50)</td>
<td>0.11</td>
</tr>
</tbody>
</table>
RRV-TV Surveillance, MN

- Intussusception identified among infants:
  - ages 1-11 months
  - hospitalized with confirmed intussusception
  - vaccinated during 11/1/98-6/30/99 (62,916 doses sold)
- 5/18 cases were vaccinated
- age range vaccinated vs. unvaccinated: 3-5 vs. 5-9 months
- Onset- interval ranged from 6-14 days
- Assuming 85% of RV doses were used
  - rate w/i 1 week of vaccination = 292/100,000 infant-years
  - vs. NY State background = 51/100,000 infant-years
Summary of "Signal"

- VAERS:
  - ~ Same number of cases as expected by chance alone, assuming 100% reporting
  - Clustering of onset-intervals 3-5 days post-vax, consistent with biologic plausibility
  - Earlier "age-shift" in cases following RV compared to the background rate

- NCK: consistent
- MN: consistent
## Rotavirus Vaccine & Intussusception: Validation Studies

<table>
<thead>
<tr>
<th>Design</th>
<th>Setting</th>
<th>Peak RR (dose 1, 3-7 days)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case-control</td>
<td>19 states</td>
<td>35.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cohort</td>
<td>10 MCO's</td>
<td>31.0</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

**Notes:**
- **RR** refers to Relative Risk.