Influenza Vaccine and Multiple Sclerosis

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Centers for Disease Control and Prevention
Outline

• Influenza vaccination of patients with MS
  – Multiple Sclerosis Council Review and Clinical Practice Guidelines

• Influenza vaccination as a risk factor for the development of MS and optic neuritis (ON)
  – Vaccine Safety Datalink (VSD) case-control study
• Questions addressed
  – Risk of potentially vaccine-preventable infectious diseases in patients with MS?
  – Do potentially vaccine-preventable infectious diseases increase the risk of MS exacerbations?
  – Does vaccination increase the risk of exacerbations?
  – Effectiveness of vaccines in patients with MS?
MS Council Review: Methods

• Search strategy
  – MEDLINE
  – HealthSTAR
  – CINAHL
  – Reference lists of included articles

• Articles screened by two independent reviewers

• Summary of evidence (AAN criteria), including meta-analysis, by Duke University*

* Rutschmann OT et al. Neurology 2002;59:1837-43
MS Council Review: Summary of General Findings

• There is conflicting evidence on the risk of common infectious diseases in the MS population

• There is definitive evidence for an increased risk of MS exacerbations during the weeks around an infectious episode

• There is insufficient evidence regarding the efficacy of immunization in patients with MS
MS Council Review: Influenza vaccination and Risk of MS Exacerbations

- There is definitive evidence against a substantial increased risk of MS exacerbation after influenza vaccine
#### RCT’s of Influenza Vaccine and MS Exacerbations

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Sample Size</th>
<th>Exacerbations (vax vs placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Miller 1997</strong></td>
<td>RCT</td>
<td>49 vaccine, 54 placebo</td>
<td>3 vs 2 (4 weeks), 11 vs 6 (6 months)</td>
</tr>
<tr>
<td><strong>Mokhtarian 1997</strong></td>
<td>RCT</td>
<td>11 vaccine, 8 placebo</td>
<td>1 vs 1 (4 weeks), 3 vs 2 (6 months)</td>
</tr>
<tr>
<td><strong>Myers 1977</strong></td>
<td>RCT</td>
<td>33 vaccine, 33 placebo</td>
<td>2 vs 4 (3 weeks), 4 vs 4 (3 months)</td>
</tr>
</tbody>
</table>
## Meta-analysis of RCT’s of Influenza Vaccine and MS Exacerbations

<table>
<thead>
<tr>
<th>Interval post-vaccination</th>
<th>Rate difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-4 weeks</td>
<td>0.0% (-6.9% to 6.9%)</td>
</tr>
<tr>
<td>3-6 months</td>
<td>6.1% (-4.1% to 16.3%)</td>
</tr>
</tbody>
</table>
Other Studies of Influenza Vaccine and MS Exacerbations

• 1 retrospective case-crossover
• 4 prospective cohort
• 3 retrospective cohort
• Variable design, size and quality
• Generally, do not provide evidence of increased occurrence of exacerbations after vaccination
Recommendation of the Multiple Sclerosis Council

- Influenza vaccine has been shown to be safe for patients with multiple sclerosis.
- Physicians should recommend that patients with MS who meet CDC indications consider receiving influenza vaccination.
Is Influenza Vaccine a Risk Factor for the Development of Demyelinating Disease?

- Theoretical
  - Immunological stimulation → increase risk
  - Protect against flu infection → decrease risk
- Case reports (e.g., MS, optic neuritis, encephalomyelitis)
  - 23 cases after swine flu vaccine
  - 12 cases after other influenza vaccines
- No evidence from epidemiological studies
- Difficult to interpret causality from case reports
Vaccine Safety Datalink (VSD) Study*

Objectives

• To assess the association between vaccination, including influenza, and the development of demyelinating diseases of the central nervous system in adults

• To evaluate risk according to timing of vaccination, particularly recent vaccination

*In press: Archives of Neurology, April 2003
Methods: study design and population

• Design: case - control study
• Population: Vaccine Safety Datalink (VSD):
  – Collaboration between CDC and several large Health Maintenance Organizations (HMOs)
  – Databases linking demographic and vaccination records to clinic and hospital discharge records
  – Initiated in 1991 to study vaccine safety issues
Methods: case ascertainment

Screen automated outpatient encounter and hospital discharge data from 1995 - 1999 at three HMOs with most complete outpatient data

Confirm incident cases by review of medical chart

Obtain informed consent and conduct telephone interview
Case Definition

• Physician diagnosis of MS or ON in medical record

• Alternative case definitions
  – Diagnosis by a specialist
  – International Panel criteria for MS (2 clinical demyelinating events separated in space and time)

• Onset date = date of first symptom (Poser 1994)
Methods: selection of controls

Select up to 3 controls per case from automated HMO member files, at least 1 year of HMO enrollment, match on age (within 1 year) and gender

Exclude prior diagnosis of MS or ON by review of medical charts

Obtain informed consent and conduct telephone interview
Methods: exposure assessment

• Based on medical records (paper and computerized) for vaccinations received at HMO
• Based on telephone interview for vaccinations received outside HMO
• Categorized as
  - ever/never before index date (onset date of matched case)
  - by time intervals before index date: 0-1 year, 1-5 years, and >5 years
Methods: statistical analysis

• Conditional logistic regression stratified by matching variables
• Adjusted for:
  - Family history (autoimmune and demyelinating diseases)
  - Race and ethnicity
  - Place of birth
  - Scandinavian ancestry
  - Smoking
  - Marital status
Results: case ascertainment

1159 potential cases from screening automated records

556 confirmed as incident eligible cases by chart review

440 cases contacted and participated in telephone interview (90% participated of those contacted)
Results: control selection

2047 potential controls

1334 eligible, contacted, and asked to participate

950 participated (71%)
# Characteristics of Cases and Controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases (N=440)</th>
<th>Controls (N=950)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>76%</td>
<td>77%</td>
</tr>
<tr>
<td>Age (index date)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>18-30</td>
<td>35%</td>
<td>34%</td>
</tr>
<tr>
<td>31-40</td>
<td>37%</td>
<td>38%</td>
</tr>
<tr>
<td>&gt;40</td>
<td>22%</td>
<td>22%</td>
</tr>
</tbody>
</table>
### Characteristics (cont’d)

<table>
<thead>
<tr>
<th>Race/ethnicity</th>
<th>Cases (N=440)</th>
<th>Controls (N=950)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White, not Hisp.</td>
<td>71%</td>
<td>71%</td>
</tr>
<tr>
<td>Black, not Hisp.</td>
<td>12%</td>
<td>8%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>9%</td>
<td>11%</td>
</tr>
<tr>
<td>Asian, Pac. Isl.</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td>Other</td>
<td>5%</td>
<td>5%</td>
</tr>
</tbody>
</table>
Influenza Vaccination Status of Cases and Controls

Ever vaccinated (before index date)

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>73 (16.6%)</td>
<td>177 (18.6%)</td>
</tr>
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</table>
Relative Risk* of Demyelinating Disease Associated with Influenza Vaccination

<table>
<thead>
<tr>
<th>Case Definition</th>
<th>MS (332 cases**)</th>
<th>ON (108 cases**)</th>
<th>Either (440 cases**)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD Dx</td>
<td>0.7 (0.5-1.1)</td>
<td>1.2 (0.6-2.3)</td>
<td>0.8 (0.6-1.2)</td>
</tr>
<tr>
<td>Specialist Dx</td>
<td>0.9 (0.6-1.3)</td>
<td>1.0 (0.5-2.0)</td>
<td>0.9 (0.6-1.3)</td>
</tr>
<tr>
<td>International Panel Criteria</td>
<td>1.0 (0.6-1.4)</td>
<td>--</td>
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</tr>
</tbody>
</table>

*Adjusted odds ratio (95% confidence interval); **MD Dx
Timing of Influenza Vaccination and Risk of Demyelinating Disease

<table>
<thead>
<tr>
<th>Years before index date</th>
<th>Odds ratio* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>0.8 (0.5-1.4)</td>
</tr>
<tr>
<td>1-5</td>
<td>1.1 (0.7-1.7)</td>
</tr>
<tr>
<td>&gt;5</td>
<td>0.6 (0.3-1.1)</td>
</tr>
</tbody>
</table>

*Adjusted, never vaccinated as referent
Discussion: Strengths

- Large, population-based study
- Included both MS and ON
- Data on both men and women
- Recently diagnosed cases to minimize recall bias
- Medical record data reduced reliance on recall
- Results robust under different case definitions and exposure measures
Discussion: limitations

• Recall bias:
  – for vaccinations outside HMO, relied on telephone interview
  – Comparison with HMO records indicated recall of vaccination (including date of vaccination) similar between cases and controls
  – Analyses excluding self-reported vaccinations had same results as main analysis
## Comparison of Results (Odds Ratios) According to Source of Vaccination Data

<table>
<thead>
<tr>
<th>Influenza vax</th>
<th>Vaccination Information</th>
<th>Records+Interview</th>
<th>Records only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ever/never</td>
<td>0.9</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>0.8</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>1-5 years</td>
<td>1.1</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>&gt;5 years</td>
<td>0.6</td>
<td>0.5</td>
<td></td>
</tr>
</tbody>
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Conclusion

The results of the VSD case-control study do not support the hypothesis that influenza vaccine causes or triggers the development of multiple sclerosis or optic neuritis.
Acknowledgements

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