Vaccines and MS: Update

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Disclosures

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Research: Actelion, Novartis, Opexa
Immunobiological product containing one or more immunizing agents

Goal is to mimic 1° immune response, leading to protective long term immunity

Classification
- live attenuated vaccine
- noninfectious vaccines

Neurologic complications of vaccination are rare, typically monophasic, and show good clinical recovery


Globally, infectious diseases are most common cause of childhood death

In the US childhood vaccinations have prevented approx 322 million illnesses, 21 million hospitalizations, 732,000 deaths in the last decade

- net savings $300 billion direct costs, >$1 trillion total societal costs

Vaccination considered one of the most lifesaving medical interventions in human history

*Phil Trans R Soc 2015; 370:20140340
Types of Vaccines

- Live attenuated vaccines
- Inactivated vaccines
- Subunit vaccines
- Toxoid vaccines
- Conjugate vaccines
- Recombinant vector vaccines

Live Attenuated Vaccines

- Derived from disease-causing virus or bacteria
- Closest to natural infection, good immune response
- Attenuated/weakened in lab; remote possibility of reversion to virulent form
- Pathogen must grow/replicate in vaccinee
  - affected by circulating antibodies
- Relatively small dose given
- Generally effective with one dose (except orals)
  - can be damaged by heat, light
Live Attenuated Vaccines

- Not used in immunocompromised; may have uncontrolled pathogen growth
- Needs to be refrigerated
- Most involve viruses more than bacteria
- Current vaccines: measles, mumps, rubella; varicella; yellow fever; influenza (intranasal) polio (oral)
- Current bacterial vaccines: BCG, oral typhoid

Inactivated Vaccines

- Microbes killed with chemicals, heat, or radiation
- More stable, safer
- No refrigeration
- Weaker immune response (extra doses/boosters), mostly humoral
- Inactivated whole virus vaccines (polio, rabies, hepatitis A)
Involve microbe antigens/epitopes (1-20+) that best stimulate immune system

- Low adverse reactions

- Antigen source either to grow microbes and use chemicals to break apart, or use recombinant DNA technology (recombinant subunit vaccine)

- Hepatitis B, influenza, HPV recombinant subunit vaccines

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**Toxoid Vaccines**

- Used for diseases due to bacterial toxins

- Toxins inactivated by formalin (toxoids), safe for vaccines

- Diphtheria, tetanus vaccines
**Conjugate Vaccines**

- Special type of subunit vaccine
- Pure cell wall polysaccharide bacterial coat conjugated to antigens or toxoids, to boost potency
- *H. influenza* type B, pneumococcal, meningococcal are conjugate polysaccharide vaccines
- Also have pneumococcal, meningococcal, *Salmonella typhi* (Vi) pure polysaccharide vaccines

**DNA Vaccines**

- Experimental
- Inject microbe genes
- Cannot produce the infection
- Relatively easy, inexpensive
- Host cells express microbe antigens
- Naked DNA, or mixed with molecules
Experimental

Use attenuated carrier virus/bacteria to introduce target microbial DNA

Recombinant Vector Vaccines

Current Recommendations

Influenza
- inactivated recombinant, live attenuated
- annual vaccination for all aged 6 months or older

Tetanus, diphtheria, acellular pertussis (Td/Tdap)
- one dose to pregnant women during each pregnancy (27-36 weeks)
- one time dose of Td/Tdap, then Td booster every 10 years

Varicella
- all non-immune adult should receive 2 doses of single antigen vaccine
**Current Recommendations**

- **Human papillomavirus (HPV)**
  - bivalent (16, 18), quadrivalent (6, 11, 16, 18), nonavelent (6, 11, 16, 18, 31, 33, 45, 52, 58)
  - females receive bivalent or quadrivalent HPV vaccines in 3 dose series
  - males receive HPV 4 in 3 doses series
  - typically age 11/12, or ages 13-21 years
  - recommended in unvaccinated immunocompromised

- **Zoster**
  - single dose for those aged 60 or older

**Current Recommendations**

- **Measles mumps rubella (MMR)**
  - all born in or after 1957 should have had 1-2 doses

- **Pneumococcal 13 and 23 valent polysaccharide vaccines (PCV13, PCV23)**
  - inactivated
  - recommended when there is risk factor

- **Meningococcal quadrivalent conjugate (Men-ACYW) meningococcal polysaccharide (MPSV4) vaccine**
  - inactivated
  - 1 or more doses recommended when there is risk factor
**Current Recommendations**

- Hepatitis A and hepatitis B
  - recommended when there is risk factor
  - 2 to 3 doses
- *H. influenza* type B
  - recommended when there is risk factor

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**MS and Vaccinations**

- Are vaccines good for MS?
- Can vaccines cause MS or MS disease activity?
- Can MS patients get live vaccines?
- How should the VZV vaccine be used in MS?
- Are there DMTs where vaccines are an issue?
Several studies find \( \uparrow \) relapse rate during infection “at risk” period (2 weeks prior, 5 weeks post infection)

- Upper respiratory tract infections more common than GI infections
- Adenoviruses, rhinoviruses especially implicated
- \( \uparrow \) Risk considered to reach level A evidence


Bacterial infections also implicated

- Infection-related relapses may be more severe
- Only 9%-41% of infections associated with relapses

Conclusion: viral and bacterial infections can induce/trigger relapses

Vaccinations can avoid infection

Avoiding infection should lower relapse risk

MS patients may be on treatments that increase risk for infection

Therefore vaccinations are beneficial (so long as they are relatively safe)

Should not vaccinate during or immediately after relapse onset

Case crossover study evaluated MS patients with relapse between 1993-1997

N=643

2.3% vaccinated in 8 week risk period vs. 2.8-4% vaccinated during control periods

Conclusion: vaccinations did not increase short term risk of relapse

*NEJM 2001; 344:319
Evidence supports strategies to minimize infectious diseases that can trigger MS relapses

Influenza, hepatitis B, varicella, and tetanus vaccines are safe

Patients with serious relapse should defer vaccination for 4-6 weeks

Inactivated vaccines generally safe, including for MS on IFNβs, GAs, fingolimod, teriflunomide, dimethyl fumarate, natalizumab, alemtuzumab

Live attenuated vaccines generally not recommended

should not receive following course of alemtuzumab

special concern with chronic steroids, cyclophosphamide, azathioprine, mitoxantrone

Unclear risks when close family member receives live virus vaccines

*NMSS; Living Well with MS
Injectable seasonal flu vaccine
- studied extensively, considered safe regardless of DMT
- for alemtuzumab should be given 6 weeks before cycle
- standard (vs. high dose) recommended
- live attenuated (nasal spray) not recommended

Hepatitis B vaccine
- recommended for those at risk
- in 2002 IOM found no associated with MS onset

HPV vaccine
- small case series linked to demyelinating syndromes
- large scale registries (nearly 800,000) found no link

Varicella and zoster vaccines
- can consider prior to starting fingolimod, alemtuzumab
Yellow fever

Hepatitis B

Human papilloma virus (HPV)

SS RNA viral infection endemic in South America, Africa

Transmitted by blood-sucking insects

Rural and urban forms; mortality 5% to 40%, but only 1 in 7 develop symptoms

Vaccination involves live attenuated virus, 17D vaccine

Uses 2 substrains 17D, 17D-204

Neurologic disease (encephalitis, meningitis) may occur

*Autoimm Dis 2014; ID473170
Immunosuppressive/immunomodulatory therapies are contraindication

- Associated with ↑ relapses, MRI activity in one small case series (N=7)

*Arch Neurol 2011; 68:1267

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MS and Yellow Fever Vaccine*

- Contains viral envelope protein; recombinant DNA vaccine
- Involves 2-3 vaccinations
- Early reports of association with MS were not confirmed in multiple studies
- Vaccine is considered safe for MS
- Speculated that it may be immunologically better for MS to avoid natural infection (IL17, osteopontin)

Two vaccines have been used: Gardasil (HPV-16, 18, 6, 11) and Cervarix (HPV-16, 18)

Given to females and males, to prevent cervical and anal cancer, genital warts

Initial reports of immune-mediated complications appear not to be true link

In Denmark/Sweden population-based cohort study, quadrivalent vaccine not associated with MS/demyelinating risk

*Kaiser Permanente Southern California EHR 2008-2011; nested case control study
780 incidence cases of CNS acute demyelinating disease, 3,885 controls

MS (54.7%), ON (22.7%), TM (15.6%), other CIS (4.2%), ADEM (2.7%)

No association between hepatitis B, HPV, or any other vaccine and risk for CNS disease over next 3 years

*JAMA Neurol 2014; 71:1566
Vaccines and Risk of CNS Demyelinating Disease*

- Younger individuals (<50 years) showed ↑ risk of CNS disease in 30 days after any vaccination (influenza, tetanus, diphtheria, pertussis)
- Short term risk accelerated transition to overt disease

*JAMA Neurol 2014; 71:1566

Influenza Vaccination in MS*

- Literature review indicates specific MS concern with influenza
  - MS at higher risk for influenza related hospitalization in Swedish cohort (↑ relative risk 3.57); risk of mortality 5.19
  - US MS deaths peak coincident with MS pneumonia
  - influenza ↑ relapse risk (33% of infected MS in one study)

*Neurology 2015; 84:872
Influenza vaccination in untreated MS evaluated
   no MS issues found
Vaccination in patients on DMT
   IFNβ: pooled 3 studies involved >200 MS, 500 untreated MS or healthy controls; comparable efficacy (mouse model IFNβ protects against influenza A)
   GA: single study; lower titers vs. healthy controls

*Neurology 2015; 84:872

Influenza Vaccination in MS*

   mitoxantrone: single study documented marked interference
   natalizumab: 2 studies vs. healthy controls showed conflicting results (lower protection vs. no difference)
   fingolimod: reported not impaired (recent study notes ↓ response rates)
   teriflunomide: TERIVA study mounted effective response (slightly ↓ 14 mg dose)

*Neurology 2015; 84:872
**Vaccination Trial in Fingolimod**

- Blinded, randomized, multicenter placebo controlled
  - 2:1 fingolimod 0.5 mg (N=95) vs. placebo (N=43) for 12 weeks
  - all but 2 completed study
- At week 6 received seasonal influenza vaccine (3 strains), and TT booster dose
- Antibodies evaluated at baseline, and post 3, 6 weeks

*Neurology* 2015; 84:872

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- Influenza responder rate 54% vs. 85% at 3 weeks, 43% vs. 75% at 6 weeks
- TT responder rate 40% vs. 61%, 38% vs. 49%
- Most of fingolimod group able to mount response to novel/recall antigens and most met regulatory criteria
- However, response rates reduced

*Neurology* 2015; 84:872
**Immunization on Natalizumab**

N=60 RRMS randomized to receive single tetanus toxoid (TT) (recall antigen) and 3 keyhole limpet hemocyanin (neoantigen) shots either 2 months pre, or 6 months post starting natalizumab

Titers evaluated at 28 days

All achieved protective levels of anti-TT IgG; responder proportion to both vaccines was similar

Natalizumab did not affect response to 1° or 2° immunization

*J Neurol Sci 2014; 22

**VZV Vaccines**

Varivax

- for those never infected with VZV
- live attenuated OKA strain (≥13 virus subpopulations)
- given in two doses (98-99% protection against varicella) one month apart
- ≥2,000 PFU
Zostavax (Merck vaccine)
- for those previously infected with VZV
- single vaccine to prevent zoster (↓ 51%; ↓ severity by 61%)
- more potent
- approved for ≥50 years of age
- contraindicated in pregnancy, 1°/acquired immunodeficiency, h/o anaphylaxis to gelatin/neomycin/vaccine component
- ≥19,400 PFU

HZ/su GlaxoSmithKline recombinant vaccine subunit
- Single VZV glycoprotein in ASO\textsubscript{1b} adjuvant
  - given in 2 doses
- 97.2% efficacy in preventing zoster
  - ≥age 50, not immunocompromised
  - no ↓ efficacy with age (vs. Zostavax)

*NEJM 2015; April 28
**INFβ**: normal humoral and cellular immune responses to influenza vaccine

**GA**: no known issues

**Natalizumab**: normal humoral response to influenza vaccine; response to tetanus, KLH adequate

**Teriflunomide**: TERIVA study: immune response mounted to influenza; response to rabies vaccine, DTH skin result to recall antigens unaffected (healthy controls)

*PlosONE 2013; 8:e78532; Neurol Res 2012; 34:730; Neurology 2013; 81:552, 872

**Dimethyl fumarate**: tetanus being evaluated; live vaccines not recommended

**Fingolimod**: humoral response to influenza, tetanus toxoid, pneumococcal vaccine, KLH decreased; DTH skin reaction ↓ to candida, tetanus toxoid; prescreening for VZV serology; vaccinated prior to drug initiation if Ab is low or negative, then wait one month; avoid live vaccines on therapy, and for 2 months post therapy

*PlosONE 2013; 8:e78532; Neurol Res 2012; 34:730; Neurology 2013; 81:552, 872
Alemtuzumab: pilot study indicated normal vaccine responses to DTP, meningococcus, pneumococcus in majority

- patients within a few months of therapy did not respond
- recommended to vaccinate pre-therapy, or wait at least 6 months post therapy and measure antibody levels at 4 weeks

*PlosONE 2013; 8:e78532; *Neurol Res* 2012; 34:730; *Neurology* 2013; 81:552, 872

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**Vaccines As MS Therapy**

- T cell, T cell receptor; DNA; recombinant T cell receptor ligand vaccines
- BCG vaccine
  - attenuated mycobacterium bovis
  - reported to benefit CIS and RRMS
- EBV vaccine

*Neurology* 2014; 82:41; *Neurology* 1999; 53:1588
Vaccination with attenuated autoreactive T cells induces T cell dependent inhibition of autoimmune responses

Eliminates autoreactive T cells

Tcelna
- personalized T cell immunotherapy
- myelin reactive T cells (MOG, MBP, PLP) expanded and irradiated
- current phase IIb SPMS trial; 1° outcome brain volume loss

Neurovax
- 3 TCR peptides (overexpressed in 90% of MS)
- enhances Fox3⁺ T reg responses
- studies planned in SPMS, pediatric MS

*Curr Opin Mol Ther 2009; 11:463; Neuroscience 2015; 288:112
**MS Vaccine Therapies**

- **BHT-3009**
  - DNA vaccine to MBP
  - designed to reprogram immune system, cause immune tolerance

- **RTL 1000**
  - recombinant T cell receptor ligands (DR2α1 and β1 domains linked covalently to MOG 35-55 peptide)
  - modulates T cell functional properties, blockades immune cell infiltrating CNS
  - being evaluated for stroke

*Curr Opin Mol Ther 2009; 11:463; Neuroscience 2015; 288:112

**BCG and MS**

- In CIS trial (N=82), those randomized to BCG vs. placebo showed significantly less MRI activity (monthly MRIs x6 mos), less likely to have second clinical attack over next 5 years; after 6 months all were treated
- BCG shows anti-inflammatory properties in asthma, type 1 diabetes as well
  - induces Tregs

*Neurology 2014; 82:41; Expert Rev Clin Immunol*
EBV implicated in pathogenesis of MS

- universal seropositivity
- high EBV antibody titers before clinical presentation
- altered EBV specific CD8⁺ T cell immunity
- ↑ spontaneous EBV induced blood B cells transformation
- ↑ EBV shedding from saliva
- EBV infected B cells and plasma cells may accumulate in CNS

Proposed mechanisms

- cross reactivity with CNS antigens
- CNS bystander damage by EBV specific CD8⁺ T cells
- innate immunity activation by microRNAs
- αβ crystallin expression in EBV infected B cells (leading to oligo attack)
- EBV infection of autoreactive B cells (pathogenic autoantibodies, costimulation to autoreactive T cells)
Adoptive immunotherapy (with autologous EBV-specific CD8+ T cells) in single SPMS patient resulted in clinical improvement, ↓ MRI activity, ↓ intrathecal IgG production

Question: Could EBV vaccination prevent MS?


Killed vaccines are safe for MS
Live vaccines (such as for VZV) can be used in MS
With regard to DMTs, fingolimod has most issues
Very limited data on live vaccines while on DMTs
It will come down to risk-benefit ratio