Health benefits versus intussusception risk of rotavirus vaccination in Australia

Julie Bines

On behalf of co-authors: John Carlin, Kristine Macartney, Katherine Lee, Helen Quinn, Jim Buttery, Ruth Lopert, Peter McIntyre

1. Murdoch Children’s Research Institute, Royal Children’s Hospital and University of Melbourne
2. National Centre for Immunisation Research and Surveillance, Children’s Hospital at Westmead, Sydney, and University of Sydney
3. Therapeutic Goods Administration, Canberra, Australia
Background: Australian context

- Australia: annual birth cohort ~ 300,000
  - total population ~23 million
- National Immunisation Program (NIP)
  - delivers all included vaccines free of charge
- RotaTeq and Rotarix funded by NIP since July 2007
  - Each State/Territory chose which vaccine to use
- Vaccine coverage increased rapidly\(^1\)
  - 85% (2 or 3 doses by age 12 months)
- Intussusception
  - Australian background rate pre-vaccine of ~80 per 100,000 in first year of life \(^2\) (double that reported from US)

\(^1\) Hull et al, *Vaccine* 2013; \(^2\) Justice et al *J Pediatr Child Health* 2005
Rotavirus vaccine use in Australian NIP
Commenced July 2007

Changed to RotaTeq in 2009
Early Australian data
July 2007-Dec 2008 (18 months post introduction)

• Data sources:
  – **PAEDS** (Paediatric Active Enhanced Disease Surveillance) network
    = active case ascertainment in 4 major paediatric hospitals
  – **APSU** (Australian Paediatric Surveillance Unit) = paediatrician reporting

• Analysis: Ratio of observed to expected cases
  – expected = (non-confirmed) ICD-coded hospitalisations for IS from routine database, infants 1-<3 month, for 4 states considered

• Results (based on $n = 92$ cases)
  – 1–7 days post dose 1
    • RotaTeq: 3 cases, RR 5.3 (95% CI 1.1, 15.4)
    • Rotarix: 3 cases, RR 3.5 (95% CI 0.7, 10.1)

¹ Buttery, Danchin et al, *Vaccine* 2011
Australia-wide study of rotavirus vaccines and IS, 2007-10
Background to this extended study

- Commissioned by Australian regulator (Therapeutic Goods Administration)
- IS cases nationwide
- Hospitalization databases (5 States/Territory)
  - IS-coded hospital discharges (ICD-10 code K56.1)
- Age range: infants 1-<12 months
- 3 year observation period: July 2007-June 2010
METHODS: IS data capture

• Supplementary case ascertainment
  – Prospective active hospital-based surveillance via PAEDS network (4 State paediatric hospitals)

  • 4'sentinel'sites
  • Nurse'based'active' surveillance
  • Consent
  • Access
    ○ UR
    ○ ACIR
    ○ Path/Radiology
    ○ GP'records
  • Stool'sample

• IS confirmed on chart review in all cases
  – confirmation of Brighton level 1 diagnostic certainty
METHODS: Vaccination Status

• Vaccination history obtained from Australian Childhood Immunisation Register (ACIR)
  – >98% coverage of vaccinations
  – Important: ascertainment of cases independent of vaccine status

• For case-control analysis:
  – ACIR used to identify age-matched controls (within 1 day of birth)
  – 10 controls per case randomly selected
  – Matched on gender, State
METHODS: Analysis

• Self controlled case-series (SCCS)
  – Conditional Poisson regression compares at-risk interval with other follow-up time, \textit{within individuals} (Farrington/Whitaker, 1996/2006)
  – Age adjustment critical
  – Multiple sensitivity analyses

• Case-control method
  – Conditional logistic regression within matched sets

• Both approaches: risk assessed for pre-specified periods post-vaccination
  – 1-7 days, 8-21 days
Summary of intussusception case ascertainment

State-based admissions data
- NSW = 108
- NT = 3
- QLD = 75
- VIC = 58
- WA = 38
  Total cases = 282

PAEDS data
- NSW = 53
- VIC = 44
- WA = 32
- SA = 24
  Total cases = 153

Combined dataset*
- NSW = 109 (1)
- NT = 3 (0)
- QLD = 75 (0)
- VIC = 69 (11)
- WA = 40 (2)
- SA = 24 (24)
  Total cases = 320 (38)

6 cases: no ACIR record found
8 cases: incomplete rotavirus vaccination record+

Cases for SCCS analysis
n = 306

5 cases: received both RV1 and RV5
10 cases: received non-standard vaccine for state

Cases for case-control analysis
n = 291
Primary results: SCCS \((n = 306\) cases of IS\)

<table>
<thead>
<tr>
<th></th>
<th>Dose 1, 1-7 days</th>
<th>Dose 1, 8-21 days</th>
<th>Dose 2, 1-7 days</th>
<th>Dose 2, 8-21 days</th>
<th>Dose 3, 1-7 days</th>
<th>Dose 3, 8-21 days</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RV1</strong></td>
<td>6.76 (2.40, 19.01)</td>
<td>3.45 (1.33, 8.94)</td>
<td>2.84 (1.10, 7.34)</td>
<td>2.11 (0.97, 4.62)</td>
<td>1.77 (0.81, 3.88)</td>
<td>0.56 (0.17, 1.82)</td>
</tr>
<tr>
<td><strong>RV5</strong></td>
<td>9.89 (3.70, 26.42)</td>
<td>6.32 (2.78, 14.37)</td>
<td>2.81 (1.16, 6.80)</td>
<td>1.77 (0.81, 3.88)</td>
<td>0.75 (0.18, 3.11)</td>
<td>0.56 (0.17, 1.82)</td>
</tr>
</tbody>
</table>

P values: <0.001, 0.011, 0.031, 0.061, <0.001, 0.022, 0.155, 0.688, 0.333
Results: case-control analysis

**RV1**

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>(95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose 1, 1-7 days</td>
<td>15.61</td>
<td>(3.36, 72.57)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dose 1, 8-21 days</td>
<td>6.48</td>
<td>(1.74, 24.16)</td>
<td>0.005</td>
</tr>
<tr>
<td>Dose 2, 1-7 days</td>
<td>2.44</td>
<td>(0.80, 7.47)</td>
<td>0.118</td>
</tr>
<tr>
<td>Dose 2, 8-21 days</td>
<td>1.35</td>
<td>(0.50, 3.63)</td>
<td>0.557</td>
</tr>
</tbody>
</table>

**RV5**

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>(95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose 1, 1-7 days</td>
<td>11.74</td>
<td>(3.18, 43.37)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dose 1, 8-21 days</td>
<td>4.65</td>
<td>(1.80, 12.00)</td>
<td>0.001</td>
</tr>
<tr>
<td>Dose 2, 1-7 days</td>
<td>2.53</td>
<td>(0.89, 7.20)</td>
<td>0.081</td>
</tr>
<tr>
<td>Dose 2, 8-21 days</td>
<td>1.38</td>
<td>(0.53, 3.62)</td>
<td>0.506</td>
</tr>
<tr>
<td>Dose 3, 1-7 days</td>
<td>1.06</td>
<td>(0.23, 4.84)</td>
<td>0.935</td>
</tr>
<tr>
<td>Dose 3, 8-21 days</td>
<td>0.80</td>
<td>(0.18, 3.64)</td>
<td>0.773</td>
</tr>
</tbody>
</table>
Risk-benefit assessment

Overall impact of rotavirus vaccines on morbidity
Rotavirus hospitalisations, Australia

For children <5 years:
71% ↓ in rotavirus admissions
~7,700 admissions averted per year

### Effect of a rotavirus vaccination program on rotavirus attributable gastroenteritis and IS in Australia

<table>
<thead>
<tr>
<th>Annual Hospitalisations in children &lt; 5 years of age</th>
<th>Without vaccination program</th>
<th>With vaccination program</th>
<th>Number of events averted or caused</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotavirus-attributable gastroenteritis #</td>
<td>11073</td>
<td>4545</td>
<td>- 6528</td>
</tr>
<tr>
<td>Vaccine-attributable intussusception *</td>
<td>144</td>
<td>158</td>
<td>+14</td>
</tr>
</tbody>
</table>
A success story for post-marketing surveillance
Policy/Practice Implications

• Benefit:Risk viewed as favorable by key Australian advisory committees (ATAGI, ACSOM – TGA)

• New estimates published in 10\textsuperscript{th} Edition Australian Immunisation Handbook, March 2013

• Advice to parents/providers updated

• Changes to vaccine product information via TGA
Summary

• **BENEFITS OF ROTAVIRUS VACCINATION**
  - Associated with 71% reduced rotavirus hospitalizations

• **INTUSSUSCESSION RISK**
  - Small level of risk of Intussusception
    • similar for Rotarix and RotaTeq
    • > after the first dose
    • Detected after dose 2
  - ~ 6 additional cases of IS per 100,000 vaccinated infants
  = 14 cases annually in Australian birth cohort

• **RISK BENEFIT** continues to be judged to be highly favorable by Australian policy-makers, healthcare providers and by parents
  - Vaccine uptake remains high
Acknowledgements and Conflicts of Interest

Acknowledgements

• Health authorities of New South Wales (Sue Campbell-Lloyd, Kathryn Cannings, Nicholas Wood, Sarah Moberley), Victoria (Rosemary Lester, Julie Quinn, Lalitha Sundaresan, Thao Nguyen), Queensland (Christine Selvey, Stephen Lambert, Madeline Hall), South Australia (Paul Basso), Western Australia (Paul Effler, Dale Carcione, Tracy Markus) and the Northern Territory (Vicki Krause, Heather Cook).

• Ruth Lopert was employed by the Therapeutic Goods Administration (TGA) when the study was initiated; subsequent support from the TGA was provided by Jane Cook.

• Thanks also to co-investigators of the Paediatric Active Enhanced Disease Surveillance (PAEDS) network (Peter Richmond, Christopher Blyth, Helen Marshall, Michael Gold, Nigel Crawford, Jenny Royle, Elizabeth Elliott, Robert Booy, Nicholas Wood, Yvonne Zurynski).

Funding sources and conflicts of interest

— Funding: Therapeutic Goods Administration (TGA), Australian Government Department of Health and Ageing (for PAEDS), NSW Ministry of Health

— Peter McIntyre has received in kind support for research conducted at NCIRS from GSK and Merck.
Sensitivity analyses – SCCS and CC

SCCS
1. Smooth curve (fractional polynomial) for age adjustment using monthly and weekly age categorisation
2. Data for each vaccine analysed separately, with IS risk fitted both by month of age category and using a fractional polynomial
3. Allowing for a change in the likelihood of being vaccinated immediately after an IS event (‘healthy vaccinee effect’)
   → all minimal impact on relative incidence
4. Removal of cases who received a dose of vaccine outside of the recommended age range for that vaccine dose
   → weakening of dose-1 association for RV1

Case-control analysis
1. Restricted to cases and matched controls who received their final dose of vaccine before the recommended upper age limit
   → similar weakening of dose-1 association for RV1 as when late vaccinated cases removed from SCCS analysis
Limitations

• Case ascertainment
  – Broad: jurisdictions that were included have >95% of national population
  – Missed cases from non-included jurisdictions/non-reviewed cases unlikely to bias estimates (vaccine coverage would need to be strongly related to IS risk)

• Lack of ability to control for confounding in CC analysis due to limited data available from ACIR

• Small numbers, despite near-complete capture

• Generalizability to other settings?
Timing of IS cases with respect to doses 1 and 2 of rotavirus vaccines (Rotarix and RotaTeq)
Age-specific trends in ICD coded hospitalisations

Unpublished data derived from the National Hospital Morbidity Database – Australian Institute of Health and Welfare