VACCINAZIONI NEI PAZIENTI CON PATOLOGIE REUMATOLOGICHE: PERCHE', QUANDO E COME

Susanna Esposito
Unità di Pediatria ad Alta Intensità di Cura
Università degli Studi di Milano
Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano

PATIENTS WITH RHEUMATIC DISEASES AND RISK OF INFECTION

(Dell'Era et al., Vaccine 2011)

- Patients with rheumatic diseases (RDs) are **at greater risk of infection** than age- and gender-matched subjects without RD because of their aberrant immunity and frequent use of immunosuppressive drugs

- They are also significantly more likely to experience **infections requiring hospitalisation**, including septicemia and pneumonia

RISK OF INFECTIONS IN PATIENTS WITH RA IN COMPARISON TO CONTROLS

(From Doran MF et al. Arthr Rheumat 2002)

Infection type	Patients, no.		Infections, no.		Incidence/100 person-years (all events/person)		Rate ratio†	95% confidence interval‡
	RA	Non-RA	RA	Non-RA	RA	Non-RA		
Total	389	343	1,481	1,137	19.64	12.87	1.53	1.41–1.65
Bacteremia/septicemia	53	39	60	47	0.78	0.51	1.50	1.10–2.08
Septic arthritis	22	2	31	2	0.40	0.02	14.89	6.12–73.71
Osteomyelitis	11	1	13	1	0.17	0.01	10.63	3.39–126.81
Pneumonia	179	135	311	218	4.02	2.39	1.68	1.46–1.95
Lower respiratory tract	52	35	83	52	1.07	0.57	1.88	1.41–2.53
Urinary tract infections	234	224	658	662	8.72	7.49	1.16	1.05–1.30
Urosepsis/pyelonephritis	28	29	38	40	0.49	0.44	1.12	0.77–1.63
Skin/soft tissue	132	59	231	83	2.99	0.91	3.28	2.67–4.07
Gastroenteritis	8	7	10	8	0.13	0.09	1.46	0.68–3.28
Intra-abdominal	17	7	17	7	0.22	0.08	2.76	1.39–6.22
Other	23	15	29	17	0.38	0.19	1.99	1.22–3.36

* Defined as infections with either a positive microbiologic culture or relevant radiologic finding.
† Obtained by dividing infection incidence rates in RA patients by those in non-RA subjects.

RATES OF SERIOUS INFECTIONS IN PATIENTS WITH RHEUMATIC DISEASE

British Society for Rhematology Biologics Register

(From Dixon WG et al., Arthr Rhemat 2006)

	DMARD	Anti-TNF
Person-years	1,352	9,868
Person-years per person, median (IQR)	0.94 (0.48–1.43)	1.26 (0.75–1.96)
No. of infections	56	525
Rate of infections/1,000 person-years (95% CI)	41.4 (31.4–53.5)	53.2 (48.9–57.8)
IRR overall	Referent	1.28 (0.94–1.76)
Adjusted for age and sex	Referent	1.47 (1.07–2.01)
Adjusted for age, sex, disease severity, comorbidity, extraarticular manifestations, steroid use, and smoking	Referent	1.03 (0.68, 1.57)

* 95% CI = 95% confidence interval; IRR = incidence rate ratio (see Table 1 for other definitions).

UPTAKE OF IMMUNIZATION AMONG CHILDREN AND ADULTS WITH RHEUMATIC DISEASES

(From Doe S et al. Rheumatology 2007)

Eligibility for vaccination	Offered 'flu vaccine *n* (%)	Received 'flu vaccine *n* (%)	Offered pneumococcal vaccine *n* (%)	Received pneumococcal vaccine *n* (%)
DMARDs $n=117$	107 (92)	86 (74)	54 (46)	47 (40)
Steroids only $n=18$	14 (78)	11 (61)	8 (44)	6 (33)
Comorbidity $n=3$	2 (67)	2 (67)	1 (33)	1 (33)
Age >65 $n=15$	13 (87)	10 (67)	7 (47)	6 (40)
Not eligible $n=14$	4 (29)	4 (29)	0	0

VACCINATION COVERAGE IN CHILDREN WITH AIG IN CANADA

(Da Morin MP et al., Rheumatology 2012)

	At 2.5 years		At 10.5 years		Last clinic visit	
	N	*n* (%)	*N*	*n* (%)	*N*	*n* (%)
Rubella and mumps	198	186 (94)	118	110 (93)	200	194 (97)
Measles	198	114 (58)	118	91 (77)	200	165 (83)
Polio	198	193 (97)	118	116 (98)	200	198 (99)
Diphtheria/tetanus	198	197 (99)	118	94 (80)	200	160 (80)
Pertussis	198	197 (99)	118	94 (80)	200	155 (78)
Meningococcus C	47	40 (85)	–	–	49	45 (92)
Hepatitis B	–	–	–	–	98	80 (82)
Haemophilus influenzae type B	198	172 (87)	–	–	–	–
Pneumococcus	31	27 (87)	–	–	–	–
Varicella[a]	12	11 (92)	–	–	14	12 (86)
Complete vaccination status	198	103 (52)	118	80 (68)	200	121 (61)

N: number of children who should have received the vaccine as per the Quebec immunization programme. [a]Not included in the complete vaccination status.

VACCINATION AWARENESS AND UPTAKE IN PATIENTS WITH RHEUMATIC CONDITIONS

(From Fahy WA et al. Rheumatology 2006)

	Age <65 (%)	>65 (%)
Patients aware of influenza vaccine	96	100
Influenza vaccination discussed by health practitioner	89	100
Vaccinated against influenza	46	81
Patients aware of pneumococcal vaccine	65	96
Pneumococcal vaccination discussed by health practitione	42	92
Vaccinated against pneumococcus	12	54

PROBLEMI CONNESSI CON L'USO DEI VACCINI NEI PAZIENTI CON MALATTIA REUMATOLOGICA

(Dell'Era et al., Vaccine 2011)

- Possibilità di riattivazione della malattia di base
- Minore sicurezza, specie nell'utilizzo dei vaccini a base di agenti infettivi vivi attenuati
- Minore immunogenicità e, quindi, più bassa efficacia protettiva

VACCINE-RELATED RISK OF AUTOIMMUNE REACTIONS

(Dell'Era et al., Vaccine 2011)

- The vaccines with the largest number of reports of RD induction are the hepatitis B virus (HBV), influenza, and measles, mumps and rubella (MMR) vaccines
- Only a few of these involved young children
- All of the case-control studies that have analysed the safety of vaccines in large groups of subjects have found no increase in the incidence of autoimmune manifestations after its administration

INFLUENZA VACCINATION AND AUTOIMMUNE REACTIONS

(Dell'Era et al., Vaccine 2011)

- Vasculitis, Henoch-Schoenlein purpura and, very rarely, reactive arthritis and cryoglubulinemia have been described after the administration of influenza vaccine
- Vaccination does not worsen the clinical situation, and that the few cases of increased joint involvement can be attributed to expected fluctuations in disease activity
- Guillain-Barré syndrome occurred with one swine influenza vaccine in 1976, but this association has not been observed since then

CLINICAL SCORES AND BIOMARKERS OF DISEASE ACTIVITY BEFORE AND AFTER AS03-ADJUVANTED INFLUENZA VACCINE

(From Gabay C et al. Arthr Rheumat 2011)

	At baseline		At follow-up *		
	N (%)	Median (IQR)	N (%)	Median (IQR)	p
Rheumatoid arthritis	82		82		
DAS28-CRP	78 (95.1)	3.30 (2.58-4.05)	77 (95.1)	3.32 (2.61-4.09)	0.40
RADAI	71 (86.6)	3.56 (1.73-5.19)	75 (86.6)	3.19 (1.80-4.28)	0.23
HAQ	77 (93.9)	0.75 (0.12-1.62)	78 (93.9)	1.00 (0.25-1.75)	0.29
Spondyloarthropathies					
Axial SpA	28		28		
BASDAI	24 (85.7)	4.85 (3.30-6.22)	24 (85.7)	3.31 (1.66-4.62)	0.06
Psoriatic arthritis	17		17		
DAS28-CRP	12 (70.6)	2.78 (2.22-3.03)	14 (70.6)	2.46 (1.99-3.16)	0.47
HAQ	16 (94.1)	0.06 (0.00-0.87)	16 (94.1)	0.06 (0.00-0.65)	0.11
Systemic Lupus Erythematosus	18		18		
SLEDAI	18 (100.0)	1.5 (0.00-2.00)	17 (100.0)	1.00 (0.00-2.00)	0.68
ANCA-associated vasculitis	10		10		
BVAS	9 (90.0)	1.00 (0.00-2.00)	9 (90.0)	1.00 (0.00-1.00)	0.18
Creatinine, mM/l	10 (100.0)	85.5 (70.0-106.8)	10 (100)	92.0 (78.8-102.8)	0.10

* 4-6 weeks after Dose 2

ANCA : anti-neutrophil cytoplasmic antibodies; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BVAS: Birmingham Vasculitis Activity Score; DAS28-CRP: Disease Activity Score including C-reactive protein; HAQ: Stanford Health Assessment Questionnaire; IQR: interquartile range; RADAI: Rheumatoid Arthritis Disease Activity Index; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SpA, spondyloarthropathies

EFFECT OF INFLUENZA VACCINATION (*) ON DISEASE ACTIVITY

(From Elkayam O et al. Semin Arthritis Rheum2010)

	RA (n = 43)		AS (n = 18)	
	Week 0	Week 4 to 6	Week 0	Week 4 to 6
ESR (mm/h)(SD)	40 (16)	46 (15)	3.5 (2.9)	4.5 (3.3)
	$P = 0.05$		$P = 0.01$	
C-reactive protein (mg/l)(SD)	14 (16)	13 (1.9)	14.6 (19)	20 (25)
	$P = 0.6$		$P = 0.09$	
DAS (SD)	3.48 (1.45)	3.23 (1.38)		
	$P = 0.31$			
BASDAI (SD)			3.41 (2.3)	3.26 (2.5)
			$P = 0.9$	

ESR, erythrocyte sedimentation rate; DAS, disease activity score; BASDAI, Bath ankylosing spondylitis activity index.

* not-adjuvanted TIV

SAFETY OF MF-59 ADJUVANTED INFLUENZA VACCINE IN PEDIATRIC PATIENTS WITH JIA

(Dell'Era et al., Vaccine 2012)

Adverse events	JIA patients treated with DMARDs ($n=30$)	JIA patients treated with etanercept ($n=30$)	Healthy controls ($n=30$)
Local reactions, no. (%)			
Erythema	2(6.7)	3(10.0)	3(10.0)
Swelling/induration	12(40.0)	11(36.7)	11(36.7)
Pain	13(43.3)	11(36.7)	12(40.0)
At least one local event	13(43.3)	11(36.7)	12(40.0)
Systemic reactions, no. (%)			
Fever ≥38 °C	7(23.3)	4(13.3)	5(16.7)
Rhinitis	9(30.0)	8(26.7)	7(23.3)
Malaise	6(20.0)	8(26.7)	8(26.7)
Sleepiness	6(20.0)	4(13.3)	5(16.7)
Changed eating habits	8(26.7)	4(13.3)	5(16.7)
Vomiting	2(6.7)	2(6.7)	1(3.3)
Diarrhea	2(6.7)	1(3.3)	2(6.7)
At least one systemic event	9(30.0)	8(26.7)	8(26.7)
At least one local or systemic event	9(30.0)	11(36.7)	12(40.0)
Required drugs for local or systemic events	4(13.3)	3(10.0)	5(16.7)
Serious adverse events	1(3.3)	1(3.3)	0(0.0)

Association between Gardasil administration and autoimmune disorders in patients with JIA and controls

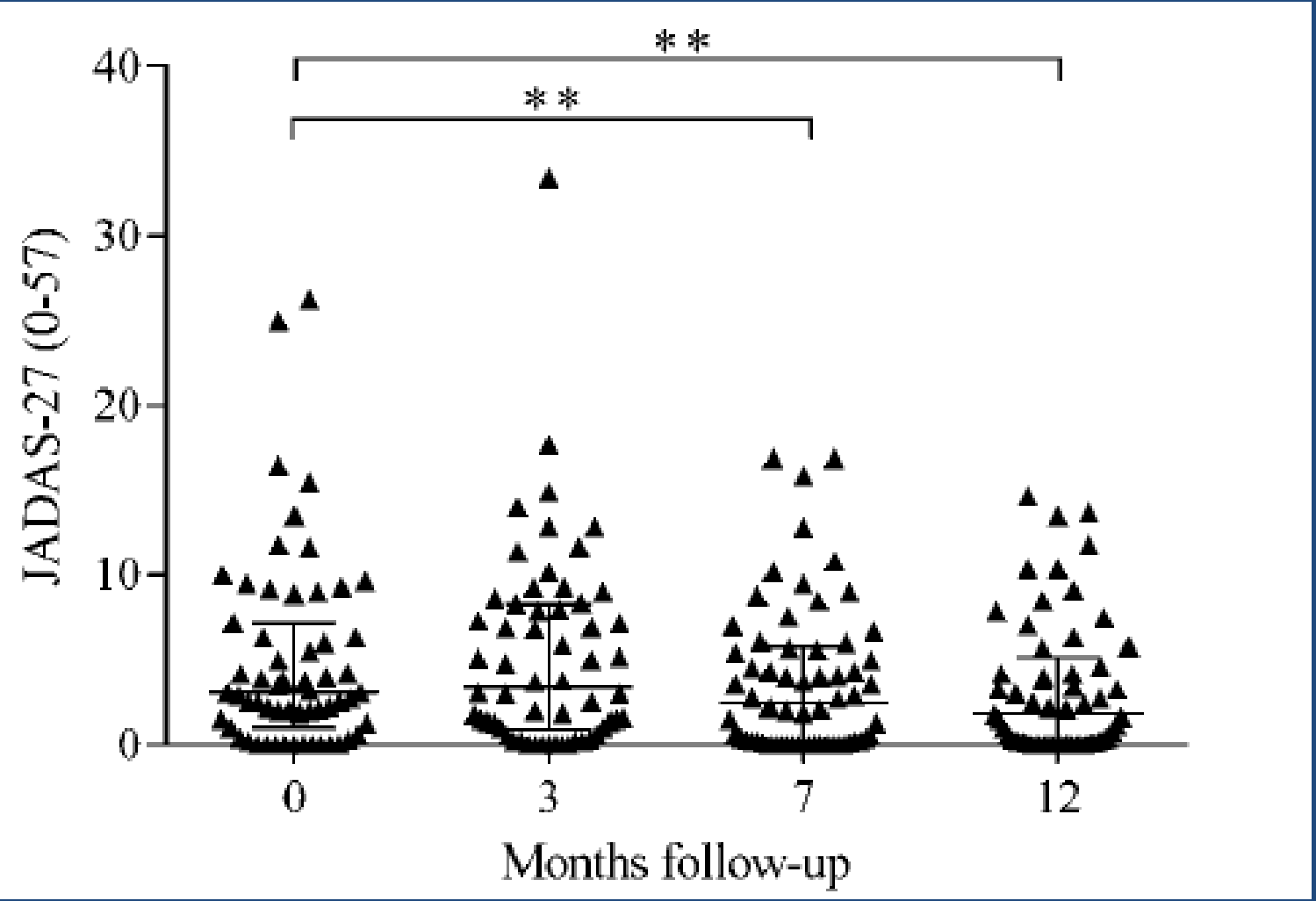
(From Grimaldi-Bensouda L et al., J Intern Med 2014)

Analysis (*n* cases/*n* controls)	Cases exposed *n* (%)	Controls exposed *n* (%)	Crude OR[b] (95% CI)	Adjusted OR[b] (95% CI)
For definite cases and confirmed Gardasil vaccinations in primary time window[a]:				
All ADs combined				
211 of 875	25 (11.8)	192 (21.9)	0.5 (0.3–0.7)[c]	0.9 (0.5–1.5)[c]
With personal or family history of AD: 20 of 55	3 (15.0)	15 (27.3)	0.5 (0.1–1.9)[d]	1.1 (0.2–5.9)[d]
Without personal or family history of AD: 137 of 602	19 (13.9)	139 (23.1)	0.5 (0.3–0.9)[d]	0.8 (0.5–1.5)[d]
ADs separately				
Idiopathic thrombocytopenic purpura: 40 of 183	6 (15.0)	33 (18.0)	0.8 (0.3–2.2)[c]	1.0 (0.4–2.6)[c]
Connective tissue disorders: 49 of 200	6 (12.2)	37 (18.5)	0.6 (0.2–1.5)[c]	0.8 (0.3–2.4)[c]
Central demyelination: 83 of 290	4 (4.8)	48 (16.6)	0.3 (0.1–0.7)[c]	0.3 (0.1–0.9)[c]
Guillain–Barré syndrome: 15 of 91	0 (0.0)	7 (7.7)	–	–
Type 1 diabetes: 38 of 202	9 (23.7)	41 (20.3)	1.2 (0.5–2.9)[c]	1.2 (0.4–3.6)[c]

AD, autoimmune disorder; ATD, autoimmune thyroid disorder; OR, odds ratio; CI, confidence interval.
[a]Primary time window A was ≤6 months before the index date for ITP, ≤2 months for Guillain–Barré syndrome and ≤24 months for the other ADs. For each case–control set, the relevant time window was used according to the AD. [b]ORs were calculated whenever there were three or more patients in each cell considered. [c]Crude ORs were calculated using unconditional logistic regression; adjusted ORs were calculated using conditional logistic regression and controlled for the multivariate risk score and a personal or family history of AD. [d]Crude and adjusted ORs were calculated using unconditional logistic regression; adjusted ORs controlled for the multivariate risk score and matching factors.

DISEASE ACTIVITY IN PATIENTS WITH JIA RECEIVING CERVARIX

(From Heijstek et al., Ann Rheum Dis 2013)



SAFETY OF CERVARIX IN ADOLESCENTS WITH JIA

(Esposito et al., Vaccine 2012)

- Among 21 patients with JIA, the incidence of solicited and unsolicited local and systemic reaction during the 14 days following each of the HPV doses was similar to that observed in healthy controls
- In most cases, the local and systemic reactions were recorded in the first two days after vaccine administration, did not require drug treatment, and their mild to moderate symptoms lasted for no more than 2 days
- No variation in both JADAS-27 score and in laboratory tests was demonstrated

Table 1. Clinical characteristics, medications used, response to varicella vaccine, and occurrence of vaccine-related rash in 25 vaccinated patients*

Patient	Age, years	Disease type	Disease activity†	Medication used			Anti–VZV-IgG titers‡		Vaccine-related rash
				MTX, mg/m²/week	Prednisone, mg/day	Other	4–6 weeks	1 year	
1	3	Juvenile DM	No	12	2		78	400§	No
2	12	Vasculitis	Yes	20	10		<50	55	No
3	2	Juvenile scleroderma	Yes	20	7.5		<50	<50	No
4	7	Juvenile DM	Yes	15	10	Cyclosporine (3 mg/kg/day)	<50	<50	No
5	14	Oligoarticular JIA	No	12	0		60	<50	No
6	4	Polyarticular JIA	Yes	15	10		947§	290§	No
7	13	Systemic JIA	Yes	25	5	Leflunomide (10 mg/day)	192§	330§	Yes
8	5	Polyarticular JIA	No	15	0		120§	<50	No
9	5	Polyarticular JIA	No	13	0		62	56	No
10	4	Polyarticular JIA	Yes	20	5		120§	<50	No
11	5	Polyarticular JIA	Yes	16.6	0		567§	485§	No
12	8	Polyarticular JIA	Yes	20	0		<50	<50	No
13	7	Systemic JIA	Yes	20	9	Cyclosporine (3 mg/kg/day)	1,458§	1,300§	Yes
14	4	Systemic JIA	No	15	0		130§	2,800§	No
15	8	Polyarticular JIA	No	15	0		635§	140§	No
16	6	Systemic JIA	Yes	18	10		<50	<50	No
17	12	Polyarticular JIA	Yes	15	0		64	55	No
18	15	Polyarticular JIA	No	13	0		<50	<50	No
19	6	Juvenile scleroderma	Yes	25	20		947§	210§	No
20	4	Oligoarticular JIA	No	19	0		335§	820§	Yes
21¶	5	Juvenile scleroderma	Yes	16.6	7.5	Penicillamine (13 mg/kg/day)	947§	340§	No
22¶	9	Polyarticular JIA	Yes	22	0		335§	150§	No
23¶	11	Systemic JIA	No	18	0		3,316§	ND	No
24¶	13	Juvenile DM	Yes	20	10		982§	ND	No
25¶	19	Juvenile DM	No	13	5	Cyclosporine (3.5 mg/kg/day)	2,230§	ND	No

From Pileggi et al., Arthritis Care & Research 2010

Disease activity parameters assessed 1 and 3 months before and after varicella vaccination in patients with JIA

(From Pileggi et al., Arthritis Care & Research 2010)

	Before, mean (95% CI)	After, mean (95% CI)	P†
No. of joints with active arthritis	3.2 (1.4–5)	1.8 (0.8–2.8)	0.009‡
No. of joints with limited range of motion	0.8 (0.3–1.3)	0.7 (0.3–1.2)	0.94
C-HAQ score	0.4 (0.1–0.6)	0.3 (0.1–0.4)	0.19
Parent's global assessment of overall well-being§	2.1 (0.8–3.5)	1.6 (0.6–2.7)	0.23
Physician's global assessment of disease activity§	2.4 (1–3.8)	1.7 (0.7–2.8)	0.077
ESR, mm/hour	26.6 (18–35)	24.3 (18–31)	0.56

* 95% CI = 95% confidence interval. C-HAQ = Childhood Health Assessment Questionnaire; ESR = erythrocyte sedimentation rate.
† By Wilcoxon's signed rank test.
‡ Significant, $P < 0.05$.
§ Measured on a 10-cm visual analog scale.

VACCINATIONS AND IMMUNE RESPONSE

- Few studies available
- Few therapies evaluated
- Correlates of protection not always very clear

EFFECT OF DRUG COMBINATIONS IN RHEUMATOID PATIENTS ON ANTIBODY RESPONSE

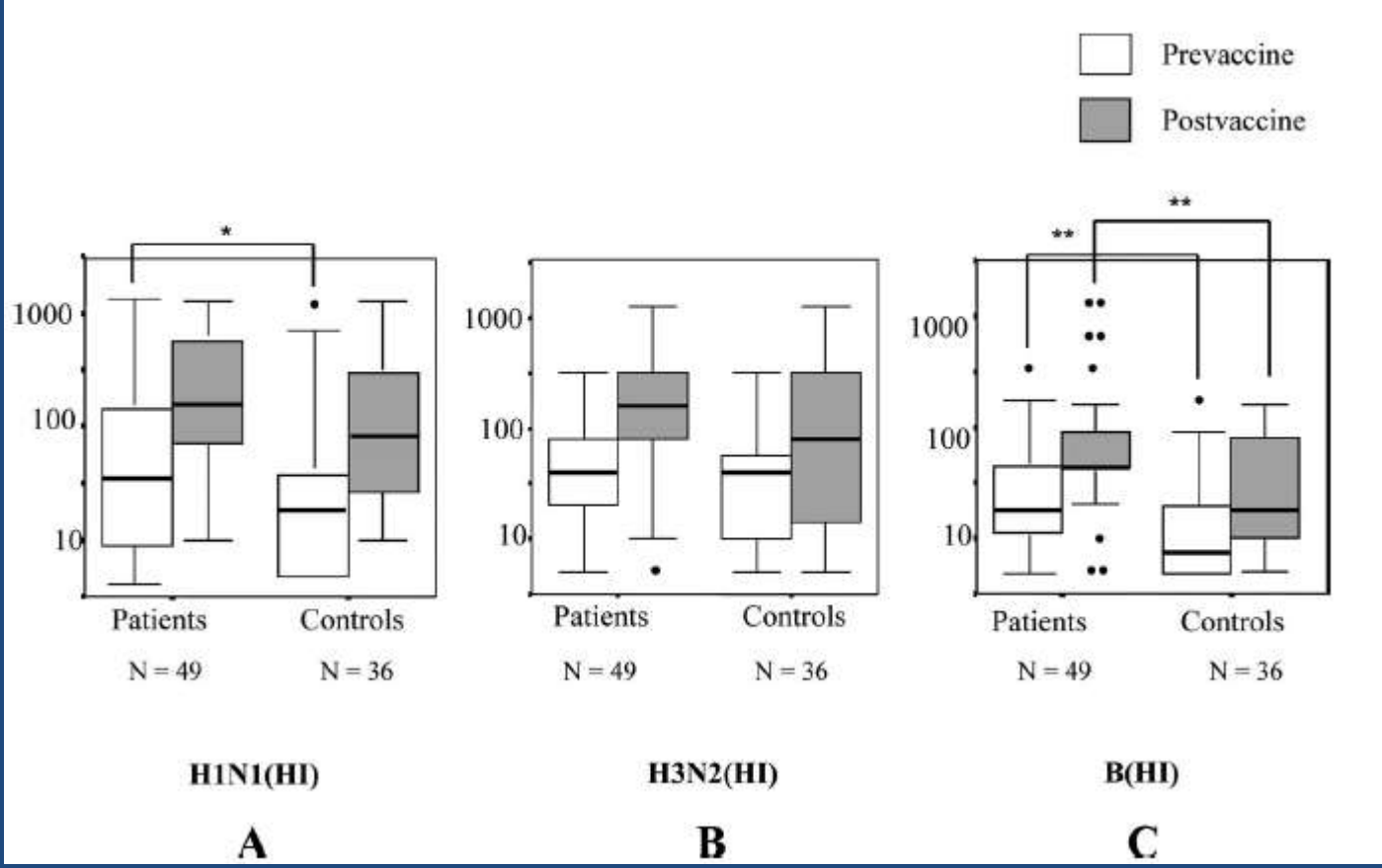
(From Brezinschek HP et al., Curr Opinion Rheumatol 2008)

Antibody response	Vaccine	DMARD	Additional TNF-Therapy
Decreased	Influenza vaccine	Methotrexate	Etanercept, infliximab
	Influenza vaccine	–	Etanercept, infliximab
	Pneumococcal vaccine	Methotrexate	–
	Pneumococcal vaccine	Methotrexate	Adalimumab
	Pneumococcal vaccine	Methotrexate	Etanercept, infliximab
Not decreased	Influenza vaccine	Methotrexate	–
	Influenza vaccine	Methotrexate	Adalimumab
	Influenza vaccine	Methotrexate	Etanercept, infliximab
	Pneumococcal vaccine	Methotrexate	Infliximab
	Pneumococcal vaccine	–	Adalimumab
	Pneumococcal vaccine	–	Etanercept, infliximab
	Hepatitis B vaccine	Methotrexate	–

DMARD, disease-modifying antirheumatic drug; TNF, tumor necrosis factor.

IMMUNOGENICITY OF INFLUENZA VACCINE IN CHILDREN WITH RHEUMATIC DISEASES RECEIVING IMMUNOSUPPRESSIVE AGENTS

(From Ogimi C et al., Pediatr Infect Dis J 2011)



GMT OF HI AB AGAINST INFLUENZA ANTIGENS IN EACH GROUP OF RA, RECEIVING INFLIXIMAB, AND CONTROLS

(From Elkayam O et al., Semin Arthritis Rheum 2010)

	RA Controls (n = 23)		RA + INF1 (n = 13)		RA + INF 2 (n = 7)		RA + INF (n = 20)	
	Week 0	Week 4 to 6	Week 0	Week 4 to 6	Week 0	Week 4 to 6	Week 0	Week 4 to 6
A/New Caledonian	2.72 (2.1)	4.1 (1.8)	2.5 (2)	4.2 (2)	2.9 (2.2)	3.9 (2)	3.1 (3.6)	4.7 (1.3)
P value	$P = 0.02$		$P < 0.01$		$P = 0.12$		$P < 0.01$	
A/Wisconsin	2.5 (2.3)	4.3 (2)	2.1 (2.2)	4.1 (2)	3.2 (2.2)	4.7 (2.4)	2.8 (2.2)	5.3 (1.7)
P value	$P < 0.01$		$P < 0.01$		$P = 0.06$		$P < 0.01$	

B Table 4 Geometric Mean Titers (GMT) of HI Antibodies (μg/mL) Against Influenza Antigens in Each Group of RA, AS, and Controls Before and 4 weeks After Influenza Virus Vaccination

	AS + INF (18)		AS + INF1 (n = 9)		AS + INF2 (n = 9)		Healthy controls (n = 17)	
	Week 0	Week 4 to 6	Week 0	Week 4 to 6	Week 0	Week 4 to 6	Week 0	Week 4 to 6
A/New Caledonian	1.75 (2.1)	4.3 (2)	0.7 (1.4)	3.8 (1.8)	2.7 (2.2)	4.7 (2)	3.4 (1.8)	4.8 (1.3)
P value	$P < 0.01$		$P = 0.03$		$P = 0.01$		$P < 0.01$	
A/Wisconsin	1.87 (2.2)	4.4 (1.7)	1.6 (2)	4.4 (1.2)	2.1 (2.6)	2.3 (2.4)	2.8 (1.8)	5.2 (1.2)
P value	$P < 0.01$		$P = 0.02$		$P = 0.03$		$P < 0.01$	
B/Malaysia	0.53 (1.24)	2.6 (2.2)	1.6 (2)	4.4 (1.2)	2.1 (2.6)	2.3 (2.4)	0.7 (1.5)	2.7 (2)
P value	$P < 0.01$		$P < 0.01$		$P = 0.01$		$P < 0.01$	

RA + INF, RA patients treated with infliximab; RA + INF1, RA patients vaccinated on same day as infliximab; RA + INF2, RA patients vaccinated 3 weeks after infliximab; AS + INF, AS patients treated with infliximab; AS + INF1, AS patients vaccinated on same day as infliximab; AS + INF2, AS patients vaccinated 3 weeks after infliximab.

GMT (fold increase) of antibodies against A/H1N1, A/H3N2 and B influenza strains in children with JIA and healthy controls

(From Dell'Era L et al., Vaccine 2012)

	JIA treated with DMARDs	JIA treated with etanercept	Healthy controls
A/H1N1			
Baseline	57.4§	48.3§	49.9§
28 ± 3 days	1833.8 (31.9)*	773.6 (16.0)^	1693.1 (33.9)*
90 ± 3 days	1067.7 (18.6)*	463.4 (9.6)	1324.5 (26.5)*
A/H1N1			
Baseline	23.5§	36.4§	31.4§
28 ± 3 days	686.2 (29.2)	724.5 (19.9)^	756.0 (24.1)
90 ± 3 days	406.3 (17.3)	295.1 (8.1)	469.9 (15.0)
B			
Baseline	11.9§	6.1	16.3§
28 ± 3 days	187.7 (15.8)*	61.2 (10.0)	210.6 (12.9)*
90 ± 3 days	162.6 (13.7)*	33.3 (5.5)	193.3 (11.9)*

* $p < 0.05$ vs JIA patients treated with etanercept; § $p < 0.05$ from baseline to 28±3 and 90±3 days post-dose within group; ^ $p < 0.05$ from 28±3 to 90±3 days post-dose within group

		PRE			POST1			POST2		
		GMT	CI95inf	CI95sup	GMT	CI95inf	CI95sup	GMT	CI95inf	CI95sup
DMARD	No	13	1.1	152	269	9.7	7479	422	23.5	7602
	Yes	12.9	0.9	181	123	3.1	4949	259	10.4	6449
	p-value		0.84			0.03			0.14	
MTX	No	12.5	0.9	172	164	4.2	6371	318	10.2	9890
	Yes	13.4	1.0	179	128	3.3	5059	247	16.3	3733
	p-value		0.39			0.34			0.13	
SSZ or HCQ	No	12.6	1.0	163	130	3.6	4614	266	12.8	5546
	Yes	14.1	0.9	220	237	4.6	12101	372	10.3	13350
	p-value		0.77			0.14			0.18	
LEF	No	13.2	1.0	171	161	4.2	6139	298	13.7	6464
	Yes	11.1	0.6	195	82.7	2.1	3271	224	5.4	9380
	p-value		0.23			0.19			0.76	
AZA, CYC or MMF	No	14.0	0.9	209	153	3.7	6353	302	13.4	6826
	Yes	8.2	1.5	45	100	4.4	2311	223	7.4	6725
	p-value		0.06			0.50			0.52	
TNF-α antagonists	No	13.6	1.1	173	117	3	4645	255	8.7	7453
	Yes	12	0.8	175	186	5	6883	340	20.2	5732
	p-value		0.27			0.12			0.46	
Oral steroids	No	13.4	0.9	208	132	4.1	4223	317	17.6	5694
	<10mg	10.8	1.1	107	142	3.1	6471	301	10.1	8973
	>=10mg	14.7	1.4	155	380	3.5	41539	152	2.6	8795
	p-value		0.49			0.3			0.57	
B cell depletion	No	13.1	0.9	195	157	4.7	5316	324	18.2	5779
	Yes	11.4	1.9	70	84	0.9	7808	118	1.3	10315
	p-value		0.83			0.2			0.09	
Time since last cycle	<12 weeks	10.3	1.4	77	30.7	0.4	2204	33.0	0.2	5533
	12-24 weeks	9.8	0.8	117	48.0	7.0	328	197	184	210
	>24 weeks	12.9	2.3	72	235	2.2	25095	370	17.8	7683
	p-value		0.89			0.13			0.08	

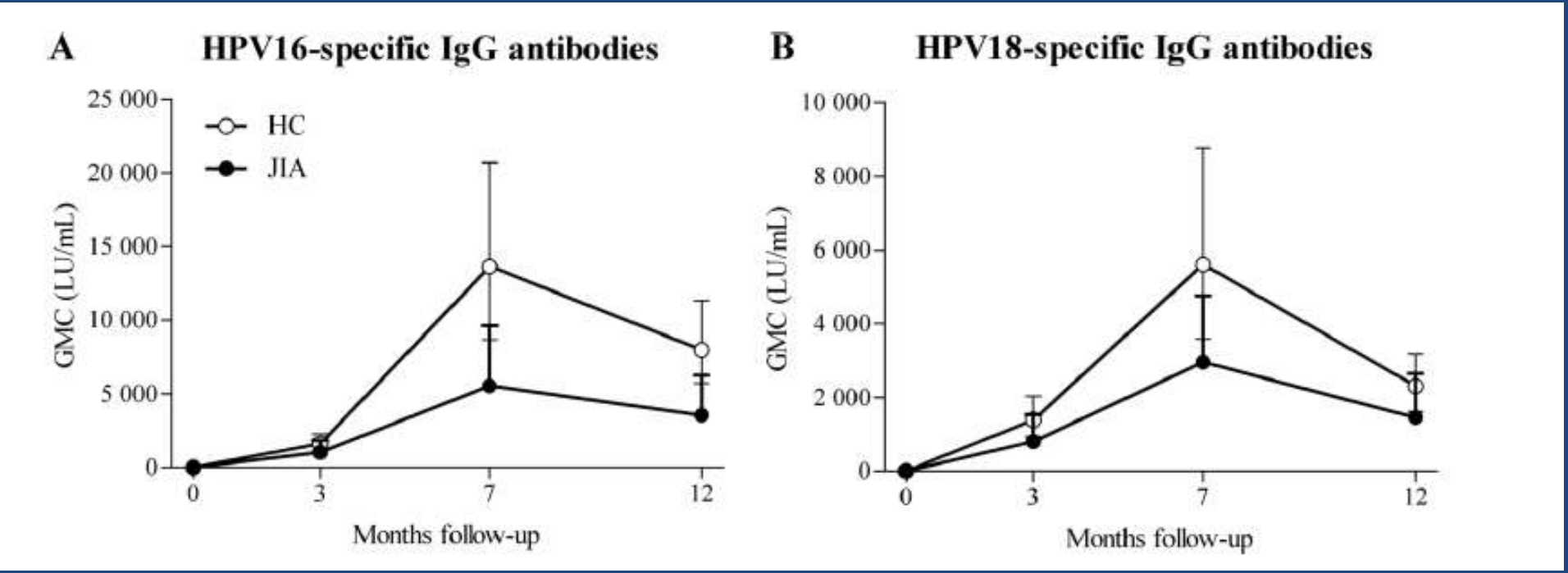
PRE: prior to vaccination; POST1 and POST2: after one and two doses of vaccine, respectively

Impact of therapy on AS03-adjuvanted pandemic influenza vaccine response

(From Gabay C et al. Arthr Rheumat 2011)

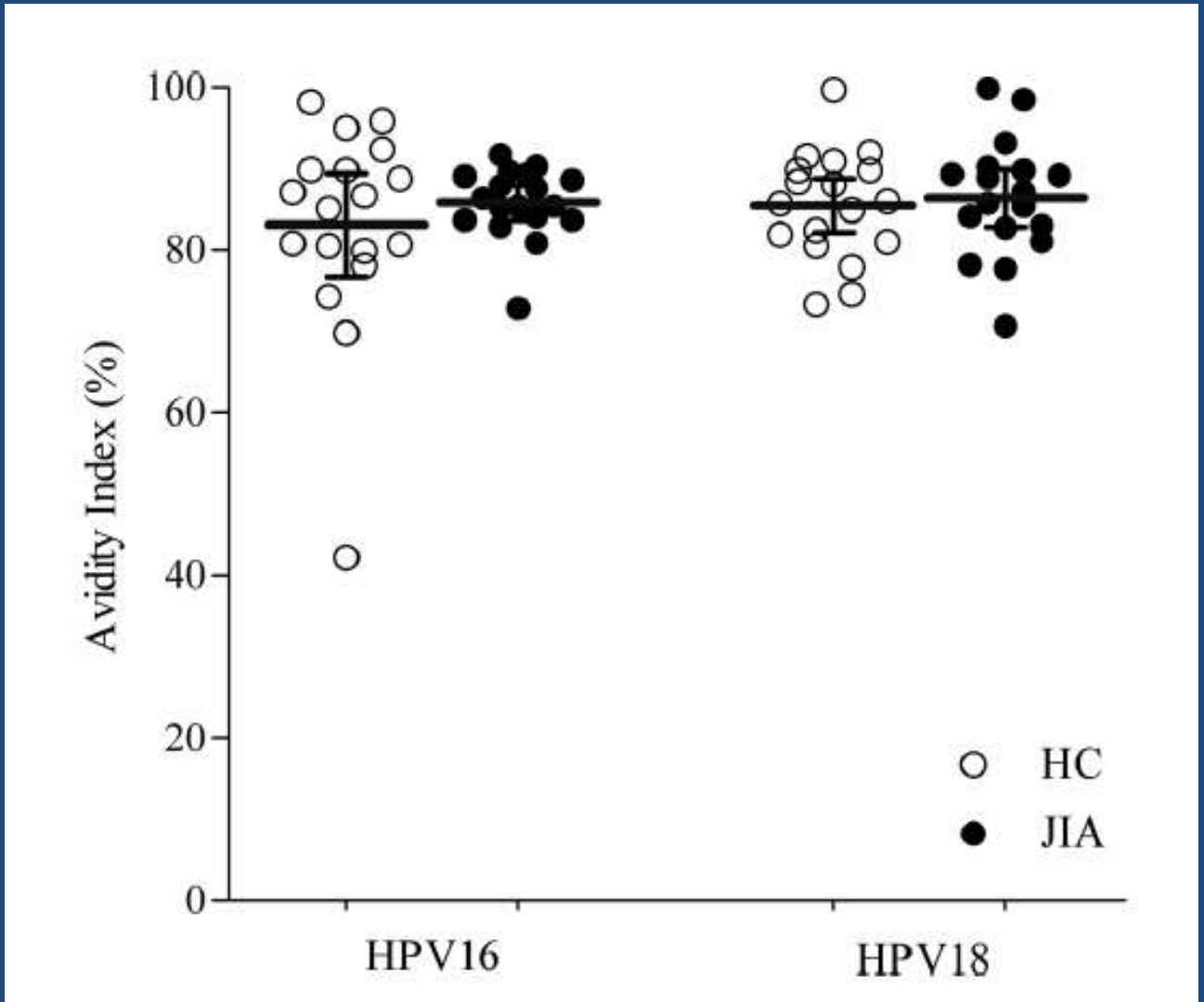
ANTIBODY RESPONSE IN PATIENTS WITH JIA AND CONTROLS RECEIVING CERVARIX

(From Heijstek et al., Ann Rheum Dis 2013)



AVIDITY INDEX OF SPECIFIC HPV16/18 ANTIBODIES IN PATIENTS WITH JIA AND CONTROLS AFTER CERVARIX

(From Heijstek et al., Ann Rheum Dis 2013)



IMMUNOGENICITY OF CERVARIX IN ADOLESCENTS WITH JIA

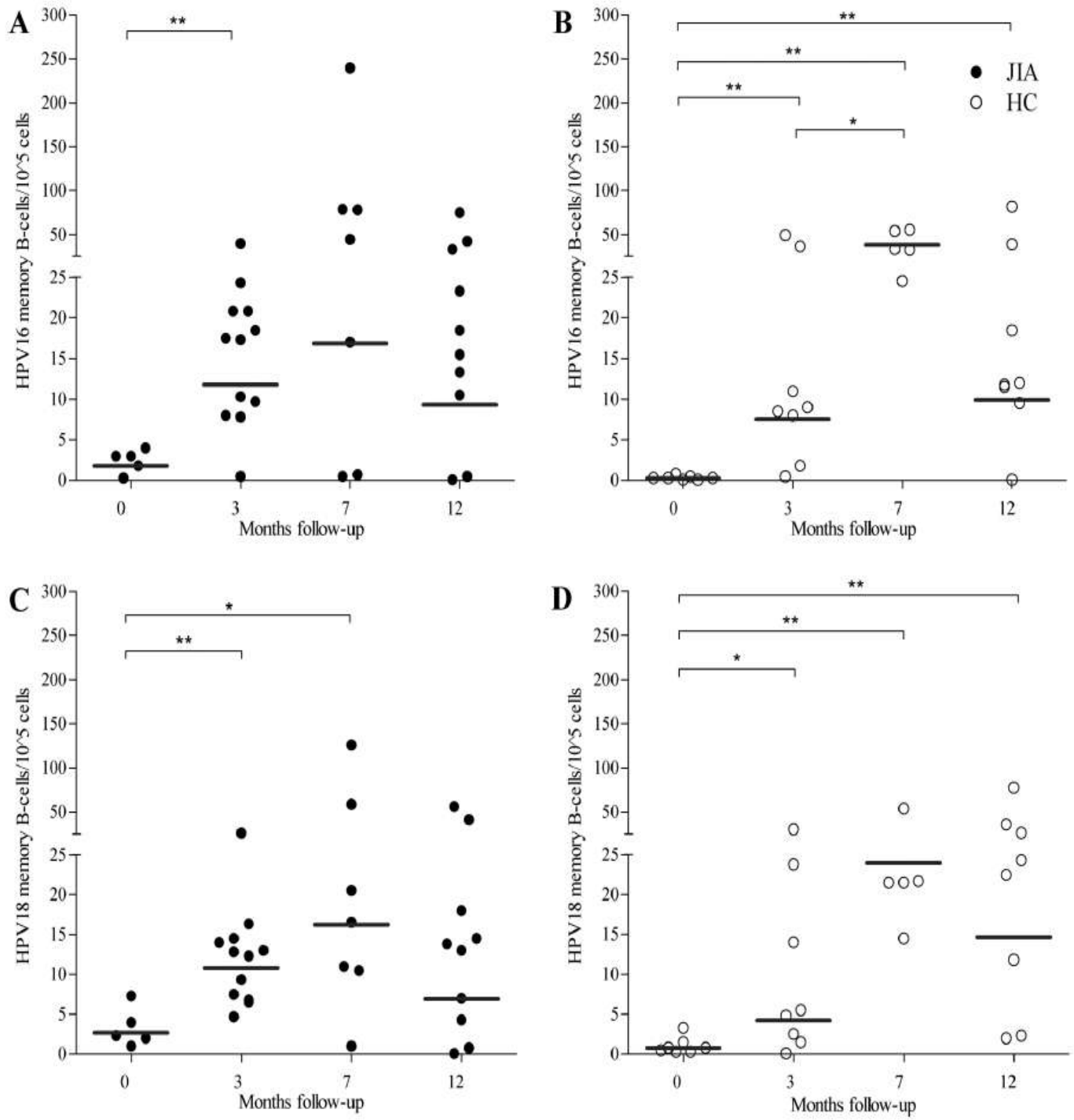
(Esposito et al., Expert Rev Vaccines 2014)

Aims: To evaluate the immunogenicity, safety and tolerability of the bivalent HPV vaccine in female patients with juvenile idiopathic arthritis (JIA).

Methods: 21 patients with JIA aged 12–25 years and 21 healthy controls were enrolled and received three doses of the bivalent HPV vaccine.

Results: All of the subjects were seronegative at baseline and seroconverted after the scheduled doses. The JIA patients showed significantly lower HPV16 neutralising antibody titres than controls 1 month after the administration of the third dose ($p < 0.05$), whereas no significant difference was observed in HPV18 neutralising antibody titres. Local and systemic reactions were similarly frequent in the patients and controls, and there were no significant changes in 27-joint juvenile arthritis disease activity score or laboratory tests.

Conclusion: The bivalent HPV vaccine is safe in patients with stable JIA and regardless of the use of medications the vaccine assures an adequate degree of protection for a certain time.

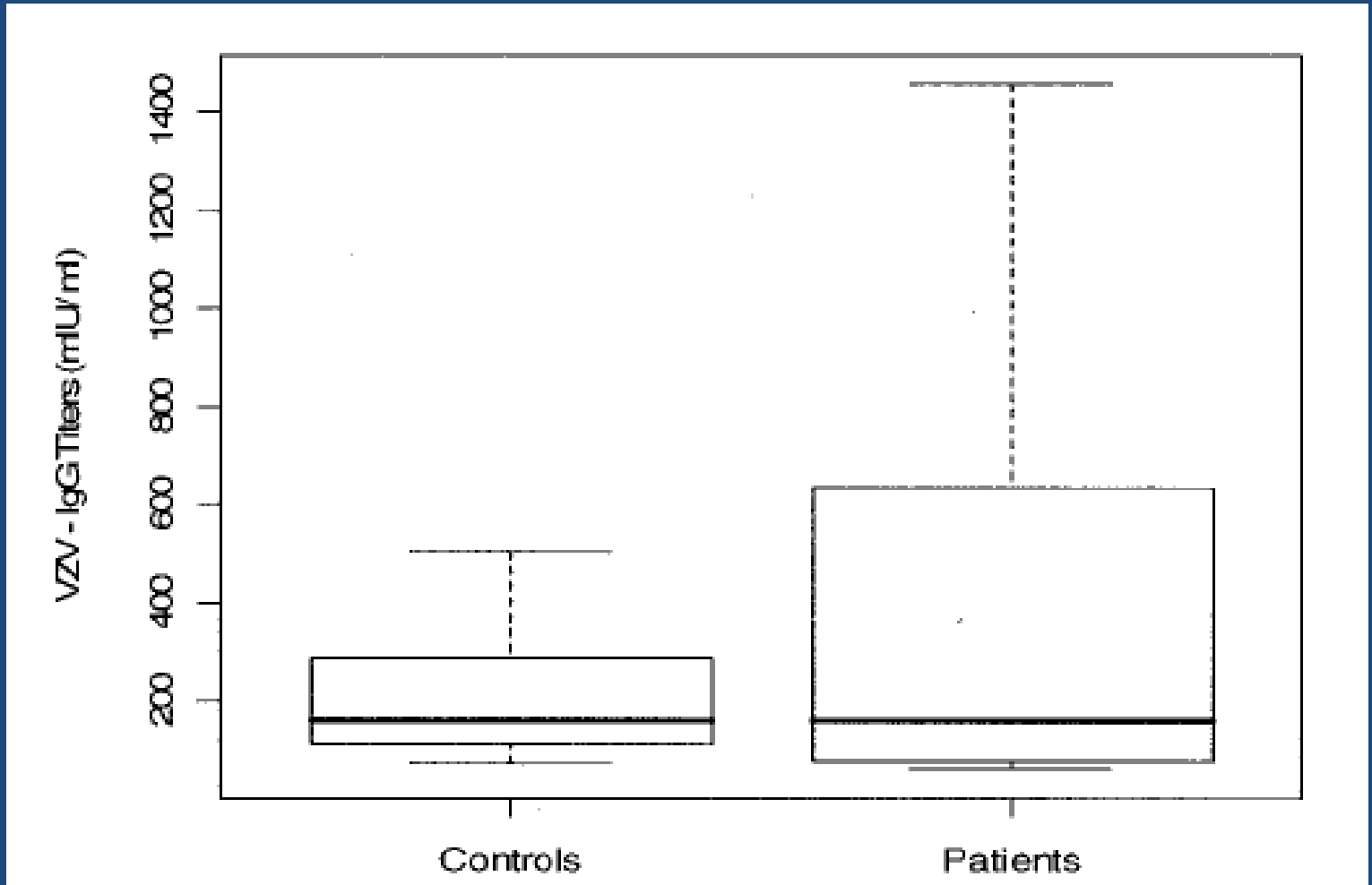


Geometric mean numbers of HPV16/18 B memory cells in children wih JIA and controls after Cervarix

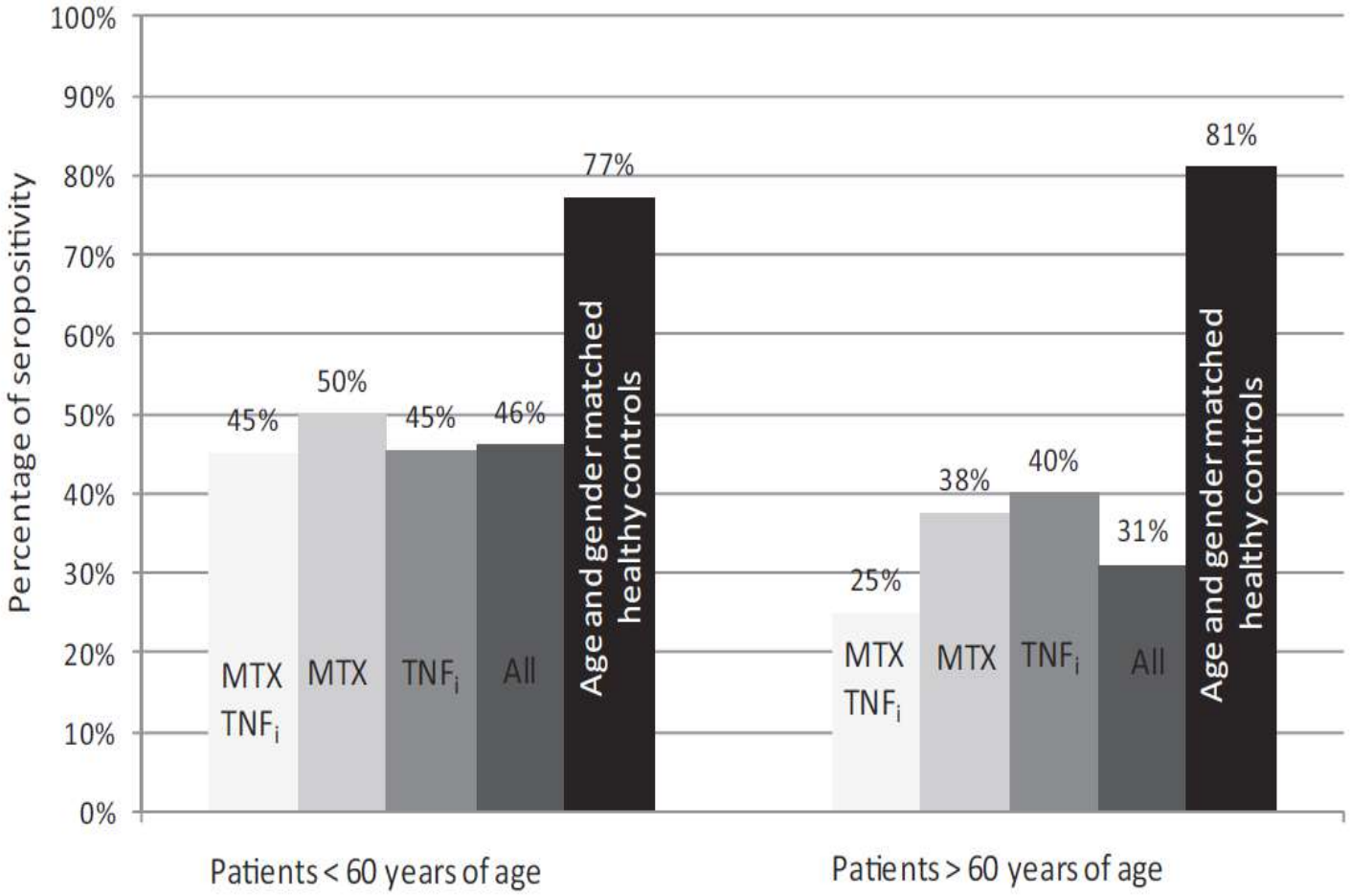
(From Heijstek et al., Ann Rhem Dis 2013)

ANTIBODY LEVELS IN PATIENTS WITH JIA AND CONTROLS 1 MONTH AFTER VARICELLA VACCINATION

(From Pileggi et al., Arthritis Care & Research 2010)



TBE VACCINE IN RA PATIENTS TREATED WITH IMMUNOSUPPRESSIVE DRUGS



Brodin Hertzell et al., Vaccine 2016

Risposta alle vaccinazioni nel soggetto con patologia reumatica in funzione della terapia

(Da Heijstek et al., Autoimmunity Review 2011)

Corticosteroidi

Nessun effetto negativo né sulla sieroconversione né sui livelli anticorpali.

La massima parte degli studi include soggetti che ricevono bassi dosaggi di farmaci (< 2mg/kg/die di prednisone).

In un solo studio sono utilizzati dosaggi elevati. In questo è stato somministrato il vaccino antivaricella senza effetti negativi neppure sulla riattivazione della malattia.

Risposta alle vaccinazioni nel soggetto con patologia reumatica in funzione della terapia

(Da Heijstek et al. ,Autoimmunity Review 2011)

DMARDs

- Il Methotrexate è il farmaco di questo gruppo più spesso utilizzato.
- I dati disponibili indicano che il suo utilizzo **non sembra interferire, in genere, con la risposta immune nè con il rischio di comparsa di eventi avversi**, inclusa la riattivazione della malattia. In qualche caso si è notata una live minore risposta immune senza significativa riduzione della sieroconversione.
- Gli studi con questi farmaci sono, tuttavia, pochi, molto diversi tra loro per tipo di terapia utilizzata ed è, quindi, impossibile trarre conclusioni definitive.

Risposta alle vaccinazioni nel soggetto con patologia reumatica in funzione della terapia

(Da Heijstek et al., Autoimmunity Review 2011)

Biologici

La somministrazione di anti-TNFalpha sembra evocare livelli anticorpali specifici lievemente inferiori senza, tuttavia, riduzione significativa del livello di protezione indotto.

Non sembra essere presente alcun rischio aggiuntivo di eventi avversi gravi nè di riattivazione della patologia.

I vaccini a base di virus vivi attenuati non vengono raccomandati per timore di favorire l'insorgenza della malattia che si vuole profilassare. Esistono, tuttavia, dati che sembrano suggerire la possibilità di somministrare qusti vaccini senza rischi.

La letteratura disponibile per gli altri biologici è estrememente limitata (i dati su rituximab sono negativi!!)

RACCOMANDAZIONI GENERALI PER LE VACCINAZIONI NEI SOGGETTI CON PATOLOGIA REUMATICA

In attesa di ulteriori studi:

- Vaccinare soggetti con malattia non attiva
- Somministrare secondo il calendario raccomandato tutti vaccini a base di agenti infettivi uccisi o frazioni di essi (inclusi influenza e HPV)
- Nei soggetti in terapia altamente immunosoppressiva può essere considerato il monitoraggio dei livelli anticorpali per somministrazione di richiami
- Non somministrare i vaccini a base di agenti infettivi vivi anche se attenuati (MPR, VZV, BCG, LAIV) in corso di terapie altamente immunosoppressive (biologici). Valutare casi particolari in presenza di epidemie o di situazioni a rischio

LIVE ATTENUATED VACCINES
(Papadopoulou et al., Clin Rheumatol 2015)

Vaccine	Recommendation
VZV–HZV	Adult patients: • If previously exposed to VZV, patients should be vaccinated, preferably before the initiation of synthetic or biologic DMARDs. • Vaccination may be considered during treatment with short-term or low to moderate doses of steroid therapy (<14 days, or <20 mg/day of prednisone or equivalent), or MTX <0.4 mg/kg/week, or azathioprine <3 mg/kg/day. • Vaccination during treatment with biologic DMARDs is not recommended [7,8]. Pediatric patients: • Vaccination, ideally before initiation of immunosuppressive therapy, in cases with a negative history for VZV infection or vaccination. • Booster vaccination can be considered in patients on MTX <15 mg/m^2/week or low-dose steroids [9].
BCG	Adult patients: • Vaccination may be considered for previously unvaccinated, tuberculin-negative travelers depending on the destination of travel, as well as for persons exposed to *M. tuberculosis* due to their professional activities. • BCG should not be administered before appropriate time following discontinuation of immunosuppressive drugs has elapsed [6,7]. Pediatric patients living in endemic areas should be vaccinated prior to starting immunosuppressive therapy [9].

GRAZIE PER L'ATTENZIONE