VACCIMUS: VACCINES AND THE RISK OF RELAPSE IN MULTIPLE SCLEROSIS

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Hepatitis B vaccination in France

• 1980s: Recommended for at-risk individuals
• 1991: Compulsory for health professionals
• 1994: Recommended for newborn and adolescents
• 1994-95: Vaccination campaign implemented in schools
• In total: 25 million vaccinated 1991-98, including 18 million 1994-96
Pharmacovigilance Alerts in France

- 1991-94: French neurologist/MS specialist reports having observed several cases to l’Agence Française du Médicament
  - Cases were rare
  - Risk assessment not possible
  - Warning about Hep. B vaccination in MS patients
  - Proposal to implement epidemiological approaches
1996: New media campaign

- Additional investigations of spontaneous reports of demyelinating and autoimmune disorders inconclusive

1997: Decision to sponsor epidemiological studies

1998: Several epidemiological studies launched

- GPRD study (Sturkenboom et al, 1999)
- French Agency case-control study (Fourrier et al, 1999)
- Nurses’ health cohort study (Ascherio et al, 2001)
- VACCIMUS study (Confavreux et al, 2001)
MUTLIPLE SCLEROSIS

- Relapses
- Onset
- Limitation to walking
- cane
- Wheelchair
- age
- time
- handicap

30 40 50 60
Vaccines

Onset

Relapse
Other epidemiological studies

Vaccines

Onset
VACCIMUS Project

Vaccines

Relapse
VACCIMUS: Objective

- To assess whether vaccinations increase the risk of a relapse in patients with multiple sclerosis

Confavreux et al: NEJM 2001;344:319-326
VACCIMUS: Organisation

- Principal Investigators:
  - Pr Christian Confavreux (neurologist) CHU, Lyon, France
  - Pr Samy Suissa (epidemiologist), McGill University, Montreal, Canada.

- 6 participating centers (France-4; Spain, Switzerland)

- Monitoring: MAPI Clinical research

- Scientific Advisory Committee:
  - Dr Rachid Salmi, Université de Bordeaux
  - Dr Alastair Compston, Cambridge University, UK
  - Dr Elisabeth Miller, Public Health Laboratory, London, UK

- Funding: Aventis Pasteur and Aventis Pasteur MSD

Confavreux et al: NEJM 2001;344:319-326
VACCIMUS: Design Challenges

- MS highly variable disease with unknown prognostic factors
- Cases of relapse relatively straightforward to identify
- Controls would be complex (variable relapse times, unmeasured confounding factors)
- Therefore: used a case-crossover design, similar to a case-control study where cases are used as both cases and as their own controls
Case-crossover design

- Transient exposures (drugs, foods, activities)
- Acute risk: of equal magnitude and known effect-time after each exposure
- Cases only
- Rate ratio estimated by comparing exposures between risk period and control period(s)
Case-crossover design

Control periods

Risk period

Cases only (MS relapse)
VACCIMUS: Case identification

- Subjects with MS with a relapse occurring during 1993-1997
- Identified from computerised database from 6 of the European centers in the EDMUS network
- MS relapse definite or probable (Poser criteria)
- Consent letter for inclusion into study

Confavreux et al: NEJM 2001;344:319-326
VACCIMUS: Case definition

- **Index relapse**: First definite or probable MS relapse to occur during 1993-1997
- Medical record obtained to validate MS relapse
- Relapse followed by an outpatient visit or hospitalisation within 2 months of the onset
- Relapse preceded by a relapse-free period of 12 months or more

*Confavreux et al: NEJM 2001;344:319-326*
VACCIMUS: Exposure information

- Interviews and questionnaires to assess vaccination history (1992-97)
- Validation from vaccination records
- Sub-study among random sample of 97 subjects reporting no vaccination to confirm non-vaccination (0/89)

Confavreux et al: NEJM 2001;344:319-326
VACCIMUS: Design

- Case-crossover design
- Target 600 cases (RR=2; $\alpha = .05$; power=90%)
- A 2-month risk period
- Four 2-month control periods per subject (8 months)

Confavreux et al: NEJM 2001;344:319-326
VACCIMUS Study: Case-crossover design

Possible previous relapses

Index relapse

Visit or hospitalisation

4 control periods of 2 months

2-month risk period

Source: NEJM 2001;344:319-326
VACCIMUS: Subjects

- 1,037 eligible subjects identified in EDMUS with a relapse during 1993-97
- 1,009 were requested to participate
- 960 subjects accepted
- First 643 subjects included in the study

Confavreux et al: NEJM 2001;344:319-326
VACCIMUS: Vaccinations

- 260 subjects of the 643 (40%) with 1 or more confirmed vaccination in 1992-97
- 960 vaccinations reported between 1992-97
- 89 (14%) subjects received a vaccination during 12 months prior to onset of index relapse
- These patients received 135 vaccinations

Confavreux et al: NEJM 2001;344:319-326
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>None (n=383)</th>
<th>1992-97 (n=260)</th>
<th>Prior year (n=89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex (%)</td>
<td>68%</td>
<td>72%</td>
<td>78%</td>
</tr>
<tr>
<td>Age at index relapse – years</td>
<td>39–10</td>
<td>37–11</td>
<td>37–11</td>
</tr>
<tr>
<td>Last known Kutzke disability score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Range</td>
<td>0–8</td>
<td>0–9</td>
<td>0–7</td>
</tr>
<tr>
<td>Type of initial symptoms (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optic neuritis only</td>
<td>22</td>
<td>24</td>
<td>25</td>
</tr>
<tr>
<td>Brain-stem symptoms only</td>
<td>15</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Long tract symptoms only</td>
<td>46</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td>Mixed symptoms</td>
<td>15</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>Other or unknown</td>
<td>2</td>
<td>2</td>
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Source: NEJM 2001;344:319-326
# Characteristics of 643 patients with a relapse of MS by vaccination

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<tr>
<td><strong>Course of disease – no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapsing – remitting</td>
<td>73</td>
<td>80</td>
<td>82</td>
</tr>
<tr>
<td>Secondary progressive</td>
<td>24</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>Progressive relapsing</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>Years of disease at index relapse</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>7</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Range</td>
<td>1–43</td>
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<td>1–43</td>
</tr>
<tr>
<td>No. Of relapses prior to index relapse</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>3</td>
<td>2</td>
<td>2</td>
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<td>Range</td>
<td>1–25</td>
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*Source: NEJM 2001;344:319-326*
# Control prevalence of vaccination in the 12 months preceding the index relapse

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<th>Periods before the index relapse</th>
<th>Prevalence (%) (N=643)</th>
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<td>1 – 2 month (risk period)</td>
<td>??</td>
</tr>
<tr>
<td>3 – 4 months (1&lt;sup&gt;st&lt;/sup&gt; control period)</td>
<td>3.0</td>
</tr>
<tr>
<td>5 – 6 months (2&lt;sup&gt;nd&lt;/sup&gt; control period)</td>
<td>2.8</td>
</tr>
<tr>
<td>7 – 8 months (3&lt;sup&gt;rd&lt;/sup&gt; control period)</td>
<td>4.0</td>
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<tr>
<td>9 – 10 months (4&lt;sup&gt;th&lt;/sup&gt; control period)</td>
<td>3.0</td>
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<tr>
<td>11 – 12 months</td>
<td>2.6</td>
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Source: NEJM 2001;344:319-326
Prevalence of vaccination in the study period preceding the index relapse

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<tr>
<td>1 – 2 month (risk period)</td>
<td>2.3</td>
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<tr>
<td>3 – 4 months (1\textsuperscript{st} control period)</td>
<td>3.0</td>
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Two-month risk of relapse associated with exposure to specific vaccines

<table>
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<th>Type of vaccine</th>
<th>% Exposed</th>
<th>Rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk period</td>
<td>Control periods</td>
</tr>
<tr>
<td>Any vaccine</td>
<td>2.3</td>
<td>3.2</td>
</tr>
<tr>
<td>Tetanus alone</td>
<td>0.6</td>
<td>0.8</td>
</tr>
<tr>
<td>Combined tetanus</td>
<td>0.3</td>
<td>1.2</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>0.6</td>
<td>0.9</td>
</tr>
<tr>
<td>Influenza</td>
<td>0.8</td>
<td>0.7</td>
</tr>
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Source: NEJM 2001;344:319-326
VACCIMUS: Study limitations

Study excludes patients with frequent relapses (within 12 months of each other; ~ 25% for a given episode), although must apply throughout entire 1993-97 period

Study excludes minor relapses

Power of 90% for rate ratio of 2 for all vaccines, but lower for specific vaccines

Case-crossover design assumes constancy of exposure (shown) and equality of risk after each exposure (shown)
VACCIMUS: Study strengths

- Case-crossover design uses cases only and avoids difficulties of control selection and confounding often present in case-control studies.
- Time-constant confounders adjusted for.
- High response rate and validation of vaccination information.
- Results unaffected by change in length of effect period.
- High power for rate ratio of 2 for all vaccines.
CONCLUSION

• Vaccination does not appear to increase the short-term risk of a relapse among patients with multiple sclerosis