Narcolepsy after vaccination with Pandemrix: - Update in Sweden 2009-2012

Report by the Medical Products Agency
- SMI meeting 2012-10-03

Ingemar Persson and MPA team
I. The *Signal* from ADR reports, in the summer of 2010

No. reports / month

- **Signal cases**
- **Media attention**

<table>
<thead>
<tr>
<th>Month</th>
<th>No. reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>maj-10</td>
<td>1</td>
</tr>
<tr>
<td>jun-10</td>
<td>2</td>
</tr>
<tr>
<td>10-jul</td>
<td>3</td>
</tr>
<tr>
<td>10-aug</td>
<td>4</td>
</tr>
<tr>
<td>10-sep</td>
<td>5</td>
</tr>
<tr>
<td>okt-10</td>
<td>25</td>
</tr>
<tr>
<td>nov-10</td>
<td>6</td>
</tr>
<tr>
<td>dec-10</td>
<td>7</td>
</tr>
<tr>
<td>Under pågående bedömning</td>
<td>2</td>
</tr>
</tbody>
</table>
HCP reports on Narcolepsy to MPA, July 2012 - # cases with cataplexy, and/or diagnostic work-up

<table>
<thead>
<tr>
<th>Age range</th>
<th>Males</th>
<th>Females</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 4</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>5-9</td>
<td>28</td>
<td>18</td>
<td>46</td>
</tr>
<tr>
<td>10-14</td>
<td>29</td>
<td>36</td>
<td>65</td>
</tr>
<tr>
<td>15-19</td>
<td>29</td>
<td>24</td>
<td>53</td>
</tr>
<tr>
<td>20-24</td>
<td>8</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>25 +</td>
<td>6</td>
<td>11</td>
<td>17</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Summary</td>
<td>102</td>
<td>94</td>
<td>196</td>
</tr>
</tbody>
</table>

Age range: 4-60 yrs; 4-19 yrs: 166 cases, 85%  
Median age: males 11.9 yrs, females 13.7 yrs, all 13.3 yrs
Time of reporting to MPA vs first recorded symptoms - HCP reports to MPA, ≤ 19 yrs (until Sept. 13, 2011)
II. A registry based cohort study of narcolepsy after vaccination with Pandemrix’

Study population = inhabitants in 4 counties (57%)

Vaccination registries

Vaccinated subjects - Risk time

Databases: diagnosis, ICD10 47.4

Incidence # cases/100’ p-yrs

Non-vaccinated subjects - Risk time

Incidence # cases/100’ p-yrs
Incidence rates and Relative Risk of Narcolepsy  
- Follow-up through December 2010 (≤ 15 months)

<table>
<thead>
<tr>
<th>Age group</th>
<th>Vaccinated</th>
<th></th>
<th></th>
<th></th>
<th>Unvaccinated</th>
<th></th>
<th></th>
<th></th>
<th>Vaccinated vs unvaccinated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>#Events</td>
<td>Risk time*</td>
<td>Rate</td>
<td>95% CI</td>
<td>#Events</td>
<td>Risk time*</td>
<td>Rate</td>
<td>95% CI</td>
<td>RR</td>
</tr>
<tr>
<td>≤ 19</td>
<td>38</td>
<td>9.355</td>
<td>4.06</td>
<td>(2.87-5.58)</td>
<td>6</td>
<td>6.188</td>
<td>0.97</td>
<td>(0.36-2.11)</td>
<td>4.19</td>
</tr>
<tr>
<td>20 +</td>
<td>26</td>
<td>22.457</td>
<td>1.16</td>
<td>(0.76-1.70)</td>
<td>26</td>
<td>27.149</td>
<td>0.96</td>
<td>(0.63-1.40)</td>
<td>1.21</td>
</tr>
</tbody>
</table>

*100 000 person-years
Conclusions from Registry Study, March 2011

• Children / adolescents (≤ 19 years)
  – Relative risk: 4-fold risk increase risk of narcolepsy
  – Absolute risk: 3 additional cases /100’revaccinated subjects

  – The magnitude of the excess risk is uncertain
    • Enhanced detection in vaccinated subjects?
    • Incidence based on time of diagnosis biased?

• Adults (20 + years)
  – No indication of a change in the risk
III. Case Inventory Study
- Age ≤ 19 years, disease onset 2009-2010

- Population rates, 81 cases with cataplexy
- Risk estimation, 76 cases

- **Pre-Pandemic**: 0.31/100’ p-yrs
- **Pandemic-vaccination**: 5.78/100’ p-yrs
- **Post Pandemic-vaccination**: 0.79/100’ p-yrs
### 2a. Incidence rates and risk estimates, by vaccination status

<table>
<thead>
<tr>
<th>Vaccinated</th>
<th>Non-vaccinated</th>
<th>Vaccinated vs non-vaccinated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of cases, person-years(^1), incidence rates/100’</strong></td>
<td><strong>No. of cases, person-years(^1,2), incidence rates/100’</strong></td>
<td><strong>Relative Risk (RR)</strong>&lt;br&gt;<strong>Absolute Risk (AR)</strong>&lt;br&gt;<strong>95% CI</strong></td>
</tr>
<tr>
<td>All</td>
<td>69 / 1624’ = 4.2</td>
<td>7 / 1093’ = 0.64</td>
</tr>
</tbody>
</table>
### 2b. Incidence rates and risk estimates, by vaccination status and *time window* of exposure

<table>
<thead>
<tr>
<th>Time window</th>
<th>Vaccinated</th>
<th>Non-vaccinated</th>
<th>Vaccinated vs non-vaccinated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases/ person-years: incidence rates / 100’</td>
<td>No. of cases / person-years: incidence rates / 100’</td>
<td>RR (95% CFI)</td>
</tr>
<tr>
<td>No. of months after vaccination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 3 months</td>
<td>53 / 377’ = 14.1</td>
<td>0.64 / 100’</td>
<td>RR = 22 (10 - 43.4)</td>
</tr>
<tr>
<td>&gt; 3 months</td>
<td>16 / 1247’ = 1.3</td>
<td>0.64 / 100’</td>
<td>RR = 2.0 (0.8 – 4.9)</td>
</tr>
</tbody>
</table>
Methodological issues

• **Stimulated detection / reporting bias?**
  A possibility, but….
  – Focus on narcolepsy *with cataplexy, a severe, specific, symptom*

  – Onset of symptoms in 98% of cases *before August 2010*
    • 78% of these had onset date *recorded* in the medical records, before August 2010

• **Earlier onset of narcolepsy after vaccination in susceptible subjects**
  – Incidence peak followed by dip? Time pattern…..
Overall conclusions by the MPA, June 2011

- **Established** association for narcolepsy (with cataplexy) in *children/adolescents*

- **In Case Inventory Study:**
  - *Relative risk:* 7-fold increase, highest risk ≤ 3 months
  - *Absolute risk:* 3.6 additional cases per 100’ vaccinated subjects

- No evidence (data) of an excess risk in *adults* (≥ 20 yrs)

- Need for a variety of investigations on causal *mechanisms* and *susceptibility*
  - Vitally important: wide implications for understanding vaccine safety
Research issues

- Risk relationship in 20+ age group?
- Incidence pattern over time in exposed subjects?
- Susceptibility factors?
- Risk modifying factors?
- Narcolepsy in other countries? Other H1N1 vaccines?
- Narcolepsy phenotype in exposed cases?
- Clues from research on mechanisms?
**Ongoing research, coordinated by the MPA**

- **MPA and Karolinska Institute**
  - Extended registry study of neurological / immune related ADRs
    - Follow-up of *narcolepsy* diagnosed through 2011, in 7 counties of Sweden
- **Karolinska Institute**
  - Case-control study
    - Risk factors, interactions
    - Immunological mechanisms
      - Biobanking
      - Cellular immune response, autoantibodies, genotype
      - Animal model
- **Swedish Institute Communicable Disease Control**
  - Ecological study of narcolepsy incidence pattern
- **HCPs**
  - Clinical follow-up: Quality registry
MPA team

- Nils Feltelius, Maria Szirmai, Charlotte Backman:
  - Advice, coordination, logistics
- Charlotta Bergquist, Agneta Aust-Kettis, Rebecca Chandler:
  - Vaccine expertise
- Birgitta Grundmark:
  - Pharmacovigilance, ADR reporting
- Tomas Salmonson: PI
- Ingemar Persson: Project leader