PAEDIATRIC RHEUMATOLOGY EUROPEAN ASSOCIATION

Vaccination working party

- This educational talk is for the use of PRES members for learning and for teaching activities.
- Add your hospital affiliation when giving the talk.

Vaccinations in pediatric rheumatology educational talk

PRES Vaccination working party

https://www.pres.eu/committee-and-wp/working-parties.html

PRES PAEDIATRIC RHEUMATOLOGY EUROPEAN ASSOCIATION

Outline

- Introduction
- Vaccination with non-live, inactivated vaccines
- Vaccination with live attenuated vaccines
- Current recommendation- EULAR, ACIP, national recommendations

PRES PAEDIATRIC RHEUMATOLOGY EUROPEAN ASSOCIATION

Introduction

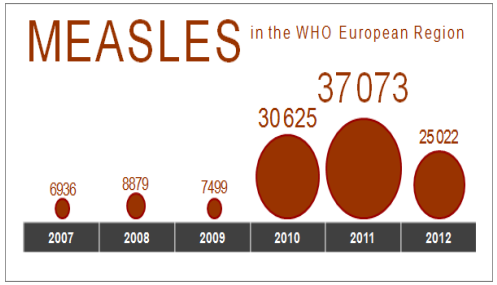
- Importance / Benefits
- Immunogenicity
- Safety / Adverse events

PRES PAEDIATRIC RHEUMATOLOGY EUROPEAN ASSOCIATION

Introduction / Importance

- *Chronically ill patients*
  - Immune dysregulation
  - Immunosuppressive treatment
- Complications of immunosupressive treatment in pediatric rheumatic patients

- Infections
  - Upper sinus infections
  - Bacterial infections (including vaccine-preventable ones)
  - VZV & measles
  - Tuberculosis
  - Opportunistic infections



Hurd A et al Curr Rheumatol Rep. 2013
Beukelman T et al Arthritis Rheum. 2012

Introduction / Importance

PAEDIATRIC RHEUMATOLOGY EUROPEAN ASSOCIATION

- Do children with PRD need vaccinations?
- Increased frequency of infections
  - High morbidity and mortality
  - Risk of disease flare post infection

- Epidemiological changes
  - Changes in consistency of populations (social, demographic)
  - Migration
  - Changes in incidence of infectious agents
  - Heard immunity is severly affected

Health in Europe 5

Migration and health in an increasingly diverse Europe

Bernd Rechel, Philipa Mladovsky, David Ingleby, Johan P Mackenbach, Martin McKee

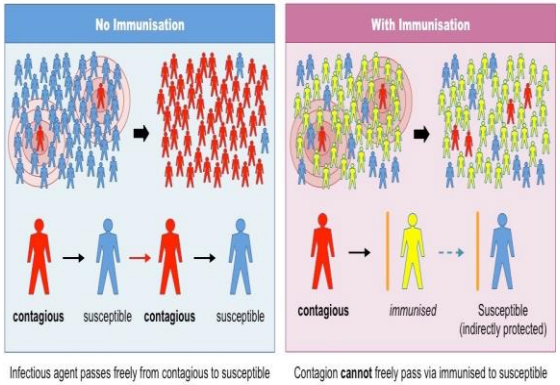
The share of migrants in European populations is substantial and growing, despite a slowdown in immigration after the global economic crisis. This paper describes key aspects of migration and health in Europe, including the scale of

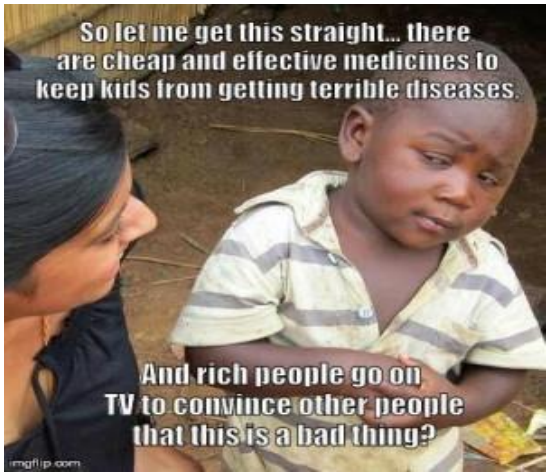
Lancet 2013; 381: 1235–45
Published Online

PAEDIATRIC RHEUMATOLOGY EUROPEAN ASSOCIATION

Introduction / Importance

- Heard immunity
- Reduced vaccination coverage
- Anti-vaccine movement
- Immigrants-refugees
- Family translocations for financial reasons





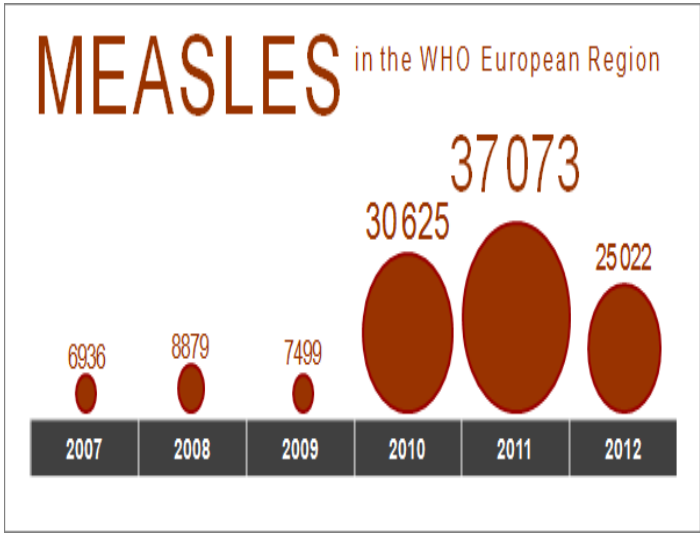
Pavlopoulou *et al. BMC Public Health* 2013, **13**:908
http://www.biomedcentral.com/1471-2458/13/908

BMC Public Health

RESEARCH ARTICLE Open Access

Immunization coverage and predictive factors for complete and age-appropriate vaccination among preschoolers in Athens, Greece: a cross- sectional study

Ioanna D Pavlopoulou[1*], Koralia A Michail[2†], Evangelia Samoli[3†], George Tsiftis[4] and Konstantinos Tsoumakas[1]



Introduction
Immunosuppression and immunizations

- Is it immunogenic / effective?
- Is it safe?
- Does it cause disease flare?

Shoenfeld Y et al Vaccination and autoimmunity-'vaccinosis': a dangerous liaison? Autoimmun 2000

Introduction / Immunogenicity

- “Good”
- Based on various national immunizations schedules
- Epidemiology PRD (time on disease onset)
- …mainly booster doses
- Type of immunosuppressive treatment
- Population under test
- Effectiveness >>> immunogenicity

PRES PAEDIATRIC RHEUMATOLOGY EUROPEAN ASSOCIATION

Introduction / Safety

- "Good"
- Up-to-date no study regarding vaccination in patients with PRD on immunomodulating showed evidence of vaccine unsafety
- The "usual" adverse events after vaccination

- fever, pain at injection site, local reddens
- Adverse events mainly transient
- NO evidence of increased risk for serious adverse events/complications

Cope JU et al Pediatrics 2015

Wraith DC et al Lancet 2003

Offit PA et al Pediatrics 2003

Molina V et al Autoimmunity 2005

PRES PAEDIATRIC RHEUMATOLOGY EUROPEAN ASSOCIATION

PAEDIATRIC RHEUMATOLOGY EUROPEAN ASSOCIATION

Introduction / Safety

- Diseases activity after vaccination?

- NO vaccination has been linked to causing disease flaring

Zonneveld E et al Arthritis Rheum 2007
Heijstek MW et al JAMA 2013
Maritsi D et al Rheumatology 2016

- No association detected regarding onset of a novel autoimmune disease

Verstraeten T et al. Vaccine 2008
Arnheim-Dahlstrom L et al BMJ 2013

Live Attenuated Vaccines in Pediatric Rheumatic Diseases are Safe:

Multicenter, retrospective data collection

Veronica Moshe MD
Pediatric Rheumatology Fellow
Meir & Shaare Zedek Medical Centers, Israel

PReS Vaccination Working Party

a joint congress with PReS

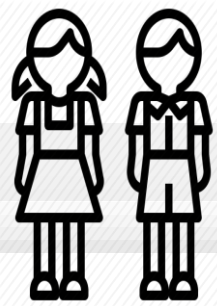
Study Objective

- **Study team**: PReS Vaccination Working Party

- **Objective:** To obtain a higher level of evidence to support recommendation guidelines for live booster vaccination (MMR-V) of pediatric rheumatology patients who are receiving:
  - DMARDs, corticosteroids with or without biological treatment

Study Methods

Retrospective study



234 pediatric patients

13 centers from 10 countries

Study Methods

- All patients received a **live attenuated booster vaccine (MMR-V) during immunosuppressive treatment**
- Questionnaires
- **Demographics, disease types and activity, therapies and adverse effects** after vaccination were reported

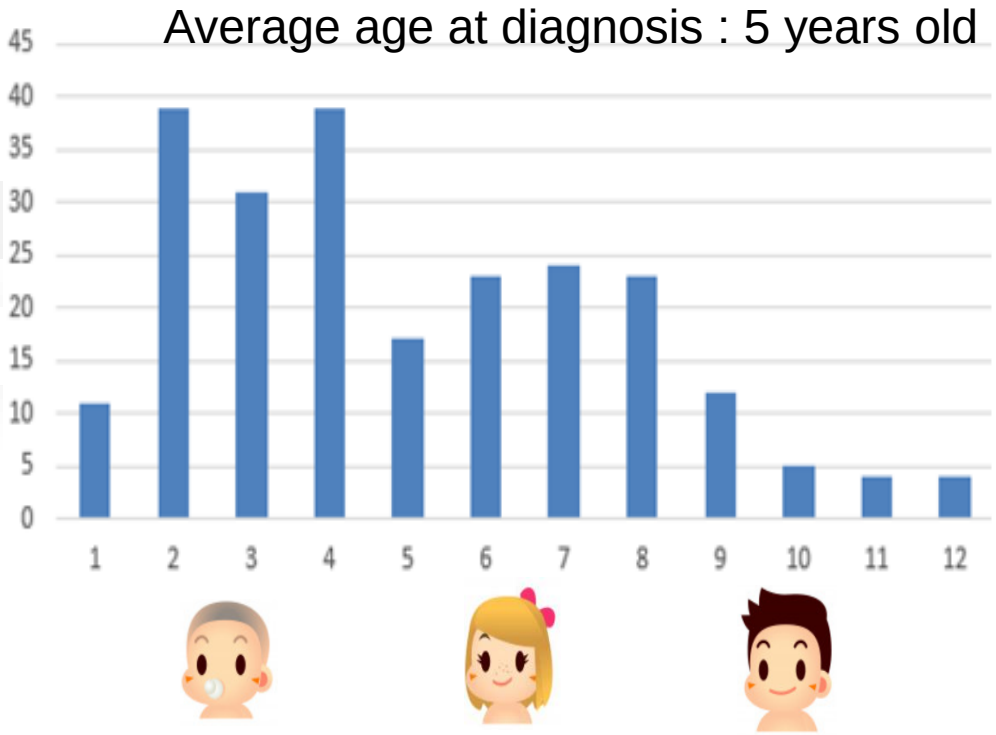
Demographic Characteristics

Female :

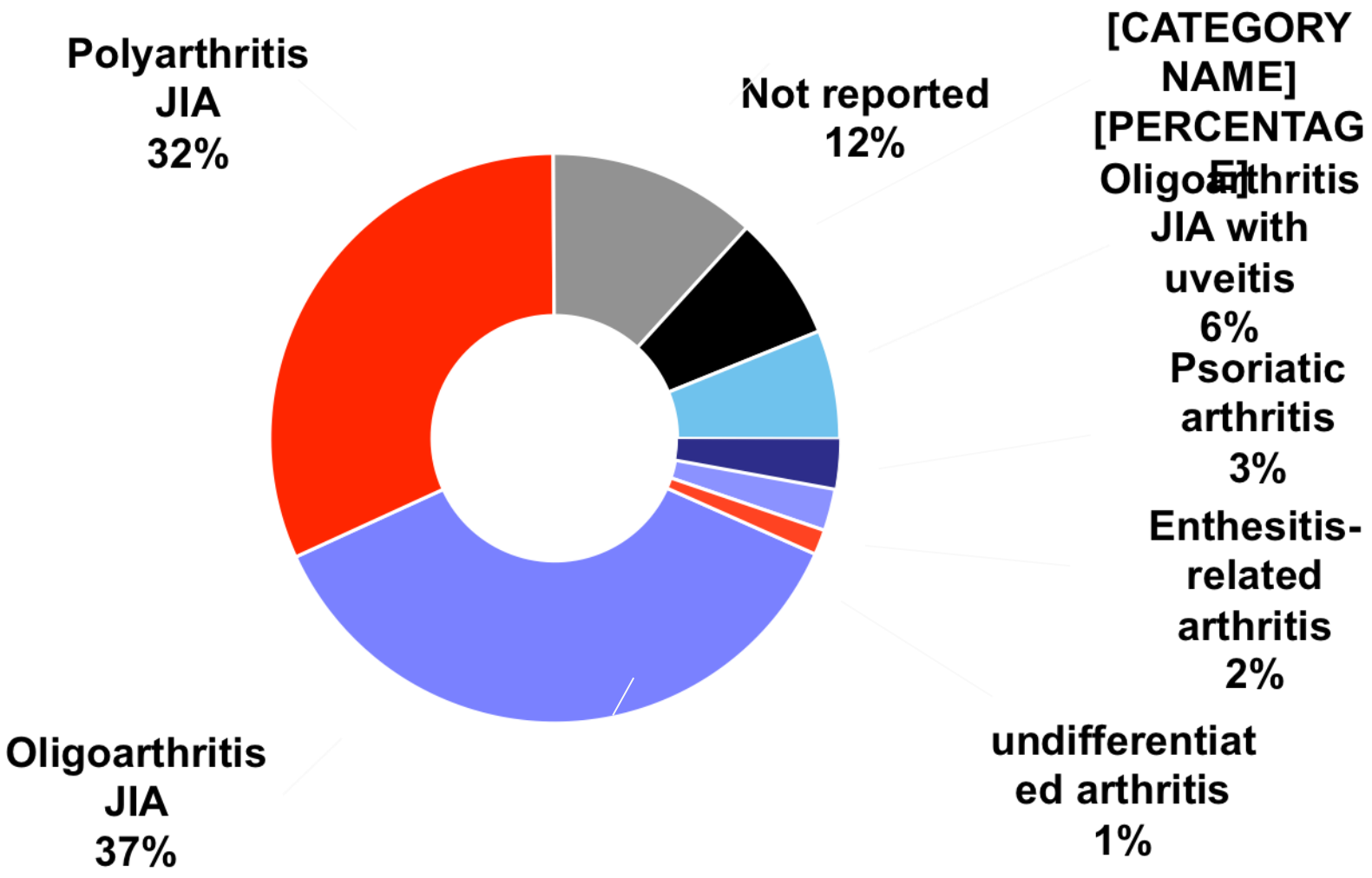
70%

Male :

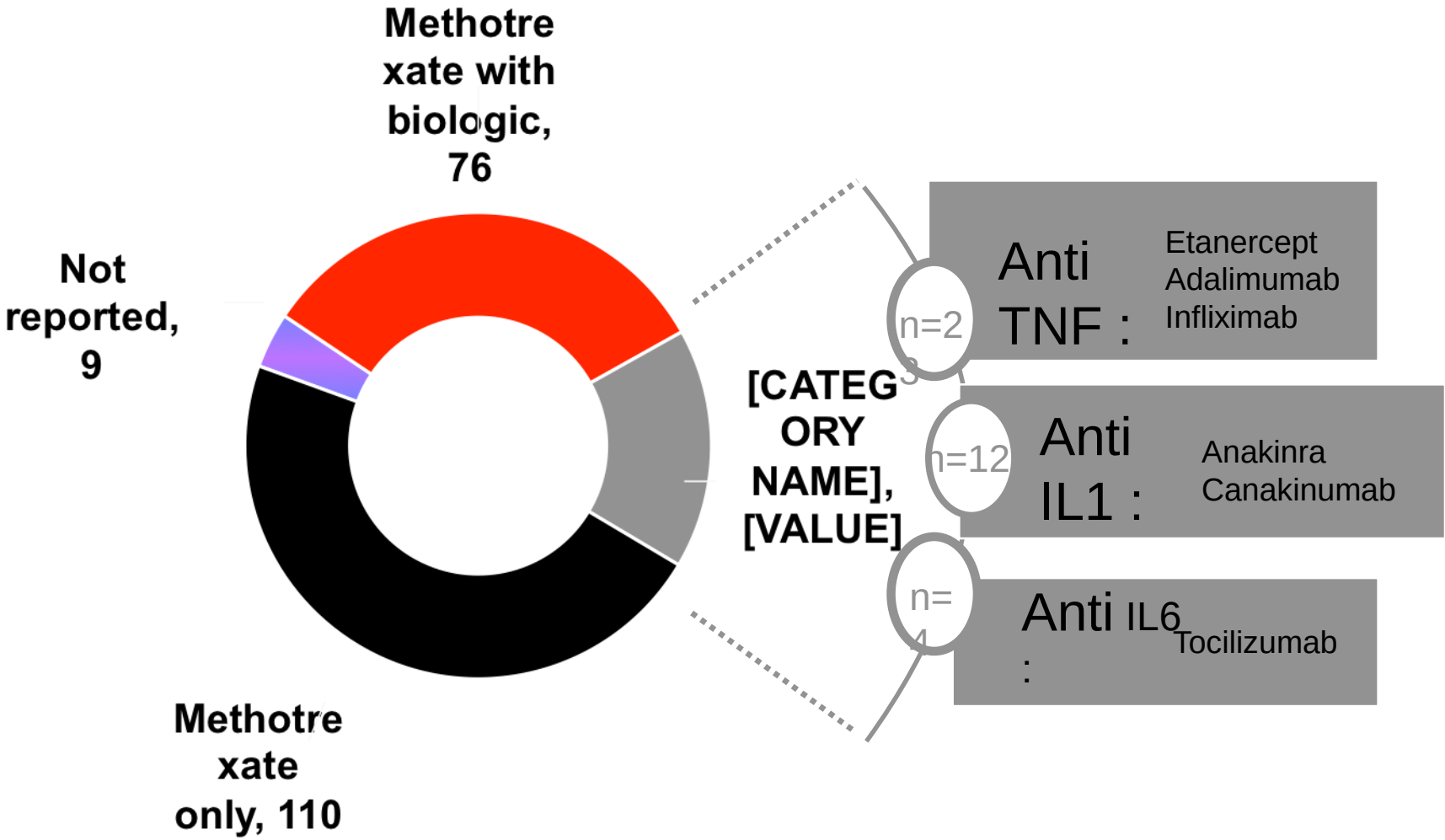
30%



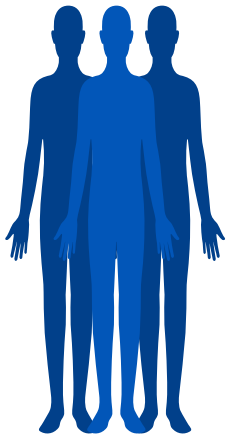
Proportion of JIA sub-types



Patient Therapy (N=234)

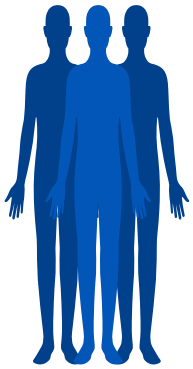


Adverse events after booster of live attenuated vaccine during methotrexate therapy



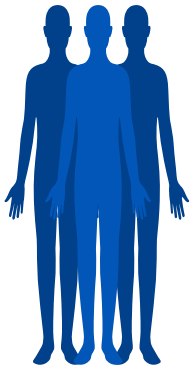
110

Total patients treated with MTX only



107

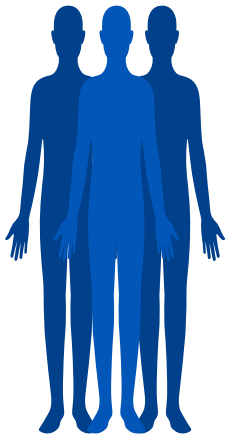
No adverse events
No flares



3

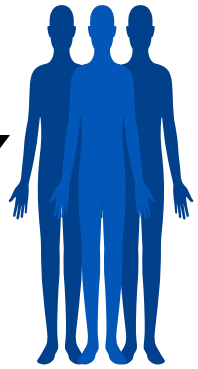
Local adverse events

Adverse events after booster of live attenuated vaccine during methotrexate and biologic therapy



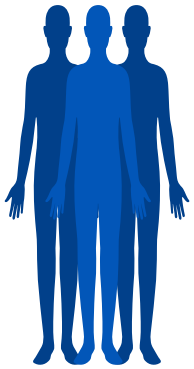
76

Total patients treated with MTX and biologics



69

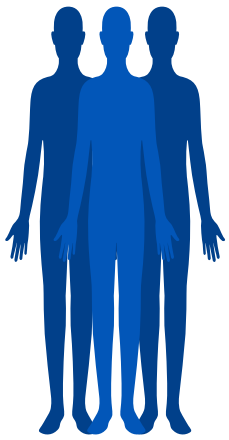
No adverse events
No flares



7

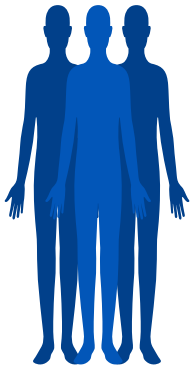
4 local adverse events
3 flu-like symptoms

Adverse events after booster of live attenuated vaccine during biologic therapy



39

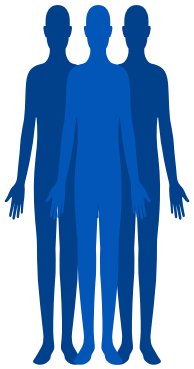
Total patients treated with biologic only



38

No adverse events

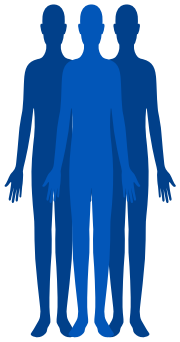
No flares



1

Fever

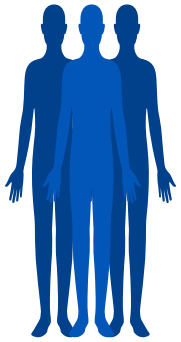
Summary of results



97.2%

No adverse events

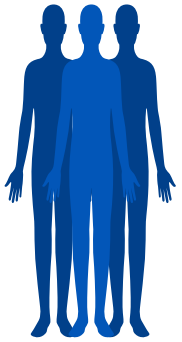
Methotrexate



91%

No adverse events

Methotrexate with biologics



97.4%

No adverse events

Biologics only

Conclusions

PAEDIATRIC RHEUMATOLOGY EUROPEAN ASSOCIATION

- **Our findings confirm and extend the current PReS recommendations**

  "live-attenuated vaccines can be considered"

- **The study implies that patients can be safely vaccinated with MMR-V booster vaccines, regardless of their age, diagnosis or therapy**

- **A prospective study to achieve a high grade of evidence is in the planning stages and we will begin soon**

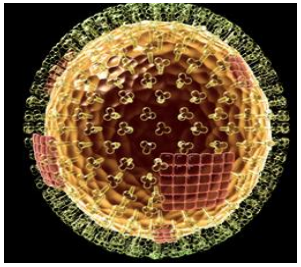
Vaccination with non-live, inactivated vaccines

Vaccination with non-live, inactivated vaccines

- Influenza vaccine
- Conjugated pneumococcal vaccine (7)
- Polysaccharide pneumo-vaccine (23)
- Hepatitis A
- Hepatitis B
- HPV
- DTaP-tetanus
- Men C

PRES PAEDIATRIC RHEUMATOLOGY EUROPEAN ASSOCIATION

Influenza vaccine (non-live)



- 15 studies (JIA-cSLE-IBD)
- Immunogenic and safe
- Reduced immunogenicity when subjects are on corticosteroids
- Reduced immunogenicity in patients on biologics
- Recommended on an annual basis for patients with PRD

Woerner A et al Hum Vaccine 2011
Aikawa NE et al J Rheumatol 2012
Toplak N et al Clin Exp Rheum 2012
Carvalho LM et al Pediatr Rheumatol Online 2013

Conjugated Pneumococcal vaccine (PCV-7)

- 2 studies (47 JIA-505 RA)
- Immunogenic and safe
- Reduced response in patients with anti-TNFa (< MTX)
- Reduced antibody titers compared to HC

Farmakis E et al Vaccine. 2010
Kapetonvic FC et al Arthritis and Rheumatism 2012

PRES PAEDIATRIC RHEUMATOLOGY EUROPEAN ASSOCIATION

Polysaccharide pneumococcal vaccine (PPV-23)

- 2 studies (37 JIA, 27 jSLE)
- Immunogenic and safe
- Adequate response (anti-TNFα> MTX)
- Reduced pneumo-specific-IgG titers

PAEDIATRIC RHEUMATOLOGY EUROPEAN ASSOCIATION

Quartier P et al Ann Rheum Dis 2011
Aikawa N et al Vaccine 2015

Hepatitis A

- 7 studies (JIA, SLE, auto-inflammatory)
- Immunogenic and safe
- MTX+/-anti-TNFα
- Reduced immunological memory
- Recommended based on individual assessment (independent of treatment received)

Moses J et al Inflamm Bowel Dis. 2011

Erguven Met al J Chin Med Assoc. 2011
Maritsi D et al Rheumatology 2016
Maritsi D et al Clin Exp Rheumatology 2017

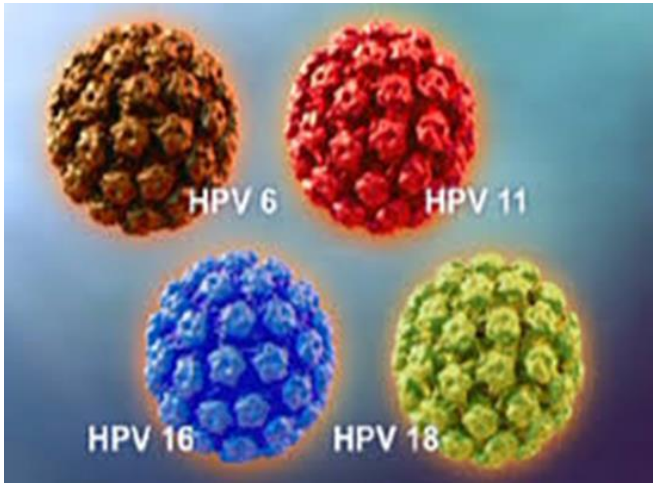
Hepatitis B

- 3 studies (JIA-IBD)
- Immunogenic and safe
- Adequate response independently of treatment
- Reduced HBV-specific titers
- Recommendation to adhere to national vaccination programs

Kasapcopur O et al Ann Rheum Dis. 2004
Moses J et al Am J Gastroenterol. 2012

PAEDIATRIC RHEUMATOLOGY EUROPEAN ASSOCIATION

HPV

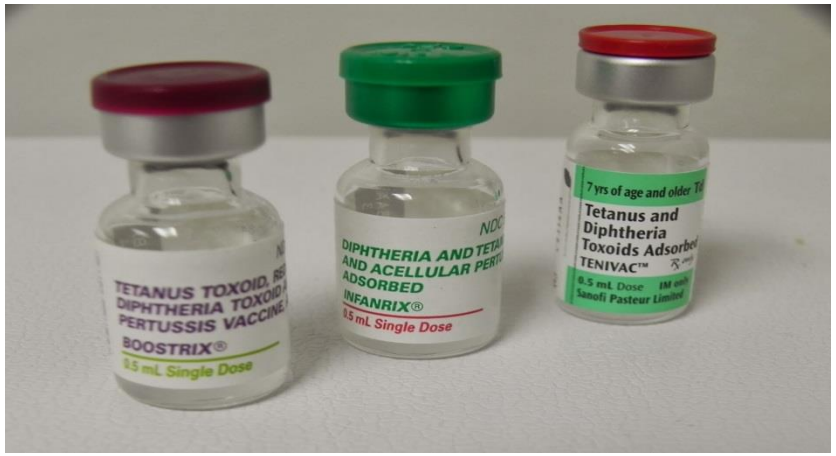


- 4 studies (JIA, jSLE)
- Immunogenic and safe
- No flare
- No novel autoimmune disease
- Reduced virus-specific antibody tiers

Heijstek MW et al. Ann Rheum Dis. 2014
Esposito S et al. Expert Rev Vaccines. 2014

Booster DTaP-tetanus (adult type

- 4 studies on immunogenicity and safety
- Good response
- Recommendation: may be given independently of PRD or treatment received.



Hoyeraal HM et al Ann Rheum Dis. 1974
Kashef S et al Iran J Immunol. 2008
Denman EJ et al Ann Rheum Dis. 1970
Miyamoto M et al Lupus. 2011

PAEDIATRIC RHEUMATOLOGY EUROPEAN ASSOCIATION

Vaccination with live attenuated vaccines

Vaccination with live attenuated vaccines

- MMR/ repeat MMR or MMRV/ repeat MMRV
- repeat VZV
- BCG

PAEDIATRIC RHEUMATOLOGY EUROPEAN ASSOCIATION

PReS Recommendations

It is recommended to **withhold live-attenuated vaccines** in patients on high-dose DMARDs, high-dose corticosteroids or biological agents.

However, vaccination can **be considered** on **a case-to-case** basis, weighing the risk of infections vs. the hypothetical risk of inducing infections by vaccination**.**

Grade of recommendation D

PAEDIATRIC RHEUMATOLOGY EUROPEAN ASSOCIATION

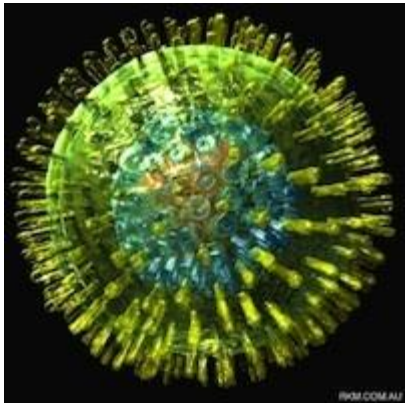
MMR (repeat dose)

- 3 studies
- MTX and or anti-TNFa
- Immunogenic
- Safe (no vaccine-induced disease, no flare)
- Individual assessment based on need versus safety

Heijstek MW et al Ann Rheum Dis 2007
Borte S et al Rheumatology 2009

PAEDIATRIC RHEUMATOLOGY EUROPEAN ASSOCIATION

VZV



- Live attenuated vaccine
- 3 studies
- Steroids, MTX, anti-TNFa
- Relatively safe
- Suboptimal seroconversion rates
- Could be administered in PRD provided no
  - High dose of steroids
  - High dose DMARD's
  - Biologics

Toplak N Vaccine 2015

Pileggi GS et al Arthritis Care Res 2010

Lu Y et al J Pediatr Gastroenterol Nutr 2010

Groot N et al Vaccine 2017

BCG

- Not recommended in children with PRD on immunosuppressive treatment

Hoyeraal HM et al Ann Rheum Dis. 1974
Kashef S et al Iran J Immunol. 2008
Denman EJ et al Ann Rheum Dis. 1970
Miyamoto M et al Lupus. 2011

Data needed …

- Tetravalent vaccine (DTaP-polio)
- Hib
- Quadrivalent Men vaccine (A,C,Y,W)
- Men B
- Typhoid
- Cholera

- BCG
- Yellow fever
- Herpes zoster vaccine (young patients)

Need for repeat dose(s)?

- ?? Induction of long-term immunological memory
- Secondary immune dysregulation-long term immunosuppressive treatment
- Need for studies assessing long-term immunity conveyed by vaccines in pediatric age
- Long-term follow-up of seroprotection rate and antigen-specific-titers

Need to repeat??

- 4 studies assessing antibody titers in children immunized prior to disease onset
- 650 patients (JIA, jSLE)
- Reduced antibody titers for
  - HBV
  - Men C
  - Mumps
  - Rubella
  - Diphtheria
  - Tetanus
  - Measles -SLE only

Heijstek MW et al Ann Rheum Dis. 2012
Maritsi D et al. Clin Exp Rheumatol. 2013
Stoof SP et al Ann Rheum Dis. 2014

Current recommendations

- EULAR recommendations
- ACIP recommendations
- National recommendations
- CDC recommendations

EULAR recommendations for vaccination in paediatric patients with rheumatic diseases

M W Heijstek,[1] L M Ott de Bruin,[1] M Bijl,[2] R Borrow,[3,4] F van der Klis,[5] I Koné-Paut,[6] A Fasth,[7] K Minden,[8] A Ravelli,[9] M Abinun,[10] G S Pileggi,[11] M Borte,[12] N M Wulffraat[1]

- Asplenic/complement deficient pts should be vaccinated with PPV23- Men (A,C,Y,W)
- MTX ->check response to pneumococcus-specific strains (PPV 23)

- All pts should receive adult type tetanus vaccine (TT)
- New guidelines are in press…

PRES PAEDIATRIC RHEUMATOLOGY EUROPEAN ASSOCIATION

Conclusions

- Adequate seroprotection rates
  - Non-live vaccines->immunogenic (even in patients with combined immunosuppression)
  - Relatively reduced quantative antibody production

- Accelerated antibody loss
  - Repeat dose(s) may be required

- Vaccines are safe regarding common adverse events and flare of the underlying PRD
- There is a need for long term data regarding immunogenicity, effectiveness and safety

PReS Vaccination Working Party Prospective Study

BE PART OF IT!

JOIN US!

PAEDIATRIC RHEUMATOLOGY EUROPEAN ASSOCIATION

https://www.pres.eu/committee-and-wp/working-parties.html