Febrile events following administration of four brands of 2010 and 2011 inactivated seasonal influenza vaccine in NZ infants and children

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Background: NZ influenza vaccination programme

• Variety of brands, change from year to year

• 2010 most widely used in children ≥6m
  – Vaxigrip® (sanofi-pasteur), Fluvax® (CSL), and Influvac® (Solvay)
  – Funded for high risk and “those a GP considered at high risk of complications” at GP discretion

• 2011
  – Fluarix® 6mos +
  – Fluvax® >8 years
  – Funded for high risk
Background: 2010 febrile reactions

- April 2010 Western Australia detected increase in spontaneous reporting of febrile convulsions, single brand Fluvax®?
  - Estimated 3.3 per 1000 doses within 4-6 hours in ≤ 5’s¹
- April 2010 NZ no signals from NZ passive surveillance (CARM)
  - 24th April total of 4 reports
- Rapid analysis of ED and admission data for Auckland region children’s hospitals (1.5 million)
  - No more FC than normally expected (~25 each per week)

Background to NZ investigations

• In 2010 NZ well placed to assess febrile events associated with several brands of TIV during same season in same population ≤5 years

• Pilot study found fever occurred significantly more frequently within 24 hours of Fluvax® compared with Vaxigrip® RR 4.33 (2.44–7.70)

Objectives

– Determine the risk for febrile convulsion following administration of Vaxigrip to infants and children ≤5 years in 2010

– Determine the rates of febrile events occurring within 24 hours after vaccination in recipients of Vaxigrip®, Fluvax® and Fluarix® in 2010 and 2011

Petousis-Harris H, Poole T, Booy R, Turner N. Fever following administration of two inactivated influenza vaccines – a survey of parents of New Zealand infants and children 5 years of age and under. Vaccine 2011;29:2933–7
Methodology

• Two retrospective telephone surveys of parents of children 6months – 8 years – 2010 & 2011
• Cohort of ~260,000 children
• Study participants from 184 NZ general practices
• Practice nurse identified (via PMS) consecutive influenza vaccinees and called by telephone
• Administered brief 6 (7) item survey
• Vaccine identified by batch number

Outcome Definitions

• Confirmed febrile convulsive seizure
  • Presence of fever ≥38°C AND
  • Level 1 of diagnostic certainty – witnessed sudden loss of consciousness AND generalised, tonic, clonic, tonic-clonic, or atonic motor manifestations. OR
  • Level 2 of diagnostic certainty – history of unconsciousness AND generalised, tonic, clonic, tonic-clonic, or atonic motor manifestations. OR
  • Level 3 of diagnostic certainty – history of unconsciousness AND other generalised motor manifestations.

• Fever either reported or measured
  – If measured then defined as ≥38°C
  – further defined into ≥38°C, ≥39°C and ≥40°C.

• Fever AND presence of organ symptoms:
  – Neurological
  – Gastrointestinal
  – Musculoskeletal
  – Malaise/other

• All major events incl. ED, GP consults were clinician confirmed

Bonhoeffer J. Fever as an Adverse Event following Immunisation Case Definition and Guidelines of Data Collection, analysis and Presentation. Vaccine 2003:1-6
Data Analysis

• Binary logistic regression to assess the outcome variables of fever alone and in association with convulsion, rigor, altered consciousness, vomiting and other symptoms to determine significance and odds ratios between the explanatory variable vaccine brand.

• Multivariable analysis for fever occurring within 24 h using logistic regression. Explanatory variables were vaccine, ethnicity, gender, dose, history of health problems and age at vaccination.

• Recall bias assessed using logistic regression
  – Outcome
    • fever recalled within 24 hours or not
  – Explanatory variables
    • Lag time from vaccination to survey
    • Vaccine
    • Age and age squared in months
    • Summer/winter (May-Oct, Nov-Apr)
Results

FEBRILE REACTIONS FOLLOWING 2010-2011 TIV

Petousis-Harris H, Poole T, Turner N, Reynolds G. Febrile events including convulsions following the administration of four brands of 2010 and 2011 inactivated seasonal influenza vaccine in NZ infants and children: The importance of routine active safety surveillance. *Vaccine* (2012), http://dx.doi.org/10.1016/j.vaccine.2012.05.052
Flow of recruitment

Children identified by practice as having received Influenza vaccine

- 3962

Parents able to be contacted
- 3635 (92%)

Parents unable to be contacted
- 327 (8%)

Completed survey
- 3620 (99%)

Survey meet criteria
- 3603 (99%)

Survey unable to be used (outside age)
- 17 (1%)

2010

Parents declined survey
- 15 (1%)

Children identified by practice as having received Influenza vaccine

- 518

Parents able to be contacted
- 486 (94%)

Parents uncontactable
- 32 (6%)

Parents completed survey
- 485 (99.8%)

Parents declined survey
- 1 (1.2%)

2011
Comparison of febrile convulsions and other febrile associated events following administration of four brands of inactivated influenza vaccine in NZ infants and children 2010-2011
Febrile events following administration of 4078 doses of four brands of inactivated influenza vaccine in NZ infants and children 2010-2011

![Graph showing febrile events following administration of different influenza vaccines.](image-url)
Children aged five to eight years.

- 252 children aged 5-8 years
- Febrile problem still evident in this age group
- But not beyond

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fluvax® OR (95%CI)</th>
<th>Vaxigrip® OR (95%CI)</th>
<th>Influvac® OR (95%CI)</th>
<th>Fluarix® OR (95%CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever within 24 hours</td>
<td>7 (23%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
<td>&lt;0.0000</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0.04 (0.00 - 0.31)</td>
<td>0</td>
<td>0.03 (0.00 – 0.22)</td>
<td></td>
</tr>
</tbody>
</table>

Results from multivariable analysis evaluating factors associated with reporting of fever within 24 hours after 4088 doses of inactivated influenza vaccine in NZ children aged 6 months to 8 years of age.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vaccine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluvax®</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Vaxigrip®</td>
<td>0.21 (0.16 – 0.27)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Influvac®</td>
<td>0.54 (0.36 – 0.81)</td>
<td></td>
</tr>
<tr>
<td>Fluarix®</td>
<td>0.10 (0.05 – 0.20)</td>
<td></td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
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<tr>
<td>European</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Maori</td>
<td>0.50 (0.36 – 0.71)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pacific Island</td>
<td>0.32 (0.22 – 0.47)</td>
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<tr>
<td>Asian</td>
<td>0.91 (0.63 – 1.30)</td>
<td></td>
</tr>
<tr>
<td>MELAA</td>
<td>0.99 (0.48 – 2.10)</td>
<td></td>
</tr>
<tr>
<td>Indian</td>
<td>1.09 (0.71 – 1.67)</td>
<td></td>
</tr>
<tr>
<td><strong>Gender (male vs. female)</strong></td>
<td>0.90 (0.71 – 1.25)</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>Dose (dose 2 compared to dose 1)</strong></td>
<td>0.56 (0.41 – 0.75)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Health problems (nil vs. ≥1)</strong></td>
<td>0.98 (0.77 – 1.25)</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>Age (months)</strong></td>
<td>0.99 (0.98 – 1.00)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

[1] Middle Eastern, Latin American, African
[2] Continuous variable assessed as one unit offsets from the mean
Conclusions and considerations

• We found risk of febrile convulsions following a single brand of flu vaccine to be 35 per 10,000 doses
  — wDTP 6-9 per 100,000, MMR 25-34 per 100,000

• UK enhanced passive surveillance found 2/10,000 and 1.4/10,000 following H1N1¹
  — = No excess in reporting

• US VSD found increased risk for seizure post TIV, particularly with concomitant PCV13²

Conclusions and considerations

• Similar 2010 survey in NSW found rates of febrile events 6-7% post non-Fluvax and 45% post Fluvax\(^1\)
• Perth survey 2010 Influvac >17% and 57% following Fluvax\(^2\)
• Speculate difference in NZ findings could be due to the lower rates among Polynesian children contributing to our sample.

Conclusions and considerations

• Not all brands/years equivalent – even with same antigens!
• Implications for National Immunisation programme planning and maintaining public confidence
• Simple cost effective survey at the start of each season is a rapid and economical approach to this
Thank you

Conflicts of interest

HPH, TP, NT and GR have no conflicts of interest to declare.

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- sanofi pasteur
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