Protocol for proposed guideline project: Neurologic adverse events following immunizations

Proposal of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology

Authors

John Halperin, MD, FAAN1; Richard Dubinsky, MD, FAAN, MPH2; Melissa Armstrong, MD, MSc3; Brian Callaghan, MD4; Frank DeStefano, MD, MPH5; Jonathan Duffy, MD, MPH6; Peter Kang, MD7; Nina Schor, MD, PhD, FAAN8; James Sejvar, MD9; Amber Stock, MPH10; Thomas S.D. Getchius11; Shannon Merillat, MLIS12; Max Wiznitzer, MD, FAAN11; Lisa Geng12

1. Overlook Medical Center, Atlantic Neuroscience Institute, Summit, NJ
2. Department of Neurology, University of Kansas Medical Center, Kansas City
3. Department of Neurology, University of Maryland, Baltimore
4. Department of Neurology, University of Michigan Health System,
5. US Centers for Disease Control and Prevention, Atlanta, GA
6. US Centers for Disease Control and Prevention, Atlanta, GA
7. Department of Pediatrics, University of Florida College of Medicine, Gainesville
8. University of Rochester Medical Center, Rochester, NY
9. US Centers for Disease Control and Prevention, Atlanta, GA
10. American Academy of Neurology, Minneapolis, MN
11. American Academy of Neurology, Minneapolis, MN
Address correspondence to
American Academy of Neurology:
guidelines@aan.com

Approved by the Guideline Development, Dissemination, and Implementation Subcommittee on July 18, 2015. All comments submitted during the 30-day public comment period in which this protocol is posted will be reviewed by the author panel members. Although all comments will be considered, author panel members will not specifically respond to individual comments online.

**STUDY FUNDING**

This practice advisory protocol was developed with financial support from the American Academy of Neurology. Authors who serve as AAN subcommittee members or methodologists, or who are AAN staff members (JH, RD, MA, BC, AS, TSDG, SM), were reimbursed by the AAN for expenses related to travel to subcommittee meetings where drafts of manuscripts were reviewed.
DISCLOSURES

Dr. Halperin serves on the editorial boards of The Neurologist and ACP PIER; receives royalties from the publisher of the book Encephalitis; has received honoraria for continuing medical education (CME) lectures; has received research support from the US Centers for Disease Control and Prevention (CDC); has given expert testimony, prepared an affidavit, and acted as witness or consultant regarding the defense of several physicians in medical malpractice cases, including accusations of failure to diagnose Lyme disease, and aided the Connecticut Department of Health in proceedings against a physician who repeatedly treated nonexistent Lyme disease; and serves on the Neurology Level of Evidence editorial board.

Richard Dubinsky serves on a scientific advisory board for Allergan Pharmaceuticals; receives funding for travel from Allergan Pharmaceuticals, the Huntington Study Group, and the American Academy of Neurology (AAN); serves as an associate editor for Neurology; has received honoraria from and served on a speakers bureau for Allergan Pharmaceuticals; and has received research support from Allergan Pharmaceuticals, the National Institutes of Health (NIH), and the Agency for Healthcare Research and Quality (AHRQ). His wife holds stock in Abbott Laboratories.

Melissa Armstrong serves on the Level of Evidence editorial board for Neurology but does not receive financial compensation; receives royalties for co-editing Parkinson’s Disease: Improving Patient Care (Oxford University Press); serves as an evidence-based methodologist for the AAN; has received honoraria for teaching at the 2014 and 2015 AAN Annual Meetings and the 2013 and 2014 International Congresses of Parkinson’s Disease and Movement Disorders, and
for serving as faculty on the AAN EBM Online Curriculum; has served as a local investigator for studies sponsored by Abbvie, The Parkinson Study Group (PSG), PSG/Biotie, the Huntington Study Group, and the CHDI Foundation; is a 2015 recipient of a career development award from the AHRQ (1K08HS024159-01).

Brian Callaghan has served on a scientific advisory board through Kaiser Permanente funded by a Patient-Centered Outcomes Research Institute grant and has received research support from Impeto Medical and the NIH (K23 grant award).

Frank DeStefano is employed by the CDC.

Jonathan Duffy reports no disclosures.

Peter Kang has served on the DMD advisory board, sponsored by Sarepta Therapeutics, and an advisory board sponsored by Fate Therapeutics; has received funding for travel from the AAN, the Massachusetts Medical Society, Amy and Friends, and Sarepta Therapeutics; serves on journal editorial boards for Pediatrics and Pediatrics Neurology; has received honoraria from Fondazione Cariplo, Health Matters CME, American College of Medical Genetics, Third Rock Ventures, Muscular Dystrophy Association Telethon, and American Clinical; has received funding from the Veterans Administration and from the NIH (grant review honoraria); has received research support from Genzyme, Sarepta Therapeutics, the NIH, and the Muscular Dystrophy Association; and has acted as an expert witness in a vaccine injury compensation program case (HRSA). His spouse holds a patent related to gene therapy.
Nina Schor serves on the scientific advisory board for the Make-A-Wish foundation; has received funding for travel from the AAN, the Child Neurology Foundation, the American Pediatric Society, the University of California in Los Angeles, Boston Children’s Hospital, and Nemours; has served on editorial boards for *MedLink Neurology*, *Practice Update: Neurology*, *Journal of Child Neurology*, and *Pediatric Neurology*; receives royalties for publishing from Elsevier for *Nelson’s Textbook of Pediatrics* and *Swaiman’s Pediatric Neurology: Principles and Practice*; has received honoraria from the University of California in Los Angeles, Boston Children’s Hospital, and Weill Cornell Medical School; received research support from the Eunice Kennedy Shriver National Institute of Child Health and Human Development of the NIH, and from the following academic entities: Crosby’s Fund for Pediatric Research at Wilmot Cancer Center, University of Rochester, and Golisano Children’s Hospital at University of Rochester.

James Sejvar reports no disclosures.

Amber Stock is a full-time employee of the American Academy of Neurology.

Thomas S.D. Getchius is a full-time employee of the American Academy of Neurology.

Shannon Merillat is a full-time employee of the American Academy of Neurology.
Max Wiznitzer serves on the editorial board for the *Lancet Neurology* and the *Journal of Child Neurology*, has received honoraria for speaking at meetings of the AAN and American Academy of Pediatrics, and has served as an expert witness for the US Department of Health and Human Service by providing written opinions and hearing testimony and prepared an affidavit for a medical malpractice case related to the Vaccine Injury Compensation Program.

Lisa Geng reports no disclosures.

**DESCRIPTION OF AAN DOCUMENT TYPES**

This protocol is the planning document for one of four AAN document types: focused systematic review, comprehensive systematic review, practice advisory (based on a systematic review), or practice guideline (based on a systematic review). The term *Guideline* is the general term that refers to all AAN evidence-based documents. Because it is for planning purposes only, this protocol document is not a substitute for the complete Guideline.
GUIDELINE PROJECT PROTOCOL

Guideline project development plan

This proposed project will be developed in accordance with the processes described in the 2011 edition of the AAN clinical practice guideline development process manual (as amended). The authors of this Guideline project intend to develop an evidence-based practice guideline based on the systematic review the authors also will develop. The AAN Guideline Development, Dissemination, and Implementation Subcommittee (GDDI) will make the final determination of whether the systematic review will inform an evidence-based practice guideline or a practice advisory. This protocol will be posted for public comment. A patient representative is included on the panel.

Timeline

We provide the following tentative timeline for development of the systematic review:

Panel formation: Completed by March 2015

Draft of protocol presented to the AAN GDDI: July 2015

Protocol posted for public comment: December 2015

Literature search: Completed by January 2015

Panel review of abstracts: Completed by January 2016

Screening of full-text articles: Completed by April 2016

Review of full-text articles and data extraction: Completed by July 2016

Development of evidence tables: Completed by August 2016

First manuscript draft presented to the AAN GDDI: Completed and presented to GDDI August 2016
Composition of the author panel

In March 2015, a multidisciplinary panel consisting of 12 physicians, 2 AAN staff members (TG, SM), and 1 patient representative was recruited to develop this guideline project. The physicians include content experts (JH, BC, FD, JD, PK, NS, JS, AS, MW), a methodology expert (MA), GDDI members (JH, RD, BC), and 1 patient representative (LG). All authors were required to submit an online conflict of interest (COI) declaration and copies of their CVs. The panel leadership, consisting of the lead author (JH), the AAN methodologist (MA), and the AAN staff members (TG, SM), reviewed the COI forms and CVs for financial and intellectual COI. These documents were specifically screened to exclude both those individuals with a clear financial conflict and those whose professional and intellectual bias would diminish the credibility of the review in the eyes of the intended users. The panel composition was recommended to the AAN GDDI leadership, who further reviewed the list of proposed authors and those authors’ letters of intent, and provided final approval. In accordance with AAN policy, the lead author (JH) has no COIs. Two of the 12 authors were determined to have COIs (PK, MW). These authors will not be permitted to review or rate the evidence; rather, they will be used in an advisory capacity to help with the validation of the key questions, the scope of the literature search, and the identification of seminal articles to validate the literature search. The panel members with COIs will be allowed to participate in the recommendation development process, following the standards recommended by the Institute of Medicine (Standard 2). This panel was solely responsible for the final decisions about the design, analysis, and reporting of the review, which was then submitted for approval to the AAN GDDI.
Introduction to proposed project topic and rationale for this practice guideline

Since publication in 1999 of the original AAN guideline on this subject, there have been both increasing public concern about potential neurologic complications of immunization and substantial information documenting that this risk is statistically very low. From a neurologist’s perspective, the topic involves 2 discrete elements – what is the risk of neurologic complications following immunization of healthy individuals, and what is the risk of immunization in individuals who have already had a neurologic disorder, particularly one that is immunologically mediated? The purpose of this Guideline is to systematically review all high-quality controlled trials, whether randomized or nonrandomized, that address these questions. On the basis of this systematic review, we will develop recommendations regarding immunizations in these populations.

Clinical questions

1. In healthy individuals receiving immunizations, what neurologic complications occur, and how frequently, and how do these risks compare to the risks associated with the natural history of the targeted infection?

2. In patients with neurologic disease, are immunizations safer than the natural history of the disease, as measured by neurologic consequences of the immunizations and the natural history of the disease?

3. In patients taking immune-suppressive medications for neurologic disease, are there additional complications of immunization compared with the natural history of the disease?

Note: This may include related evidence in other diseases, separately identified.
4. In individuals who have recently received immunizations, what symptoms and clinical findings are indicative of an adverse neurologic reaction to the immunization and should lead to further investigation?

5. In individuals who have an adverse neurologic reaction to an immunization, which treatments improve outcome (function, cognition, etc.) compared with the natural history of neurologic adverse effects of immunizations?

Rationale for the clinical questions

Immunization has been one of the most important weapons in the reduction or near elimination of many infectious diseases. As with any medical intervention, there is well-documented attendant risk, although with most current vaccines, these are quite infrequent. Most recently, there has been an apparent increased incidence of narcolepsy in individuals vaccinated with a 2009 European influenza vaccine used during the 2009 H1N1 influenza pandemic. There appears to be some increase in the incidence of Guillain–Barré syndrome following vaccination with other influenza vaccines. On the other hand, many infections can have a far greater impact on patients who are chronically debilitated by neurologic diseases or are immune compromised by treatment of such diseases. When those neurologic diseases have an underlying immune mechanism, the advisability of vaccine-induced immune stimulation raises legitimate theoretical concerns. Superimposed on these well-substantiated concerns has been a widespread concern that early childhood immunizations could lead to autism or other disorders. As more data have accumulated pertinent to these questions, we determined this to be an appropriate time to update our literature review and guidance. Notably, this project excludes questions regarding multiple sclerosis and immunization, as this topic is being addressed in a separate guideline.
**Consideration of patient preferences**

The guideline panel includes a representative with personal experience relating to possible neurologic adverse events from immunization. This individual participated in formation of the clinical questions and drafting the project protocol and will participate in development of recommendations. Inclusion of this individual resulted in the addition of 2 questions that were not in the original scope of the guideline: (1) characterizing the specific symptoms children develop following immunization that portend neurologic complications and (2) what therapeutic options can be helpful in individuals who experience neurologic complications of vaccination.

Patient views and preferences will also be obtained through public comment on the project protocol and draft guideline.

**Relevant special populations and multiple morbidities**

Findings related to age, sex, and race/ethnicity are considered for all systematic reviews and guidelines. For this guideline specifically, because a large proportion of vaccinations is performed in children, and because there has been considerable concern regarding a possible relationship between immunization and neurodevelopmental issues, pediatrics will be a particular area of focus, though studies involving adults will also be examined. Since individuals (children and adults) with neurologic disease are particularly susceptible to adverse outcomes in infectious diseases, this population is also the subject of a specific question. Patients taking immunosuppressive medications for their neurologic disease are another special population considered in this guideline. As outlined in the search strategy, we will seek evidence specifically related to these populations in our search strategy and will formulate
recommendations regarding them to whatever extent supported by available high-quality evidence.

**Literature search strategy**

A medical librarian will perform a comprehensive literature search to obtain the relevant studies. The panel developed the search terms described below on the basis of the proposed clinical questions, and the research librarian will perform literature searches of the MEDLINE, Cochrane, and EMBASE databases, and the grey literature, using the following search strategy:

**Keywords**

a. Question 1

i. Chickenpox or diphtheria or h. flu or H1N1 or hepatitis A or hepatitis B or herpes zoster or human papilloma virus or influenza or measles or mumps or rubella or meningococcus or pertussis or pneumococcus or polio or rabies or rotavirus or shingles or tetanus or varicella

1. AND: (vaccination or immunization)

2. AND Complications or autism or Guillain Barre or Bell’s palsy or stroke or epilepsy or seizures or postural orthostatic hypotension tachycardia syndrome

ii. Chickenpox or diphtheria or h. flu or H1N1 or hepatitis A or hepatitis B or herpes zoster or human papilloma virus or influenza or measles or mumps or rubella or meningococcus or pertussis or pneumococcus or polio or rabies or rotavirus or shingles or tetanus or varicella
1. AND incidence AND ([nervous system and complications] or autism or Guillain Barre or Bell’s palsy or stroke or epilepsy or seizures or mortality)

b. Question 2

i. Chickenpox or diphtheria or h. flu or H1N1 or hepatitis A or hepatitis B or herpes zoster or human papilloma virus or influenza or measles or mumps or rubella or meningococcus or pertussis or pneumococcus or polio or rabies or rotavirus or shingles or tetanus or varicella

ii. AND (vaccination or immunization)

iii. AND (Bell’s palsy or muscular dystrophy or Charcot Marie Tooth or myasthenia or Guillain Barre syndrome or acute/chronic inflammatory demyelinating polyneuropathy or epilepsy or cerebral palsy or ADEM or tic disorders or narcolepsy or CRPS or developmental delay or static encephalopathy or autism spectrum or Dravet or myopathies or myositis or mitochondrial disorder or other CNS or other PNS)

c. Question 3

i. Immunosuppressed or immunocompromised

ii. AND vaccination

iii. AND Chickenpox or diphtheria or h. flu or H1N1 or hepatitis A or hepatitis B or herpes zoster or human papilloma virus or influenza or measles or mumps or rubella or meningococcus or pertussis or pneumococcus or polio or rabies or rotavirus or shingles or tetanus or varicella
iv. AND complications

d. Question 4

i. immunization

ii. AND Chickenpox or diphtheria or h. flu or H1N1 or hepatitis A or hepatitis B or herpes zoster or human papilloma virus or influenza or measles or mumps or rubella or meningococcus or pertussis or pneumococcus or polio or rabies or rotavirus or shingles or tetanus or varicella

iii. Early symptoms of neurologic complications

e. Question 5

i. Question 1.1

ii. AND treatment

2. Databases to be searched (e.g., MEDLINE, EMBASE, Current Contents): PubMed/
MEDLINE, EMBASE, Cochrane

3. Years to be included in the search: 1999–2015 (present)

4. Inclusion and exclusion criteria

  • Languages to be included: All

  • Selected study population:
    
    o Human subjects: Yes
    
    o Animal studies: No

  • Disease in question or closely related diseases to be included: Neurologic disorders, immunizations, adverse effects

Disease to be excluded: multiple sclerosis
Interventions to be included: immunizations

Interventions to be excluded: none

Outcomes to be included: all

Outcomes to be excluded: none

Types of studies to be included:

1. Randomized, controlled clinical trial
2. Cohort or case control or case series
3. Meta-analyses

Standard exclusion criteria:

i. Not relevant to the clinical question
ii. Unrelated disease*
iii. Outside of study population*
iv. Article not peer reviewed

*Strong related information from other diseases and populations may be considered during recommendation development but are not part of the systematic review.

Types of participants

The general population at risk for communicable diseases: children, adults, elders, men and women, all ethnic/racial groups, worldwide

People with chronic neurologic disorders, primarily those involving immunosuppressive therapies (e.g., myasthenia gravis), or immune-mediated diseases (acute inflammatory
demyelinating polyneuropathy, chronic inflammatory demyelinating polyneuropathy, CNS sarcoid)

Multiple sclerosis is excluded because a guideline on the topic of multiple sclerosis and immunization is already in process.

Types of intervention

Therapy: Immunizations against endemic infectious diseases (diphtheria or h. flu or H1N1 or hepatitis A or hepatitis B or influenza or measles or meningococcus or mumps or pneumococcus or pertussis or polio or rabies or rubella or tetanus or varicella)

Types of outcome measures

Neurologic complications of immunizations (primarily encephalitis, transverse myelitis and cerebellitis, but also worsening of underlying neurologic disease; autism).

This should be compared with the neurologic consequences of the diseases for which immunizations are offered.
1 DISCLAIMER

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18 CONFLICT OF INTEREST

The American Academy of Neurology is committed to producing independent, critical, and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms
were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects. Drafts of the guideline have been reviewed by at least three AAN committees, a network of neurologists, Neurology peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com. For complete information on this process, access the 2011 AAN process manual.9
REFERENCES


