

Immunizations and MULTIPLE SCLEROSIS

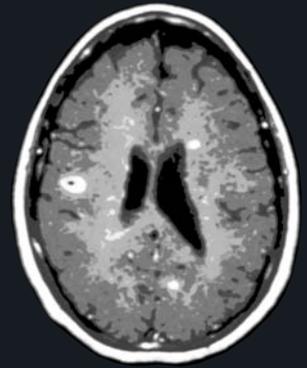
**Evidence-Based
Management Strategies for
Immunizations in
Multiple Sclerosis**



**Multiple Sclerosis Council
for Clinical Practice Guidelines**

Administrative and financial support provided by
Paralyzed Veterans of America

■ CLINICAL
■ PRACTICE
■ GUIDELINES



■ IMMUNIZATIONS



Multiple Sclerosis Council
for Clinical Practice Guidelines

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American Academy of Neurology
American Academy of Physical Medicine and Rehabilitation
American Congress of Rehabilitation Medicine
American Neurological Association
American Occupational Therapy Association
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American Psychological Association
American Society of Neuroradiology
American Society of Neurorehabilitation
American Speech-Language-Hearing Association
Association of Academic Physiatrists
Association of Rehabilitation Nurses
Canadian Neurological Association
Consortium of Multiple Sclerosis Centers
Eastern Paralyzed Veterans Association
International Organization of Multiple Sclerosis Nurses
Kaiser-Permanente Health Maintenance Organization
National Multiple Sclerosis Society
Paralyzed Veterans of America
Rehabilitation in Multiple Sclerosis
U.S. Department of Veterans Affairs

■ CLINICAL
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**Evidence-Based
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for Immunizations in
Multiple Sclerosis Patients**



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Fatigue and Multiple Sclerosis

Urinary Dysfunction and Multiple Sclerosis

Disease Modifying Therapies in Multiple Sclerosis

*Fatigue and Multiple Sclerosis: What You Should Know.
A Guide for People with Multiple Sclerosis*



November 2001

This guide has been prepared based on scientific and professional information available in 2001. Users of this guide should periodically review this material to ensure that the advice herein is consistent with current reasonable clinical practice.

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FOREWORD

Professional organizations from all sectors of the health-care community have embraced the development, use, and evaluation of practice guidelines through which they collate and evaluate empirical evidence and expert opinion. Generally, the goals of these practice guidelines are to reduce inappropriate care and improve patient outcomes, reduce health-care costs, enhance quality assurance, and improve medical education. Their benefit is in documenting the advice of clinical experts, documenting the clinical research, and assessing the clinical significance of conflicting research findings.

Many public and private health-care organizations are involved in developing practice guidelines, and the scope of topics researched and methodologies used is quite diverse. The choices of topics and methods reflect each organization's major practice concerns, the empirical evidence available on those topics, and, just as importantly, the resources available to the organization for developing the guidelines. Whenever possible, clinical practice guidelines are based on empirical evidence and in those cases the recommendations are graded on the quality of evidence. Nonetheless, expert opinion remains an integral part of guideline development "because reliable scientific evidence is lacking for most clinical practices" (S.H. Woolf, 1992. Practice guidelines: a new reality in medicine. II Methods of developing guidelines. *Archives of Internal Medicine* 152: 946–52).

I am pleased to present these clinical practice guidelines on immunizations in multiple sclerosis (MS) patients to the health-care community. These guidelines and others developed by the Multiple Sclerosis Council for Clinical Practice Guidelines reflect both the published research on this topic as well as the expert opinion of the panel members. That expert opinion has been supported in turn by the expert consensus of a broad range of clinicians who are MS specialists.

This topic, the use of immunizations by people with MS, is different from other issues included in this series of guidelines. It addresses the appropriateness of preventive measures that are recommended for the general population. In this document we consider what exceptions to the general standards of care should be made for people with MS. The recommendations that we consider are those of the Centers for Disease Control and Prevention. This is a topic that many community neurologists, general practitioners, and nurses have raised as being important for guideline development. It is a common concern among clinicians and patients, there is large variability in the practice of immunizing patients with MS, and it is likely that this guideline will help to standardize practice.

These guidelines are written for health-care professionals to assist them in clinical decision making. We anticipate that the document will be useful to clinicians in discussing MS and its symptoms with their patients and in making treatment decisions. We also expect the publication will be useful to individuals and organizations responsible for allocating health-care resources.

People with MS come from all walks of life and live with a broad range of disability. Their care is provided by many types of health-care professionals in varied settings. For this reason, the guidelines have been developed for a range of patients, clinicians, and treatment settings. Adaptability has been a guiding principle of the Multiple Sclerosis Council for Clinical Practice Guidelines, whose members represent the major professional and consumer MS groups, and of the members of the Guidelines Development Panel, who also reflect this provider and consumer diversity.

These guidelines will be of benefit only if they are studied, used, evaluated, and updated. The council welcomes the responsibility of ensuring the current and future value of these guidelines as part of its ongoing activities. However, we will be successful in this effort only with the participation of you, the health-care providers who use this document. We look forward to your comments on these guidelines and encourage you to undertake the investigations for future research recommended in this publication.

We are grateful to the Paralyzed Veterans of America for convening and providing ongoing support to the representatives of the 21 organizations that constitute the Multiple Sclerosis Council for Clinical Practice Guidelines. PVA's concern for the well-being of people with MS and its commitment to ensuring that appropriate care is available to every person with MS are an example to us all.

Deborah M. Miller, Ph.D.
Chair, MS Council for Clinical Practice Guidelines

ACKNOWLEDGEMENTS

The chair and members of the MS & Immunizations Guidelines Development Panel wish to express special appreciation for the leadership and encouragement shown by the 21 organizations that make up the Multiple Sclerosis Council for Clinical Practice Guidelines and their representatives. We especially appreciate the contributions of the 13 professionals who provided expert review of the final draft. The efforts of all of these groups have been crucial in establishing the expert consensus that underpins these recommendations.

Assistance in conducting the literature review was provided by the staff of the Center for Clinical Health Policy Research at Duke University, especially, David B. Matchar, MD, Douglas C. McCrory, MD, MHSc, Olivier Rutschmann, MD, MPH, and Jane Kolimaga, MA. Their assistance was essential to the successful completion of these guidelines.

The Guidelines Development Panel is indebted to the leaders and staff of the Paralyzed Veterans of America, who provided organizational, administrative, and financial support to the Guidelines Development Panel. In particular, the panel recognizes Lara Chisa, project administrator of the MS Council, who demonstrated her organizational and management skills throughout this project; John Carswell, associate executive director of the Health Policy Department, who championed the cause of PVA members who have MS; Fred Cowell, staff director of that department, who made sure that the project was appropriately staffed; James A. Angelo, Patricia E. Scully, and Christine Campbell of the Communication Department who provided editing, design, indexing, and production; medical writer Jane Saiers, PhD; medical editor Joellen Talbot, who provided excellent technical and editorial review; and legal reviewer William H. Archambault of Goodman, West & Filetti, PLLC, Charlottesville, VA. Finally, we are grateful for the steadfast commitment and advocacy of PVA's senior officers, including Immediate Past President Homer S. Townsend, Jr., National President Joseph L. Fox, Sr., Executive Director Del McNeal, Deputy Executive Director John C. Bollinger, and the entire PVA board of directors.

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THE MULTIPLE SCLEROSIS COUNCIL

Two separate organizational efforts stimulated the 1997 formation of the Multiple Sclerosis Council for Clinical Practice Guidelines. The first of these efforts was formalized in 1995 when the American Academy of Neurology, the Consortium of Multiple Sclerosis Centers, and the National Multiple Sclerosis Society established the interorganizational Collaborative Group for Multiple Sclerosis Management Strategies (CGMSMS). The term “management strategies” was used in this collaboration because of concern that, although the recommendations would be based on all available empirical evidence, development of the recommendations would be largely dependent on expert consensus. In that same year, CGMSMS formed a steering committee, which established criteria for topic selection and management strategy development, and convened management strategies development panels on two topics—fatigue and bladder dysfunction.

The second organizational effort was initiated by the Paralyzed Veterans of America. To better serve the approximately 30 percent of PVA members who experience multiple sclerosis, the organization made a board-level decision in 1997 to commit resources for developing practice guidelines for MS. This commitment paralleled the guidelines support PVA had been providing to the spinal cord injury community since 1995, through the Consortium of Spinal Cord Medicine. In making these resources available, PVA also ensured that its only influence on the recommendations generated through the MS-guidelines effort would be through its one voting member on the council. In 1997 the two organizational efforts were integrated, and the Multiple Sclerosis Council for Clinical Practice Guidelines was established. This merger allowed a greater number of organizations to participate and a more ambitious schedule for producing the guidelines to be set.

The Multiple Sclerosis Council for Clinical Practice Guidelines is made up of 21 representatives from key MS professional and consumer organizations. A multidisciplinary group, it includes civilian and military representatives who have experience in fee-for-service and managed care payment systems, as well as in academic, group, and individual practice settings. These representatives and their organizations are listed on page ix. Each member organization is responsible for providing the following:

- Appointment to the council of one member with expertise in the topic area.
- High-level professional and technical peer review of the guidelines materials.
- Dissemination and application of the guidelines through the organization’s educational offerings.
- Organizational endorsement of the completed practice guidelines and related products.

In addition, each member of the council participates in one of three advisory subcommittees: the Methodological and Scientific Review Advisory Subcommittee; the Topic Selection and Panel Recruitment Advisory Subcommittee; or the Peer Review, Dissemination, and Outcomes Evaluation Advisory Subcommittee.

Dissemination of the guidelines is through the member organizations and other key societies, including publication in *Neurology*, the journal of the American Academy of Neurology. Evaluation of the guidelines is the responsibility of the Multiple Sclerosis Council for Clinical Practice Guidelines, which will consider the guidelines’ utility, their impact on clinical outcomes, and the need for revision as new information becomes available.

INTRODUCTION

Multiple sclerosis, one of the most common causes of nontraumatic neurologic disability, is a chronic, inflammatory, immune-mediated disease characterized by central nervous system demyelination. Its etiology is unknown, but may involve both genetic and environmental factors (1–5). Some evidence suggests that infectious agents may influence the development and clinical course of multiple sclerosis (1–5). Viruses in particular have been hypothesized to play a role in causing multiple sclerosis and in triggering exacerbations of the disease. The possibility that viruses or other infectious agents are responsible for development or exacerbation of multiple sclerosis raises questions about the risks and benefits of antimicrobial immunizations:

- Immunizations stimulate the immune system and health-care providers and patients have raised the concern that immunizations may trigger exacerbations in patients with multiple sclerosis (1). Influenza and hepatitis B are two vaccines where particular concern has been raised about safety. The administration of live attenuated vaccines, such as varicella and measles/mumps/rubella, might be of special concern.
- On the other hand, some evidence suggests that exacerbations of multiple sclerosis may occur more frequently during viral infections that might be prevented by vaccinations (6, 7). If so, prevention of viral infections by vaccination might reduce the risk of exacerbations of multiple sclerosis.

These considerations have led health-care providers who care for patients with multiple sclerosis to seek information on the utility and safety of immunizations in multiple sclerosis.

Purpose and Scope

These guidelines were developed to provide clinicians with the information they need to evalu-

ate the risks and benefits of immunization in patients with multiple sclerosis. The guidelines proffer practical advice that will assist clinicians in adopting a systematic, evidence-based approach to weighing the risks and the benefits of vaccination and to deciding whether or not to immunize an adult patient with multiple sclerosis.

These guidelines consider all common immunizations, including influenza, hepatitis B, diphtheria/tetanus (given either for routine vaccination or for wound management), varicella, Bacille Calmette-Guérin (BCG), pneumococcus, measles/mumps/rubella, hepatitis A, and other vaccines (polio, typhoid, yellow fever, and rabies). The guidelines are intended to supplement but not to replace other information and tools clinicians rely upon to make decisions about immunization in multiple sclerosis.

Goals

The goals of the guidelines are to:

- Provide clinicians with the best available evidence about the utility and safety of immunizations in patients with multiple sclerosis
- Provide clinicians with a practical decision-making tool for assisting in immunization-related decisions with the aim of improving the quality of care for individuals with multiple sclerosis
- Stimulate additional clinical research into the use of immunizations in patients with multiple sclerosis

The remainder of this document describes the methods employed in developing the guidelines, explains the treatment algorithms arising from the guideline, and reviews recommendations for future research. Considered together, the evidence available to date suggests that immunizations are safe for patients with multiple sclerosis.

METHODS

These guidelines, based on a review of the published evidence on the safety and efficacy of vaccines for patients with multiple sclerosis, were prepared by the MS & Immunizations Guidelines Development Panel, which is comprised of a multidisciplinary team of individuals with expertise relevant to evaluating the utility and safety of immunization in patients with multiple sclerosis.

In developing the guidelines for immunization in patients with multiple sclerosis, the MS & Immunizations Guidelines Development Panel followed a multiphasic process that integrates the methodologies of the Collaborative Group for Multiple Sclerosis Management Strategies and the Consortium for Spinal Cord Medicine.

- During phase I, the parameters of the guidelines were determined. It was determined that the guidelines would apply to adult patients with multiple sclerosis and involve the following common immunizations: influenza, hepatitis B, diphtheria/tetanus (for both routine vaccination and wound management), varicella, BCG, pneumococcus, measles/ mumps/rubella, hepatitis A, and other vaccines (polio, typhoid, yellow fever, and rabies).
- Phase II was devoted to constructing, based on panel members' expert opinion, proto-algorithms for each of the immunizations identified in phase I.
- During phase III, the panel, working with methodologists expert in medical literature review, data extraction, and data synthesis, defined a strategy for searching and reviewing the medical literature in order to identify information relevant to refining the proto-algorithms. Relevant publications were identified using the procedure outlined in table 1. Two physicians independently reviewed all relevant publications and

assigned levels of evidence to them according to criteria developed by the American Academy of Neurology (see table 2).

- The guidelines were developed during phase IV as the panel expanded the proto-algorithm and wrote the supporting annotations based upon the literature. If the available scientific data were insufficient to support a recommendation, the panel noted the insufficiency and developed one based on expert opinion.

Table 1. Literature Review Methodology

- The panel identified specific topics to be included in the literature searches and guided the development of inclusion and exclusion criteria so that the publications identified through the literature searches would be appropriately focused.
- The primary literature source was MEDLINE, a computerized, bibliographical database maintained by the National Library of Medicine. MEDLINE searches were supplemented by thorough searches of the reference lists of all articles and review articles identified for the project.
- The literature searches identified 667 potentially relevant abstracts of articles published between 1966 and February 2001. These abstracts were reviewed by the panel, which determined whether the information appeared to meet the criteria for being retrieved from the library for a more critical screening and possibly the data abstraction. The number of abstracts selected for full-text review was 280.
- Each of the 280 articles that the panel identified for possible data abstraction was retrieved in full-text form and reviewed independently by two physicians, who determined whether the article met the inclusion and exclusion criteria. The 69 articles determined to meet the criteria were summarized in the form of evidence tables for panel evaluation. The two physicians assigned a level of evidence to each of the 69 articles. Finally, 21 articles were found to be relevant and used in the development of the guidelines (see appendix A).

Table 2. American Academy of Neurology Evidence Classification Scheme

Rating of recommendation	Translation of evidence to recommendations	Rating of Therapeutic Article	Rating of Programmatic Article
<p>A = Established as effective, ineffective, or harmful for the given condition in the specified population</p>	<p>Level A rating requires at least one convincing class I study or at least two consistent, convincing class II studies</p>	<p>Class I: Prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population. The following are required:</p> <ul style="list-style-type: none"> a. primary outcome(s) is/are clearly defined b. exclusion/inclusion criteria are clearly defined c. adequate accounting for drop-outs and crossovers with numbers sufficiently low to have minimal potential for bias d. relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences. 	<p>Class I: Evidence provided by a prospective study of a broad spectrum of persons who may be at risk for developing the outcome (e.g., target disease, work status). The study measures the predictive ability using an independent gold standard for case definition. The predictor is measured in an evaluation that is masked to clinical presentation and the outcome is measured in an evaluation that is masked to the presence of the predictor.</p>
<p>B = Probably effective, ineffective, or harmful for the given condition in the specified population</p>	<p>Level B rating requires at least one convincing class II study or at least three consistent class III studies</p>	<p>Class II: Prospective matched group cohort study in a representative population with masked outcome assessment that meets a-d above OR an RCT in a representative population that lacks one criterion a-d.</p>	<p>Class II: Evidence provided by a prospective study of a narrow spectrum of persons at risk for having the condition or by a retrospective study of a broad spectrum of persons with the condition compared to a broad spectrum of controls. The study measures the prognostic accuracy of the risk factor using an acceptable independent gold standard for case definition. The risk factor is measured in an evaluation that is masked to the outcome.</p>
<p>C = Possibly effective, ineffective, or harmful for the given condition in the specified population</p>	<p>Level C rating requires at least two convincing and consistent class III studies</p>	<p>Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment.</p>	<p>Class III: Evidence provided by a retrospective study where either the persons with the condition or the controls are of narrow spectrum. The study measures the predictive ability using an acceptable independent gold standard for case definition. The risk factor is measured in an evaluation that is masked to the outcome.</p>
<p>U = Data inadequate or conflicting. Given current knowledge, treatment is unproven.</p>		<p>Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion.</p>	<p>Class IV: Any design where the predictor is not applied in a masked evaluation OR evidence provided by expert opinion or case series without controls.</p>

- After the panel had agreed on the guidelines, a draft manuscript was sent for review and comment to several outside experts who had not been involved in the development process. The revised guidelines were also sent to the 21 representatives of the Multiple Sclerosis Council for Clinical Practice Guidelines and to as many as three additional reviewers from each member organization for review and comment.

Role of the Centers for Disease Control Guidelines

The Centers for Disease Control and Prevention (CDC) have developed guidelines for immunizations for adults. These recommendations are summarized in appendix B. The panel used the CDC recommendations as a foundation for developing its guidelines for patients with multiple sclerosis; the underlying position of the panel was to recommend that the CDC guidelines for adult immunizations be followed unless the panel considered the evidence to show that a vaccine was unsafe for patients with multiple sclerosis.

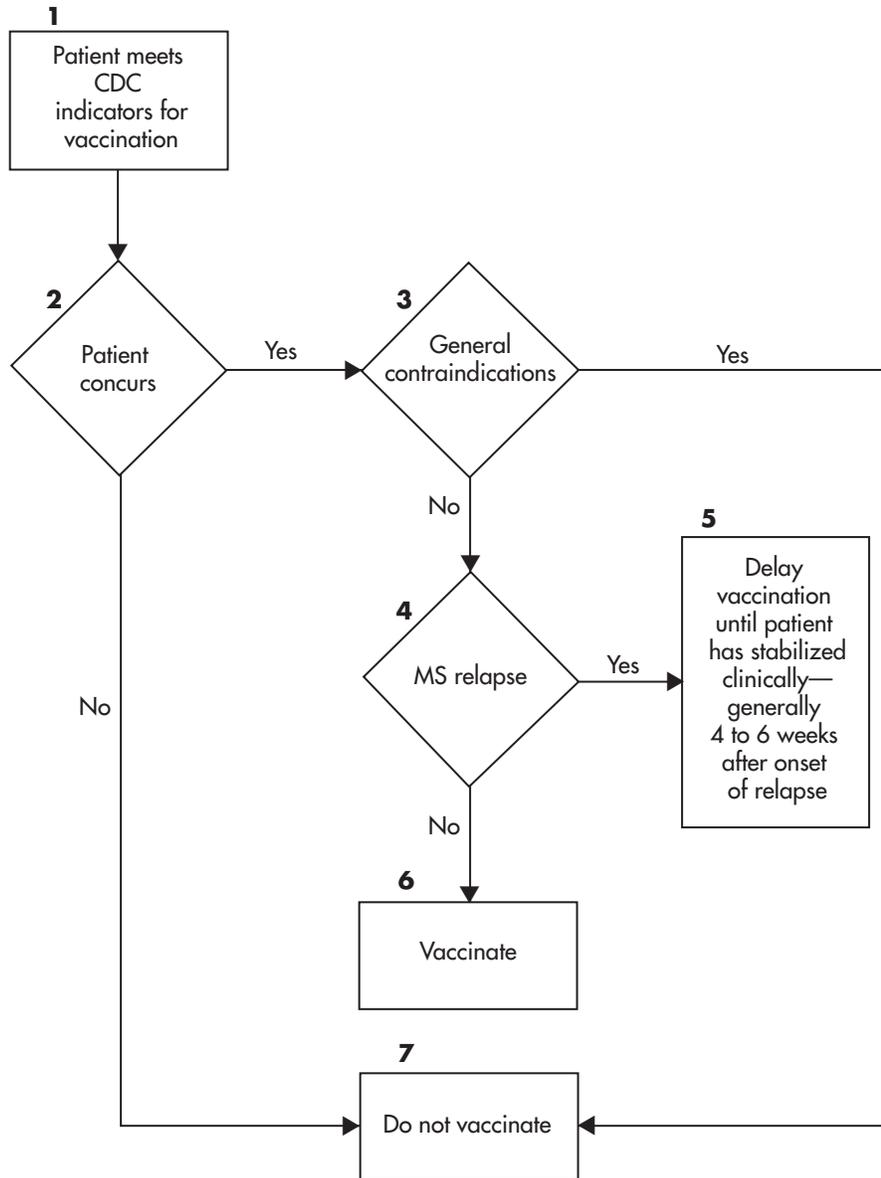
The consensus of the panel was that, in the absence of evidence of lack of safety, patients with multiple sclerosis should not be denied access to health-preserving and potentially life-saving vaccines.

Using the Treatment Algorithms

To maximize the utility of the guidelines, the panel condensed the recommendations into two treatment algorithms with accompanying annotations for each vaccination. Each algorithm is a flow chart intended to guide clinicians in making decisions about the use of a specific immunization for patients with multiple sclerosis. Diamond-shaped boxes indicate decision nodes, and rectangular or square boxes indicate evaluation and treatment nodes.

The annotations for each vaccination categorize the level of recommendation (Level A, B, or C) according to criteria developed by the American Academy of Neurology (see table 2). The panel wrote annotations to the algorithms only for vaccines in common use in the United States and with one or more class I, II, or III publications on safety in multiple sclerosis. Recommendations for other vaccines are discussed in a separate section following the algorithms and annotations.

Algorithm 1: Influenza (A), Hepatitis B (B), Varicella (C), and Diphtheria/Tetanus—Routine (D)



ALGORITHM 1: Influenza (A), Hepatitis B (B), Varicella (C), and Diphtheria/Tetanus— Routine (D) Treatment Recommendations

Annotations to Algorithm 1: Influenza Vaccination (A)

1.A-1 Patient meets CDC indications for Influenza Vaccination

Influenza vaccination has been shown to be safe for patients with multiple sclerosis (8-19): **Level A Recommendation** (see Table 3).

Physicians should recommend that patients with multiple sclerosis who meet CDC indications (see appendix A) consider receiving influenza vaccination. The CDC recommends that the following groups receive the influenza vaccination:

- Adults 50 years of age and older
- Residents of nursing homes or other facilities that care for patients with chronic medical conditions
- Individuals at least 6 months of age with chronic cardiovascular or pulmonary disorders, including asthma
- Individuals at least 6 months of age with chronic metabolic diseases (including diabetes), renal dysfunction, hemoglobinopathies, or immunosuppressive or immunodeficiency disorders
- Women who will be in their second or third trimester of pregnancy during influenza season
- Individuals 6 months to 18 years of age receiving long-term aspirin therapy
- Groups, including household members and caregivers, who can infect high-risk persons
- Any person at least 6 months of age who wishes to reduce the likelihood of becoming ill with influenza

MS patients who spend most or all of their time in a wheelchair or motorized cart or are bed-bound have impaired pulmonary function and should receive yearly influenza vaccination as indicated in the CDC guidelines (3rd indication above). MS patients who are on chronic corticosteroid therapy, including monthly infusions with high dose methylprednisolone, or immunosuppres-

sants, such as mitoxantrone, cyclophosphamide, azathioprine, and methotrexate, should receive yearly influenza vaccination as indicated in the CDC guidelines (4th indication above). It is important to note, however, that the recombinant interferons and glatiramer acetate are not immunosuppressants. Finally, MS patients requesting influenza vaccination for protection from influenza should be given the vaccine per the CDC guidelines (last indication above).

While many MS patients will meet the above indications for influenza vaccination as described above, some patients will not, such as young, otherwise healthy MS patients who are fully ambulatory. There is divided opinion among experts over whether all MS patients should receive yearly influenza vaccination, including patients who do not meet any of the CDC indications for vaccination. Those experts that advocate giving all MS patients yearly influenza vaccination argue that (1) it is safe to do so and (2) it will reduce the risk of patients developing influenza that might precipitate a relapse or worsening of MS symptoms (6, 15, 16, 20–24). However, other experts argue that many of their MS patients who do not meet CDC indications for vaccination report that they never or rarely develop influenza and these experts see no reason to recommend that these patients receive influenza vaccination, particularly in patients who do not want to receive the vaccination and question the need for vaccination. For MS patients who do not meet the CDC indications for influenza vaccination as discussed above, the MS & Immunizations Guidelines Development Panel recommends that physicians inform these patients that there is divided opinion among experts about whether or not they should receive influenza vaccination and discuss the basis for the difference of opinion; the final decision should be made by these patients in consultation with their physicians.

The components of the influenza vaccine change annually; the risk of neurologic complications is not necessarily similar between vaccines with differing components.

1.A-2 Patient concurs

Patients need to be involved in the decision-making process.

1.A-3 General contraindications

CDC contraindications for the influenza vaccine are anaphylactic allergy to eggs and acute febrile illness. Prophylactic use of neuraminidase inhibitors may be considered in patients with contraindications to the influenza vaccine.

1.A-4 Relapse of multiple sclerosis

Randomized controlled trials of influenza vaccination have generally excluded patients experiencing relapses of multiple sclerosis and there are therefore no research studies to indicate whether it is safe to give influenza vaccination in the midst of a relapse. The neurologists on the guidelines development panel and most neurologists reviewing the guidelines do not give the influenza vaccine when patients are in the midst of a significant relapse (i.e., one that causes motor symptoms or severe sensory symptoms that have affected the patient's usual ability to carry out daily activities) or who are receiving corticosteroids for a relapse. The rationale for delaying vaccination is that the vaccination might cause side effects, such as fever, that could worsen the relapse. In addition, if patients receive corticosteroids for a relapse, the corticosteroids might decrease the effectiveness of the vaccination. However, these experts do not delay vaccinations in patients experiencing minor, nondisabling relapses, such as those causing only sensory symptoms or in patients who have asymptomatic gadolinium-enhancing lesions on magnetic resonance imaging. The panel recognizes that there is no scientifically valid research to support the practice of delaying vaccination during clinically significant relapses or for relapses treated with corticosteroids. This recommendation is therefore based solely on expert opinion.

1.A-5 Delay vaccination until patient has stabilized clinically—generally 4 to 6 weeks after onset of relapse.

Expert opinion recommends delaying influenza vaccination until patients have stabilized or have begun to improve from the relapse, typically 4–6 weeks after the start of the relapse. If patients are treated with corticosteroids for a relapse, influenza vaccination should be delayed until 4 weeks after the last dose of corticosteroid.

Annotations to Algorithm 1: Hepatitis B Vaccination (B)**1.B-1 Patient meets CDC indications for Hepatitis B vaccination**

Hepatitis B is a serious and potentially life-threatening illness from which patients at high risk of exposure based on CDC indications should be protected.

The CDC indications for hepatitis B vaccination include:

- People with occupational risk of exposure to blood or blood-contaminated fluids
- Clients and staff of institutions for the developmentally disabled
- Hemodialysis patients
- Recipients of clotting-factor concentrates
- Household contacts and sex partners of those chronically infected with HBV
- Family members of adoptees from countries where HBV infection is endemic, if adoptees are HbsAg+
- Certain international travelers
- Injecting drug users
- Men who have sex with men
- Heterosexual men and women with multiple sex partners or a recent episode of a sexually transmitted disease
- Inmates of long-term correctional facilities
- All unvaccinated adolescents

There have been concerns raised that the hepatitis B vaccination may induce the risk of developing MS but recent publications do not support them (11, 28-32). Because of these concerns, some physicians have questioned the safety of the hepatitis B vaccination for MS patients. However, limited evidence suggests that the hepatitis B vaccination is safe for patients with multiple sclerosis (11). **Level C Recommendation.**

1.B-2 Patient concurs

The patient should be involved in the decision-making process.

1.B-3 General contraindications

The CDC contraindication for the hepatitis B vaccine is an anaphylactic allergy to yeast.

1.B-4 Relapse of multiple sclerosis

There are no research studies to indicate whether it is safe to give the hepatitis B

vaccine in the midst of a relapse. The neurologists on the guidelines development panel and most neurologists reviewing the guidelines do not give elective prophylactic vaccinations when patients are in the midst of a significant relapse (i.e., one that causes motor symptoms or severe sensory symptoms that have affected the patient's usual ability to carry out daily activities) or who are receiving corticosteroids for a relapse. The rationale for delaying vaccination is that the vaccination might cause side effects, such as fever, that could worsen the relapse. In addition, if patients receive corticosteroids for a relapse, the corticosteroids might decrease the effectiveness of the vaccination. However, these experts do not delay vaccinations in patients experiencing minor, nondisabling relapses, such as those causing only sensory symptoms or in patients who have asymptomatic gadolinium-enhancing lesions on magnetic resonance imaging. The panel recognizes that there is no scientifically valid research to support the practice of delaying vaccination during clinically significant relapses or for relapses treated with corticosteroids. This recommendation is therefore based solely on expert opinion.

1.B-5 Delay vaccination until patient has stabilized clinically—generally 4 to 6 weeks after onset of relapse.

Expert opinion recommends delaying vaccination until patients have stabilized or have begun to improve from the relapse, typically 4–6 weeks after the start of the relapse. If patients are treated with corticosteroids for a relapse, hepatitis B vaccination should be delayed until 4 weeks after the last dose of corticosteroid.

Annotations to Algorithm 1: Varicella Vaccination (C)

1.C-1 Patient meets CDC indications for Varicella vaccine

In adults, primary varicella infection carries a small risk of severe complications, particularly in immunosuppressed patients, and teratogenicity. Limited evidence suggests that varicella immunization is safe for patients with multiple sclerosis (25).

Level C recommendation.

For patients with multiple sclerosis who meet CDC high-risk criteria (see appendix B), the panel recommends administering the varicella vaccine if the patient is seronegative for varicella.

The CDC recommends that the varicella vaccine be administered to

- People of any age without a reliable history of varicella disease or vaccination or who are seronegative for varicella
- Susceptible adolescents or adults living in households with children
- All susceptible health-care workers
- Susceptible family contacts of immunocompromised patients
- Susceptible people in the following groups who are at high risk for exposure:
 - people who live or work in environments in which transmission of varicella is likely (e.g., teachers of young children, day care employees, residents and staff in institutional settings) or can occur (e.g., college students, inmates and staff of correctional institutions, military personnel)
 - nonpregnant women of childbearing age
 - international travelers

1.C-2 Patient concurs

The patient should be involved in the decision-making process.

1.C-3 General contraindications

CDC contraindications for the varicella vaccine include:

- Anaphylactic allergy to gelatin or neomycin
- Untreated, active tuberculosis

- Immunosuppressive therapy or immunodeficiency* (including HIV infection)
- Family history of congenital or hereditary immunodeficiency in first-degree relatives, unless the immune competence of the recipient has been clinically substantiated or verified by a laboratory
- Immune globulin preparation or blood/blood product received during the preceding 5 months
- Pregnancy

1.C-4 Relapse of multiple sclerosis

There are no research studies to indicate whether it is safe to give varicella vaccine in the midst of a relapse. The neurologists on the guidelines development panel and most neurologists reviewing the guidelines do not give elective prophylactic vaccinations when patients are in the midst of a significant relapse (i.e., one that causes motor symptoms or severe sensory symptoms that have affected the patient's usual ability to carry out daily activities) or who are receiving corticosteroids for a relapse. The rationale for delaying vaccination is that the vaccination might cause side effects, such as fever, that could worsen the

relapse. In addition, if patients receive corticosteroids for a relapse, the corticosteroids might decrease the effectiveness of the vaccination. However, these experts do not delay vaccinations in patients experiencing minor, nondisabling relapses, such as those causing only sensory symptoms or in patients who have asymptomatic gadolinium-enhancing lesions on magnetic resonance imaging. The panel recognizes that there is no scientifically valid research to support the practice of delaying vaccination during clinically significant relapses or for relapses treated with corticosteroids. This recommendation is therefore based solely on expert opinion.

1.C-5 Delay vaccination until patient has stabilized clinically—generally 4 to 6 weeks after onset of relapse.

Expert opinion recommends delaying vaccination until patients have stabilized or have begun to improve from the relapse, typically 4-6 weeks after the start of the relapse. If patients are treated with corticosteroids for a relapse, varicella vaccination should be delayed until 4 weeks after the last dose of corticosteroid.

*Human recombinant interferons and glatiramer acetate are not immunosuppressants and are not contraindications for receiving varicella or other live attenuated virus vaccines. Patients with multiple sclerosis who are on chronic corticosteroid therapy or are receiving treatment with immunosuppressants (e.g., mitoxantrone, azathioprine, methotrexate, or cyclophosphamide) may be immunosuppressed, and the safety of administering varicella or other live attenuated virus vaccinations is unknown.

Annotations to Algorithm 1: Diphtheria/Tetanus Vaccination— Routine (D)

1.D-1 Patient meets CDC indications for diphtheria/tetanus vaccination (routine):

Tetanus is a serious and potentially life-threatening illness from which patients at high risk of exposure based on CDC indications (see appendix B) should be protected. The CDC recommends that all adults be vaccinated for diphtheria/tetanus and that all adolescents be assessed at 11–12 or 14–16 years of age and immunized if no dose was received during the previous five years. Limited evidence suggests that the tetanus vaccination is safe for patients with multiple sclerosis (11).

Level C recommendation.

1.D-2 Patient concurs

The patient should be involved in the decision-making process.

1.D-3 General contraindications

CDC contraindications for the diphtheria/tetanus vaccine are a neurologic or severe hypersensitivity reaction to prior dose.

1.D-4 Relapse of multiple sclerosis

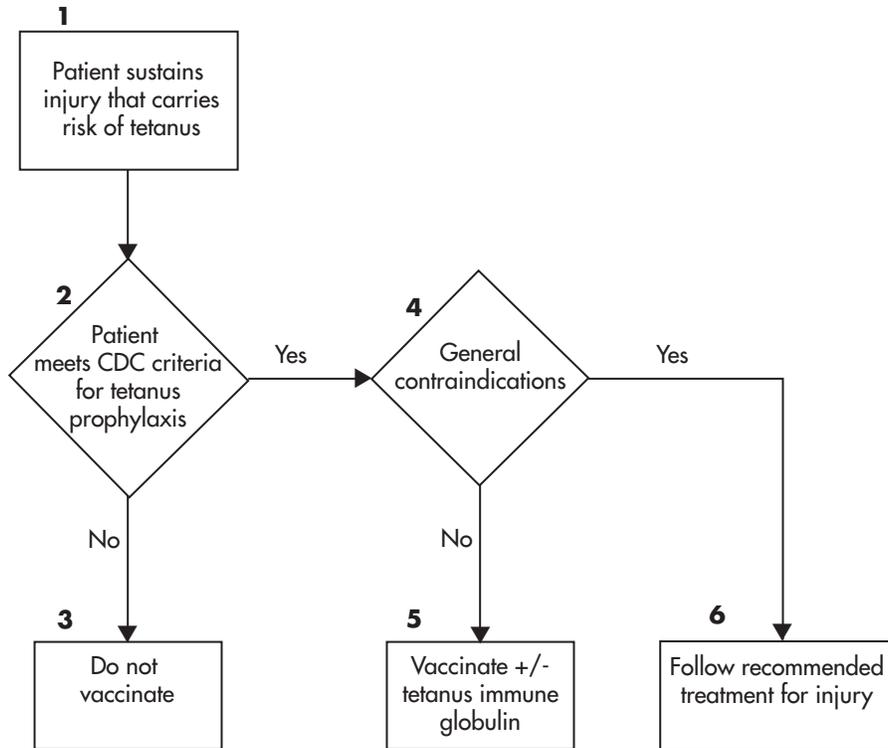
There are no research studies to indicate whether it is safe to give diphtheria/tetanus vaccine in the midst of a relapse. The neurologists on the guidelines development panel and most neurologists reviewing the guidelines do not give elective prophylactic vaccinations when patients are in the midst of a significant relapse (i.e., one that causes

motor symptoms or severe sensory symptoms that have affected the patient's usual ability to carry out daily activities) or who are receiving corticosteroids for a relapse. The rationale for delaying vaccination is that the vaccination might cause side effects, such as fever, that could worsen the relapse. In addition, if patients receive corticosteroids for a relapse, the corticosteroids might decrease the effectiveness of the vaccination. However, these experts do not delay vaccinations in patients experiencing minor, nondisabling relapses, such as those causing only sensory symptoms or in patients who have asymptomatic gadolinium-enhancing lesions on magnetic resonance imaging. The panel recognizes that there is no scientifically valid research to support the practice of delaying vaccination during clinically significant relapses or for relapses treated with corticosteroids. This recommendation is therefore based solely on expert opinion.

1.D-5 Delay vaccination until patient has stabilized clinically—generally 4 to 6 weeks after onset of relapse.

Expert opinion recommends delaying vaccination until patients have stabilized or have begun to improve from the relapse, typically 4–6 weeks after the start of the relapse. If patients are treated with corticosteroids for a relapse, diphtheria/tetanus vaccination should be delayed until 4 weeks after the last dose of corticosteroid.

Algorithm 2: Diphtheria/Tetanus Vaccination— Wound Management



ALGORITHM 2: Diphtheria/Tetanus Vaccination—Wound Management Treatment Recommendations

Annotations to Algorithm 2:

2.1 Patient sustains an injury that carries risk of tetanus

Tetanus is a serious and potentially life-threatening illness from which patients at high risk of exposure based on CDC indications (see appendix B) should be protected. Limited evidence suggests that the tetanus vaccine is safe for patients with multiple sclerosis (11). **Level C Recommendation.**

2.2 Patient meets CDC criteria for prophylaxis

The CDC recommends that among patients with three or more previous tetanus toxoid doses, the diphtheria/tetanus vaccine should be given for clean, minor wounds only if more than 10 years have elapsed since the last dose. For other wounds, the CDC recommends that the diphtheria/tetanus vaccine be given only if more than 5 years has elapsed since the last dose.

For patients with less than three or an unknown number of prior tetanus toxoid doses, the diphtheria/tetanus vaccine should be given for clean, minor wounds. For other wounds, both the diphtheria/tetanus vaccine and tetanus immune globulin should be given.

2.3 Vaccination not necessary

For patients with at least three previous tetanus toxoid doses, vaccination is not necessary for clean, minor wounds if fewer than 10 years has elapsed since the last dose or for other wounds if fewer than 5 years has elapsed since the last dose.

2.4 General contraindications

CDC contraindications for the diphtheria/tetanus vaccine include a neurologic or severe hypersensitivity reaction to a prior dose.

2.5 Vaccinate +/- tetanus immune globulin

The CDC recommends that tetanus immune globulin be given to patients with fewer than three previous tetanus toxoid doses or with an unknown number of prior doses unless their wounds are clean and minor.

2.6 Follow recommended treatment for injury

Follow the recommended treatment for wound patient who cannot receive the diphtheria/tetanus vaccination.

OTHER IMMUNIZATIONS

Little or no published evidence exists regarding the safety in multiple sclerosis of a number of other vaccines, including BCG, pneumococcus, MMR, and hepatitis A. Consequently, the panel's recommendations for these vaccines are based primarily on expert opinion. In developing recommendations for these immunizations, the panel used the CDC guidelines as a foundation; the underlying position of the panel was to recommend that the CDC recommendations for adult immunizations be followed unless the panel considered the evidence to show that a vaccine was not safe for patients with multiple sclerosis (see appendix B). The consensus of the panel was that in the absence of evidence of lack of safety, patients with multiple sclerosis should not be denied access to health-preserving and potentially life-saving vaccines. As with the immunizations considered in algorithm 1, vaccination for patients experiencing a relapse of multiple sclerosis should be delayed until the patient has stabilized clinically, generally 4 to 6 weeks after onset of relapse.

BCG (Bacille Calmette-Guérin for Tuberculosis)

BCG is used in some countries to reduce the risk of tuberculosis, a serious and potentially life-threatening disease. Limited evidence suggests that the BCG vaccination is safe for patients with multiple sclerosis (26). **Level B recommendation.**

In the United States, the CDC recommends against BCG vaccination because of the low risk of infection with *M. tuberculosis*, the variable effectiveness of the BCG vaccine against pulmonary tuberculosis, and the vaccine's interference with the ability to determine tuberculin reactivity. In the United States, use of the BCG vaccination as a tuberculosis prevention strategy is reserved for selected individuals who meet specific criteria. According to the CDC, BCG vaccination may be considered for health-care workers who are employed in settings in which the

likelihood of transmission and subsequent infection with *M. tuberculosis* strains resistant to isoniazid and rifampin is high, provided that comprehensive TB infection-control precautions have been implemented in the workplace and have not been successful. BCG vaccination is not recommended for either HIV-infected children or HIV-infected adults because of the potential adverse reactions associated with use of the vaccine in those individuals.

RECOMMENDATION

In countries where BCG is recommended, expert opinion recommends that the immunization guidelines for the general population should be applied to patients with multiple sclerosis.

Pneumococcus Vaccination

Pneumococcal pneumonia and meningitis are serious and potentially life-threatening illnesses. No published evidence addressing the safety of pneumococcal vaccination in patients with multiple sclerosis was found in the literature searches conducted for this project.

RECOMMENDATION

Expert opinion recommends that the CDC guidelines for the general population should be applied to patients with multiple sclerosis. Respiratory infections such as pneumococcal pneumonia may be particularly debilitating for nonambulatory patients with multiple sclerosis. Patients with compromised pulmonary function, such as wheelchair-dependent or bed-bound patients, should be immunized with the pneumococcal vaccine.

MMR (Measles/Mumps/Rubella) Vaccination

Measles, mumps, and rubella are serious illnesses. No substantial published evidence addressing the safety of these vaccines in patients with multiple sclerosis was found in the literature searches conducted for this project (15).

RECOMMENDATION

Expert opinion recommends that the CDC guidelines for the general population should be applied to patients with multiple sclerosis. Serologic testing should be considered before giving the vaccine to test for immunity that may preclude the need for a vaccination.

Hepatitis A Vaccination

Hepatitis A is a serious illness. No substantial published evidence addressing the safety of this vaccine in patients with multiple sclerosis was found in the literature searches conducted for this project.

RECOMMENDATION

Expert opinion recommends that the CDC guidelines for the general population should be applied to patients with multiple sclerosis.

Other Vaccines

Published evidence for safety in patients with multiple sclerosis was inconclusive for polio, typhoid, and yellow fever (15, 27). Similarly, no substantial evidence was identified for other vaccines such as rabies.

RECOMMENDATION

These vaccines are effective in preventing serious illnesses and expert opinion recommends that they should be made available to patients with multiple sclerosis as indicated for the general population. The rabies vaccine in particular might be considered for individuals such as veterinarians or animal laboratory workers who frequently work with animals.

RECOMMENDATIONS FOR FUTURE RESEARCH

Based on their review of the published literature, panel members concluded that there is a paucity of data on the safety of common vaccines in patients with multiple sclerosis. They recommended that more randomized, controlled trials on vaccines be conducted in MS patients and identified several specific areas of interest:

1. Hepatitis B can be a serious disease, and it is important that all individuals have access to this vaccine unless the vaccine itself poses an undue safety hazard with multiple sclerosis. The panel determined that a trial to evaluate the safety of the hepatitis B vaccine in patients should be a high priority to heighten physicians' confidence in administering the vaccine to their MS patients. The trial should also evaluate the immunological response to the vaccine to address concerns that patients with MS have poorer response to vaccines.
2. Some of the literature reviewed by the panel suggests that the influenza vaccine may not be as effective in patients with MS as in the general population. The panel cited the need for additional research on the efficacy of the influenza vaccine in protecting against influenza and in reducing the risk of influenza-related MS relapses. However, the panel acknowledged that only a randomized, controlled trial requiring a large number of patients—and therefore one impractical to conduct—would constitute definitive evidence of efficacy. A more limited trial evaluating the antigenic response to influenza vaccine might be easier to realize.
3. One small pilot trial suggests that the BCG vaccine may reduce the number of exacerbations of MS (26). The panel suggests that a controlled clinical trial be conducted to examine the efficacy of the BCG vaccine in patients with multiple sclerosis.
4. Another small pilot trial suggests that the varicella vaccine may reduce MS disease activity (25). The panel suggests that a controlled clinical trial be conducted to examine the efficacy of the varicella vaccine in patients with multiple sclerosis.

REFERENCES

- (1) Poser CM. Notes on the pathogenesis of multiple sclerosis. *Clin Neurosci* 1994; 2:258-65.
- (2) Sadovnick AD, Armstrong H, Rice GP, Bulman D, Hashimoto L, Paty DW, et al. A population-based study of multiple sclerosis in twins: update. *Ann Neurol* 1993; 33:281-5.
- (3) Sadovnick AD, Baird PA, Ward RH. Multiple sclerosis: updated risks for relatives. *Am J Med Genet* 1988; 29:533-41.
- (4) Jersild C, Fog T, Hansen GS, Thomsen M, Svejgaard A, Dupont B. Histocompatibility determinants in multiple sclerosis, with special reference to clinical course. *Lancet* 1973; 2:1221-5.
- (5) Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. *N Engl J Med* 2000; 343:938-52.
- (6) Andersen O, Lygner PE, Bergstrom T, Andersson M, Vahlne A. Viral infections trigger multiple sclerosis relapses: a prospective seroepidemiological study. *Journal of Neurology* 1993; 240:(7)417-22.
- (7) Panitch HS, Bever CT, Katz E, Johnson KP. Upper respiratory tract infections trigger attacks of multiple sclerosis in patients treated with interferon. *J Neuroimmunol* 1991; 36:(Suppl 1)125.
- (8) Miller AE, Morgante LA, Buchwald LY, Nutile SM, Coyle PK, Krupp LB, et al. A multicenter, randomized, double-blind, placebo-controlled trial of influenza immunization in multiple sclerosis. *Neurology* 1997; 48:(2)312-4.
- (9) Mokhtarian F, Shirazian D, Morgante L, Miller A, Grob D, Lichstein E. Influenza virus vaccination of patients with multiple sclerosis. *Multi Scler* 1997; 3:(4)243-7.
- (10) Myers LW, Ellison GW, Lucia M, Novom S, Holevoet M, Madden D, et al. Swine influenza virus vaccination in patients with multiple sclerosis. *J Infect Dis* 1977 Dec; 136 Suppl:S546-54 1977; 136:(Suppl)S546-54.
- (11) Confavreux C, Suissa S, Sadding P, Bourdes V, Vukusic S. Vaccinations and the risk of relapse in multiple sclerosis. *New Engl J Med* 2001; 344:(5)319-26.
- (12) Bamford CR, Sibley WA, Laguna JF. Swine influenza vaccination in patients with multiple sclerosis. *Arch Neurol* 1978; 35:(4)242-3.
- (13) Salvetti M, Pisani A, Bastianello S, Millefiorini E, Buttinelli C, Pozzilli C. Clinical and MRI assessment of disease activity in patients with multiple sclerosis after influenza vaccination. *J Neurol* 1995; 242:(3)143-6.
- (14) Salvetti M, Pisani A, Bastianello S, Millefiorini E, Buttinelli C, Pozzilli C. Influenza immunization in multiple sclerosis. *Neurology* 1997; 49:(5)1474-5.
- (15) Sibley WA, Foley JM. Infection and immunization in multiple sclerosis. *Ann NY Acad Sci* 1965; 122: 457-68.
- (16) De Keyser J, Zwanikken C, Boon M. Effects of influenza vaccination and influenza illness on exacerbations in multiple sclerosis. *J Neurol Sci* 1998; 159:(1)51-3.
- (17) Sibley WA, Bamford CR, Laguna JF. Influenza vaccination in patients with multiple sclerosis. *JAMA* 1976; 236:(17)1965-6.
- (18) Kurland LT, Molgaard CA, Kurland EM, Wiederholt WC, Kirkpatrick JW. Swine flu vaccine and multiple sclerosis. *JAMA* 1984; 251:(20)2672-5.
- (19) Michielsens B, Wilms G, Marchal G, Carton H. Serial magnetic resonance imaging studies with paramagnetic contrast medium: assessment of disease activity in patients with multiple sclerosis before and after influenza vaccination. *Eur Neurol* 1990; 30:(5)258-9.
- (20) Edwards S, Zvartau M, Clarke H, Irving W, Blumhardt LD. Clinical relapses and disease activity on magnetic resonance imaging associated with viral upper respiratory tract infections in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1998; 64:(6)736-41.
- (21) Panitch HS. Influence of infection on exacerbations of multiple sclerosis. *Ann Neurol* 1994; 36 Suppl:S25-8.
- (22) Sibley WA, Bamford CR, Clark K. Clinical viral infections and multiple sclerosis. *Lancet* 1985; 1:(8441)1313-5.
- (23) Gay D, Dick G, Upton G. Multiple sclerosis associated with sinusitis: case-controlled study in general practice. *Lancet* 1986; 1:(8485)815-9.
- (24) Narod S, Johnson-Lussenburg CM, Zheng Q, Nelson R. Clinical viral infections and multiple sclerosis. *Lancet* 1985; ii:16-6.
- (25) Ross RT, Nicolle LE, Cheang M. The varicella zoster virus: a pilot trial of a potential therapeutic agent in multiple sclerosis. *J Clin Epidemiol* 1997; 50:(1)63-8.
- (26) Ristori G, Buzzi MG, Sabatini U, Giugni E, Bastianello S, Viselli F, et al. Use of Bacille Calmette-Guerin (BCG) in multiple sclerosis. *Neurology* 1999; 53:(7)1588-9.
- (27) Miller H, Cendrowski W, Shapira K. Multiple sclerosis and vaccination. *Br Med J* 1967; 2:(546)210-3.
- (28) Ascherio A, Zhang SM, Hernan MA et al. Hepatitis B vaccination and the risk of multiple sclerosis. *New Engl J Med* 2001; 344(5):327-32.
- (29) Sadovnik, AD, Scheifele DW. School-based hepatitis B vaccination programme and adolescent multiple sclerosis. *Lancet* 2000; 355(9203):549-50.
- (30) Shaw FE Jr, Graham DJ, Guess HA et al. Postmarketing surveillance for neurologic adverse events reported after hepatitis B vaccination. Experience of the first three years [Review] *Am J Epidemiol* 1988 127(2): 337-52.
- (31) Tourbah A, Gout O, Libau R et al. Encephalitis after hepatitis B vaccination: recurrent disseminated encephalitis or MS? *Neurology* 1999; 53(2):396-401.
- (32) Zipp F, Weil JG, Einhaupl KM. No increase in demyelinating disease after hepatitis b vaccination [letter]. *Nat Med* 1999; 5(9):964-5.

APPENDIX A: Summary of Included Articles (Tables 3 & 4)

List of Included Articles

1. Andersen O, Lygner PE, Bergstrom T, Andersson M, Vahlne A. Viral infections trigger multiple sclerosis relapses: a prospective seroepidemiological study. *Journal of Neurology* 1993;240:417–22.
2. Edwards S, Zvartau M, Clarke H, Irving W, Blumhardt LD. Clinical relapses and disease activity on magnetic resonance imaging associated with viral upper respiratory tract infections in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1998;64:736–41.
3. Panitch HS. Influence of infection on exacerbations of multiple sclerosis. *Ann Neurol* 1994;36 Suppl:S25–8.
4. Sibley WA, Bamford CR, Clark K. Clinical viral infections and multiple sclerosis. *Lancet* 1985;1:1313–5.
5. Sibley WA, Foley JM. Infection and immunization in multiple sclerosis. *Ann NY Acad Sci* 1965;122:457–68.
6. De Keyser J, Zwanikken C, Boon M. Effects of influenza vaccination and influenza illness on exacerbations in multiple sclerosis. *J Neurol Sci* 1998;159:51–3.
7. Narod S, Johnson-Lussenburg CM, Zheng Q, Nelson R. Clinical viral infections and multiple sclerosis. *Lancet* 1985;ii:165–6.
8. Gay D, Dick G, Upton G. Multiple sclerosis associated with sinusitis: case-controlled study in general practice. *Lancet* 1986;1:815–9.
9. Ristori G, Buzzi MG, Sabatini U, et al. Use of Bacille Calmette-Guerin (BCG) in multiple sclerosis. *Neurology* 1999;53:1588–9.
10. Ross RT, Nicolle LE, Cheang M. The varicella zoster virus: a pilot trial of a potential therapeutic agent in multiple sclerosis. *J Clin Epidemiol* 1997;50:63–8.
11. Confavreux C, Suissa S, Saddier P, Bourdes V, Vukusic S. Vaccinations and the risk of relapse in multiple sclerosis. *New Engl J Med* 2001;344:319–26.
12. Miller AE, Morgante LA, Buchwald LY, et al. A multi-center, randomized, double-blind, placebo-controlled trial of influenza immunization in multiple sclerosis. *Neurology* 1997;48:312–4.
13. Mokhtarian F, Shirazian D, Morgante L, Miller A, Grob D, Lichstein E. Influenza virus vaccination of patients with multiple sclerosis. *Mult Scler* 1997;3:243–7.
14. Myers LW, Ellison GW, Lucia M, et al. Swine influenza virus vaccination in patients with multiple sclerosis. *J Infect Dis* 1977 Dec;136 Suppl:S546–54 1977; 136:S546–54.
15. Bamford CR, Sibley WA, Laguna JF. Swine influenza vaccination in patients with multiple sclerosis. *Arch Neurol* 1978;35:242–3.
16. Salvetti M, Pisani A, Bastianello S, Millefiorini E, Buttinelli C, Pozzilli C. Clinical and MRI assessment of disease activity in patients with multiple sclerosis after influenza vaccination. *J Neurol* 1995;242:143–6.
17. Salvetti M, Pisani A, Bastianello S, Millefiorini E, Buttinelli C, Pozzilli C. Influenza immunization in multiple sclerosis. *Neurology* 1997;49:1474–5.
18. Sibley WA, Bamford CR, Laguna JF. Influenza vaccination in patients with multiple sclerosis. *JAMA* 1976;236:1965–6.
19. Kurland LT, Molgaard CA, Kurland EM, Wiederholt WC, Kirkpatrick JW. Swine flu vaccine and multiple sclerosis. *JAMA* 1984;251:2672–5.
20. Michielsens B, Wilms G, Marchal G, Carton H. Serial magnetic resonance imaging studies with paramagnetic contrast medium: assessment of disease activity in patients with multiple sclerosis before and after influenza vaccination. *Eur Neurol* 1990;30:258–9.

Table 3. Studies exploring the risk of relapses or exacerbations of MS symptoms in patients with MS after infectious episodes

Patients included in the analyses	Study Design	Level of evidence	Infection types	Main findings	Ref
60 patients —67% female —Mean age 30 yrs —46 patients had ≥ 1 relapse	Prospective cohort	Class II (narrow spectrum of persons)	URI (98%) GI infections (2%)	RR of relapse during a 4 week period (-1 to +3) around the infectious episode, compared to other periods: 1.3 (p=0.0477)	1
41 patients included in a randomized controlled trial of IFN- $\beta 1\alpha$ —68% female —Median age 35 yrs	Prospective cohort	Class II (narrow spectrum of persons)	URI	OR of attack rates of exacerbations during a 4 week period (-2 to +2) around the infectious episode, compared to other periods: 2.0 (1.3-3.2)	2
30 patients included in randomized controlled trial of IFN- β	Prospective cohort	Class II (narrow spectrum of persons)	URI	MS attack rates: —2.92 per year during "at risk" periods (-1 week to +5 weeks around URI) —1.16 per year during "not at risk" periods	3
170 patients with MS —61% female —Mean age 34.7 yrs 134 controls: —63% female —mean age 34.4 yrs	Prospective cohort with concurrent controls	Class II (narrow spectrum of persons)	Colds, flu, GI, herpes	Incidence of infections (%/month): —Colds: 4.5% (MS) vs. 7.9% (controls) —Flu: 1.2% vs. 1.9% —GI: 0.8% vs. 2.0% —Herpes: 0.03% vs. 0.3% Exacerbation rate: —0.64 per year during "at risk" periods (-2 week to +5 weeks around infection) —0.23 per year during "not at risk" periods	4
34 patients with MS followed for 461 patient-months —69 attacks of MS —82 infections	Prospective cohort	Class II (narrow spectrum of persons)	URIs (70%) GI infections (14%) Other bacterial infections (16%)	33/69 (48%) MS attacks associated with infection 33/82 (40%) associated with MS exacerbation	5
34 patients with MS —46 MS attacks	Prospective cohort	Class II (narrow spectrum of persons)	Herpes, RSV	Increase in antibodies to herpes in one patient related to MS attack Increase in antibodies to RSV in one patient related to MS attack	5

Continued

<p>233 patients, of which 40 patients reporting influenza symptoms: —36 relapsing patients with MS —4 primary progressive patients</p>	<p>Retrospective cohort</p>	<p>Class IV (no masked evaluation)</p>	<p>Influenza illness</p>	<p>Number of relapses during a 6 week period following the influenza illness: —12/36 in relapsing MS group —2/4 in the primary progressive group</p>	<p>6</p>
<p>39 patients with MS 39 community controls</p>	<p>Case-control</p>	<p>Class IV (no masked evaluation)</p>	<p>Colds (coronavirus)</p>	<p>Monthly cold frequency: —13.3% in patients with MS —13.7% in controls Rate of MS exacerbation: > 3 times higher in cold months than in non-cold months (p = 0.028)</p>	<p>7</p>
<p>92 patients with MS compared to different control groups</p>	<p>Case-control</p>	<p>Class IV (no masked evaluation)</p>	<p>Sinusitis</p>	<p>Sinusitis were significantly more frequent in MS than in control patients Rate of MS attacks: —0.025 per patient per year during the periods around the sinusitis (-2 mo to + 6 mo) —0.012 per patient per year out of these periods</p>	<p>8</p>

Table 4. Studies exploring the risk of relapses or exacerbation of MS symptoms in patients with MS after immunization

Patients included in the analyses	Study Design	Level of evidence	Infection types	Main findings	Ref
Live attenuated vaccines					
14 patients with relapsing-remitting MS	Single cross-over	Class II (inclusion/exclusion criteria not clearly stated)	BCG	Number of exacerbations: —6 months before BCG: 9 —6 months after BCG: 1 Mean number of active MRI lesions: —6 months before BCG: 2.27 —6 months after BCG: 0.98	9
20 patients with MS, 18 controls	Prospective cohort	Class II (narrow spectrum of persons)	Sabin polio	Antibody response: —55% of patients with MS —44% of controls No cases of MS exacerbation observed	5
45 patients with MS	Pilot prospective clinical trial	Class III (patients served as own controls)	Varicella	Clinical changes at 12 months after vaccination: —14 patients improved —4 worsened —29 unchanged	10
Inactivated vaccines					
89 participants of the European Database for Multiple Sclerosis	Retrospective case-crossover study	Class III (narrow spectrum of persons)	Tetanus Combine Te Hepatitis B Influenza	RR (95% CI) of relapse if vaccinated during the 2 months before the relapse (risk period) vs. vaccinated during the 8 month period before the risk period: 0.71 (0.40-1.26)	11
104 patients with relapsing-remitting MS —49 receiving influenza vaccine —54 receiving placebo	Randomized controlled trial	Class I (good quality RCT)	Influenza	Exacerbations: —4 weeks follow-up: 3 (vaccine) vs. 2 (placebo), p=NS —6 months follow-up: 11 (vaccine) vs. 6 (placebo), p=NS Influenza episodes: —7 (vaccine) vs. 3 (placebo)	12
19 patients with relapsing-remitting MS —11 receiving influenza vaccine —8 receiving placebo	Randomized controlled trial	Class I (good quality RCT)	Influenza	Exacerbations: —4 weeks follow-up: 1 (vaccine) vs. 1 (placebo), p=NS —6 months follow-up: 3 (vaccine) vs. 2 (placebo), p=NS Influenza episodes: —2 (vaccine) vs. 1 (placebo)	13

Continued

60 patients with relapsing-emitting MS, 6 patients with progressive MS —33 receiving influenza vaccine —33 receiving placebo	Randomized controlled trial	Class II (inclusion/exclusion criteria not reported)	Influenza	Exacerbations: —3 weeks follow-up: 2 (vaccine) vs. 4 (placebo), p=NS —3 months follow-up: 4 (vaccine) vs. 4 (placebo), p=NS Influenza episodes: not reported	14
127 patients with MS: —65 receiving vaccine —62 not vaccinated	Prospective cohort	Class II (narrow spectrum of persons)	Swine Influenza	Episodes of deterioration: —vaccinated: 0.031 per patient-month —not vaccinated: 0.032 per patient-month	15
6 patients with MS followed 12 months before and 12 months after vaccine	Prospective cohort	Class II (narrow spectrum of persons)	Influenza	5 patients had no change before and after the vaccine 1 patient shifted to the progressive form of the disease	16, 17
24 patients with MS (16 relapsing-remitting MS, 8 progressive MS)	Prospective cohort	Class II (narrow spectrum of persons)	Influenza	1 patient developed optic neuritis 24 hours after vaccine	5
233 patients with MS —180 relapsing MS, 80 vaccinated —53 primary progressive MS, 24 vaccinated	Retrospective cohort	Class IV (no masked evaluation)	Influenza	Exacerbation during the 6 weeks following the vaccine: —4/80 in the relapsing group Influenza episodes: —36 relapsing patients Exacerbation after influenza: 13/36	6
152 patients with MS: —93 vaccinated (209 inoculations) —59 not vaccinated	Retrospective cohort	Class IV (no masked evaluation)	Influenza	1 patient developed retrobulbar neuritis 24 hours after influenza vaccine	18
31 patients with MS	Retrospective cohort	Class IV (no masked evaluation)	Influenza	No difference in exacerbation rate before and after immunization	19
11 patients with relapsing-remitting MS	Prospective cohort	Class IV (no masked evaluation)	Influenza	No MS exacerbation during the 3 weeks following the vaccine	20

APPENDIX B: Summary of Adolescent/Adult Immunization Recommendations

Agent	Indications	Primary Schedule	Contraindications	Comments
Tetanus and Diphtheria Toxoids Combined (Td)	<p>All adults</p> <p>All adolescents should be assessed at 11–12 or 14–16 years of age and immunized if no dose was received during the previous 5 years.</p>	<p>Two doses 4–8 weeks apart, third dose 6–12 months after the second. No need to repeat doses if the schedule is interrupted.</p> <p>Dose: 0.5 mL intramuscular (IM)</p> <p>Booster: At 10-year intervals throughout life.</p>	<p>Neurologic or severe hypersensitivity reaction to prior dose.</p>	<p>WOUND MANAGEMENT: Patients with three or more previous tetanus toxoid doses: (a) give Td for clean, minor wounds only if more than 10 years since last dose; (b) for other wounds, give Td if over 5 years since last dose.</p> <p>Patients with less than 3 or unknown number of prior tetanus toxoid doses: give Td for clean, minor wounds and Td and TIG (tetanus immune globulin) for other wounds.</p>
Influenza Vaccine	<p>a. Adults 50 years of age and older.</p> <p>b. Residents of nursing homes or other facilities for patients with chronic medical conditions.</p> <p>c. Persons ≥ 6 months of age with chronic cardiovascular or pulmonary disorders, including asthma.</p> <p>d. Persons ≥ 6 months of age with chronic metabolic diseases (including diabetes), renal dysfunction, hemoglobinopathies, immunosuppressive or immunodeficiency disorders.</p> <p>e. Women in their 2nd or 3rd trimester of pregnancy during influenza season.</p> <p>f. Persons 6 mo.–18 years of age receiving long-term aspirin therapy.</p> <p>g. Groups, including household members and caregivers, who can infect high risk persons.</p>	<p>Dose: 0.5 mL intramuscular (IM)</p> <p>Given annually, each fall.</p>	<p>Anaphylactic allergy to eggs.</p> <p>Acute febrile illness.</p>	<p>Depending on season and destination, persons traveling to foreign countries should consider vaccination.</p> <p>Any person ≥ 6 months of age who wishes to reduce the likelihood of becoming ill with influenza should be vaccinated.</p> <p>Avoiding subsequent vaccination of persons known to have developed GBS within 6 weeks of a previous vaccination seems prudent; however, for most persons with a GBS history who are at high risk for severe complications, many experts believe the established benefits of vaccination justify yearly vaccination.</p>
Pneumococcal Polysaccharide Vaccine (PPV)	<p>a. Adults 65 years of age and older.</p> <p>b. Persons ≥ 2 years with chronic cardiovascular or pulmonary disorders including congestive heart failure, diabetes mellitus, chronic liver disease, alcoholism, CSF leaks, cardiomyopathy, COPD, or emphysema.</p> <p>c. Persons ≥ 2 years with splenic dysfunction or asplenia, hematologic malignancy, multiple myeloma, renal failure, organ transplantation or immunosuppressive conditions, including HIV infection.</p> <p>d. Alaskan Natives and certain American Indian populations.</p>	<p>One dose for most people*</p> <p>Dose: 0.5 mL intramuscular (IM) or subcutaneous (SC)</p> <p>*Persons vaccinated prior to age 65 should be vaccinated at age 65 if 5 or more years have passed since the first dose. For all persons with functional or anatomic asplenia, transplant patients, patients with chronic kidney disease, immunosuppressed or immunodeficient persons, and others at highest risk of fatal infection, a second dose should be given—at least 5 years after first dose.</p>	<p>The safety of PPV during the first trimester of pregnancy has not been evaluated. The manufacturer's package insert should be reviewed for additional information.</p>	<p>If elective splenectomy or immunosuppressive therapy is planned, give vaccine 2 weeks ahead, if possible.</p> <p>When indicated, vaccine should be administered to patients with unknown vaccination status. All residents of nursing homes and other long-term care facilities should have their vaccination status assessed and documented.</p>

Continued

<p>Measles and Mumps Vaccines**</p>	<p>a. Adults born after 1956 without written documentation of immunization on or after the first birthday. b. Health-care personnel born after 1956 who are at risk of exposure to patients with measles should have documentation of two doses of vaccine on or after the first birthday or of measles seropositivity. c. HIV-infected persons without severe immunosuppression. d. Travelers to foreign countries. e. Persons entering post-secondary educational institutions (e.g., college).</p>	<p>At least one dose. (Two doses of measles-containing vaccine if in college, in health-care profession, or traveling to a foreign country with second dose at least 1 month after the first.) Dose: 0.5 mL subcutaneous (SC)</p>	<p>a. Immunosuppressive therapy or immunodeficiency including HIV-infected persons with severe immunosuppression. b. Anaphylactic allergy to neomycin. c. Pregnancy. d. Immune globulin preparation or blood/blood product received in preceding 3–11 months.</p>	<p>Women should be asked if they are pregnant before receiving vaccine, and advised to avoid pregnancy for 30 days after immunization.</p>
<p>Rubella Vaccine**</p>	<p>a. Persons (especially women) without written documentation of immunization on or after the first birthday or of seropositivity. b. Health-care personnel who are at risk of exposure to patients with rubella and who may have contact with pregnant patients should have at least one dose.</p>	<p>One dose. Dose: 0.5 mL subcutaneous (SC)</p>	<p>Same as for measles and mumps vaccines.</p>	<p>Women should be asked if they are pregnant before receiving vaccine, and advised to avoid pregnancy for 3 months after immunization.</p>
<p>Hepatitis B Vaccine</p>	<p>a. Persons with occupational risk of exposure to blood or blood-contaminated body fluids. b. Clients and staff of institutions for the developmentally disabled. c. Hemodialysis patients. d. Recipients of clotting-factor concentrates. e. Household contacts and sex partners of those chronically infected with HBV. f. Family members of adoptees from countries where HBV infection is endemic, if adoptees are HbsAg+. g. Certain international travelers. h. Injecting drug users. i. Men who have sex with men. j. Heterosexual men and women with multiple sex partners or a recent episode of a sexually transmitted disease. k. Inmates of long-term correctional facilities. l. All unvaccinated adolescents.</p>	<p>Three doses: second dose 1–2 months after the first, third dose 4–6 months after the first. No need to start series over if schedule interrupted. Can start series with one manufacturer's vaccine and finish with another. Dose (Adult): intramuscular (IM) Recombivax HB®: 10 µg/1.0 mL (green cap) Engerix-B®: 20 µg/1.0mL (orange cap) Dose (Adolescents 11–19 years): intramuscular (IM) Recombivax HB®: 5 µg/0.5 mL (yellow cap) Engerix-B: 10 µg/0.5 mL (light blue cap) Booster: None presently recommended.</p>	<p>Anaphylactic allergy to yeast.</p>	<p>a. Persons with serologic markers of prior or continuing hepatitis B virus infection do not need immunization. b. For hemodialysis patients and other immunodeficient or immunosuppressed patients, vaccine dosage is doubled or special preparation is used. c. Pregnant women should be sero-screened for HbsAG and, if positive, their infants should be given post-exposure prophylaxis beginning at birth. d. Post-exposure prophylaxis: consult ACIP recommendations, or state or local immunization program.</p>

Continued

Summary of Adolescent/Adult Immunization Recommendations *continued*

Agent	Indications	Primary Schedule	Contraindications	Comments
<p>Poliovirus Vaccine: IPV–Inactivated Vaccine; OPV–Oral (live) Vaccine</p>	<p>Routine vaccination of those ≥ 18 years of age residing in the United States is not necessary. Vaccination is recommended for the following high-risk adults:</p> <ul style="list-style-type: none"> a. Travelers to areas or countries where poliomyelitis is epidemic or endemic. b. Members of communities or specific population groups with disease caused by wild polioviruses. c. Laboratory workers who handle specimens that may contain polioviruses. d. Health-care workers who have close contact with patients who may be excreting wild polioviruses. e. Unvaccinated adults whose children will be receiving OPV. 	<p>Unimmunized adolescents/adults: IPV is recommended—two doses at 4–8 week intervals, third dose 6–12 months after second (can be as soon as 2 months). Dose: 0.5 mL subcutaneous (SC) or intramuscular (IM) Partially immunized adolescents/adults: Complete primary series with IPV (IPV schedule shown above). OPV is no longer recommended for use in the United States.</p>	<p>IPV: Anaphylactic reaction following previous dose or to streptomycin, polymyxin B, or neomycin.</p>	<p>In instances of potential exposure to wild poliovirus, adults who have had a primary series of OPV or IPV may be given 1 more dose of IPV. Although no adverse effects have been documented, vaccination of pregnant women should be avoided. However, if immediate protection is required, pregnant women may be given IPV in accordance with the recommended schedule for adults.</p>
<p>Varicella Vaccine</p>	<ul style="list-style-type: none"> a. Persons of any age without a reliable history of varicella disease or vaccination, or who are seronegative for varicella. b. Susceptible adolescents and adults living in households with children. c. All susceptible health-care workers. d. Susceptible family contacts of immunocompromised persons. e. Susceptible persons in the following groups who are at high risk for exposure: <ul style="list-style-type: none"> —persons who live or work in environments in which transmission of varicella is likely (e.g., teachers of young children, day care employees, residents and staff in institutional settings) or can occur (e.g., college students, inmates and staff of correctional institutions, military personnel) —nonpregnant women of childbearing age —international travelers 	<p>For persons < 13 years of age, one dose. For persons 13 years of age and older, two doses separated by 4–8 weeks. If >8 weeks elapse following the first dose, the second dose can be administered without restarting the schedule. Dose: 0.5 mL subcutaneous (SC)</p>	<ul style="list-style-type: none"> a. Anaphylactic allergy to gelatin or neomycin. b. Untreated, active TB c. Immunosuppressive therapy or immunodeficiency (including HIV infection). d. Family history of congenital or hereditary immunodeficiency in first-degree relatives, unless the immune competence of the recipient has been clinically substantiated or verified by a laboratory. e. Immune globulin preparation or blood/blood product received in preceding 5 months. f. Pregnancy. 	<p>Women should be asked if they are pregnant before receiving varicella vaccine, and advised to avoid pregnancy for one month following each dose of vaccine.</p>

Continued

<p>Hepatitis A Vaccine</p>	<p>a. Persons traveling to or working in countries with high or intermediate endemicity of infection. b. Men who have sex with men. c. Injecting and non-injecting illegal drug users. d. Persons who work with HAV-infected primates or with HAV in a research laboratory setting. e. Persons with chronic liver disease. f. Persons with clotting factor disorders. g. Consider food handlers, where determined to be cost-effective by health authorities or employers.</p>	<p>HAVRIX®: Two doses, separated by 6–12 months. Adults (19 years of age and older)—Dose: 1.0 mL intramuscular (IM); Persons 2–18 years of age: Dose: 0.5 mL (IM). VAGTA®: Adults (18 years of age and older): Two doses, separated by 6 months. Dose: 1.0 mL intramuscular (IM); Persons 2–17 years of age: Two doses, separated by 6–18 months; Dose: 0.5 mL (IM)</p>	<p>A history of hypersensitivity to alum or the preservative 2-phenoxyethanol</p>	<p>The safety of hepatitis A vaccine during pregnancy has not been determined, though the theoretical risk to the developing fetus is expected to be low. The risk of vaccination should be weighed against the risk of hepatitis A in women who may be at high risk of exposure to HAV.</p>
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Adapted from the recommendations of the Advisory Committee on Immunization Practices (ACIP) by the Centers for Disease Control. Foreign travel and less commonly used vaccines such as typhoid, rabies, and meningococcal are not included.

** These vaccines can be given in the combined form measles-mumps-rubella (MMR). Persons already immune to one or more components can still receive MMR.

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