Approaches to Assessing Intussusception Risk in Developing Countries

Jacqueline Tate
Centers for Disease Control and Prevention
Atlanta, GA, USA
Intussusception  
“Naturally Occurring” or Baseline  

- Etiology not well defined  
- Uncommon: 74 cases per 100,000 infants  
  - Incidence varies by region and age  
- Peak incidence coincides with age at vaccination
Global rates of intussusception

Jiang et al. PLOS one 2013
Baseline rate of intussusception varies substantially by age early in life

Tate et al. Pediatrics 2008
Intussusception and Rotavirus Vaccines

• **RotaShield** – introduced 1998 – United States
  – Tetravalant rhesus human reassortant vaccine
  – No risk of IS identified in clinical trials but post-licensure surveillance for IS recommended
  – Post-licensure evaluations identified association between RotaShield and IS
    • 1 excess cases of IS per every ~10,000 vaccinees

• **US Decision**
  – Safety concerns overshadowed benefit considerations
  – Risk of IS, though small, considered unacceptable
  – Vaccine withdrawn from the US market
Intussusception and Currently Available Rotavirus Vaccines (RotaTeq and Rotarix)

• No risk of IS identified in clinical trials
  – Pre-licensure trials large (60,000-70,000 infants each)……but powered to exclude relative risk of 10 within 0-42 days of any dose
  – Monitoring of hundreds of thousands of infants needed to exclude smaller risk

• Post-licensure evaluations performed in Australia, Brazil, Mexico, and United States
## Benefits vs. Risks of Vaccination

Estimated possible risk: 1-5 excess intussusception cases per 100,000 vaccinated infants

<table>
<thead>
<tr>
<th>Country</th>
<th>Diarrhea Hospitalizations (Deaths) Prevented</th>
<th>Intussusception Cases (Deaths) Caused</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mexico</td>
<td>11,600 (663)</td>
<td>41 (2)</td>
</tr>
<tr>
<td>Brazil</td>
<td>69,600 (640)</td>
<td>55 (3)</td>
</tr>
<tr>
<td>Australia</td>
<td>7,000 (0)</td>
<td>6 (0)</td>
</tr>
<tr>
<td>US</td>
<td>53,000 (16)</td>
<td>48 (0)</td>
</tr>
</tbody>
</table>
Use of rotavirus vaccines reaffirmed by regulatory agencies

• Post-licensure intussusception data reviewed by
  – WHO’s Global Advisory Committee on Vaccine Safety
  – Regulatory agencies and immunization advisory committees in many countries including US ACIP

• These groups unanimously reaffirmed the recommendation for use of rotavirus vaccine
  – Real-world benefits of vaccination including decreases in diarrhea mortality and hospitalizations far outweigh the possible short-term risk of intussusception
Why continue to monitor intussusception in developing countries?

• Sparse data on intussusception in these settings
  – Diagnostic differences and differences in access to care
• No large safety trials conducted in Africa or Asia
  – Rotavirus vaccines have modest efficacy but high rotavirus disease burden results in substantial impact
• Regional data needed for benefit-risk analyses
  – Studies to be conducted in several representative countries using common protocol
  – Useful to have benefit-risk data from same settings
Safety monitoring post-licensure

• Surveillance
  – Signal generation

• Hypothesis testing—observational studies
  – Cohort
  – Case-control
  – Case-series
Brighton Collaboration Case Definition
Level 1 of Diagnostic Certainty

**Surgical:** demonstration of invagination of the intestine at surgery;

and/or

**Radiologic:** demonstration of invagination of the intestine by either air or liquid contrast enema; or
demonstration of an intra-abdominal mass by abdominal ultrasound with specific characteristic features that is proven to be reduced by hydrostatic enema on post-reduction ultrasound;

and/or

**Autopsy:** demonstration of invagination of the intestine.
Surveillance

• **Observed cases of intussusception**
  – e.g.: reporting network – trends over time

• **Expected number of cases**
  – Baseline rate of intussusception
  – Number of children vaccinated (age-stratified)
  – **UNKNOWN in most settings**

• **Challenging for rare event and low level risk**
Other safety assessment options

• **Case-control**
  – Smaller sample size
  – Potential bias due to control selection and confounders
  – Logistical challenges of enrolling controls

• **Self-controlled case-series**
  – Combines power and simplicity of cohort
  – Economy of case-control
  – Reduced confounding
  – Uses only data on case-patients
  • Cases effectively act as own controls
What exactly is the case-series?
Simplified explanation

Incidence rate ratio = 1

Vaccination

Control Period  
RISK Period  
Control Period

Age in weeks
Real intussusception scenario: rates vary during age of vaccine recommendation
Baseline rate of intussusception in younger and older infants

IS Rate (per 100,000)

<table>
<thead>
<tr>
<th>Age of Child in Days</th>
<th>IS Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-90 days</td>
<td>10</td>
</tr>
<tr>
<td>90-180 days</td>
<td>30</td>
</tr>
</tbody>
</table>
Same **RELATIVE RISK** (2-fold) results in greater **ABSOLUTE RISK** in older infants.
Intussusception Onset after Dose 1 in Brazil versus Mexico
### Risk of Intussusception

<table>
<thead>
<tr>
<th>Dose</th>
<th>Risk window (days)</th>
<th>Cases</th>
<th>Incidence ratio (95% confidence interval)</th>
<th>Odds ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose 1</td>
<td>1-7</td>
<td>4 (1.2%)</td>
<td>1.2 (0.4 to 3.7)</td>
<td>1.4 (0.4 to 5.0)</td>
</tr>
<tr>
<td>Mexico</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose 1</td>
<td>1-7</td>
<td>24 (8.7%)</td>
<td>5.9 (3.4 to 10.5)</td>
<td>6.3 (2.8 to 14.4)</td>
</tr>
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</table>

**1 to 2 excess cases of IS per 100,000 children vaccinated**

*Case-series adjusted for age in 14 day interval; denominators used for risk-window percents include unvaccinated and cases >21 days; Case-series model only includes post-exposure intussusception events; total child-months of follow-up = 62.5 within 1-7 days and 2004 child-months for the cases outside the 1-21 day risk window*
Summary

• Post-marketing intussusception and rotavirus surveillance are important for understanding risk-benefit balance

• Low-level intussusception risk has been detected in some settings mainly during 1\textsuperscript{st} week after dose 1

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

• Additional data needed from developing country settings where benefit-risk balance may be different
  – Case-series approach offers an efficient mechanism to identify risk of intussusception