INTUSSUSCEPTION SURVEILLANCE

How hard should we look?
1999

• March:
  • Rotashield licensed
  • VAERS search term established for intussusception (IS)

• July:
  • 15 cases after 1.8 million doses of vaccine administered
    • 13 following 1\textsuperscript{st} dose; 12 within a week of Rotashield vaccine
  • \textbf{AAP/CDC Alert - Possible Association of IS with Rotashield}

• November:
  • Recommendation for use withdrawn

Set a new threshold for safety surveillance
  future candidates would look for an excess risk of 1 in every 10,000 recipients
Second Generation Vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Vaccine recipients</th>
<th>Placebo recipients</th>
<th>Risk window</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotarix (RV1)</td>
<td>6/31,673</td>
<td>7/31,552</td>
<td>31 days after each dose</td>
</tr>
<tr>
<td>Rotateq (RV5)</td>
<td>6/34,837</td>
<td>5/34,788</td>
<td>42 days after each dose</td>
</tr>
</tbody>
</table>

- Demonstrated futility of looking for small “time restricted” risks within the context of phase III trials
- Reasonable power only to pick up risks larger than those with the Rotashield vaccine.
Intussusception Incidence Rates

Jiang J et al; 2013
Intussusception Surveillance in India

Limited literature on intussusception surveillance

- Bahl, 2009: Population based passive surveillance in Delhi
  - *Incidence 18 per 100,000 (? data capture limited*)
- Bhowmick, 2009: Retrospective, hospital record based study at Vellore
  - *31 Level 1 cases in a 3 ½ year period*
- Nagpur and Lucknow, 75 cases over 3 years, no denominator

Bahl et al, JID 2009; Bhowmick et al, J Pop Health Nutr 2009; Awasthi et al, J Ped Child Health 2009
Rotavac Phase III Trial

- Pragmatic trial – to represent real life impact in a phase III trial
  - Community based recruitment
  - Community based follow up
  - Minimize exclusions to absolute contraindications
  - Geographically representative
  - Representative of Urban / Rural differences
  - C- administration of EPI vaccines and OPV
- Maximize the number of vaccine recipients to study safety
  - 2:1 ratio of vaccine: placebo
Rotavac Phase III Trial

- Safety concerns
  - A placebo controlled trial was ethically acceptable only when adequate measures to mitigate avoidable morbidity and mortality was in place
  - Health seeking is a complex phenomena – even when access to health is assured
  - Blood in stool and vomiting are relatively common childhood problems and parents may delay accessing care
Rotavac Phase III trial

- Intussusception surveillance primarily for participant safety
  - Ensuring early access to care imperative
- Very intensive screening for potential cases of intussusception.
  - All families provided a mobile phone
  - Access to 24*7 study team (call center)
  - Dedicated team evaluated GE & Suspected Intussusception
- Criteria were
  - Blood in stool OR
  - Vomiting more than 3 times in one hour OR
  - Abdominal lump OR
  - Abdominal distension
N = number of subjects; E = number of events; Excluded* = history of abdominal distension unaccompanied by increase in abdominal girth or another sign or symptom of intussusception; Not classified = inadequate information for classifying by Brighton criteria.
Rotavac Phase III Trial

1361 Possible intussusception events based on the trial screening criteria

• 914 in the Rotavac group and 447 in the placebo group
• 15% of all children screened by ultrasound
Rotavac Trial

- 1361 possible intussusception (suspected)
  - 15% of all children received an USG – some several times!
- 11 cases met Brighton level 1 criteria
  - 8 among vaccine recipients and 3 among placebo recipients
- All reduced conservatively
  - 6 pneumatically
  - 5 by barium
  - none required surgery
- The incidence rate of confirmed intussusception
  - Vaccine recipients 94/100,000 child-years (95% CI, 41 to 185)
  - Placebo recipients 71/100,000 child-years (95% CI, 15 to 206)

Temporal Profile of Intussusception Cases

John et al, Vaccine 2014,
Key observations – Rotavac surveillance

There were **no events** in the 7, 14, 28 day risk windows after any dose of vaccine

The first case in a vaccine **recipient** was **112 days** after the third dose

The first case in a placebo recipient was **36 days** after the third dose

Inadequate power to detect events of the magnitude noted in PMS with other rotavirus vaccines
Further observations

- Blood in stools was a trigger in 1179 events among 903 children.
- Several transient intussusception events were detected.
- Incidence of **ultrasound-diagnosed intussusception**
  - 200/100,000 child-years (95% CI, 120, 320) in the vaccine arm
  - 141/100,000 child-years (95% CI, 50, 310) among those receiving placebo.
Conclusions

• Large Phase III studies do not provide reasonable confidence to exclude small risks
• Risks larger than observed with Rotashield unlikely from available evidence
• Active search for intussusception reveals many transient intussusceptions as well as intussusceptions that received very early intervention
• How do these intussusceptions compare with other intussusceptions in similar settings?
  • Presentation
  • Interventions
  • Outcomes
PASSIVE HOSPITAL BASED SURVEILLANCE
The Vellore Experience..
## Passive, Hospital-based Surveillance

<table>
<thead>
<tr>
<th></th>
<th>Passive surveillance</th>
<th>Active surveillance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Period</strong></td>
<td>Jan 2010-Aug 2013</td>
<td>Apr 2011-Aug 2013</td>
</tr>
<tr>
<td><strong>Criteria for evaluation</strong></td>
<td>Presentation at hospital</td>
<td>Vaccine trial protocol</td>
</tr>
<tr>
<td><strong>Number</strong></td>
<td>61</td>
<td>16 (from 444 USGs)</td>
</tr>
</tbody>
</table>

Brighton level 1: 59 vs. 7

Brighton level 2: 2 vs. 6

No. requiring surgery: 31 (50.8%) vs. 0 (0%)

Non-operative reduction: 28 (45.9%) vs. 7 (43.8%)

Resolved spontaneously: 2 (3.3%) vs. 9 (56.2%)

Jehangir et al, Vaccine 2014
Comparison of vaccine trial and hospital based surveillance in Vellore

<table>
<thead>
<tr>
<th>Variable</th>
<th>Passive surveillance (n=59)</th>
<th>Active surveillance (n=16)</th>
<th>P value Fisher’s exact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence of intestinal obstruction</td>
<td>27 (45.8)</td>
<td>2 (12.5)</td>
<td>0.020</td>
</tr>
<tr>
<td>Evidence of intestinal ischemia</td>
<td>55 (93.2)</td>
<td>9 (56.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Conservative treatment before referral</td>
<td>31 (52.5)</td>
<td>1 (6.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Requiring intervention</td>
<td>57 (96.7)</td>
<td>7 (43.8)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Jehangir et al, Vaccine 2014
Lessons learnt

• An active surveillance system resulted in a safety net for intussusception and other illness, such that potentially serious illnesses were identified and managed early
• Despite the very active surveillance, no risk of intussusception greater than that seen with Rotashield was identified
• However, a number of IS events that resolved spontaneously were identified
• The IS cases seen in the trial were very mild compared to the IS cases who usually present to hospital in an area with excellent health care access, leading to questions about how comparable the cases detected in this trial might be to cases in other trials
Conclusions

Low-level intussusception risk has been detected in some settings.

Proven benefits of vaccination far outweigh potential short-term low-level risk.

Post marketing intussusception and rotavirus surveillance important for understanding risk-benefit balance.
Acknowledgements

• Investigators of the Rotavac trial
• Study teams
• The Intussusception Adjudication Committee
• The Data Safety and Monitoring Board
• Department of Biotechnology
• PATH
• Susan Jehangir and the Paediatric Surgery Department at CMC
• More information tomorrow at Sangeeth Rajkumar’s Presentation
QUESTIONS