Hospital based sentinel surveillance for AEFI - the PAEDS network

Nick Wood on behalf of PAEDS investigators
Lieu Trinh, Heather Gidding, Han Wang, Jocelynne McRae, Elizabeth Elliott, Yvonne Zurynski, Peter McIntyre, Robert Booy, Peter Richmond, Helen Marshall, Chris Blyth, Mike Gold, Jim Buttery, Nigel Crawford, Michael Nissen and Kristine Macartney
Outline

- PAEDS – a description
- Specific AEFI conditions
  - Intussusception
  - Febrile seizures
- Benefits of PAEDS
Surveillance Systems

- Event
  - Yes
    - Spontaneous REPORTS
  - No

- Vaccine
  - Yes
  - No
PAEDS – a description

- 5 sentinel sites – tertiary paediatric hospitals
- Nurse based active surveillance
- Consent – no consent
- Access and review
  - Medical records
  - ACIR
  - Path/Radiology
  - GP records
- Specific case reports
- Biological samples
- Based on IMPACT - Canada
PAEDS - conditions

- **Vaccine preventable diseases**
  - Varicella
  - Pertussis
  - Influenza

- **AEFI**
  - Intussusception
  - Febrile seizures

- **Acute flaccid paralysis**

- **Encephalitis -pilot**
Intussusception: PAEDS Aug 2007 to Apr 2013

QUESTIONS

- Is vaccine proximate IS (within 21 days of a dose of RV vaccine) associated with:
  - A different clinical phenotype?
  - Family history IS?
  - Different outcomes?

- Stool sample
Aug 2007 - April 2013

- 478 confirmed cases
- 317 Male (66%)
- Median Age = 10 months
- Stool samples collected = 223 (47%)
- Rotavirus Vaccination = 403 (84%)
  Rotarix®, GSK = 161 (40%)
  Rotateq®, Merck = 236 (59%)
  Unknown = 6 (1%)
Brighton Collaboration IS Case definition
Level 1 of Diagnostic Certainty

- Surgical criteria:
  - The demonstration of invagination of the intestine at surgery;
    - and/or

- Radiologic criteria:
  - The demonstration of invagination of the intestine by either air or liquid contrast enema; or
  - The 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 criteria demonstration of intestinal invagination
### Intussusception: Overview of Data (2007 - 2012)

<table>
<thead>
<tr>
<th>Brighton Level *</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>397 (83)</td>
</tr>
<tr>
<td>Level 2</td>
<td>73 (15)</td>
</tr>
<tr>
<td>Level 3</td>
<td>6 (1)</td>
</tr>
</tbody>
</table>

*Please note there was a change in reporting of Brighton level classification from Definite, Probable and Possible to level 1, level 2 and level 3.

![Graph showing Brighton level by gender](chart.png)

**PAEDS**
Paediatric Active Enhanced Disease Surveillance
Intussusception: BC
Level 1

- 397 cases
  - 49 vaccine proximate
    - Mean age 136 days
  - 348 non vaccine proximate
    - Mean age 344 days
- No deaths
- No difference in:
  - Gender
  - Site of IS
  - Family history of IS

Map courtesy: Andras Bogdanovits & Clare Brazenor DH Vict
Intussusception BC Level 1: Outcomes

- **Vaccine proximate**
  - Increased risk surgery
    - Vaccine proximate 18 of 49 had surgery
    - Non-proximate 68 of 348 underwent surgery
      - $P=0.006$
  - Not increased risk bowel resection
    - Prox 8 of 49 vs Non-prox 29 of 348
      - $P=0.06$
  - Increased length of stay
    - Vaccine prox median 2 (range 0-73)
    - Non-proximate median 1 (range 0-58)
      - $P=0.005$
Intussusception Risk and Disease Prevention Associated With Rotavirus Vaccines in Australia’s National Immunization Program

John B. Carlin,1,2 Kristine K. Macartney,5,6,7 Katherine J. Lee,1,2 Helen E. Quinn,5,6 Jim Buttery,1,3,4 Ruth Lopert,8 Julie Bines,1,2 and Peter B. McIntyre5,6,7

1Murdoch Children’s Research Institute, Royal Children’s Hospital, 2Department of Paediatrics, University of Melbourne, 3Infectious Diseases Department, Monash Children’s Hospital, and 4Department of Paediatrics, Monash University, Melbourne; 5National Centre for Immunisation Research & Surveillance, 6Discipline of Paediatrics and Child Health, University of Sydney, and 7Department of Microbiology and Infectious Diseases, The Children’s Hospital at Westmead, Sydney; and 8Therapeutic Goods Administration, Canberra, Australia

(See the Editorial Commentary by Parashar and Orenstein on pages 1435–7.)

Results. Based on 306 confirmed cases of IS, the relative incidence of IS in the 1–7-day period after the first vaccine dose, was 6.8 (95% confidence interval, 2.4–19.0; \( P < .001 \)) for RV1, and 9.9 (95% confidence interval, 3.7–26.4; \( P < .001 \)) for RV5. There was a smaller increased risk 1–7 days after the second dose of each vaccine. The case-control analysis gave similar results. We estimate an excess of 14 IS cases and \( >6500 \) fewer gastroenteritis hospitalizations in young children annually in Australia after vaccine introduction.
Conclusions

- Small excess cases associated with RV vaccination
- Vaccine proximate cases
  - Younger
  - Some evidence more severe
    - Increased surgery but not resection
    - Increased LOS
- Active surveillance critical to define features/outcomes
Febrile seizures, measles and varicella containing vaccines

What is the risk in Australian children?

Presentation to the PHAA14th National Immunisation Conference, Melbourne June 2014
MMRV – Measles Mumps Rubella and Varicella vaccine and febrile seizures

USA (ProQuad, Merck and Co)
  • 2-fold increased risk of FS post vaccination with MMRV as dose 1 – compared with children given MMR and VV

Canada and Germany (Priorix-Tetra, GSK)
  • 2-fold increased risk similar to ProQuad

Australia
  o MMRV as dose 2 of measles-containing vaccine - age 18 months from July 1st 2013
  o “MMRV Vaccine Safety Surveillance Plan”
    o Surveillance for FS added - funded by Dept of Health

**Aims**

To describe

- Clinical and epidemiologic characteristics of FS (vaccine and non-vaccine proximate)
- Association between FS and
  - MMR and Varicella vaccine
  - MMRV vaccine
Methods

FS surveillance
Children aged 0-5 years, 5 PAEDS hospitals

Retrospective
Jan 2012 – April 2013
ICD-coded FS cases (ICD10 code R56.0)

No chart review or parent contact
Vaccines recorded on ACIR + age, date of presentation

Self controlled case series analysis --
relative incidence post MMR dose 1 and varicella vaccine
Children aged 11-23 months

Vaccine attributable risk of additional FS
Calculated using excess applied to baseline incidence (extrapolated using data from NSW Health ED collection)

Prospective
May 2013 - ongoing
active surveillance - all FS ED/hosp records/ICD coded

Case confirmation/clinical details
FS history, Vaccine history (parents/ACIR)

Self controlled case series analysis
– relative incidence post MMRV
Children aged 11-23 months
(Wood et al, PHAA 2014)
Results

Timing of MMR 1 and varicella vaccination in relation to age at first FS presentation (N=1,761) ICD-coded FS cases
Jan 2012 to April 30, 2013
Febrile seizures occurring within 30 days after MMR 1 or varicella vaccine
Relative incidence of FS following MMR dose 1 in children aged 11 to < 24 months of age

<table>
<thead>
<tr>
<th>FS episode*</th>
<th>RI (95% CI) -1 to -13 days</th>
<th>P value</th>
<th>RI (95% CI) 5-12 days</th>
<th>P value</th>
<th>RI (95% CI) 13-30 days</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>0.26 (0.12-0.56)</td>
<td>0.001</td>
<td>1.90 (1.26-2.86)</td>
<td>0.002</td>
<td>0.84 (0.56-1.25)</td>
<td>0.394</td>
</tr>
<tr>
<td>Repeat</td>
<td>0.30 (0.15-0.62)</td>
<td>0.001</td>
<td>1.93 (1.30-2.88)</td>
<td>0.001</td>
<td>0.84 (0.57-1.25)</td>
<td>0.394</td>
</tr>
</tbody>
</table>

- 2-fold increased risk of FS occurring in the 5-12 days post MMR dose 1
- No increase in FS 13-30 days post MMR dose 1
- Children who have had recent FS less likely to get MMR in next 2 weeks
What does that 2-fold ‘increased risk’ mean?

Attributable risk of FS post MMR dose 1
- 24 extra FS per 100,000 vaccinated children (95% CI: 7-50 per 100,000)
- 1 excess per 4200 children vaccinated
- Background rate
  - ~ 500-1000 FS per 100,000 children aged 12-24 months per year
- Comparable to other studies from 1980’s-2000’s UK, USA and Scandinavia
  - Including data linkage study in South Australia (Gold et al, Vaccine 2010)
Methods

FS surveillance
Children aged 0-5 years, 5 PAEDS hospitals

Retrospective
Jan 2012 – April 2013
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No chart review or parent contact
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Self controlled case series analysis – relative incidence post MMRV
Children aged 11-23 months

PAEDS Paediatric Active Enhanced Disease Surveillance
Enhanced clinical data – prospective n=1668 cases

- Indigenous status
- Risk factors
- Type and length of seizure
- Other potential causes
- Investigations
- Compare vaccine proximate vs vaccine distant cases
- Outcome
- SCCS on MMRV
## National Adverse Events Following Immunisation (AEFI) reporting form

### Vaccinated person’s details

**Personal details**

<table>
<thead>
<tr>
<th>Field</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surname</td>
<td></td>
</tr>
<tr>
<td>First name</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Male, Female, Unknown</td>
</tr>
<tr>
<td>Date of Birth</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Months or Years</td>
</tr>
<tr>
<td>Street address</td>
<td></td>
</tr>
<tr>
<td>Suburb</td>
<td></td>
</tr>
<tr>
<td>State</td>
<td></td>
</tr>
<tr>
<td>Postcode</td>
<td></td>
</tr>
<tr>
<td>Name of parent/guardian</td>
<td>(if relevant)</td>
</tr>
<tr>
<td>Phone</td>
<td>Landline (inc. area code) or mobile</td>
</tr>
</tbody>
</table>

### Adverse event details

<table>
<thead>
<tr>
<th>Field</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of event Date:</td>
<td></td>
</tr>
<tr>
<td>Onset of event Time:</td>
<td></td>
</tr>
<tr>
<td>Description of events, including timeline of occurrences:</td>
<td></td>
</tr>
<tr>
<td>Management of event (tick as many as apply)</td>
<td>None, Nurse assessment, GP assessment, Hospital emergency department, Hospital admission, Number of days (if applicable), Date of discharge, Unknown, Other, please specify</td>
</tr>
<tr>
<td>Please specify the treatment/care provided (e.g. antibiotics, adrenaline, advice, counselling, etc.):</td>
<td></td>
</tr>
</tbody>
</table>
Strengths of PAEDS

- Limitations of passive surveillance – well known
- Highly detailed clinical and vaccine outcome information
  - > data linkage studies
- Compare severity of vaccine proximate and vaccine distant cases

- Measure risk – SCCS

- Biological samples
  - Stool from IS cases
  - Genetic analysis in FS cases
Requirements

- Accurate case definition of condition
  - Eg – infant seizures vs Intussusception

- Time and labour
  - consent

- Vaccine history
  - ACIR vs patient contact
  - Time lag to ACIR entry
Acknowledgments

Children’s Hospital at Westmead, Sydney
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Women’s and Children’s Hospital Adelaide
Investigators: Associate Professor Mike Gold, Associate Professor Helen Marshall
PAEDS surveillance nurses: Chris Heath, Mary Walker

Princess Margaret Hospital, Perth
Investigators: Associate Professor Peter Richmond, Associate Professor Christopher Blyth
PAEDS surveillance nurses: Chris Robins, Carol Orr, Cazz Finucane

Royal Children’s Hospital, Queensland
Investigators: Associate Professor Michael Nissen, Dr Anne Kynaston
PAEDS surveillance nurse: Sonia Dougherty
Clinical features: BC Level 1

No difference

- Vomiting
- Diarrhoea
- Recurrent jelly stool
- fever
- AXR abN rate
Clinical features: BC Level 1

No difference
- Vomiting
- Diarrhoea
- Recurrent jelly stool
- fever
- AXR abN rate

Vaccine-prox ↑
- PR blood
- Hypovolaemic shock
Relative incidence of FS following varicella vaccine in children aged 11 to < 24 months of age

<table>
<thead>
<tr>
<th>Age range</th>
<th>RI (95% CI) -1 to -13 days</th>
<th>P value</th>
<th>RI (95% CI) 5-12 days</th>
<th>P value</th>
<th>RI (95% CI) 13-30 days</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>11-&lt;24 mo</td>
<td>0.86 (0.56-1.35)</td>
<td>0.520</td>
<td>0.64 (0.34-1.19)</td>
<td>0.158</td>
<td>0.71 (0.47-1.08)</td>
<td>0.109</td>
</tr>
<tr>
<td>17-&lt;24 mo</td>
<td>1.19 (0.75-1.89)</td>
<td>0.451</td>
<td>0.65 (0.34-1.25)</td>
<td>0.193</td>
<td>0.75 (0.49-1.15)</td>
<td>0.193</td>
</tr>
</tbody>
</table>

- No increased risk of FS post varicella vaccine given alone
Other findings.....

- Insufficient children had MMR1 and VV on same day to compare risk for both vaccines given together
- Very few FS occur in children > 3 years
- no risk of FS with MMR 2\textsuperscript{nd} dose at age 4 years

Children offered enrolment in \textbf{NHMRC funded study} (Wood et al) - long term developmental outcomes
- genetic analysis for epilepsy-associated genes