# Role of biologics on vaccination in rheumatic diseases

Nico Wulffraat

Sao Pedro 2015

University Medical Center
*Utrecht*

# Concerns about vaccinating PedRD

University Medical Center Utrecht

1. Is vaccination safe under medication, esp biologicals
   - Effect of vaccination on disease activity
   - Risk of inducing infection with live-attenuated virus vaccines (MMR, VZV)

2. Does vaccination induce protection?
   - Serological response
   - Infection prevention

For the audience:

Do you give MMR or VZV during
   - Inactive disease
   - Active disease

# Similar immune responses to immunisation in RA, treated with biologicals and MTX

University Medical Center Utrecht

- Etanercept and MTX (retrospective, 1)
  - Response to influenza same for Etanercept as MTX
- Adalimumab and MTX (RCT, 2)
  - Adequate pneumococcal vaccine response 37.4% (controls 40%) and similar % of protective antibody titers in both groups.
  - Lower influenza vaccine response (51.5% vs 63.3%)
- Certolizumab and MTX (RCT, 3):
  - In patients without baseline antibodies: Lower pneumococcal immune responses (54.5% vs 62.5). Overall, 50.5 vs 54.1% had adequate titers
- Tociluzimab and MTX (RCT, 4)
  - 60.0% vs 70.8% responded to PPV23

1: Kapetanovic , Rheumatol 2007 Apr;46(4):608-11. 2: Kaine, J Rheumatol 2007 Feb;34(2):272-9. 3: Kivitz, J Rheumatol 2014 Apr;41(4):648-57) 4: Bingham, ARD 2014, Jan 21.

# Recommendations for adults

University Medical Center Utrecht

**Table 2** Recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases with level of evidence, strength of recommendations and results of Delphi voting per recommendation

| Recommendation | Category of evidence | | | Strength of recommendation | Mean (SD) level of agreement by Delphi voting (VAS) |
|---|---|---|---|---|---|
| | Increased incidence of VP infection | Efficacy of vaccination | Harms of vaccination | | |
| The vaccination status should be assessed in the initial investigation of patients with AIIRD | – | | | D | 9.50 (0.97) |
| Vaccination in patients with AIIRD should ideally be administered during stable disease | – | | | D | 8.88 (1.26) |
| Live attenuated vaccines should be avoided whenever possible in immunosuppressed patients with AIIRD | IV | | | D | 9.25 (1.13) |
| Vaccination in patients with AIIRD can be administered during the use of DMARDs and TNFα blocking agents, but should ideally be administered before starting B cell-depleting biological therapy | II | | | B | 9.13 (1.02) |
| Influenza vaccination should be strongly considered for patients with AIIRD | III | Ib | Ib | B–C | 9.00 (1.10) |
| 23-valent polysaccharide pneumococcal vaccination should be strongly considered for patients with AIIRD | III | Ib | Ib | B–C | 8.19 (1.38) |
| Patients with AIIRD should receive tetanus toxoid vaccination in accordance with recommendations for the general population. In case of major and/or contaminated wounds in patients who received rituximab within the last 24 weeks, passive immunisation with tetanus immunoglobulin should be administered | – | II | II | B–D | 9.19 (1.11) |
| Herpes zoster vaccination may be considered in patients with AIIRD | III | – | IV | C–D | 8.00 (1.59) |
| HPV vaccination should be considered in selected patients with AIIRD | III | – | – | C–D | 8.44 (1.41) |
| In hyposplenic/asplenic patients with AIIRD, influenza, pneumococcal, *Haemophilus influenzae* b and meningococcal C vaccinations are recommended | IV | | | D | 9.50 (0.82) |
| Hepatitis A and/or B vaccination is only recommended in patients with AIIRD at risk | – | II* | III* | D | 9.13 (0.89) |
| Patients with AIIRD who plan to travel are recommended to receive their vaccinations according to general rules, except for live attenuated vaccines which should be avoided whenever possible in immunosuppressed patients with AIIRD | – | | | D | 9.25 (1.24) |
| BCG vaccination is not recommended in patients with AIIRD | III | – | – | D | 9.38 (1.09) |

*For hepatitis B only

AIIRD, autoimmune inflammatory disease; BCG, Bacillus Calmette-Guérin; DMARD, disease-modifying antirheumatic drug; HPV, human papillomavirus; TNF, tumour necrosis factor; VAS, visual analogue scale; VP, vaccine-preventable.

Van Assen, ARD 2011, Mar;70(3):414-22

# What about immunising children using biologics

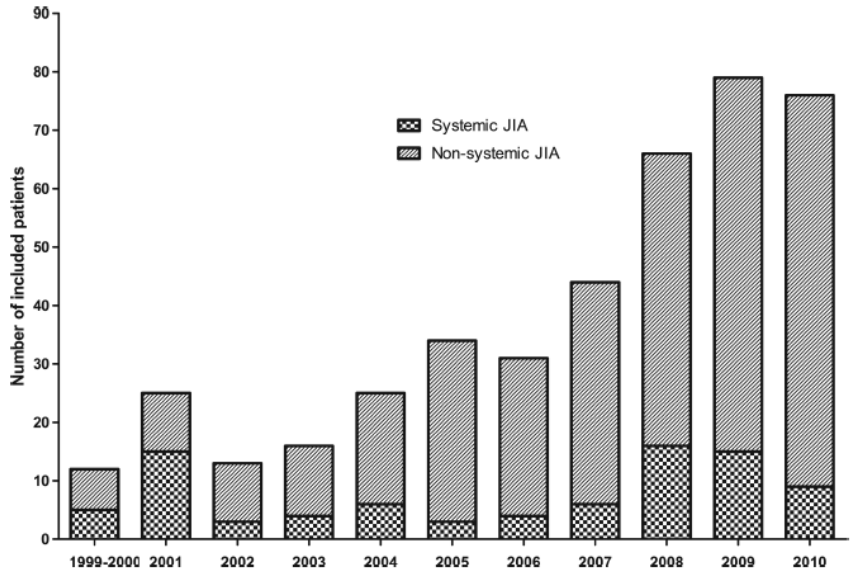
University Medical Center Utrecht

**Increasing numbers of indications and different biologics since 1999**

**JIA: most common pediatric rheumatic disease treated with biologics**

**Existing international network of expert pediatric rheumatology centers**

Figure 1 Number of biologically naive patients with non-systemic and systemic juvenile idiopathic arthritis (JIA) who started biological treatment between 1999 and 2010.




Otten, ARD 2014

# Vaccinations in PedRD: Men C

University Medical Center Utrecht

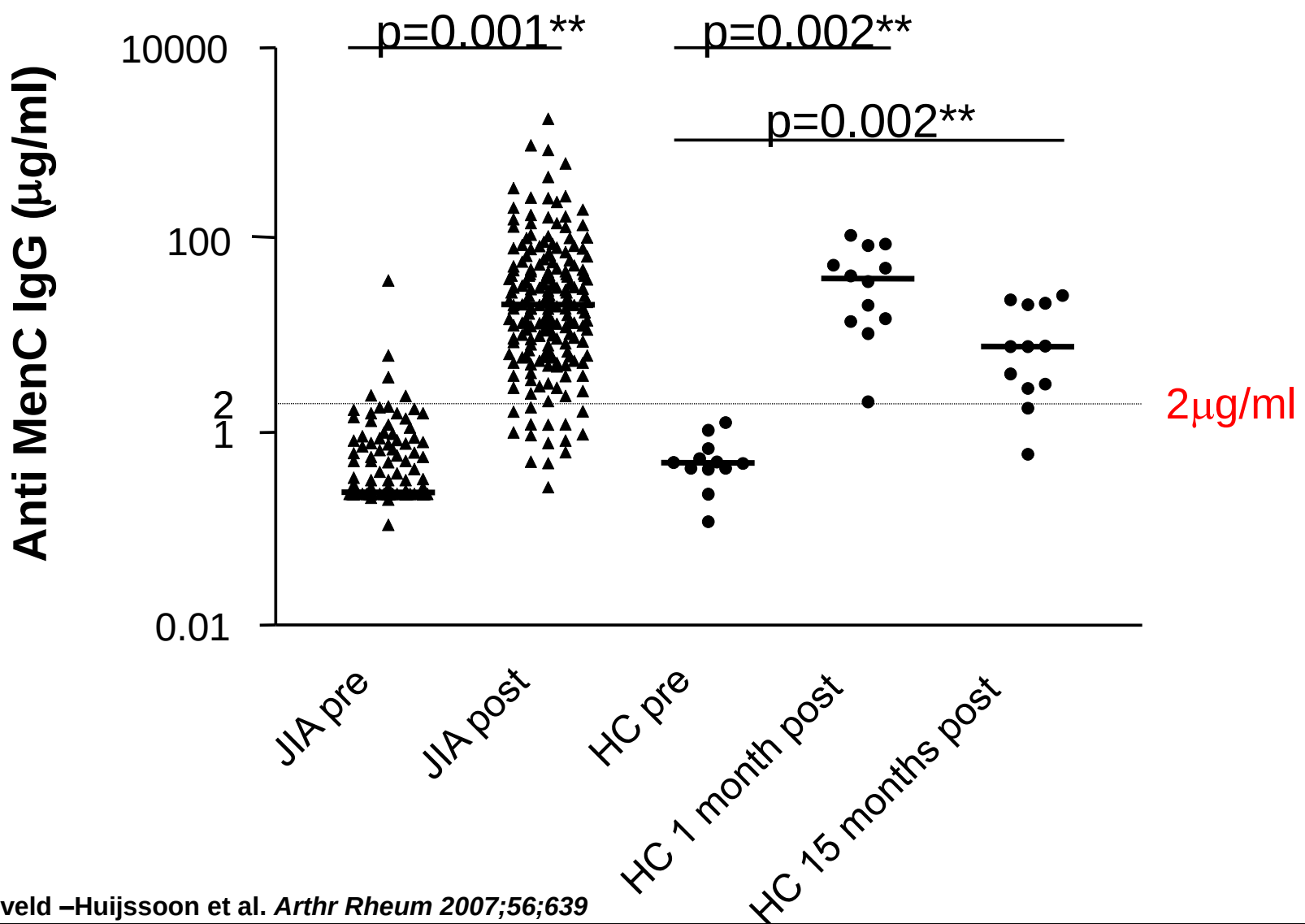
Meningococcal C vaccination in JIA

- Prospective observational cohort: good immunogenicity (1)
- Long term follow-up (4-10y)(2)
- Low numbers of patients with biologics

(1)Zonneveld-Huyssoon, 2007 Feb;56(2):639-46.
(2) Stoof, 2013 ARD 2014;73:728–734.
doi:10.1136

# Anti MenC IgG levels rise after MenC vaccination

University Medical Center Utrecht




Zonneveld –Huijssoon et al. *Arthr Rheum 2007;56;639*

# Effect of biologicals on MenC Titers?

University Medical Center Utrecht

**Table 2** Characteristics of different age cohorts at time of MenCC vaccination and during follow-up

| Characteristic* | Cohort according to age at time of vaccination | | | | p Value |
|---|---|---|---|---|---|
| | 13–19 years (n=21) | 9.0–12.9 years (n=41) | 5–8.9 years (n=48) | 1–4.9 years (n=17) | |
| Female (%) | 16 (76) | 26 (63) | 26 (54) | 11 (65) | 0.371 |
| Median number of available samples (range)† | 3 (1–6) | 3 (1–8) | 3 (1–10) | 3 (1–6) | 0.128 |
| JIA subtype | | | | | 0.377 |
| Oligoarticular JIA (%) | 5 (24) | 12 (29) | 9 (19) | 8 (47) | |
| Extended oligoarticular/polyarticular JIA (%) | 11 (52) | 21 (51) | 29 (60) | 5 (29) | |
| Other JIA (%) | 5 (24) | 8 (20) | 10 (21) | 4 (24) | |
| Medication use at time of MenCC vaccination | | | | | |
| Patients on methotrexate (%) | 9 (43) | 18 (44) | 13 (27) | 2 (12) | 0.062 |
| Patients on biologicals (%)‡ | 2 (10) | 4 (10) | 1 (2) | 0 (0) | 0.247 |
| Start of treatment after MenCC vaccination | | | | | |
| Patients starting with methotrexate (%) | 6 (29) | 17 (42) | 31 (65) | 12 (71) | 0.008 |
| Mean time (years) elapsed since MenCC vaccination (±SD) | 3.2 (±2.1) | 3.0 (±1.9) | 3.3 (±2.1) | 2.9 (±1.7) | 0.926 |
| Patients starting with biologicals (%)§ | 5 (24) | 18 (44) | 21 (44) | 9 (53) | 0.282 |
| Mean time (years) elapsed since MenCC vaccination (±SD) | 3.4 (±1.9) | 5.5 (±1.3) | 4.7 (±1.7) | 4.7 (±2.4) | 0.140 |
| Estimated t½ MenC-specific IgG antibodies (years, 95% PI) | 2.3 (1.7–3.4) | 2.9 (2.3–3.9) | 6.6 (3.3–16.1) | 5.1 (1.7–13.5) | n/a |

*Unless otherwise indicated, frequencies (percentage) are depicted.
†Twenty-one patients only had one serum sample available.
‡Six patients used tumour necrosis factor (TNF)α blocking agents (4 etanercept, 2 infliximab), and 1 patient from the 5–8.9 years cohort used an interleukin (IL)-6 antagonist (tocilizumab) at time of MenCC vaccination. In one of the patients initially treated with etanercept, rituximab and later abatacept were started during follow-up after treatment with etanercept had failed.
§Of the patients in whom biologicals were commenced after vaccination, the IL-1 receptor antagonist anakinra was started in nine patients. Three of these patients were aged 9–13 years, 5 were 5–8.9 years, and 1 was 1–4.9 years at time of MenCC vaccination. In all other patients, TNFα blocking agents (40 etanercept, 4 infliximab) were initiated.
JIA, juvenile idiopathic arthritis; MenCC, meningococcal serotype C conjugate; n/a, not applicable; PI, predictive interval; t½, half-life.

# Men C in JIA (n=127): long term follow-up

University Medical Center Utrecht

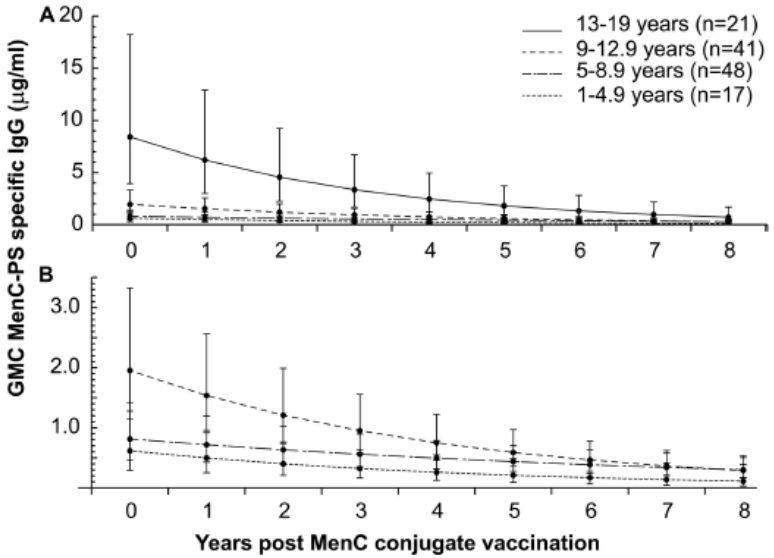



Figure 1 Kinetics of MenC polysaccharide-specific IgG concentrations according to age at time of vaccination in patients with juvenile idiopathic arthritis. All age groups are outlined in A. In B, the lines of

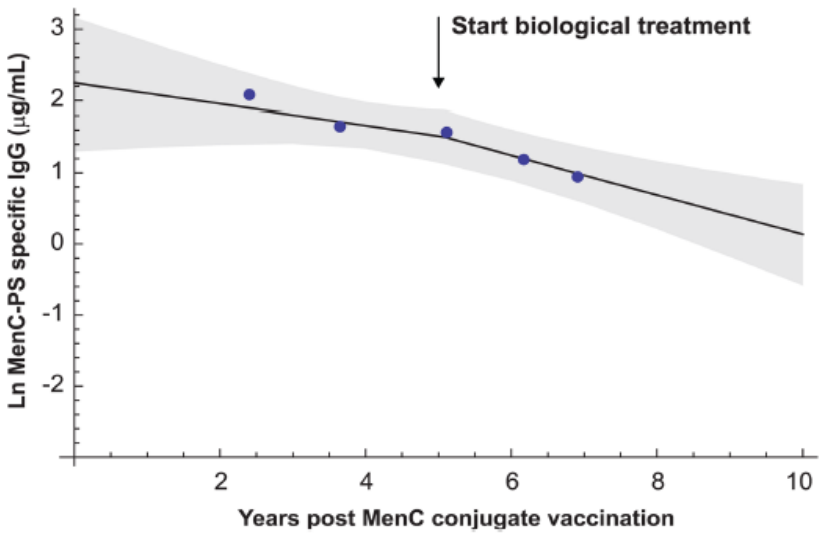



Figure 4 Example of MenC-specific IgG concentrations decline before and after starting treatment with biologicals in one patient. This

Stoof & Heijstek, ARD 2012,

# Live attenuated Vaccinations in PedRD

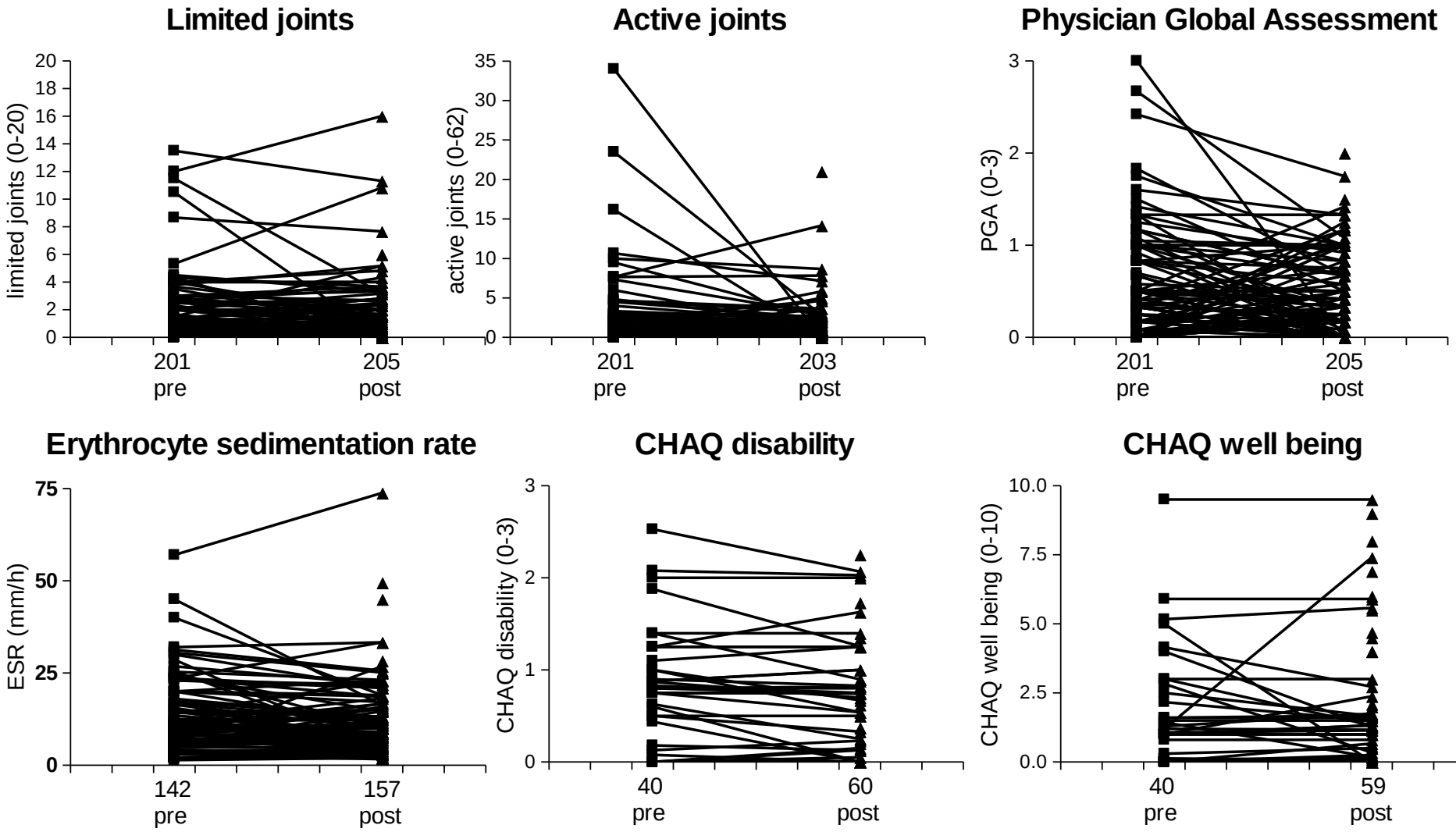
University Medical Center Utrecht

- MMR vaccination in JIA patients
  - Retrospective safety analysis
  - Retrospective immunogenicity analysis (serology)
  - Prospective randomized controlled trial
    - Clinical, serological and immunological analysis

# Retrospective study: No effect of MMR booster on disease activity

University Medical Center Utrecht

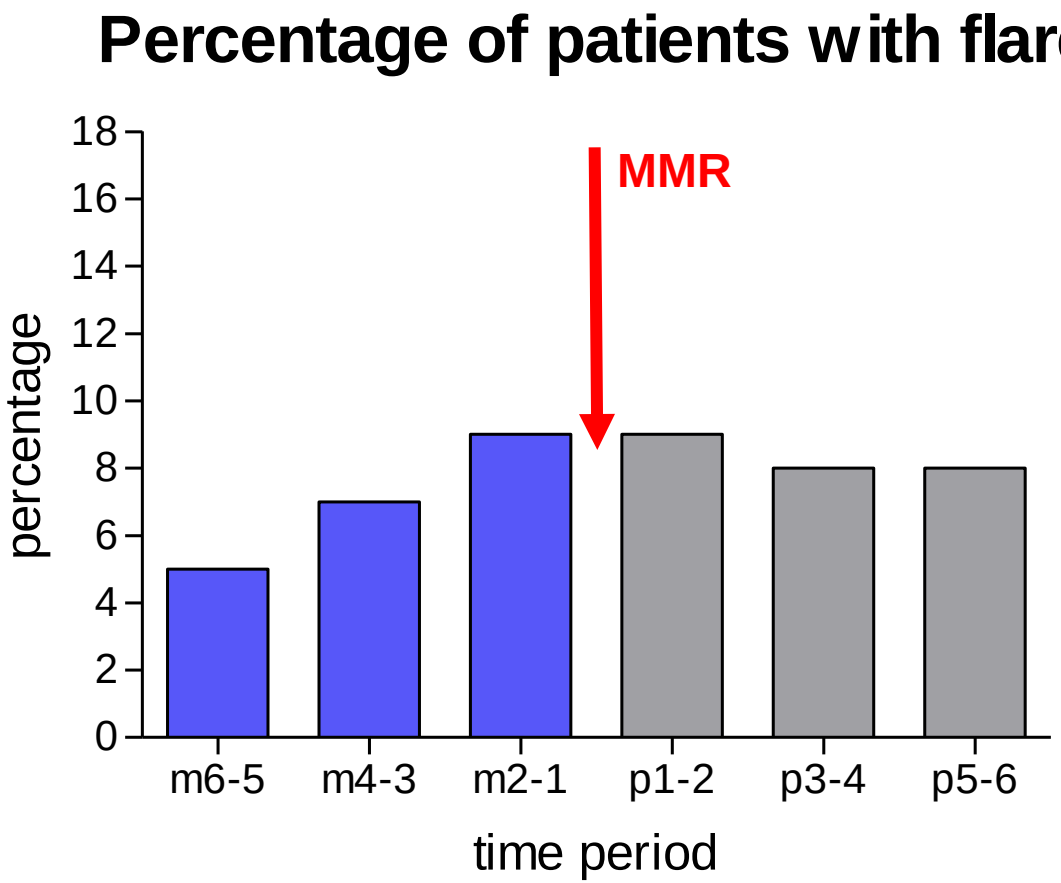
* All P-value Wilcoxon SR test: NS




**Heijstek et al.** ***Ann Rheum Dis. 2007 Oct;66(10):1384-7***

# Percentage of patients with a flare similar before and after MMR booster (n=207)

University Medical Center Utrecht



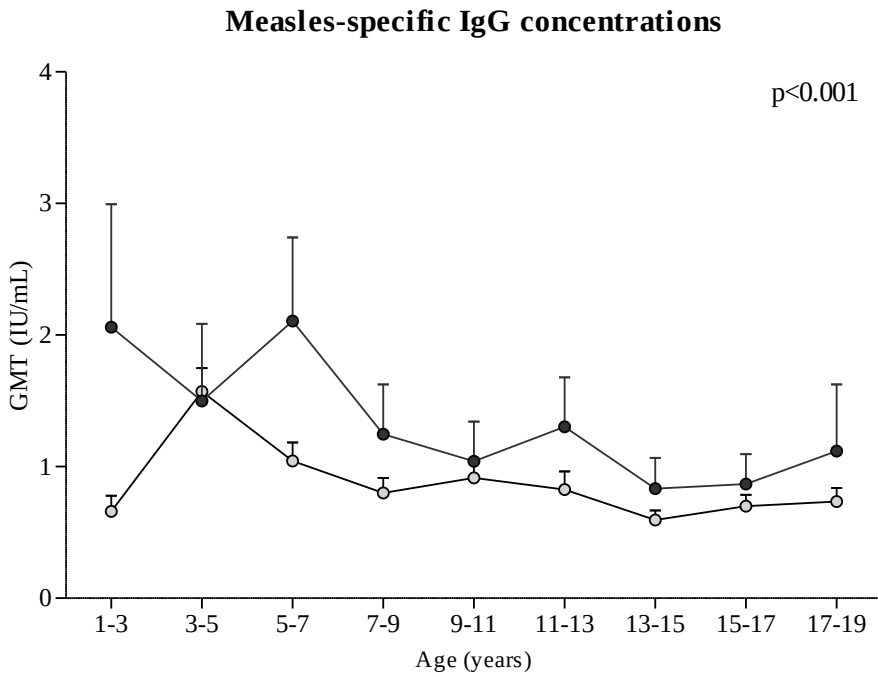

Heijstek et al. *Ann Rheum Dis. 2007 Oct;66(10):1384-7*

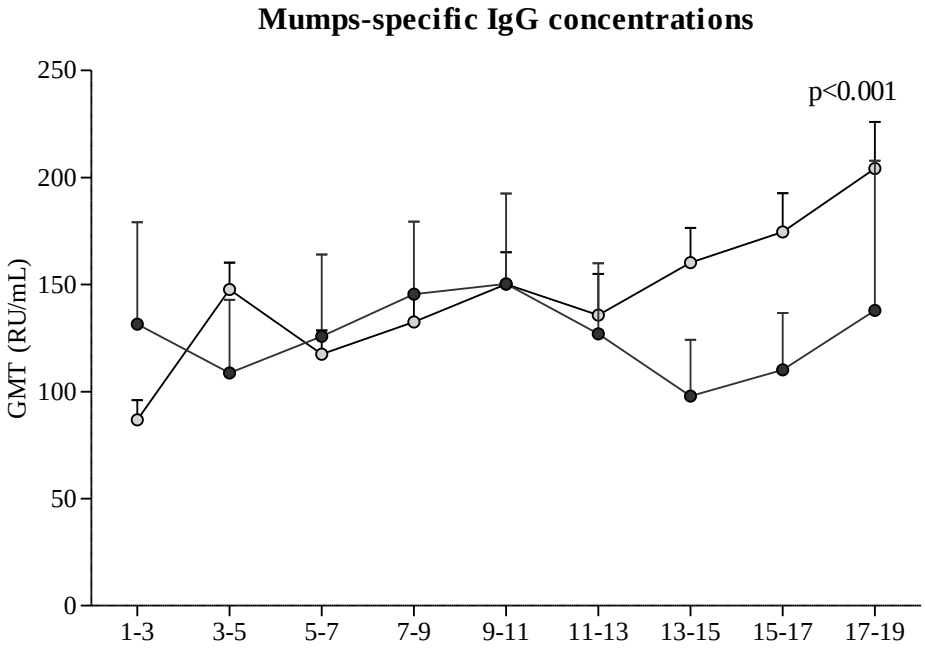
"VAccinatie bij ARTritis"
VAART

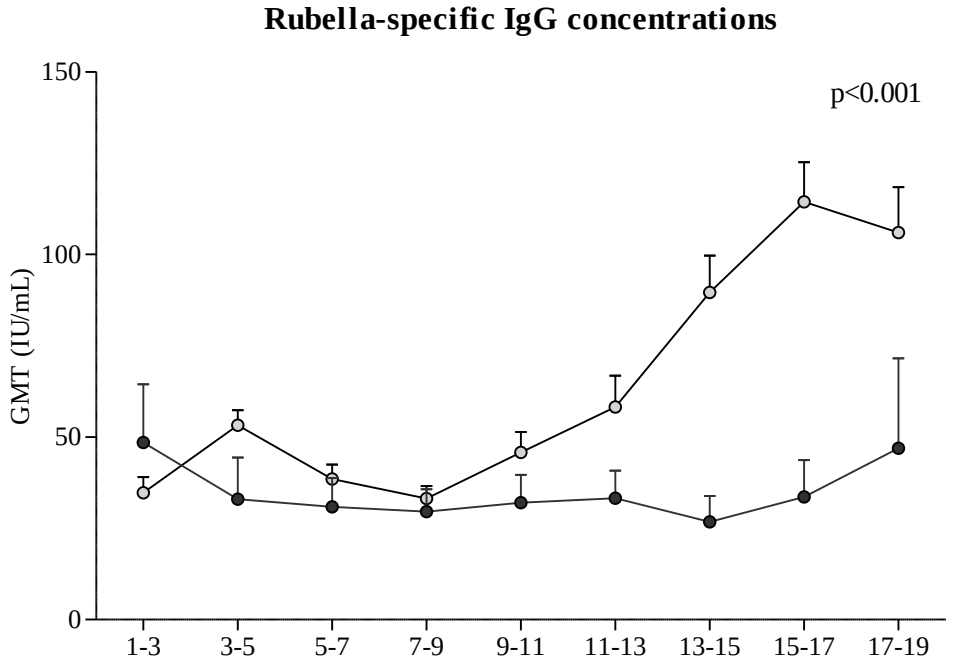
# Higher MV-GMT in JIA
# Mumps and RV-GMT lower

Healthy control (n=2173)

JIA (n=400)



# Prevalence of protective antibody levels lower in JIA, except for MV

University Medical Center Utrecht

| Protective antibody levels | OR* | 95%-CI | P-value |
|---|---|---|---|
| Measles | 1.4 | 0.8-2.5 | 0.233 |
| Mumps | 0.4 | 0.3-0.6 | <0.001 |
| Rubella | 0.4 | 0.3-0.7 | 0.001 |
| Diphtheria | 0.1 | 0.06-0.2 | <0.001 |
| Tetanus | 0.1 | 0.05-0.3 | <0.001 |

Corrected for number of vaccinations, age

**Heijstek et al.** ***ARD 2012***

# MMR immunisation during biological treatment

University Medical Center Utrecht

Retrospective analysis (Borte, 2009)

- MMR booster in 10 JIA children with etanercept and low dose MTX
- Similar immunogenicity compared with MTX monotherapy

Prospective analysis (Heijstek 2013)

- RCT for MMR booster in 137 JIA patients
- No worsening of disease activity
- MTX and biologics did not affect humoral responses, but low patient numbers precluded definite conclusions.

# Effects of the Live Attenuated Measles-Mumps-Rubella Booster Vaccination on Disease Activity in Patients With Juvenile Idiopathic Arthritis

## A Randomized Trial

Marloes W. Heijstek, MD
Sylvia Kamphuis, MD, PhD
Wineke Armbrust, MD
Joost Swart, MD
Simone Gorter, MD
Lara D. de Vries, MD
Gaby P. Smits, MSc
Pieter G. van Gageldonk, BASc
Guy A. M. Berbers, PhD
Nico M. Wulffraat, MD, PhD

**Importance** The immunogenicity and the effects of live attenuated measles-mumps-rubella (MMR) vaccination on disease activity in patients with juvenile idiopathic arthritis (JIA) are matters of concern, especially in patients treated with immunocompromising therapies.

**Objectives** To assess whether MMR booster vaccination affects disease activity and to describe MMR booster immunogenicity in patients with JIA.

**Design, Setting, and Participants** Randomized, multicenter, open-label clinical equivalence trial including 137 patients with JIA aged 4 to 9 years who were recruited from 5 academic hospitals in the Netherlands between May 2008 and July 2011.

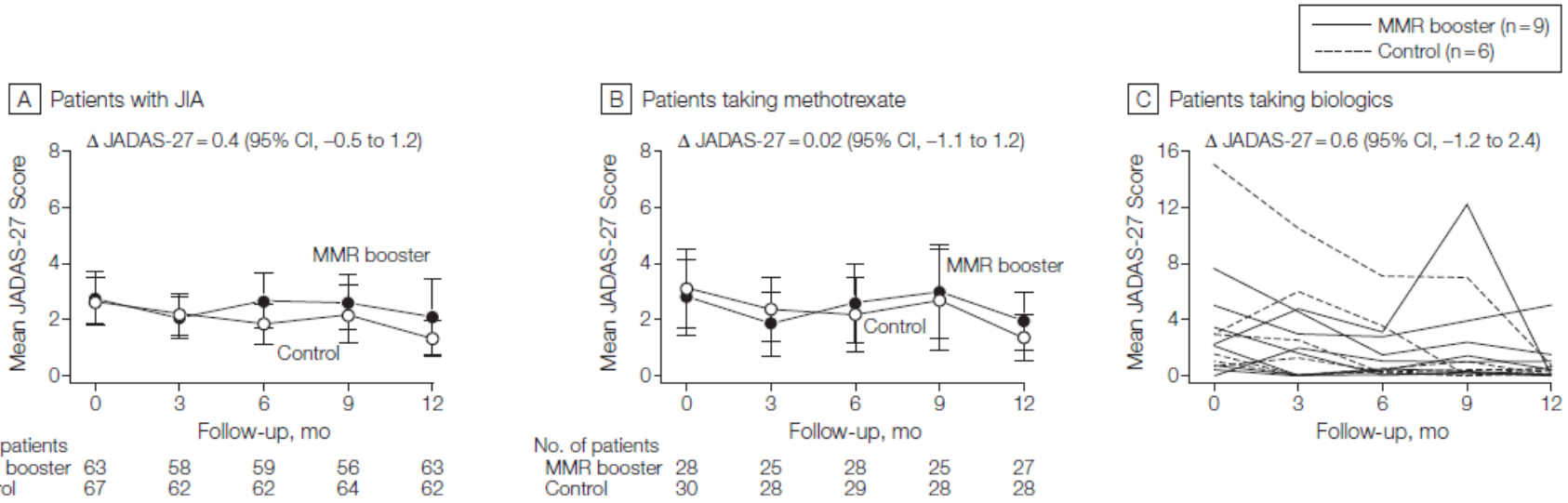
**Intervention** Patients were randomly assigned to receive MMR booster vaccination (n=68) or no vaccination (control group; n=69). Among patients taking biologics, these treatments were discontinued at 5 times their half-lives prior to vaccination.

**Main Outcomes and Measures** Disease activity as measured by the Juvenile Arthritis Disease Activity Score (JADAS-27), ranging from 0 (no activity) to 57 (high activity). Disease activity in the year following randomization was compared between revaccinated patients and controls using a linear mixed model. A difference in JADAS-27 of 2.0 was the equivalence margin. Primary immunogenicity outcomes were seroprotection rates and MMR-specific antibody concentrations at 3 and 12 months.

JUVENILE IDIOPATHIC ARTHRITIS (JIA) is the most common childhood rheumatic disease, with a prevalence between 16 and 150

University Medical Center Utrecht

**Figure 2.** Mean Disease Activity Levels During 12 Months of Follow-up by Randomization Group




JADAS-27 indicates Juvenile Arthritis Disease Activity Score including 27 joints; JIA, juvenile idiopathic arthritis; MMR, measles-mumps-rubella. Error bars indicate 95% CIs. Δ indicates the difference in JADAS-27 scores over time between randomization groups.

# What about HPV?

University Medical Center Utrecht

- HPV is associated with cervical dysplasia and cancer
- In healthy women HVP vaccination is effective
- HPV related cervical pathology is increased in adults with RA and SLE

But:

- The HPV adjuvans may cause adverse reactions (ASIA syndrome)
- Only few studies on HPV in SLE exist

Kim SC, ARD 2015 Jul;74(7):1360-7.; Mok, ARD 2013;72:659-664

# Safety on vaccins, an ongoing debate

University Medical Center Utrecht

- Hawkes D (1): The current studies involving human cases are so diverse, in both external stimuli and in resulting conditions, that there is currently a lack of reproducible evidence for any consistent relationship between adjuvant and autoimmune condition.

- Schoenfeld (2) et al postulate an ASIA syndrome (autoimmune syndrome induced by adjuvants or silicone exposure)
  - Chronic fatique syndrome, sick building syndrome, SJIA, SLE, breast implants
- **In the** VAERS database cases of pyrexia, myalgia and arthralgia or arthritis were reported with 3.6 cases per 100,000 doses of HPV (3)

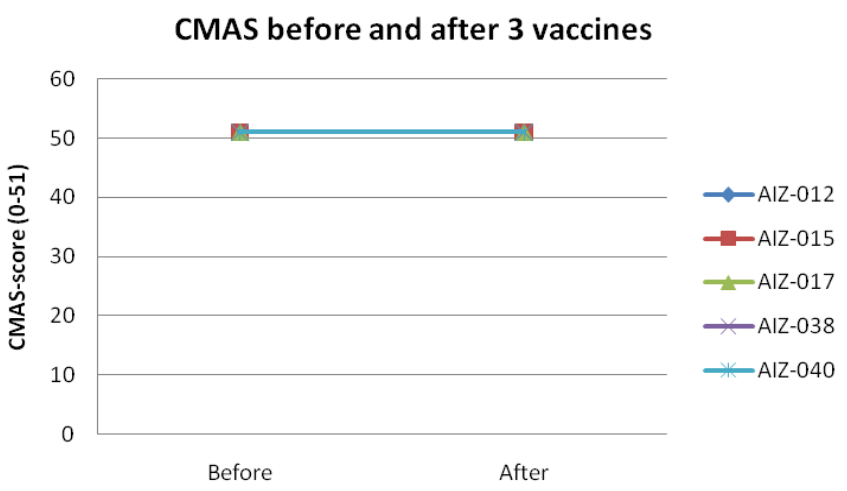

1:J Autoimmun 2015 May;59:77-84;

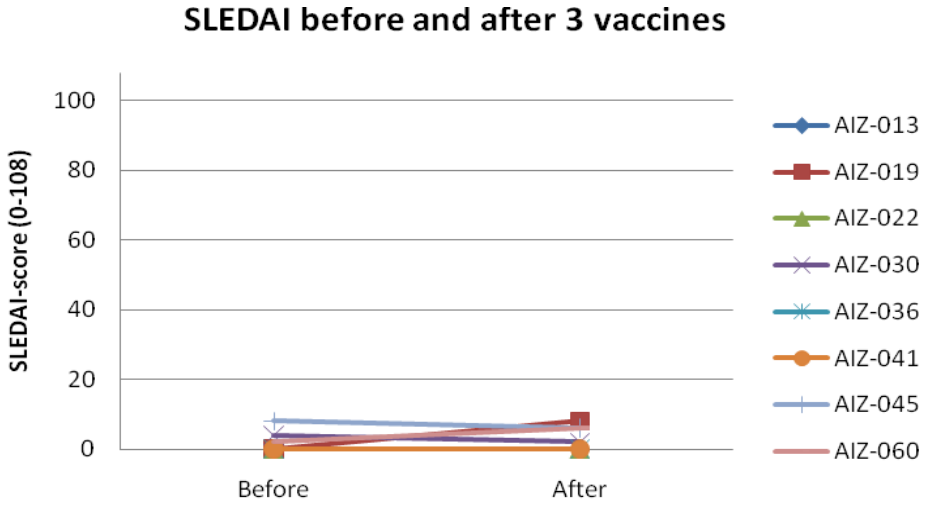
2: Clin Rheumatol. 2015 Jan 22.

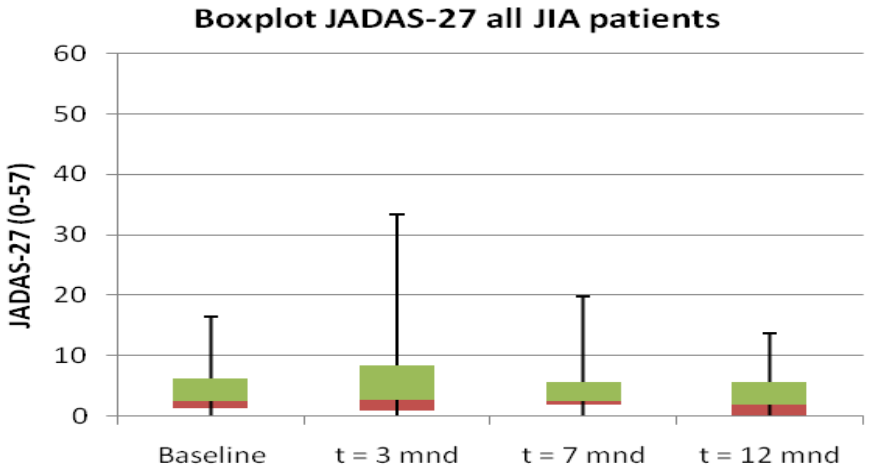
3: Immunol Res 2015 Feb;61(1-2):90-6

# Disease activity does not increase after HPV vaccination

University Medical Center Utrecht

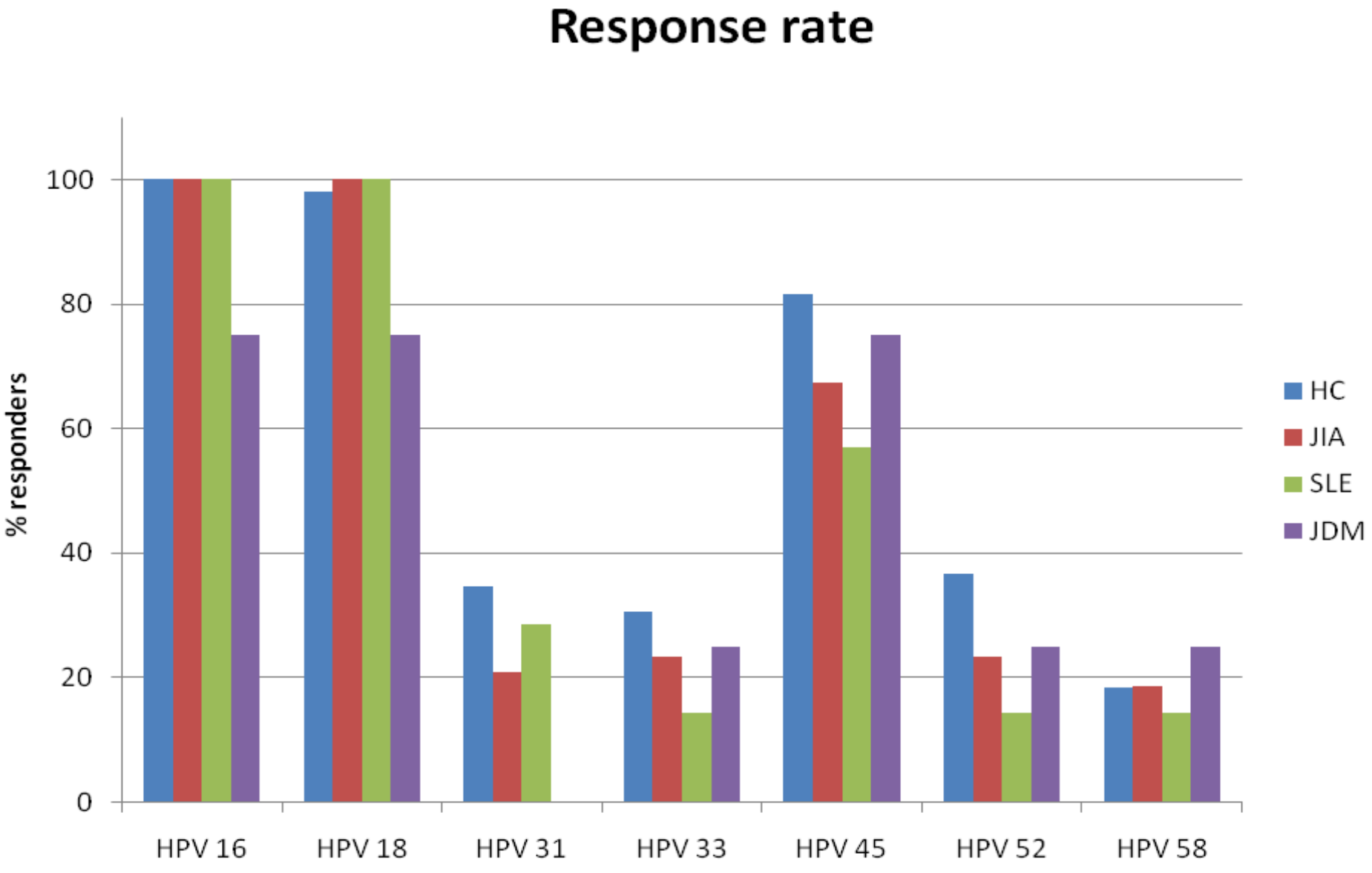


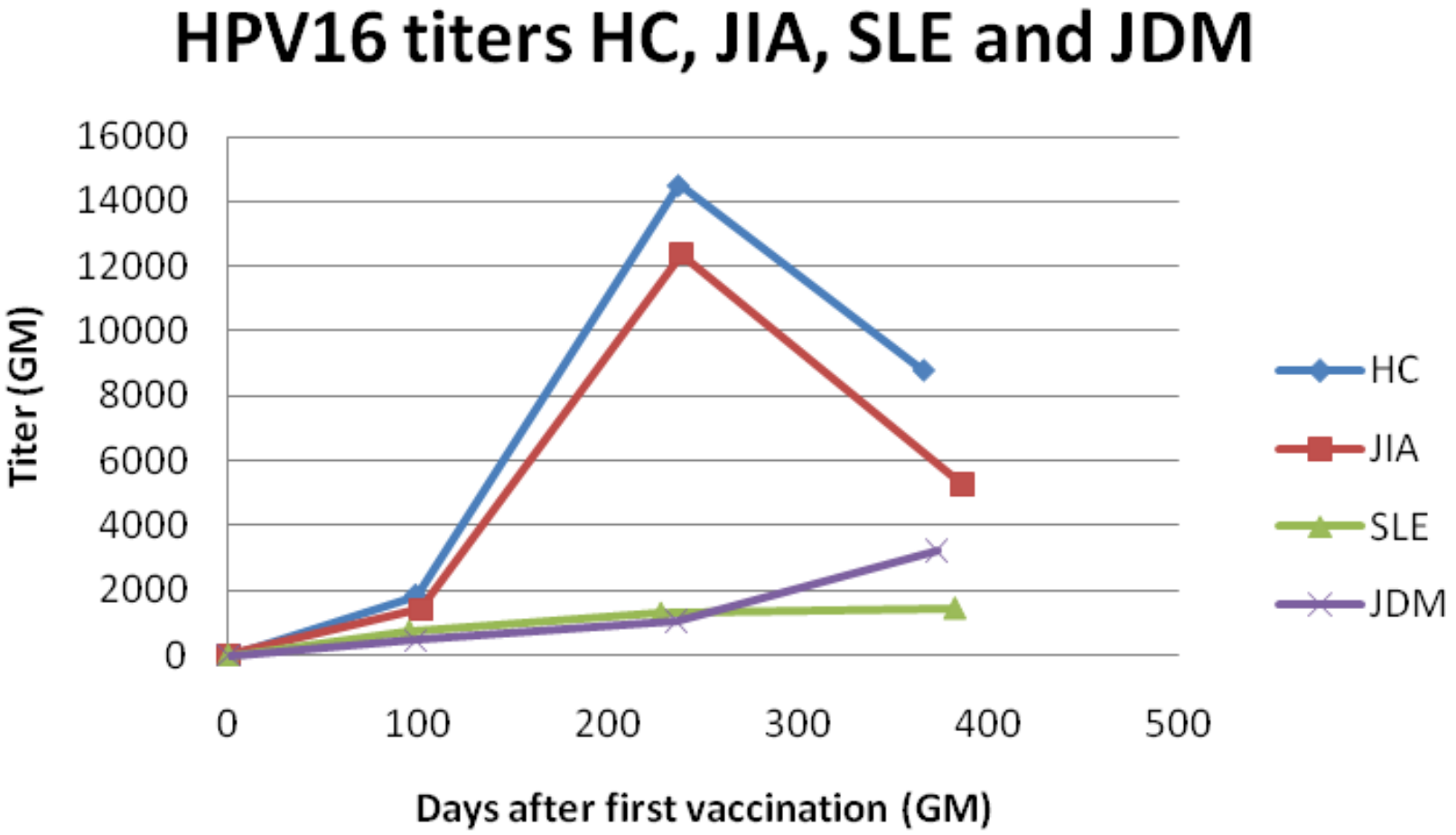
# Response rate similar for HPV 16-18

University Medical Center Utrecht



# Lower HPV-antibody levels in SLE / JDM

University Medical Center Utrecht



# HPV vaccine in SLE

University Medical Center Utrecht

- Mean SLEDAI scores do not increase following vaccination (low patient numbers).
- Seropositivity post-vaccine was high for HPV 6, 11, 16 and 18.

- However, vaccination-induced HPV16/18-specific antibody concentrations seemed lower

- Quadrivalent HPV vaccine seems generally safe and well tolerated in this series of adolescents and young women with SLE, with no increase in mean SLEDAI scores, but larger studies are needed


**•Soybilgic, PROJ 2013 Aug 7;11:29**

**•Mok, ARD 2013;72:659-664**

**•Heijstek MW, J Rheum 2013 Sep;40(9):1626-7.**

# EULAR task force: recommendations

University Medical Center Utrecht

R. Borrow, UK
L. Ott de Bruin, NL
N. Wulffraat, NL
M. Bijl, NL
A. Fasth, SWE
M. Heijstek, NL
M. Abinun, UK
F. van der Klis, NL
A. Ravelli, IT
I. Koné-Paut, FR
K. Minden, GE
G.Pileggi, BRA
M. Borte, GE

**Heijstek & Ott de Bruin, Ann Rheum Dis. 2011 Oct;70(10):1704-12.**

# Antirheumatic drugs and vaccinations

University Medical Center Utrecht

Safety

- Non-live vaccines are safe when on MTX, GCs, anti-TNF alpha, RTX
- Live-attenuated boosters seem safe when on low dose MTX or GCs
- Live-attenuated vaccines may be considered when on MTX, GCs, anti-TNF alpha, RTX on a case-by-case basis

Immunogenicity

- Good when on MTX, low dose GCs or anti-TNF alpha
  - except for PPV23 when on MTX
- Possibly lower when on high dose GCs (>20mg/day or >2mg/kg/day)
- Much lower until 6 months after RTX

**Heijstek & Ott de Bruin, Ann Rheum Dis. 2011 Oct;70(10):1704-12.**

# EULAR Recommendations
# Non-live vaccines

University Medical Center Utrecht

- Non-live vaccins safe in PedRD, including patients on GCs, DMARDS and anti-TNF alpha
- Annual influenza vaccination should be considered in all PedRD patients
- Hib, pneumococcal and meningococcal vaccines
  - recommended for patients with low complement or asplenia
  - should be considered in patients on high dose IS drugs
- HPV vaccination advised for SLE patients

**Heijstek & Ott de Bruin, Ann Rheum Dis. 2011 Oct;70(10):1704-12.**

# EULAR recommendations live-attenuated vaccines

University Medical Center Utrecht

- Patients on high dose DMARDS, high dose GCs or biologicals: withhold live-attenuated vaccines
  - can be considered on a case-to-case
- In patients on low dose MTX or GCs: Boosters vaccinations (MMR, VZV, YFV) can be considered
- Consider VZV vaccination in case of negative history for VZV infection / vaccination

**Heijstek & Ott de Bruin, Ann Rheum Dis. 2011 Oct;70(10):1704-12**
**Pileggi Arthritis Care Res (Hoboken). 2010 Jul;62(7):1034-9.**
**Groot & Heijstek, Current Rheum Reports 2015 Jul;17(7):519. doi: 10.1007/s11926-015-0519**

# Vaccination in AIRD: Friend or foe?

University Medical Center Utrecht

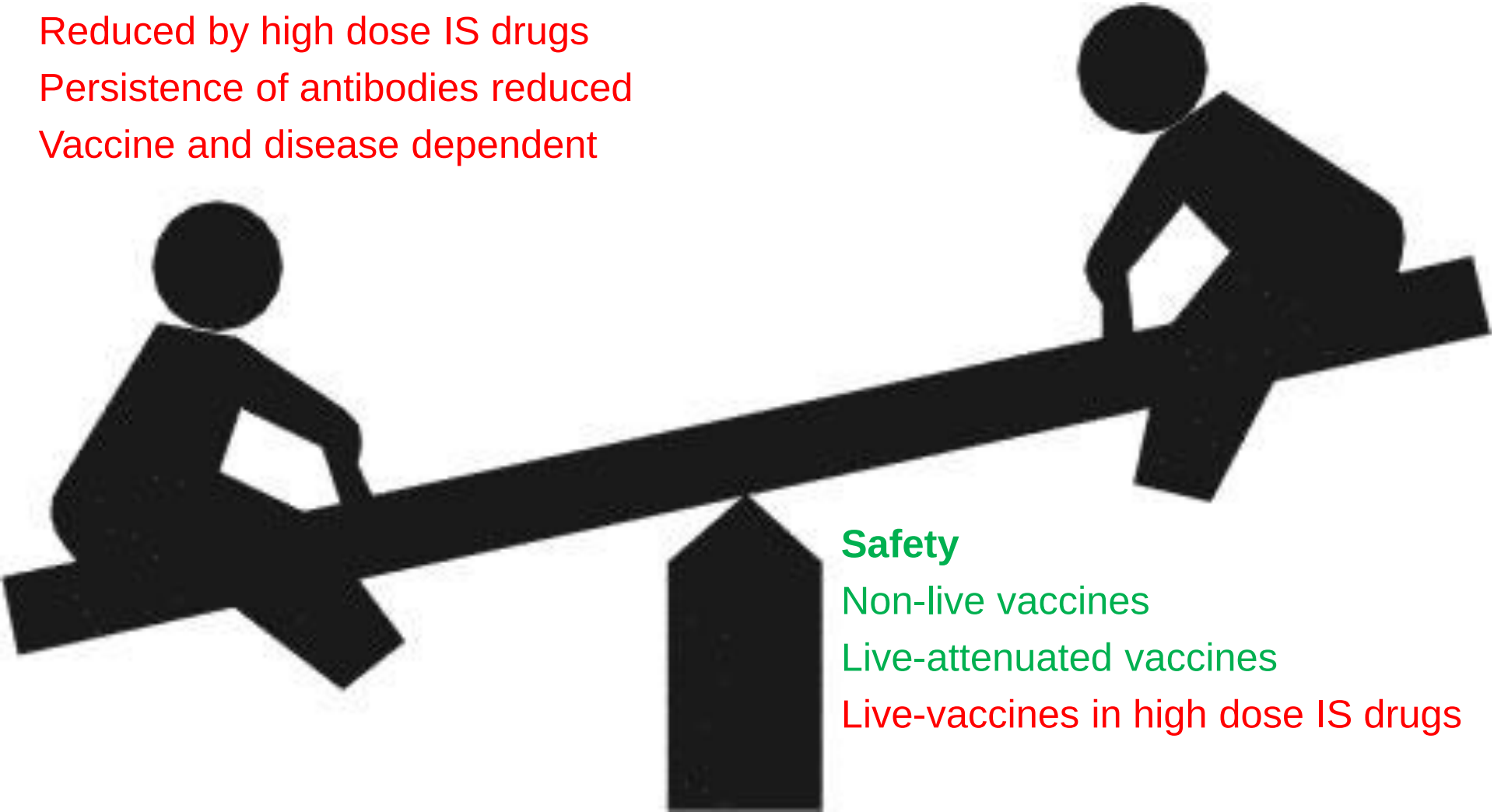
**Efficacy**

Generally effective in AIRD without drugs

Reduced by high dose IS drugs

Persistence of antibodies reduced

Vaccine and disease dependent



**Safety**

Non-live vaccines

Live-attenuated vaccines

Live-vaccines in high dose IS drugs

# Acknowledgements

University Medical Center Utrecht

**UMCU**
**Berent Prakken**
**Bas Vastert**
**Joost Swart**
**Prakken-lab**
**Marloes Heijstek**
**Noortje Groot**
**Sytze de Roock**
**Wilco de Jager**

**RIVM**
**Guy Berbers**
**Pieter vd Gageldonk**
**Fiona vd Klis**

**PHYSICIANS**
**Wineke Armbrust, UMC Groningen**
**Simone Gorter, UMC Maastricht**
**Sylvia Kamphuis, EMC Rotterdam**
**Mare Pileggi, Rib Preito, Brasil**

Reumaresearch
www.reumaresearch.nl

gsk GlaxoSmithKline