Assessment of intussusception risk in Mexican infants under 9 months of age after administration of pentavalent rotavirus vaccine.

Background

• During its use in Mexico (2007-2010), RV1 was associated with intussusception
  – Risk: 5.8, (95%CI:2.6–13.0)
• Since 2011, Mexico shifted to RV5.
Objective

• Estimate the risk of intussusception with RV5 in Universal Immunization Program in México in the first 30 days after vaccination
Methods

• Self-Controlled Case Series
• Estimate intussusception risk after each dose of RV5.
• Active surveillance: 14 public hospitals through the country.
• Vaccination status determined by card or immunization records from health facilities.
• Relative incidence as measure of risk comparison
• Analysis in MS Excel, EpilInfo7 and R.
Selection criteria

• Inclusion
  – Age: ≥6 weeks & ≤ 8 months 29 days.
  – Brighton Collaboration criteria for definitive diagnosis of intussusception
  – Informed consent by parents

• Exclusion
  – Intestinal anatomical conditions
Results

• Included
  – 210 infants
  – 60% male
  – First, second and third RV5 doses received in 94%, 88%, and 78% respectively.

• Excluded
  – Anatomical conditions: 10
    • Meckel’s diverticulum 8, malrotation 1, colonic incomplete fixation 1
  – Participation not accepted by parents 5
  – No definitive diagnosis 3
Distribution by age of symptom onset

Age in weeks at symptom onset

Cases
Age in weeks

Age in weeks
6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40
Number of cases by age at vaccination before symptom onset (any dose) and by time of symptom onset after vaccination.
After first dose. 1 to 7 days.
R.I.: 3.6 (95% C.I.: 1.4-9.3, p=0.008).

Once adjusted by age effect and the presence of the other doses
After second dose. 22 to 31 days.
R.I.: 2.6 (95% C.I.: 1.5-4.4, p=0.001).
After third dose. 22 to 31 days.
R.I.: 2.8 (95% C.I.: 1.6-4.9, p<0.001).
Table 1. Age adjusted intussusception risk estimates by RV5 dose and time of symptom onset after vaccination

<table>
<thead>
<tr>
<th>Risk window. Days after Vaccination</th>
<th>Relative Incidence</th>
<th>95%CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 to 7</td>
<td>3.6</td>
<td>1.4-9.3</td>
<td><strong>0.008</strong></td>
</tr>
<tr>
<td>8 to 14</td>
<td>1.1</td>
<td>0.3-4.6</td>
<td>0.932</td>
</tr>
<tr>
<td>15 to 21</td>
<td>0.5</td>
<td>0.6-3.5</td>
<td>0.455</td>
</tr>
<tr>
<td>22 to 31</td>
<td>1.9</td>
<td>0.8-4.7</td>
<td>0.176</td>
</tr>
<tr>
<td><strong>Dose 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 to 7</td>
<td>1.3</td>
<td>0.5-3.5</td>
<td>0.666</td>
</tr>
<tr>
<td>8 to 14</td>
<td>0.8</td>
<td>0.2-2.4</td>
<td>0.632</td>
</tr>
<tr>
<td>15 to 21</td>
<td>2.2</td>
<td>1.1-4.4</td>
<td><strong>0.034</strong></td>
</tr>
<tr>
<td>22 to 31</td>
<td>2.6</td>
<td>1.5-4.4</td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td><strong>Dose 3</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 to 7</td>
<td>2.1</td>
<td>0.9-4.6</td>
<td>0.072</td>
</tr>
<tr>
<td>8 to 14</td>
<td>0.7</td>
<td>0.2-2.2</td>
<td>0.537</td>
</tr>
<tr>
<td>15 to 21</td>
<td>0.7</td>
<td>0.2-2.3</td>
<td>0.570</td>
</tr>
<tr>
<td>22 to 31</td>
<td>2.8</td>
<td>1.6-4.9</td>
<td><strong>&lt;0.001</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age in Days</th>
<th>Relative Incidence</th>
<th>95%CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age effect</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>113 to 217</td>
<td>12.0</td>
<td>6.4-22.6</td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td>218 to 274</td>
<td>12.2</td>
<td>6.1-24.7</td>
<td><strong>&lt;0.001</strong></td>
</tr>
</tbody>
</table>

Events=210. Rsquare= 0.053 (max possible= 0.266). Likelihood ratio test= 161.5 on 15 df, p=0. Wald test= 103.9 on 15 df, p=<0.0001. Score (logrank) test = 143.6 on 15 df, p=0.000
Applying the risk of three doses

To

• Proportions of intussusception incidence by age group reported for Mexico
• For the prevaccine incidence of intussusception in México
  – 2006
• And proportion of infants vaccinated at different ages:
  • 1 additional case / 7508 vaccinated infants,
    or
  • 295 vaccine-related cases / cohort of about 2 million
Conclusions

• Slight increase in risk after any dose of RV5.
• Possible reason for the observed risk increase in second and third doses
  – Some children received accelerated schedule: 6 weeks of age and next doses after 4 weeks intervals.
  – None infant with “accelerated” schedule developed intussusception within risk window after first dose.
Conclusions

• Additional cases attributable to RV5 (294 yearly) are surpassed by
  – 205,909 cases,
  – 11,662 hospitalizations and
  – 959 deaths

• Averted in México every year.