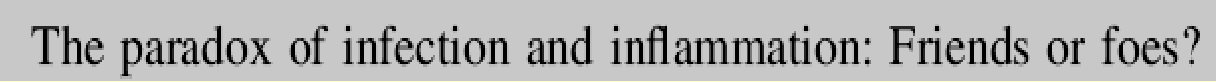
CARA A CARA 4
VACUNAS Y ENFERMEDADES AUTOINMUNES

Presentador: Antonio Gil Aguado

Ponente: Angel Robles Marhuenda

Hospital General

INFECCIÓN Y ENFERMEDADES AUTOINMUNES



The paradox of infection and inflammation: Friends or foes?

INFECCIÓN Y AUTOINMUNIDAD

Una pareja no siempre bien avenida

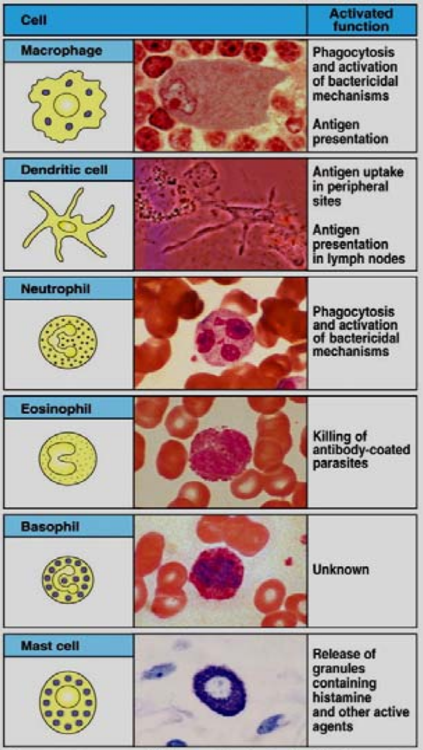
Goya: “Duelo a garrotazos”

LA INFECCIÓN EN EL LES

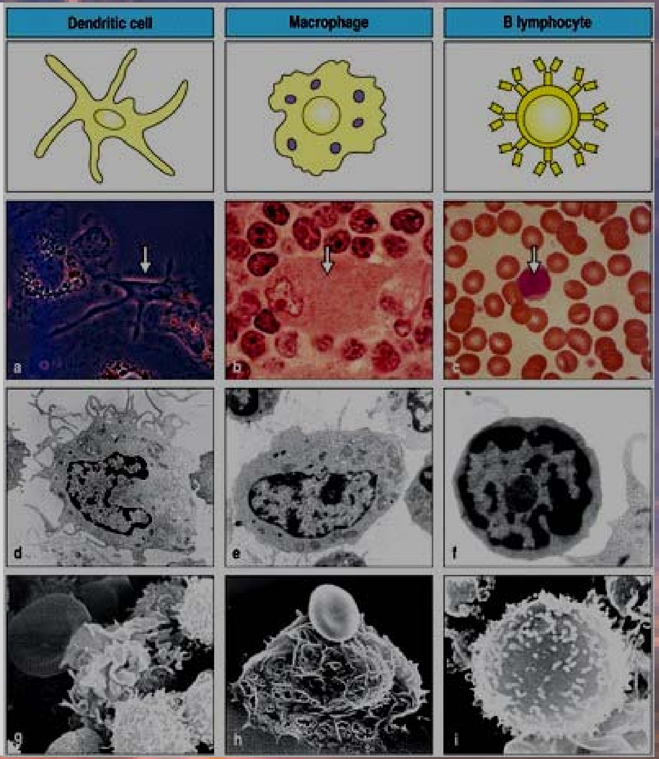
Hipótesis viral del LES

- Protagonismo en su génesis (VEB, CMV, PVB19, VHC, VIH, HTLV-1)
- Inducción de autoanticuerpos
- Inducción de actividad
- Modulación de la actividad del LES

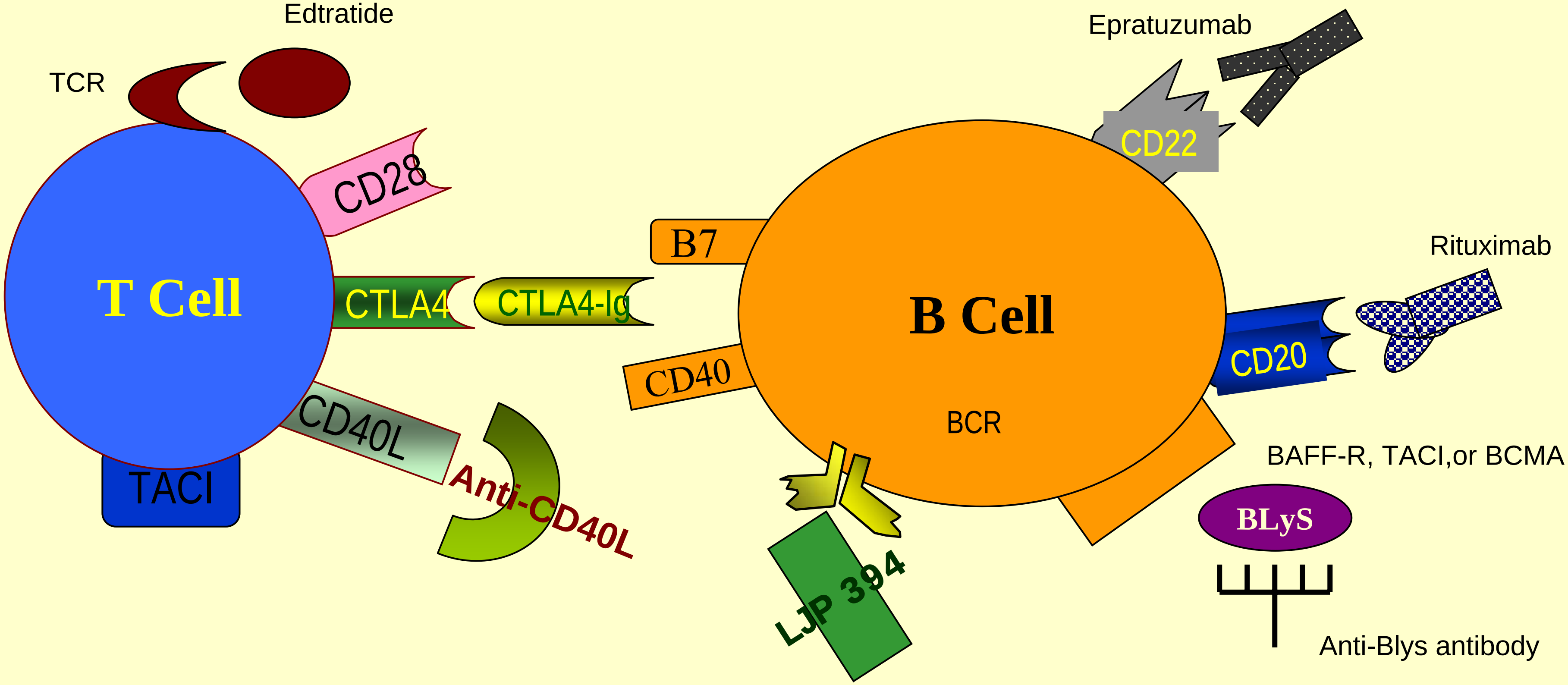
PROGRESO DE LA MEDICINA



Cell	Activated function
Macrophage	Phagocytosis and activation of bactericidal mechanisms Antigen presentation
Dendritic cell	Antigen uptake in peripheral sites Antigen presentation in lymph nodes
Neutrophil	Phagocytosis and activation of bactericidal mechanisms
Eosinophil	Killing of antibody-coated parasites
Basophil	Unknown
Mast cell	Release of granules containing histamine and other active agents



Targets of Biologic Agents


Edtratide
TCR
Epratuzumab
CD22
CD28
T Cell
B7
CTLA4
CTLA4-Ig
B Cell
Rituximab
CD40
CD20
CD40L
BCR
TACI
BAFF-R, TACI,or BCMA
Anti-CD40L
BLyS
LJP 394
Anti-Blys antibody

1.- Anti-antígenos de superficie	**4.- Interacción de presentación antigénica**
2.- Bloqueo de coestimulación linfocitaria	**5.- Tolerancia antigénica**
3.- Anti-citocinas	**6.- Anti-idiotipo**

PROGRESO DE LA MEDICINA

> 2000

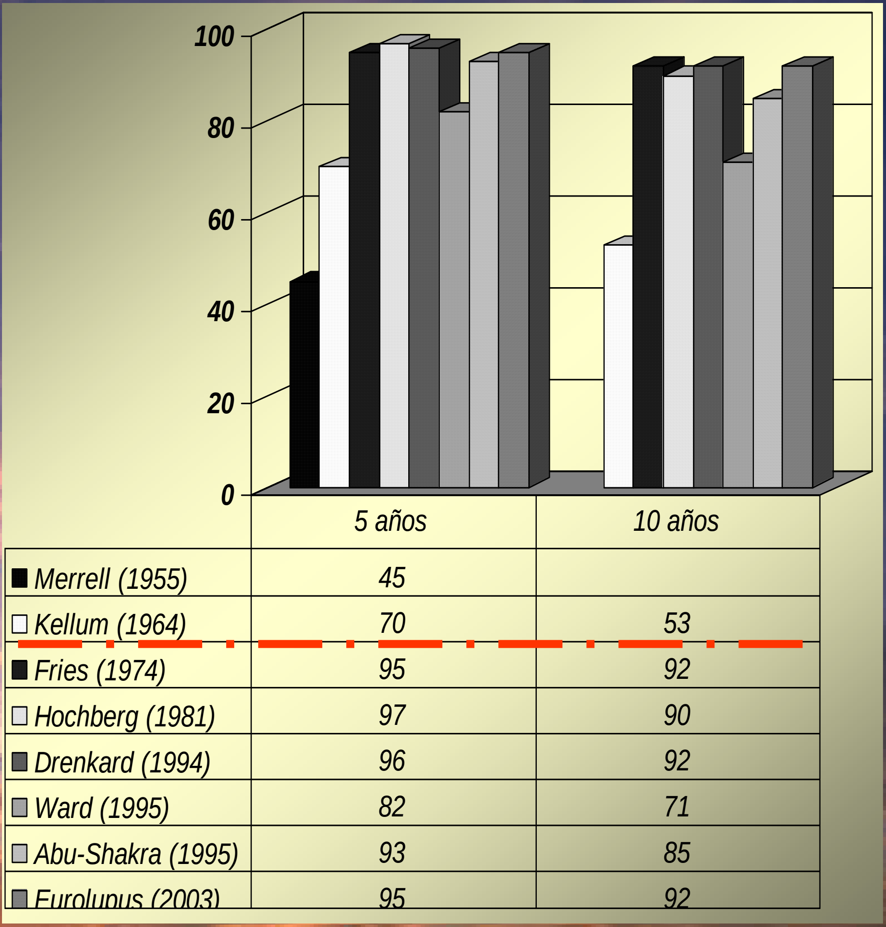
- ● **POSITIVO**

❑ **Mayor supervivencia:**

LES (1954)*	<50%
LES (2000’)	>85%
VNS (1950’)**	10%
VNS (2000’)	>75%

* John Hopkins H, a los 4 años

< 1955

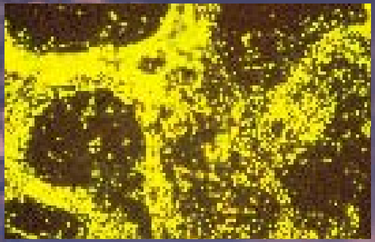


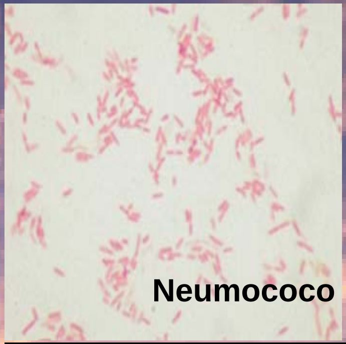
	5 años	10 años
■ Merrell (1955)	45	
□ Kellum (1964)	70	53
■ Fries (1974)	95	92
□ Hochberg (1981)	97	90
■ Drenkard (1994)	96	92
□ Ward (1995)	82	71
□ Abu-Shakra (1995)	93	85
■ Eurolupus (2003)	95	92

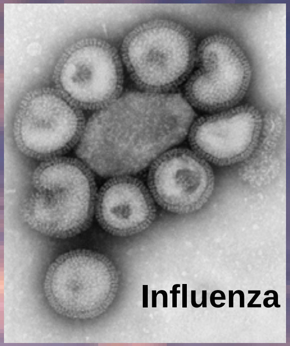
PROGRESO DE LA MEDICINA

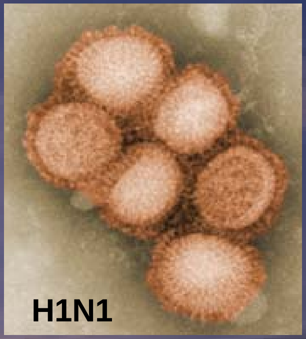
- NEGATIVO

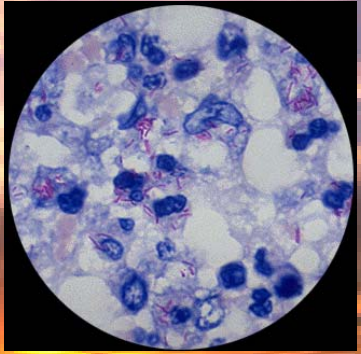
☐ Emergencia de una población de pacientes altamente susceptible a complicaciones (infecciones, vasculares, osteoporosis, etc)











LA INFECCIÓN EN EL LES

PROBLEMAS

- Causa importante de morbi-mortalidad
- Dificultad para su reconocimiento
- Espectro amplio de patógenos
- Problemática elección de antibioterapia empírica

INCIDENCIA DE INFECCIONES EN EL LES

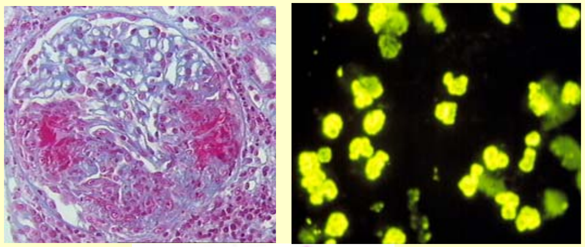
Carpenter	1958-65	40 / 53%	Urinaria	67%
Staples	1960-69	23 / 57%	Urinaria	28%
Ginzler	1966-76	223 / 67%	Urinaria	20%
Platt	1958-81	70 / 78%	Cutánea	45%
Font	1986-89	120 / 34%	Cutánea	31%
Ferrer			rinaria	33%
Ladrón			rinaria	31%
De Luis			rinaria	31%
Juega			rinaria	57%
Formiga	1975-91	145 / 22%	Respirat	33%
Eurolupus	1990-00	1.000 / 36%	Urinaria	47%
TOTAL	**1958-00**	**1.853 / 49%**	**Urinaria**	**35%**

Responsable del 25% de los ingresos

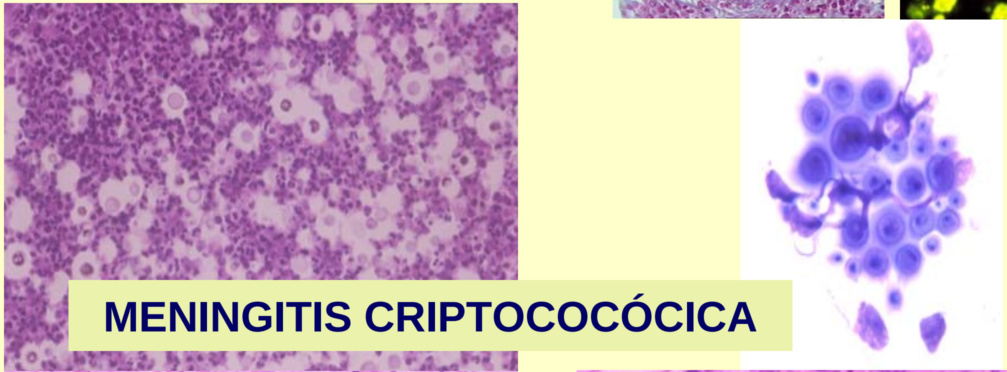
ESPECTRO DE LA INFECCIÓN EN EL LES

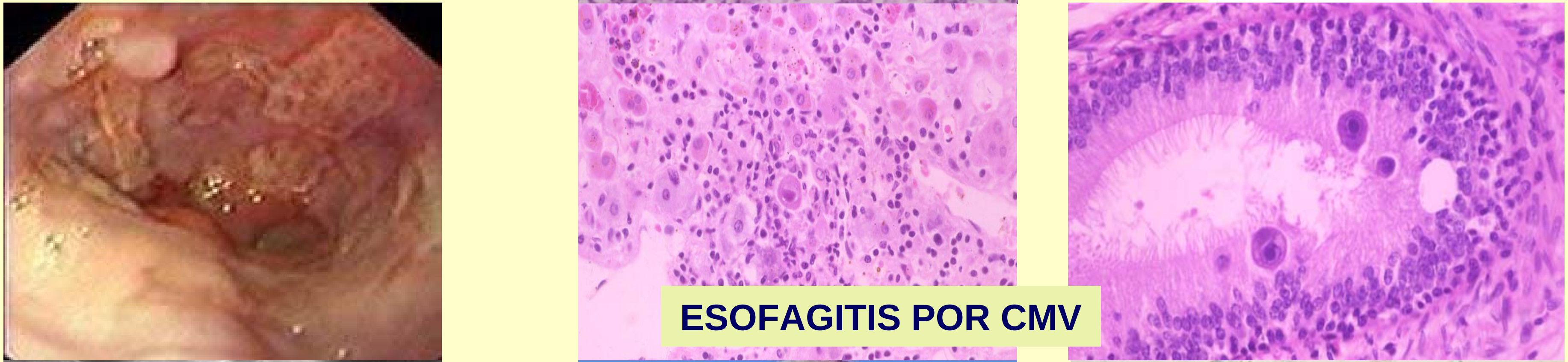
- **Predominio de infecciones urinarias y cutáneas**
- **Neumonías y sepsis: infecciones más severas**
- **Enterobacterias (*Klebsiella*) en pacientes activos**
- **Bacilos Gram + (*S aureus*) en pacientes inactivos**
- **Bacilos Gram (-) en infecciones respiratorias**
- **Infecciones recidivantes por *Salmonella***
- **Tuberculosis: presentación atípica**
- **Infecciones virales: Herpes zoster diseminado**
- **Infecciones oportunistas: *Listeria, Candida, Aspergillus, Pneumocystis, Toxoplasma, Leishmania, CMV, Nocardia***

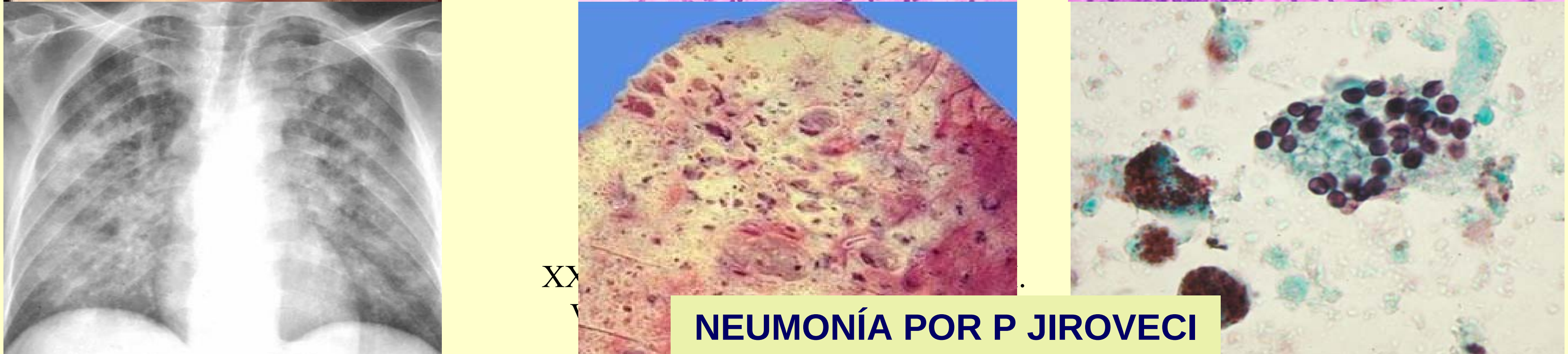
Poliangeitis microscópica:



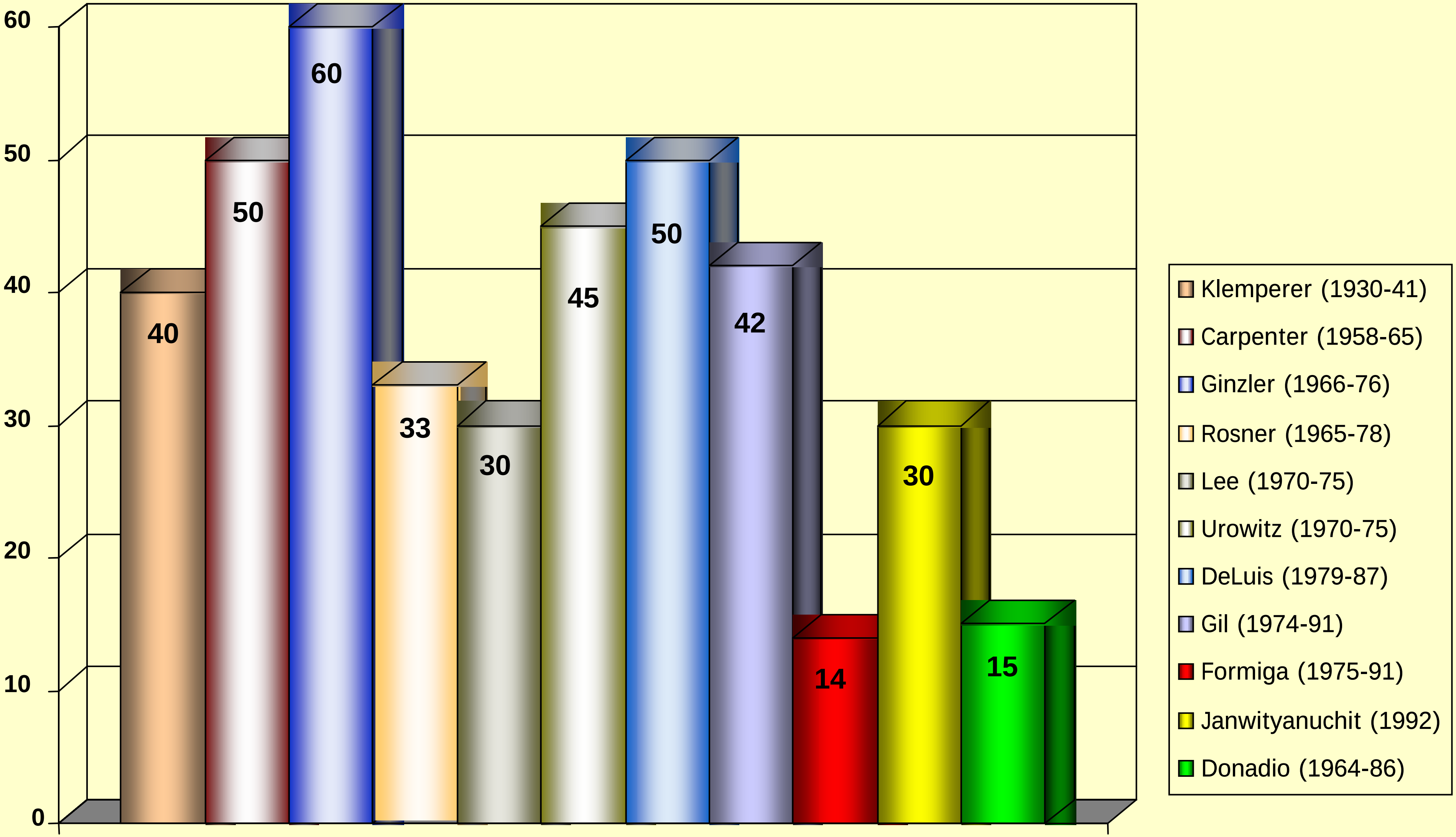
Tratamiento: Corticoides (bolus) + Ciclofosfamida


MENINGITIS CRIPTOCOCÓCICA

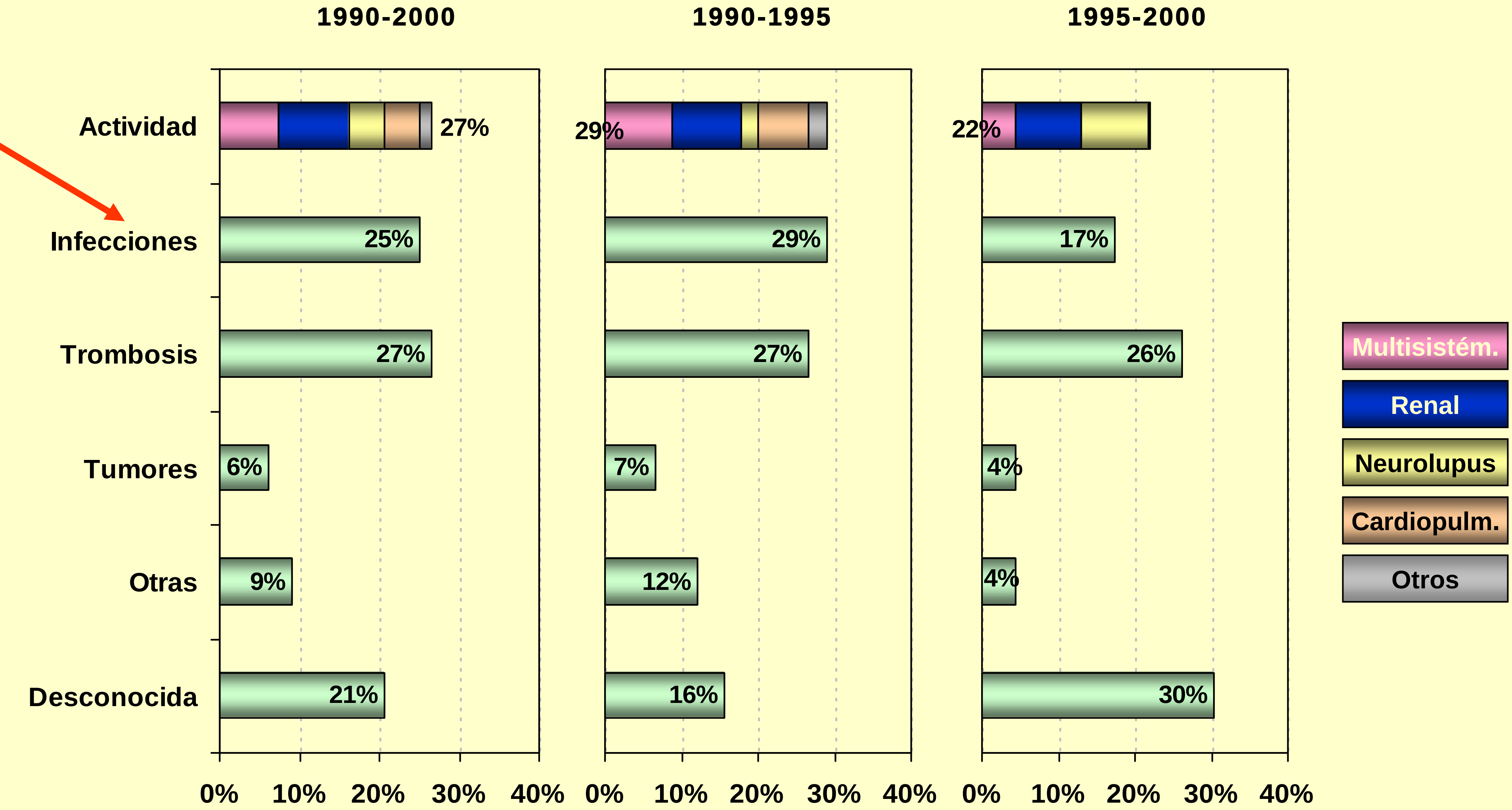

ESOFAGITIS POR CMV

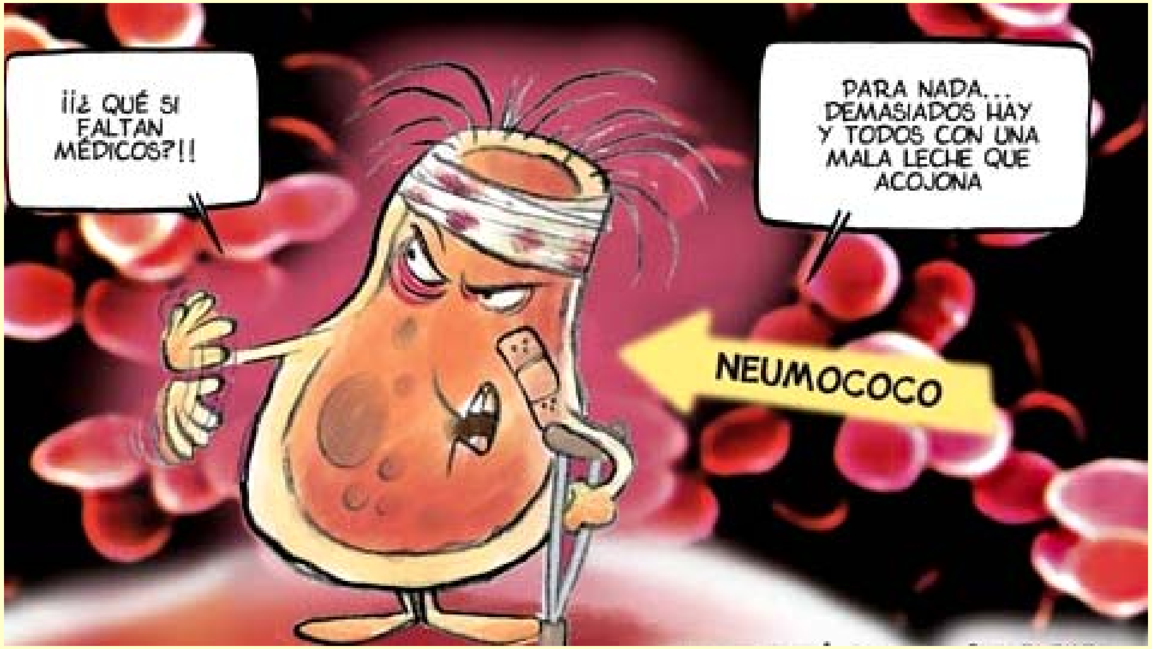

NEUMONÍA POR P JIROVECI

INFECCIÓN Y MORTALIDAD EN EL LES



EUROLUPUS: CAUSAS DE MORTALIDAD SEGÚN PERIODO DE TIEMPO




¡¡¿ QUÉ SI FALTAN MÉDICOS?!!
PARA NADA... DEMASIADOS HAY Y TODOS CON UNA MALA LECHE QUE ACOJONA
NEUMOCOCO

Un buen médico es como una buena célula:cuando hace falta se parten en dos

VACUNAS Y EAS

1. ¿Están indicadas?
2. ¿Son eficaces?
3. ¿Son seguras?
   - ¿Inducen EAS?
   - ¿Inducen actividad de la enfermedad?
   - ¿Potenciales efectos adversos en EAS?

4. Recomendaciones vacunales

XXX Congreso Nacional de la Sociedad Española de Medicina Interna

VIII Congreso de la Sociedad de Medicina Interna Comunidad Valenciana

SEMI

VACUNAS
Y
ENFERMEDADES AUTOINMUNES SISTÉMICAS

Angel Robles Marhuenda
Servicio de Medicina Interna

SaludMadrid
Hospital Universitario La Paz
Comunidad de Madrid

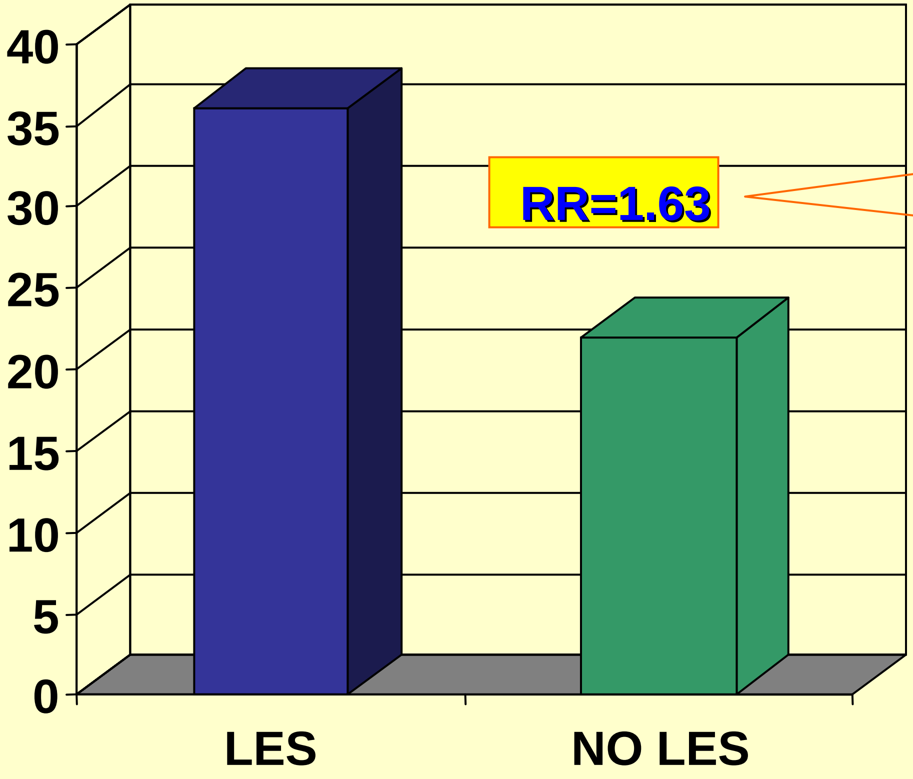
VACUNAS Y E.A.S.

- ¿Están indicadas?
- ¿Son eficaces?
- ¿Son seguras?
  - ¿Inducen EAS?
  - ¿Inducen actividad de la enfermedad?
  - ¿Potenciales efectos adversos en EAS?

- Recomendaciones vacunales

¿Están indicadas?

Infections in SLE: a prospective and controlled study of 110 pateints.



NEUMONÍA-INF.RESPIR.
I.T.U.
BACTERIEMIA (piel y p.b.)

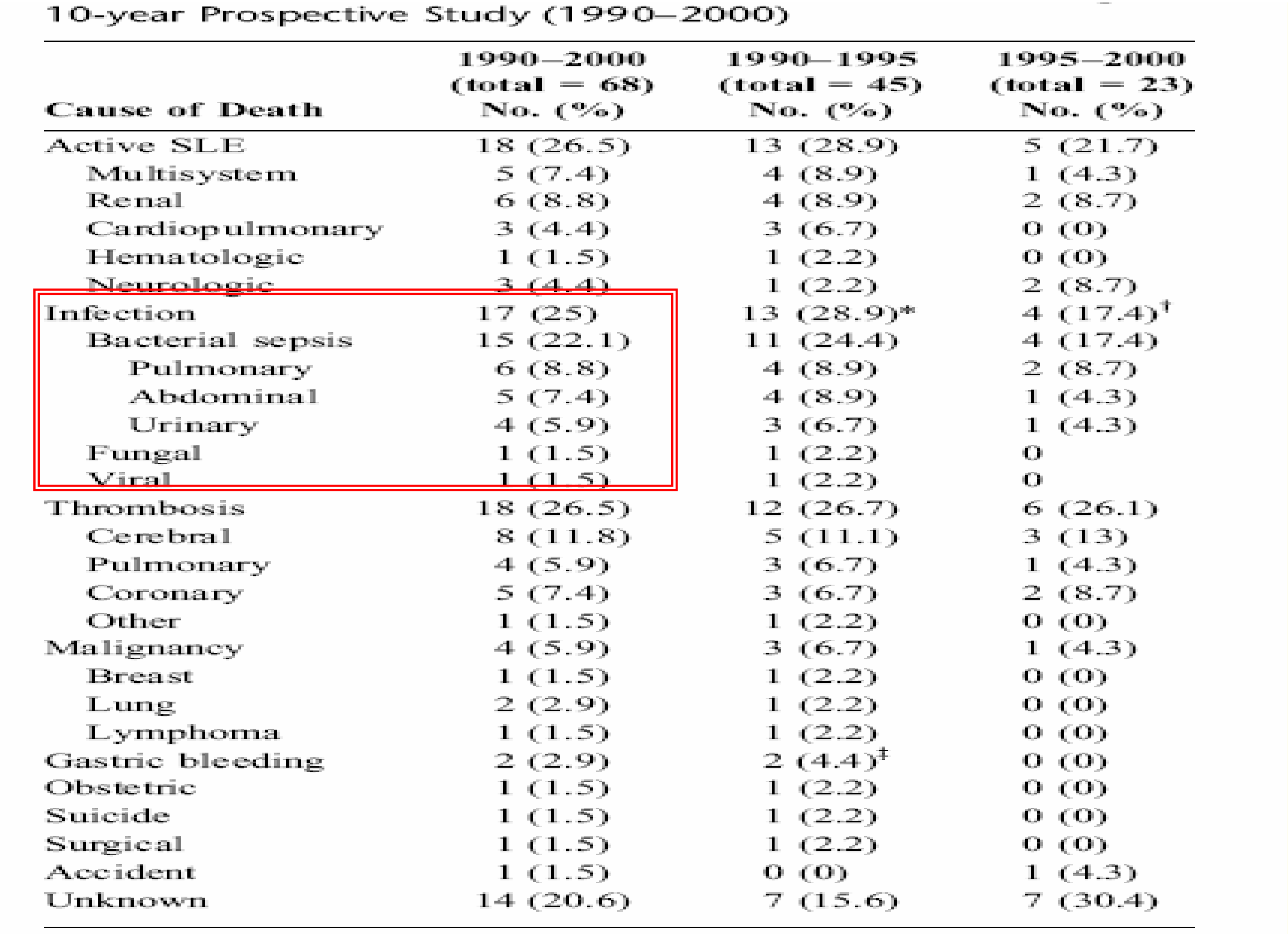
NEUMOCOCO
E.COLI
S.AUREUS
INFLUENZA
HERPES ZOSTER

Lupus; 2006: 584-9.

Best Practice & Research Clinical Rheumatology
Vol. 16, No. 2, pp. 281–291, 2002

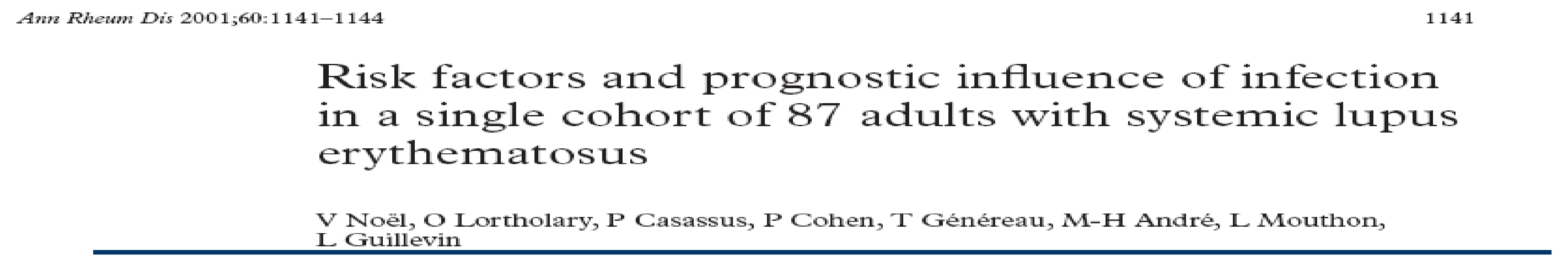
Morbidity and Mortality in Systemic Lupus Erythematosus During a 10-Year Period

(*Medicine* 2003;82:299–308)



10-year Prospective Study (1990–2000)

Cause of Death	1990–2000 (total = 68) No. (%)	1990–1995 (total = 45) No. (%)	1995–2000 (total = 23) No. (%)
Active SLE	18 (26.5)	13 (28.9)	5 (21.7)
Multisystem	5 (7.4)	4 (8.9)	1 (4.3)
Renal	6 (8.8)	4 (8.9)	2 (8.7)
Cardiopulmonary	3 (4.4)	3 (6.7)	0 (0)
Hematologic	1 (1.5)	1 (2.2)	0 (0)
Neurologic	3 (4.4)	1 (2.2)	2 (8.7)
Infection	17 (25)	13 (28.9)*	4 (17.4)†
Bacterial sepsis	15 (22.1)	11 (24.4)	4 (17.4)
Pulmonary	6 (8.8)	4 (8.9)	2 (8.7)
Abdominal	5 (7.4)	4 (8.9)	1 (4.3)
Urinary	4 (5.9)	3 (6.7)	1 (4.3)
Fungal	1 (1.5)	1 (2.2)	0
Viral	1 (1.5)	1 (2.2)	0
Thrombosis	18 (26.5)	12 (26.7)	6 (26.1)
Cerebral	8 (11.8)	5 (11.1)	3 (13)
Pulmonary	4 (5.9)	3 (6.7)	1 (4.3)
Coronary	5 (7.4)	3 (6.7)	2 (8.7)
Other	1 (1.5)	1 (2.2)	0 (0)
Malignancy	4 (5.9)	3 (6.7)	1 (4.3)
Breast	1 (1.5)	1 (2.2)	0 (0)
Lung	2 (2.9)	1 (2.2)	0 (0)
Lymphoma	1 (1.5)	1 (2.2)	0 (0)
Gastric bleeding	2 (2.9)	2 (4.4)‡	0 (0)
Obstetric	1 (1.5)	1 (2.2)	0 (0)
Suicide	1 (1.5)	1 (2.2)	0 (0)
Surgical	1 (1.5)	1 (2.2)	0 (0)
Accident	1 (1.5)	0 (0)	1 (4.3)
Unknown	14 (20.6)	7 (15.6)	7 (30.4)



Ann Rheum Dis 2001;60:1141–1144

Risk factors and prognostic influence of infection in a single cohort of 87 adults with systemic lupus erythematosus

V Noël, O Lortholary, P Casassus, P Cohen, T Généreau, M-H André, L Mouthon, L Guillevin

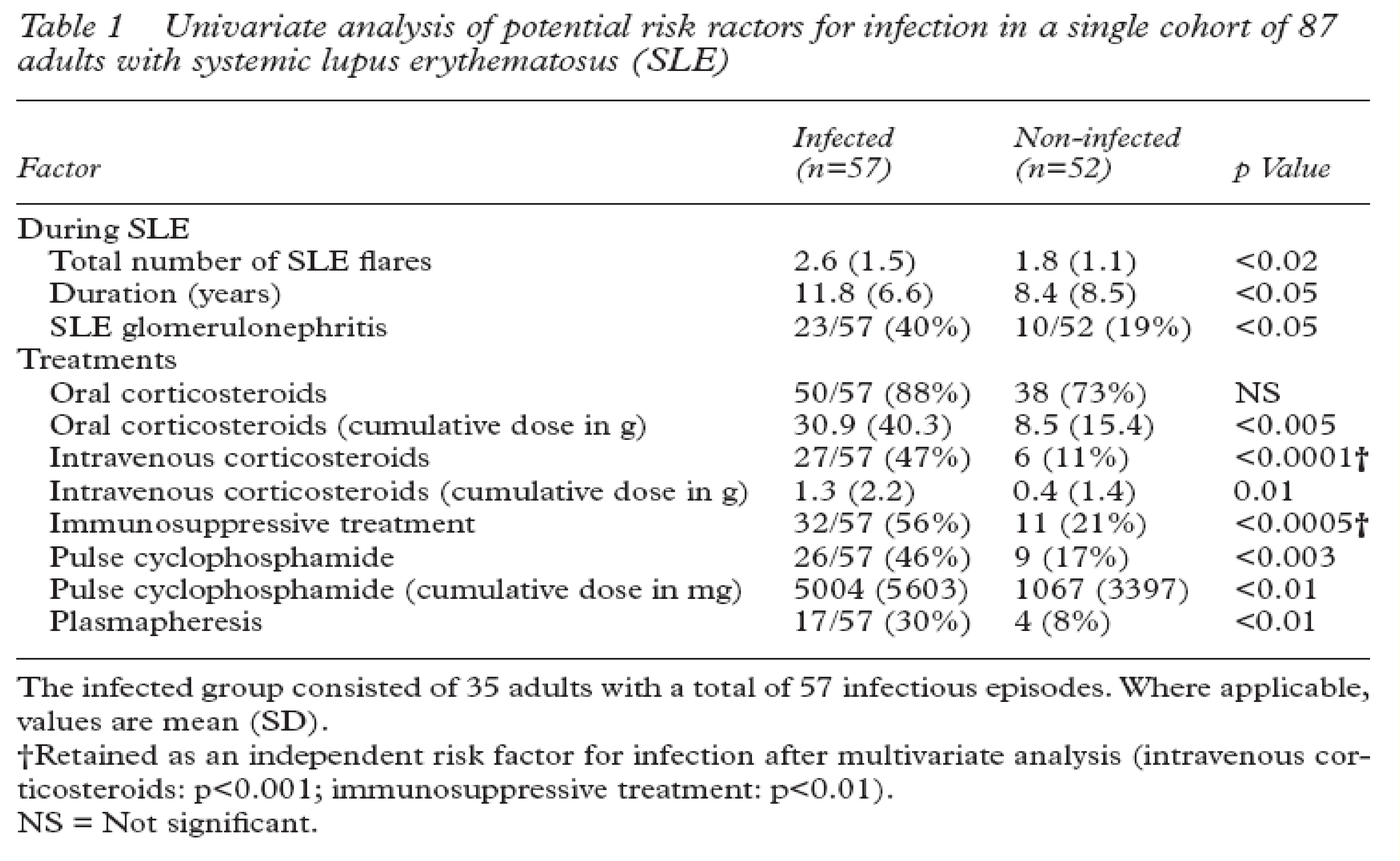


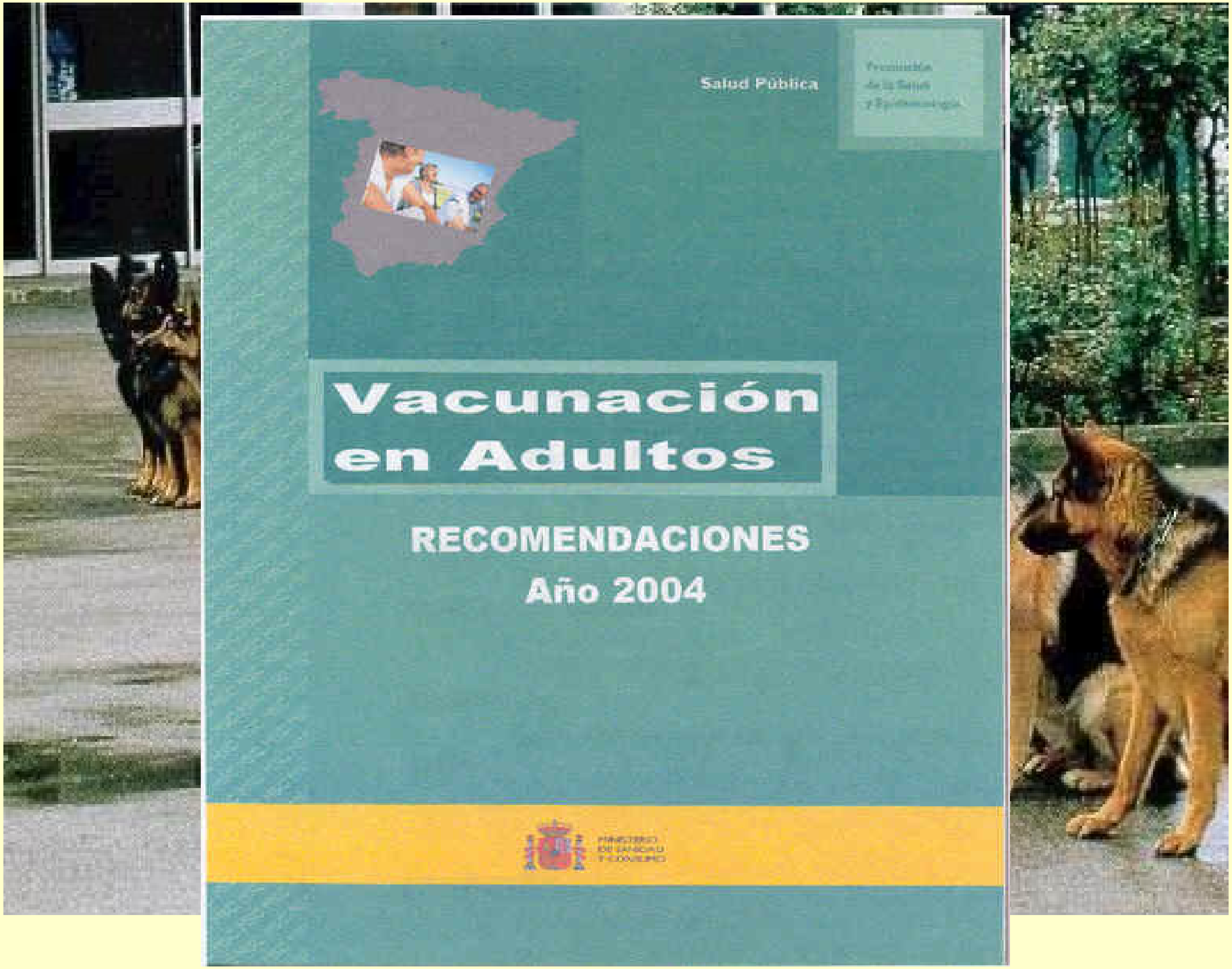
Table 1 Univariate analysis of potential risk ractors for infection in a single cohort of 87 adults with systemic lupus erythematosus (SLE)

Factor	*Infected (n=57)*	*Non-infected (n=52)*	*p Value*
During SLE			
Total number of SLE flares	2.6 (1.5)	1.8 (1.1)	<0.02
Duration (years)	11.8 (6.6)	8.4 (8.5)	<0.05
SLE glomerulonephritis	23/57 (40%)	10/52 (19%)	<0.05
Treatments			
Oral corticosteroids	50/57 (88%)	38 (73%)	NS
Oral corticosteroids (cumulative dose in g)	30.9 (40.3)	8.5 (15.4)	<0.005
Intravenous corticosteroids	27/57 (47%)	6 (11%)	<0.0001†
Intravenous corticosteroids (cumulative dose in g)	1.3 (2.2)	0.4 (1.4)	0.01
Immunosuppressive treatment	32/57 (56%)	11 (21%)	<0.0005†
Pulse cyclophosphamide	26/57 (46%)	9 (17%)	<0.003
Pulse cyclophosphamide (cumulative dose in mg)	5004 (5603)	1067 (3397)	<0.01
Plasmapheresis	17/57 (30%)	4 (8%)	<0.01

The infected group consisted of 35 adults with a total of 57 infectious episodes. Where applicable, values are mean (SD).

†Retained as an independent risk factor for infection after multivariate analysis (intravenous corticosteroids: $p<0.001$; immunosuppressive treatment: $p<0.01$).

NS = Not significant.



Salud Pública

Promoción
de la Salud
y Epidemiología

Vacunación en Adultos

RECOMENDACIONES
Año 2004

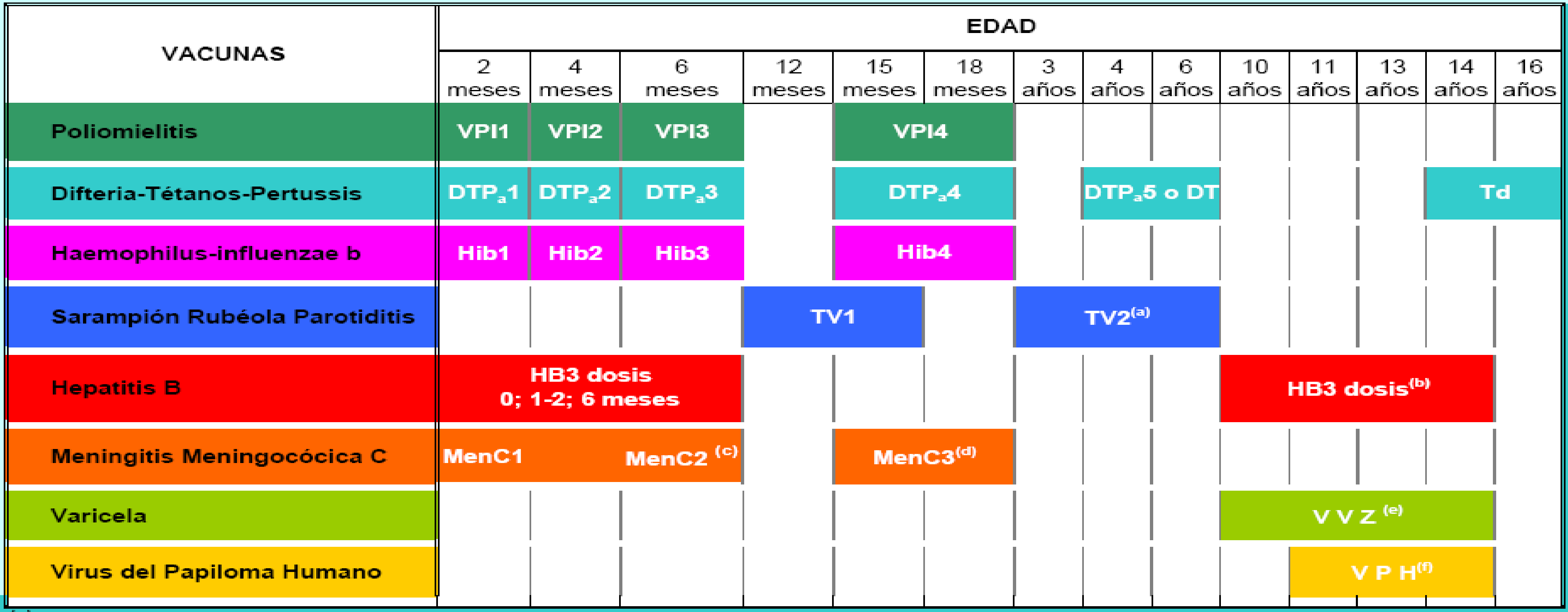
MINISTERIO
DE SANIDAD
Y CONSUMO

Vacunas recomendadas

CONSEJO INTERTERRITORIAL DEL SISTEMA NACIONAL DE SALUD

CALENDARIO DE VACUNACIONES RECOMENDADO (2007)

Aprobado por el Consejo Interterritorial el 10 de octubre de 2007



VACUNAS	EDAD													
	2 meses	4 meses	6 meses	12 meses	15 meses	18 meses	3 años	4 años	6 años	10 años	11 años	13 años	14 años	16 años
Poliomielitis	VPI1	VPI2	VPI3		VPI4									
Difteria-Tétanos-Pertussis	DTP$_a$1	DTP$_a$2	DTP$_a$3		DTP$_a$4			DTP$_a$5 o DT					Td	
Haemophilus-influenzae b	Hib1	Hib2	Hib3		Hib4									
Sarampión Rubéola Parotiditis				TV1			TV2(a)							
Hepatitis B	HB3 dosis 0; 1-2; 6 meses									HB3 dosis(b)				
Meningitis Meningocócica C	MenC1		MenC2 (c)		MenC3(d)									
Varicela										V V Z (e)				
Virus del Papiloma Humano											V P H(f)			

(a) Niños no vacunados en este rango de edad, recibirán la segunda dosis entre los 11-13 años..

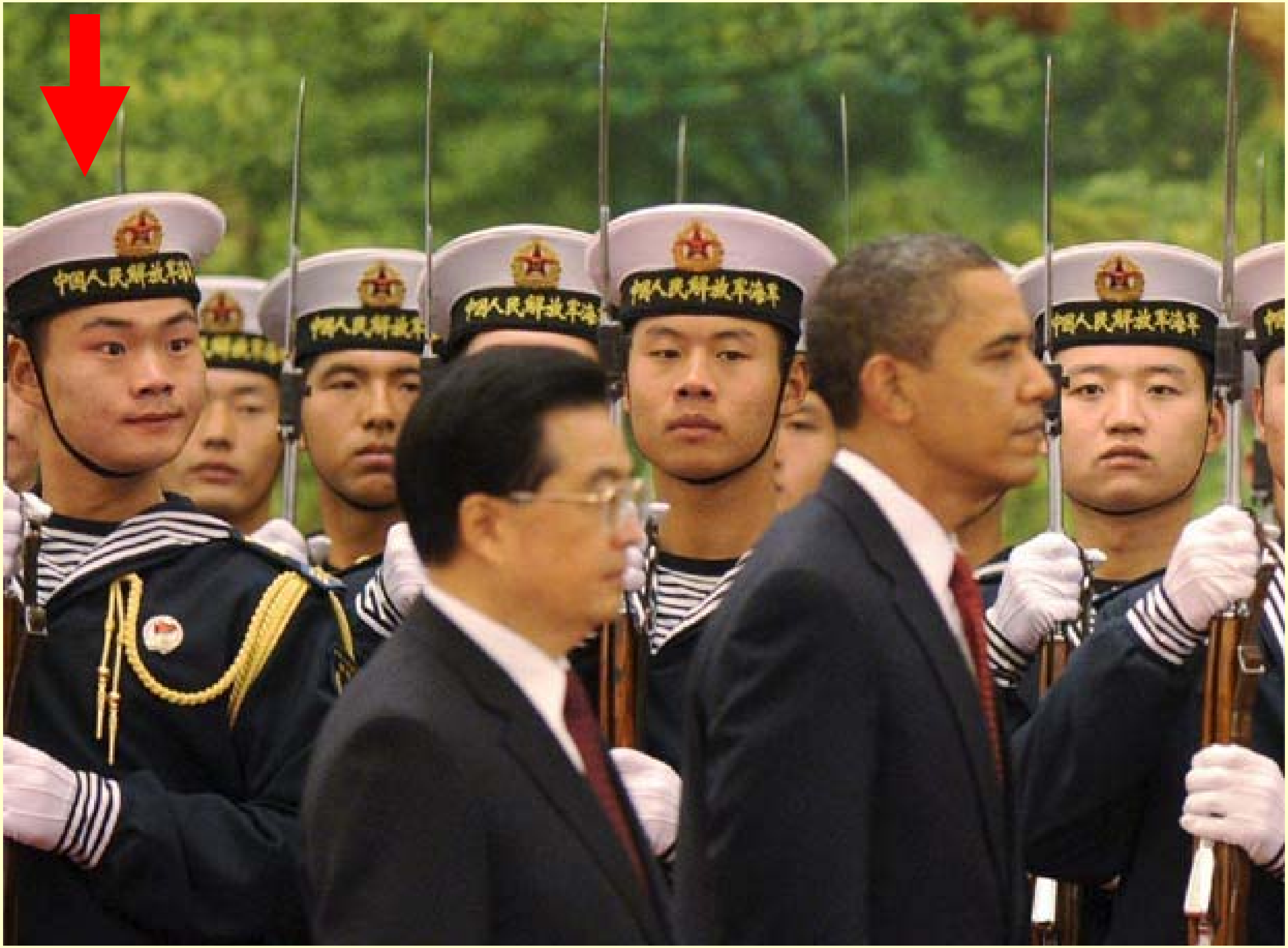
(b) Niños que no han recibido la primovacunación en la infancia.

(c) Se administrarán dos dosis de vacuna MenC entre los 2 y 6 meses de vida separadas entre sí al menos dos meses.

(d) Se recomienda administrar una dosis de recuerdo a partir de los doce meses de vida.

(e) Personas que refieran no haber pasado la enfermedad ni haber sido vacunadas con anterioridad, siguiendo indicaciones de la ficha técnica.

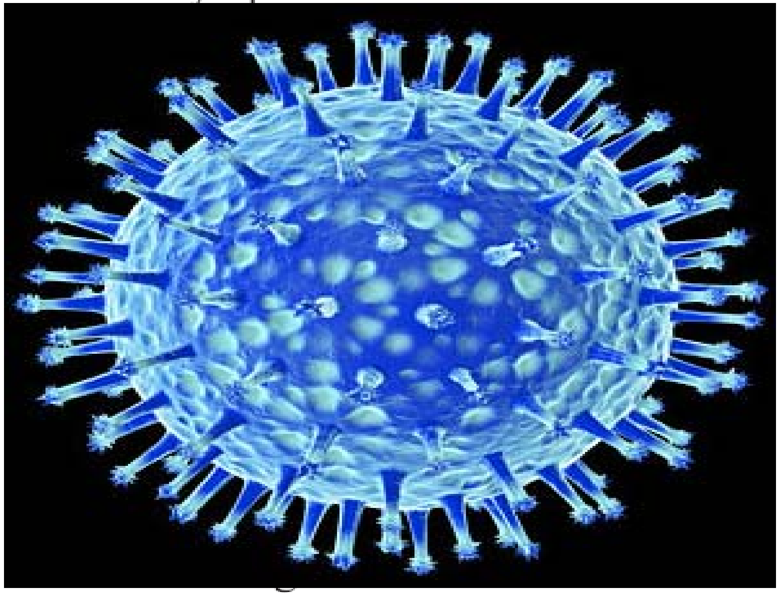
(f) Vacunar en una única cohorte a las niñas entre los 11-14 años de edad.


中国人民解放军海军

¿Son eficaces?

Table 1
Response rates to immunization in persons with impaired immunity

Vaccine	Condition	Response rate (%)[a]
Measles	Malnutrition	83–86
	Bone marrow transplantation	77
	HIV infection	25–77
Mumps and rubella	Bone marrow transplantation	64–75
	Acute lymphoblastic leukemia	100
Poliovirus	HIV infection	>80 (IPV or OPV) 61–88 (IPV)
Varicella	Renal disease	100
	Acute lymphoblastic	88–91
		88–98
		77
		67
		66
Hepatitis B virus		43–82
		44–54
		50–80
		24–43
		73
		46
Influenza	Renal disease; chronic renal failure	66
	Renal disease, hemodialysis	25–100
	Renal disease; transplant	18–93
	Systemic lupus erythromytosis	Normal, decreased if on immunosuppression
	Cancer	24–71
	Bone marrow transplant	18–60
	HIV infection	15–80



Immunol Allergy Clin N Am 23 (2003) 605–634

Safety and efficacy of influenza vaccination in systemic lupus erythematosus patients with quiescent disease

Ann Rheum Dis 2006;65;913-918

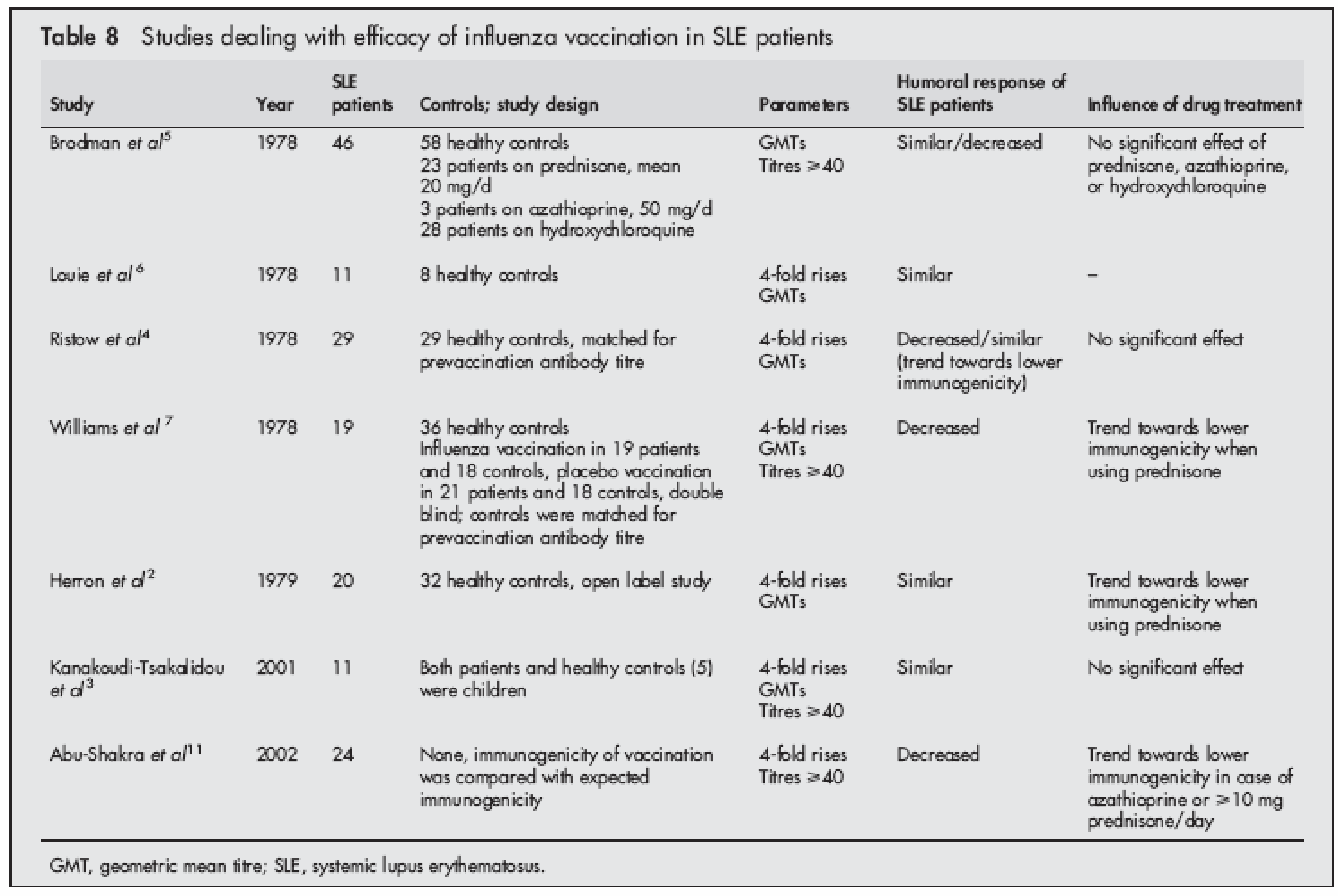


Table 8 Studies dealing with efficacy of influenza vaccination in SLE patients

Study	Year	SLE patients	Controls; study design	Parameters	Humoral response of SLE patients	Influence of drug treatment
Brodman *et al*[5]	1978	46	58 healthy controls 23 patients on prednisone, mean 20 mg/d 3 patients on azathioprine, 50 mg/d 28 patients on hydroxychloroquine	GMTs Titres ≥40	Similar/decreased	No significant effect of prednisone, azathioprine, or hydroxychloroquine
Louie *et al*[6]	1978	11	8 healthy controls	4-fold rises GMTs	Similar	–
Ristow *et al*[4]	1978	29	29 healthy controls, matched for prevaccination antibody titre	4-fold rises GMTs	Decreased/similar (trend towards lower immunogenicity)	No significant effect
Williams *et al*[7]	1978	19	36 healthy controls Influenza vaccination in 19 patients and 18 controls, placebo vaccination in 21 patients and 18 controls, double blind; controls were matched for prevaccination antibody titre	4-fold rises GMTs Titres ≥40	Decreased	Trend towards lower immunogenicity when using prednisone
Herron *et al*[2]	1979	20	32 healthy controls, open label study	4-fold rises GMTs	Similar	Trend towards lower immunogenicity when using prednisone
Kanakoudi-Tsakalidou *et al*[3]	2001	11	Both patients and healthy controls (5) were children	4-fold rises GMTs Titres ≥40	Similar	No significant effect
Abu-Shakra *et al*[11]	2002	24	None, immunogenicity of vaccination was compared with expected immunogenicity	4-fold rises Titres ≥40	Decreased	Trend towards lower immunogenicity in case of azathioprine or ≥10 mg prednisone/day

GMT, geometric mean titre; SLE, systemic lupus erythematosus.

Safety and efficacy of influenza vaccination in systemic lupus erythematosus patients with quiescent disease

Ann Rheum Dis 2006;65;913-918

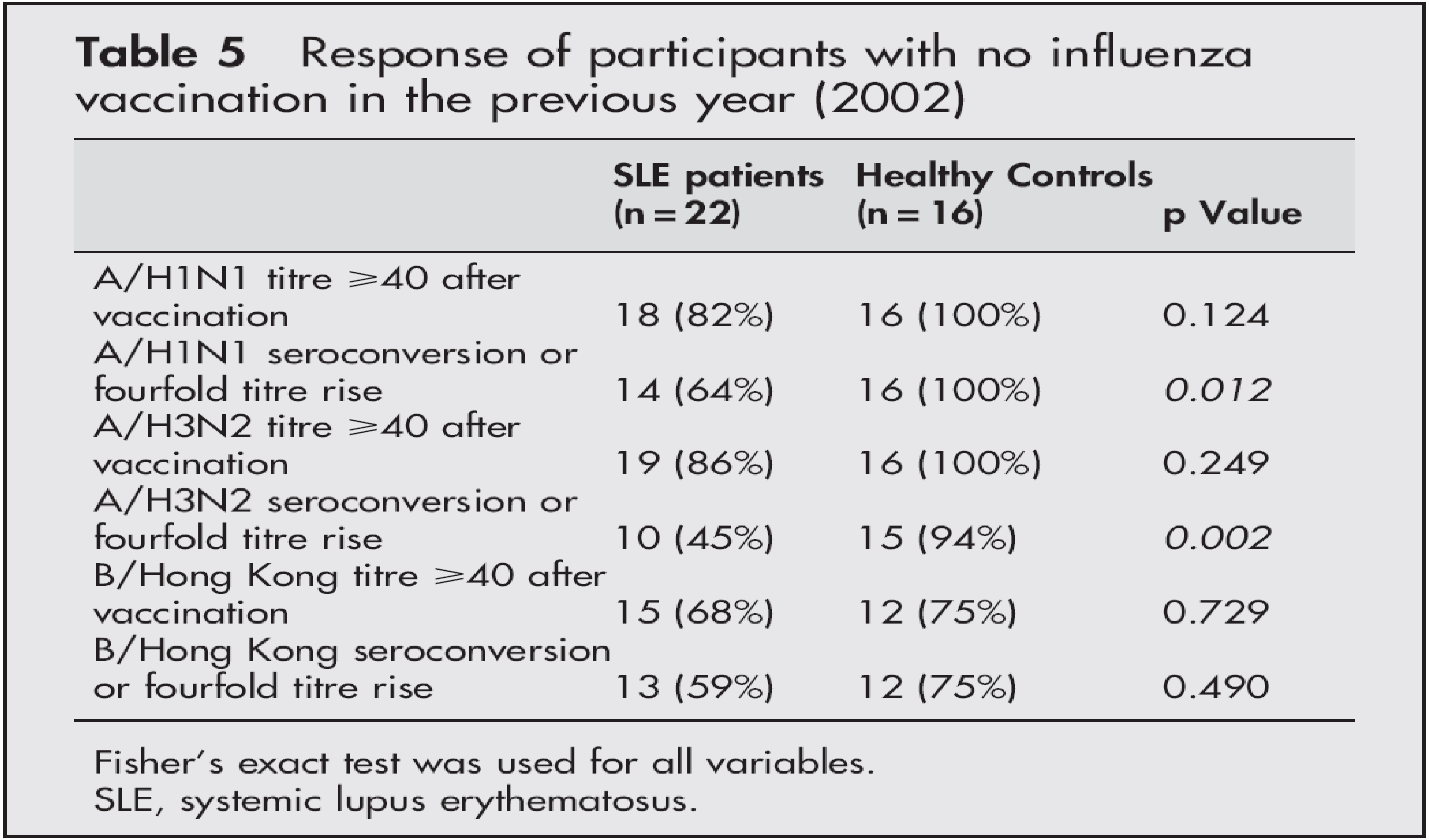


Table 5 Response of participants with no influenza vaccination in the previous year (2002)

	SLE patients (n = 22)	Healthy Controls (n = 16)	p Value
A/H1N1 titre ⩾40 after vaccination	18 (82%)	16 (100%)	0.124
A/H1N1 seroconversion or fourfold titre rise	14 (64%)	16 (100%)	*0.012*
A/H3N2 titre ⩾40 after vaccination	19 (86%)	16 (100%)	0.249
A/H3N2 seroconversion or fourfold titre rise	10 (45%)	15 (94%)	*0.002*
B/Hong Kong titre ⩾40 after vaccination	15 (68%)	12 (75%)	0.729
B/Hong Kong seroconversion or fourfold titre rise	13 (59%)	12 (75%)	0.490

Fisher's exact test was used for all variables.
SLE, systemic lupus erythematosus.

Safety and efficacy of influenza vaccination in systemic lupus erythematosus patients with quiescent disease

Ann Rheum Dis 2006;65;913-918

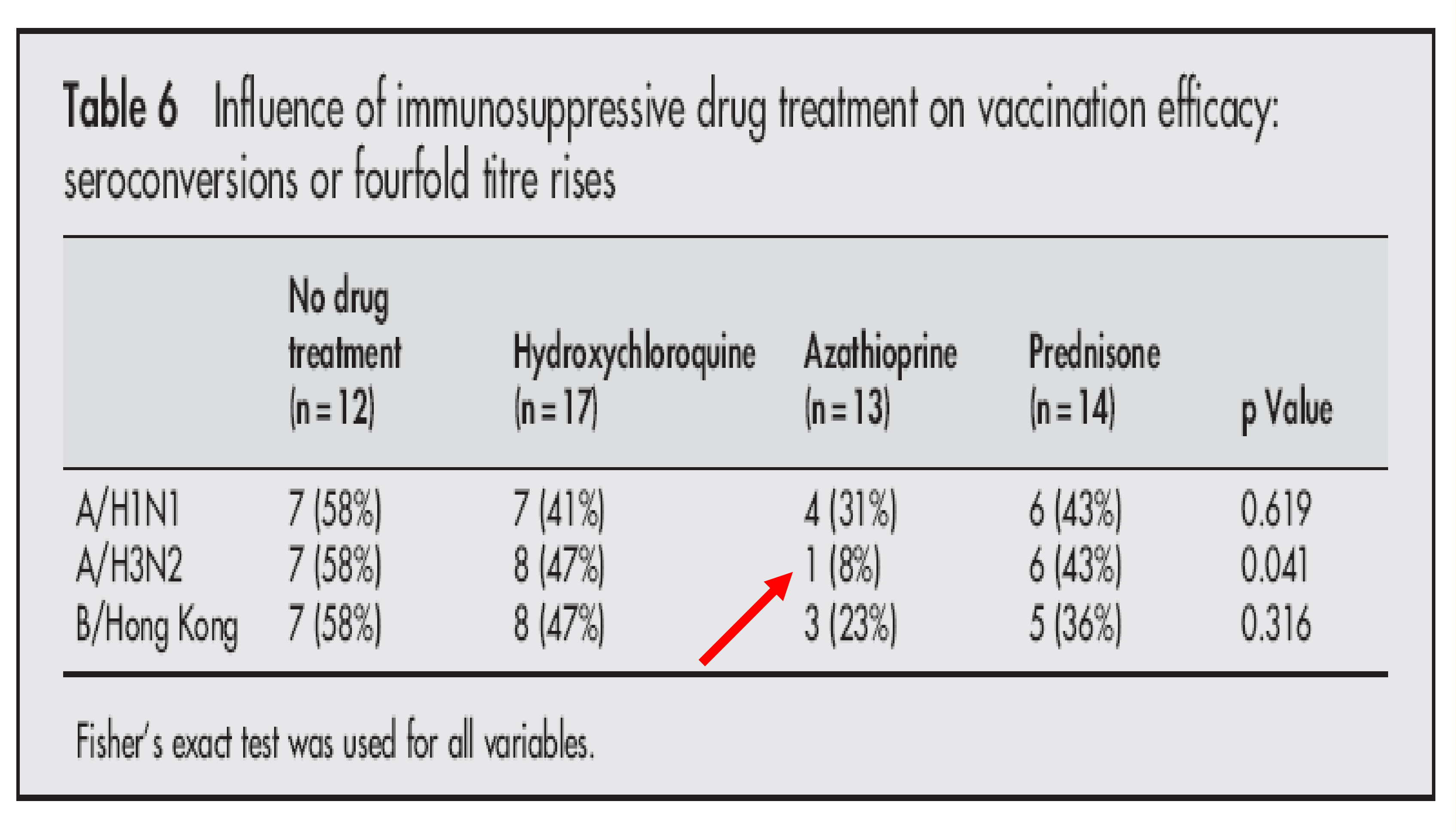
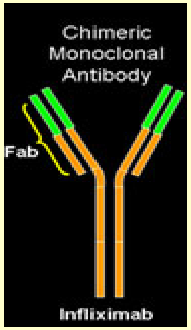


Table 6 Influence of immunosuppressive drug treatment on vaccination efficacy: seroconversions or fourfold titre rises

	No drug treatment (n = 12)	Hydroxychloroquine (n = 17)	Azathioprine (n = 13)	Prednisone (n = 14)	p Value
A/H1N1	7 (58%)	7 (41%)	4 (31%)	6 (43%)	0.619
A/H3N2	7 (58%)	8 (47%)	1 (8%)	6 (43%)	0.041
B/Hong Kong	7 (58%)	8 (47%)	3 (23%)	5 (36%)	0.316

Fisher's exact test was used for all variables.



Vaccination against influenza in rheumatoid arthritis: the effect of disease modifying drugs, including TNFα blockers

Ann Rheum Dis 2006;**65**:191–194.

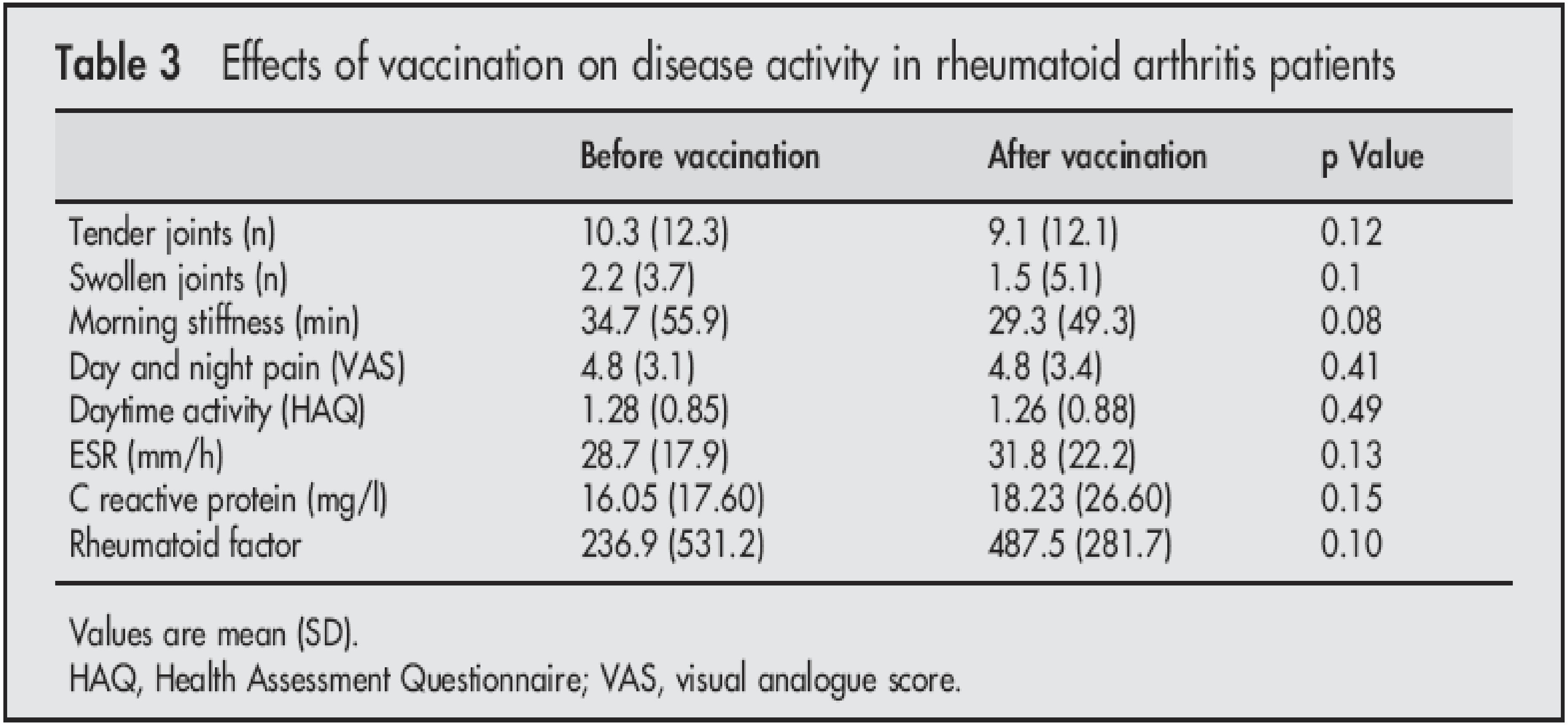


Table 3 Effects of vaccination on disease activity in rheumatoid arthritis patients

	Before vaccination	After vaccination	p Value
Tender joints (n)	10.3 (12.3)	9.1 (12.1)	0.12
Swollen joints (n)	2.2 (3.7)	1.5 (5.1)	0.1
Morning stiffness (min)	34.7 (55.9)	29.3 (49.3)	0.08
Day and night pain (VAS)	4.8 (3.1)	4.8 (3.4)	0.41
Daytime activity (HAQ)	1.28 (0.85)	1.26 (0.88)	0.49
ESR (mm/h)	28.7 (17.9)	31.8 (22.2)	0.13
C reactive protein (mg/l)	16.05 (17.60)	18.23 (26.60)	0.15
Rheumatoid factor	236.9 (531.2)	487.5 (281.7)	0.10

Values are mean (SD).
HAQ, Health Assessment Questionnaire; VAS, visual analogue score.

Vaccination against influenza in rheumatoid arthritis: the effect of disease modifying drugs, including TNFα blockers

Ann Rheum Dis 2006;65:191–194.

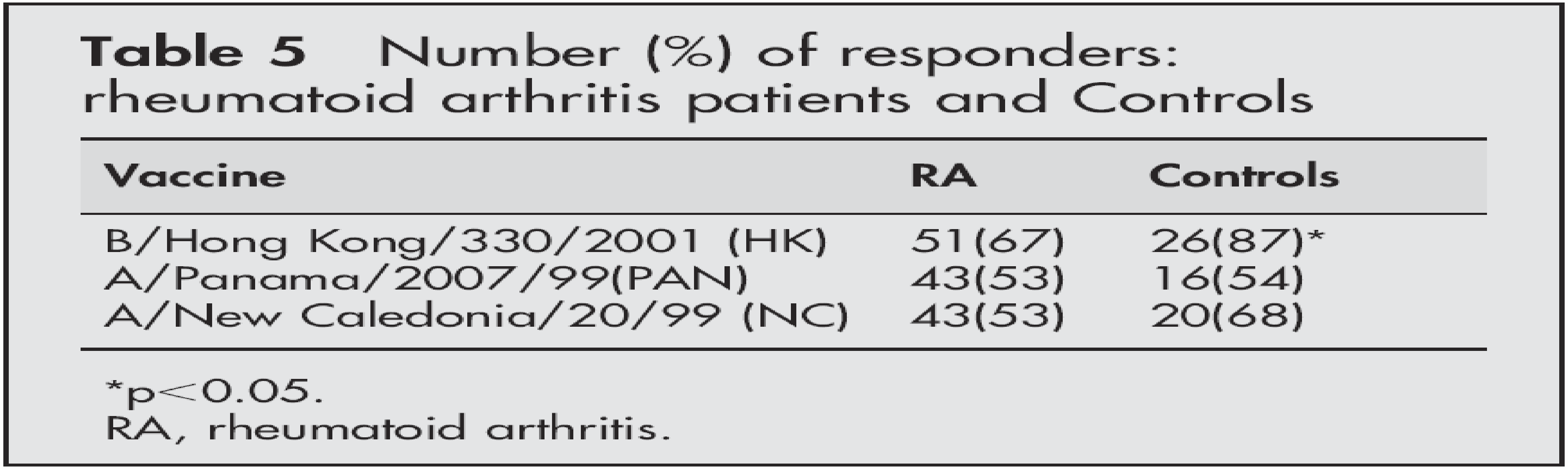


Table 5 Number (%) of responders: rheumatoid arthritis patients and Controls

Vaccine	RA	Controls
B/Hong Kong/330/2001 (HK)	51(67)	26(87)*
A/Panama/2007/99(PAN)	43(53)	16(54)
A/New Caledonia/20/99 (NC)	43(53)	20(68)

*p<0.05.
RA, rheumatoid arthritis.

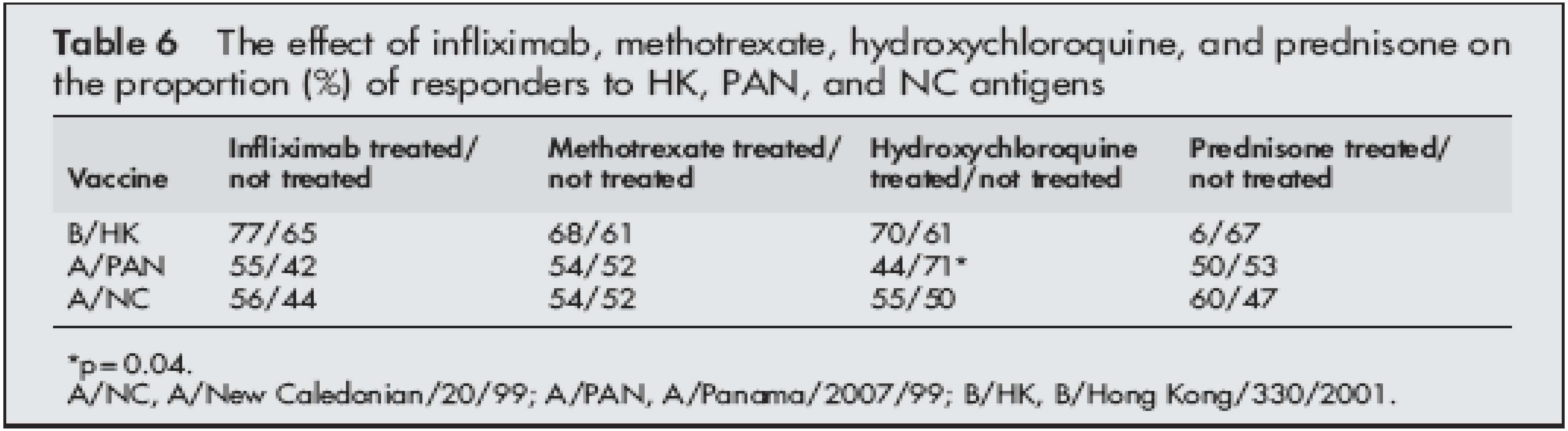


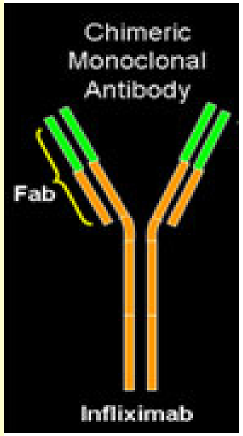
Table 6 The effect of infliximab, methotrexate, hydroxychloroquine, and prednisone on the proportion (%) of responders to HK, PAN, and NC antigens

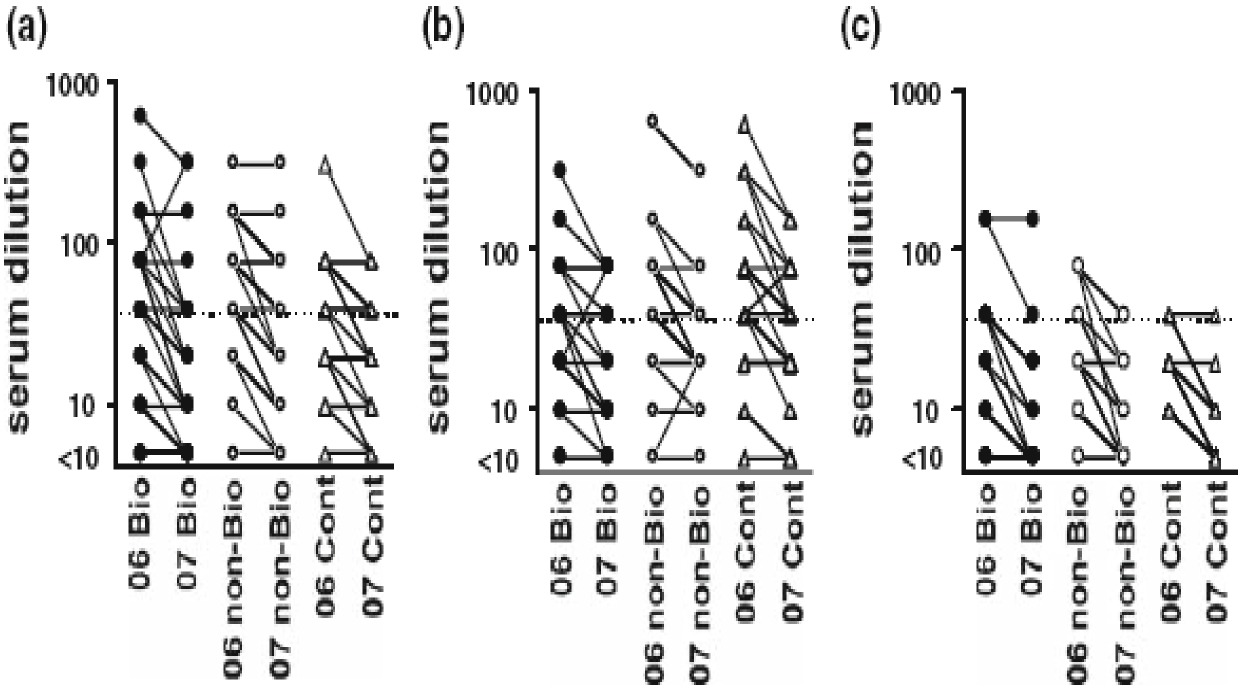
Vaccine	Infliximab treated/not treated	Methotrexate treated/not treated	Hydroxychloroquine treated/not treated	Prednisone treated/not treated
B/HK	77/65	68/61	70/61	6/67
A/PAN	55/42	54/52	44/71*	50/53
A/NC	56/44	54/52	55/50	60/47

*p=0.04.
A/NC, A/New Caledonian/20/99; A/PAN, A/Panama/2007/99; B/HK, B/Hong Kong/330/2001.

Reevaluation of antibody titers 1 year after influenza vaccination in patients with rheumatoid arthritis receiving TNF blockers

Mod Rheumatol (2009) 19:216–218


Chimeric Monoclonal Antibody
Fab
Infliximab



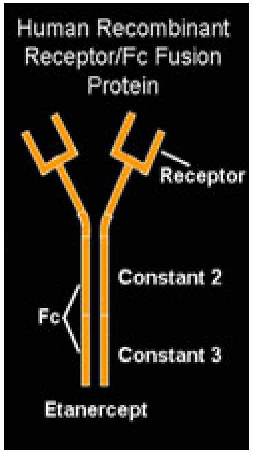
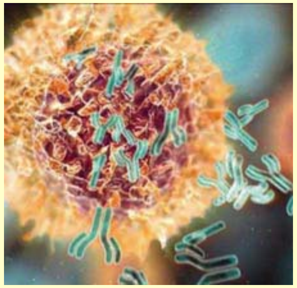

Human Recombinant Receptor/Fc Fusion Protein
Receptor
Constant 2
Fc
Constant 3
Etanercept

Fig. 1 One year follow-up of antibody titers against influenza antigens after vaccination. Antibody titers of individual subject for A/New Caledonia/20/99 (H1N1) (a), A/Hiroshima/52/2005 (H3N2) (b), and B/Malaysia/2506/2004 (c) were measured 4–6 weeks after vaccination for the 2006/2007 season (06) and 1 year after the vaccination (07), in RA patients receiving anti-TNF biologics (*Bio*), not receiving any biologics (*non-Bio*), and healthy controls (*Cont*). The *dotted line* represents the lower limit of protective titer (×40). Antibody titers at 06, those at 07, and the ratio of the titers at 07 to those at 06 were all compared by the Mann–Whitney test, showing that groups are not significantly different from one another ($P > 0.05$). Note that each line may represent more than one individual who had the same antibody titers



Vaccination against influenza in patients with rheumatoid arthritis: the effect of rituximab on the humoral response

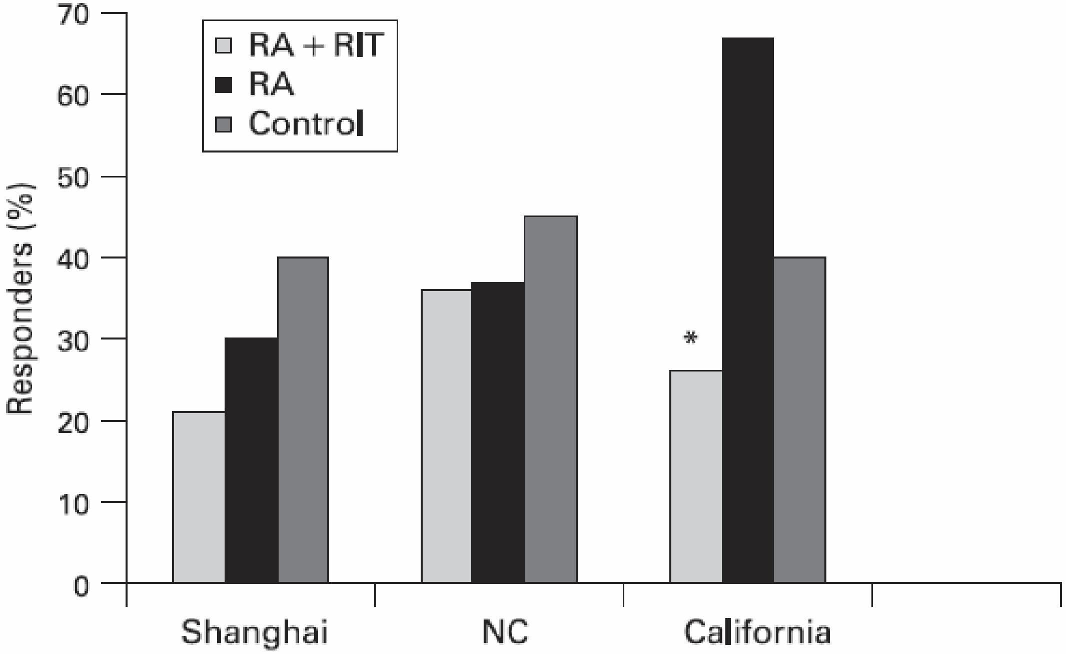


Figure 2 Percentages of responders among both groups of patients with rheumatoid arthritis (RA) and controls. NC, New Caledonian; RIT, rituximab. $^*p<0.05$.

Ann Rheum Dis 2008;67;937-941

Poor serological responses upon influenza vaccination in patients with rheumatoid arthritis treated with rituximab

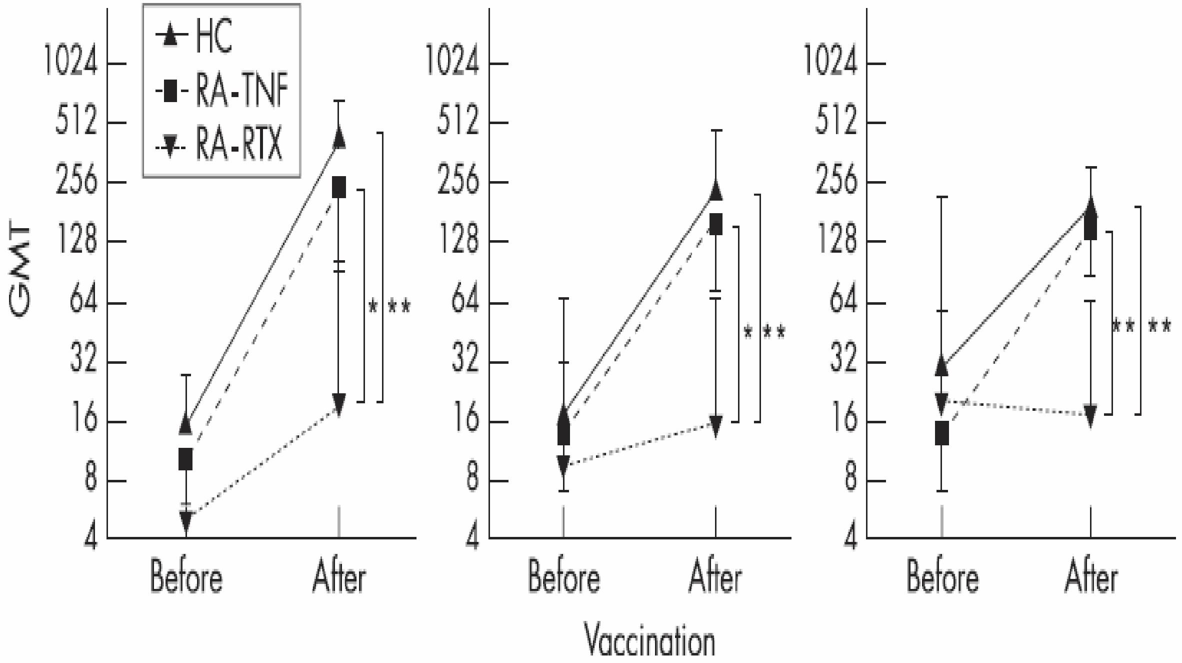


Figure 1 Pre and postvaccination serum geometric mean titres (GMT), with 95% confidence intervals, against influenza A/H3N2, A/H1N1 and influenza B for a group of patients with rheumatoid arthritis (RA) treated with rituximab (RA–RTX; n = 4), compared with RA patients treated with anti-tumour necrosis factor (TNF; RA–TNF; n = 19) and healthy controls (HC; n = 20). $^{*}p \leqslant 0.02$; $^{**}p \leqslant 0.001$.

Ann Rheum Dis 2007;66;1402-1403

¿Y CON LA GRIPE A?

SWINE INFLUENZA EPIDEMIC

NEW JERSEY 1976

A/New Jersey/76 Hsw1N1

109 Pacientes con LES

2 Brotes renales

Ann Int Med 1978;88:786-789 /790-792

Immunogenicity and Safety of Pneumococcal Vaccination in Patients with Rheumatoid Arthritis or Systemic Lupus Erythematosus

Clinical Infectious Diseases 2002;34:147–53

Table 1. Clinical characteristics of patients with systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA) and control subjects who underwent pneumococcal vaccination.

Immunogenicity and Safety of Pneumococcal Vaccination in Patients with Rheumatoid Arthritis or Systemic Lupus Erythematosus

Clinical Infectious Diseases 2002;34:147–53

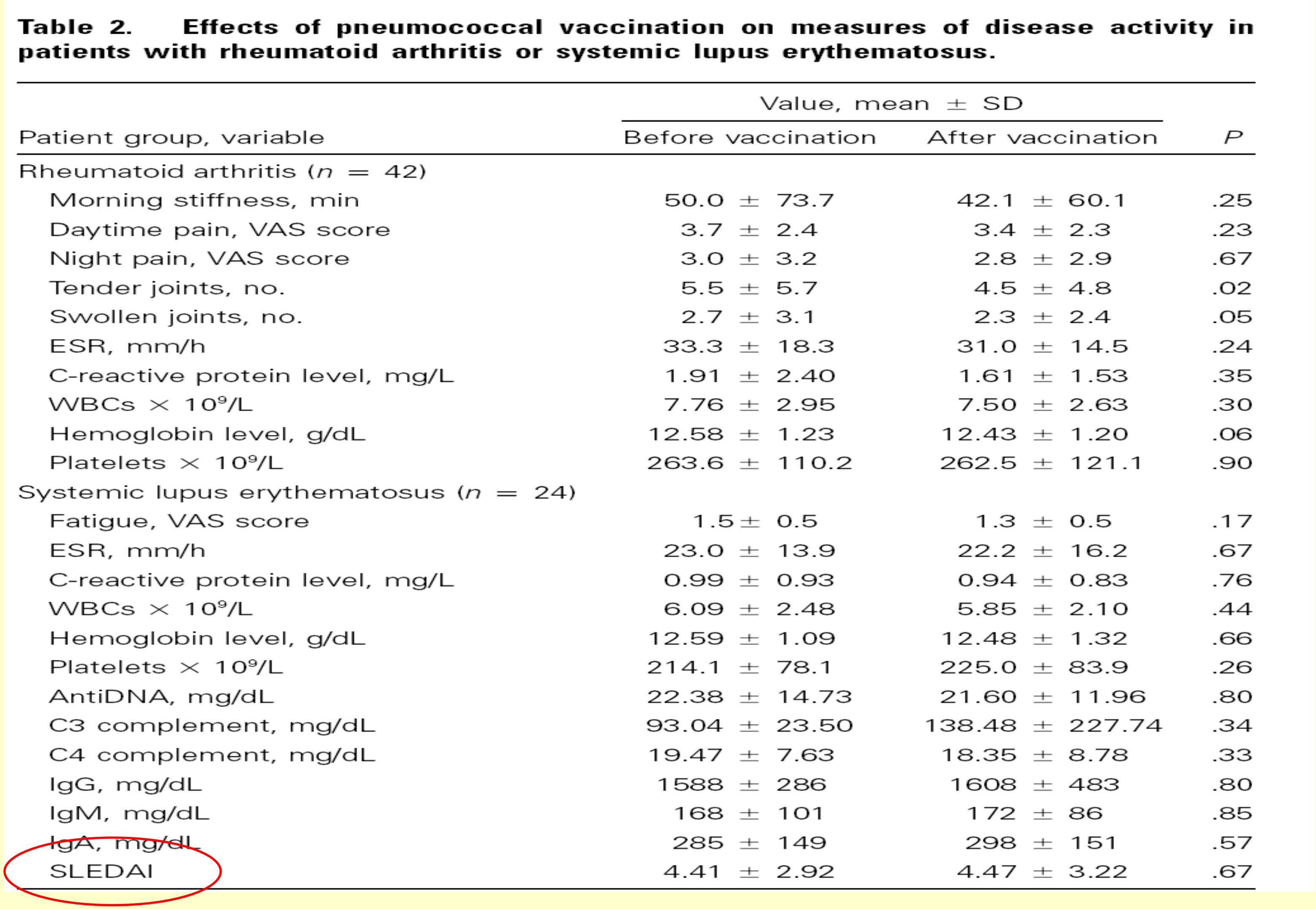


Table 2. Effects of pneumococcal vaccination on measures of disease activity in patients with rheumatoid arthritis or systemic lupus erythematosus.

Patient group, variable	Value, mean ± SD Before vaccination	 After vaccination	P
Rheumatoid arthritis (*n* = 42)			
Morning stiffness, min	50.0 ± 73.7	42.1 ± 60.1	.25
Daytime pain, VAS score	3.7 ± 2.4	3.4 ± 2.3	.23
Night pain, VAS score	3.0 ± 3.2	2.8 ± 2.9	.67
Tender joints, no.	5.5 ± 5.7	4.5 ± 4.8	.02
Swollen joints, no.	2.7 ± 3.1	2.3 ± 2.4	.05
ESR, mm/h	33.3 ± 18.3	31.0 ± 14.5	.24
C-reactive protein level, mg/L	1.91 ± 2.40	1.61 ± 1.53	.35
WBCs × 10^9/L	7.76 ± 2.95	7.50 ± 2.63	.30
Hemoglobin level, g/dL	12.58 ± 1.23	12.43 ± 1.20	.06
Platelets × 10^9/L	263.6 ± 110.2	262.5 ± 121.1	.90
Systemic lupus erythematosus (*n* = 24)			
Fatigue, VAS score	1.5 ± 0.5	1.3 ± 0.5	.17
ESR, mm/h	23.0 ± 13.9	22.2 ± 16.2	.67
C-reactive protein level, mg/L	0.99 ± 0.93	0.94 ± 0.83	.76
WBCs × 10^9/L	6.09 ± 2.48	5.85 ± 2.10	.44
Hemoglobin level, g/dL	12.59 ± 1.09	12.48 ± 1.32	.66
Platelets × 10^9/L	214.1 ± 78.1	225.0 ± 83.9	.26
AntiDNA, mg/dL	22.38 ± 14.73	21.60 ± 11.96	.80
C3 complement, mg/dL	93.04 ± 23.50	138.48 ± 227.74	.34
C4 complement, mg/dL	19.47 ± 7.63	18.35 ± 8.78	.33
IgG, mg/dL	1588 ± 286	1608 ± 483	.80
IgM, mg/dL	168 ± 101	172 ± 86	.85
IgA, mg/dL	285 ± 149	298 ± 151	.57
SLEDAI	4.41 ± 2.92	4.47 ± 3.22	.67

Immunogenicity and Safety of Pneumococcal Vaccination in Patients with Rheumatoid Arthritis or Systemic Lupus Erythematosus

Clinical Infectious Diseases 2002;34:147–53

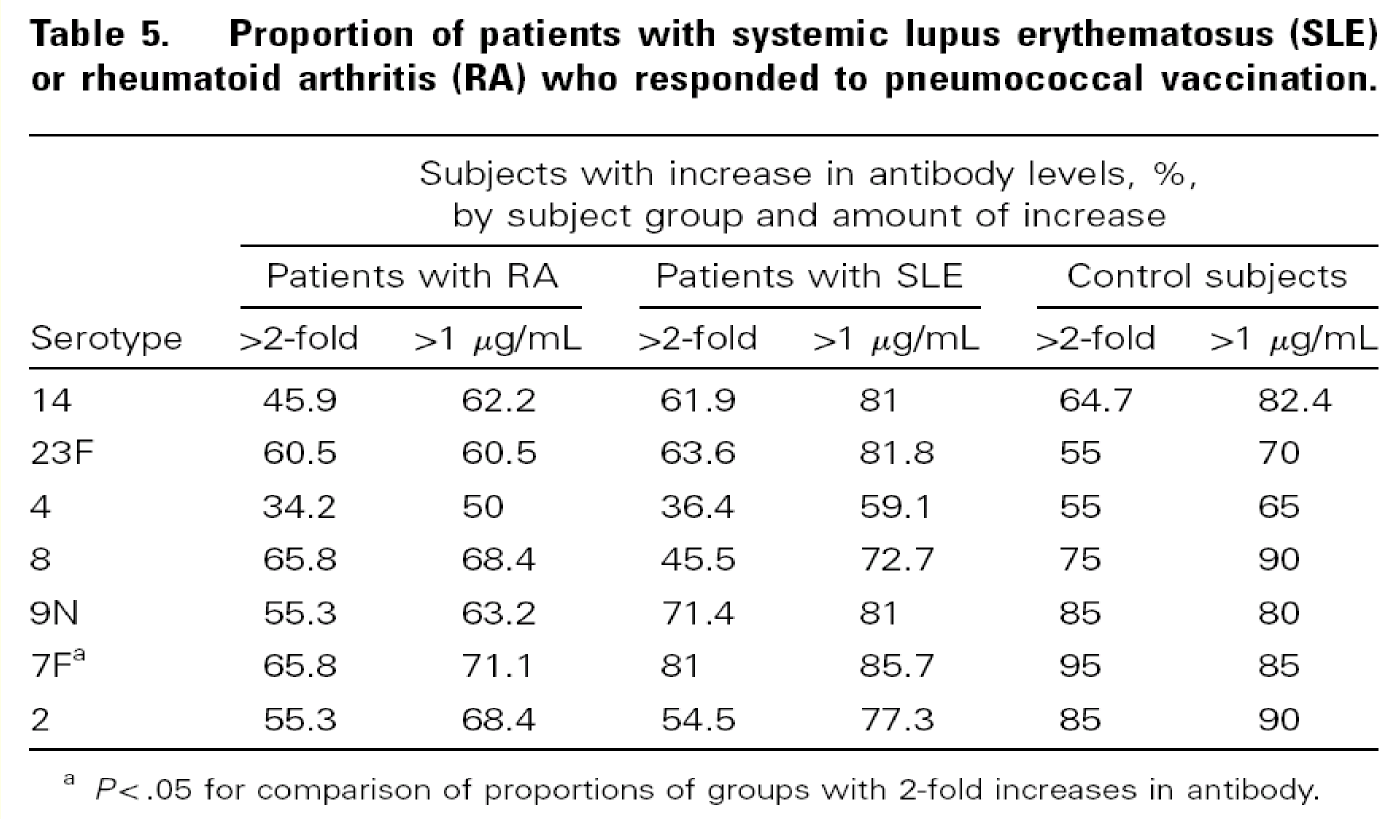
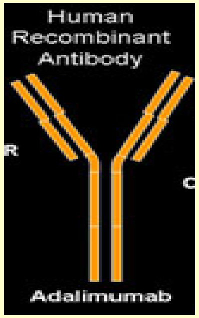


Table 5. Proportion of patients with systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA) who responded to pneumococcal vaccination.

	Subjects with increase in antibody levels, %, by subject group and amount of increase					
	Patients with RA		Patients with SLE		Control subjects	
Serotype	>2-fold	>1 μg/mL	>2-fold	>1 μg/mL	>2-fold	>1 μg/mL
14	45.9	62.2	61.9	81	64.7	82.4
23F	60.5	60.5	63.6	81.8	55	70
4	34.2	50	36.4	59.1	55	65
8	65.8	68.4	45.5	72.7	75	90
9N	55.3	63.2	71.4	81	85	80
7F[a]	65.8	71.1	81	85.7	95	85
2	55.3	68.4	54.5	77.3	85	90

[a] $P < .05$ for comparison of proportions of groups with 2-fold increases in antibody.



Immune Responses Following Administration of Influenza and Pneumococcal Vaccines to Patients with Rheumatoid Arthritis Receiving Adalimumab

. (J Rheumatol 2007;34:272–9)

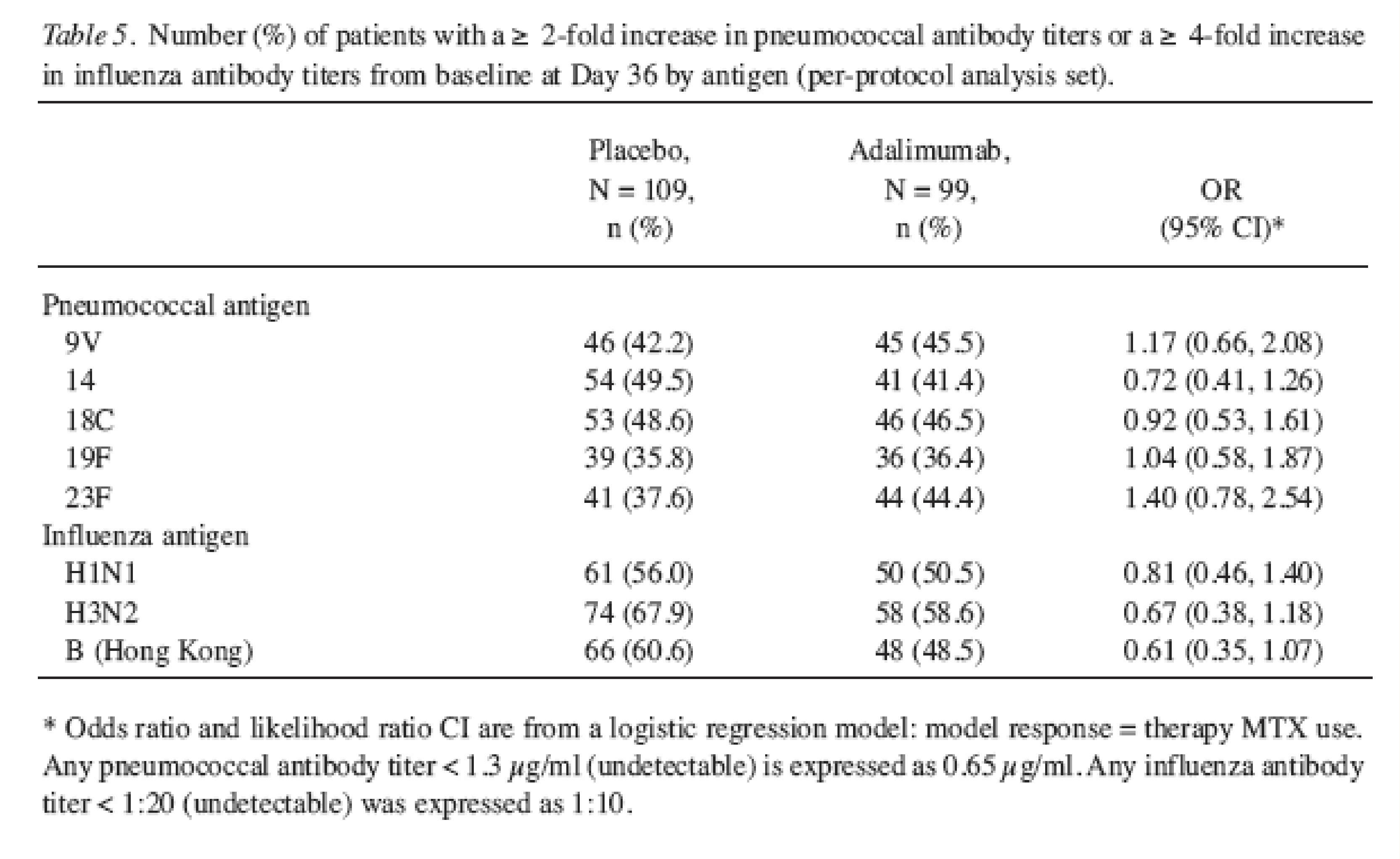


Table 5. Number (%) of patients with a ≥ 2-fold increase in pneumococcal antibody titers or a ≥ 4-fold increase in influenza antibody titers from baseline at Day 36 by antigen (per-protocol analysis set).

	Placebo, N = 109, n (%)	Adalimumab, N = 99, n (%)	OR (95% CI)*
Pneumococcal antigen			
9V	46 (42.2)	45 (45.5)	1.17 (0.66, 2.08)
14	54 (49.5)	41 (41.4)	0.72 (0.41, 1.26)
18C	53 (48.6)	46 (46.5)	0.92 (0.53, 1.61)
19F	39 (35.8)	36 (36.4)	1.04 (0.58, 1.87)
23F	41 (37.6)	44 (44.4)	1.40 (0.78, 2.54)
Influenza antigen			
H1N1	61 (56.0)	50 (50.5)	0.81 (0.46, 1.40)
H3N2	74 (67.9)	58 (58.6)	0.67 (0.38, 1.18)
B (Hong Kong)	66 (60.6)	48 (48.5)	0.61 (0.35, 1.07)

* Odds ratio and likelihood ratio CI are from a logistic regression model: model response = therapy MTX use. Any pneumococcal antibody titer < 1.3 μg/ml (undetectable) is expressed as 0.65 μg/ml. Any influenza antibody titer < 1:20 (undetectable) was expressed as 1:10.

Influence of methotrexate, TNF blockers and prednisolone on antibody responses to pneumococcal polysaccharide vaccine in patients with rheumatoid arthritis

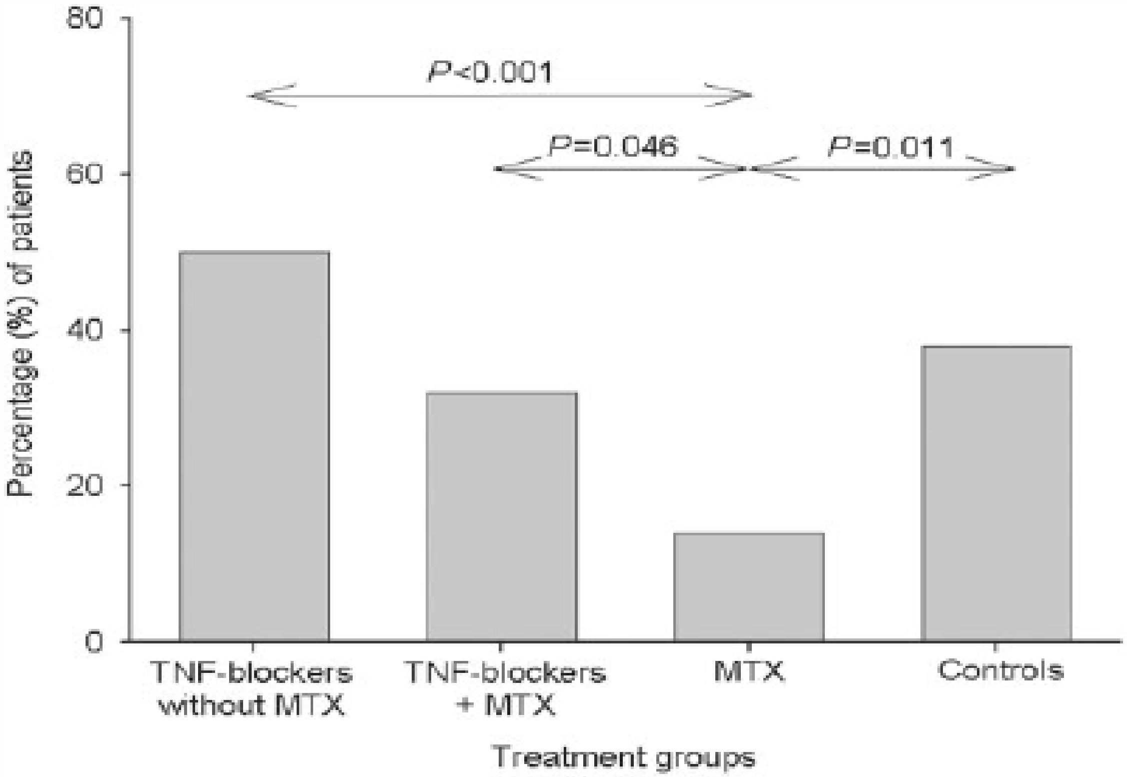


Fig. 3. Percentage of patients with immune response, defined as ≥2-fold increase in antibody level to both 23F and 6B. For details of groups see legend to Fig. 1. Significant differences are shown.

Rheumatology 2006;45:106–111

Immunization of patients with rheumatoid arthritis with antitumor necrosis factorα therapy and methotrexate

Current Opinion in Rheumatology 2008, 20:295–299

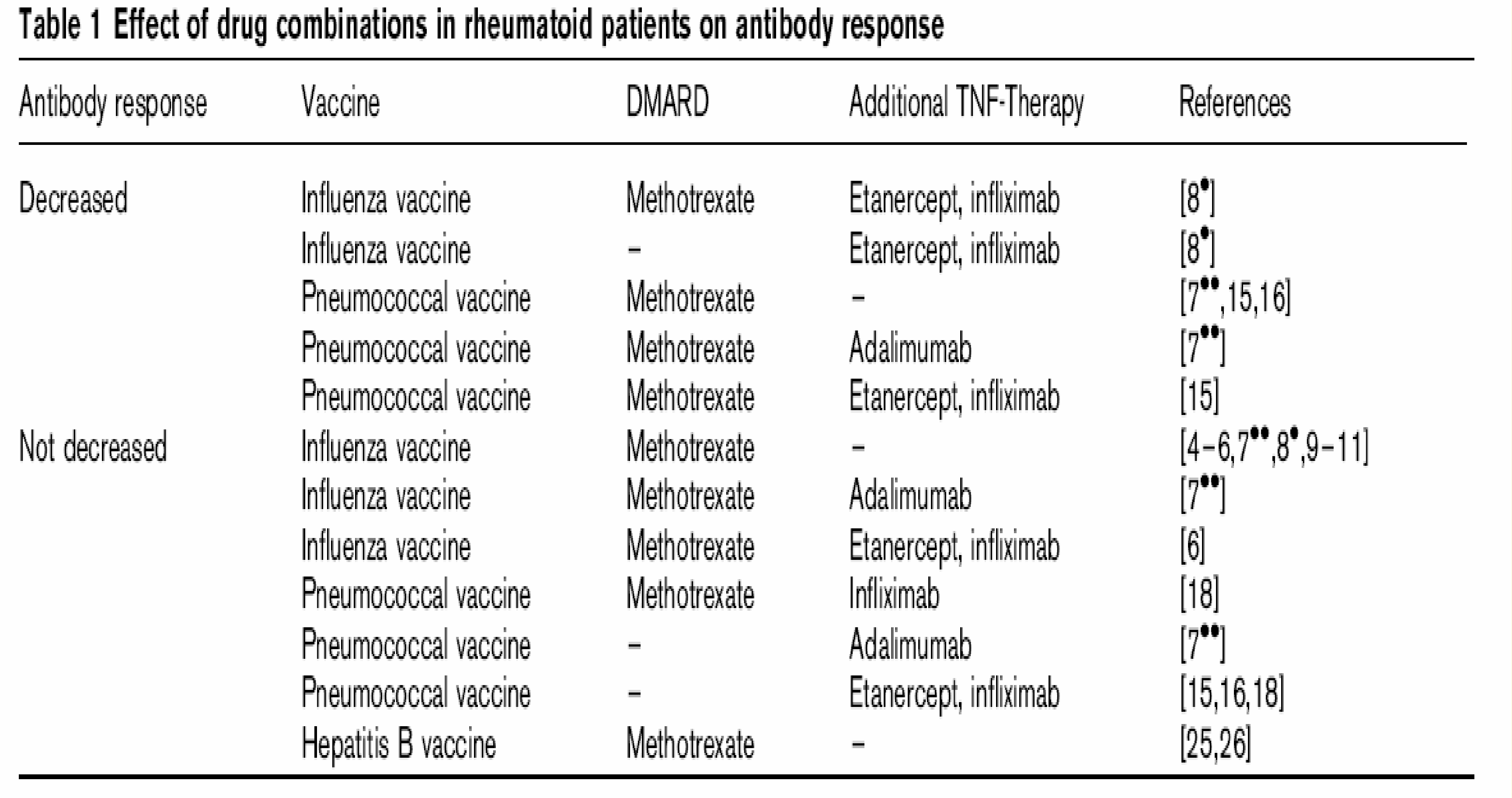
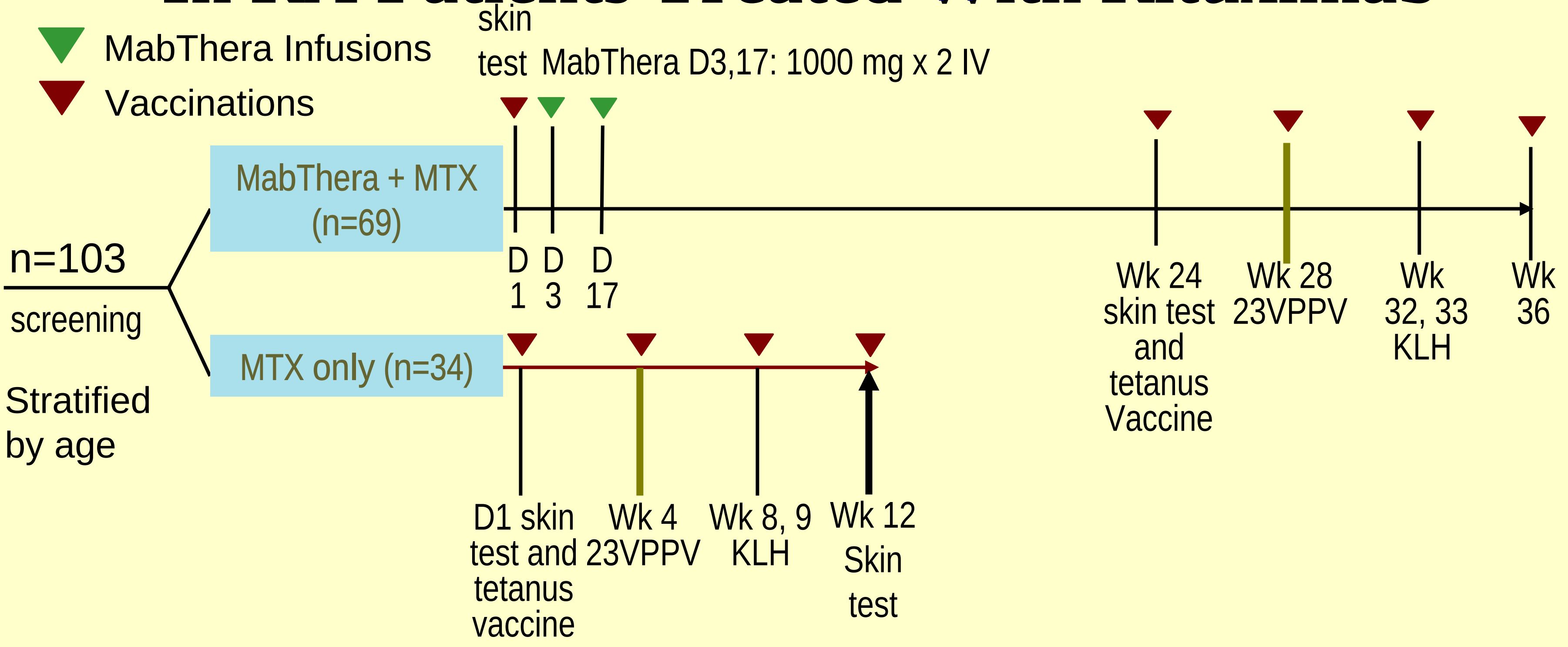


Table 1 Effect of drug combinations in rheumatoid patients on antibody response

Antibody response	Vaccine	DMARD	Additional TNF-Therapy	References
Decreased	Influenza vaccine	Methotrexate	Etanercept, infliximab	[8$^{\bullet}$]
	Influenza vaccine	–	Etanercept, infliximab	[8$^{\bullet}$]
	Pneumococcal vaccine	Methotrexate	–	[7$^{\bullet\bullet}$,15,16]
	Pneumococcal vaccine	Methotrexate	Adalimumab	[7$^{\bullet\bullet}$]
	Pneumococcal vaccine	Methotrexate	Etanercept, infliximab	[15]
Not decreased	Influenza vaccine	Methotrexate	–	[4–6,7$^{\bullet\bullet}$,8$^{\bullet}$,9–11]
	Influenza vaccine	Methotrexate	Adalimumab	[7$^{\bullet\bullet}$]
	Influenza vaccine	Methotrexate	Etanercept, infliximab	[6]
	Pneumococcal vaccine	Methotrexate	Infliximab	[18]
	Pneumococcal vaccine	–	Adalimumab	[7$^{\bullet\bullet}$]
	Pneumococcal vaccine	–	Etanercept, infliximab	[15,16,18]
	Hepatitis B vaccine	Methotrexate	–	[25,26]

AntiTNF > Metotrexate

A Controlled Clinical Trial (SIERRA) To Evaluate Primary And Recall Responses To Immunizations In RA Patients Treated With Rituximab



▼ MabThera Infusions

▼ Vaccinations

skin test

MabThera D3,17: 1000 mg x 2 IV

n=103

screening

Stratified by age

MabThera + MTX (n=69)

D 1

D 3

D 17

Wk 24 skin test and tetanus Vaccine

Wk 28 23VPPV

Wk 32, 33 KLH

Wk 36

MTX only (n=34)

D1 skin test and tetanus vaccine

Wk 4 23VPPV

Wk 8, 9 KLH

Wk 12 Skin test

MTX=methotrexate; TT=Tetanus Toxoid;23VPPV=23-Valent Pneumococcal Polysaccharide; KLH=Keyhole Limpet Hemocyanin

MABTHERA®
RITUXIMAB
B CELL THERAPY. LASTING SUCCESS.

Roche

Tetanus toxoid vaccine response at Week 4 following vaccination

	MabThera + MTX n=64	MTX n=26
Four-fold titer increase (primary endpoint); n (%)	25 (39.1)	11 (42.3)
Difference (95% CIs); %	-3.2 (-25.7, 19.2)	
Two-fold titer increase (secondary endpoint); n (%)	35 (54.7)	16 (61.5)
Difference (95% CIs); n (%)	-6.9 (-29.2, 15.5)	

Patients treated with MabThera + MTX had comparable humoral response to a recall protein antigen compared with patients treated with MTX alone

MABTHERA®
RITUXIMAB
B CELL THERAPY. LASTING SUCCESS.

Roche

Positive responses to pneumococcal serotypes

	MabThera + MTX n=63	MTX n=28
Patients with 2-fold titer rise to ≥1 serotype	36 (57%)	23 (82%)
Difference (95% CIs); %	-25.0 (-43.7, -6.3)	

Positive responses to pneumococcal serotypes in MabThera plus MTX-treated patients were decreased compared with MTX alone

MABTHERA®
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Influenza vaccination of patients with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA)

Clinical & Developmental Immunology, June–December 2006

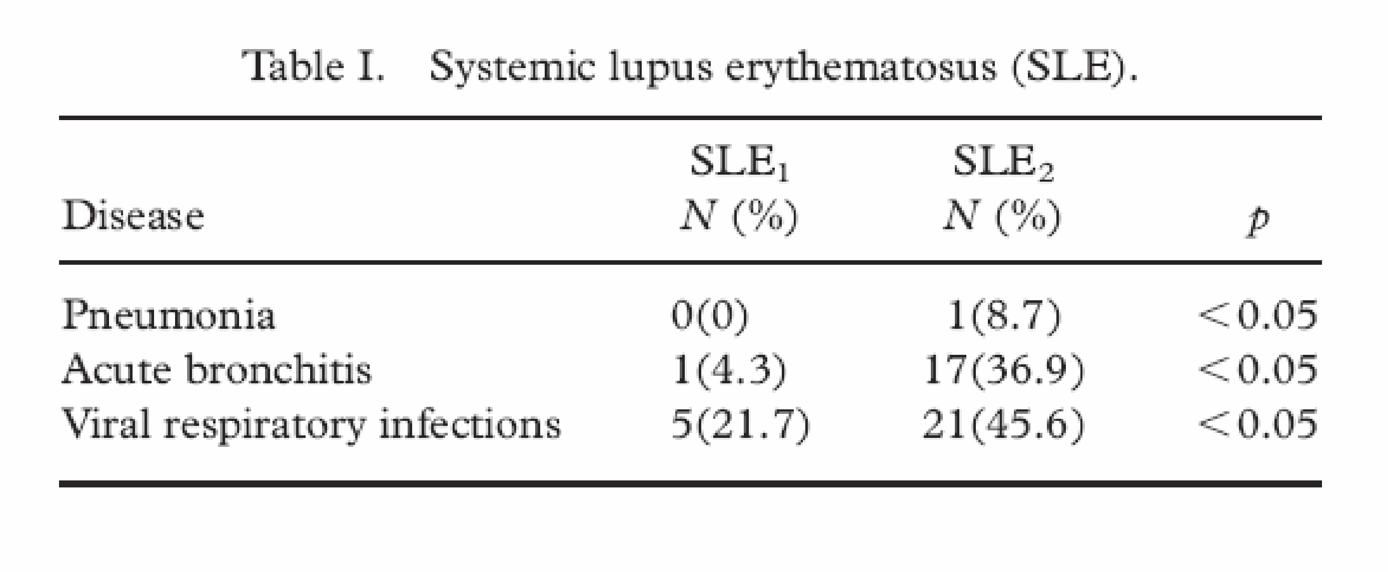


Table I. Systemic lupus erythematosus (SLE).

Disease	SLE_1 *N* (%)	SLE_2 *N* (%)	p
Pneumonia	0(0)	1(8.7)	<0.05
Acute bronchitis	1(4.3)	17(36.9)	<0.05
Viral respiratory infections	5(21.7)	21(45.6)	<0.05

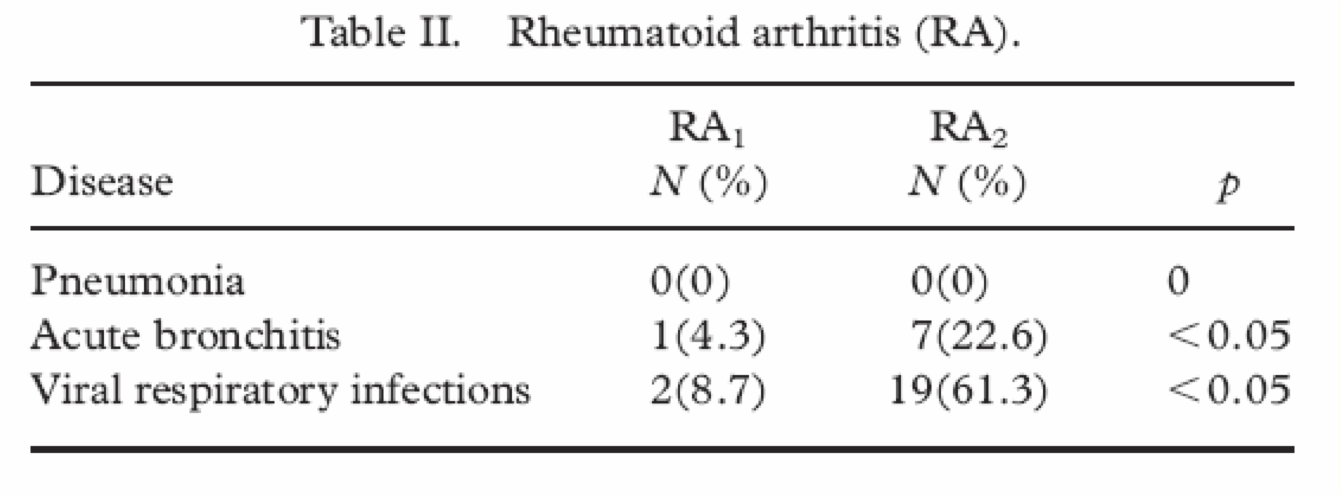
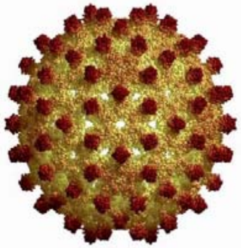
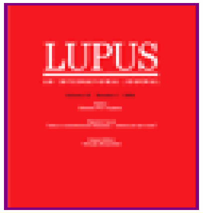


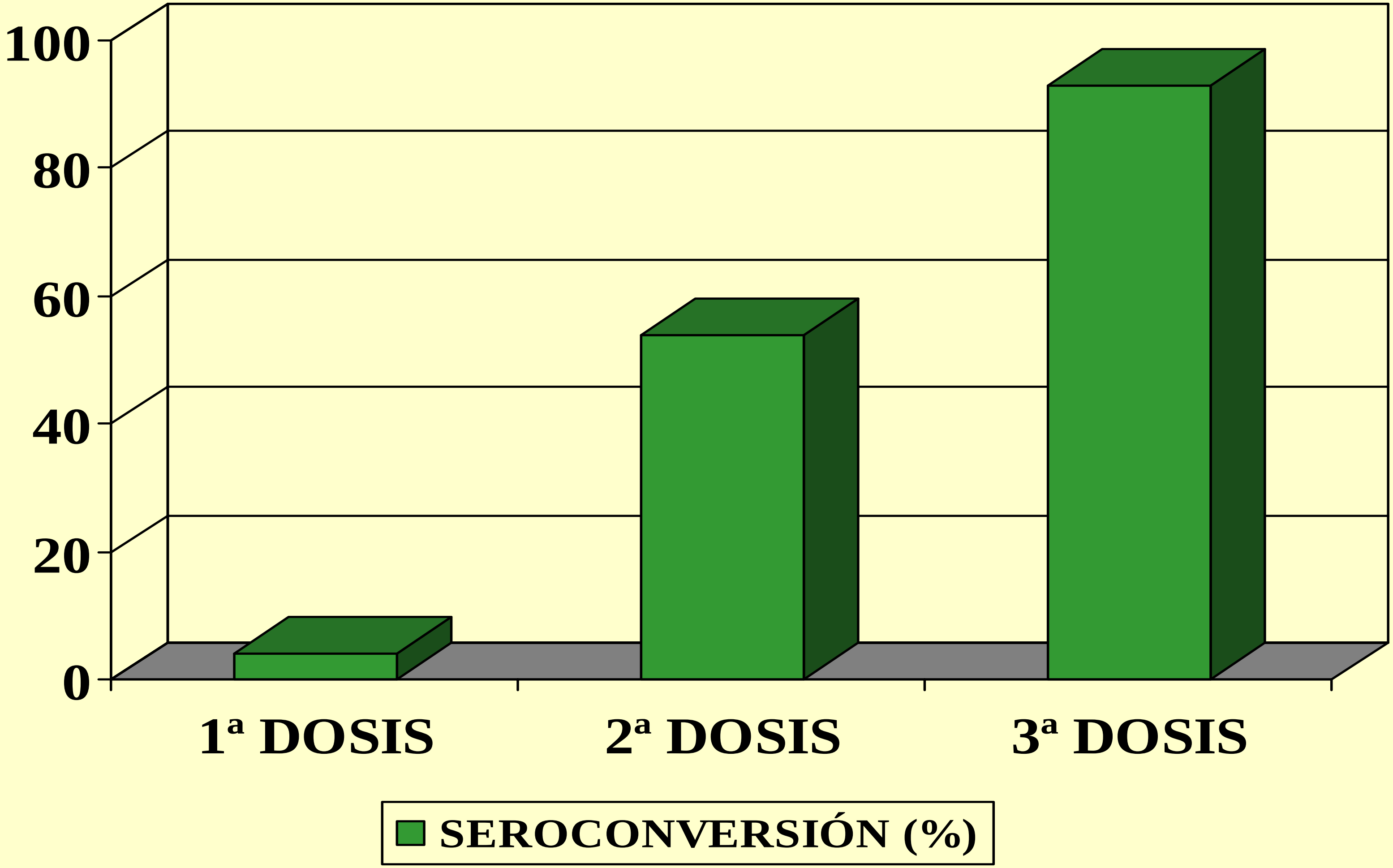
Table II. Rheumatoid arthritis (RA).

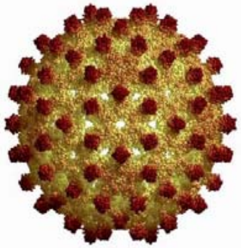
Disease	RA_1 *N* (%)	RA_2 *N* (%)	p
Pneumonia	0(0)	0(0)	0
Acute bronchitis	1(4.3)	7(22.6)	<0.05
Viral respiratory infections	2(8.7)	19(61.3)	<0.05

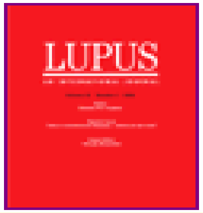




PDF
Safety and efficacy of hepatitis B vaccine in systemic lupus erythematosus
Kuruma et al. *Lupus.*2007; 16: 350-354







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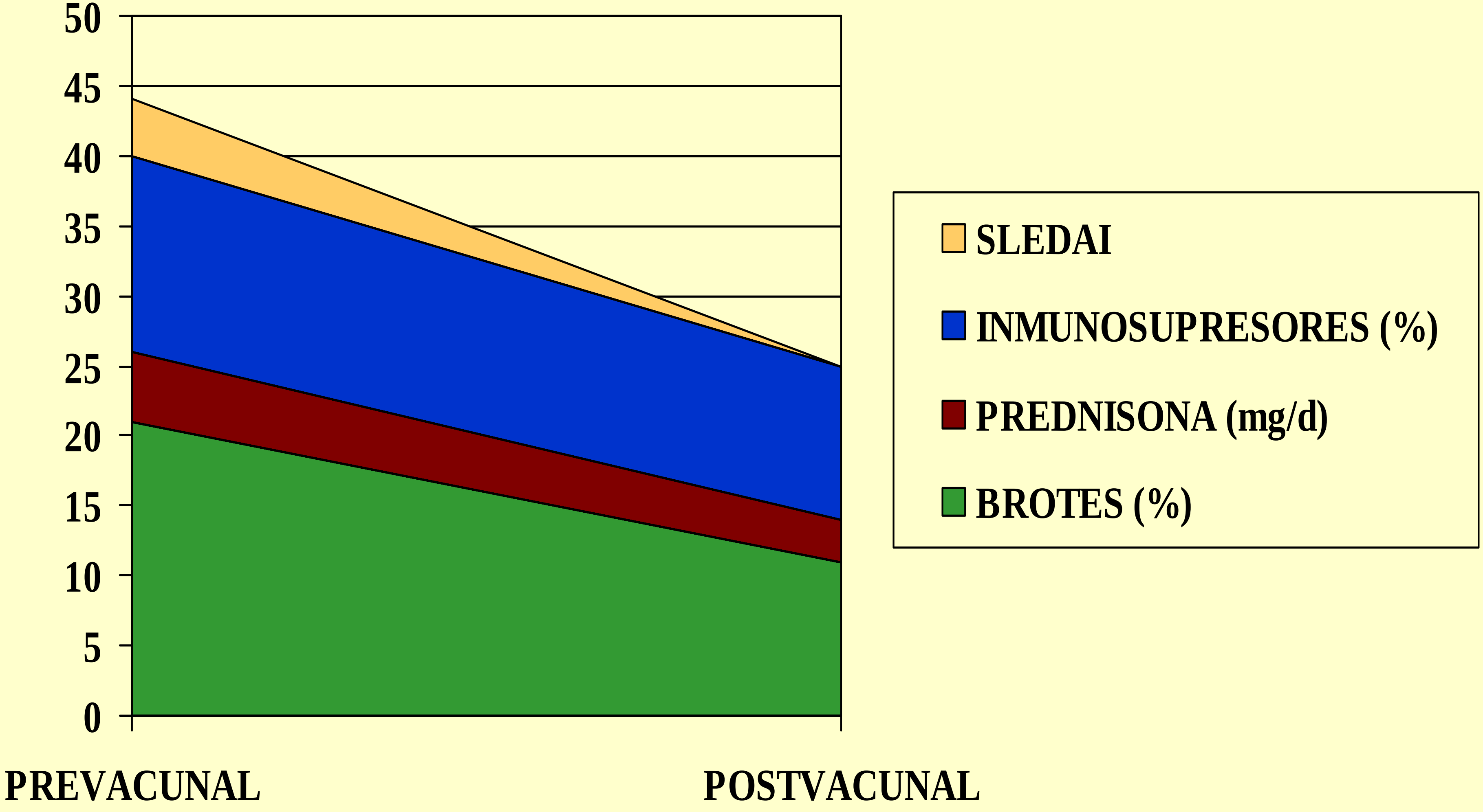
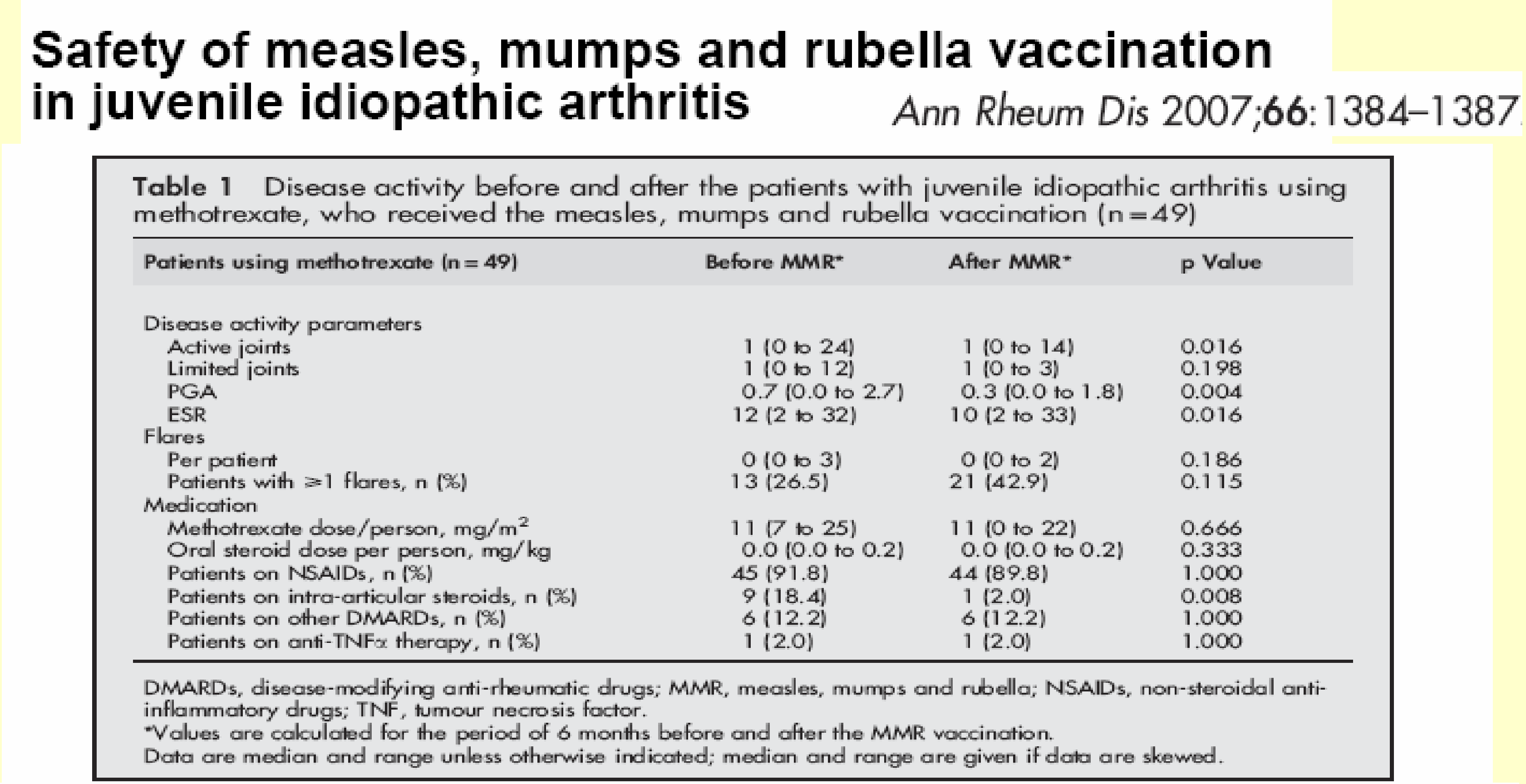
Safety and efficacy of hepatitis B vaccine in systemic lupus erythematosus
Kuruma et al. *Lupus*.2007; 16: 350-354





Safety of measles, mumps and rubella vaccination in juvenile idiopathic arthritis

Ann Rheum Dis 2007;**66**:1384–1387.

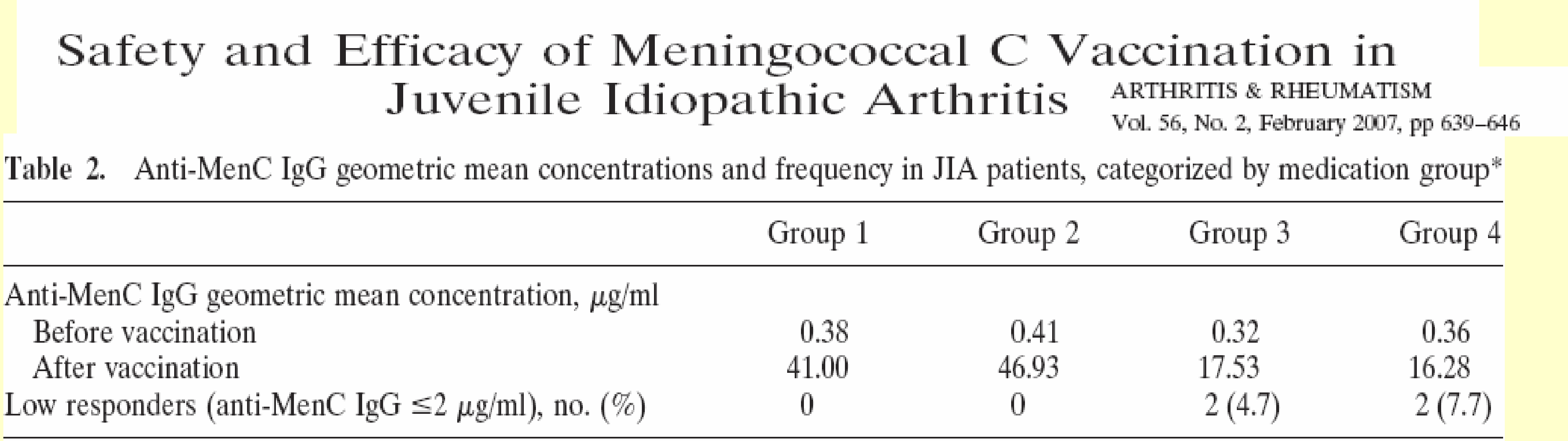
Table 1 Disease activity before and after the patients with juvenile idiopathic arthritis using methotrexate, who received the measles, mumps and rubella vaccination (n = 49)

Patients using methotrexate (n = 49)	Before MMR*	After MMR*	p Value
Disease activity parameters			
Active joints	1 (0 to 24)	1 (0 to 14)	0.016
Limited joints	1 (0 to 12)	1 (0 to 3)	0.198
PGA	0.7 (0.0 to 2.7)	0.3 (0.0 to 1.8)	0.004
ESR	12 (2 to 32)	10 (2 to 33)	0.016
Flares			
Per patient	0 (0 to 3)	0 (0 to 2)	0.186
Patients with ≥1 flares, n (%)	13 (26.5)	21 (42.9)	0.115
Medication			
Methotrexate dose/person, mg/m^2	11 (7 to 25)	11 (0 to 22)	0.666
Oral steroid dose per person, mg/kg	0.0 (0.0 to 0.2)	0.0 (0.0 to 0.2)	0.333
Patients on NSAIDs, n (%)	45 (91.8)	44 (89.8)	1.000
Patients on intra-articular steroids, n (%)	9 (18.4)	1 (2.0)	0.008
Patients on other DMARDs, n (%)	6 (12.2)	6 (12.2)	1.000
Patients on anti-TNFα therapy, n (%)	1 (2.0)	1 (2.0)	1.000

DMARDs, disease-modifying anti-rheumatic drugs; MMR, measles, mumps and rubella; NSAIDs, non-steroidal anti-inflammatory drugs; TNF, tumour necrosis factor.

*Values are calculated for the period of 6 months before and after the MMR vaccination.

Data are median and range unless otherwise indicated; median and range are given if data are skewed.



Safety and Efficacy of Meningococcal C Vaccination in Juvenile Idiopathic Arthritis

ARTHRITIS & RHEUMATISM
Vol. 56, No. 2, February 2007, pp 639–646

Table 2. Anti-MenC IgG geometric mean concentrations and frequency in JIA patients, categorized by medication group*

	Group 1	Group 2	Group 3	Group 4
Anti-MenC IgG geometric mean concentration, μg/ml				
Before vaccination	0.38	0.41	0.32	0.36
After vaccination	41.00	46.93	17.53	16.28
Low responders (anti-MenC IgG ≤2 μg/ml), no. (%)	0	0	2 (4.7)	2 (7.7)

¿Son seguras?

- ¿Inducen EAS?
- ¿Inducen actividad de la enfermedad?
- ¿Potenciales efectos adversos en EAS?

¿Son seguras?

- ¿Inducen EAS?
- ¿Inducen actividad de la enfermedad?
- ¿Potenciales efectos adversos en EAS?

Vaccination may be Associated with Autoimmune Diseases

Moshe Tishler MD[1] and Yehuda Shoenfeld MD[2]

IMAJ 2004;6:430–432

Table 1. Autoimmune diseases reported after vaccination

Disease	Type of vaccine	Ref
Systemic lupus erythematosus	HBV, tetanus, anthrax	30
Rheumatoid arthritis	HBV, tetanus, typhoid/paratyphoid, MMR	29
Multiple sclerosis	HBV	18, 23, 24
Reactive arthritis	BCG, typhoid, DPT, MMR, HBV, influenza	15, 29, 31
Polymyositis/dermatomyositis	BCG, smallpox, diphtheria, DPT	14, 15
Polyarteritis nodosa	Influenza, pertussis, HBV	14, 15
Guillain-Barré syndrome	Influenza, polio, tetanus	16, 21, 22
Diabetes mellitus – type I	HiB	19, 26, 27
Idiopathic thrombocytopenia	MMR, HBV	14, 15

HBV = hepatitis B virus, BCG = Bacillus Calmette-Guerin, DPT = diphtheria-tetanus, MMR = measles-mumps-rubella

Vaccination and autoimmune disease: what is the evidence?

Lancet 2003; **362:** 1659–66.

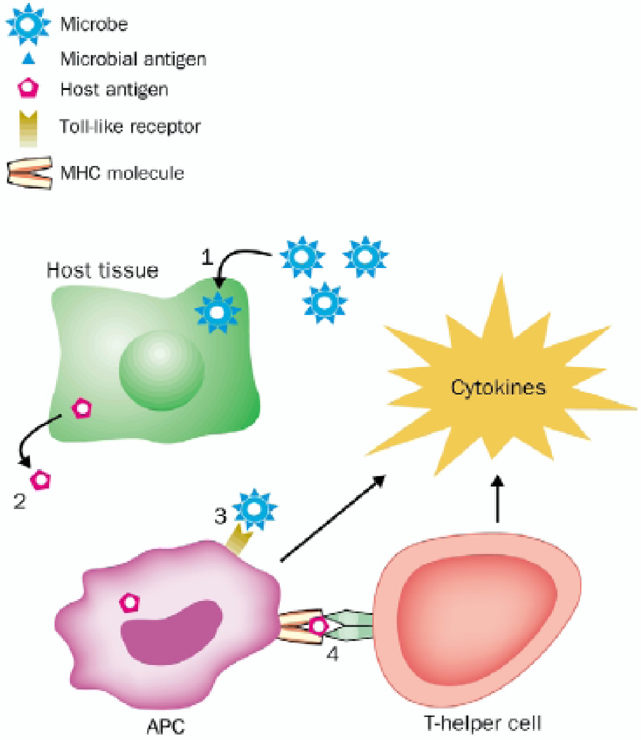
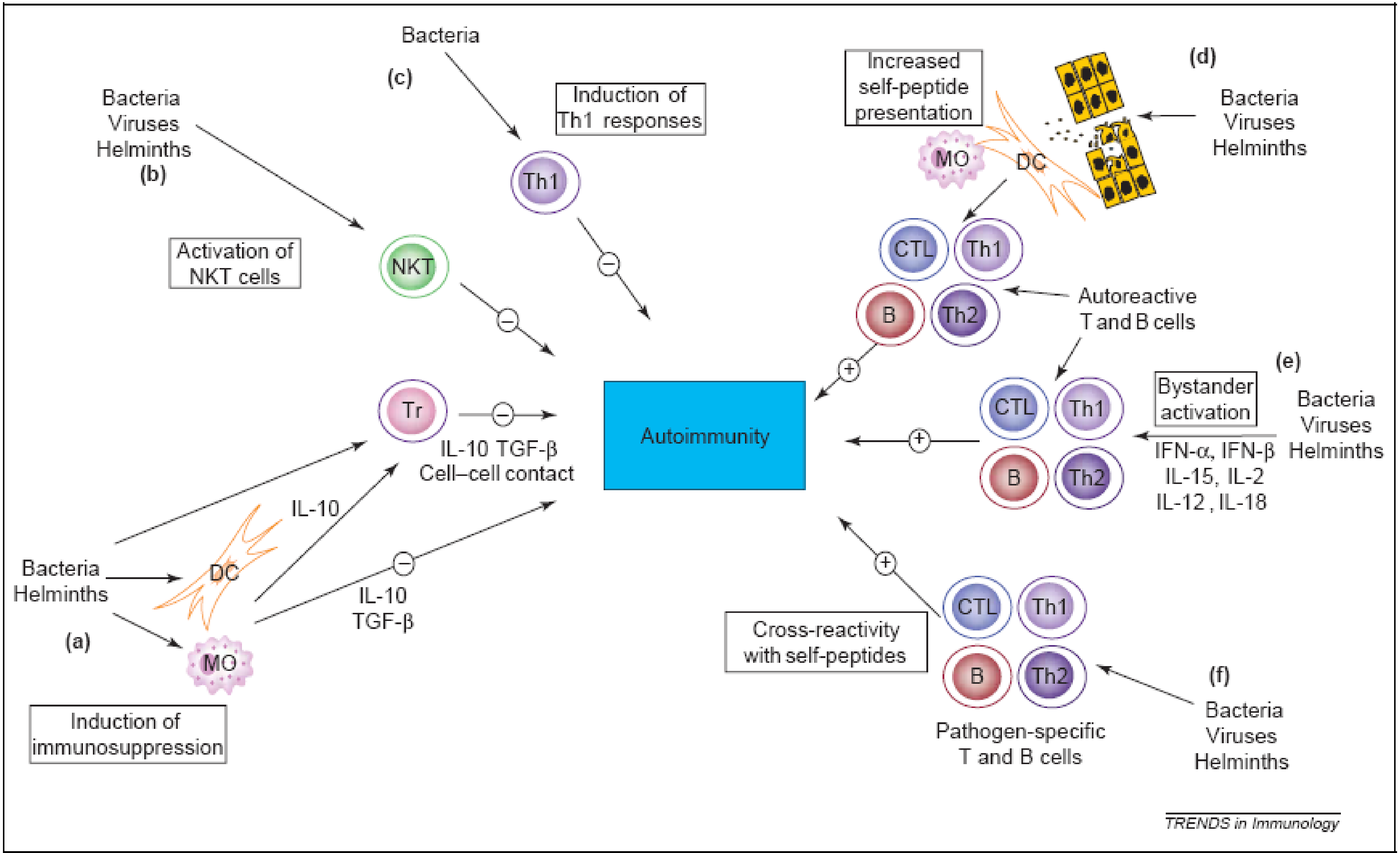


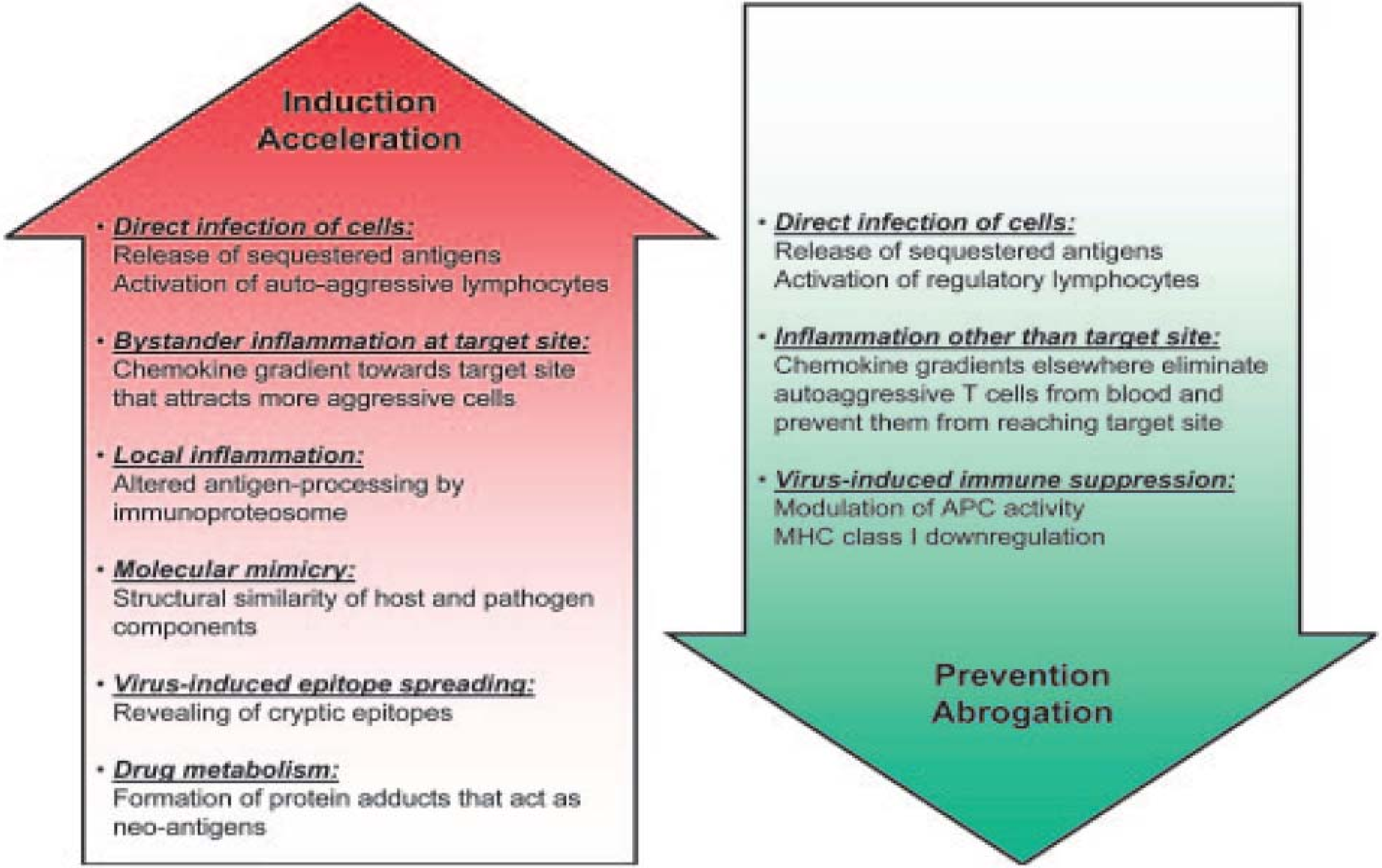
Figure 2: **Mechanisms of infection-induced autoimmunity**
APC=antigen presenting cell. Microbial infection of host tissue leads to tissue damage (1) and release of self-antigen (2). Microbial molecules engage Toll-like receptors on APCs, resulting in up-regulation of MHC and co-stimulatory molecule expression and secretion of cytokines (3). Up-regulation of self-antigen expression by APCs activates autoreactive T cells, leading to a burst of cytokine secretion, local inflammation, and recruitment of additional autoreactive lymphocytes (4).

Induction, exacerbation and inhibition of allergic and autoimmune diseases by infection

TRENDS in Immunology Vol.26 No.5 May 2005


Bacteria
(c)
Induction of Th1 responses
Th1
Bacteria
Viruses
Helminths
(b)
Activation of NKT cells
NKT
Tr
IL-10 TGF-β
Cell–cell contact
Autoimmunity
IL-10
Bacteria
Helminths
DC
(a)
MO
IL-10
TGF-β
Induction of immunosuppression
Increased self-peptide presentation
MO
DC
(d)
Bacteria
Viruses
Helminths
CTL
Th1
B
Th2
Autoreactive T and B cells
(e)
Bystander activation
Bacteria
Viruses
Helminths
CTL
Th1
B
Th2
IFN-α, IFN-β
IL-15, IL-2
IL-12 , IL-18
Cross-reactivity with self-peptides
CTL
Th1
B
Th2
Pathogen-specific T and B cells
(f)
Bacteria
Viruses
Helminths

TRENDS in Immunology



Induction
Acceleration

- ***Direct infection of cells:***
  Release of sequestered antigens
  Activation of auto-aggressive lymphocytes
- ***Bystander inflammation at target site:***
  Chemokine gradient towards target site that attracts more aggressive cells
- ***Local inflammation:***
  Altered antigen-processing by immunoproteosome
- ***Molecular mimicry:***
  Structural similarity of host and pathogen components
- ***Virus-induced epitope spreading:***
  Revealing of cryptic epitopes
- ***Drug metabolism:***
  Formation of protein adducts that act as neo-antigens

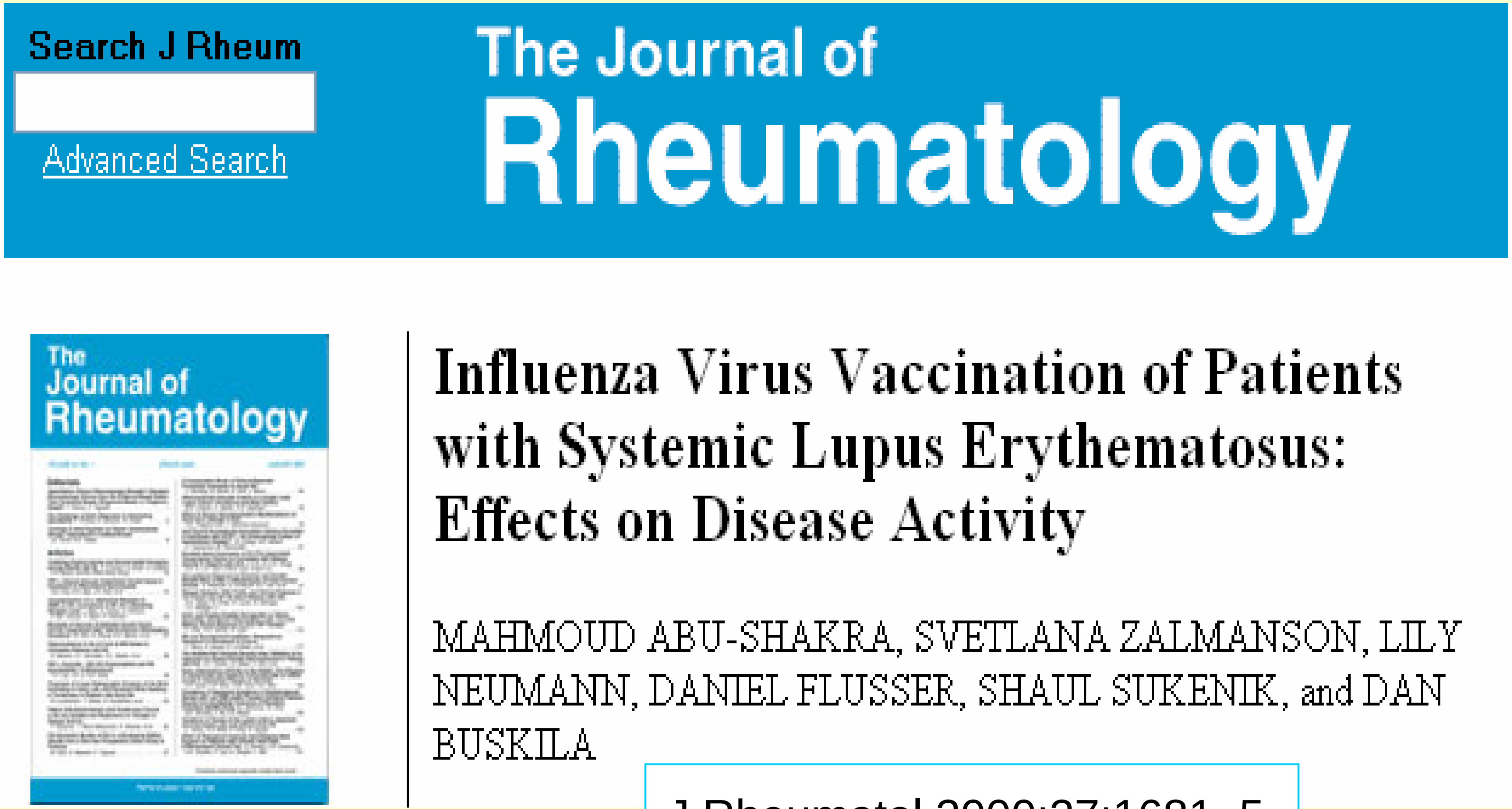
- ***Direct infection of cells:***
  Release of sequestered antigens
  Activation of regulatory lymphocytes
- ***Inflammation other than target site:***
  Chemokine gradients elsewhere eliminate autoaggressive T cells from blood and prevent them from reaching target site
- ***Virus-induced immune suppression:***
  Modulation of APC activity
  MHC class I downregulation

Prevention
Abrogation

FIGURE 2. Summary of putative mechanisms involved in the initiation or abrogation of autoimmune disorders. *Immunology*, 2005, 174: 7481–7486.

¿Son seguras?

- ¿Inducen EAS?
- **¿Inducen actividad de la enfermedad?**
- ¿Potenciales efectos adversos en EAS?



The Journal of Rheumatology

Influenza Virus Vaccination of Patients with Systemic Lupus Erythematosus: Effects on Disease Activity

MAHMOUD ABU-SHAKRA, SVETLANA ZALMANSON, LILY NEUMANN, DANIEL FLUSSER, SHAUL SUKENIK, and DAN BUSKILA

J Rheumatol 2000;27:1681–5

NO AUMENTAN EL NÚMERO NI LA GRAVEDAD DE LOS BROTES

Influenza vaccine administration in patients with systemic lupus erythematosus and rheumatoid arthritis
Safety and immunogenicity

Vaccine 24 (2006) 3217–3223

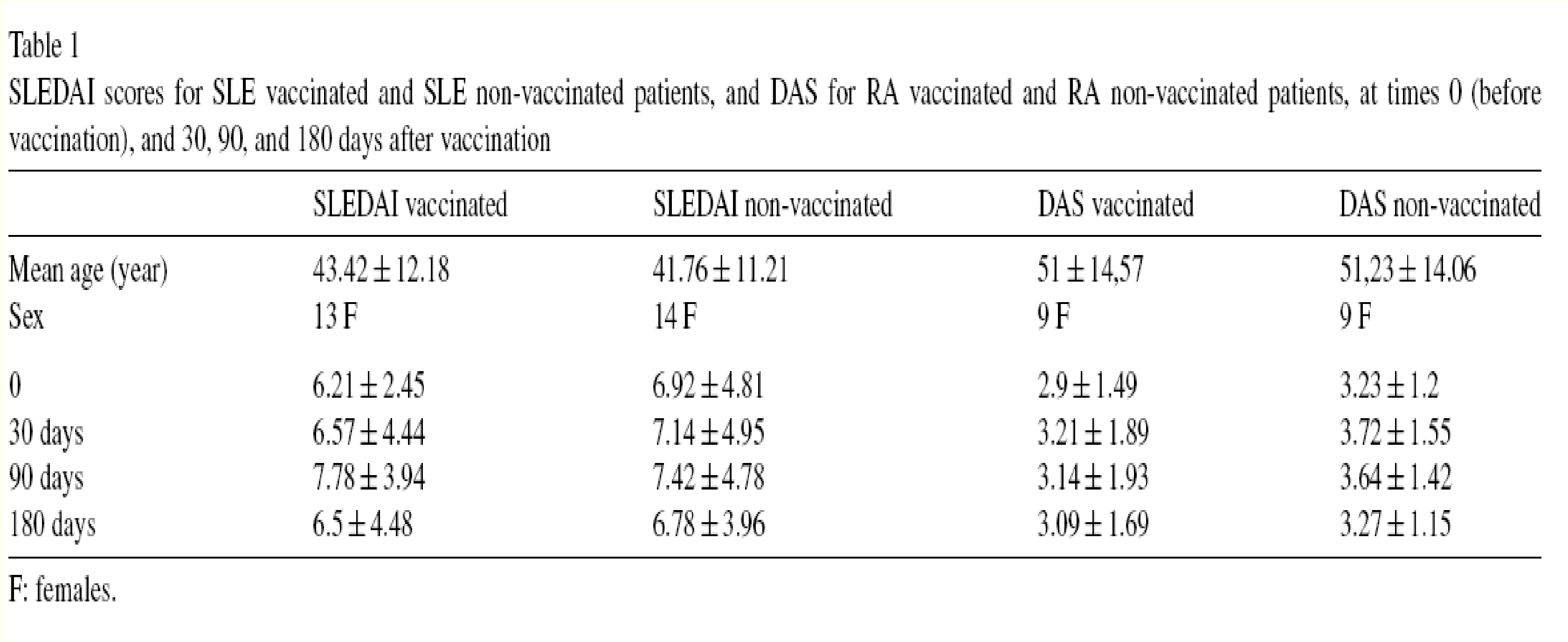
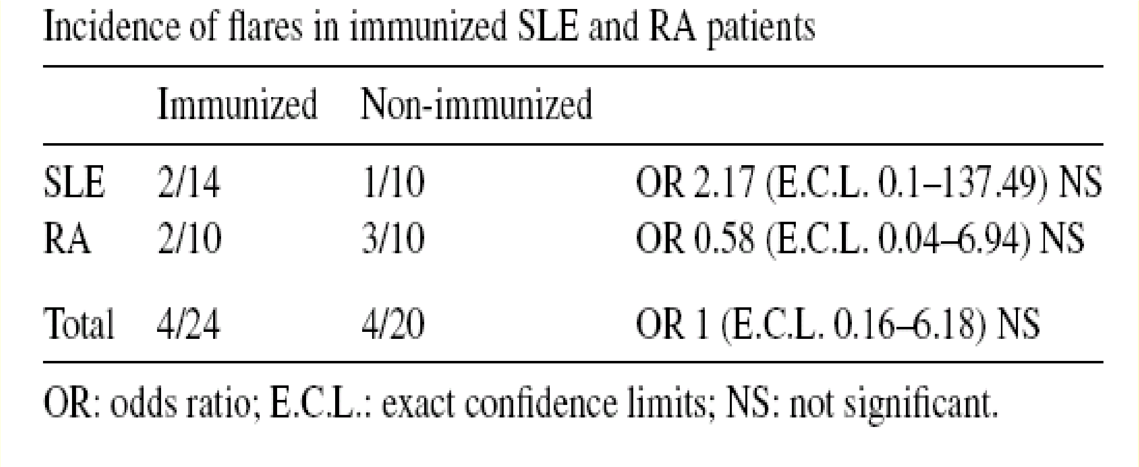


Table 1

SLEDAI scores for SLE vaccinated and SLE non-vaccinated patients, and DAS for RA vaccinated and RA non-vaccinated patients, at times 0 (before vaccination), and 30, 90, and 180 days after vaccination

	SLEDAI vaccinated	SLEDAI non-vaccinated	DAS vaccinated	DAS non-vaccinated
Mean age (year)	43.42 ± 12.18	41.76 ± 11.21	51 ± 14,57	51,23 ± 14.06
Sex	13 F	14 F	9 F	9 F
0	6.21 ± 2.45	6.92 ± 4.81	2.9 ± 1.49	3.23 ± 1.2
30 days	6.57 ± 4.44	7.14 ± 4.95	3.21 ± 1.89	3.72 ± 1.55
90 days	7.78 ± 3.94	7.42 ± 4.78	3.14 ± 1.93	3.64 ± 1.42
180 days	6.5 ± 4.48	6.78 ± 3.96	3.09 ± 1.69	3.27 ± 1.15

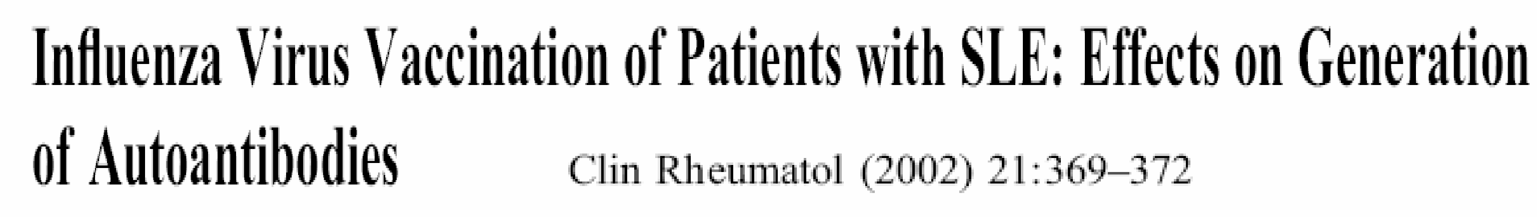
F: females.



Incidence of flares in immunized SLE and RA patients

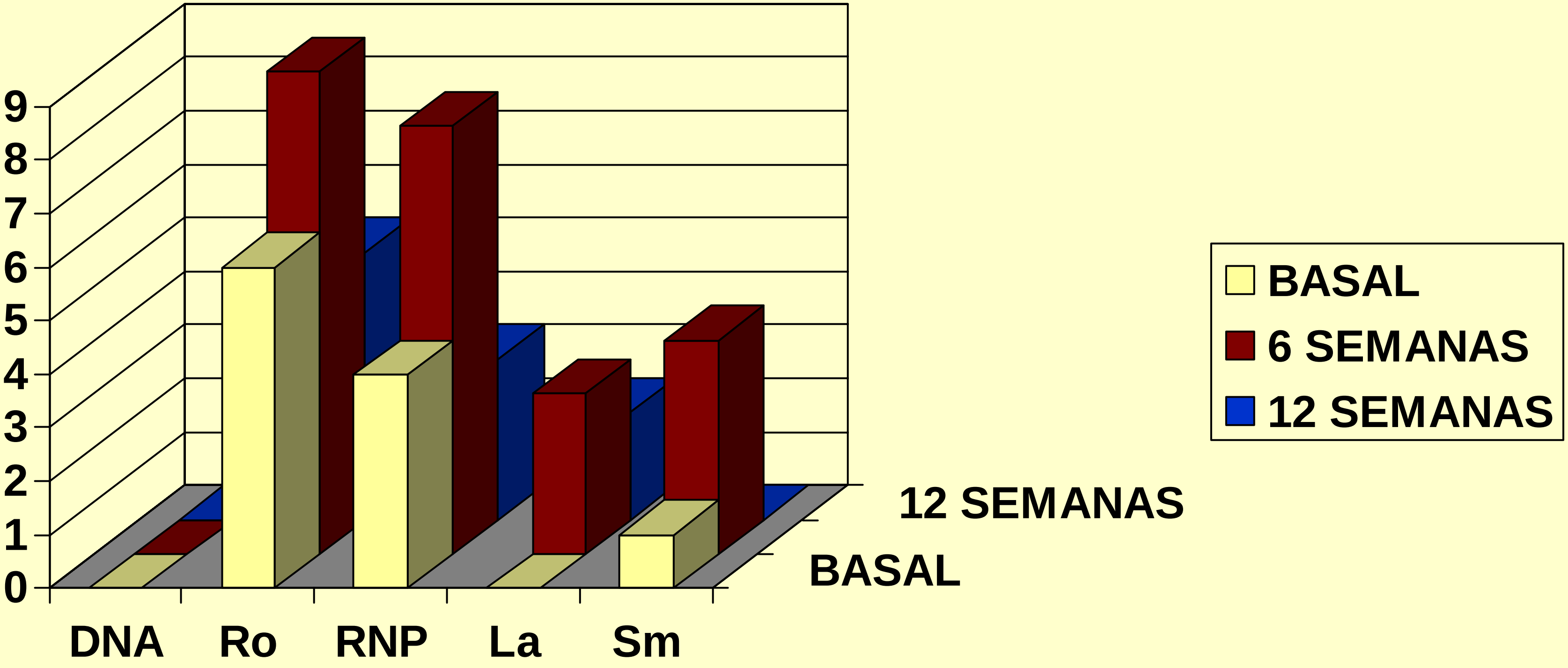
	Immunized	Non-immunized	
SLE	2/14	1/10	OR 2.17 (E.C.L. 0.1–137.49) NS
RA	2/10	3/10	OR 0.58 (E.C.L. 0.04–6.94) NS
Total	4/24	4/20	OR 1 (E.C.L. 0.16–6.18) NS

OR: odds ratio; E.C.L.: exact confidence limits; NS: not significant.



Influenza Virus Vaccination of Patients with SLE: Effects on Generation of Autoantibodies

Clin Rheumatol (2002) 21:369–372



Sin significación clínica

¿Son seguras?

- ¿Inducen EAS?
- ¿Inducen actividad de la enfermedad?
- **¿Potenciales efectos adversos en EAS?**

¿EFECTOS SECUNDARIOS PARTICULARES EN E.A.S.?

- **NO DEMOSTRADA MAYOR EFECTOS SECUNDARIOS**
- **MEJOR TOLERANCIA EFECTOS SECUNDARIOS LEVES**
- **DESCRITOS CASOS POTENCIALMENTE MÁS GRAVES QUE EN LA POBLACIÓN GENERAL**

RECOMENDACIONES VACUNACIÓN

HIDROXICLOROQUINA
PREDNISONA < 20 MG /D

GRIPE
NEUMOCOCO

CUANTIFICAR

TOXOIDES
VHB

PREDNISONA >20 MG/ D
AZATIOPRINA
ANTI-TNF

CALENDARIO
INFANTIL

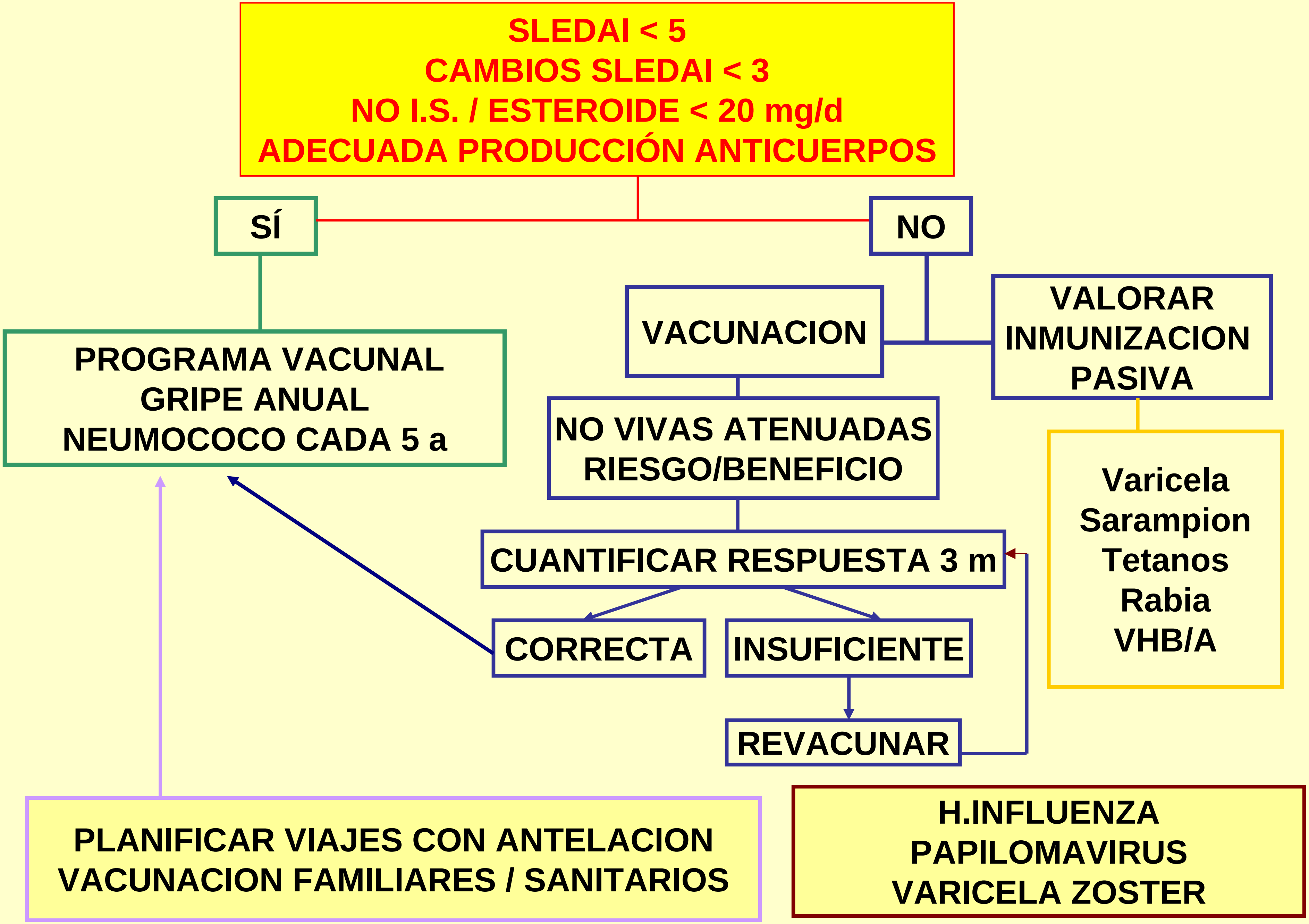
CICLOSPORINA?
MICOFENOLATO?
CICLOFOSFAMIDA?

VIVAS
ATENUADAS

METOTREXATE

REVACUNAR

RITUXIMAB
ABATACEPT



SLEDAI < 5
CAMBIOS SLEDAI < 3
NO I.S. / ESTEROIDE < 20 mg/d
ADECUADA PRODUCCIÓN ANTICUERPOS

SÍ

PROGRAMA VACUNAL
GRIPE ANUAL
NEUMOCOCO CADA 5 a

NO

VACUNACION

NO VIVAS ATENUADAS
RIESGO/BENEFICIO

CUANTIFICAR RESPUESTA 3 m

CORRECTA

INSUFICIENTE

REVACUNAR

VALORAR
INMUNIZACION
PASIVA

Varicela
Sarampion
Tetanos
Rabia
VHB/A

PLANIFICAR VIAJES CON ANTELACION
VACUNACION FAMILIARES / SANITARIOS

H.INFLUENZA
PAPILOMAVIRUS
VARICELA ZOSTER

CONCLUSIONES

- VACUNAR ANTES DE INMUNOSUPRIMIR
- MONITORIZAR RESPUESTA
  - REVACUNAR
- POLIVALENTES
- EVITAR VIVAS ATENUADAS
  - BROTE
  - USO DE INMUNOSUPRESORES
  - Embarazadas
- VIGILANCIA CLÍNICA POSTVACUNAL
  - NO DEMOSTRADO MÁS RIESGO
- INMUNIDAD DE GRUPO

VACCINATION

Rheumatology 2006;45:9–10

Editorial

Vaccinate your immunocompromised patients!

T. Glück