Mellen Center Approach: MS and vaccination.

Q: Do vaccinations cause MS?

A: Best evidence at present from numerous case control studies does not support a link between any vaccination and causation of MS. A nested case-control study (Langer-Gould 2014) did not show an association between HepB vaccination, HPV vaccination, or any vaccination and the risk of MS and other central nervous system demyelinating disease in the next three years. A systematic review of immunization and the risk of developing MS (Farez, Correale 2011) found no increased risk of MS after vaccination with following agents: BCG, Hepatitis B, Influenza, Measles-Mumps-Rubella. The risk of MS appeared reduced after tetanus or diphtheria vaccination.

A single retrospective case control study in 47 MS patients receiving VZV vaccination showed improvement in 29.8%, deterioration in 8.5%, and no change in 61.7%. Four patients developed a mild vaccine-associated chickenpox. The significance of this study is unclear at the present time.

References:


Q: Is there any evidence that vaccinations either cause or precipitate relapses of MS?

A: There does not appear to be any evidence that vaccinations cause or precipitate relapses in people known to have MS. A practice advisory from the American Academy of Neurology (Rutschmann et al 2002) found strong evidence against an increased risk of MS exacerbation after influenza immunization. There is limited data related to other specific vaccinations increasing relapse rate. A randomized blinded trial of influenza vaccination in patients with relapsing MS showed no difference in attack rate between treated and placebo treated patients (Miller et al 1997).

At the Mellen Center we recommend that patients get the influenza vaccination shot (not the FluMist live inactivated vaccine) annually. Our opinion is that the risk of influenza in the MS population outweighs any risk of the influenza vaccine. Note that each year’s vaccine varies, and so this may change depending on information emerging with future vaccination cycles.

Reference:


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**Q: What are the recommendations for vaccinations in adults now?**

A: Attached is the recommended Adult Immunization Schedule for the United States for 2016. There are no additional vaccination recommended for the MS population (see below for specific medications and vaccination recommendations). Our recommendation is that MS patients receive the standard schedule of vaccinations for their age and other individual characteristics unless they are on specific medications with an impact on response to vaccination (see below). **MS patients should try to avoid live attenuated vaccines where possible** (see below)

Reference: Attachment - [http://www.cdc.gov/vaccines/schedules/hcp/adult.html](http://www.cdc.gov/vaccines/schedules/hcp/adult.html)

**Q: Should any specific vaccinations or types of vaccinations be avoided and if so why?**

A: Inactivated vaccines are generally considered safe for people with MS including those taking a disease modifying therapy. Live attenuated vaccines are generally not recommended for a person with MS because their ability to cause disease is weakened but not totally inactivated. We note that this is a theoretical risk and that there is no high quality evidence showing an increased risk in the MS population of live attenuated vaccines at this time.

**Q: Do any of the DMTs we use have an effect on the safety or efficacy of vaccination?**

A: Corticosteroids, particularly long term daily use, might have an impact on the efficacy or response to vaccination. However, organ transplantation patients on long term steroids do not show an impaired immune response to influenza or pneumococcal vaccinations (Briggs 1980). The response has not been evaluated in MS patients, but generally corticosteroids are not used in an ongoing fashion other than as intermittent pulse therapy in MS. **When patients with MS are treated with a course of steroids, at the Mellen Center we recommend deferring immunization until 6 weeks after steroids are completed.**

Interferons do not seem to interfere with immune responses in MS patients and may have an antiviral effect. In a prospective study of 88 MS patients treated with interferon beta-1a and 77 untreated patients with MS, similar proportions (93 and 90% respectively) developed protective immune responses after receiving seasonal influenza vaccination (Schwid et al 2005). There is no evidence that glatiramer acetate affects the safety or efficacy of vaccination (glatiramer acetate package insert).

There is no evidence of an effect of natalizumab on the safety or efficacy of vaccination.

A study evaluating immune responses in MS patients going onto fingolimod vs placebo showed that while most patients mounted an effective immune reaction, there was a lower response rate compared with placebo patients (Kappos et al 2015). Teriflunomide treated patients generally mounted an

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effective immune response to immunization with seasonal influenza vaccine (Bar-Or et al 2013). Patients with MS treated with daclizumab mount normal immune response to influenza vaccination (Lin et al 2016)

See below for specific discussions of fingolimod and alemtuzumab. Other than specific recommendations for certain DMTs, there is no overall increase in safety risk for MS patients from vaccinations.

Rituximab has been used off label for refractory MS and for neuromyelitis optica. At present there is no literature on vaccinations and rituximab specific to MS. Results of immunization in patients with rheumatic conditions on rituximab vary from preserved response to immunization (Bingham 2010, Arad 2011, rheumatoid arthritis patients) to reduced (Albert 2006, lupus patients). These studies are confounded by the immunological abnormalities in the patients prior to treatment. In light of the lack of data, at the Mellen Center we would recommend required immunizations be given 6 weeks prior to initiation of rituximab if possible.

References:


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Q: Should any vaccines be used before starting DMTs and if so under what circumstances?

A: Fingolimod (Gilenya), a sphingosine 1-phosphate receptor modulator approved for relapsing MS, may increase the risk of dissemination and potentially life threatening varicella zoster (VZV infections). At the Mellen Center we check for VZV antibodies before initiating fingolimod therapy. If immunity is not demonstrated by elevated VZV titers, we initiate chicken pox (two-step) vaccination prior to initiating fingolimod. Optimally checking for the development of VZV antibodies prior to beginning medication would be prudent. Having elevated VZV titers does not guarantee against developing zoster infections (anecdotal communication). At the Mellen Center we recommend waiting 1 month after last VZV immunization to initiate fingolimod.

Alemtuzumab (Lemtrada) is a humanized monoclonal antibody directed against CD52. CD52 is a cell surface antigen present on T and B cells. Alemtuzumab depletes circulating T and B cells for variable amounts of time; over months T and B cell lines repopulate, with B cells usually repopulating over 6 months and T cells over 12 months. Because of this profound immunological effect, LIVE ATTENUATED VACCINES should not be used after initiation of alemtuzumab due to an increased risk of infection. Live attenuated vaccines include: Live Attenuated Flu Vaccine (LAIV, nasal spray), MMR, chickenpox, and Zostavax (herpes zoster). Vaccines which are not live include: tetanus toxoid boosters and injectable influenza vaccine.

One study showed retained immune competence related to prior vaccination after treatment with alemtuzumab (McCarthy C, et al 2013)

We recommend that any required vaccinations be given 6 weeks before initiating alemtuzumab to ensure an adequate immunological response before lymphocyte depletion. A similar recommendation is reasonable for other major immunosuppressive regimen (e.g. cyclophosphamide, bone marrow transplantation, rituximab, etc.)

References:


Q: Should patients having a relapse avoid immunizations?

A: There is limited data on this group of patients. The National MS Society advises that people experiencing a serious relapse affecting the ability to carry out activities should defer vaccination until 4-6 weeks after the onset of the relapse.

Reference:

http://www.nationalmssociety.org/Living-Well-With-MS/Health-Wellness/Vaccinations

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Q: What about the use of shingles vaccine (Zostavax, live-virus to prevent shingles) in older patients with MS?

A: There is no high quality evidence about shingles vaccine in the MS population. At present at the Mellen Center we recommend patients have this vaccination unless on immunosuppressing medications. This is consistent with recommendations from the National MS society.

Q. What about specific vaccinations for travel?

A: The CDC does not have specific recommendations for travel vaccination for the MS patient. Care should be taken with patients on strong immunosuppressing regimens similar to that for bone marrow transplant patients. Most patients with MS will not conform to this designation. Reviewing the data for travel immunization in immunocompromised individuals may be helpful in those patients on alemtuzumab, cyclophosphamide, rituximab, daclizumab or other major immunosuppressing medication regimens. At the Mellen Center we advise our patients travelling to at risk countries to seek infectious disease counselling before travelling.

Reference:

### Additional materials:


<table>
<thead>
<tr>
<th>Disease or pathogen</th>
<th>Use in USA</th>
<th>Type of vaccine</th>
<th>Use in MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria</td>
<td>All individuals</td>
<td>Inactivated vaccine</td>
<td>Possibly assoc. with decreased risk of MS</td>
</tr>
<tr>
<td>Influenza</td>
<td>All individuals</td>
<td>Inactivated vaccine (SC)</td>
<td>Recommended</td>
</tr>
<tr>
<td>Human papilloma virus</td>
<td>Females 12-13 years old</td>
<td>Inactivated vaccine</td>
<td>Inadequately investigated in MS</td>
</tr>
<tr>
<td>Measles, mumps, rubella</td>
<td>&lt; 50 with lack of immunity, &gt;50 if at risk</td>
<td>Live attenuated vaccine</td>
<td>Ms relapse risk not increased; not recommended if immunosuppressed</td>
</tr>
<tr>
<td>Meningococcal meningitis</td>
<td>At-risk individuals</td>
<td>Inactivated vaccine</td>
<td>Inadequately investigated in MS</td>
</tr>
<tr>
<td>Pertussis</td>
<td>All adults, combined with diphtheria and tetanus</td>
<td>Inactivated vaccine</td>
<td>Insufficient data in MS</td>
</tr>
<tr>
<td>Pneumococcus</td>
<td>At risk and those &gt;65</td>
<td>Inactivated vaccine</td>
<td>Insufficient data in MS, consider before immunosuppression</td>
</tr>
<tr>
<td>Tetanus</td>
<td>All individuals</td>
<td>Inactivated vaccine</td>
<td>Possibly associated with reduced risk of MS; no restrictions</td>
</tr>
<tr>
<td>Varicella</td>
<td>Individuals lacking evidence of immunity</td>
<td>Live attenuated vaccine</td>
<td>MS relapse risk not increased by vaccine; not recommended with immunosuppressive therapy; initiate prior to starting fingolimod if no immunity</td>
</tr>
<tr>
<td>Zoster reactivation</td>
<td>Individuals &gt;60</td>
<td>Live attenuated vaccine</td>
<td>Not studied in MS</td>
</tr>
</tbody>
</table>
Additional materials:

National MS Society recommendations on MS and vaccination:

http://www.nationalmssociety.org/Living-Well-With-MS/Health-Wellness/Vaccinations#section-1

General recommendations

The Academy of Neurology, in collaboration with the Immunization Panel of the Multiple Sclerosis Council for Clinical Practice Guidelines, published a summary of evidence and recommendations regarding immunizations and MS. They concluded that:

- The evidence supports strategies to minimize the risk of acquiring infectious diseases that may trigger MS relapses (also called attacks or exacerbations).
- The influenza, hepatitis B, varicella and tetanus vaccines are safe for people with MS.
- Decisions about the potential benefits and risks of any given immunization should be made in consultation with your healthcare providers, including your family physician and neurologist.

Special considerations

- People who are experiencing a serious relapse that affects their ability to carry out activities of daily living should defer vaccination until 4-6 weeks after the onset of the relapse.
- Inactivated vaccines are generally considered safe for people with MS, including those who are taking an interferon medication (Avonex®, Betaseron®, Extavia®, Plegridy™, Rebif®), Aubagio®, Copaxone®, Gilenya®, Glatopa®, Lemtrada®, Novantrone, Tecfidera® or Tysabri®.
- Live, attenuated vaccines are generally not recommended for a person with MS because their ability to cause disease has been weakened but not totally inactivated.
- People on therapies that suppress the immune system, such as Cytoxan, Imuran, Novantrone, Rheumatrex® and/or chronic corticosteroid therapy, should consult their neurologist before taking any live-virus vaccine.
- A person should not receive a live-virus vaccine following a course of Lemtrada.
- MS experts are not in agreement about the risks for a person with MS whose close family member receives a live-virus vaccine. The family should discuss with the neurologist how best to handle this situation.

Specific recommendations for people with MS

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1. Influenza vaccine

2015-2016 Injectable Seasonal Flu Vaccine (includes H1N1)

The 2015-16 inactivated seasonal influenza (flu) immunization is manufactured by several different companies under different brand names. Each is a single injection that provides immunity to three or four different flu viruses. Trivalent vaccines protect against three types of flu: the A/California/7/2009 (H1N1) pdm09-like virus; the A/Switzerland/971/2013 (H3N2)-like virus; the B/Phuket/3073/2013-like virus (a B/Yamagata lineage virus). Quadrivalent vaccines protect against the same three viruses plus an additional B virus (B/Brisbane/60/2008-like virus).

The 2015-16 inactivated seasonal flu immunization is recommended by the Centers for Disease Control and Prevention (CDC) for everyone over 6 months of age. The seasonal flu vaccine has been studied extensively in people with MS and is considered quite safe, regardless of the disease-modifying therapy they are taking. **However, individuals being treated with Lemtrada® should be given the inactivated flu vaccine six weeks before receiving their Lemtrada infusion.**

A high-dose inactivated flu vaccine (Fluzone High Dose) is available for people over age 65. The Centers for Disease Control does not specifically recommend the high-dose vaccine for people over age 65 and the high-dose vaccine has not been studied in people with MS of any age. For these reasons, the National MS Society continues to support influenza vaccination (flu shots) for people with MS but recommends that only the standard dose be used. If additional data for Fluzone high dose in MS patients become available, the recommendation may be revised.

FluMist is a live-virus flu vaccine (sometimes called LAIV for "live attenuated influenza vaccine") that is delivered via a nasal spray. **This live-virus vaccine is not recommended for people with MS.**

2. Hepatitis B vaccine.

Recommended for all children, adolescents, and adults at risk of contracting this potentially life-threatening disease. In 2002 the National Academy of Sciences’ Institute of Medicine (IOM) determined that there is no association between hepatitis B vaccination and the onset of MS.

3. Human papillomavirus vaccine (Gardasil).

Designed to prevent the HPV 6, 11, 16 and/or 18-related cervical cancer, cervical dysplasias, vulvar and vaginal dysplasias, and condyloma acuminate in girls and women ages 9 to 26. One case report (Waldemann et al., 2009) described the onset of acute disseminated encephalomyelitis following the second immunization with Gardasil and Sutton et al. (2009) reported five patients who presented with multifocal or atypical demyelination syndromes within 21 days of the second or third immunization (three of whom had previously experienced clinical isolated episodes of neurological dysfunction). However, a recent large-scale study of patient registries in Denmark and Sweden (see below) found no
increased risk of developing MS among nearly 800,000 who received this vaccine. Use of Gardasil should be preceded by a discussion between patient and physician regarding benefits and risks.

4. Shingles vaccine (Zostavax).

A live-virus vaccine to prevent shingles. MS neurologists do not recommend live-virus vaccines for people with MS because these vaccines can lead to an increase in disease activity. However, Zostavax is an exception because most people have had chicken pox earlier in their lives and therefore already have the virus in their bodies. Each person needs to discuss the potential benefits and risks of this vaccine with her or his healthcare provider.

5. Smallpox vaccine.

While this vaccine has not been studied in people with MS, it should be made available to any person with MS directly exposed to smallpox as the risks associated with not getting vaccinated would be too great.


This vaccine should be considered by people with MS who have never had chicken pox, lack evidence of prior immunity, and are considering starting an MS medication that has the potential to suppress cell mediated immunity – for example, Gilenya (fingolimod) and Lemtrada (alemtuzumab). The vaccine should be taken six weeks before starting the MS therapy.

Studies of Vaccine Safety and Effectiveness in People with MS

Some, but not all, immunizations have been evaluated for safety and efficacy in people with MS:

A study by the Vaccines in Multiple Sclerosis Study Group published in 2001 in the New England Journal of Medicine found that vaccination for tetanus, hepatitis B or influenza did not appear to increase the short-term risk of relapses (also called attacks or exacerbations) in people with MS.

A study by the National Immunization Program of the Centers for Disease Control and Prevention, published in the Archives of Neurology in 2003, found that vaccination against hepatitis B, influenza, tetanus, measles, or rubella did not increase a person’s risk of developing MS or optic neuritis (which is often a first symptom of MS).
A small, unblinded study, published in the Archives of Neurology in 2011, of people with relapsing-remitting MS who received the yellow fever vaccination prior to travel, found a significantly increased risk of MS relapses during the six weeks following the vaccination when compared to the remainder of the two-year follow-up period. For people with MS who must travel to areas where yellow fever is common, the increased relapse risk needs to be carefully weighed against the likelihood of exposure to yellow fever – which is a potentially fatal illness.

A study of nearly four million girls and women identified in nationwide patient registries in Denmark and Sweden, published in JAMA, found no increased risk of developing MS among nearly 800,000 who received quadrivalent human papillomavirus vaccine (Gardasil), designed to prevent cervical cancer.

A review of data from the complete electronic medical health records of Kaiser Permanente Southern California between 2008 and 2011, published in JAMA Neurology, found no long-term association of vaccines with MS or any other acquired central nervous system demyelinating disease.
### Additional materials:

For current adult vaccination schedule: [http://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html](http://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html)

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### Recommended Adult Immunization Schedule—United States - 2016

**Note:** These recommendations must be read with the footnotes that follow containing number of doses, intervals between doses, and other important information.

#### Figure 1. Recommended immunization schedule for adults aged 19 years or older, by vaccine and age group

<table>
<thead>
<tr>
<th>VACCINE</th>
<th>AGE GROUP</th>
<th>19-26 years</th>
<th>27-49 years</th>
<th>50-59 years</th>
<th>60-64 years</th>
<th>≥ 65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza*</td>
<td>1 dose annually</td>
<td>Substitute Tdap forTd once, then Td booster every 10 yrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetanus, diphtheria, pertussis (Tdap)*</td>
<td>2 doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varicella</td>
<td>3 doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human papillomavirus (HPV) females*</td>
<td>3 doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human papillomavirus (HPV) males*</td>
<td>3 doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interm</td>
<td>1 dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mumps, measles, rubella (MMR)*</td>
<td>1 or 2 doses depending on indication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumococcal 13-valent conjugate (PCV13)*</td>
<td>1 dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumococcal 23-valent polysaccharide (PPSV23)*</td>
<td>1 or 2 doses depending on indication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis A*</td>
<td>2 or 3 doses depending on vaccine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B*</td>
<td>3 doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningococcal C polysaccharide (MenC) or meningococcal (MCV4)*</td>
<td>1 or more doses depending on indication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningococcal 4-valent conjugate (MenACWY or MenB)*</td>
<td>2 or 3 doses depending on vaccine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemophilus influenza type b (Hib)*</td>
<td>1 or more doses depending on indication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Recommended for all persons who need the immunization, regardless of age.

**Footnotes:**

- Recommended for all persons who need the immunization, regardless of age.
- Recommended for persons who are at an increased risk of serious vaccine-preventable disease.
- Recommended for persons with a history of Guillain-Barré syndrome (GBS).
- Recommended for persons with a history of Guillain-Barré syndrome (GBS).
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