

Influenza Vaccine and Multiple Sclerosis

Frank DeStefano

National Immunization Program

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

Immunizations and MULTIPLE SCLEROSIS

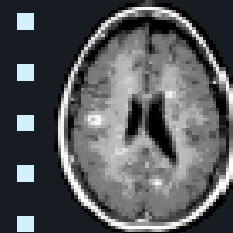
**Evidence-Based
Management Strategies for
Immunizations in
Multiple Sclerosis**



**Multiple Sclerosis Council
for Clinical Practice Guidelines**

Administrative and Financial support provided by
Paralyzed Veterans of America

- CLINICAL
- PRACTICE
- GUIDELINES



- IMMUNIZATIONS

MS Council Literature Review

- 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

Study	Design	Sample Size	Exacerbations (vax vs placebo)
Miller 1997	RCT	49 vaccine 54 placebo	3 vs 2 (4 weeks) 11 vs 6 (6 months)
Mokhtarian 1997	RCT	11 vaccine 8 placebo	1 vs 1 (4 weeks) 3 vs 2 (6 months)
Myers 1977	RCT	33 vaccine 33 placebo	2 vs 4 (3 weeks) 4 vs 4 (3 months)

Meta-analysis of RCT's of Influenza Vaccine and MS Exacerbations

Interval post-vaccination	Rate difference (95% CI)
3-4 weeks	0.0% (-6.9% to 6.9%)
3-6 months	6.1% (-4.1% to 16.3%)

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 >5years

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

Characteristic	Cases (N=440)	Controls (N=950)
Female	76%	77%
Age (index date)		
<18	6%	5%
18-30	35%	34%
31-40	37%	38%
>40	22%	22%

Characteristics (cont'd)

Race/ethnicity	Cases (N=440)	Controls (N=950)
White, not Hisp.	71%	71%
Black, not Hisp.	12%	8%
Hispanic	9%	11%
Asian, Pac. Isl.	3%	5%
Other	5%	5%

Influenza Vaccination Status of Cases and Controls

Ever vaccinated (before index date)

Cases	Controls
73 (16.6%)	177 (18.6%)

Relative Risk* of Demyelinating Disease Associated with Influenza Vaccination

Case Definition	MS (332 cases**)	ON (108 cases**)	Either (440 cases**)
MD Dx	0.7 (0.5-1.1)	1.2 (0.6-2.3)	0.8 (0.6-1.2)
Specialist Dx	0.9 (0.6-1.3)	1.0 (0.5-2.0)	0.9 (0.6-1.3)
International Panel Criteria	1.0 (0.6-1.4)	--	--

*Adjusted odds ratio (95% confidence interval); **MD Dx

Timing of Influenza Vaccination and Risk of Demyelinating Disease

Years before index date	Odds ratio* (95% CI)
<1	0.8 (0.5-1.4)
1-5	1.1 (0.7-1.7)
>5	0.6 (0.3-1.1)

*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

Influenza vax	Vaccination Information	
	Records+Interview	Records only
Ever/never	0.9	0.9
<1 year	0.8	0.8
1-5 years	1.1	1.1
>5 years	0.6	0.5

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

- Group Health Cooperative : Lisa Jackson, Patti Benson
- Northwest Kaiser: John Mullooly
- Northern California Kaiser: Steve Black and Henry Shinefield
- CDC: Tom Verstraeten, Katie Okoro and Robert Chen

