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MENACTRIMS
Middle East North Africa Committee for Treatment and Research in Multiple Sclerosis

5th MENACTRIMS CONGRESS

December 6-7, 2019
Intercontinental Dubai Festival City
Dubai, United Arab Emirates

In collaboration with

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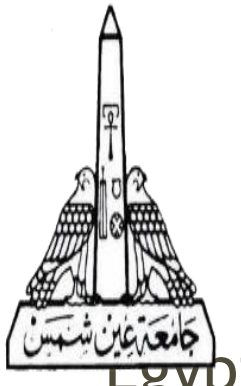
Immunization In MS



Magd Zakaria
Professor of Neurology
Ain Shams University,
Egypt

Disclosures and Disclaimer

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Prof. Magd Zakaria has received honoraria for lectures and advisory boards from:

- Bayer Schering
- Biogen (Biologix).
- Merck Serono.
- Novartis
- Roche
- Sanofi-Genzyme

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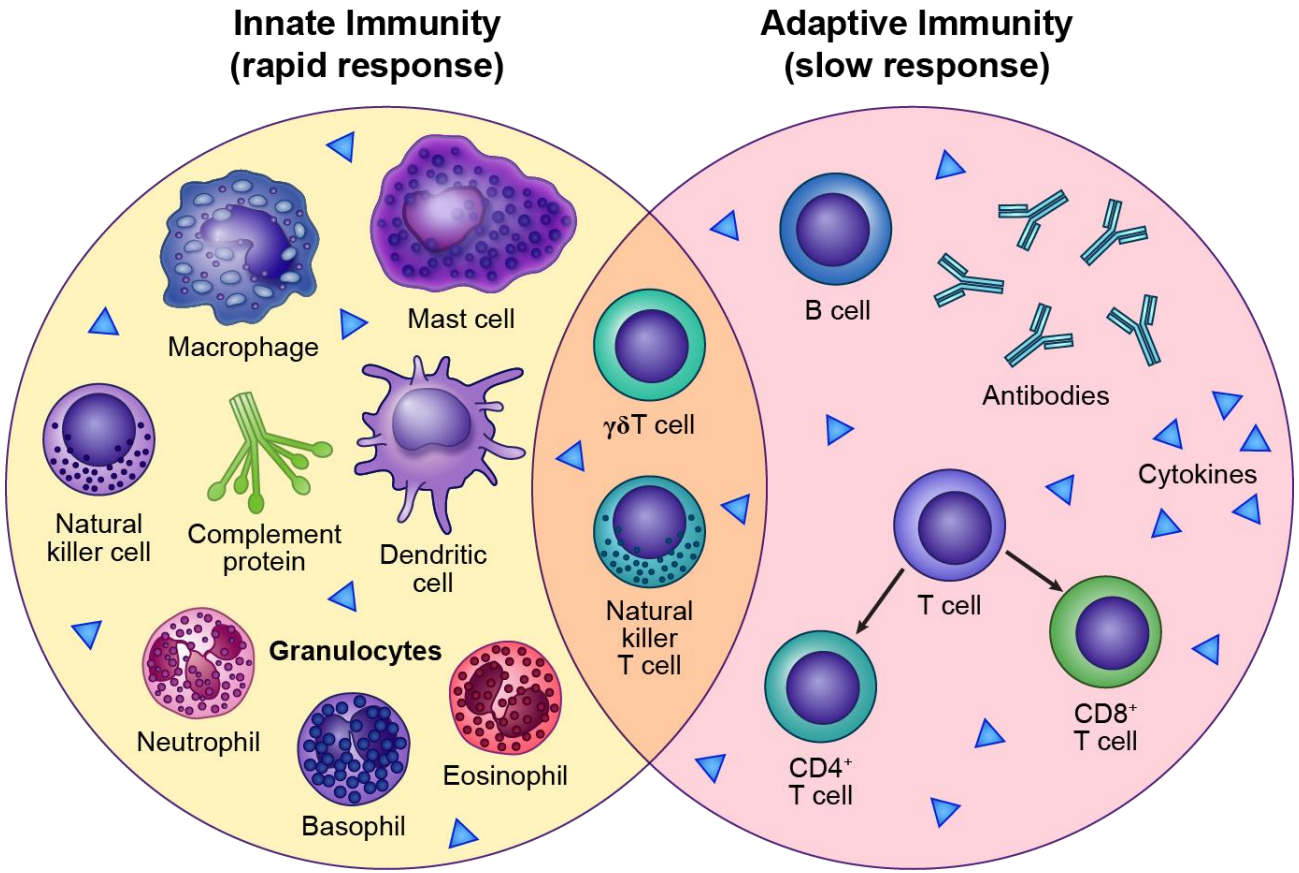
Basic Immunology

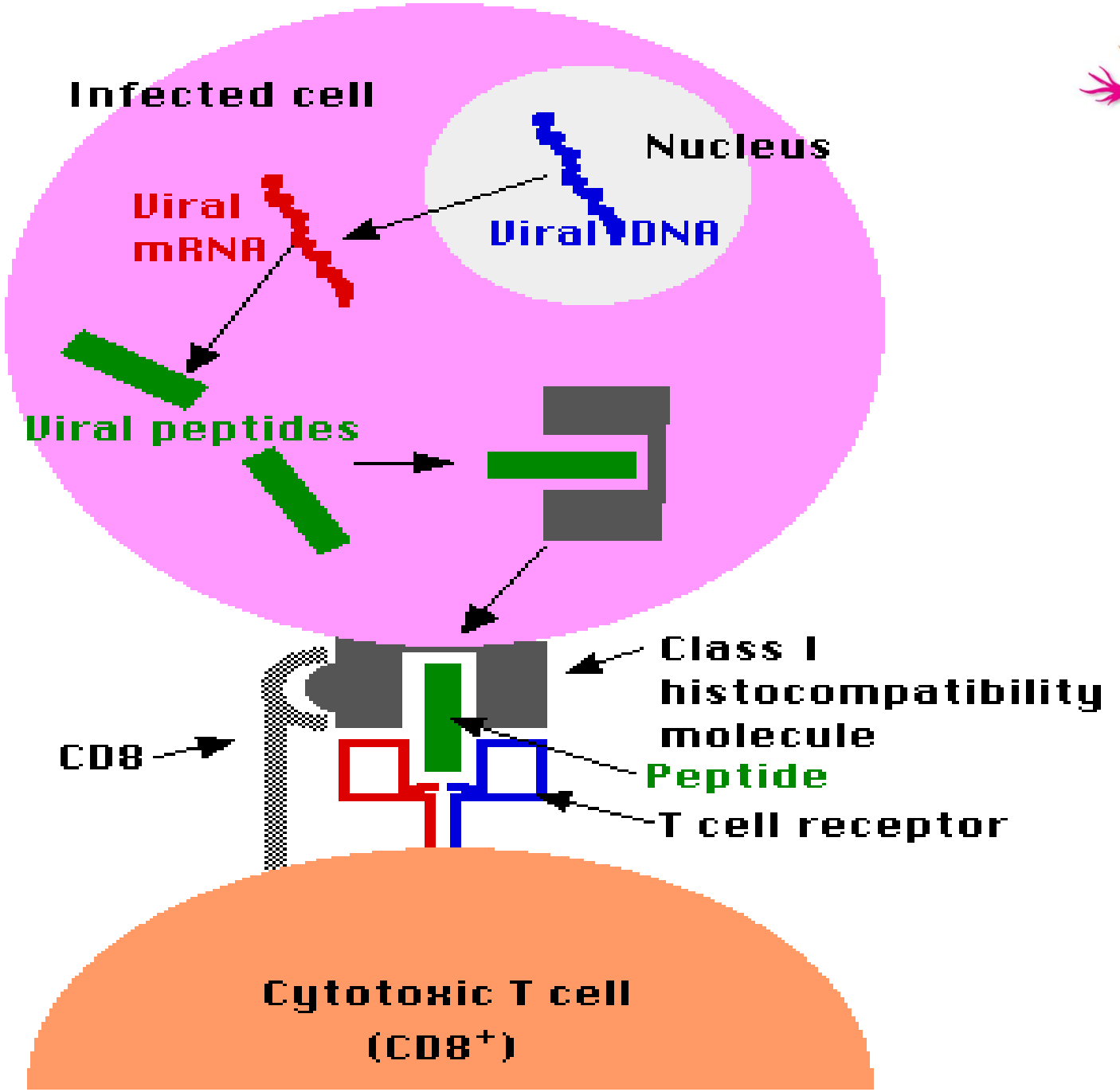
Non specific with no memory

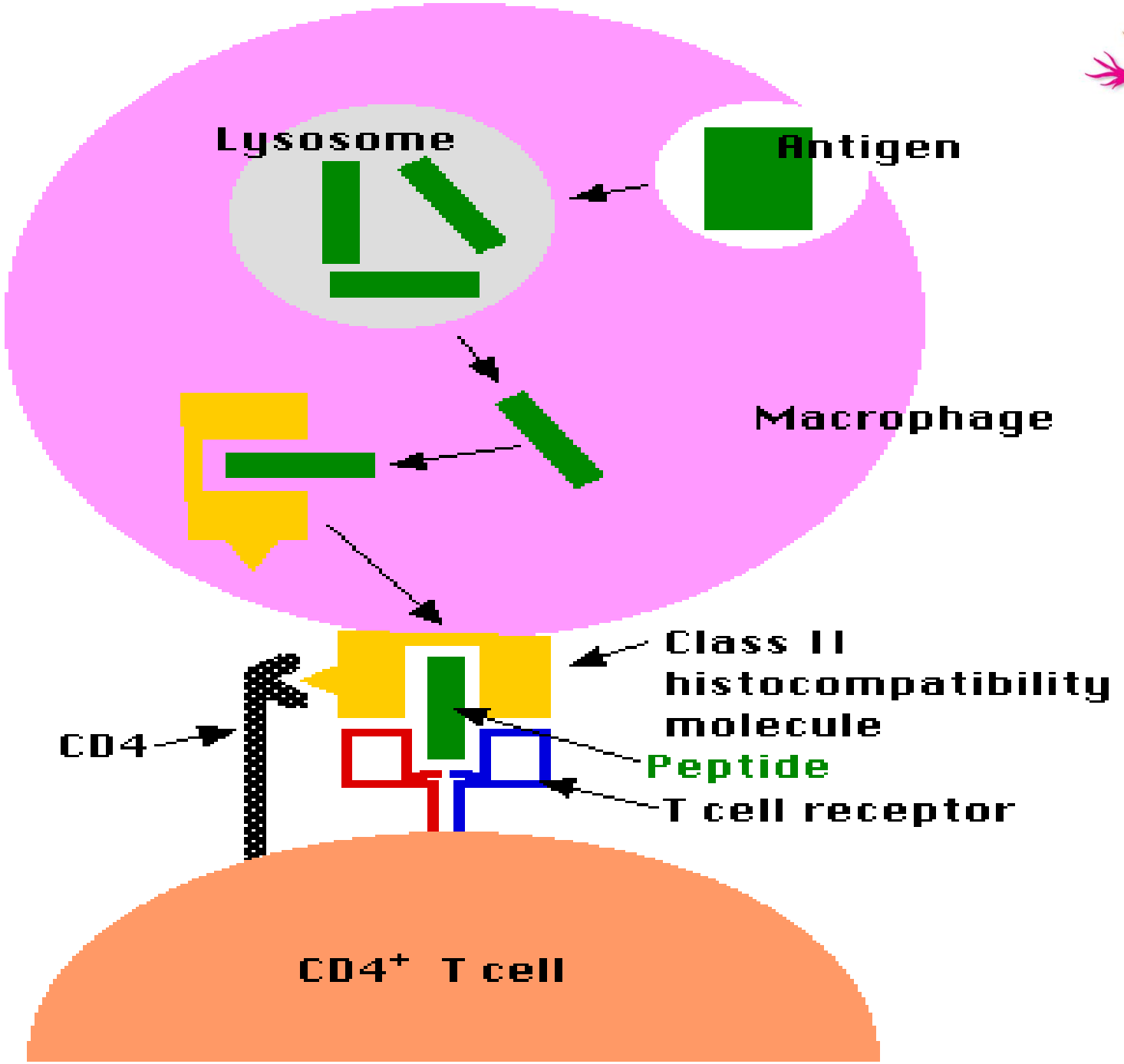
Specific with memory

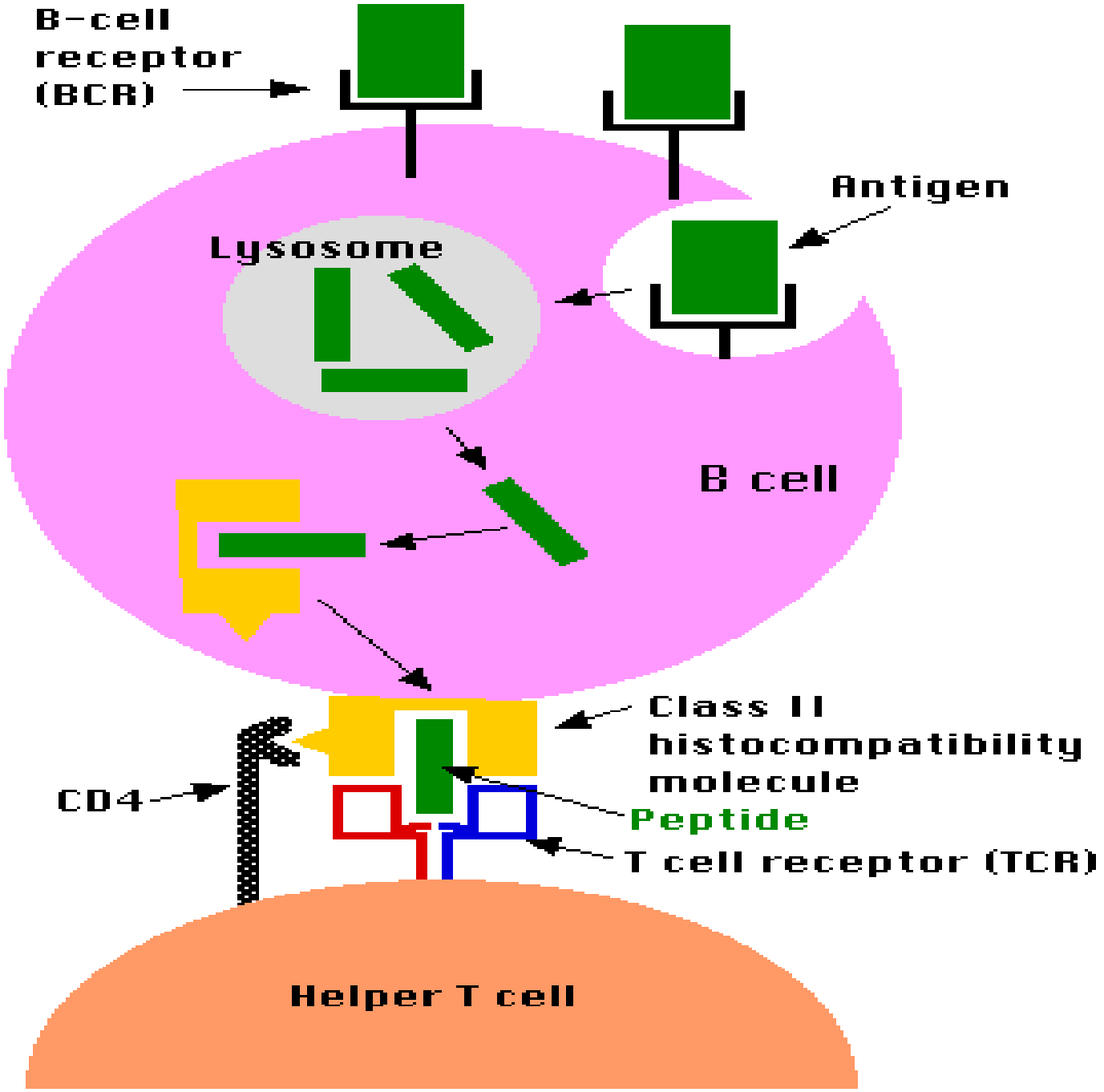
Innate vs adaptive immunity

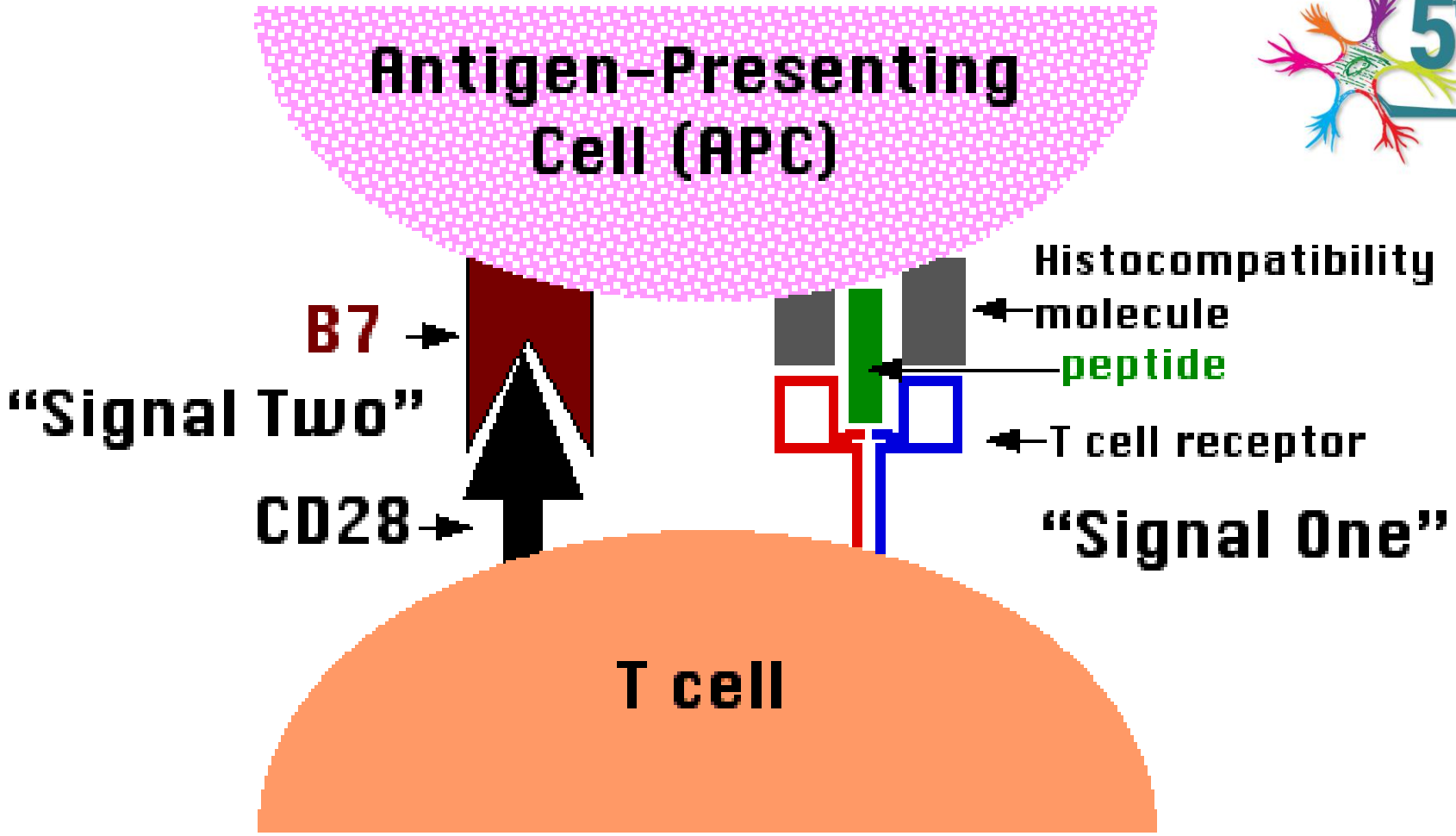


Dranoff G. *Nat Rev Cancer.* 2004;4:11-22.[1]

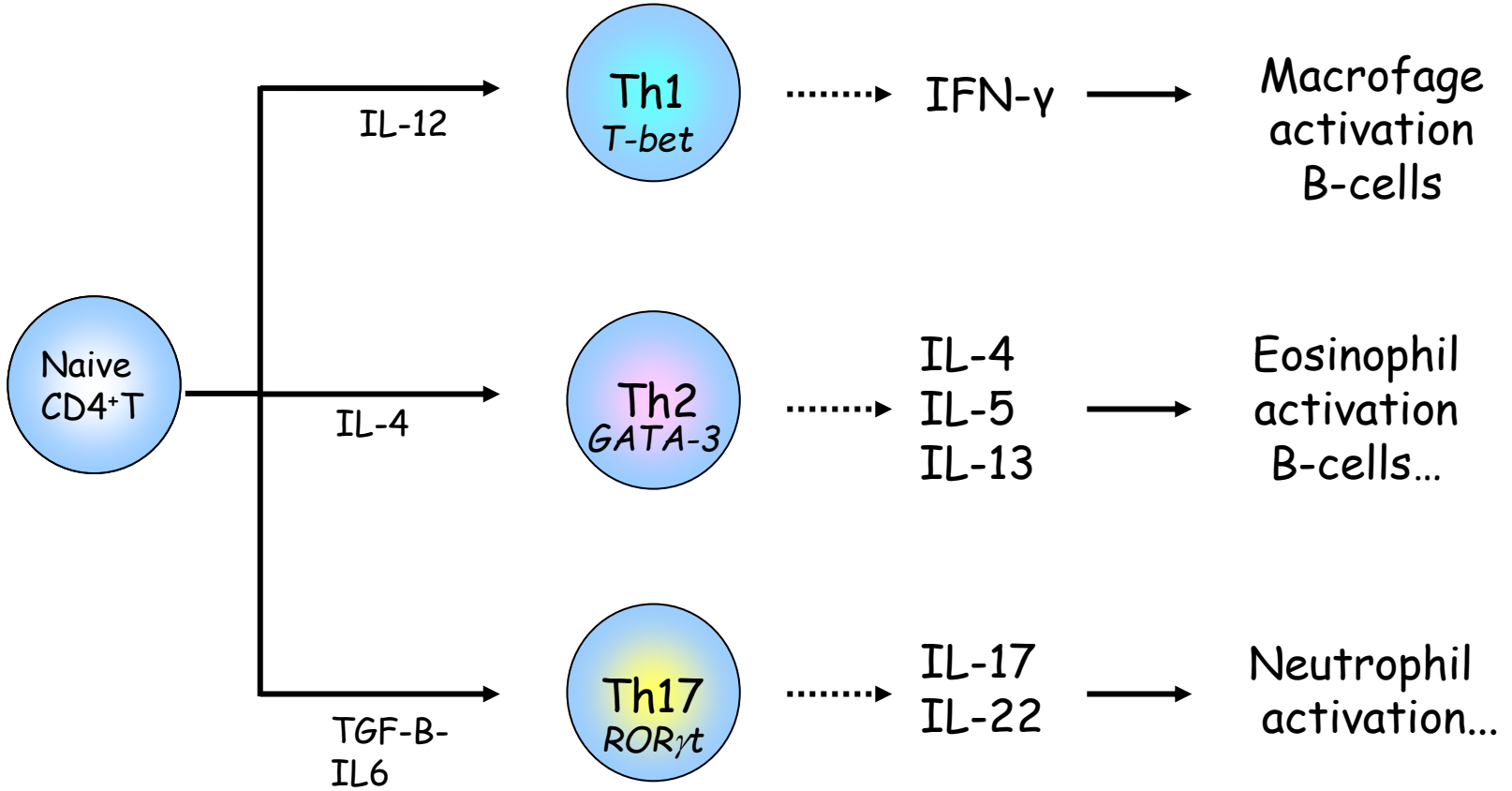

Infected cell
Nucleus
Viral mRNA
Viral DNA
Viral peptides
Class I histocompatibility molecule
CD8
Peptide
T cell receptor
Cytotoxic T cell
(CD8+)


Lysosome
Antigen
Macrophage
Class II histocompatibility molecule
CD4
Peptide
T cell receptor
CD4+ T cell


B-cell receptor (BCR)
Antigen
Lysosome
B cell
Class II histocompatibility molecule
CD4
Peptide
T cell receptor (TCR)
Helper T cell



One method of the "co-stimulation" needed to activate T cells. If the T cell fails to receive "signal two", it dies by apoptosis. (B7 comes in two forms: B7-1 [CD80] and B7-2 [CD86].


Naive CD4+T
IL-12
Th1
T-bet
IFN-γ
Macrofage activation
B-cells
IL-4
Th2
GATA-3
IL-4
IL-5
IL-13
Eosinophil activation
B-cells…
TGF-B-
IL6
Th17
RORγt
IL-17
IL-22
Neutrophil activation…

T Cell Activation

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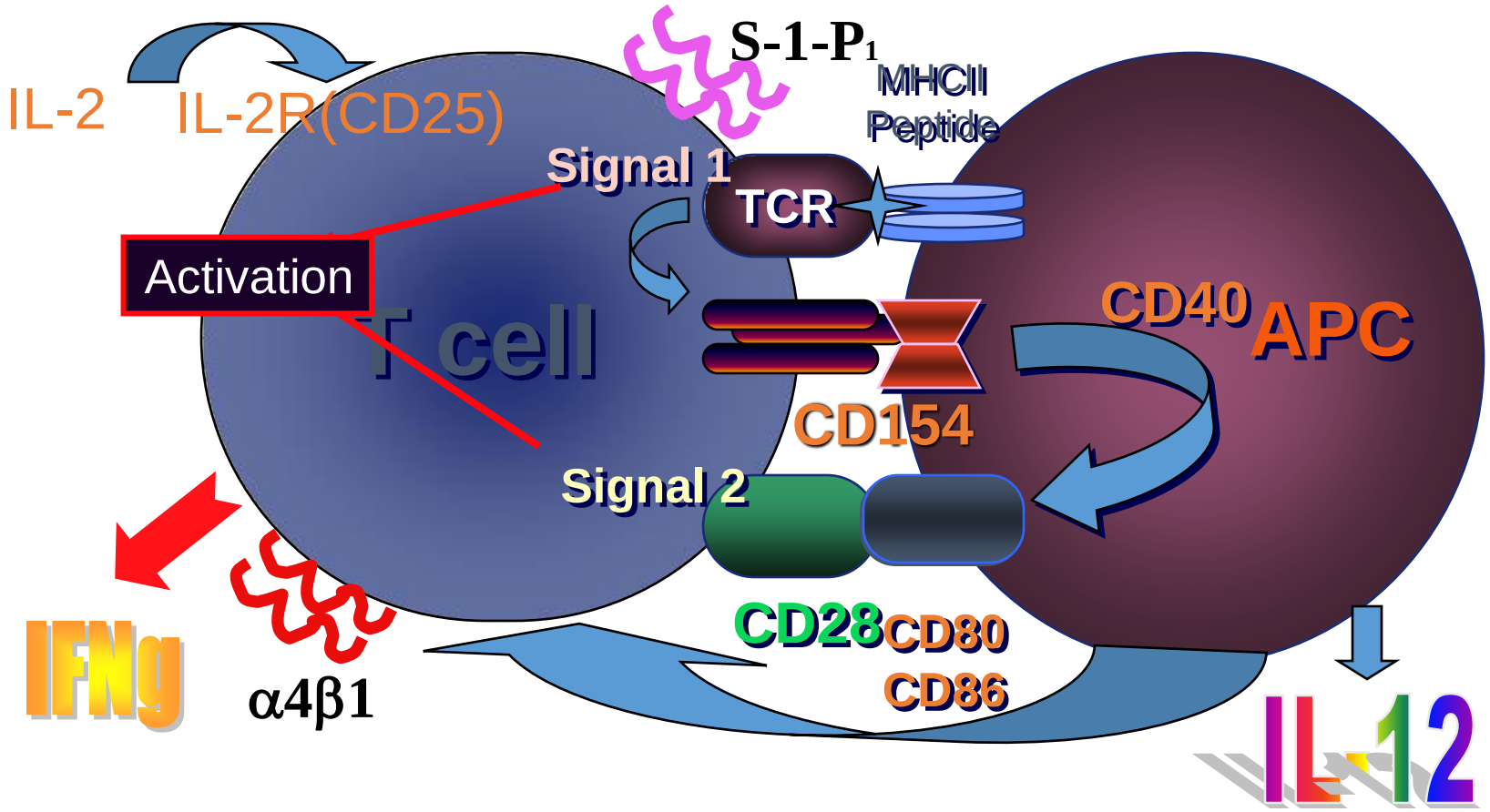

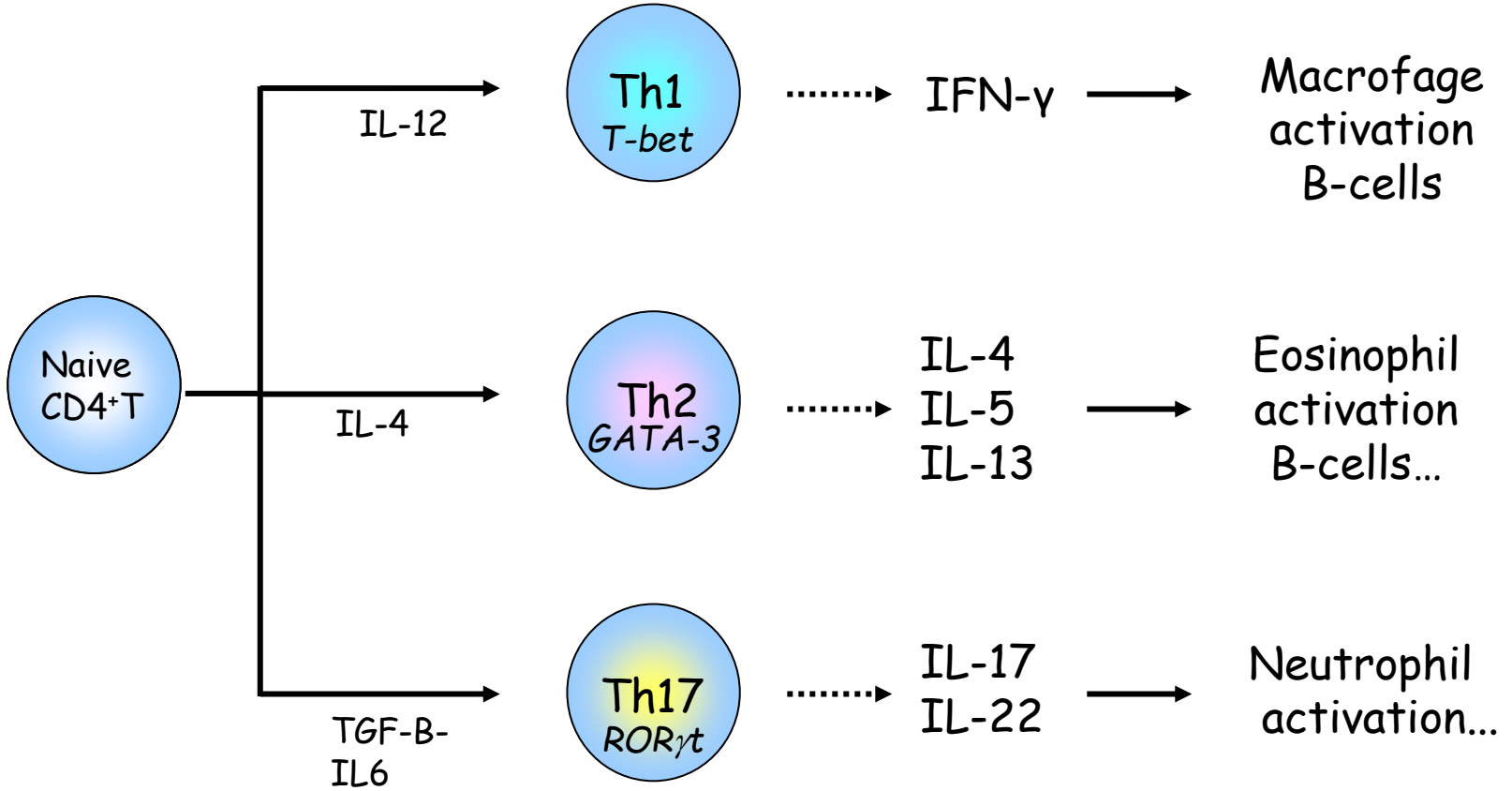
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IL-5
IL-13
Eosinophil activation
B-cells…
TGF-B-
IL6
Th17
RORγt
IL-17
IL-22
Neutrophil activation…

B cells express different surface markers throughout development

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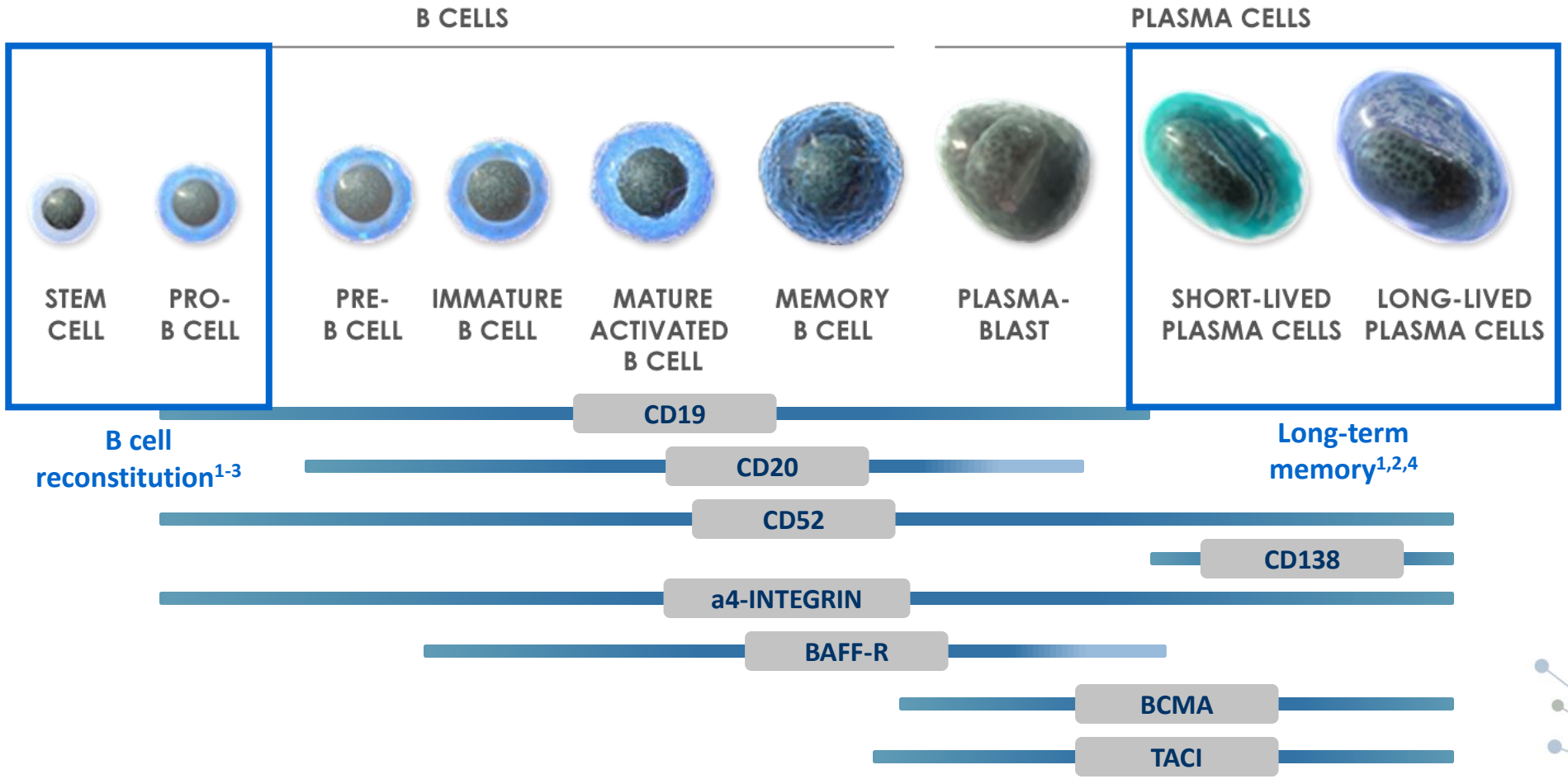
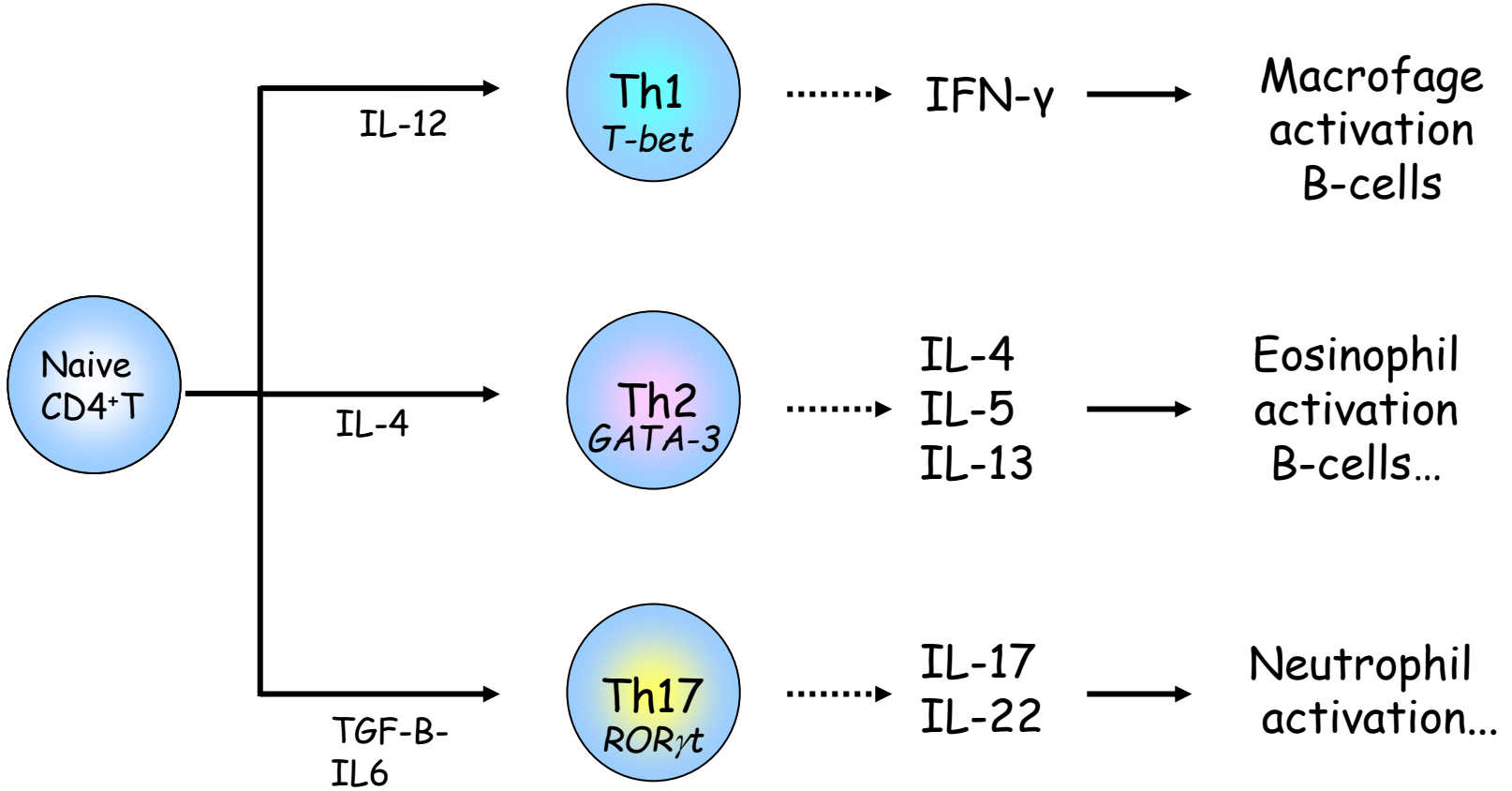


BAFF, B cell activating factor; BCMA, B cell maturation antigen; TACI, transmembrane activator and calcium-modulator and cytophilin ligand interactor

Image adapted from Krumbholz M, *et al*. *Nat Rev Neurol* 2012;8:613-23.

1. Stashenko P, *et al*. *J Immunol* 1980;125:1678-85. **2.** Loken MR, *et al*. *Blood* 1987;70:1316-24. **3.** Tedder TF, Engel P. *Immunol Today* 1994;15:450-4; **4.** Dilillo DJ, *et al*. *J Immunol* 2008;180:361-71.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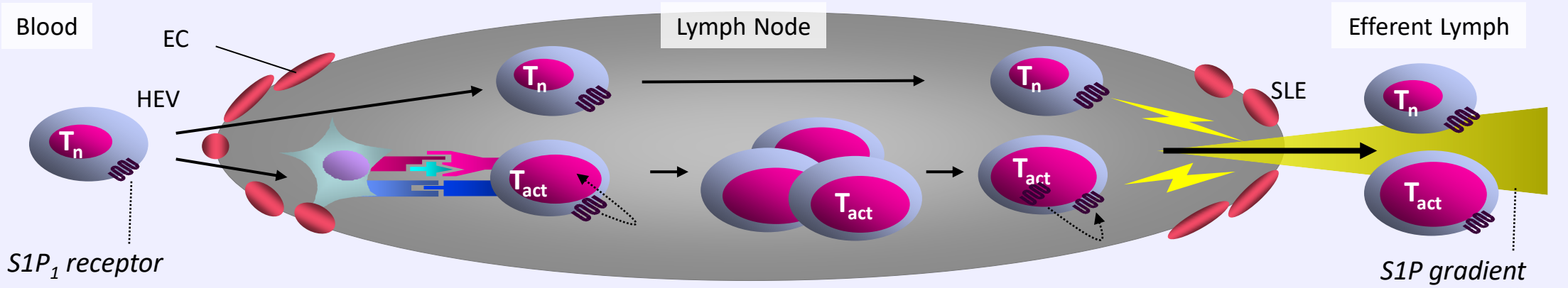
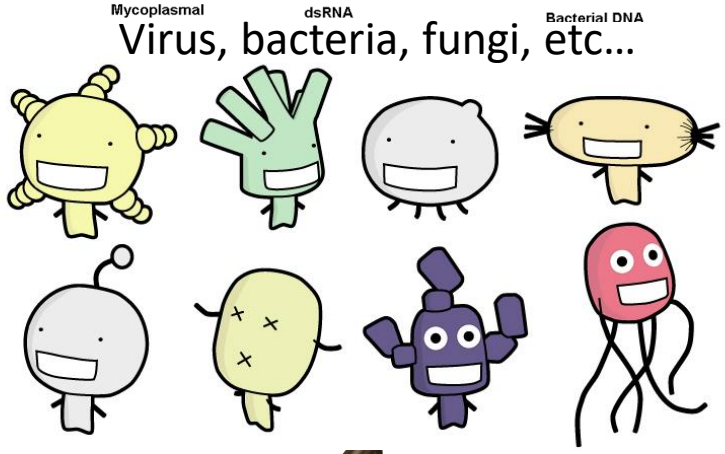
IL-13
Eosinophil activation
B-cells…
TGF-B-
IL6
Th17
RORγt
IL-17
IL-22
Neutrophil activation…

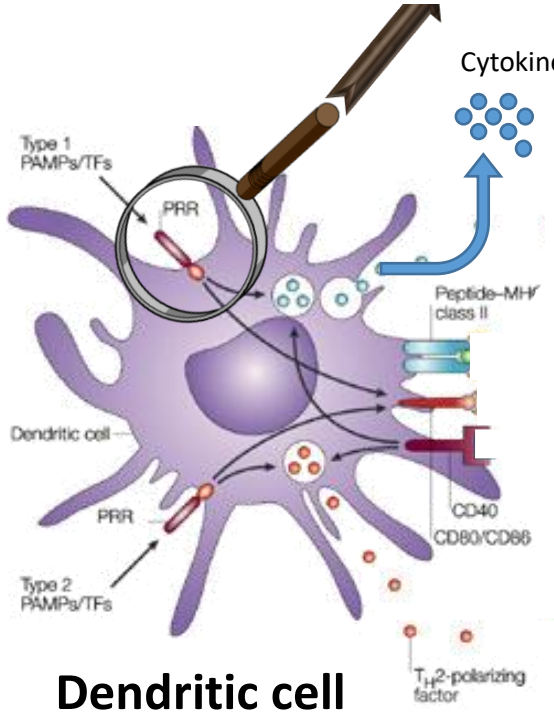
Regulation of Lymphocyte Egress from Lymph Nodes

Physiological role of $S1P_1$ during the induction of an immune response



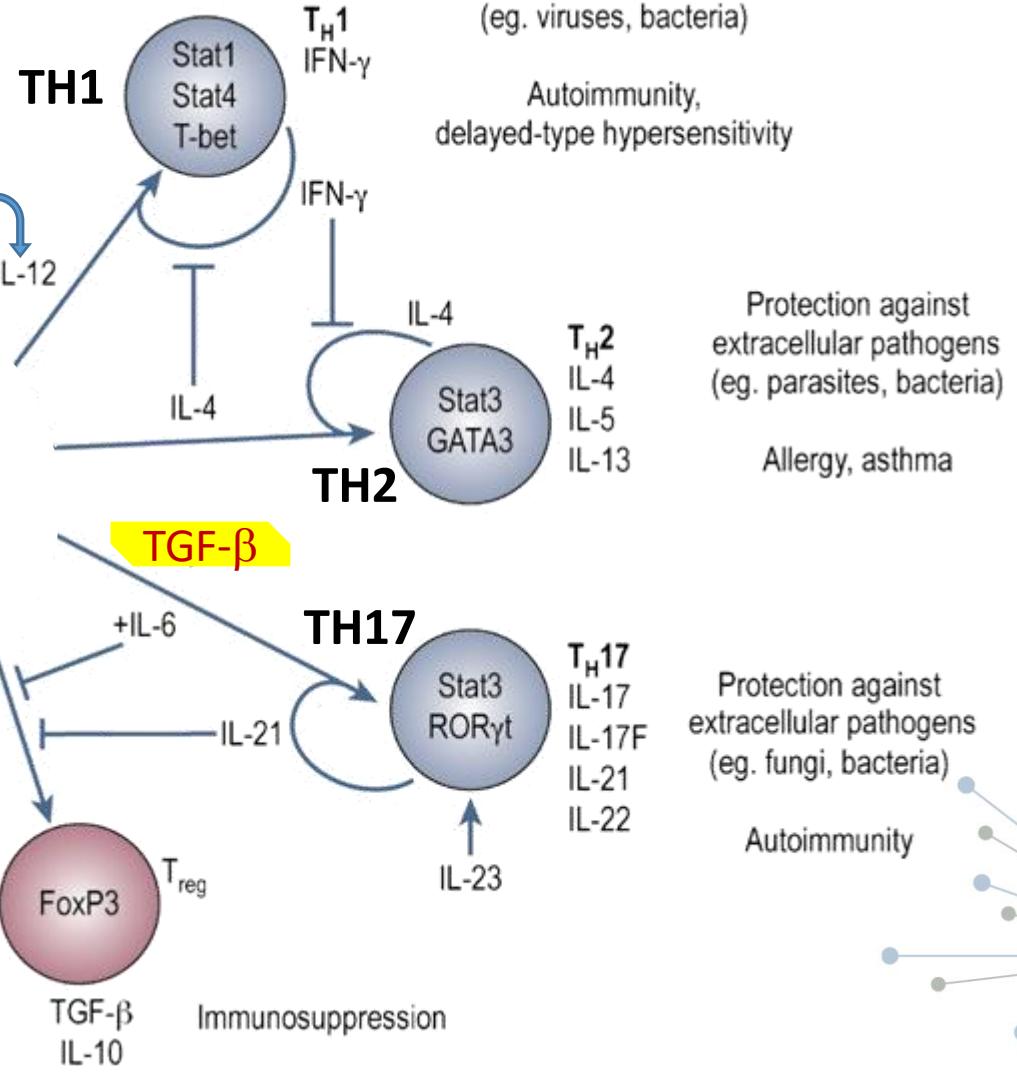
Virus, bacteria, fungi, etc…





Dendritic cell

Cytokines (TNF-a, IL-6, IL-12, etc.)



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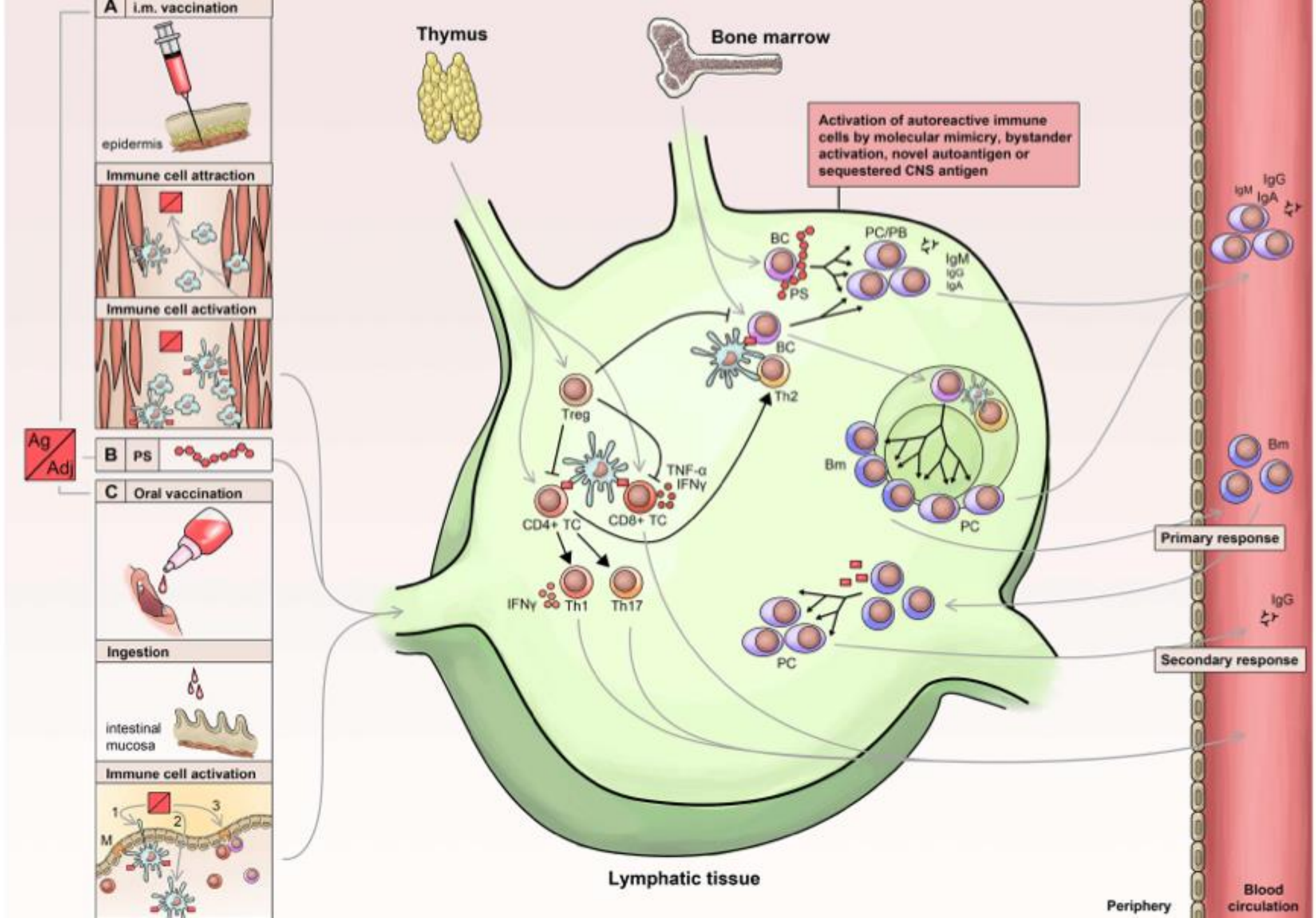
Vaccine Immunology

What is a Vaccine?

- A vaccine is an antigenic material that stimulate adaptive immunity to a disease. Vaccines can prevent the effects of infection by many pathogens. Vaccine's are generally considered to be the most effective method of preventing infectious diseases. The material administered can either be live but weakened forms of either bacteria or viruses, killed or inactivated forms of these pathogens, or purified material such as proteins.


A i.m. vaccination
epidermis
Immune cell attraction
Immune cell activation
Ag
Adj
B PS
C Oral vaccination
Ingestion
intestinal mucosa
Immune cell activation
1
2
3
M
Thymus
Bone marrow
Activation of autoreactive immune cells by molecular mimicry, bystander activation, novel autoantigen or sequestered CNS antigen
BC
PC/PB
PS
IgM IgG IgA
BC
Th2
Treg
TNF-α IFNγ
CD4+ TC
CD8+ TC
IFNγ
Th1
Th17
Bm
PC
PC
IgM IgG IgA
Bm
Primary response
IgG
Secondary response
Lymphatic tissue
Periphery
Blood circulation

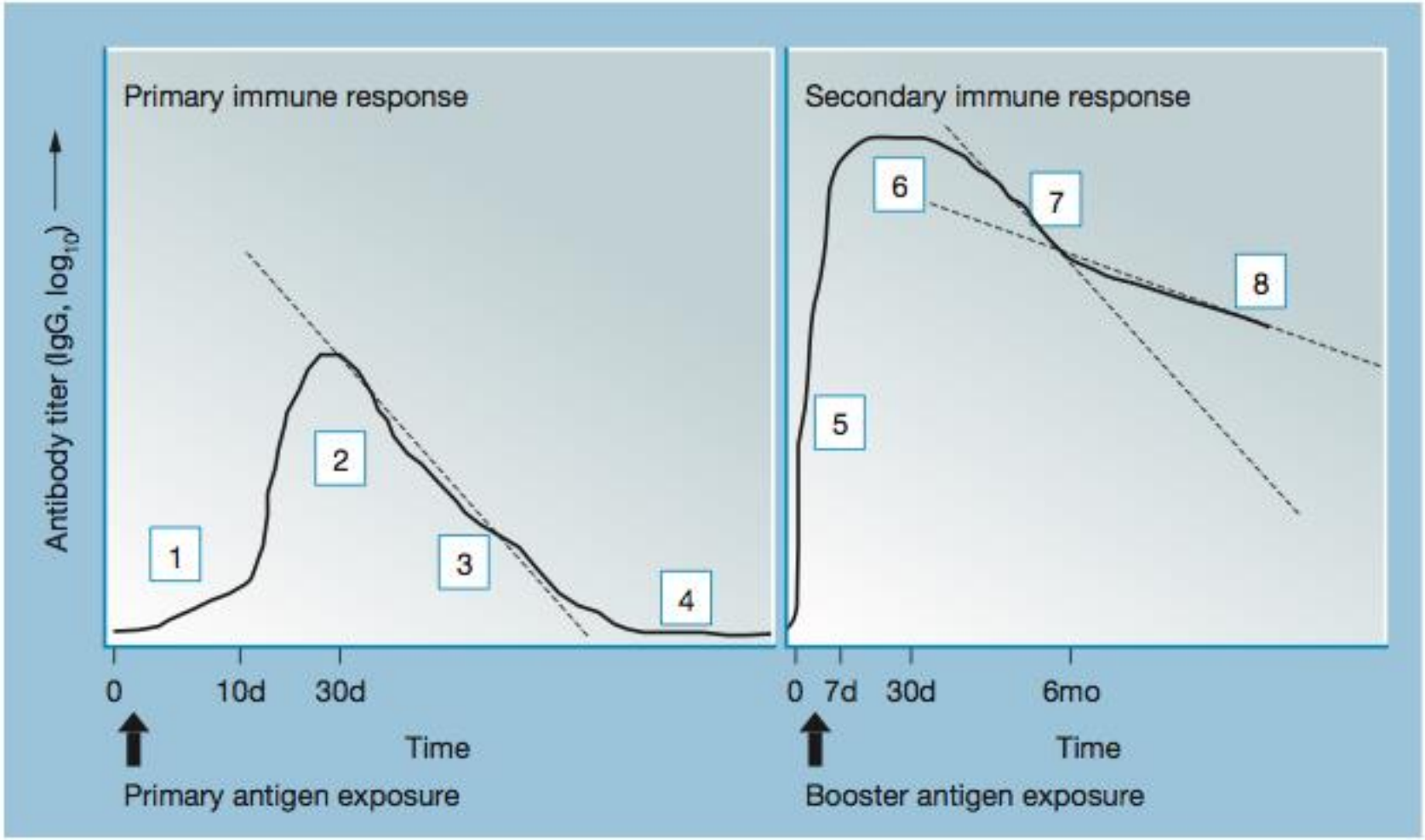


Figure 2.3. Correlation of antibody titers to the various phases of the vaccine response. The initial antigen exposure elicits an extrafollicular response *(1)* that results in the rapid appearance of low IgG antibody titers. As B cells proliferate in germinal centers and differentiate into plasma cells, IgG antibody titers increase up to a peak value *(2)*, usually reached 4 weeks after immunization. The short life span of these plasma cells results in a rapid decline of antibody titers *(3)*, which eventually return to baseline levels *(4)*. In secondary immune responses, booster exposure to antigen reactivates immune memory and results in a rapid (<7 days) increase *(5)* of IgG antibody titer. Short-lived plasma cells maintain peak antibody levels *(6)* during a few weeks—after which serum antibody titers decline initially with the same rapid kinetics as following primary immunization *(7)*. Long-lived plasma cells that have reached survival niches in the bone marrow continue to produce antigen-specific antibodies, which then decline with slower kinetics *(8)*. Note: This generic pattern may not apply to live vaccines triggering long-term IgG antibodies for extended periods.

Immunity

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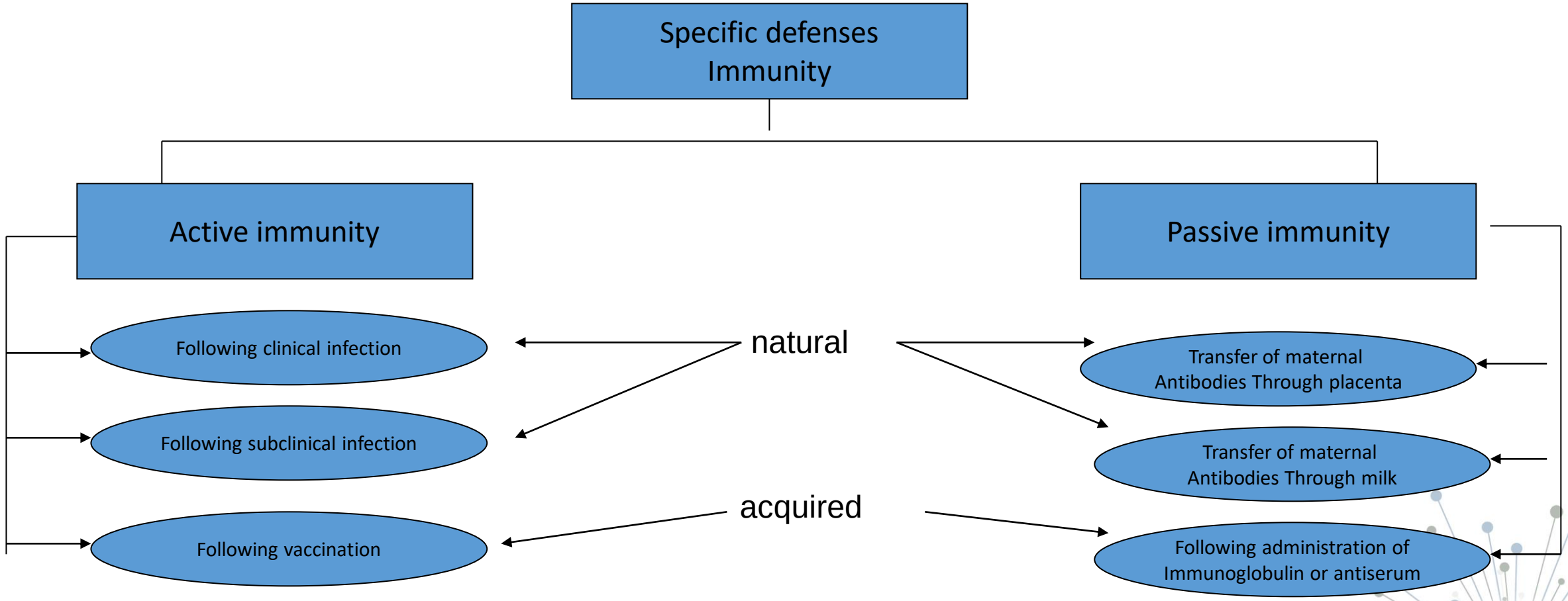

Types of vaccines

	Live Attenuated vaccines	Killed Inactivated vaccines	Toxoids	Cellular fraction vaccines	Recombinant vaccines
	•BCG •Typhoid oral •Plague •Oral polio (sabin). •Yellow fever •Measles •Mumps •Rubella •Intranasal Influenza •Typhus •Varicella •Zoster	•Typhoid •Cholera •Pertussis •Plague •Rabies •Salk polio •Intra-muscular influenza •Japanese encephalitis •Hepatitis A	•Diphtheria •Tetanus	•Meningococcal polysaccharide vaccine •Pneumococcal polysaccharide vaccine •Hepatitis B polypeptide vaccine	•Hepatitis B vaccine •Zoster •HPV •Meningococcal B

COMPARISON OF ATTENUATED (LIVE) AND INACTIVATED (KILLED) VACCINES

Characteristic	Attenuated vaccine	Inactivated vaccine
Production	Selection for avirulent organisms: virulent pathogen is grown under adverse culture conditions or prolonged passage of a virulent human pathogen through different hosts	Virulent pathogen is inactivated by chemicals or irradiation with γ-rays
Booster requirement	Generally requires only a single booster	Requires multiple boosters
Relative stability	Less stable	More stable (advantageous for Third World countries where refrigeration is limited)
Type of immunity induced	Produces humoral and cell-mediated immunity	Produces mainly humoral immunity
Reversion tendency	May revert to virulent form	Cannot revert to virulent form

Site and Route of administration Generalized response Primary focal LN responce

J Neurol (2017) 264:1035–1050
DOI 10.1007/s00415-016-8263-4

REVIEW

Vaccines and multiple sclerosis: a systematic review

Mia Topsøe Mailand[1] · Jette Lautrup Frederiksen[2]

Received: 20 July 2016 / Revised: 6 August 2016 / Accepted: 8 August 2016 / Published online: 7 September 2016

Table 2 Overview of results

Author, country	Design	Cases/controls	Gender ratio (M/F)	Mean age	Frequency of MS	Risk of MS onset	Risk of relapse	Follow-up	Comment/conclusion
HBV									
Langer-Gould A, et al. USA	Nested case–control study	780/3885	0.44	39.3	ND	OR 1.36 (0.77–2.42)	ND	<3 years	No increased risk of MS onset
Eftekharian et al., Iran	Case–control study	250/250	0.43	33	ND	1.29 (0.89–1.78)	ND	Indefinite	No increased risk of MS onset
Mikaeloff, et al. France	Case–control study	349/2941	0.81 (cases) 0.85 (controls)	9.3 (cases) 9.0 (controls)	ND	OR 0.74 (0.54–1.02)	OR 0.74 (0.54–1.02)	<3 years	No increased risk of acute inflammatory demyelinating of CNS. However, significantly increased risk of MS onset >3 years for patients vaccinated with Engerix B: OR 2.77 (1.23–6.24)
Ramagopalan SV, et al. Canada	Case–control study	13,524/ 7216	0.36 (cases) 2.41 (controls)	49 (cases) 52.9 (controls)	ND	OR 0.92 (0.84–1.91)	ND	Indefinite	No increased risk of MS onset
Mikaeloff et al. France	Case–control study	143/1122	0.57 (cases) 0.62 (controls)	11.5 (cases) 11.3 (controls)	ND	OR 1.03 (0.62–1.69)	ND	<3 years	No increased risk of MS onset
M. N. Hocine et al. France	Self-controlled case-series method	289/289	ND	ND	ND	OR 1.35 (0.66–2.79) OR 1.78 (0.97–3.77)	ND	0–60 days 61–365 days	No increased risk of CNS demyelinating events or MS onset
Mikaeloff, et al. France	Retrospective cohort study	33/323	0.79 (cases) 1.08 (controls)	9.2	ND	HR 0.78 (0.32–1.89) HR 1.09 (0.53–2.24)	ND	<3 years at any time (5.8 years)	No increased risk of MS onset after first episode of CNS inflammatory demyelinating disease in childhood and HBV vaccination
Ozakbas S, et al. Turkey	Comparative study	Group I: 11 Group II: 71 Group III: 20	I: 0.57 II: 0.51 III: 0.54	I: 27.75 II: 30.16 III: 34.4	ND	ND	ND	2 years	No increased risk of MS onset (also no difference in HLA-type or disease progression)
Geier DA, et al. USA (VAERS)	Case–control study	MS: 65/1591	MS: 0.24	35 (median)	ND	OR 5.2 (1.9–20)	OR 14 (2.3–560)	Indefinite	Increased risk of MS onset
Hernán MA, et al. UK	Nested case–control study	163/1604	0.46 (cases) 0.44 (controls)	Median 36.7 (cases) 36.3 (controls)	ND	OR 3.1 (1.5–6.3)	ND	<3 years	Increased risk of MS onset
DeStefano F, et al. USA	Case–control study	309/950	0.31 (cases) 0.30 (controls)	ND	ND	OR 0.8 (0.5–1.4)	OR 1.2 (0.5–1.3)	Indefinite	No increased risk of MS onset
Touzé E, et al. France	Case–control study	236/355	0.03 (cases) 0.29 (controls)	33.6 (cases) 34.2 (controls)	ND	OR 1.8 (0.7–4.6) OR 0.9 (0.4–2.0)	ND	<2 months 2–12 moths	No increased risk of MS onset
Ascherio A, et al. USA	Nested case–control study	192/645	Only female	37.6 (cases) 38.1 (controls)	ND	OR 0.9 (0.5–1.6) OR 0.7 (0.3–1.8)	ND	Indefinite <2 years	No increased risk of MS onset
Confavreux C, et al. Europe	Case-crossover study	643 (260/383)	0.39 (cases) 0.47 (controls)	37 (cases) 39 (controls)	ND	ND	OR 0.67 (0.20–2.17)	2 months	No increased risk of relapse
Sadovnick AD, et al. France	Undefined	288,657/ 41,237	ND	11–17 years	3.12/ 100.000 (HBV) 1.73/	ND	ND	Indefinite	No significant difference between incidence of MS in prevaccination and postvaccination era

					(nonHBV)				
HPV									
Scheller NM, et al. Denmark and Sweden	Retrospective cohort study Case-series study	788986/ 3,189,285 (cohort) 339/3993 (case-series)	Only female	25.5	6.12/100.000 (HPV) 21.54/100.000 (nonHPV)	OR 0.90 (0.70–1.15) OR 1.05 (0.79–1.38)	ND	<2 years	No increased risk of MS onse other CNS demyelinating diseases OR 1.00 (0.80–1.2 after qHPV vaccination
Langer-Gould A, et al. USA	Nested case–control study	92/459	Only female	(9–27 years)	ND	OR 1.60 (0.79–3.25)	ND	<3 years	No increased risk of MS onse after qHPV vaccination
Grimaldi-Bensouda L, et al. France	Case–control study	83/290	Only female	21.4 (casers) 21.2 (controls)	ND	OR 0.3 (0.1–0.9)	ND	<2 years	No increased risk of MS onse after qHPV vaccination
Pellegrino P, et al. USA, Australia and Europe	Undefined	46 mio. (USA) 7 mio. (Australia)	Only female	ND	0.08/100,000 doses (USA) 0.14/ 100,000 doses (Australia)	ND	ND	ND	No increased risk of MS onse after qHPV vaccination (do not distinguish between MS onset and progression)
Chao C, et al. USA	Cohort study	189,629	Only female	ND	MS: 3/100,000 Estimated nonVac: 14/100,000	RR 1.37 (0.74–3.40)	ND	180 days	No increased risk of MS onse after qHPV vaccination (do not distinguish between MS onset and progression)
Seasonal influenza and H1N1									
Auriel E, et al. Israel	Undefined	49/77	0,4 (cases) 0625 (controls)	45,4 (cases) 39,1 (controls)	ND	ND	ND	>8 weeks	No neurological adverse ever after vaccination against seasonal influenza or H1N1 → no increased risk relapse
Farez MF, et al. Argentina	Self-controlled case-series method	60 cases	ND	37	ND	ND	RR 0.51 (0.18–1.47)	90 days	No increased risk of relapse a vaccination against H1N1
Bardays C, et al. Sweden	Retrospective cohort study	1,024,019/ 921,005	1.12 (cases) 0.86 (controls)	ND	ND	ND	HR 1.17 (0.53–2.57) HR 0.71 (0.45–1.12)	<6 weeks >6 weeks	No increased risk of relapse a vaccination against H1N1
McNicholas N, et al. UK	Case-crossover study	18/12	ND	ND	ND	ND	RR 6.0 (1.4–26.2)	3 weeks	Increased risk of relapse after vaccination against H1N1 (seasonal influenza)
Ramagopalan SV, et al. Canada	Case–control study	14,135/7569	0.36 (cases) 2.38 (controls)	49 (cases) 52.9 (controls)	ND	OR 1.02 (0.96–1.09)	ND	Indefinite	No increased risk of MS onse after influenza vaccination
Hernán MA, et al. UK	Nested case–control study	163/1604	0.46 (cases) 0.44 (controls)	Median 36.7(cases) 36.3 (controls)	ND	OR 1.0 (0.5–1.02)	ND	<3 years	No increased risk of MS onse after influenza vaccination
Zorzon M, et al. Italy	Case–control study	140/131	ND	ND	ND	OR 1.6 (0.7–3.3)	ND	Indefinite	No increased risk of MS onse after influenza vaccination
DeStefano F, et al. USA	Case–control study	309/950	0.31 (cases) 0.30 (controls)	ND	ND	OR 0.7 (0.5–1.1)	ND	Indefinite	No increased risk of MS onse after influenza vaccination

Table 2 continued

Author, country	Design	Cases/controls	Gender ratio (M/F)	Mean age	Frequency of MS	Risk of MS onset	Risk of relapse	Follow-up	Comment/conclusion
Moriabadi NF, et al. Germany	Clinical trials	12/28	0.5 (cases) 0.87 (controls)	41.1 (cases) 31.1 (controls)	ND	ND	ND	16 weeks	Steady levels of CNS autoantibodies (MBP and MOG) before and after vaccination against seasonal influenza and H1N1 (MS patients and healthy controls) → No increased risk of relapse after influenza vaccination
Confavreux C, et al. Europe	Case-crossover study	643 (260vac/383nonVac)	0.39 (cases) 0.47 (controls)	37 (cases) 39 (controls)	ND	ND	OR 1.08 (0.37–3.10)	2 months	No increased risk of relapse after influenza vaccination
De Keyser J, et al. Holland	Case–control study	90/36	44	ND	ND	ND	ND	6 weeks	Greater risk of relapse (33 %) after influenza infection than after seasonal influenza and H1N1 vaccination (5 %) in RR MS patients p value <0.0001
Mokhtarian F, et al. USA	Clinical trials	19 (11vac/8placebo)/9	0.36 (cases)	40.2	ND	ND	ND	4 weeks	Inconclusive
Miller AE, et al. USA	Randomized double-blind placebo-controlled trial	49/54	ND	ND	ND	ND	ND	6 weeks	No increased risk of relapse after influenza vaccination
Salvetti M, et al. Italy	Clinical trials	6 cases	0.2	31.7	ND	ND	ND	45 days	No increase in numbers of relapses, EDSS or permeability of BBB (MRI) → No increased risk of relapse, except for patients with aggressive disease progression
Michielsens B, et al. Belgium	Clinical trials	11 cases	ND	ND	ND	RR 0.45 (0035–5843)	ND	3 weeks	No increase in lesions or plaques (MRI) after influenza vaccination → No increased risk of relapse after influenza vaccination
Bamford, et al. USA	Clinical trials	65/62	ND	ND	ND	ND	ND	ND	No increased risk of relapse after vaccination against H1N1
Myers LW, et al. USA	Randomized double-blind, placebo-controlled study	33/33 (22 untreated)	Vaccine: 0.32 Placebo: 0.74 Untreated: 0.57	Vaccine: 43 Placebo: 43 Untreated: 44	ND	ND	ND	3 weeks (follow-up 3 months)	No increased risk of relapse after vaccination against H1N1
Alter M, et al. USA	Case–control study	36/72	ND	ND	ND	ND	1.31 (0.02–68.00)[a]	Indefinite	No increased risk of relapse after vaccination against H1N1
Sibley WA, et al. USA	Case–control study	93/59	ND	ND	ND	ND	ND	ND	No increased risk of relapse after vaccination against influenza
Sibley WA, et al. USA	Undefined	24 cases	ND	ND	ND	ND	ND	ND	No increased risk of relapse after vaccination against H1N1
MMR									
Ahlgren C, et al. Sweden	Case–control study	206/888	0.43 (cases) 0.73 (controls)	ND	ND	OR 1.13 (0.62–2.05)	ND	Indefinite	No overall increased risk of MS debut after vaccination against MMR. Positive association between late vaccination (>10 years of age) and MS

J Neurol (2011) 258:1053–1065

Author, country	Design	Cases/controls	Gender ratio (M/F)	Mean age	Frequency of MS	Risk of MS onset	Risk of relapse	Follow-up	Comment/conclusion
Ahlgren C, et al. Sweden	Cohort study	ND	C I: 0.48 C II: 0.44 C III: 0.32 C IV: 0.32	ND	CI (f/m): 14.98/6.97 CII (f/m): 15.28/6.61 CIII (f/m): 12.29/3.85 CIV (f/m): 4.96/1.18	ND	ND	Indefinite	Incidence of MS in 4 cohorts born in different periods with different vaccination programs. (CI: rubella vaccine, CII: two-dose MMR, CIII: monovalent measles vaccine, CVI: combined MMR) compared to cohort born before introduction of listed vaccines → No increased risk of MS debut after introduction of the MMR vaccination
Ramagopalan SV, et al. Canada	Case–control study	10.521/5593	0.35 (cases) 2.31 (controls)	49 (cases) 52.9 (controls)	ND	Ms[a]: OR 1.08 (1.00–1.16) Mp[b]: OR 1.09 (1.01–1.17) R[c]: OR 1.09 (1.00–1.17)	ND	Indefinite	No increased risk of MS debut after vaccination against MMR
Pekmezovic T, et al. Serbia	Case–control study	110/110	0.43	34.4 (cases) 35.0 (controls)	ND	Ms: OR 1.0 (0.5–1.9) Mp: OR 2.0 (0.2–5.7)	ND	Indefinite	No increased risk of MS debut after vaccination against measles or mumps
Zorzon M, et al. Italy	Case–control study	140/131	ND	ND	ND	Ms: OR 50.4 (6.8–373.3) Mp: OR 51.4 (6.9–381.2) R: OR 6.2 (2.3–15.3)	ND	Indefinite	Increased risk of MS debut after vaccination against measles, mumps and rubella
DeStefano F, et al. USA	Case–control study	309/950	0.31 (cases) 0.30 (controls)	ND	ND	OR 0.9 (0.4–1.8)	ND	Indefinite	No increased risk of MS after vaccination against MMR. Ms: OR 0.9 (0.3–1.8), R: OR 0.7 (0.4–1.0)
Kurtzke JF, et al. Faroe Islands	Case–control study	23/127	1.56 (cases) 0.87 (controls)	ND	ND	ND	ND	Indefinite	No increased risk of MS debut after vaccination against MMR
Bansil S, et al. India	Case–control study	56/147	0.6 (cases) 0.71 (controls)	34.1 (cases) 33.4 (controls)	ND	OR 0.7	ND	Indefinite	No increased risk of MS debut after vaccination against MMR
Zilber N, et al. Israel	Case–control study	93/94	0.56 (cases)	ND	ND	OR 0.16 (0.06–0.41)[d]	ND	Indefinite	No increased risk of MS debut after vaccination against MMR
Varicella									
Zorzon M, et al. Italy	Case–control study	140/131	ND	ND	ND	OR 41.6 (5.6–309.6)	ND	Indefinite	Increased risk of MS debut after vaccination against varicella
Variola									
Pekmezovic T, et al. Serbia	Case–control study	110/110	0.43	34.4 (cases) 35.0 (controls)	ND	OR 0.9 (0.5–1.7)	ND	Indefinite	No increased risk of MS debut after vaccination against smallpox
Kurtzke JF, et al. Faroe Islands	Case–control study	23/127	1.56 (cases) 0.87 (controls)	ND	ND	OR 0.23 (0.14–0.36)[d]	ND	Indefinite	No increased risk of MS debut after vaccination against smallpox. Significantly less smallpox vaccination coverage

Bansil S, et al. India	Case–control study	56/147	0.6 (cases) 0.71 (controls)	34.1 (cases) 33.4 (controls)	ND	OR 0.9	ND	Indefinite	No increased risk of MS debut after vaccination against smallpox
Casetta I, et al. Italy	Case–control study	104/150	0.49 (cases) 0.60 (controls)	45.6 (cases) 47.17 (controls)	ND	ND	ND	Indefinite	No increased risk of MS debut after vaccination against smallpox
Andersen E, et al. Denmark	Case–control study	81/243	ND	ND	ND	ND	ND	Indefinite	No increased risk of MS debut after vaccination against smallpox
Alter M, et al. USA	Case–control study	36/72	ND	ND	ND	OR 1.57 (0.37–6.65)	ND	Indefinite	No increased risk of MS debut after vaccination against smallpox
Rabies									
Bansil S, et al. India	Case–control study	56/147	0.6 (cases) 0.71 (controls)	34.1 (cases) 33.4 (controls)	ND	OR 1.9	ND	Indefinite	No increased risk of MS debut after vaccination against rabies
Yellow Fever									
Farez MF, et al. Argentina	Self-controlled case-series study	7 (RR MS)	0.4	45	ND	RR 12.778 (4.28–38.13)	ND	5 weeks	Increased risk of relapse after vaccination against yellow fever
TBE									
Baumhackl U, et al. Germany	Clinical trials	15/15	0.36 (cases) 0.25 (controls)	ND	ND	OR 0.67 (0.13–3.38)	ND	18 weeks	No increased risk of relapse after vaccination against TBE
Tetanus									
Mikaeloff, et al. France	Retrospective cohort study	82/191	1.00 (cases) 0.67 (controls)	9.2	ND	HR 0.99 (0.58–1.67) HR 1.08 (0.63–1.83)	ND	<3 years at any time (5.8 years)	No increased risk of MS debut after first episode of CNS inflammatory demyelinating disease in childhood and tetanus vaccination
Pekmezovic T, et al. Serbia	Case–control study	110/110	0.43	34.4 (cases) 35.0 (controls)	ND	OR 1.5 (0.5–5.1)	ND	Indefinite	No increased risk of MS debut after vaccination against tetanus
Hernán MA, et al. UK	Nested case–control study	163/1604	0.46 (cases) 0.44 (controls)	Median 36.7 (cases) 36.3 (controls)	ND	OR 0.6 (0.4–1.0)	ND	<3 years	No increased/decreased risk of MS debut after vaccination against tetanus
DeStefano F, et al. USA	Case–control study	309/950	0.31 (cases) 0.30 (controls)	ND	ND	OR 0.6 (0.4–0.8)	ND	Indefinite	Decreased risk of MS debut after vaccination against tetanus
Confavreux C, et al. Europe	Case-crossover study	643 (260/383)	0.39 (cases) 0.47 (controls)	37 (cases) 39 (controls)	ND	ND	OR 0.75 (0.23–2.46)	2 months	No increased risk of relapse after vaccination against tetanus
De Keyser J, Holland	Undefined	13 cases	0.63	56	ND	ND	ND	6 weeks	No increased risk of relapse after vaccination against tetanus
Kurtzke JF, et al. Faroe Islands	Case–control study	23/127	1.56 (cases) 0.87 (controls)	ND	ND	OR 0.46 (0.27–0.77)[d]	ND	Indefinite	Decreased risk of MS debut after vaccination against tetanus
Bansil S, et al. India	Case–control study	56/147	0.6 (cases) 0.71 (controls)	34.1 (cases) 33.4 (controls)	ND	OR 0.6	ND	Indefinite	Decreased risk of MS debut after vaccination against tetanus (DPT[c])
Zilber N, et al.	Case–control study	93/94	0.56 (cases)	ND	ND	OR 0.52 (0.40–0.68)[d]	ND	Indefinite	Decreased risk of MS after

Author, country	Design	Cases/controls	Gender ratio (M/F)	Mean age	Frequency of MS	Risk of MS onset	Risk of relapse	Follow-up	Comment/conclusion
Compston DA, et al. UK	Case–control study	177/164	0.47 (cases) 0.89 (controls)	32.2 (cases) 33.7 (controls)	ND	ND	ND	Indefinite	No increased risk of MS debut after vaccination against tetanus
Alter M, et al. USA	Case–control study	36/72	ND	ND	ND	OR 0.57 (0.31–1.01)[d]	ND	Indefinite	No increased risk of MS debut after vaccination against tetanus
Diphtheria									
Pekmezovic T, et al. Serbia	Case–control study	110/110	0.43	34.4 (cases) 35.0 (controls)	ND	OR 0.8 (0.4–1.9)	ND	Indefinite	No increased risk of MS debut after vaccination against diphtheria
Kurtzke JF, et al. Faroe Islands	Case–control study	23/127	1.56 (cases) 0.87 (controls)	ND	ND	OR 0.44 (0.26–0.74)[d]	ND	Indefinite	No increased risk of MS debut after vaccination against diphtheria
Casetta I, et al. Italy	Case–control study	104/150	0.49 (cases) 0.60 (controls)	45.6 (cases) 47.17 (controls)	ND	ND	ND	Indefinite	No increased risk of MS debut after vaccination against diphtheria
Andersen E, et al. Denmark	Case–control study	81/243	ND	ND	ND	ND	ND	Indefinite	No increased risk of MS debut after vaccination against diphtheria
Alter M, et al. USA	Case–control study	36/72	ND	ND	ND	OR 0.48 (0.30–0.76)[d]	ND	Indefinite	Decreased risk of MS debut after vaccination against diphtheria
Polio									
Pekmezovic T, et al. Serbia	Case–control study	110/110	0.43	34.4 (cases) 35.0 (controls)	ND	OR 1.1 (0.6–2.0)	ND	Indefinite	No increased risk of MS debut after vaccination against polio
Zorzon M, et al. Italy	Case–control study	140/131	ND	ND	ND	OR 0.8 (0.07–2.8)	ND	Indefinite	No increased risk of MS debut after vaccination against polio
Kurtzke JF, et al. Faroe Islands	Case–control study	23/127	1.56 (cases) 0.87 (controls)	ND	ND	OR 0.74 (0.18–2.97)[d]	ND	Indefinite	No increased risk of MS debut after vaccination against polio
Bansil S, et al. India	Case–control study	56/147	0.6 (cases) 0.71 (controls)	34.1 (cases) 33.4 (controls)	ND	OR 0.5	ND	Indefinite	No increased risk of MS debut after vaccination against polio
Zilber N, et al. Israel	Case–control study	93/94	0.56 (cases)	ND	ND	OR 0.07 (0.04–0.13)[d]	ND	Indefinite	Decreased risk of MS debut after vaccination against polio (live, attenuated)
Casetta I, et al. Italy	Case–control study	104/150	0.49 (cases) 0.60 (controls)	45.6 (cases) 47.17 (controls)	ND	ND	ND	Indefinite	No increased risk of MS debut after vaccination against polio
Berr C, et al. France	Case–control study	63/63	0.37	ND	ND	ND	ND	Indefinite	No increased risk of MS debut after vaccination against polio. Positive association between late vaccination and MS
Andersen E, et al. Denmark	Case–control study	81/243	ND	ND	ND	ND	ND	Indefinite	No increased risk of MS debut after vaccination against polio
Alter M, et al. USA	Case–control study	36/72	ND	ND	ND	OR 0.37 (0.20–0.69)[d]	ND	Indefinite	No increased risk of MS debut after vaccination against polio

Table 2 continued

Author, country	Design	Cases/controls	Gender ratio (M/F)	Mean age	Frequency of MS	Risk of MS onset	Risk of relapse	Follow-up	Comment/conclusion
Pertussis									
Pekmezovic T, et al. Serbia	Case–control study	110/110	0.43	34.4 (cases) 35.0 (controls)	ND	OR 1.0 (0.6–1.8)	ND	Indefinite	No increased risk of MS debut after vaccination against pertussis
Kurtzke JF, et al. Faroe Islands	Case–control study	23/127	1.56 (cases) 0.87 (controls)	ND	ND	OR 0.42 (0.12–1.48)	ND	Indefinite	No increased risk of MS debut after vaccination against pertussis
Alter M, et al. USA	Case–control study	36/72	ND	ND	ND	OR 0.93[d]	ND	Indefinite	No increased risk of MS debut after vaccination against pertussis
Typhoid fever									
Kurtzke JF, et al. Faroe Islands	Case–control study	23/127	1.56 (cases) 0.87 (controls)	ND	ND	OR 0.68 (0.07–6.20)[d]	ND	Indefinite	No increased risk of MS debut after vaccination against typhoid fever
Zilber N, et al. Israel	Case–control study	93/94	0.56 (cases)	ND	ND	OR 1.87 (1.41–2.49)[d]	ND	Indefinite	Decreased risk of MS debut after vaccination against typhoid fever
Compston DA, et al. UK	Case–control study	177/164	0.47 (cases) 0.89 (controls)	32.2 (cases) 33.7 (controls)	ND	ND	ND	Indefinite	No increased risk of MS debut after vaccination against typhoid fever. Positive association between late vaccination and MS
Alter M, et al. USA	Case–control study	36/72	ND	ND	ND	OR 0.81 (0.05–13.20)[d]	ND	Indefinite	No increased risk of MS debut after vaccination against typhoid fever
Cholera									
Casetta I, et al. Italy	Case–control study	104/150	0.49 (cases) 0.60 (controls)	45.6 (cases) 47.17 (controls)	ND	ND	ND	Indefinite	No increased risk of MS debut after vaccination against cholera
BCG									
Pekmezovic T, et al. Serbia	Case–control study	110/110	0.43	34.4 (cases) 35.0 (controls)	ND	OR 1.3 (0.5–4.1)	ND	Indefinite	No increased risk of MS debut after BCG vaccination
Zorzon M, et al. Italy	Case–control study	140/131	ND	ND	ND	OR 1.0 (0.4–2.6)	ND	Indefinite	No increased risk of MS debut after BCG vaccination
Ristori G, et al. Denmark	Crossover trial	12 cases	0.4	30.6	ND	ND	ND	6 months	Decreased risk of relapse after BCG vaccination
Bansil S, et al. India	Case–control study	56/147	0.6 (cases) 0.71 (controls)	34.1 (cases) 33.4 (controls)	ND	OR 0.9	ND	Indefinite	No increased risk of MS debut after BCG vaccination
Casetta I, et al. Italy	Case–control study	104/150	0.49 (cases) 0.60 (controls)	45.6 (cases) 47.17 (controls)	ND	ND	ND	Indefinite	No increased risk of MS debut after BCG vaccination
Berr C, et al. France	Case–control study	63/63	0.37	ND	ND	ND	ND	Indefinite	No increased risk of MS debut after BCG vaccination
Andersen E, et al. Denmark	Case–control study	81/243	ND	ND	ND	OR 1.00	ND	Indefinite	No increased risk of MS debut after BCG vaccination

retrospective cohort studies with an inherent risk of confounding and bias. In addition, MS is a relatively rare disease making it difficult (and costly) to obtain sufficient cases. Recall bias is one of the problems associated with retrospective studies, and especially, earlier studies are prone to this type of bias, since interviews are used to gather information of vaccination status instead of medical records. Some of the newer studies retrieve information of vaccination from big medical databases, such as VAERS and EMA. However, these sources of information are not immune to bias and certain problems arise from this form of passive surveillance systems, e.g., under reporting, differential reporting (over reporting of serious adverse events), and stimulated reporting (over reporting after media coverage of specific adverse events). Adding to that the reports of adverse events vary greatly in quality and

Conclusion

Since vaccine controversies abound, care must be taken in making conclusions. Based on an analysis of the literature on PubMed, the following vaccines do not seem to increase the risk of developing MS: vaccination against HBV, HPV, seasonal influenza, MMR, variola, tetanus, diphtheria, polio, or BCG. Further research on the association between MS onset and vaccination against H1N1, varicella, rabies, pertussis, typhoid fever, and cholera might yield enough evidence to confirm or reject association, especially for the potential protective role of tetanus- and diphtheria vaccinations. However, such studies would require large populations of patients, great expense, and years of involvement of many professionals to reach a conclusion and may, therefore, not be justified.

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frontiers in Immunology

REVIEW
published: 07 August 201
doi: 10.3389/fimmu.2019.0188

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Vaccination in Multiple Sclerosis: Friend or Foe?

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CONCLUSION

Theoretically, an increased immune response against different types of vaccines, such as live attenuated viruses, inactive attenuated viruses, or portions of bacteria and viruses, could trigger increased immune response to self-antigens (45, 58, 96), but an increased risk for MS itself or increased relapse rates after vaccination have not been show (with exception for YF) in case-control studies (7). There is, however, evidence that infections can trigger relapses in MS (96–104), which is why vaccination of MS patients should be pursued in order to reduce the risk of infections. To assure the best vaccination success, immunization and immunosuppressive treatments have to be well timed.

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HARE August 27, 2019; 93 (9) ARTICLE

A large case-control study on vaccination as risk factor for multiple sclerosis

Alexander Hapfelmeier, Christiane Gasperi, Ewan Donnachie, Bernhard Hemmer

First published July 30, 2019. DOI: https://doi.org/10.1212/WNL.0000000000008012

Abstract

Objective To investigate the hypothesis that vaccination is a risk factor for multiple sclerosis (MS) by use of German ambulatory claims data in a case-control study.

Methods Using the ambulatory claims data of the Bavarian Association of Statutory Health Insurance Physicians covering 2005–2017, logistic regression models were used to assess the relation between MS (n = 12,262) and vaccinations in the 5 years before first diagnosis. Participants newly diagnosed with Crohn disease (n = 19,296) or psoriasis (n = 112,292) and participants with no history of these autoimmune diseases (n = 79,185) served as controls.

Results The odds of MS were lower in participants with a recorded vaccination (odds ratio [OR] 0.870, $p < 0.001$ vs participants without autoimmune disease; OR 0.919, $p < 0.001$ vs participants with Crohn disease; OR 0.973, $p = 0.177$ vs participants with psoriasis). Lower odds were most pronounced for vaccinations against influenza and tick-borne encephalitis. These effects were consistently observed for different time frames, control cohorts, and definitions of the MS cohort. Effect sizes increased toward the time of first diagnosis.

Conclusions Results of the present study do not reveal vaccination to be a risk factor for MS. On the contrary, they consistently suggest that vaccination is associated with a lower likelihood of being diagnosed with MS within the next 5 years. Whether this is a protective effect needs to be addressed by future studies.

Multiple Sclerosis and Related Disorders 31 (2019) 173–188

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Review article

Immunization and multiple sclerosis: Recommendations from the French multiple sclerosis society☆

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1 Are vaccines associated with an increased risk of MS?
2 Are vaccines associated with an increased risk of relapse in MS or a worsening of disability?
3 Are vaccines as effective in people with MS as in the general population (regardless of treatment)?
4 Are vaccines as effective in people with MS exposed to disease-modifying treatments?
5 What methods of prevention should be offered to patients with MS?

Table 3
Summary of the recommendations of the French Multiple Sclerosis Society (SFSEP) on immunization and multiple sclerosis (MS).

Question 1: Are vaccines associated with an increased risk of MS?	
1. Vaccines, in general, are not associated with an increased risk of MS or occurrence of a first demyelinating episode of the central nervous system, including hepatitis B and human papillomavirus vaccines.	Level B
Question 2: Are vaccines associated with an increased risk of relapse or worsening of disability in MS?	
2a. Vaccines, in general, are not associated with an increased risk of relapse in patients with MS.	Level B
An increased risk of relapse after vaccination against yellow fever cannot be excluded.	Level C
2b. Influenza and BCG vaccines have no impact on the short-term accumulation of disability.	Level C
Impact of other vaccines on disability has not been studied yet.	
Question 3: Are vaccines as effective in people with MS as in the general population (regardless of treatment)?	
3. Available data on the efficacy of inactivated vaccines, in patients with MS and without disease-modifying treatment suggest that it is similar to the general population, particularly for mono-and trivalent influenza vaccines.	Level C
No studies are available for live attenuated vaccines.	

Question 4: Are vaccines as effective in people with MS exposed to disease-modifying treatments?

4a. Interferon bêta — Level B

The vaccine response to influenza of patients treated with interferon beta is not decreased compared to healthy controls and untreated MS. — Level C

The vaccine response to Meningococcus, Pneumococcus, and Diphtheria-Tetanus, in patients treated with interferon beta, is not decreased compared to healthy controls and untreated MS.

The other vaccines were not studied.

4b. Glatiramer acetate — Level C

The vaccine response to influenza in patients with MS treated with glatiramer acetate may be reduced compared to healthy controls and untreated MS.

The other vaccines were not studied.

4c. Dimethylfumarate — Level C

The vaccine response to Meningococcus, Pneumococcus and diphtheria-tetanus vaccines in patients with MS treated with dimethylfumarate appears to be comparable to that of MS treated with interferon beta. — Expert recommendati

Due to the risk of lymphopenia it is advised to apply immunization recommendations for immunocompromised patients.

4d Teriflunomide — Level B

The vaccine response to influenza in patients treated with teriflunomide is decreased compared to MS treated with interferon beta. — Expert recommendati

The other vaccines were not studied.

It is advised to apply immunization recommendations for immunocompromised patients.

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P633

An Open-label Study to Assess the Immune Response to Vaccination in Patients with Relapsing Forms of Multiple Sclerosis Treated with Delayed-release Dimethyl Fumarate Compared to Non-pegylated Interferon

von Hehn C,[1] Howard J,[2] Liu S,[1] Meka V,[1] Pultz J,[1] Sheikh SI[1]

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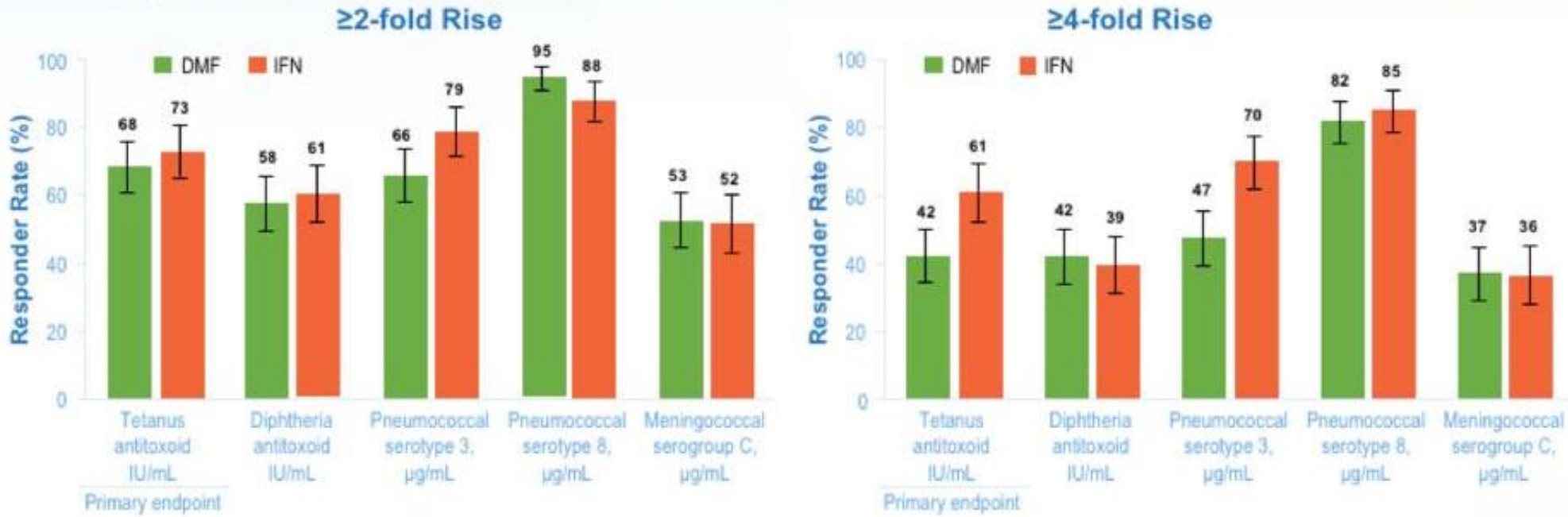
Conclusions

- Overall, patients receiving DMF can mount an effective immune response to recall antigens, neo-antigens and T-cell–independent antigens.
  - This response is comparable to that in IFN-treated patients.
  - In general, a 2- to 4-fold or higher increase above the pre-treatment levels of a specific vaccine antibody titre is considered an appropriate vaccine response.[6,7]
  - DMF-treated patients reached a similar degree of seroprotection from vaccination as patients receiving IFNs.
- No new safety concerns were seen in DMF-treated patients following these vaccinations.

Vaccine study: responders

Proportion of Responders with ≥2- and ≥4-fold Rise at 4 Weeks Compared with Prevaccinated Level[1]



- Patients taking TECFIDERA may receive non-live vaccines; no clinical data are available on the efficacy and safety of live attenuated vaccines in patients taking TECFIDERA[2]
  - This language should be adjusted to align with local labelling[3,4]

Mean responder rate is shown; error bars indicate standard error. DMF=dimethyl fumarate; IU=international unit.

1. von Hehn C et al. Presented at ECTRIMS; September 14–17, 2016; London, UK. P633; 2. Biogen, data on file; 3. TECFIDERA (dimethyl fumarate) [prescribing information]. Cambridge, MA: Biogen Inc; 2017;

Question 4: Are vaccines as effective in people with MS exposed to disease-modifying treatments?

4a. Interferon bêta — Level B

The vaccine response to influenza of patients treated with interferon beta is not decreased compared to healthy controls and untreated MS. — Level C

The vaccine response to Meningococcus, Pneumococcus, and Diphtheria-Tetanus, in patients treated with interferon beta, is not decreased compared to healthy controls and untreated MS.

The other vaccines were not studied.

4b. Glatiramer acetate — Level C

The vaccine response to influenza in patients with MS treated with glatiramer acetate may be reduced compared to healthy controls and untreated MS.

The other vaccines were not studied.

4c. Dimethylfumarate — Level C

The vaccine response to Meningococcus, Pneumococcus and diphtheria-tetanus vaccines in patients with MS treated with dimethylfumarate appears to be comparable to that of MS treated with interferon beta. — Expert recommendati

Due to the risk of lymphopenia it is advised to apply immunization recommendations for immunocompromised patients.

4d Teriflunomide — Level B

The vaccine response to influenza in patients treated with teriflunomide is decreased compared to MS treated with interferon beta. — Expert recommendati

The other vaccines were not studied.

It is advised to apply immunization recommendations for immunocompromised patients.

Teriflunomide effect on immune response to influenza vaccine in patients with multiple sclerosis

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"Teriflunomide-treated patients generally mounted a lower but effective immune responses to seasonal influenza vaccination, consistent with preservation of protective immune responses"

TERIVA: Proportion of Patients With ≥2- or ≥4-fold Increase in Titer

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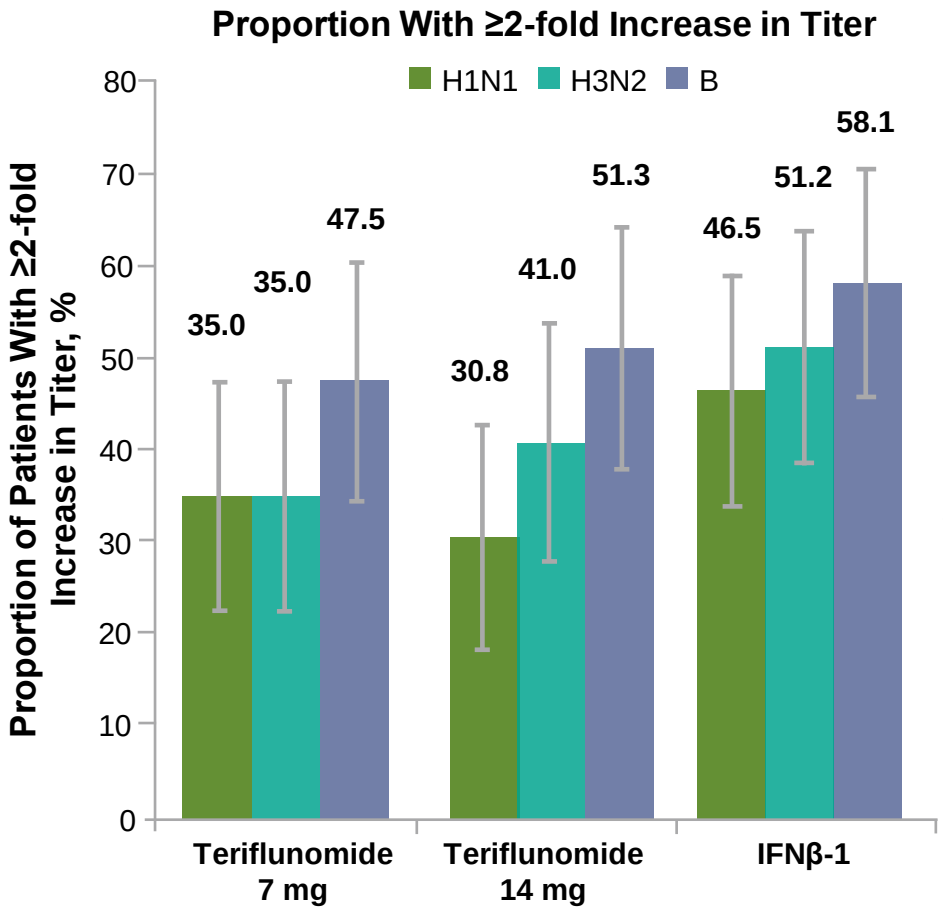

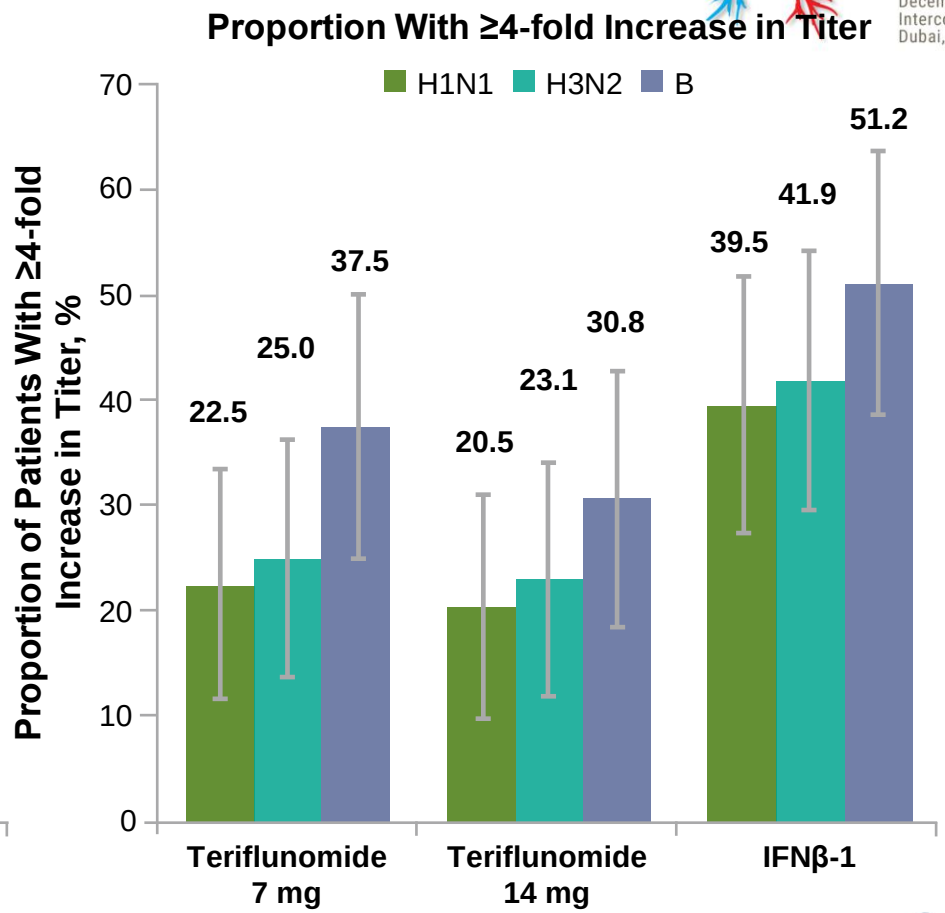

- A slightly higher proportion of patients in the IFNβ-1 group achieved ≥2-fold or ≥4-fold increase in titer compared with the teriflunomide groups[a]
  - The proportions were similar between both teriflunomide groups

[a]TERIVA was not designed or powered to make direct comparisons between immune responses in the teriflunomide groups and the IFNβ-1 reference population. IFN, interferon.

Bar-Or et al. *Neurology*. 2013;81:552.

Randomized study of teriflunomide effects on immune responses to neoantigen and recall antigens

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Philippe Truffinet, MD
Meg Church, MS
Francoise Menguy-Vacheron, PhD

Correspondence to
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"Following vaccination, geometric mean titers for rabies antibodies were lower with teriflunomide than with placebo. However, teriflunomide did not limit the ability to achieve seroprotective titers against this neoantigen. Evaluation of DTH showed that teriflunomide had no adverse impact on the cellular memory response to recall antigens."

Classification of evidence	**This study provides Class II evidence that in normal subjects treated with teriflunomide, antibody titer responses to rabies vaccination are lower than with placebo but sufficient for sero-protection**

:. Mitoxantrone — Level C

ıe vaccine response to influenza in patients treated with mitoxantrone is insufficient compared to :althy controls. — Expert recommendati

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is advised to apply immunization recommendations for immunocompromised patients.

. Natalizumab — Level B

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ı. Alemtuzumab — Expert recommendati

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. Ocrelizumab — Level B

ıe vaccine response in patients treated with ocrelizumab is effective but decreased after 12 weeks for tanus, Pneumococcus and influenza compared with non-treated and interferon beta-treated MS. — Expert recommendati

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Journal of the Neurological Sciences 341 (2014) 22–27

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Natalizumab treatment shows no clinically meaningful effects on immunization responses in patients with relapsing-remitting multiple sclerosis☆

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ARTICLE INFO

Article history:
Received 1 November 2013
Received in revised form 4 March 2014
Accepted 18 March 2014
Available online 26 March 2014

Keywords:
Multiple sclerosis
Natalizumab
Immunization
Vaccines
Immunoglobulins
Lymphocytes
Immunity
Humoral

ABSTRACT

Natalizumab is an immunomodulatory drug approved for the treatment of multiple sclerosis. This randomized, multicenter, open-label study evaluated natalizumab's effects on immunization responses to a recall antigen (tetanus toxoid [TT]) and a neoantigen (keyhole limpet hemocyanin [KLH]) in patients with relapsing forms of multiple sclerosis (MS). Natalizumab-naive relapsing MS patients were randomized (1:1; n = 30 per group) to receive TT and KLH immunizations either without natalizumab treatment (control) or after 6 months of natalizumab treatment (natalizumab group). An adequate response to immunization was defined as an increase to at least twofold in specific serum immunoglobulin G (IgG) 28 days after the first immunization. All evaluable patients achieved protective levels of anti-TT IgG antibodies, and the proportion of responders to this recall antigen, as well as to primary immunization with KLH, was similar in the presence and absence of natalizumab. This indicates that natalizumab treatment does not appear to affect responses to primary or secondary immunization in a clinically meaningful way.

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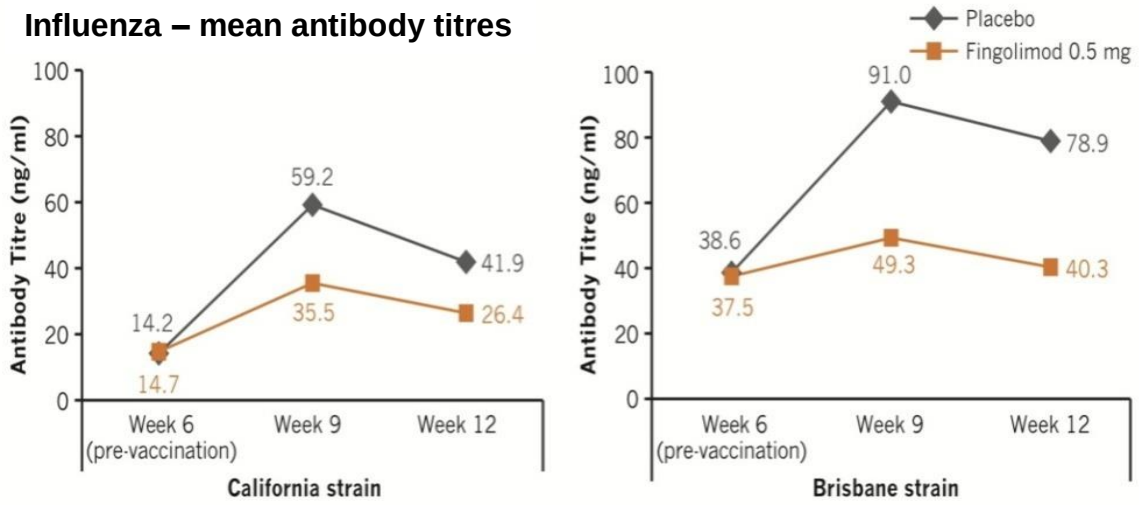
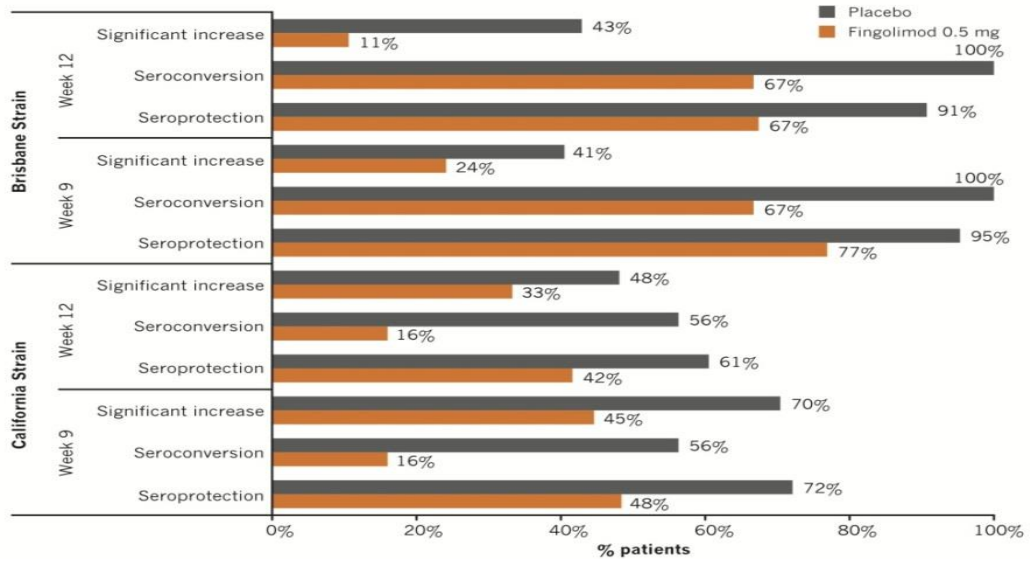
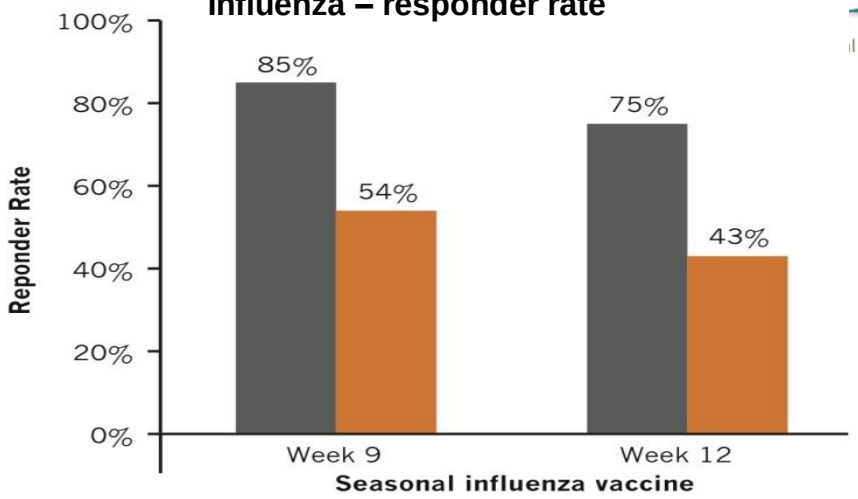
Influenza vaccination under fingolimod therapy

Influenza – mean antibody titres





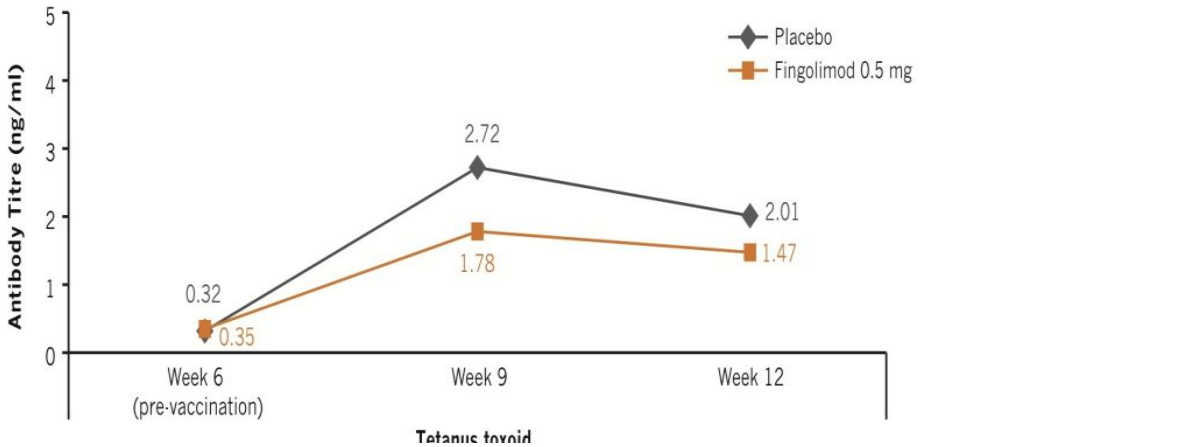
Influenza – responder rate

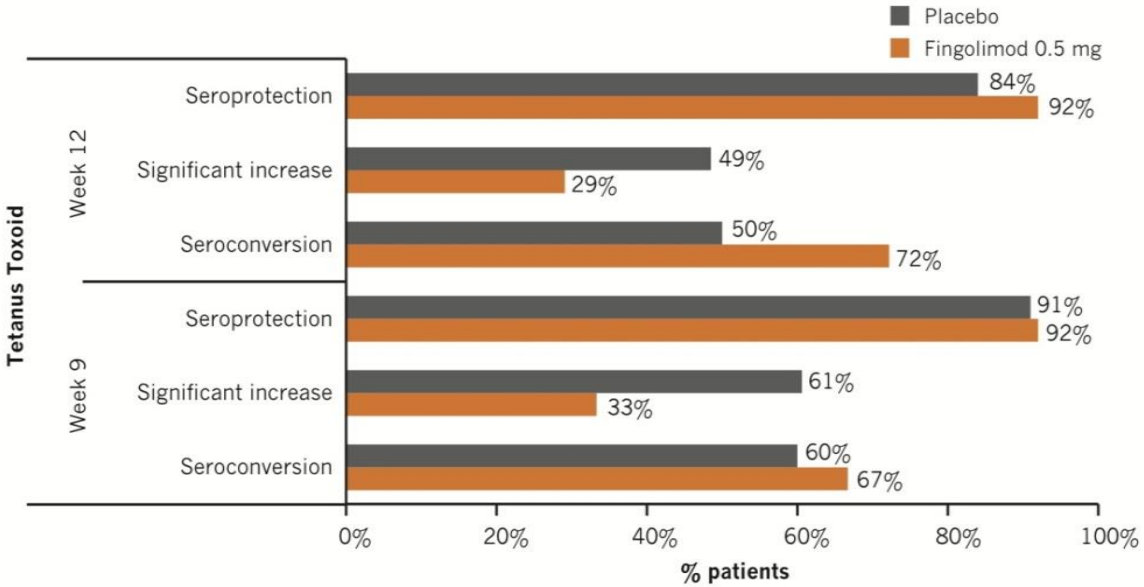


- Antibody titres showed an increase but were numerically lower in the fingolimod 0.5mg group compared to placebo
- Fewer patients responded to a de novo vaccination with seasonal influenza vaccine in the fingolimod 0.5 mg treatment group than in the placebo group
- A higher proportion of patients in the placebo treatment group compared to fingolimod 0.5mg fulfilled the criteria for seroprotection, seroconversion, and significant increase in antibody titre

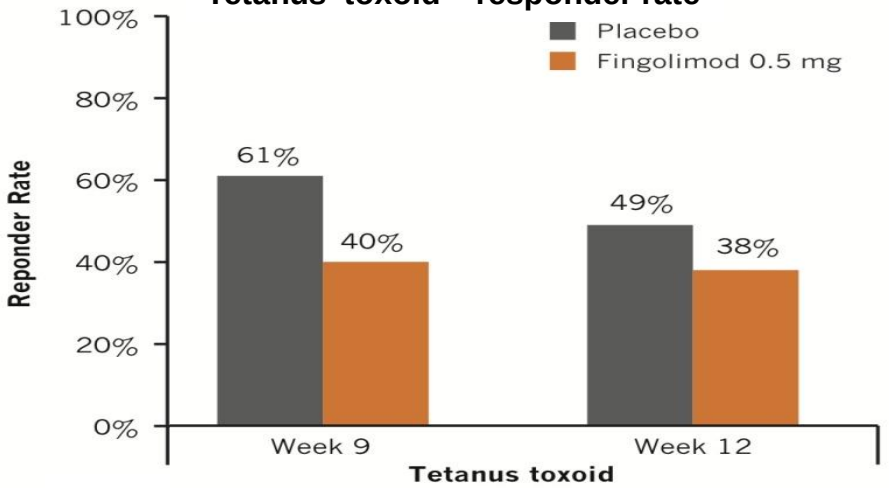
*Seroconversion: Involves the development of detectable specific antibodies in blood serum post-vaccination or post immunization. **Seroprotection: Involves attaining post-vaccination antibody levels which fulfill 50% probability of clinical protection if exposed to infection. Responder: 4-fold increase in antibody levels marks responders versus non-responders.

Tetanus toxoid – mean antibody titres





Tetanus toxoid – responder rate



- A higher proportion of patients in the placebo treatment group compared to fingolimod 0.5mg fulfilled the criteria for significant increase (≥4-fold) in antibody titre

- Seroconversion was higher in the fingolimod 0.5 mg group compared to placebo

- Seroprotection titres were reached in almost all patients in the two groups, with a slightly higher proportion in the fingolimod 0.5 mg group (92% Versus 84%) 12 weeks post-vaccination).

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Immune competence after alemtuzumab treatment of multiple sclerosis

Claire L. McCarthy, MRCP, PhD
Orla Tuohy, MB
D. Alastair S. Compston, FRCP, PhD
Dinakantha S. Kumararatne, FRCPath, DPhil
Alasdair J. Coles, FRCP, PhD
Joanne L. Jones, MRCP, PhD

"In this small historically controlled pilot study, we demonstrated i) retained humoral immunologic memory (in the form of antibodies against common viruses and response to recall antigens), and ii) the retained ability to mount a humoral immune response against a novel antigen after treatment with alemtuzumab"

Correspondence to Dr. McCarthy: dr.claire.mccarthy@gmail.com

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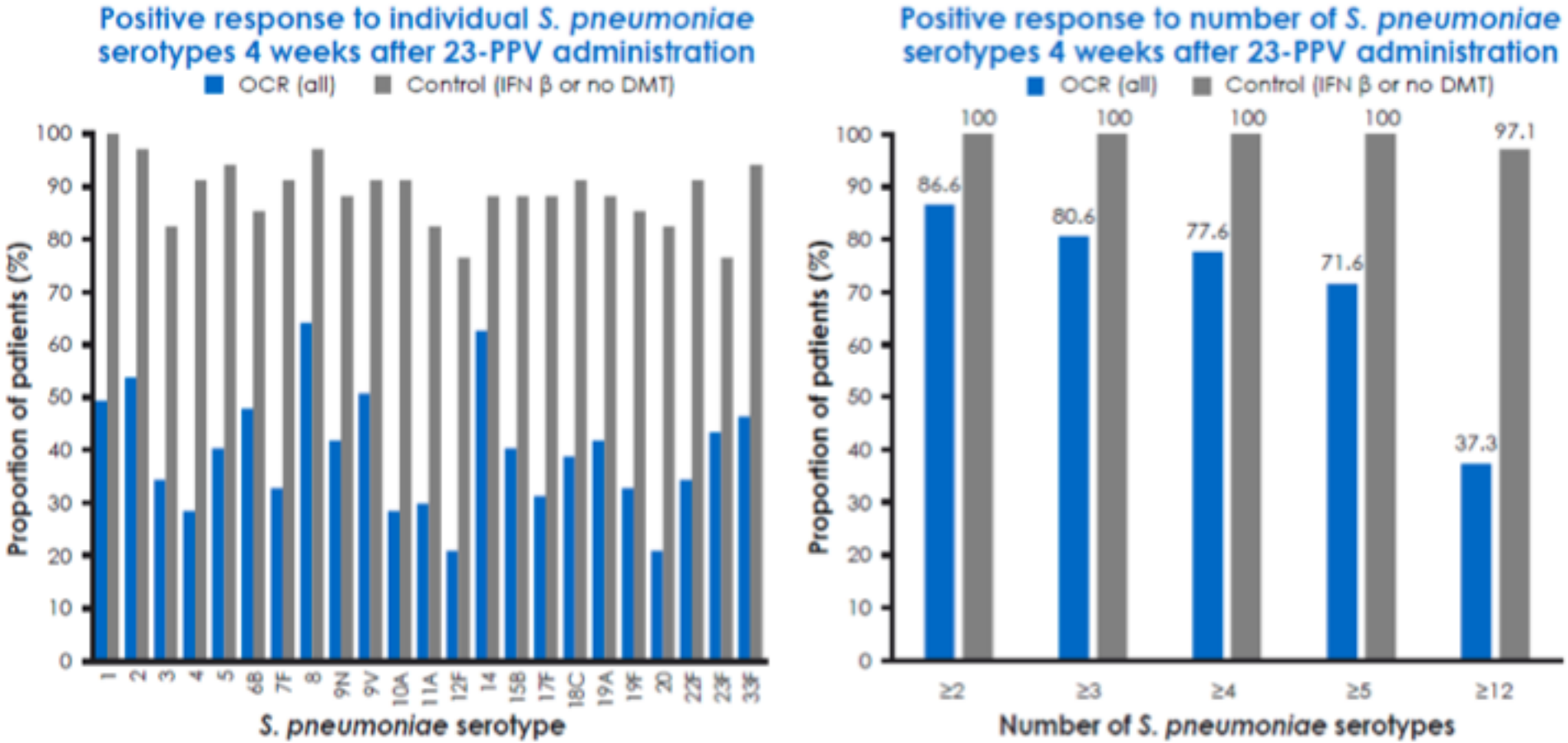
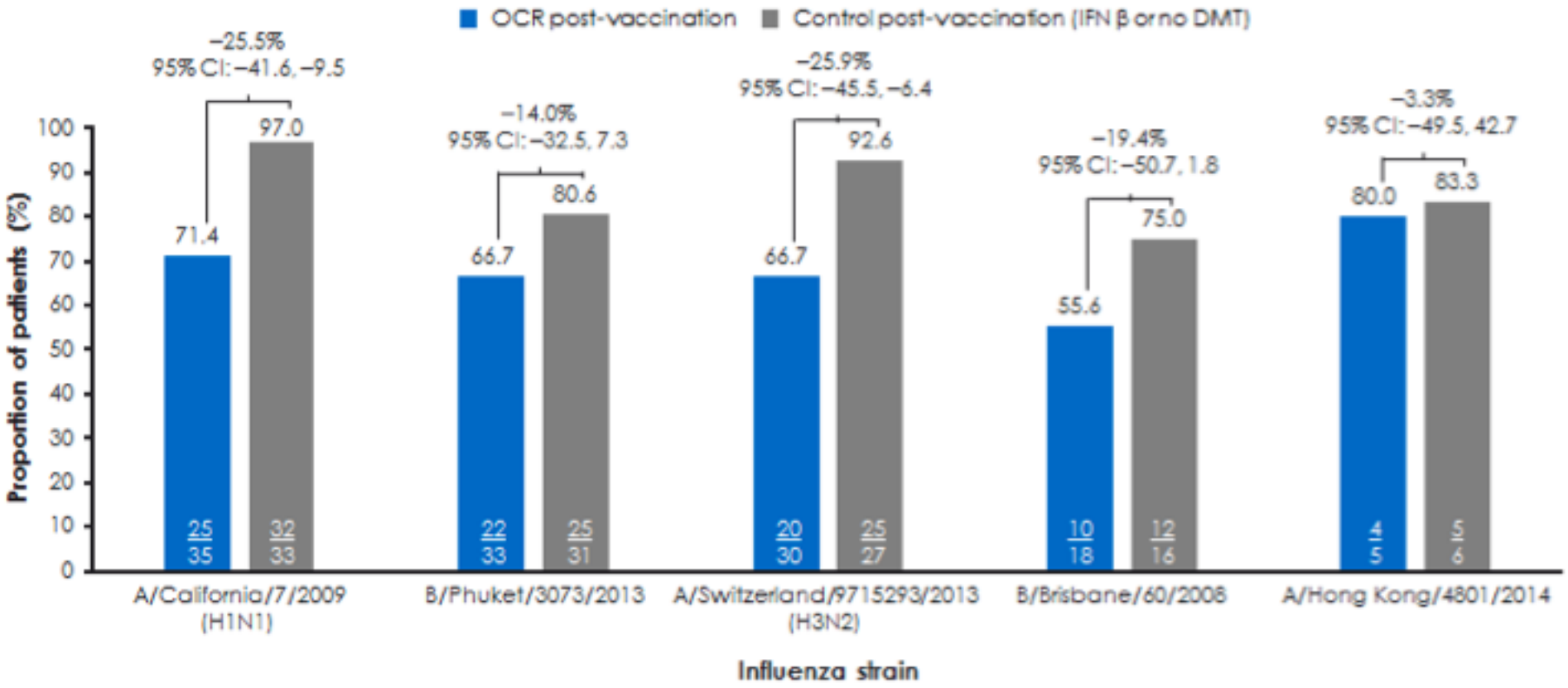
Figure 1: Response (IgG) to Pneumococcal Vaccine[9]



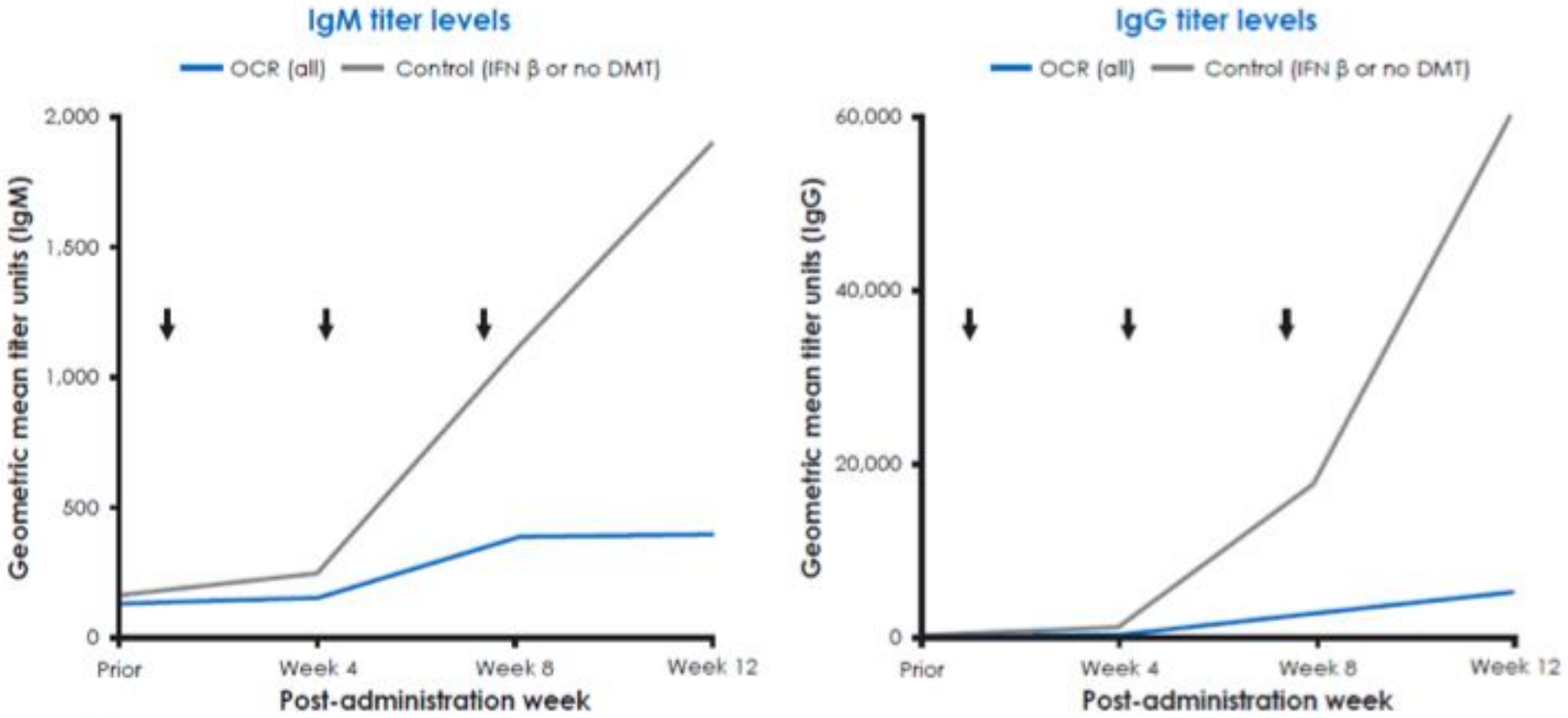
Notes: Positive response: 2-fold increase or a >1 µg/mL rise in titer level (IgG), compared with pre-vaccination levels.
Abbreviations: 23-PPV=23-valent pneumococcal polysaccharide vaccine; DMT=disease-modifying therapy; IFN=interferon; IgG=immunoglobulin G; OCR=Ocrevus

Figure 2: Seroprotection to Individual Strains of the Influenza Virus[9]



Notes: Seroprotection defined as a specific hemagglutination inhibition titer >40.
Abbreviations: DMT=disease-modifying therapy; IFN=interferon; OCR=Ocrevus.

Figure 3: IgM and IgG Responses to KLH Neoantigen[9]



Notes: ↓KLH administration

Abbreviations: DMT=disease-modifying therapy; IFN=interferon; IgG=immunoglobulin G; IgM=immunoglobulin M; KLH=keyhole limpet hemocyanin; OCR=Ocrevus.

Question 5: What prevention methods should be offered to patients with MS?

5a. The vaccination schedule of the general population should be applied to any patient with MS unless there is a specific contraindication.	Recommendation of the Haut Conseil de la Santé Publique, article L3111-1, Code de la Santé Publique
5b. It is recommended to update the vaccination schedule as soon as possible after the diagnosis of MS and before any disease-modifying treatment is introduced.	Recommendation of the Haut Conseil de la Santé Publique, article L3111-1, Code de la Santé Publique
5c. Seasonal flu vaccination is recommended for patients with MS who are treated with immunosuppressive drugs or with a significant disability (or any other reason recommended for influenza vaccination) unless there is a specific contraindication. For the other MS patients, seasonal flu vaccination can be proposed annually.	Recommendation of the Haut Conseil de la Santé Publique, article L3111-1, Code de la Santé Publique Expert recommendation
5d. There is no restriction for vaccines associated with immunomodulators (interferon beta and glatiramer acetate).	Level B
5e. During treatment with immunosuppressants and in any other case of immunosuppression, live attenuated vaccines are contraindicated. Recommended vaccines are those of the vaccination schedule for the general population and vaccines specifically recommended in immunocompromised patients (influenza and Pneumococcus in particular). It is not recommended to vaccinate during relapse requiring high dose steroid therapy (expert recommendation).	Recommendation of the Haut Conseil de la Santé Publique, article L3111-1, Code de la Santé Publique Expert recommendation
5f. It is recommended to provide the immediate entourage of an immunocompromised person with the vaccination schedule, seasonal influenza vaccination and varicella vaccination in case of negative serology.	Recommendation of the Haut Conseil de la Santé Publique, article L3111-1, Code de la Santé Publique

EDITORIAL

Vaccination

Not a trigger for MS

E. Ann Yeh, MD, MA, and Jennifer Graves, MD, PhD, MAS

Neurology® 2019;93:377-378. doi:10.1212/WNL.0000000000008000

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Vaccinations revolutionized medicine in the 20th century with the near or total elimination of disabling, life-threatening infections. Yet, despite clear benefits to public health, suspicion of ill effects related to vaccines has risen in recent years. In large part, this fear of vaccination has been fueled by poorly designed, inaccurate, or even fraudulent studies[1–3] linking vaccinations to adverse outcomes. While more recent large and well-designed studies have assuaged concerns about vaccines,[4] some public mistrust remains. The recent resurgence of measles and resultant public health crisis across the United States, with more than 700 cases in 2019—the greatest number since 1994—highlights this growing distrust.[5] Distrust in vaccines is centered primarily on questions of their potential to cause health problems, among them behavioral and autoimmune disease. With this background in mind, it is no surprise, then, that one of the most common queries that patients and families ask physicians dealing with a chronic immune-mediated disorder like multiple sclerosis (MS) is as follows: Did this or any vaccine cause or trigger MS?

RELATED ARTICLE

A large case-control study on vaccination as risk factor of multiple sclerosis
Page 386

5th MENACTRIMS CONGRESS
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Published Ahead of Print on August 28, 2019 as 10.1212/WNL.0000000000008157

SPECIAL ARTICLE LEVEL OF RECOMMENDATION

Practice guideline update summary: Vaccine-preventable infections and immunization in multiple sclerosis

Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology

Mauricio F. Farez, MD, MPH, Jorge Correale, MD, Melissa J. Armstrong, MD, MSc, Alexander Rae-Grant, MD, David Gloss, MD, Diane Donley, MD, Yolanda Holler-Managan, MD, Norman J. Kachuck, MD, Douglas Jeffery, MD, Maureen Beilman, Gary Gronseth, MD, David Michelson, MD, Erin Lee, Julie Cox, MFA, Tom Getchius, James Sejvar, MD, and Pushpa Narayanaswami, MD

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Neurology® 2019;93:1-11. doi:10.1212/WNL.0000000000008157

Table 1 Recommendation statements[a] for general care for individuals with multiple sclerosis when considering immunization and vaccine-preventable infections

Recommendation number	Recommendation statement and level
1	1a. Clinicians should discuss with their patients the evidence from the systematic review regarding immunization in MS (Level B).
	1b. Clinicians should explore patients' opinions, preferences, and questions regarding immunizations at clinical visits to be able to effectively address the optimal immunization strategy for each patient, in keeping with the patient's MS status, values, and preferences (Level B).
2	Clinicians should recommend that patients with MS follow all local vaccine standards (e.g., from the US CDC, WHO, and local regulatory bodies), unless there is a specific contraindication (e.g., active treatment with ISIM agents) (Level B).
3	Clinicians should weigh local risks of vaccine-preventable diseases when counseling individuals with MS regarding vaccination (Level B).
4	Clinicians should recommend that patients with MS receive the influenza vaccination annually, unless there is a specific contraindication (e.g., previous severe reaction) (Level B).

Abbreviations: CDC = Centers for Disease Control and Prevention; ISIM = immunosuppressive or immunomodulating; MS = multiple sclerosis; WHO = World Health Organization.

[a] Level A is the strongest recommendation level and is denoted by the use of the helping verb must. These recommendations are rare. Level B corresponds to the helping verb should. Such recommendations are more common, as the requirements are less stringent but are still associated with confidence in the rationale and a favorable benefit-risk profile. Level C corresponds to the helping verb may. These recommendations represent the lowest allowable recommendation level that the American Academy of Neurology considers useful within the scope of clinical practice and can accommodate the highest degree of practice variation.

Table 2 Recommendation statements regarding immunization in the setting of immunosuppressive or immunomodulating medication use

Recommendation number	Recommendation statement and level
5	5a. Clinicians should counsel patients with MS about infection risks associated with specific ISIM medications and treatment-specific vaccination guidance according to the prescribing instructions for ISIM medications when one of these treatments is being considered for use (Level B).
	5b. Physicians should assess or reassess vaccination status of patients with MS before prescribing ISIM therapy and should vaccinate patients with MS, according to local regulatory standards and guided by treatment-specific infectious risks, at least 4–6 weeks before initiating ISIM therapy as advised by specific prescribing information (Level B).
	5c. Clinicians may discuss the advantage of vaccination with patients as soon as possible after MS diagnosis, regardless of initial therapeutic plans, to prevent future delays in initiation of ISIM therapies (Level C based on variation in patient preferences).
6	6a. Clinicians must screen for certain infections (e.g., hepatitis, tuberculosis, and VZV) according to prescribing information before initiating the specific ISIM medication planned for use (Level A) and should treat patients testing positive for latent infections (e.g., hepatitis and tuberculosis) before MS treatment according to individual ISIM prescribing information (Level B based on feasibility and cost relative to benefit).
	6b. In high-risk populations or in countries with high burden (in the case of tuberculosis), clinicians must screen for latent infections (e.g., hepatitis and tuberculosis) before starting MS treatment with ISIM medications even when not specifically mentioned in prescribing information (Level A) and should consult infectious disease or other specialists (e.g., liver specialists) regarding treating patients who screen positive for latent infection before treating them with ISIM medications (Level B).
7	7a. Clinicians should recommend against using live-attenuated vaccines in people with MS who currently receive ISIM therapies or have recently discontinued these therapies (Level B based on importance of outcomes).
	7b. When the risk of infection is high, clinicians may recommend using live-attenuated vaccines if killed vaccines are unavailable for people with MS who are currently receiving ISIM therapies (Level C based on variation in patient preferences, benefit relative to harm, and importance of outcomes).

TABLE 2 | Recommended vaccination in MS patients in dependency of treatment.

	FDA/EMA vaccination	FDA/EMA screening	Extended vaccination
GLAT			
IFN beta			
Cladribin	VZV	Screen for HBV, HCV	
Teriflunomid			
Fingolimod	VZV		HBV, HPV
DMF			
Rituximab	n.a.	n.a.	HBV, Pneumococcal
Ocrelizumab		Screen for HBV, HCV	HBV, Pneumococcal
Natalizumab			VZV
Alemtuzumab	VZV	Screen for HBV, HCV	HBV, Influenza, HPV and Pneumococcal

GLAT, glatiramer acetate; IFN beta, interferon beta; DMF, dimethyl fumarate; HBV, hepatitis B; HCV, hepatitis C; VZV, varicella-zoster virus; HPV, human papillomavirus; n.a., not applicable.

Table 2 Recommendation statements regarding immunization in the setting of immunosuppressive or immunomodulating medication use

Recommendation number	Recommendation statement and level
5	5a. Clinicians should counsel patients with MS about infection risks associated with specific ISIM medications and treatment-specific vaccination guidance according to the prescribing instructions for ISIM medications when one of these treatments is being considered for use (Level B).
	5b. Physicians should assess or reassess vaccination status of patients with MS before prescribing ISIM therapy and should vaccinate patients with MS, according to local regulatory standards and guided by treatment-specific infectious risks, at least 4–6 weeks before initiating ISIM therapy as advised by specific prescribing information (Level B).
	5c. Clinicians may discuss the advantage of vaccination with patients as soon as possible after MS diagnosis, regardless of initial therapeutic plans, to prevent future delays in initiation of ISIM therapies (Level C based on variation in patient preferences).
6	6a. Clinicians must screen for certain infections (e.g., hepatitis, tuberculosis, and VZV) according to prescribing information before initiating the specific ISIM medication planned for use (Level A) and should treat patients testing positive for latent infections (e.g., hepatitis and tuberculosis) before MS treatment according to individual ISIM prescribing information (Level B based on feasibility and cost relative to benefit).
	6b. In high-risk populations or in countries with high burden (in the case of tuberculosis), clinicians must screen for latent infections (e.g., hepatitis and tuberculosis) before starting MS treatment with ISIM medications even when not specifically mentioned in prescribing information (Level A) and should consult infectious disease or other specialists (e.g., liver specialists) regarding treating patients who screen positive for latent infection before treating them with ISIM medications (Level B).
7	7a. Clinicians should recommend against using live-attenuated vaccines in people with MS who currently receive ISIM therapies or have recently discontinued these therapies (Level B based on importance of outcomes).
	7b. When the risk of infection is high, clinicians may recommend using live-attenuated vaccines if killed vaccines are unavailable for people with MS who are currently receiving ISIM therapies (Level C based on variation in patient preferences, benefit relative to harm, and importance of outcomes).

Table 3 Recommendation statement regarding immunization for individuals with multiple sclerosis during a relapse

Recommendation number	Recommendation statement and level
8	Clinicians should delay vaccination of people with MS who are experiencing a relapse until clinical resolution or until the relapse is no longer active (e.g., the relapse is no longer progressive but may be associated with residual disability), often many weeks after relapse onset (Level B).

Take Home Messages

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- Vaccination is not a risk factor for developing MS.
- Vaccination is not a risk factor for relapses or disease progression.
- Infections are risk factors for relapses.
- In MS patients not under treatment, vaccination is as effective as non MS patients.
- Vaccination programs should be completed before starting therapy, Including screening for VZV, HBV, HCV and T.B.
- Live attenuated vaccines are avoided in MS patients under treatment.

Take Home Messages

- Non live vaccines are safe in MS patients treated with immunosuppressants.
- Most immunosuppressants will result in a lower level of protection.
- Measuring the antibody titer when using immunosuppressants to ensure protection.
- Booster doses may be required.

THANK YOU

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Non Existence of MS in Egypt to the international community till 2012

- No data

Local Registries

Egypt - MS Network registry

2016 | Phase III: Launching “Egypt MS Network Registry”

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Action points:

- Launching a Web-Based Registry portal

  www.msnetworkeg.com

- First Patient enrolled in January 2016
- Successful piloting in the Biggest MSCoEs:
  1) Ain Shams university
  2) Kasr AlAiny, Cairo university
  3) Alexandria University
  4) Azhar university
- Providing centers with technical support in the form of User manuals & trainings
- Organize meetings to maintain alignment across centers and set Publication plan for Egyptian RWE by 2018.

- 5390 cases

MSBase
Neuro-Immunology Registry

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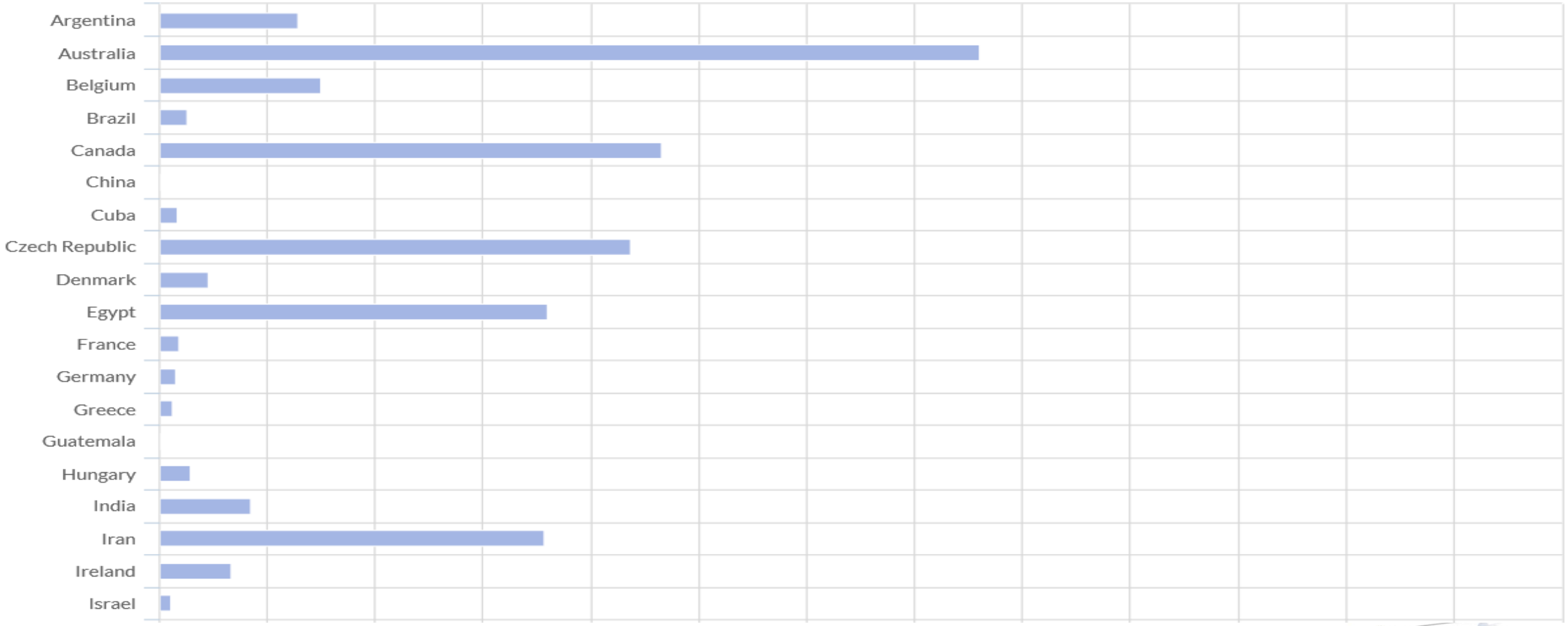
Patient Enrolments by Country



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Fingolimod
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Rituximab
Ocrelizumab
Generic of DMF

2019

Multiple Sclerosis and Related Disorders 28 (2019) 313–316

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Vitamin D and body mass index in Egyptian multiple sclerosis patients

Dina Zamzam[a], Mohamed Foad[a], Mahmoud Swelam[a], Mohamed AbdelHafez[a], Azza AbdelNasser[a], Ramy Mahmoud[b], Hany Aref[a], Magd Zakaria[a,*]

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ARTICLE INFO

Keywords:
Vitamin D
BMI
Multiple sclerosis
Egypt

ABSTRACT

Background: Vitamin D deficiency and obesity may be related to the pathogenesis and disease activity of multiple sclerosis (MS). This study aimed to assess the correlation between the serum level of 25(OH) vitamin D, body mass index (BMI) and the Expanded Disability Status Scale (EDSS) in a sample of Egyptian MS patients.
Subjects and Methods: This was an observational study that included 130 MS patients who were recruited consecutively among the patients attending the MS unit of Ain Shams University Hospital, Cairo, in the period between December 2017 and March 2018. The serum level of 25(OH) D, BMI and EDSS were recorded.

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Clinical trial

Micro-RNA 18b and interleukin 17A profiles in relapsing remitting multiple sclerosis

Mohamed Salah Mohamed[a], Eslam. M.A. El- Nahrery[b,*], Nevin Shalaby[c], Mona Hussein[d], Reda Abd El Aal[e], Magdy Mahmoud Mohamed[f]

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5th MENACTRIMS CONGRESS
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Multiple Sclerosis and Related Disorders 28 (2019) 184–188

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Risk of obstructive sleep apnea in multiple sclerosis: Frequency, clinical and radiological correlates

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ARTICLE INFO

Key words:
Multiple sclerosis
OSA

ABSTRACT

Background: Primary sleep disorder, especially, obstructive sleep apnea (OSA), are noted to occur in MS patients at higher frequency than the general population.

Multiple Sclerosis and Related Disorders 36 (2019) 101417

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Clinical trial

Magnetic resonance imaging markers of disability in Egyptian multiple sclerosis patients

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ARTICLE INFO

Keywords:
Magnetic resonance imaging
Multiple sclerosis
Disability

ABSTRACT

Background: The aim of this work was to identify the magnetic resonance imaging (MRI) markers of disability in Egyptian multiple sclerosis (MS) patients.
Subjects and methods: This retrospective observational study included 673 patients recruited from the registry of the MS unit at Ain Shams University hospitals. At the time when the MRI scans of the brain and spinal cord were

Multiple Sclerosis and Related Disorders 38 (2020) 101495

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Clinical trial

Immunoglobulin G index as a biomarker of relapse response to corticosteroids during early stages of multiple sclerosis

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ARTICLE INFO

Keywords:
Acute relapse
Biomarker
IgG index
Multiple sclerosis
Response to steroids

ABSTRACT

Background: Despite the considerable advances in disease modifying therapy in multiple sclerosis (MS), management of acute MS relapses remains understudied. The response to relapse therapy is heterogenous among patients, and the exact reason behind such response remains elusive. Identification of a reliable biomarker for relapse responsiveness would contribute considerably to optimizing the relapse outcome.

Objectives: to explore whether the immunoglobulin G (IgG) index during acute relapse contributes to relapse response to corticosteroid therapy or not

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