Rotavirus Vaccine Safety: US Postmarketing Experience

9th International Rotavirus Symposium
August 2, 2010
Johannesburg, South Africa

James Baggs, PhD
Immunization Safety Office
Centers for Disease Control and Prevention
Published Results


VAERS

- US Vaccine Adverse Event Reporting System

- National post-licensure passive surveillance system ("spontaneous reporting system") for vaccine adverse events operated by CDC and FDA

- Advantages
  - Covers US population
  - Permits monitoring for known AEs
  - Detects signals for previously unrecognized/rare AEs
  - Generates hypothesis

- Limitations
  - Risk of underreporting
  - Stimulated reporting due to media attention and other factors
  - Incomplete data
  - Lack of availability of denominator data
Post-licensure Monitoring of Intussusception in VAERS

- Monitoring does not indicate the observed number of confirmed reports to VAERS is greater than the expected number (RR=0.84, 0.61-1.17)
- Potential cluster within 1-7 days following vaccination after dose 1 (RR=1.71, 0.97-3.01)
Vaccine Safety Datalink (VSD)

Collaboration between CDC and 8 managed care organizations
Data from over 9 million members captured annually (3% of US population)
Vaccine Safety Datalink (VSD): Background

- Established in 1990
- A collaborative project among CDC and 8 managed care organizations (MCOs)
- Allows for planned immunization safety studies as well as timely investigations arising from
  - hypotheses from medical literature and pre-licensure
  - reports to the [Vaccine Adverse Event Reporting System (VAERS)](http://www.vaers.hhs.gov)
  - changes in immunization schedules, or the introduction of new vaccines
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
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
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®
# Outcome Ascertainment

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

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

** ED = Emergency department

Major Findings

• Five cases of IS within 30 days after RotaTeq® in the computerized data
  – Did not exceed expected
  – No cases within 7 days of vaccination
  – 207,621 doses included

• 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
Subsequent Analysis in VSD

- Continue surveillance for intussusception occurring 1-30 and 1-7 days after RotaTeq® vaccination
- 8 of 8 VSD sites participated
- Exposed population: children who received any dose of RotaTeq® (with or without other vaccines) from age 4 through 34 weeks
- Concurrent comparison group: children who received any immunization but not RotaTeq® from age 4-34 weeks
- Historical comparison group: age adjusted historical background rates of intussusception from VSD
- From May 2006 through May 2010
# Results of Continued Surveillance of IS 1-30 Days Following RotaTeq®

<table>
<thead>
<tr>
<th>Vaccine Dose</th>
<th>Age Range (weeks)</th>
<th>Exposed Visits</th>
<th>Exposed IS Cases 1-30 days</th>
<th>Unexposed Visits</th>
<th>Unexposed IS Cases 1-30 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-15</td>
<td>328,090</td>
<td>13</td>
<td>110,417</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>16-24</td>
<td>275,060</td>
<td>9</td>
<td>120,618</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>25-34</td>
<td>236,214</td>
<td>9</td>
<td>178,488</td>
<td>9</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>839,364</strong></td>
<td><strong>31</strong></td>
<td></td>
<td><strong>409,523</strong></td>
<td><strong>19</strong></td>
</tr>
</tbody>
</table>

* Through 05/31/2010

** Total includes only doses administered age range of 4 to 34 weeks for doses 1, 2, or 3
## Results of Continued Surveillance of IS 1-7 Days Following RotaTeq®

<table>
<thead>
<tr>
<th>Vaccine Dose</th>
<th>Age Range (weeks)</th>
<th>Exposed Visits</th>
<th>Exposed IS Cases 1-7 days</th>
<th>Unexposed Visits</th>
<th>Unexposed IS Cases 1-7 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-15</td>
<td>328,090</td>
<td>2</td>
<td>110,417</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>16-24</td>
<td>275,060</td>
<td>1</td>
<td>120,618</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>25-34</td>
<td>236,214</td>
<td>3</td>
<td>178,488</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>839,364</strong></td>
<td><strong>6</strong></td>
<td><strong>409,523</strong></td>
<td><strong>4</strong></td>
</tr>
</tbody>
</table>

* Through 05/31/2010

** Total includes only doses administered age range of 4 to 34 weeks for doses 1, 2, or 3
# Risk Ratios for IS 1-30 and 1-7 Days Following RotaTeq®

<table>
<thead>
<tr>
<th>Model</th>
<th>Risk Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>IS 1-30 Days Following RotaTeq®</td>
<td>0.81</td>
<td>0.44, 1.53</td>
</tr>
<tr>
<td>IS 1-7 Days Following RotaTeq®</td>
<td>0.81</td>
<td>0.19, 3.98</td>
</tr>
<tr>
<td>IS 1-30 Days Following RotaTeq®, Dose 1 only</td>
<td>1.46</td>
<td>0.40, 7.98</td>
</tr>
<tr>
<td>IS 1-7 Days Following RotaTeq®, Dose 1 only</td>
<td>0.67</td>
<td>0.04, 39.71</td>
</tr>
</tbody>
</table>

- Exact Poisson Regression controlling for age/dose strata
- Ages 4-34 weeks and doses 1, 2, 3
Limitations

• Cases have not yet been chart confirmed
  • Limiting to cases identified in the ER or hospital did not alter findings substantially

• Historical comparison not completed
  • However, we did identify potential temporal trends that will make the historical comparison challenging
Rates of Intussusception in the Vaccine Safety Datalink from 2001 through 2009

Year

Rates of IS per 100,000 PY

2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010

All Hosp Out

Legend:

- Green diamonds represent all cases.
- White squares represent hospital cases.
- Red triangles represent outpatient cases.
Summary

- US post marketing experience in VAERS and VSD provide no evidence that RotaTeq® receipt is associated with an increased risk for IS 1-30 days or 1-7 days following vaccination.
- Limited data available on Rotarix® in the VSD. Early analysis of VAERS data do not suggest any potential issues (FDA).
Acknowledgements

• Irene M. Shui, MPH
• Edward A. Belongia, MD, Stephanie A. Irving, MHS, Martin Kulldorff, PhD, Edwin Lewis, MPH, Rong Li, MSc, Tracy A. Lieu, MD, MPH, 4, Eric Weintraub, MPH, W. Katherine Yih, PhD, MPH, Ruihu Xia, MS
• Penina Haber, MPH, Umesh Parashar, MD, MPH, Manish Patel, MD, MPH
• 1 Department of Ambulatory Care and Prevention, Harvard Medical School and Harvard Pilgrim Health Care, Boston, MA
• 2 Marshfield Clinic Research Foundation, Marshfield, WI
• 3 Kaiser Permanente of Northern California, Oakland, CA
• 4 Division of General Pediatrics, Children’s Hospital, Boston, MA
• 5 Immunization Safety Office, Centers for Disease Control and Prevention, Atlanta, GA

• 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 official position of the Centers for Disease Control and Prevention.
Additional Slides
**Poisson maxSPRT Results: Intussusception (IS)**

<table>
<thead>
<tr>
<th>Dose</th>
<th>IS Events observed</th>
<th>IS Events expected</th>
<th>RR</th>
<th>Signal?</th>
</tr>
</thead>
<tbody>
<tr>
<td>All doses</td>
<td>5</td>
<td>6.75</td>
<td>0.74</td>
<td>NO</td>
</tr>
<tr>
<td>Dose 1</td>
<td>2</td>
<td>1.41</td>
<td>1.42</td>
<td>NO</td>
</tr>
<tr>
<td>Dose 2</td>
<td>2</td>
<td>2.76</td>
<td>0.72</td>
<td>NO</td>
</tr>
<tr>
<td>Dose 3</td>
<td>1</td>
<td>2.23</td>
<td>0.45</td>
<td>NO</td>
</tr>
</tbody>
</table>
## Rates of IS Following RotaTeq®

<table>
<thead>
<tr>
<th>Vaccine Dose</th>
<th>Age Range (weeks)</th>
<th>Exposed IS Cases 1-30 Days</th>
<th>Exposed IS Cases 1-7 days</th>
<th>Unexposed IS Cases 1-30 Days</th>
<th>Unexposed IS Cases 1-7 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-15</td>
<td>48.24</td>
<td>31.81</td>
<td>33.08</td>
<td>47.26</td>
</tr>
<tr>
<td>2</td>
<td>16-24</td>
<td>39.84</td>
<td>18.97</td>
<td>70.66</td>
<td>43.26</td>
</tr>
<tr>
<td>3</td>
<td>25-34</td>
<td>46.39</td>
<td>66.27</td>
<td>61.39</td>
<td>58.47</td>
</tr>
<tr>
<td>Total***</td>
<td></td>
<td>44.97</td>
<td>37.30</td>
<td>56.49</td>
<td>50.97</td>
</tr>
</tbody>
</table>

* Through 05/31/2010

** Rates per 100,000 PY

*** Total includes only doses administered age range of 4 to 34 weeks for doses 1, 2, or 3
## Results of Continued Surveillance of IS 1-30 Days Following RotaTeq®

<table>
<thead>
<tr>
<th>Vaccine Dose</th>
<th>Age Range (weeks)</th>
<th>Exposed Visits</th>
<th>Exposed IS Cases 1-30 days</th>
<th>Unexposed Visits</th>
<th>Unexposed IS Cases 1-30 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-15</td>
<td>328,090</td>
<td>7</td>
<td>110,417</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>16-24</td>
<td>275,060</td>
<td>7</td>
<td>120,618</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>25-34</td>
<td>236,214</td>
<td>8</td>
<td>178,488</td>
<td>5</td>
</tr>
<tr>
<td>Total**</td>
<td></td>
<td>839,364</td>
<td>22</td>
<td>409,523</td>
<td>11</td>
</tr>
</tbody>
</table>

* Through 05/31/2010, **limited to ER and hospitalized only**

** Total includes only doses administered age range of 4 to 34 weeks for doses 1, 2, or 3
## Results of Continued Surveillance of IS 1-7 Days Following RotaTeq®

<table>
<thead>
<tr>
<th>Vaccine Dose</th>
<th>Age Range (weeks)</th>
<th>Exposed Visits</th>
<th>Exposed IS Cases 1-7 days</th>
<th>Unexposed Visits</th>
<th>Unexposed IS Cases 1-7 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-15</td>
<td>328,090</td>
<td>1</td>
<td>110,417</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>16-24</td>
<td>275,060</td>
<td>1</td>
<td>120,618</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>25-34</td>
<td>236,214</td>
<td>2</td>
<td>178,488</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>839,364</strong></td>
<td><strong>4</strong></td>
<td><strong>409,523</strong></td>
<td><strong>2</strong></td>
</tr>
</tbody>
</table>

* Through 05/31/2010, limited to ER and hospitalized only

** Total includes only doses administered age range of 4 to 34 weeks for doses 1, 2, or 3