Surveillance for Guillain-Barré Syndrome after H1N1 Influenza Vaccine: A CDC Update

James J. Sejvar, MD
Division of Viral and Rickettsial Diseases
National Center for Zoonotic, Vectorborne, and Enteric Diseases

Immunization Safety Office
Centers for Disease Control and Prevention
Guillain-Barré Syndrome (GBS)

- Immune-mediated polyradiculoneuropathy
  - Acute – subacute “ascending” limb weakness with decreased reflexes
  - Cranial nerve palsies, respiratory failure
- Hypothesized mechanism: humoral or cellular immune response to antigenic stimulus, resulting in attack on nerve self-proteins
- Incidence increases with age, particularly over 50
- Characteristic clinical, laboratory, electrodiagnostic features
GBS and Antecedent “Triggers”

- Infectious illness
  - 2 / 3 reported within 6 weeks of onset
  - ILI, gastrointestinal
  - *C. jejuni*, CMV, EBV
- Surgery
- Vaccinations
  - Tetanus toxoid
  - Semple rabies
  - Influenza
GBS: “Background Rates”

- Presumes an “expected” amount of GBS within the population
- Estimated incidence varies widely
  - 0.4 – 4 / 100,000 population per year
  - N. America, Europe: 1.2 – 1.9 / 100,000
- Incidence differs by age
  - <30 yrs: <1 / 100,000
  - >75 yrs: 4 / 100,000
- GBS uncommon in children
- “Age-specific” rates
GBS and A/NJ/76 (H1N1) Vaccine

- 1976: human-to-human transmission of swine-origin H1N1 influenza virus on US military base
  - 40 million doses of vaccine among US civilians, military
  - Influenza epidemic never materialized
- “Cluster” of GBS cases noted though AE surveillance early in campaign
  - Campaign discontinued Dec. 16, 1976
- Subsequent assessment of US civilians by CDC, state health depts.
Based on 8 controlled assessments, A/NJ/76 (H1N1) influenza vaccine associated with increased risk of GBS

- RR of 7.6 (95% CI 6.7 – 8.6)
- Reporting rate of 8.6 cases / 100,000
  - Non-vaccinees: 1.7 / 100,000
- **Attributable risk** of 0.95 / 100,000 vaccinees
- Risk seen among all lots, manufacturers
- Increased risk concentrated within first 6 weeks, with peak at week 2 – 3 (suggesting biological plausibility)
- Conclusion: A/NJ/76 (H1N1) vaccine associated with small, but statistically significant increased risk of GBS in 6 weeks post-vaccination
  - Temporal pattern consistent with biological causality
  - Reason for association unknown
Most data suggest little, if any, risk of GBS following subsequent influenza vaccines

- Association between other influenza vaccine formulations and immunizations less clear
- 9 well-designed, controlled studies in the literature between 1977 and 2009
- Two suggesting a small but statistically significant increase in risk of GBS
  - Lasky et al*: increased risk following influenza vaccine for combined 1992-93 and 1993-94 seasons (RR 1.7; 95% CI 1.0 – 2.4; AR 0.06 / 100,000 vaccinations);
  - no such risk with each season separately.
- Juurlink et al#: increased risk of GBS following presumed influenza vaccination over period of 1993 – 2004 (RR 1.45, 95% CI 1.05 – 1.99)
  - No increase in incidence of hospital admissions for GBS following universal influenza vaccination in Ontario in 2000.
- Differences in methodologies, case ascertainment methods, analyses
- No clear, consistent association
- Potential GBS risk likely outweighed by influenza-associated morbidity / mortality in any particular season

What Caused the GBS Association in 1976?

- No association with particular human leukocyte antigen (HLA) haplotypes*
- Contamination of vaccine?
  - Risk distributed among all lots
  - *C. jejuni*?
- A/NJ/76 vaccine, but also other formulations, induces anti-myelin ganglioside antibodies in mice
  - Provides biological basis, but significance unclear
- No robust data suggesting a biological basis for association

2009 A/CA/H1N1 Influenza

- Swine influenza viruses cause sporadic human illness through contact with pigs

- April 2009: 2 cases in CA with novel “swine” influenza virus, with no epidemiologic relationship and no pig contact

- Continued spread
  - June 2009: “Pandemic” declared

- Concerning features
  - Ongoing transmission throughout the summer
  - Excess morbidity / morality among pregnant women, young children
A/NJ/76 (H1N1) and 2009 A/H1N1 Viruses: Similarities and Differences

- A/NJ/76 (HswN1): “classical” swine influenza virus
  - All gene segments derived from viruses since 1930

- 2009 A/H1N1: novel combination of gene segments
  - 6 genes – “triple reassortant”; gene segments from swine H1N1, North American avian and human H3N2
  - Immunologically and genetically different from A/NJ/76

- Biological properties of 2009 A/H1N1 not fully characterized
...So Why The Concern??

- Partial “swine” origin of 2009 A/H1N1 virus—first since 1976
- Could vaccine against 2009 H1N1 virus lead to similar increased GBS risk?
  - Improvements in influenza vaccine manufacturing
  - 2009 H1N1 vaccine manufactured the same as seasonal flu vaccine
- Surveillance being conducted out of “abundance of caution”
The Bottom Line...

- A/NJ/76 (H1N1) influenza vaccine associated with increased risk in adults 6 weeks following vaccine
  - Reasons unknown
  - No clear biological explanation
- Most data suggest little or no risk of GBS following subsequent influenza vaccines
- A/NJ/76 and A/CA/09 viruses differ virologically and antigenically
  - Without biological underpinning for 1976 event, unclear what significance any similarities might have on risk of vaccine
Things are different in 2009...

- 1976: No significant influenza disease
- 2009: Already associated with morbidity and mortality
  - Future epidemiology, potential virulence unknown
- Risk in 1976 may have been acceptable in the setting of significant influenza-associated disease
GBS and Influenza Illness

• Case reports of GBS following influenza / ILI

• No substantial evidence of strong association
  • No seasonal pattern of GBS
  • No increase in GBS following large epidemics

• Several reports suggest risk, but data conflicting
Surveillance for GBS Following H1N1 Vaccine: CDC Activities

- Multi-faceted approach
- VAERS
- Active, population-based surveillance—CDC Emerging Infections Program (EIP) sites
- Partnership with American Academy of Neurology
- Serum / CSF bank for anti-ganglioside antibodies
The Vaccine Adverse Event Reporting System (VAERS)

- Cornerstone of vaccine safety monitoring in the U.S.
- National passive surveillance system operated jointly by CDC and FDA; established in 1990
- The “early warning system” of vaccine safety surveillance
- Accepts reports from physicians, other health care providers, vaccine manufacturers, health departments, and the public
- “Hypothesis generating”; seeking signals of potential concern
  - Signals of concern can then be followed up by detailed, controlled studies, active surveillance
## VACCINE ADVERSE EVENT REPORTING SYSTEM

24 Hour Toll-free information line: 1-800-822-7967  
Fax number: 1-877-721-0366  
P. O. Box 1100, Rockville, MD 20849-1100

**PATIENT IDENTITY KEPT CONFIDENTIAL**

### Patient Information
- **Patient Name:** [ ]
  - Last: [ ]
  - First: [ ]
- **Address:** [ ]
- **City:** [ ]
- **State:** [ ]  **ZIP:** [ ]
- **Phone No.** [ ]

### Vaccine Information
- **Vaccine Administered by (Name):** [ ]
  - Last: [ ]
  - First: [ ]
  - MI: [ ]
- **Responsible Physician (Name):** [ ]
  - Last: [ ]
  - First: [ ]
  - MI: [ ]
- **Facility Name:** [ ]
- **Facility Address:** [ ]
  - City: [ ]
  - State: [ ]  **ZIP:** [ ]
  - Phone No.: [ ]

### Additional Information
1. **State where administered:** [ ]
2. **County where administered:** [ ]
3. **Date of Birth:** [ ] (mm / dd / yyyy)
4. **Patient Age at Vaccination:** [ ] yr [ ] mo.
5. **Sex:** [ ]
6. **Date form Completed:** [ ] (mm / dd / yyyy)

7. **Describe adverse event(s) (symptoms, signs, time course) and treatment, if any:** [ ]
8. **Check all appropriate:**
   - [ ] Patient Died (date [ ] / [ ] / [ ] (mm / dd / yyyy)
   - [ ] Life threatening illness
   - [ ] Required emergency room/doctor visit
   - [ ] Required hospitalization ( [ ] days)
   - [ ] Resulted in prolongation of hospitalization
   - [ ] Resulted in permanent disability
   - [ ] None of the above
9. **Patient recovered:** [ ]
10. **Date of vaccination:**
   - **Date:** (mm / dd / yyyy)
   - **Time:** [ AM / PM]
11. **Adverse event onset:**
    - **Date:** (mm / dd / yyyy)
    - **Time:** [ AM / PM]
VAERS: Assets and Limitations

- **Advantages**
  - National in scope, covers diverse populations
  - Able to detect rare events in a cost-effective manner
  - Rapid detection of possible signals (hypotheses to be tested)
    - Signals can then be more thoroughly assessed with active surveillance, case-control studies, assessment of linked databases, etc.

- **Limitations**
  - Reporting biases
  - Unable to provide data on incidences, background rates
  - Reports often incomplete or lack sufficient detail
  - Lack of standardized definitions of what is being reported

- **VAERS data cannot be used to determine “causality”!**
What To Report To VAERS

- "Clinically significant adverse event" following immunization
  - Adverse event of concern to healthcare provider or vaccinee / caregiver
  - Suspicion of causality is not a prerequisite to file a VAERS report
How To Submit A VAERS Report

• Online via secure website: https://vaers.hhs.gov

• Download report form: www.vaers.hhs.gov/pdf/vaers_form.pdf
  • Fax form to: 877-721-0366
  • Mail to: VAERS, PO Box 1100, Rockville, MD 208949

• Request a form, or assistance:
  • Ph: 800-822-7967
  • Email info@vaers.org
Emerging Infections Programs
A population-based, scientific, public health network

- Network of CDC and 10 state health departments
- Collaborators: local health departments, academic institutions, infection control practitioners, other federal agencies (FDA, USDA, EPA)

Activities:

1. active surveillance
2. applied epidemiology and laboratory research
3. implementation and evaluation of pilot prevention and intervention projects
4. flexible response
EIP Partnerships

State Health Departments:
- California Department of Health Services
- Colorado Dept. of Public Health & Environment
- Connecticut Department of Public Health
- Georgia Department of Human Resources
- Maryland Dept. of Mental Health and Hygiene
- Minnesota Department of Health
- New Mexico Department of Health
- New York State Department of Health
- Oregon Department of Human Services
- Tennessee Department of Health

Academic Institutions:
- University of California, Berkeley
- University of California, San Francisco
- University of Colorado Health Sciences Ctr.
- Yale University
- University of Connecticut
- Emory University
- University of Georgia
- Johns Hopkins University
- University of Maryland
- University of Minnesota
- University of New Mexico
- University of Rochester
- Oregon Health Sciences University
- Vanderbilt University
CDC EIP Surveillance

- Active, population-based, real-time surveillance
- Site-based surveillance officers
- Active outreach to neurologists
  - Informational letter
  - Telephone calls
- Information obtained on all diagnosed GBS cases
  - Medical record review
  - Telephone interview
- Public health emergency: HIPPA waived
ALL physicians (nation-wide) should report any vaccine-associated case of GBS (or any other suspected adverse event) to VAERS
ALL physicians in EIP sites should report any case of vaccine-associated GBS (or any other suspected adverse event) to VAERS.
Physicians in EIP sites should report ALL cases of GBS, regardless of vaccination status, to EIP surveillance officers*

*Exceptions in CO, GA, NY, OR
EIP Surveillance

- Analyses: H1N1-vaccinated GBS cases versus
  - “Expected” rates
  - Unvaccinated GBS cases
- Real-time assessment of reported cases, denominator (# of vaccinees)
- Weekly updates
- Ability to switch surveillance in setting of another signal (e.g., Bell’s palsy)
CDC / AAN Partnership

• Raise awareness of H1N1 vaccination issues among neurologic community

• Educational activities
  • Webinars
  • Features in AAN.com, NeurologyToday
  • Web links
GBS Specimen Bank

• Convenience collection of serum, CSF

• Clinical Immunization Safety Assessment (CISA) sites
  • Network of academic centers with vaccine subject matter experts

• Specimen bank for testing of anti-ganglioside antibodies, other biological markers
GBS and Influenza Vaccine: Re-Vaccination

- Is risk of relapse of GBS increased with subsequent influenza vaccines?
  - Data unclear
    - Pritchard et al*.; 3.5% relapse of "self-reported subjective sx" among 311 GBS patients following vaccine
    - Wijdicks et al#.; case report of person with no GBS recurrence following 15 annual influenza vaccines
  - Very limited data
  - "Theoretical" risk of relapse versus risk of morbidity / mortality due to influenza disease...

Neurologists and Public Health

- Neurologists will be crucial to GBS H1N1 surveillance activities
- Opportunity for neurologic community to assist in critically important public health response
- Opportunities for neurologists to assist in future important public health initiatives
GET A SHOT OF PROTECTION.

THE SWINE FLU SHOT.
Additional Slides

► 1976 swine flu vaccines contain (uncharacterized) GM1-like structures by BOTH cholera toxin binding assay & recognition by polyclonal anti-GM1 reagent
  - GM1 is receptor for cholera toxin and contains surface sialic acid residues
  - Patients with GBS of any cause develop antibodies to ganglioside GM1 – hypothesized “molecular mimicry”

► Mice inoculated with 1976 swine flu vaccines developed IgM & IgG anti-GM1 antibodies by EIA (not an animal model; mice not ill; no histology or nerve conduction studies; Abs not fully titered)

► Commercially-available anti-GM1 antibodies produce influenza HI titers of 1:10-1:20, but anti-asialo-GM1 (GM1 w/o sialic acid) antibodies do not

HYPOTHESIS: If sialic acid is required for full GM1 antigenicity, then HA/GM1 cross-reactivity might also require HA-sialic acid complexes, which could be produced by low NA (which cleaves HA from sialic acid).

Theory implies that HA-sialic acid complexes, but not fully NA-cleaved HA (either viral or non-viral), might present an epitope or epitopes that cross-react with (a) sialo-GM1 epitope(s)

Notes:
The pathogenesis of GBS is unknown
There is no animal model for GBS
Some post-1976 vaccines NOT associated with GBS produced similar results (anti-GM1 structures/antibody induction)
Serums from 1976 GBS cases not yet identified (has been discussed with CDC)
Not known whether HA-sialic acid complexes can be reliably produced, measured, or studied quantitatively
Not known how to vary viral NA activity experimentally?
Vaccine-Associated Neurologic Disease

- Neurologic AE
  - Neurotropic
    - Central Nervous System
  - Post-Immunization Immune-Mediated
  - "diosyncratic"
    - Peripheral Nervous System
“Phylogeny” of GBSs

Guillain-Barré Syndromes

- Acute Inflammatory Demyelinating Type (AIDP)
  - (Secondary axonal Degeneration)
- Acute motor axonal Type (AMAN)
- Acute motor and Sensory axonal type (AMSAN)
- Fisher syndrome