

## Supplemental Online Content

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**eFigure.** Flowchart of the Studied Multiple Sclerosis Cohort from the SNDS

**eTable 1.** List of SNDS Codes to Capture the Dispensing of a Multiple Sclerosis Disease-Modifying Treatment and High-Dose Corticosteroids in a Given Year

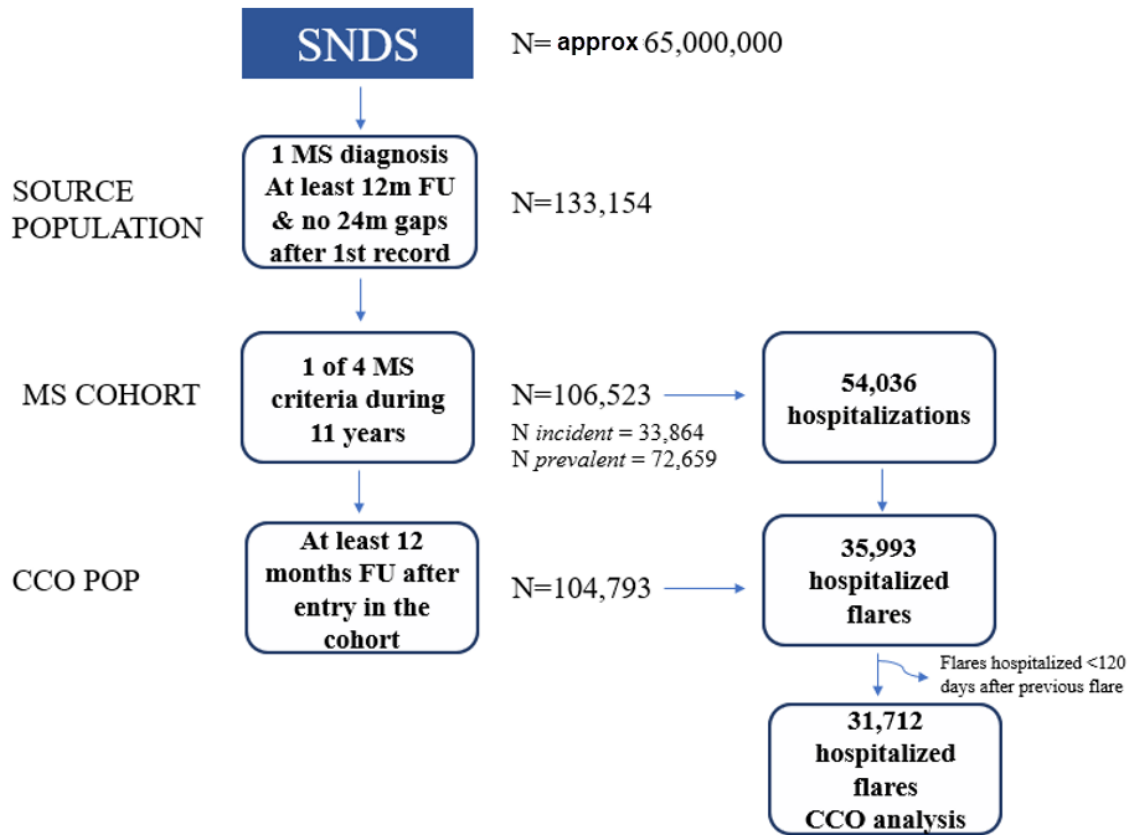
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This supplemental material has been provided by the authors to give readers additional information about their work.



**eFigure.** Flowchart of the Studied Multiple Sclerosis Cohort from the SNDS

Abbreviations: SNDS: System of National Health Databases; FU: follow-up; CCO POP: case-crossover population

**eTable 1.** List of SNDS Codes to Capture the Dispensing of a Multiple Sclerosis Disease-Modifying Treatment and High-Dose Corticosteroids in a Given Year

- MS disease-modifying therapies
  - [beta]interferon
  - dimethyl fumarate
  - fampridine
  - fingolimod
  - glatiramer acetate
  - mitoxantrone
  - monoclonal antibodies: alemtuzumab, natalizumab ocrelizumab
  - teriInfluzanamide

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- High-dose corticosteroids
  - Betamethasone arw 2mg cpr disp 20
  - Betamethasone bga 2mg cpr disp 20
  - Betamethasone eg 2mg cpr disp 20
  - Betamethasone ztv 2mg cpr disp 20
  - Betnesol 4 mg sol inj 3
  - Celestene 2mg cpr disp 20
  - Celestene 4 mg sol inj 3
  - Celestene 8mg/2ml sol inj 1
  - Celestene chrono 5,70 mg/ml inj+nec 1
  - Diprostene susp inj 1
  - Cepo medrol 80mg/2ml inj ser 1/2 ml
  - Depo-medrol 0,040 g 1 flacon de 1 ml avec seringue
  - Depo-medrol 40 mg/1 ml (acetate de methyl predniso
  - Medrol 100mg cpr 30
  - Medrol 16mg cpr 20
  - Medrol 4mg cpr 30
  - Methyl prednisolone dakota pharm 120 mg (succinate)
  - Methyl prednisolone dakota pharm 20 mg (succinate)
  - Methyl prednisolone dakota pharm 20 mg (succinate)
  - Solpredone 120 mg (methylprednisolone) 1 flacon ly
  - Solpredone 20 mg (methylprednisolone) 1 flacon lyo
  - Solumedrol 1000 mg pdr et sol inj 1
  - Solumedrol 120 mg pdr et sol inj 1
  - Solumedrol 120 mg pdr et sol inj 1
  - Solumedrol 120 mg pdr et sol inj 1

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**eTable 2. Specific Multiple Sclerosis Diagnosis Codes in the SNDS French Health Care Database**

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- Hospital discharge diagnosis with ICD-10 code for a general or a specific MS (principal, relative or associated diagnosis)
    - G35: Multiple sclerosis
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- MS-related disorders
    - F068: Other specified mental disorders due to known physiological condition
    - F078: Other personality and behavioral disorders due to known physiological condition
    - F079: Unspecified personality and behavioral disorder due to known physiological condition
    - G040: Acute disseminated encephalitis and encephalomyelitis (ADEM)
    - G048: Other encephalitis, myelitis and encephalomyelitis
    - G049: Encephalitis, myelitis and encephalomyelitis, unspecified
    - G058: Encephalitis, myelitis and encephalomyelitis in other diseases classified elsewhere
    - G111: Early-onset cerebellar ataxia
    - G112: Late-onset cerebellar ataxia
    - G122: Motor neuron disease
    - G360: Neuromyelitis Optica [Devic]
    - G368: Other specified acute disseminated demyelination
    - G369: Acute disseminated demyelination, unspecified
    - G373: Acute transverse myelitis in demyelinating disease of central nervous system
    - G378: Other specified demyelinating diseases of central nervous system
    - G379: Demyelinating disease of central nervous system, unspecified
    - G800: Spastic quadriplegic cerebral palsy
    - G801: Spastic diplegic cerebral palsy
    - G802: Spastic hemiplegic cerebral palsy
    - G810: Flaccid hemiplegia
    - G811: Spastic hemiplegia
    - G819: Hemiplegia, unspecified
    - G820: Flaccid paraplegia
    - G821: Spastic paraplegia
    - G822: Paraplegia, unspecified
    - G823: Flaccid tetraplegia
    - G824: Spastic tetraplegia
    - G825: Tetraplegia, unspecified
    - G831: Monoplegia of lower limb
    - G832: Monoplegia of upper limb
    - G833: Monoplegia, unspecified
    - G838: Other specified paralytic syndromes
    - G839: Paralytic syndrome, unspecified
    - G948: Other specified disorders of brain in diseases classified elsewhere
    - G950: Syringomyelia and syringobulbia
    - G958: Other specified diseases of spinal cord
    - G968: Other specified disorders of central nervous system
    - G969: Disorder of central nervous system, unspecified
    - G98: Other disorders of nervous system, not elsewhere classified
    - G998: Other specified disorders of nervous system in diseases classified elsewhere
    - H46: Optic neuritis
    - H471: Papilloedema, unspecified
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- H480: Optic atrophy in diseases classified elsewhere
  - H481: Retrobulbar neuritis in diseases classified elsewhere
  - H488: Other disorders of optic nerve and visual pathways in diseases classified elsewhere
  - H490: Third [oculomotor] nerve palsy
  - H491: Fourth [trochlear] nerve palsy
  - H493: Total (external) ophthalmoplegia
  - H512: Internuclear ophthalmoplegia
  - H532: Diplopia
  - H534: Visual field defects
  - H535: Color vision deficiencies
  - H538: Other visual disturbances
  - H539: Visual disturbance, unspecified
  - H540: Blindness, binocular
  - H541: Severe visual impairment, binocular
  - H542: Moderate visual impairment, binocular
  - H544: Blindness, monocular
  - H545: Severe visual impairment, monocular
  - H549: Unspecified visual impairment (binocular)
  - H55: Nystagmus and other irregular eye movements
  - H814: Vertigo of central origin
  - R201: Hypoesthesia of skin
  - R202: Paresthesia of skin
  - R203: Hyperesthesia
  - R208: Other and unspecified disturbances of skin sensation
  - R260: Ataxic gait
  - R261: Paralytic gait
  - R262: Difficulty in walking, not elsewhere classified
  - R268: Other and unspecified abnormalities of gait and mobility
  - R27: Other lack of coordination
  - R298: Other and unspecified symptoms, signs involving nervous and musculoskeletal systems
  - R4700: Recent aphasia, persisting beyond 24 hours
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**eTable 3.** Use of Vaccines in the Multiple Sclerosis Cohort According to Age Group

	<b>&lt;18 years old</b>	<b>18-34 years old</b>	<b>35-69 years old</b>	<b>≥70 years old</b>	<b>MS Cohort</b>
% Patient (N, %)	n=1,297	n=28,945	n=72,188	n=4,093	n=106,523
<b>Any vaccine</b>	642 (49.5%)	11,710 (40.5%)	32,762 (45.4%)	3,118 (76.2%)	48,232 (45.3%)
DTPPHi*	506 (39.0%)	9,831 (34.0%)	21,109 (29.2%)	794 (19.4%)	32,240 (30.3%)
Influenza	68 (5.2%)	1,694 (5.9%)	15,802 (21.9%)	2,933 (71.7%)	20,497 (19.2%)
Pneumococcus	61 (4.7%)	1,602 (5.5%)	5,230 (7.2%)	584 (14.3%)	7,477 (7.0%)
Other vaccines	269 (20.7%)	1,558 (5.4%)	1,232 (1.7%)	23 (0.6%)	3,082 (2.9%)
<i>Me/Mu/Ru</i>	47 (3.6%)	633 (2.2%)	174 (0.2%)	8 (0.2%)	862 (0.8%)
<i>HPV</i>	123 (9.5%)	121 (0.4%)	102 (0.1%)	0 (0.0%)	346 (0.3%)
<i>HBV</i>	72 (5.6%)	295 (1.0%)	383 (0.5%)	6 (0.1%)	756 (0.7%)
<i>Meningococcus</i>	61 (4.7%)	250 (0.9%)	276 (0.4%)	2 (0.0%)	589 (0.6%)
<i>Tuberculosis</i>	2 (0.2%)	79 (0.3%)	51 (0.1%)	0 (0.0%)	132 (0.1%)
<i>Varicella/zona</i>	13 (1.0%)	168 (0.6%)	160 (0.2%)	7 (0.2%)	348 (0.3%)
<i>Hepatitis A</i>	2 (0.2%)	140 (0.5%)	141 (0.2%)	0 (0.0%)	283 (0.3%)

\* Abbreviation: DTPPHi: Any of Diphtheria/Tetanus/Poliomyelitis/Pertussis/*Haemophilus Influenzae*, including DTPPHi+Hepatitis B combination

**eTable 4.** Association of Multiple Sclerosis Flare-Ups Requiring Hospitalization and Vaccines Exposure According to Age and Type of Vaccine (60-Day Time Window)

	'At-risk time windows'	'Control time windows'	Crude OR CI[95%]	Adjusted OR CI[95%]*
<b>&lt;18 years old</b>	<b>n=318</b>	<b>n=1,081</b>		
<i>DTPPHi</i> <sup>‡</sup>	7 (2.20%)	22 (2.04%)	1.08 [0.47 - 2.50]	1.10 [0.49 - 2.48]
<i>Influenza</i>	1 (0.31%)	3 (0.28%)	Not applicable	Not applicable
<i>Pneumococcus</i>	0 (0.00%)	2 (0.19%)	Not applicable	Not applicable
<b>18-34 years old</b>	<b>n=6,075</b>	<b>n=22,414</b>		
<i>DTPPHi</i> <sup>‡</sup>	62 (1.02%)	194 (0.87%)	1.18 [0.89 - 1.57]	1.17 [0.88 - 1.56]
<i>Influenza</i>	18 (0.30%)	52 (0.23%)	1.28 [0.70 - 2.35]	1.24 [0.66 - 2.32]
<i>Pneumococcus</i>	9 (0.15%)	27 (0.12%)	1.23 [0.89 - 2.56]	1.10 [0.52 - 2.34]
<b>35-69 years old</b>	<b>n=23,553</b>	<b>n=86,736</b>		
<i>DTPPHi</i> <sup>‡</sup>	132 (0.56%)	554 (0.64%)	0.88 [0.72 - 1.06]	0.86 [0.71 - 1.04]
<i>Influenza</i>	255 (1.08%)	1,062 (1.22%)	0.88 [0.77 - 1.01]	0.89 [0.78 - 1.02]
<i>Pneumococcus</i>	67 (0.28%)	194 (0.22%)	1.27 [0.97 - 1.67]	1.30 [0.98 - 1.72]
<b>≥70 years old</b>	<b>n=1,766</b>	<b>n=6,670</b>		
<i>DTPPHi</i> <sup>‡</sup>	9 (0.51%)	28 (0.42%)	1.22 [0.57 - 2.60]	1.20 [0.56 - 2.58]
<i>Influenza</i>	157 (8.89%)	517 (7.75%)	1.16 [0.95 - 1.41]	1.17 [0.96 - 1.42]
<i>Pneumococcus</i>	5 (0.28%)	21 (0.31%)	0.90 [0.35 - 2.30]	0.79 [0.31 - 1.98]

<sup>‡</sup>DTPPHi: Any of Diphtheria/Tetanus/Poliomyelitis/Pertussis/*Haemophilus Influenzae*, including DTPPHi+Hepatitis B combination

\*Adjusted for: visits with a GP, visits with a specialist, occurrence of any hospitalization for reasons other than MS and other vaccines

**eTable 5.** Sensitivity Analysis of the Association of Multiple Sclerosis Flare-Ups Requiring Hospitalization and Vaccines Exposure According to 2 Different Time Windows (30-Day Time Window and 90-Day Time Window)

	<i>'At-risk time windows'</i>	<i>'Control time windows'</i>	Crude OR CI[95%]	Adjusted OR CI[95%]*
<b>Time window = 30-day</b>				
<b>All age</b>	<b>n=31,712</b>	<b>n=125,906</b>		
Any vaccine (N, %)	392 (1.24%)	1490 (1.18%)	1.05 [0.94 - 1.17]	1.04 [0.93 - 1.17]
<i>DTPPHi</i> <sup>‡</sup>	124 (0.39%)	409 (0.32%)	1.20 [0.99 - 1.47]	1.14 [0.93 - 1.40]
<i>Influenza</i>	210 (0.66%)	924 (0.73%)	0.90 [0.78 - 1.04]	0.92 [0.79 - 1.07]
<i>Pneumococcus</i>	45 (0.14%)	144 (0.11%)	1.24 [0.90 - 1.71]	1.20 [0.86 - 1.69]
<b>Time window = 90-day</b>				
<b>All age</b>	<b>n=29,861</b>	<b>n=106,932</b>		
Any vaccine (N, %)	1047 (3.51%)	3506 (3.28%)	1.07 [1.00 - 1.15]	1.07 [1.00 - 1.14]
<i>DTPPHi</i> <sup>‡</sup>	308 (1.03%)	1056 (0.99%)	1.04 [0.92 - 1.19]	1.03 [0.91 - 1.17]
<i>Influenza</i>	633 (2.12%)	2184 (2.04%)	1.04 [0.96 - 1.13]	1.03 [0.95 - 1.12]
<i>Pneumococcus</i>	117 (0.39%)	255 (0.24%)	1.65 [1.32 - 2.05]	1.59 [1.27 - 1.99]

<sup>‡</sup>DTPPHi: Any of Diphtheria/Tetanus/Poliomyelitis/Pertussis/*Haemophilus Influenzae*, including DTPPHi+Hepatitis B combination

\*Adjusted for: visits with a GP, visits with a specialist, occurrence of any hospitalization for reasons other than MS and other vaccines