

Week 1

Session 4

# The Risk of Infections for MS Disease Modifying Treatments (DMTs)

Prevention Strategies: Vaccination

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# Safety and Immunogenicity of Vaccines in Multiple Sclerosis

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Session 4, April 14<sup>th</sup> 2021

# Are Vaccines Safe in MS Patients?

- Scientific evidence shows that vaccines in MS patients are safe
- Vaccines do not contribute to an increased MS risk, occurrence of a first demyelinating episode, higher disease activity or disability progression
- The earlier MS patients are vaccinated, the better
- Inactivated vaccines can be administered in MS patients exposed to any DMTs

# Are Vaccines Protective Enough in MS Patients?

## Untreated MS patients

- Inactivated vaccines are as effective as in the general population
- No data are available for live attenuated vaccines

## DMT-exposed patients

- Not all vaccines have been tested with every DMT
- With some DMTs, such as interferons beta, protective haemagglutination titers have been observed

## Patients under immunosuppressive therapy

- Protection is lower than healthy subjects or untreated patients
- Mode of action and lymphopenia can affect vaccine immunogenicity
- Recommendations for immunosuppressed patients should be applied

# DMTs and SARS-CoV-2 Vaccine

- Pfizer, Moderna and AstraZeneca vaccines are safe
- Immunization does not provide complete protection in general
- No live vaccines should be administered while on immunosuppressive DMTs
- Even if less active than in the general population (in case of immunosuppression), COVID-19 vaccination is recommended.



# Immunization Programme for MS Patients: Recommendations

- **Recommended vaccines for MS patients** include
  - Recommended vaccines for the general population
  - Recommended vaccines for immunocompromised patients
- **Timing may need to be adjusted to optimize vaccine responses**
  - Vaccination should be completed 4 weeks before starting immunosuppressive DMT
  - No adjustment needed for patients taking continuous DMTs only
  - Infusion dates and type of DMT should be considered in the vaccination schedule
- **Live vaccines should not be administered to immunosuppressed patients (or under steroid therapy)**
  - Existing risk of developing vaccine-related infections

# Conclusions

- Standard vaccination programme should be applied to MS patients
- Inactivated vaccines are safe for MS patients
- Patients under immunosuppressive treatment have lower responsiveness to vaccines
- When possible, vaccines should be administered before starting the treatment
- Timing of vaccination should be adjusted to optimize vaccine response
- Anti-covid 19 vaccines are recommended!



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# Immunization Strategy (Before, During and After Immunosuppression)

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Session 4, April 14<sup>th</sup> 2021

# General Considerations

## Benefits

- MS patients have high risk of infections
- Infections can worsen MS course
- Some infections are vaccine-preventable

## Risks

- Limited adverse effects (vaccines are safe for MS patients!)
- Possible lack of immunogenic response

## Guidelines and consensus documents recommend:

- Document patient's clinical and vaccine history
- Determine vaccination needs
- Optimize vaccination schedule

# Vaccination Schedule in MS Patients

	Attenuated vaccines	Inactivated vaccines
Before Immunosuppression	<ul style="list-style-type: none"><li>• Effective</li><li>• 4/6 wks before treatment onset</li></ul>	<ul style="list-style-type: none"><li>• Effective</li><li>• 4/6 wks before treatment onset</li></ul>
During Immunosuppression	<ul style="list-style-type: none"><li>• Contraindicated</li><li>• Post-exposure prophylaxis may be performed</li></ul>	<ul style="list-style-type: none"><li>• Safe</li><li>• 2 wks before treatment onset</li><li>• Accelerated vaccination schedules may be used</li><li>• Serological tests should confirm an adequate response</li></ul>
After Immunosuppression	<ul style="list-style-type: none"><li>• Can be administered after immune restoration following safety interval recommendations</li></ul>	<ul style="list-style-type: none"><li>• Can be administered anytime</li></ul>

# Recommended Vaccines for MS Patients

- It is important to **update the local routine vaccination schedule**
  - Tetanus, Diphtheria, Pertussis, Measles, Mumps, Rubella, Varicella
- **Additional vaccines** should be considered:
  - Influenza, Pneumococcus (as for high-risk populations)
  - HPV, Herpes Zoster, Hepatitis A and B (with more restricted indications)
  - Sars-CoV-2



# COVID-19 Vaccines

- No specific data for MS patients are available, but:
  - They are **expected to be safe**
  - Should be **administered 2 to 4 wks before DMTs onset** for better immunogenicity
- The **immunological context and the risk-benefit balance** should always be considered
- Can be given in case of prior Sars-CoV-2 infection
- Should be separated by at least 14 days from other vaccines
- So far, neither post-vaccination serology nor revaccination after



# Conclusions

- Vaccines have a clearly favourable benefit-risk balance for MS patients
- Live attenuated vaccines are only contraindicated during immunosuppression (including steroids courses)
- Additional vaccines for high-risk populations should be considered
- Covid-19 vaccine is expected to be safe in MS patients.

# 2 Immunization in Special Situations – Children

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Session 4, April 14<sup>th</sup> 2021

# Do Vaccines Work in Immunosuppressed Children?

No data are available for paediatric MS

- **Effective immune response is developed following Varicella Zoster vaccination** (up to 95% immunity with 2 vaccines)
- **Immunity following HPV vaccine is slightly decreased 5 years after vaccination**
- **Measles-mumps-rubella vaccination elicits immune response** (booster dose, specific lymphopenia level)
- The **H1N1 vaccine shows reduced immunogenicity under steroid therapy.**





# Are Vaccines Safe in Immunosuppressed Children?

- **Live attenuated MMR/V booster vaccines were safe** in immunosuppressed children affected by Juvenile idiopathic arthritis (JIA) and they did not lead to any disease flare
- There have been **some cases of paediatric patients developing CNS demyelination after HPV vaccination but not MS**
- A large study showed **no associations between HPV, HepB or any other vaccination and CNS Acquired Demyelinating Syndrome (ADS)**, but younger patients had an increased risk of developing first symptoms of CNS ADS up to 30 days following vaccination.



# Are Vaccines Safe in Immunosuppressed Children?

- Despite safety and efficacy data, **the complete vaccination status of children with autoimmune diseases or under immunosuppression is much lower than expected**
- **Accelerated vaccination schedules** are available if needed
- **Natalizumab treatment may overlap the immunization period** of children with very active disease



# Conclusions

- No specific data concerning vaccination in MS paediatric patients are available yet
- However, immune response is elicited by the vaccination of immunocompromised children
- Inactive vaccines are safe during immunosuppression, while live vaccines are contraindicated in most cases
- Care providers must remain vigilant in maintaining patients' vaccination status

# 3 Immunization in Special Situations – Women, Including Pregnancy

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# Vaccination in Pregnancy

## Benefits

- Prevention of maternal morbidity and mortality
- Reduction of infections
- Transfer of passive immunity to the new-born

## Infant Perspective

- Possible blunting effect of the infant's immune response (controversial)
- Breastfeeding of vaccinated women provides higher protection.

## Maternal Perspective

- Immunological changes make pregnant women more susceptible to certain infections
- Hormonal and physiological changes may lead to more severe clinical symptoms
- Response to vaccination may be altered.

# Timing of Maternal Immunization

- Inactivated vaccines are safe; live vaccines should be avoided during pregnancy
- Vaccination in the first trimester is usually avoided, with the exception of the influenza vaccine which is recommended
- Timing required for optimal transplacental transfer of maternal Abs must be considered
- Among others, pertussis and influenza vaccines are recommended.



# Vaccination of Women with MS

- Some DMTs may affect efficacy and safety of vaccines – DMT discontinuation window may be applied to vaccinate during pregnancy
- Pre-conception vaccination would be ideal
- No interference of vaccines with MS course or DMT's effectiveness
- Increased risk of infection under immunosuppressive DMTs
- Serology for Varicella (live vaccine) should be performed early on; vaccine is recommended



Vaccination status assessment and optimization is important in the light of current and future treatments (pre-conception, pregnancy, post-partum)



# Covid-19 and Pregnancy

- Similar disease in pregnant and non-pregnant women
- No evidence of fetal abnormalities or higher miscarriage rate
- Possible increased risk for premature birth
- 2-3% risk of vertical transmission

## Covid-19 Vaccine

- Not tested in pregnant women, but likely to be safe (not live vaccines)
- So far, out of 51000 vaccinated pregnant women, no risk of complications or miscarriages have been observed





# Conclusions

## In women with MS:

- Vaccines should be administered at the time of diagnosis
- Timing of vaccination must be adapted to treatment plans for better immunological response

## In pregnant women with MS and DMT:

- Live vaccines should be avoided
- Attenuated vaccines can be used during the 2nd and 3rd trimester of pregnancy, and also in the 1st trimester for flu vaccines
- Evidence on vaccines' safety and effectiveness are lacking

# 4 Immunization in Special Situations – Elderly

Dr. Bernhard Hemmer

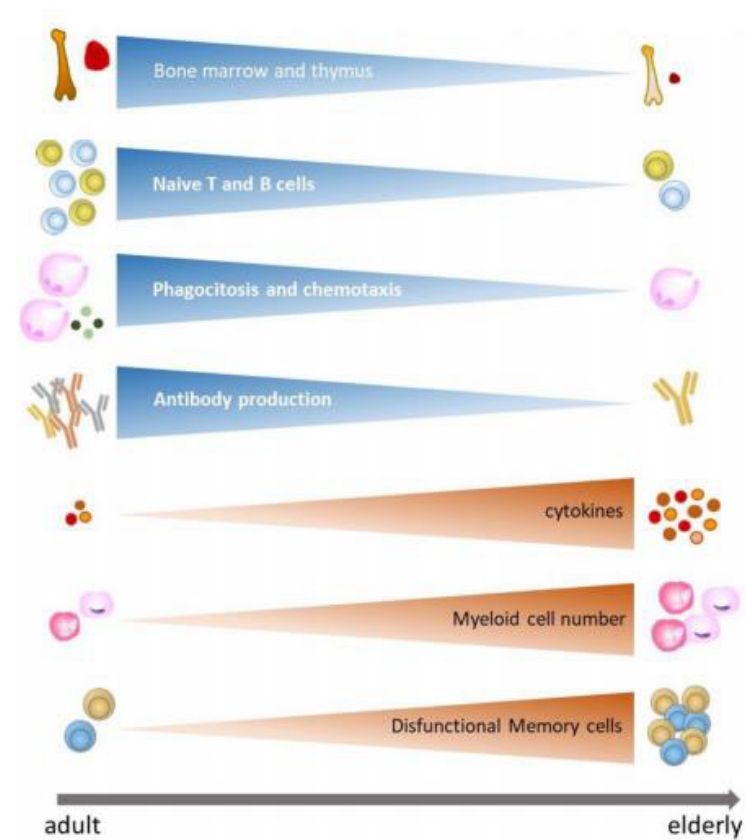
Technische Universität München, Munich, DE

Session 4, April 14<sup>th</sup> 2021

# Immunosenescence and Infections

**Elderly show significant immunological changes which lead to an impaired response to multiple infections**

- Invasive Pneumococcal disease (IPD):  
higher incidence and rate of mortality
- Herpes Zoster infection:  
increased incidence and clinical complications
- Influenza infection:  
higher rates of hospitalization and death
- Sars-CoV-2 infection:  
increased death rate



Ciabattini et al., Seminars in Immunology, 2015

# Vaccine Immune Response Associated with Aging

Immunological changes occurring with aging impair the immune response to vaccination

- **Zoster vaccine:**
  - Higher the vaccination age, higher the risk of infection
  - Protection against infection rapidly fades in elderly
- **Influenza vaccine:**
  - Antibody production is much lower in older people
  - Reduced side effects have been observed
  - Lower protection against hospitalization
  - Reduced broadness of response because of a more restricted B cell repertoire
- **Covid-19 vaccine:**
  - Lower response to vaccination, in some case insufficient protective antibody titre
  - Reduced side effects

MS patients: no specific evidence is available



# Conclusions

- **Immunosenescence is associated with increased rate of infections**
- Vaccination of elderly people elicits a weaker immune response
- New vaccines aimed at increasing the immune response in the elderly have been designed
- **No studies looked at the vaccine response in elderly people with MS.**  
Multiple factors might contribute to it

# 5 Immunization in Special Situations – International Travel

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Session 4, April 14<sup>th</sup> 2021

# General Recommendations for MS Patients Travelling

## Travel-related information

### Time

- Immunization should be discussed as early as possible
- Travel planning should start 2-3 months ahead
- In case of relapse, immunizations should be delayed

### Place

- It defines required vaccinations and time needed for immunization
- Vaccines, preventive medicines, mosquito bites, health infrastructure and other factors to be considered.

# General Recommendations for MS Patients Travelling

## Clinical status of the patient

### Treatment/immunological status

- The immune status should be assessed before planning vaccinations
- There are no safety concerns for inactivated vaccines
- Live vaccines are contraindicated in most cases – it depends on the treatment

### Immunization status

- It is important to keep the immunization status of the patients monitored (vaccination, boost, etc.)





# Vaccine-Specific Recommendations

Disease	Vaccine type	Vaccination schedule
<b>Cholera</b>	Inactivated	<ul style="list-style-type: none"> <li>2 doses, 1 to 6 weeks apart.</li> </ul>
<b>Tetanus</b>	Inactivated	<ul style="list-style-type: none"> <li>Primary vaccination before travelling</li> </ul>
<b>Tick-borne encephalitis</b>	Inactivated	<ul style="list-style-type: none"> <li>3 IM injections, rapid schedule available</li> </ul>
<b>Hepatitis A</b>	Inactivated	<ul style="list-style-type: none"> <li>2 IM injections, 6 to 12 months apart. Travelling possible with 1 injection only</li> </ul>
<b>Japanese encephalitis</b>	Inactivated	<ul style="list-style-type: none"> <li>2 IM injections 28 days apart, rapid schedule available</li> </ul>
<b>Menigoccal disease</b>	Inactivated	<ul style="list-style-type: none"> <li>1 IM injections 10 days before travelling</li> </ul>
<b>Polio</b>	Inactivated, oral attenuated	<ul style="list-style-type: none"> <li>Eradicated disease in the majority of countries. Some outbreaks exist</li> </ul>
<b>Rabies</b>	Inactivated	<ul style="list-style-type: none"> <li>3 IM injections at day 0, 7 and 21. Rapid schedule available</li> </ul>
<b>Typhoid</b>	Inactivated, oral attenuated	<ul style="list-style-type: none"> <li>Inactivated: 1 IM injection 2 weeks before travelling</li> <li>Oral attenuated: 1 capsule on day 1, 3, 5 and 7, 1 week before travelling</li> </ul>
<b>Yellow fever</b>	Live attenuated	<ul style="list-style-type: none"> <li>1 SC injection 10 days before travelling</li> </ul>

# Conclusions

- Immunizations should be discussed with MS patients
- Travelling time and destinations, as well as the immunological status of the patient should be considered
- Inactivated vaccines are safe, live attenuated vaccines may be administered upon careful risk/benefits analysis of treatment suspension.