Rotavirus Vaccines and Intussusception – Benefit/Risk Considerations

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Rotavirus is the Leading Cause Of Severe Diarrhea in Children <5 Years Globally
The face of rotavirus

Diarrhea
Vomiting
Dehydration
Shock
Death
Rotavirus is a Major Cause of Child Mortality Worldwide -- ~200,000-250,000 Annual Deaths

1 dot = 150 deaths
Rotashield -- Implemented in 1998 in US
Setback in 1999 – Rotashield Withdrawn 1 Year Later Because of Intussusception

1 intussusception per 10,000 vaccinated infants
# Risks Versus Benefits of Rotashield in US

<table>
<thead>
<tr>
<th>Rotavirus</th>
<th>Number prevented by vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doctor Visits</td>
<td>400,000</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>50,000</td>
</tr>
<tr>
<td>Deaths</td>
<td>16-36</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intussusception</th>
<th>Number caused by vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>~300-600</td>
</tr>
<tr>
<td>Deaths</td>
<td>2-4</td>
</tr>
</tbody>
</table>
US Decision

• No data on real benefit of vaccine

• Risk of IS, though small, considered unacceptable

• Vaccine withdrawn from the US market
Further Test Rotashield in Developing Countries?

- 1 death in 250 children
- 600,000 deaths/yr

- 1 IS in 10,000 vaccinees
- ~ 10,000 severe IS cases
The View from Ethicists

• Benefits in developing countries far exceed risks

• Other RV vaccines may have same risk
  – ~2-3 million preventable rotavirus deaths in 5 years

• Inaction is not a morally neutral state
  – Culpability for deaths caused by withholding vaccine

• Applying US standards to the world in unjust
The Demise of Rotashield®

• Political challenges with using “tainted” vaccine in developing countries

• Vaccine manufacture stopped production

• Abrupt demise of first vaccine licensed after 20 years of research
Will other oral rotavirus vaccines also cause intussusception?
Two Oral Rotavirus Vaccines Licensed in 2006

- Trials of 60-70,000 infants each
- Efficacy of 85%-98% against severe disease
- No increased risk of intussusception

Vesikari et al and Ruiz-Palacios et al, NEJM 2006
Rotavirus Vaccine Introductions: 55 Countries

*National introductions by WHO region as of 5 May 2014
**Not a WHO member state
RV = rotavirus vaccine

**Not a WHO member state

- Armenia
- Austria
- Belgium
- Finland
- Georgia
- Germany
- Israel
- Luxembourg
- Moldova
- United Kingdom

- Bahrain
- Iraq
- Libya
- Morocco
- Qatar
- Saudi Arabia
- Sudan
- Yemen

- Australia
- Fiji
- Marshall Islands
- Micronesia
- Palau

- Angola
- Botswana
- Burkina Faso
- Burundi
- Cameroon
- Congo, Rep.
- Ethiopia
- The Gambia
- Ghana
- Madagascar
- Malawi
- Mali
- Rwanda
- Sierra Leone
- South Africa
- Tanzania
- Zambia
- Zimbabwe

Not GAVI-eligible [34]
GAVI-eligible [26]
Post-Licensure Intussusception Data

• Mexico, Brazil, Australia, and US have identified a low-level risk of intussusception after both vaccines
  – ~1-5 cases per 100,000 vaccinated

• Key Question – How does this level of risk compare with the observed benefits?
Impact on All-Cause and Rotavirus-Specific Gastroenteritis Hospitalizations in USA

Payne DC, unpublished 2014
### Age-Specific Rotavirus Hospitalization Rate Reduction and Vaccine Coverage, USA

<table>
<thead>
<tr>
<th>Age</th>
<th>Decline in rotavirus hospitalization rate (2008 vs. 2006)</th>
<th>Rotavirus vaccine coverage in 2008 (&gt;=1 dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 year</td>
<td>66%</td>
<td>56%</td>
</tr>
<tr>
<td>1 -&lt; 2 years</td>
<td>95%</td>
<td>44%</td>
</tr>
<tr>
<td>2 -&lt; 3 years</td>
<td>85%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

*This age cohort was ineligible to receive rotavirus vaccine*

**Herd Protection?**
Effect of Rotavirus Vaccination on Death from Childhood Diarrhea in Mexico

Number of diarrhea deaths
Month-Year
Age ≤11 months
Age 12-23 months
Age 24-59 months

Richardson et al, NEJM 2010
## Benefits vs. Risks of Vaccination

<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>
WHO Safety Committee – Dec 2013

• Risk of intussusception following administration of both rotavirus vaccines
  – in particular during the first 7 days following a first dose

• Attributable risk estimates vary across studies
  – differences in the background rate of intussusception
  – sampling uncertainty in all available estimates

• Overall, findings reassuring that intussusception risk remains small compared to benefits

WER Feb 2014
Age restrictions on rotavirus vaccination

Do not give first dose after 12-15 weeks of age
Rationale for Age Restriction
Age of immunization of US infants with DTP vaccine

*Tai et al. Pediatrics 2006*
Age of DTP1 Immunization in Developing Countries

Clark et al. Lancet 2009
Benefit risk of Strict vs. Free schedule in low income countries

**STRICT**
- *First dose by 12 weeks of age*

**FREE**
- *First dose by 1 year of age*

- Assume same timing as current DTP
- Efficacy lower than in high income countries
- Assumed hypothetical risk of IS
  - RR=6 for dose 1, 3 for dose 2
- 50% fatality rate for IS

*Patel et al. Plos Med 2013*
## Risk-Benefit With and Without Age Restrictions

<table>
<thead>
<tr>
<th></th>
<th>Vaccine-associated Intussusception Deaths</th>
<th>Rotavirus Deaths Averted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine by 15 weeks</td>
<td>288</td>
<td>156,100</td>
</tr>
<tr>
<td>No age restriction</td>
<td>605</td>
<td>199,200</td>
</tr>
</tbody>
</table>

No age restriction (vs. age restriction)  

317 additional IS deaths associated  

43,100 additional rotavirus deaths averted

*Patel et al. Plos Med 2013*
Estimated rotavirus deaths averted versus intussusception deaths associated if age restrictions are removed.

Median 136 lives saved per death caused (43,100 ÷ 316)

Median 317
WHO Safety Committee – June 2009

• In many developing countries, not all children receive immunizations according to recommended schedules
  – challenges of delivering timely immunization may be most acute in countries with high rates of early childhood mortality

• The Committee recommended expanding the age eligibility for vaccination in order to maximize coverage
  – Benefits would exceed risk
Does rotavirus vaccine increase intussusception risk overall?
Rotarix Clinical Trial

<table>
<thead>
<tr>
<th></th>
<th>Vaccine group</th>
<th>Placebo group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Safety cohort N=31,673</td>
<td>Safety cohort N=31,552</td>
</tr>
<tr>
<td></td>
<td>Efficacy cohort N=10,159</td>
<td>Efficacy cohort N=10,010</td>
</tr>
</tbody>
</table>

Cases of IS
0 → 31 days

- **Vaccine group**: 6 cases
- **Placebo group**: 7 cases

Relative Risk = **0.85 (0.30 ; 2.42)**

0 → 100 days

- **Vaccine group**: 9 cases
- **Placebo group**: 16 cases

Relative Risk = **0.56 (0.25 ; 1.24)**

0 → 1 year

- **Vaccine group**: 4 cases
- **Placebo group**: 14 cases

Relative Risk = **0.28 (0.1 ; 0.81)**

*Statistical significance indicated.*
Effect of rotavirus vaccination on trends in admission of infants to hospital for intussusception

L Simonsen et al
Lancet
Trends in Intussusception Hospitalizations among US Infants <12 Months of Age

Yen C, Tate J, Steiner C et al  J Inf Dis 2012 and Tate J et al, unpublished
Acknowledgements

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