Rare AEFI
Power of international collaboration

Nigel Crawford
COI

• Investigator led- study

• Supported by bioCSL
What is Guillain-Barre Syndrome (GBS)?

- GBS is a condition of acute flaccid paralysis (weakness)
- Causes
  - Infectious
    - including campylobacter & wild type influenza
  - Post-infectious (auto-immune)
- Significant morbidity
  - 20% having persistent and significant disability
Why an issue?

2009

H1N1/09 Influenza pandemic

1976

H1N1 vaccine had an increased risk of Guillain-Barre syndrome
GUILLAIN-BARRE SYNDROME FOLLOWING VACCINATION IN THE NATIONAL INFLUENZA IMMUNIZATION PROGRAM, UNITED STATES 1976–1977

American Journal of Epidemiology 1979

The Johns Hopkins University School of Hygiene and Public Health

LAWRENCE B. SCHONBERGER et al.
What was the risk in 1976?

- relative risk of 7.6 (95% CI 6.7–8.6)
  - within 0-42 days of vaccination

- estimated one additional case of GBS per 100,000 persons vaccinated
Why did it occur?

- Suspected GM1 antibody- but no sera from patients to confirm 1976 hypothesis

- Animal models:
  - Rabbits developed anti-GM1 Ab and flaccid limb weakness when sensitised with *C. jejuni*

- Low homogeneity between HINI 1976 c/w 2009:
  - of 88.6% by nucleotide sequence
  - 90.8% by amino acid sequence

Steve Black

Importance of background rates of disease in assessment of vaccine safety during mass immunisation with pandemic H1N1 influenza vaccines

Steven Black, Juhani Eskola, Claire-Anne Siegrist, Neal Halsey, Noni MacDonald, Barbara Law, Elizabeth Miller, Nick Andrews, Julia Stowe, Daniel Salmon, Kirsten Vannice, Hector Izurieta, Aysha Akhtar, Mike Gold, Gabriel Oselka, Patrick Zuber, Dina Pfeifer, Claudia Vellozzi

GBS in Australia

- Annual incidence: 2.5 per 100,000 population
  - (560 per year in Australia, ~140 per year in Victoria)

- Males are at higher risk

- Incidence increases with age

[AIHW-ATAGI 2009]
**Victorian Background rates**

<table>
<thead>
<tr>
<th></th>
<th>Child (&lt;5 years)</th>
<th>Adolescent (5-15 years)</th>
<th>Adult (16-64 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guillain-Barre syndrome</td>
<td>1.24</td>
<td>1.18</td>
<td>2.96</td>
</tr>
<tr>
<td>Transverse myelitis</td>
<td>0.46</td>
<td>0.45</td>
<td>1.59</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>0</td>
<td>0.39</td>
<td>23.64</td>
</tr>
<tr>
<td>Optic neuritis</td>
<td>0.07</td>
<td>0.84</td>
<td>3.82</td>
</tr>
<tr>
<td>Seizures</td>
<td>696.43</td>
<td>105.22</td>
<td>111.47</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>207.76</td>
<td>89.15</td>
<td>90.84</td>
</tr>
</tbody>
</table>
# GBS Active Sites

<table>
<thead>
<tr>
<th>Site</th>
<th>Site lead investigator</th>
<th>No. expected GBS cases (12 months)</th>
<th>Provisional No. GBS cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCH</td>
<td>Nigel Crawford</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>MMC</td>
<td>Victoria Rodriguez-Caesero</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>RMH</td>
<td>Lyn Kiers</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Epworth</td>
<td>Lyn Kiers</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Cabrini</td>
<td>Tim Day</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Austin</td>
<td>Pat Charles</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Alfred</td>
<td>Allen Cheng</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>St Vincent's Hospital</td>
<td>Les Roberts</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Western Hospital</td>
<td>Tissa Wijeratne</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Geelong Hospital</td>
<td>Peter Gates</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td><strong>67</strong></td>
<td></td>
</tr>
</tbody>
</table>
GBS Active: study procedures

• Review all GBS cases (Brighton def)
  • Levels 1-4 (clinical; CSF; NCS)

• Study duration 1-year [9/09-9/10]
  • H1N1 Panvax [CSL]
  • Seasonal Trivalent Influenza Vaccine

• 10 Victorian sites
• WHO Global collaboration
SCCS

Standard Self-Controlled Case Series

Post-Vaccination Vaccinees-Only Approach

H1N1 Vaccination
Risk Period
Guillain Barré Diagnosis within risk period
Guillain Barré Diagnosis outside of risk period
GBS Active: Results

67 cases per year expected*

66 probable cases identified†

54 confirmed cases

12 excluded:
- 2 opted out
- 1 interhospital transfer
- 9 not GBS

4 excluded (symptoms onset before 30 Sep 2009)

50 cases analysed:
- 37 Brighton level 1–2
- 13 Brighton level 3–4a

* Based on background rates from the Victorian Admitted Episodes Dataset and the Victorian Emergency Minimum Dataset. † Diagnosed between 30 Sep 2009 and 30 Sep 2010.

MJA. 2012;197(10):574-78.
GBS Active: Results

• 66 potential GBS cases were identified, with complete data on 50 confirmed cases
• GBS cases aged 7–95 years
  • median 48 years
• Victorian annual incidence of GBS was 1.7 per 100 000 population

MJA. 2012;197(10):574-78.
GBS Active: Results

• The RI of GBS following monovalent vaccination was 3.4 (95% CI, 0.8–15.0)

• For TIV, there was one case in the risk period
  • RI 0.69 (95% CI, 0.08–5.64)
### Global GBS Active study

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of cases reported*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>60</td>
</tr>
<tr>
<td>Canada</td>
<td>80</td>
</tr>
<tr>
<td>China</td>
<td>42</td>
</tr>
<tr>
<td>Denmark</td>
<td>31</td>
</tr>
<tr>
<td>Finland</td>
<td>29</td>
</tr>
<tr>
<td>Israel</td>
<td>12</td>
</tr>
<tr>
<td>Mexico</td>
<td>44</td>
</tr>
<tr>
<td>Netherlands</td>
<td>80</td>
</tr>
<tr>
<td>Singapore</td>
<td>19</td>
</tr>
<tr>
<td>Spain</td>
<td>32</td>
</tr>
<tr>
<td>UK</td>
<td>40</td>
</tr>
<tr>
<td>USA</td>
<td>66</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>535</strong></td>
</tr>
</tbody>
</table>

*Cases not meeting Brighton Collaboration criteria 1 - 4A were excluded in subsequent analyses.

## Global GBS Active study

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Risk Window(s)</th>
<th>Exclusions</th>
<th>Brighton Criteria Levels</th>
<th>Relative Incidence</th>
<th>Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard SCCS</td>
<td>Days 1-42</td>
<td>• Databases (DBs) with Vaccinated Cases Only</td>
<td>1-3</td>
<td>2.86</td>
<td>(1.87, 4.34)</td>
</tr>
<tr>
<td>Standard SCCS</td>
<td>Days 1-42</td>
<td>• DBs with Vaccinated Cases Only</td>
<td>1-4A</td>
<td>3.21</td>
<td>(2.18, 4.71)</td>
</tr>
<tr>
<td>Pseudo-Likelihood</td>
<td>Days 1-42</td>
<td>• DBs with Vaccinated Cases Only</td>
<td>1-3</td>
<td>2.65</td>
<td>(1.71, 4.11)</td>
</tr>
<tr>
<td>Pseudo-Likelihood</td>
<td>Days 1-42</td>
<td>• DBs with Vaccinated Cases Only</td>
<td>1-4A</td>
<td>2.93</td>
<td>(1.97, 4.38)</td>
</tr>
<tr>
<td>Vaccinated Cases Only</td>
<td>Days 1-42</td>
<td>• Unvaccinated cases</td>
<td>1-3</td>
<td>2.65</td>
<td>(1.66, 4.24)</td>
</tr>
<tr>
<td>Standard SCCS</td>
<td>Days 1-7*</td>
<td>• DBs with Vaccinated Cases Only</td>
<td>1-3</td>
<td>2.82</td>
<td>(1.27, 6.35)</td>
</tr>
<tr>
<td></td>
<td>8-21*</td>
<td></td>
<td></td>
<td>3.76</td>
<td>(2.18, 6.46)</td>
</tr>
<tr>
<td></td>
<td>22-42*</td>
<td></td>
<td></td>
<td>2.28</td>
<td>(1.31, 3.98)</td>
</tr>
<tr>
<td>*Modeled Simultaneously</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccinated Cases Only Adjuvanted</td>
<td>Days 1-42</td>
<td>• Unvaccinated cases</td>
<td>1-3</td>
<td>1.88</td>
<td>(1.04, 3.41)</td>
</tr>
<tr>
<td>Vaccinated Cases Only Non-Adjuvanted</td>
<td>Days 1-42</td>
<td>• Unvaccinated cases</td>
<td>1-3</td>
<td>2.97</td>
<td>(1.13, 7.84)</td>
</tr>
</tbody>
</table>

Global GBS Active study

Self Controlled Case Series
Risk Period Days 1-42 Post-vaccination
Seasonality defined as periods of circulating influenza

Limitations

• Multiple (10-site) ethics in Victoria....
• WHO teleconference scheduling
International collaboration to assess the risk of Guillain Barré Syndrome following Influenza A (H1N1) 2009 monovalent vaccines


DOI: 10.1016/j.vaccine.2013.06.032

Outcomes

Expert Review of Vaccines

Reviews

Active surveillance for adverse events following immunization

Nigel W Crawford, Hazel Clothier, Kate Hodgson, Gowri Selvaraj, Mee Lee Easton, and Jim P Buttery

1 SAEFVIC, Murdoch Children's Research Institute (MCRI), Parkville,
Conclusion

• Collaboration required for rare…. but significant AEFI
• GBS Active as a ”proof of principle”
• Australia can continue to contribute to global vaccine safety initiatives
Hawthorn coach Alastair Clarkson hospitalised, diagnosed with Guillain-Barré syndrome