Post-marketing surveillance for Rotavirus Vaccines in Australia
Rotavirus Vaccines in the Australian National Immunization Program

• Birth cohort: 260,000/year

• Introduction of rotavirus vaccines into NIP: 1st July 2007

• National Immunization Program
  – Rotavirus vaccine coverage in the first 18 months of NIP
    • 87% eligible infants received at least one dose before 4 months
    • 84% eligible infants received a complete course

• Australian Childhood Immunization Register (ACIR)
  – Register of infant vaccines received
  – Incentive based registration
  – Estimated ~95% vaccines given are registered in ACIR
State-based differences in vaccine administration within the National Immunization Program

Initially Rotarix now RotaTeq

Yellow – States using Rotarix
Green – States using RotaTeq
Post-marketing surveillance activities

(1) ROUTINE PASSIVE ADVERSE EVENT REPORTING

Therapeutic Goods Administration

(2) ACTIVE INTUSSUSCEPTION SURVEILLANCE ACTIVITIES

APSU Intussusception Study
Australian Paediatric Surveillance Unit (APSU)

PAEDS Study
Paediatric Active Enhanced Disease Surveillance (PAEDS)

Additional State-based activities
Western Australia: Notifiable diseases
Northern Territory: Prospective IS Study (5 years)
Victoria: Institution and State based Study (20 years)
Monthly report card/ e-mail sent to ~1250 Australian paediatricians and surgeons from APSU: Reporting doctor completes a questionnaire detailing the case

All cases of acute IS in infants ≤ 24 months

All IS cases confirmed on *air/liquid contrast enema, ultrasound* or *surgery*

Temporal relationship between IS and receipt of a rotavirus vaccine

Clinical presentation, diagnosis, management of IS
PAEDS:
Paediatric Active Enhanced Disease Surveillance

- 4 Sentinel sites
- Nurse based surveillance
- Consent
- Access to:
  - Medical record
  - Australian Childhood Immunization Register
  - Path/radiology
  - GP records
Active Surveillance Studies: 
unique but complimentary

**APSU**
- **National** surveillance
  - Paediatricians
  - Surgeons
  - Emergency Room Dr
- Email/mail prompted reporting
- If report yes
  - mailed questionnaire
    - Date of birth, gender
    - Clinical details
    - Asked immunization status
- De-identified
  - No link to Australian Childhood Immunization Register

**PAEDS**
- 4 **Sentinel** sites in 4 States
- Nurse based surveillance
- Consent
- Access to:
  - Medical record
  - Australian Childhood Immunization Register
  - Path/radiology
  - GP records
Data analysis

- **Combined unique** patient data from PAEDS and APSU studies for each of the 4 States involved in **both** studies

- Period 18 months from commencement of National Immunization Program
  - 1\textsuperscript{st} July 2007 to 31\textsuperscript{st} December 2008

- Presented by vaccine, dose of vaccine, in 2 month age strata, in 0-7 day and 0-21 day post-vaccination risk window

- Comparison between observed vs expected IS rate
Calculation of expected Intussusception Rates

**BACKGROUND IS RATES**

- National data on all hospital admissions children less than 24 months
  *Australian Institute of Health and Welfare*
- Period July 2000- June 2006
- Age, region, outcome
- Background incidence estimated by no of cases divided by no of live births
  *Australian Bureau of Statistics*
- Incidence rates pooled for the 2 States administering RotaTeq in NIP and 2 States administering Rotarix in NIP

*Retno Palpuli & Katherine Lee, Murdoch Children’s Research Institute*
Calculation of *expected* Intussusception Rates

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**CHILD-TIME AT RISK**
- For the 4 States (*APSU and PAEDS*)
- Australian Childhood Immunization Register
- Number of children that received each vaccine by dose number
  *1st July 2007-31st December 2008*
- Time at risk for each child following each dose of vaccine (7 or 21 days) was assigned to month of age
Intussusception cases identified in 4 States with synchronous APSU and PAEDS surveillance

<table>
<thead>
<tr>
<th></th>
<th>APSU</th>
<th>PAEDS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>101 cases in 95 children</td>
<td>137 cases in 132 children</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>0-23 months of age</td>
<td>0-23 months of age</td>
</tr>
</tbody>
</table>

Duplicate notifications removed

Combined dataset (0-23 months of age)

- Ever received rotavirus vaccine
- 1st episode IS only

**Total: 92 cases**

<table>
<thead>
<tr>
<th>Days post-vaccine</th>
<th>1-7</th>
<th>8-21</th>
<th>&gt;21 (range post 21 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at IS (mths)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-&lt;3</td>
<td>6</td>
<td>4</td>
<td>4 (24-28)</td>
</tr>
<tr>
<td>3-&lt;5</td>
<td>4</td>
<td>5</td>
<td>10 (22-56)</td>
</tr>
<tr>
<td>5-&lt;7</td>
<td>0</td>
<td>3</td>
<td>19 (26-103)</td>
</tr>
<tr>
<td>7-&lt;9</td>
<td>0</td>
<td>1</td>
<td>19 (33-181)</td>
</tr>
<tr>
<td>9-&lt;12</td>
<td>0</td>
<td>0</td>
<td>11 (89-242)</td>
</tr>
<tr>
<td>&gt;12</td>
<td>0</td>
<td>0</td>
<td>6 (187-337)</td>
</tr>
</tbody>
</table>
## Observed and expected number of IS cases by age in months in jurisdictions delivering RotaTeq

<table>
<thead>
<tr>
<th>DOSE</th>
<th>AGE (months)</th>
<th>No. Vaccinated South Aust</th>
<th>No. Vaccinated Victoria</th>
<th>1 - 7 Days post-vaccine</th>
<th>1 - 21 days post-vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cases</td>
<td>Expected</td>
</tr>
<tr>
<td>1</td>
<td>1 - &lt; 3</td>
<td>24,924</td>
<td>86,629</td>
<td>3</td>
<td>0.57</td>
</tr>
<tr>
<td>1</td>
<td>3 - &lt; 5</td>
<td>876</td>
<td>2,413</td>
<td>0</td>
<td>0.04</td>
</tr>
<tr>
<td>1</td>
<td>5 - &lt; 7</td>
<td>156</td>
<td>460</td>
<td>0</td>
<td>0.01</td>
</tr>
<tr>
<td>1</td>
<td>7 - &lt; 9</td>
<td>36</td>
<td>163</td>
<td>0</td>
<td>0.01</td>
</tr>
<tr>
<td>2</td>
<td>1 - &lt; 3</td>
<td>24</td>
<td>108</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>3 - &lt; 5</td>
<td>20,329</td>
<td>70,112</td>
<td>2</td>
<td>1.5</td>
</tr>
<tr>
<td>2</td>
<td>5 - &lt; 7</td>
<td>1,794</td>
<td>6,285</td>
<td>0</td>
<td>0.19</td>
</tr>
<tr>
<td>2</td>
<td>7 - &lt; 9</td>
<td>163</td>
<td>476</td>
<td>0</td>
<td>0.02</td>
</tr>
<tr>
<td>3</td>
<td>1 - &lt; 3</td>
<td>1</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>3 - &lt; 5</td>
<td>32</td>
<td>144</td>
<td>0</td>
<td>0</td>
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<tr>
<td>3</td>
<td>5 - &lt; 7</td>
<td>15,933</td>
<td>55,061</td>
<td>0</td>
<td>1.71</td>
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<tr>
<td>3</td>
<td>7 - &lt; 9</td>
<td>2,154</td>
<td>7,742</td>
<td>0</td>
<td>0.29</td>
</tr>
<tr>
<td>TOTAL</td>
<td>1 - &lt; 9</td>
<td>66,422</td>
<td>66,422</td>
<td>5</td>
<td>4.36</td>
</tr>
</tbody>
</table>
Observed and expected number of IS cases by age in months in jurisdictions delivering Rotarix

<table>
<thead>
<tr>
<th>DOSE</th>
<th>AGE (month)</th>
<th>No. Vaccinated NSW</th>
<th>No. Vaccinated WA</th>
<th>1 - 7 Days post-vaccine</th>
<th>1 - 21 days post-vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cases</td>
<td>Expected</td>
</tr>
<tr>
<td>1</td>
<td>1 - &lt; 3</td>
<td>118,120</td>
<td>36,169</td>
<td>3</td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td>3 - &lt; 5</td>
<td>6,410</td>
<td>1,923</td>
<td>0</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>5 - &lt; 7</td>
<td>736</td>
<td>175</td>
<td>0</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>7 - &lt; 9</td>
<td>145</td>
<td>31</td>
<td>0</td>
<td>0.01</td>
</tr>
<tr>
<td>2</td>
<td>1 - &lt; 3</td>
<td>188</td>
<td>64</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>3 - &lt; 5</td>
<td>97,785</td>
<td>28,711</td>
<td>2</td>
<td>2.22</td>
</tr>
<tr>
<td></td>
<td>5 - &lt; 7</td>
<td>8,402</td>
<td>2,591</td>
<td>0</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>7 - &lt; 9</td>
<td>559</td>
<td>129</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TOTAL</td>
<td>1 - &lt; 9</td>
<td>232,620</td>
<td>69,835</td>
<td>5</td>
<td>3.16</td>
</tr>
</tbody>
</table>

* One case was recorded as occurring after 3 doses of Rotarix at 7 months of age
In Summary..........

• No evidence of an increased risk of IS following vaccination combining all doses to 9 months of age for either vaccine

• In infant 1 - < 3 months, there was a suggestive evidence of more IS cases 1 to 7 days and 1 to 21 days following dose 1
  
  1-7 days:
  • RotaTeq® RR = 5.3 (1.1,15.4)
  • Rotarix® RR = 3.5 (0.7,10.1)

  1-21 days:
  • RotaTeq® RR = 3.5 (1.3, 7.6)
  • Rotarix® RR = 1.5 (0.4, 3.9)

• No difference in clinical outcome in cases occurring within 21 days of vaccination
Key advantages and limitations

ADVANTAGES
• National active surveillance systems
• High rate of timely rotavirus vaccination within the National Immunization Program
• Australian Childhood Immunization Register reports vaccine administration with a high compliance rate ~95%
• State-based purchasing agreements allows comparison of Rotarix and RotaTeq within the National Immunization Program
• Established baseline data on intussusception in infants
• National hospital admission data – Australian Institute of Health and Welfare

DISADVANTAGES
• Limited period of surveillance of new vaccines (18 mo)
• Rare; small case numbers
• Calculation of expected rates based on 2000-6 data; reducing IS rates
Key advantages and limitations

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- National active surveillance systems
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DISADVANTAGES

- Limited period of surveillance of new vaccines (18 mo)
- Rare; small case numbers
- Calculation of expected rates based on 2000-6 data; reducing IS rates
- Potential reporting bias: APSU not PAEDS study
- Incomplete reporting: PAEDS sentinel site surveillance does not reflect all State cases but expected rate based on all State data

Victoria: Sentinel site captures between 41-69% of States cases, no bias in patient age or severity of disease based on State-based data
Why might the Australian experience differ from the US experience?

• Chance observation

• Differences in methodology
  • Australian Childhood immunization Register
  • National hospitalization data
  • Clinical management: inpatient vs outpatient, trends
Why might the Australian experience differ from the US experience?

- Chance observation
- Differences in methodology
- Regional differences in Intussusception incidence

![Incidence of acute intussusception in infants & children per 1,000 live-births or children <1 year]
Variation in “baseline” Intussusception rate in infants in different regions

<table>
<thead>
<tr>
<th>Country</th>
<th>IS hospitalization rate per 100,000 infants</th>
<th>Year</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panama</td>
<td>30.0</td>
<td>1998-2002</td>
<td>Saez-Lorens et al</td>
</tr>
<tr>
<td>United States</td>
<td>33.6</td>
<td>2001-2004</td>
<td>Tate et al</td>
</tr>
<tr>
<td>Venezuela</td>
<td>35.0</td>
<td>1998-2001</td>
<td>Perez-Schael et al</td>
</tr>
<tr>
<td>Switzerland</td>
<td>38.1</td>
<td>2003-2006</td>
<td>Buettcher et al</td>
</tr>
<tr>
<td>Latin America</td>
<td>51.0</td>
<td>2002</td>
<td>Abate et al</td>
</tr>
<tr>
<td>Chile</td>
<td>51.0</td>
<td>2000-2001</td>
<td>O’Ryan et al</td>
</tr>
<tr>
<td>New Zealand</td>
<td>65.1</td>
<td>1998-2002</td>
<td>Chen et al</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>66.0</td>
<td>1994</td>
<td>Gay</td>
</tr>
<tr>
<td>Taiwan</td>
<td>68.4</td>
<td>1999-2001</td>
<td>Ho et al</td>
</tr>
<tr>
<td>Denmark</td>
<td>68.8</td>
<td>2001</td>
<td>Kolsen-Fischer et al</td>
</tr>
<tr>
<td>Australia</td>
<td>81.0</td>
<td>2000</td>
<td>Justice et al</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>88.2</td>
<td>1997-1999</td>
<td>Nelson et al</td>
</tr>
<tr>
<td>Vietnam</td>
<td>302</td>
<td>2003</td>
<td>Bines et al</td>
</tr>
</tbody>
</table>
Variation in the proportion of IS infants treated with surgery

<table>
<thead>
<tr>
<th>Country</th>
<th>IS hospitalization rate per 100,000 infants</th>
<th>% treated by surgery</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panama</td>
<td>30.0</td>
<td>68</td>
<td>Saez-Lorens et al</td>
</tr>
<tr>
<td>United States</td>
<td>33.6</td>
<td>51</td>
<td>Tate et al</td>
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<tr>
<td>Venezuela</td>
<td>35.0</td>
<td>88</td>
<td>Perez-Schael et al</td>
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<tr>
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<td>38.1</td>
<td>23</td>
<td>Buettcher et al</td>
</tr>
<tr>
<td>Latin America</td>
<td>51.0</td>
<td>84</td>
<td>Abate et al</td>
</tr>
<tr>
<td>Chile</td>
<td>51.0</td>
<td>78</td>
<td>O’Ryan et al</td>
</tr>
<tr>
<td>Taiwan</td>
<td>68.4</td>
<td>31</td>
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</tr>
<tr>
<td>Vietnam</td>
<td>302</td>
<td>12</td>
<td>Bines et al</td>
</tr>
</tbody>
</table>
Is there any clinical implications of developing IS at a younger age?

Baseline IS data July 2001 – June 2006    Royal Children's Hospital
Conclusions

First 18 months following introduction of rotavirus vaccines into the National Immunization Program:

- Excellent uptake of vaccines (87% ≥1 dose, 84% complete course)
- Evidence of benefits of rotavirus vaccines
- Due to State-based purchasing arrangements ability to compare safety and effectiveness of Rotarix and RotaTeq within the NIP
- No increase in risk of IS at 12 months of age with either vaccine
- Increase relative risk of IS within the 0-7 day and 0-21 day post-vaccination risk window following dose 1
- The need to continue to encourage post-marketing surveillance for IS, particularly in regions with different baseline IS rates compared to US
Acknowledgements

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Sonja Ellia
Christine Heath
Marie Hobson
Christine Robins
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**CSL/Merck**

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