Agenti infettivi: ruolo eziologico primario o solo trigger?

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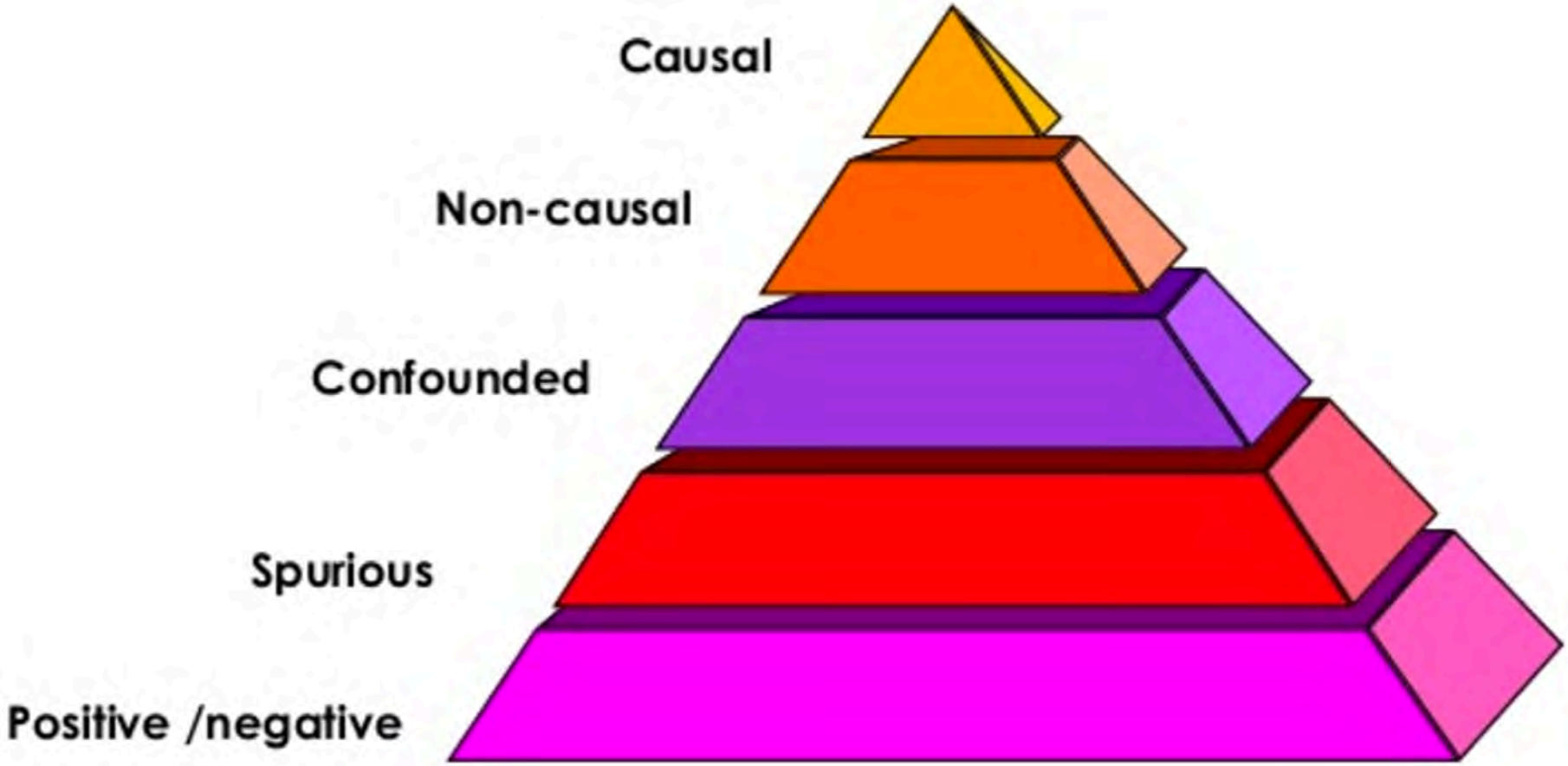
OSPEDALE SAN RAFFAELE

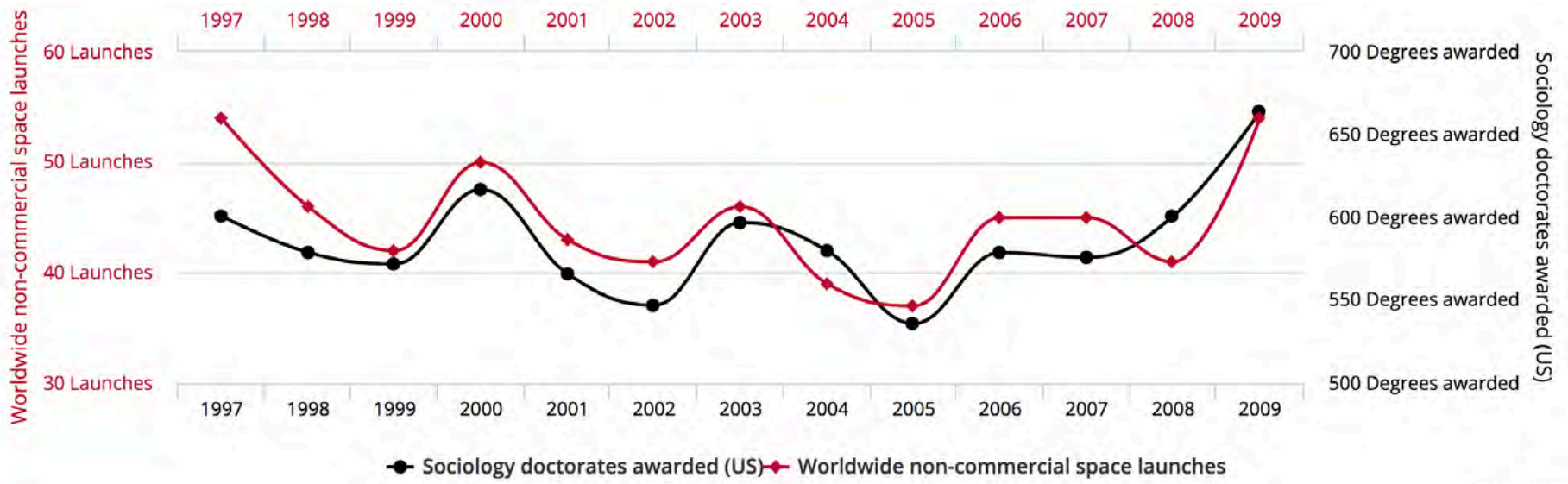
Infections in MS (and autoimmunity):

- **Causal**
- **Co-factor**
- **Protective**


Causal
Non-causal
Confounded
Spurious
Positive /negative

Worldwide non-commercial space launches
correlates with
Sociology doctorates awarded (US)

Correlation: 78.92% (r=0.78915)



tylervigen.com

Data sources: Federal Aviation Administration and National Science Foundation

Causal: EBV

-99.5% of adult MS patients EBV+, 94% of adult controls

-98.6% of children with MS EBV+, 72.1% of age-matched controls

-Almost NO MS patient EBV sero-negative

-MS patients have higher titers of EBNA Ab than control. Titers are already higher before the onset of MS

-Infectious mononucleosis increases the risk of MS significantly

-In MS patients, EBNA1-specific T cells cross-react with MBP (one report only)

-EBV-infected B cells, with evidence of reactivation, are present in MS lesions (controversial, not confirmed by others)

Table 1. Odds Ratios of Multiple Sclerosis in Epstein–Barr Virus Seronegative versus Seropositive Subjects

Study	Cases, N		Control Subjects, N		OR of MS for Seronegativity	Exact 95% CI*
	+	−	+	−		
1. Sumaya and colleagues, 1980[37]	155	2	76	5	0.2	0.02–1.24
2. Bray and colleagues, 1983[38]	309	4	363	43	0.11	0.03–0.31
3. Larsen and colleagues, 1985[39]	93	0	78	15	0	0–0.05
4. Sumaya and colleagues, 1985[40]	104	0	99	5	0	0–1.07
5. Shirodaria and colleagues, 1987[41]	26	0	24	2	0	0–5.29
6. Ferrante and colleagues, 1987[42]	29	1	31	11	0.1	0–0.76
7. Munch and colleagues, 1997[43]	137	1	124	14	0.06	0–0.44
8. Myhr and colleagues, 1998[44]	144	0	162	8	0	0–0.67
9. Wagner and colleagues, 2000[45]	107	0	153	10	0	0–0.66
10. Ascherio and colleagues, 2001[46]	143	1	269	18	0.1	0–0.68
11. Haahr and colleagues, 2004[47]	153	0	50	3	0	0–0.82
12. Sundström and colleagues, 2004[48]	234	0	693	9	0	0–1.5
13. Ponsonby and colleagues, 2005[34]	136	0	252	9	0	0–0.96
Total	1770	9	2374	152	$OR_{MH} = 0.06$	0.03–0.13[a]

[a]Cornfield confidence interval; $p < 0.000000001$.

*Calculated as described in: Mehta CR, Patel NR, Gary R. J Am Stat Assoc 1985;78:969–973.

OR = odds ratio; MS = multiple sclerosis; CI = confidence interval.

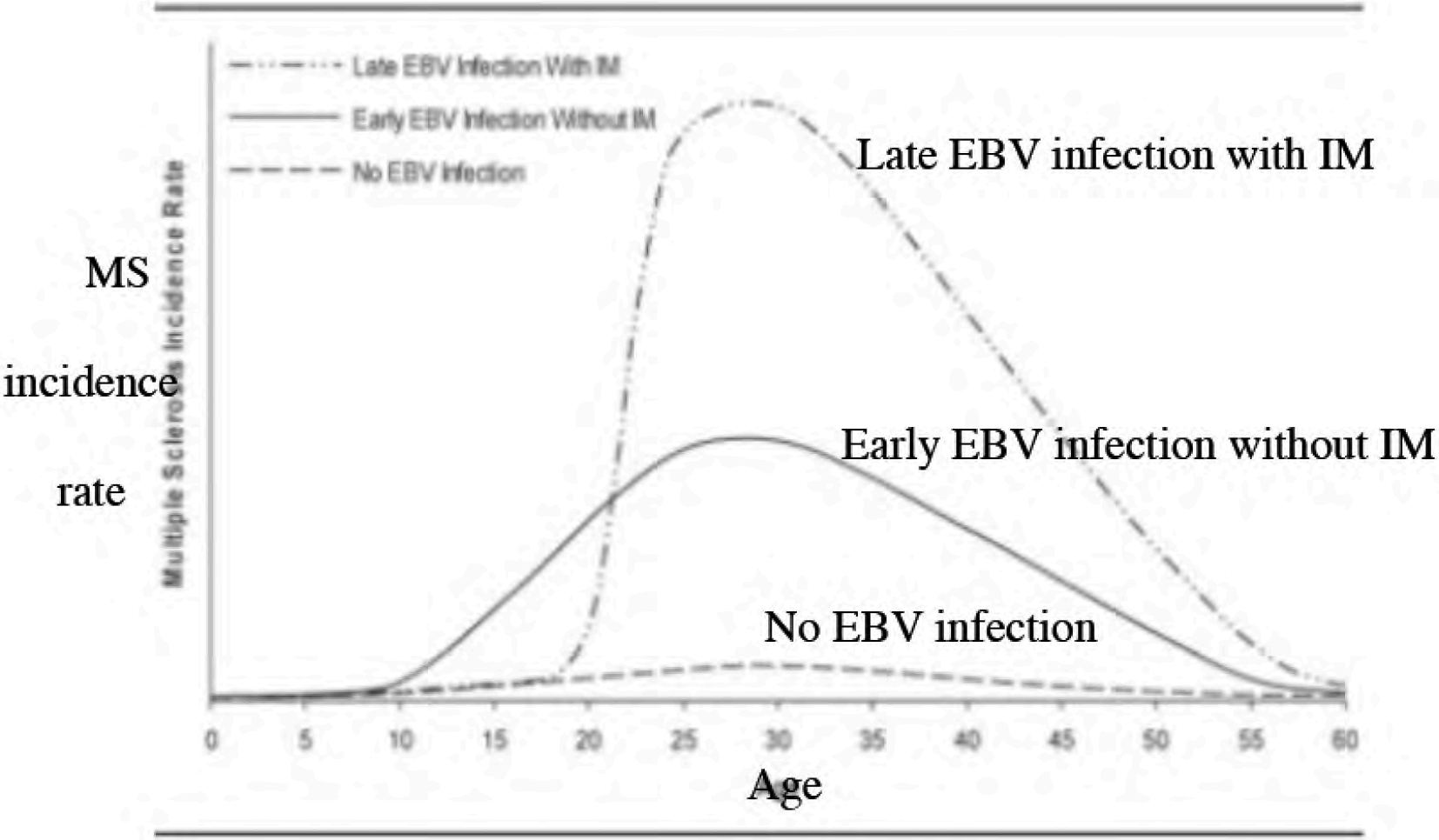
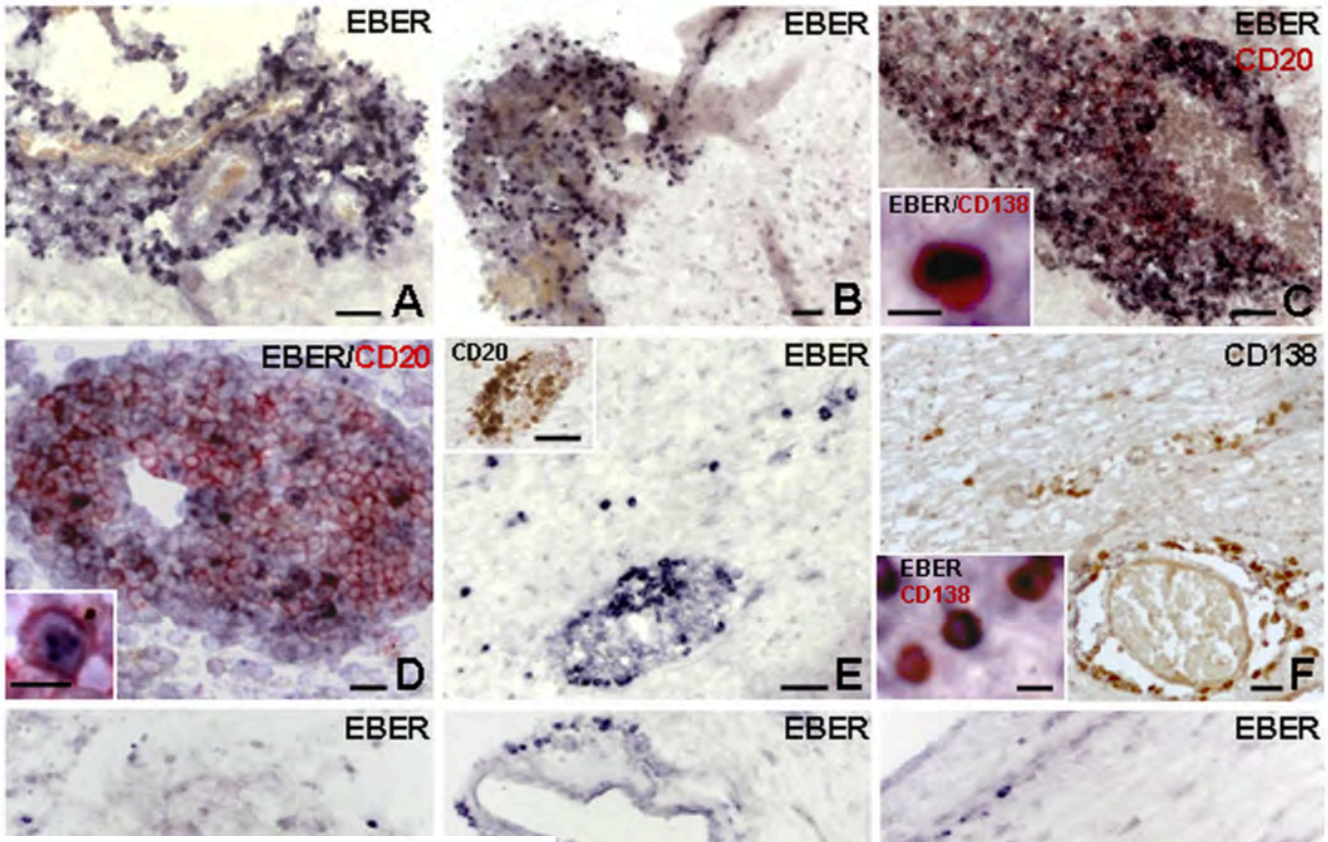


Fig 2. Schematic representation of multiple sclerosis incidence according to Epstein–Barr virus infection. Reprinted with permission from Thacker and colleagues.[54]



JEM

ARTICLE

Dysregulated Epstein-Barr virus infection in the multiple sclerosis brain

Barbara Serafini,[1] Barbara Rosicarelli,[1] Diego Franciotta,[2] Roberta Magliozzi,[3] Richard Reynolds,[3] Paola Cinque,[4] Laura Andreoni,[2] Pankaj Trivedi,[5] Marco Salvetti,[6] Alberto Faggioni,[5] and Francesca Aloisi[1]

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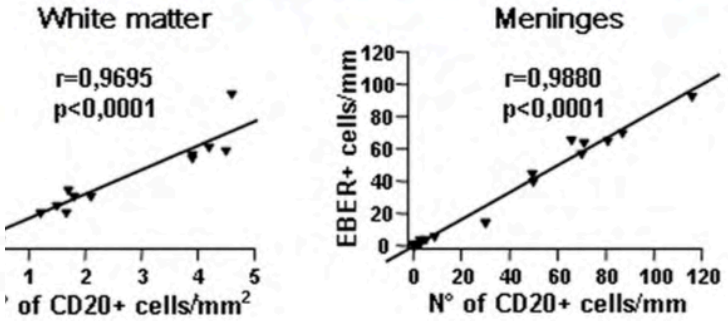


MULTIPLE SCLEROSIS JOURNAL | MSJ

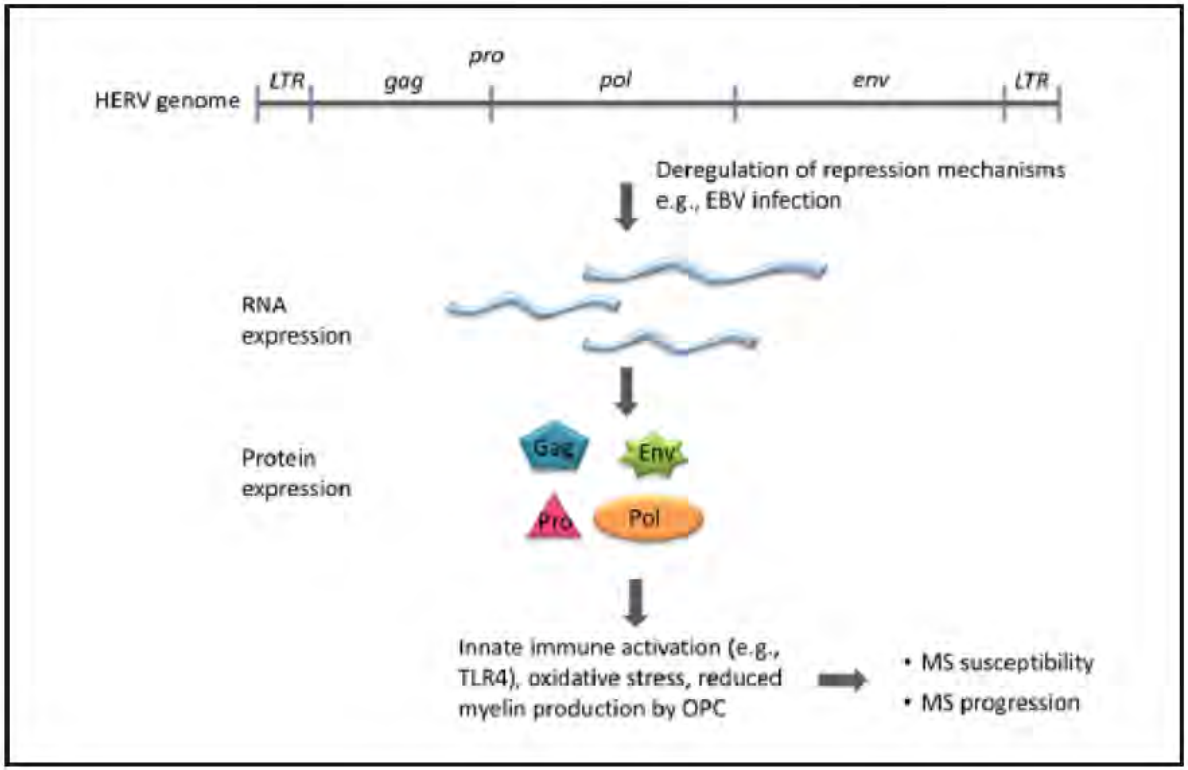
Topical Review

Human endogenous retroviruses and multiple sclerosis: Causation, association, or after-effect?

Multiple Sclerosis Journal
1–6
DOI: 10.1177/1352458517704711

Elena Morandi, Rachael E. Tarlinton, Radu Tanasescu and Bruno Gran

Perron
Ferrante
Sotgiu
Dolei



DOI 10.1007/s10517-015-3037-z

Role of Chlamydia in Multiple Sclerosis

M. V. Ivanova, N. I. Kolkova*, E. Yu. Morgunova*, Yu. P. Pashko*, N. A. Zigangirova*, and M. N. Zakharova

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 159, No. 5, pp. 605-608, May, 2015
Original article submitted May 22, 2014

Chlamydia and antibodies to them were detected by serological, molecular biological, and culture methods in the sera and cerebrospinal fluid of patients with multiple sclerosis and in the reference groups of subjects without neurological diseases. Correlations between the agent presence in the biological fluids of patients and clinical characteristics of the disease were analyzed. *C. pneumoniae* were more incident in the biological liquids of patients with multiple sclerosis than in healthy volunteers. On the other hand, the incidence of the agent in the patients was not high and its presence did not correlate with the clinical manifestations. *C. trachomatis* was equally rare in the patients and volunteers. The studies indicated the existence of a group of patients infected by *C. pneumoniae* in the cohort of patients with multiple sclerosis, but the impact of this agent for the disease course remains unclear.

Key Words: *multiple sclerosis; Chlamydia*

Sriram


"NON ME SOMIGLIA PE' NIENTE!"
JOHNNY STECCHINO

ELSEVIER

Journal of Neuroimmunology 109 (2000) 3–9

Journal of Neuroimmunology

www.elsevier.com/locate/jneuroim

Cytokines and immunity in multiple sclerosis: the dual signal hypothesis

G. Martino[a,b,*], R. Furlan[a], E. Brambilla[a], A. Bergami[a], F. Ruffini[a], M. Gironi[a,b], P.L. Poliani[a], L.M.E. Grimaldi[a,b], G. Comi[b]

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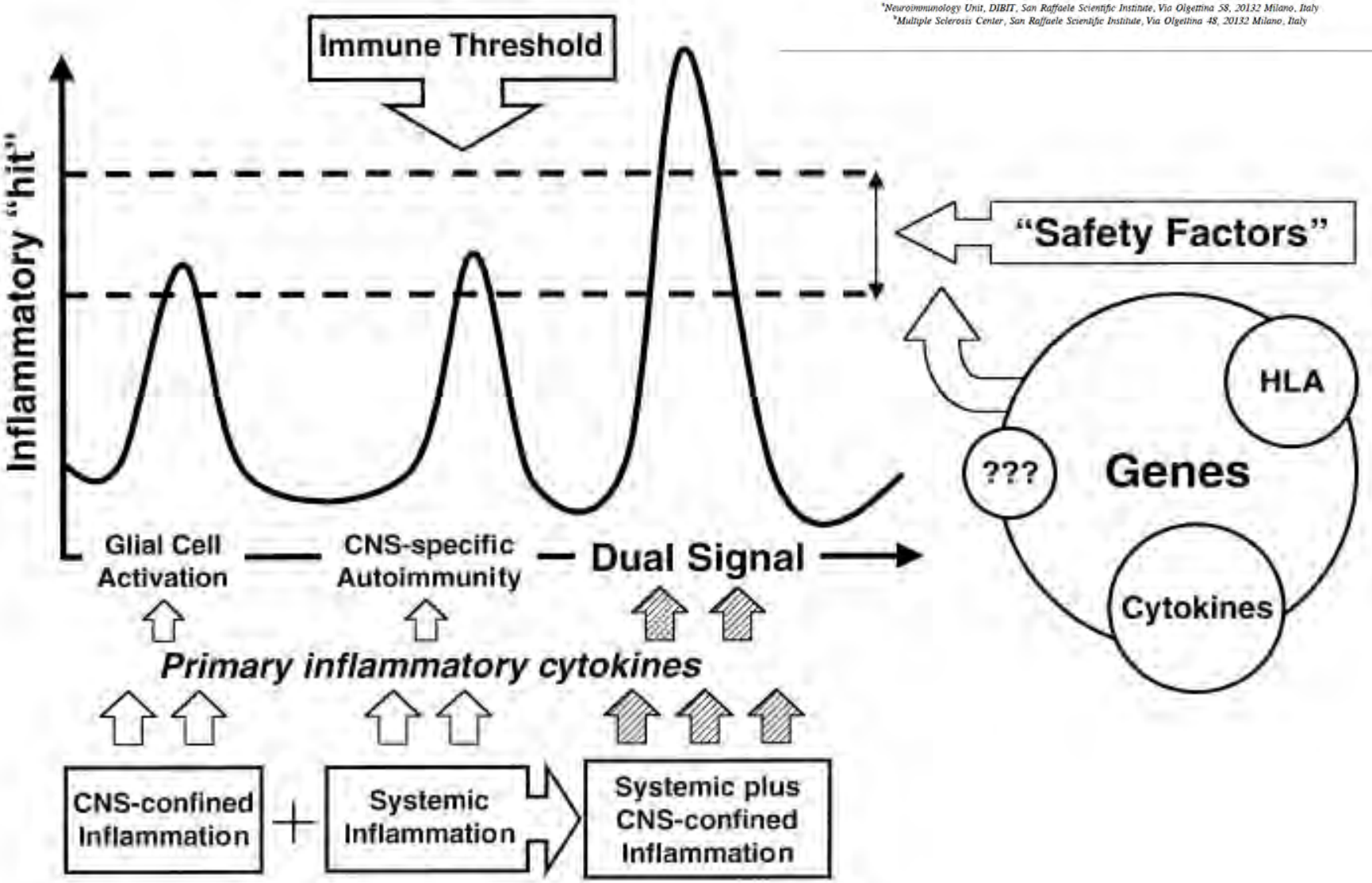
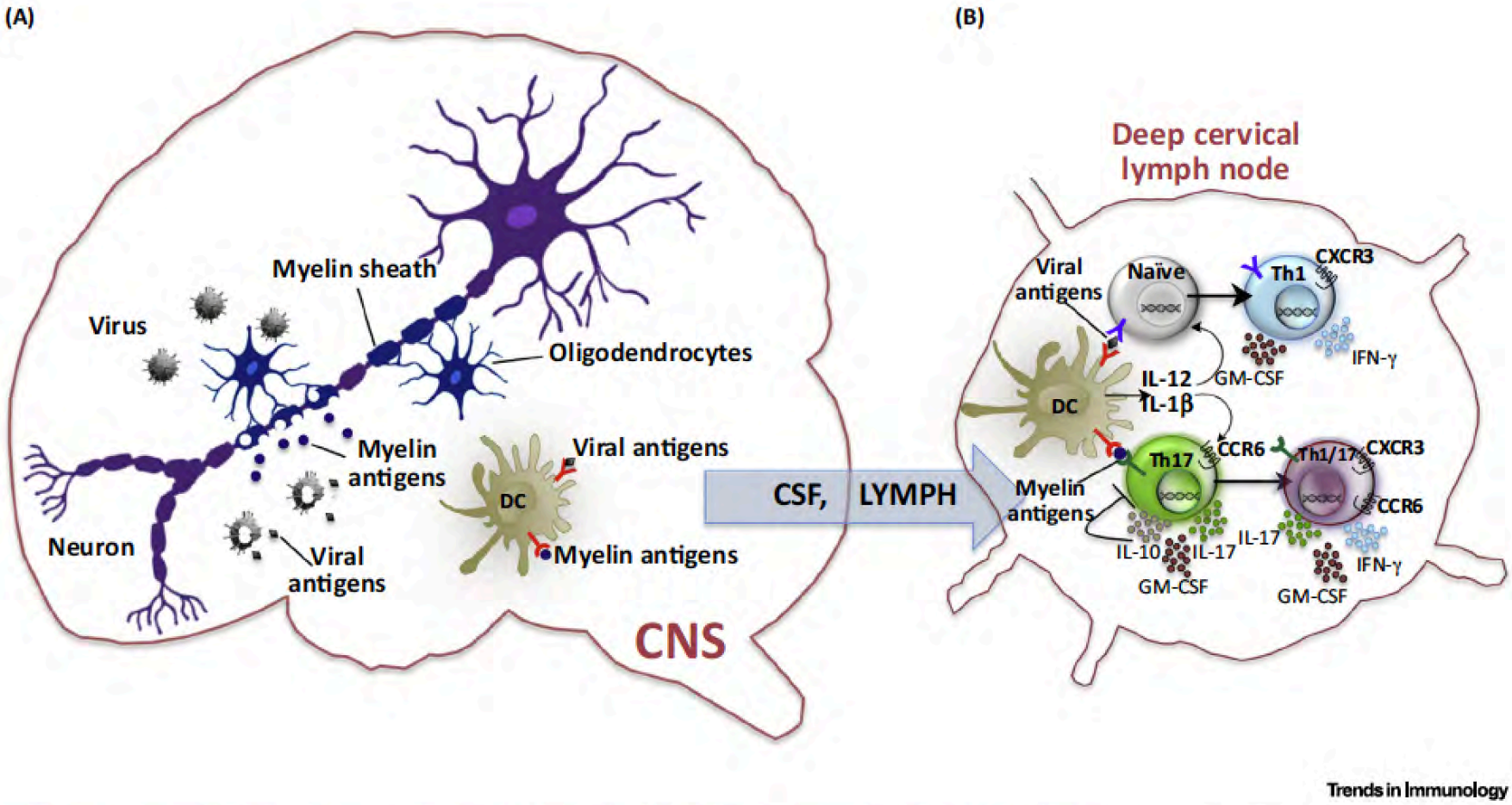




Trends in Immunology

Figure 1. Viral Infections Could Induce Bystander Generation of Pathogenic T Helper (Th)-1/17Cells. Local reactivations of neurotropic viruses in the

Prototypical infectious diseases and immune disorders

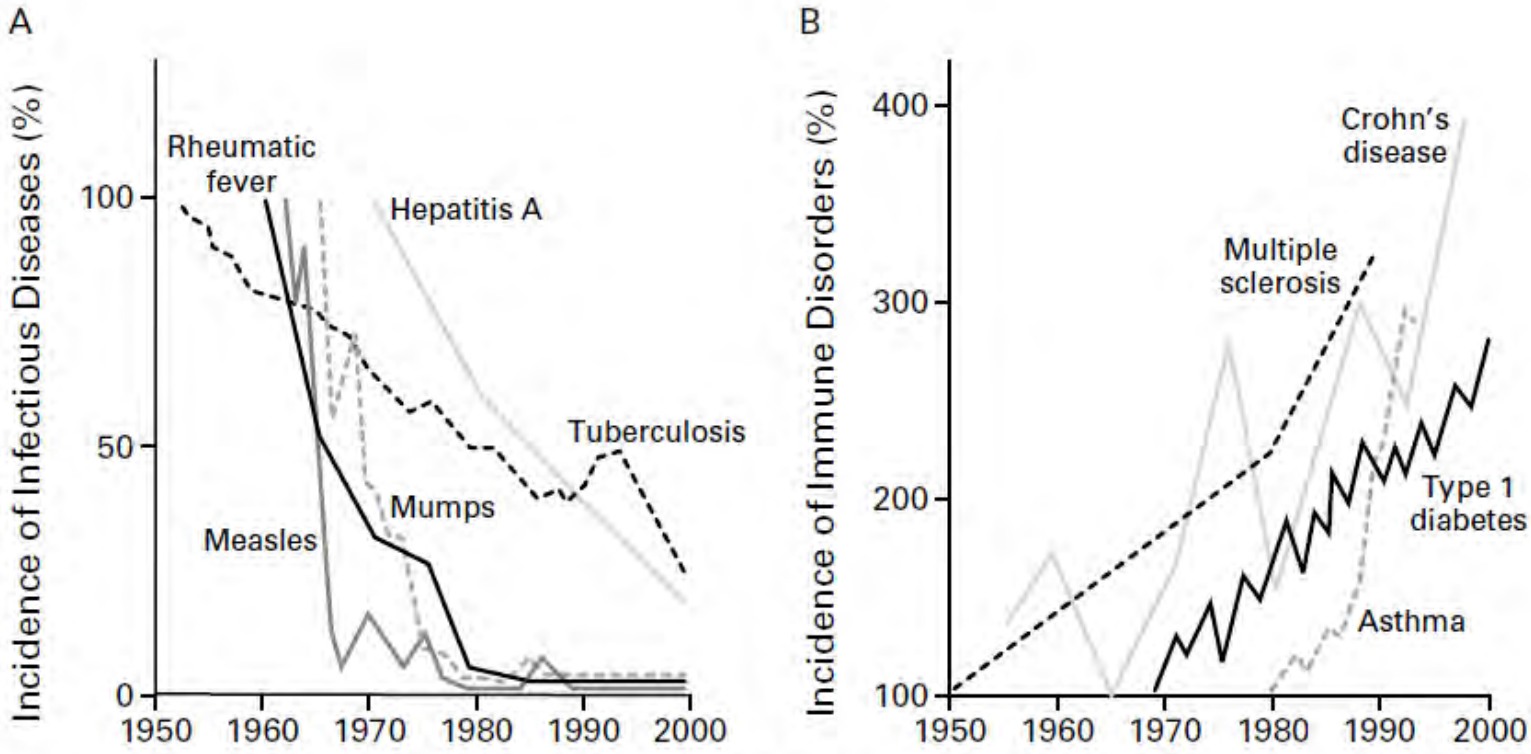


Figure 1. Inverse Relation between the Incidence of Prototypical Infectious Diseases (Panel A) and the Incidence of Immune Disorders (Panel B) from 1950 to 2000.

In Panel A, data concerning infectious diseases are derived from reports of the Centers for Disease Control and Prevention, except for the data on hepatitis A, which are derived from Joussemet et al.[12] In Panel B, data on immune disorders are derived from Swarbrick et al.,[10] Dubois et al.,[13] Tuomilehto et al.,[14] and Pugliatti et al.[15]

Bach JF. N Engl J Med 2002

Bacteria and parasites with protective effects in autoimmune disease

Table 1
Bacteria with protective effects in autoimmune disease

Organism	Autoimmune disease	Species	Reference
Mycobacterial cell wall components	EAE	Guinea pigs	[47]
B. pertussis	EAE	SJL mice	[50,51]
M. tuberculosis	EAE	SJL mice	[50]
M. bovis BCG	EAE	C57BL6 mice	Sewell et al., in preparation
M. avium	IDDM	NOD mice	[52,53]
M. bovis BCG	Adjuvant arthritis	Lewis rats	[54]

Table 2
Parasites with protective effects in autoimmune disease

Organism	Autoimmune disease	Species	Reference
S. mansoni ova	EAE	SJL mice	Qing et al., submitted
T. brucei brucei	CIA	DA rats	[63]
Malaria	Lupus syndrome	NZBxNZW mice	[66]
T. trichuria	IBD	Human	[60]
S. mansoni live infection or ova	IDDM	NOD mice	[59]

Helminth therapy

Table 1
Clinical studies of helminth therapy in human disease.

Disease	Helminth	Outcome	Reference
Multiple Sclerosis	*Trichuris suis*	Five patients with relapsing/remitting MS Fewer neurological and CNS lesions Reoccurrence of symptoms after helminth expulsion	Fleming et al. (2011)
Inflammatory Bowel Disease	*T. suis*	No adverse events observed in CD or UC CD: 12 weeks after single dose of *T. suis ova* 75% remission with a 66% relapse rate UC: 12 weeks after single dose of *T. suis ova* 100% remission with a 33% relapse rate	Summers et al. (2003)
		75.9% of CD patients responded after 12 weeks; 65.5% remitted 79.3% of CD patients responded after 24 weeks; 72% remitted	Summers et al. (2005a)
		43.3% of UC patients responded after 12 weeks compared with 16.7% of placebo Non-significant differences in remission rates observed between treatment groups	Summers et al. (2005b)
		Change in CD activity index 20 weeks p.i. Adverse events recorded include anemia, transient enteropathy and peripheral eosinophilia	Croese et al. (2006)
	Trichuris trichiura	Infection associated with clinical remission and mucosal healing Increased IL-17$^+$ and IL-22$^+$ cells compared to episodes of colitis	Pullan et al. (1994)
Allergic rhinitis	*T. suis*	No significant change in symptom score, total histamine, grass-specific IgE or change in skin prick test	Bager et al. (2010)
	Necator americanus	No significant reduction in lung function No potentiation of allergen-specific IgE	Blount et al. (2009)
		AMP-responsive asthma – no change in airway responsiveness, asthma control or allergen skin test observed	Feary et al. (2010)
Celiac Disease	*N. americanus*	No significant differences in duodenal pathology found between infected group and placebo Infected subjects reported injection site reactions and transient enteritis	Daveson et al. (2011)

MS, multiple sclerosis; CD, Crohn's disease; UC, ulcerative colitis.

Khan and Fallon. Int J Parasitol 2013

MULTIPLE SCLEROSIS JOURNAL | MSJ

Research Paper

Trichuris suis ova therapy in relapsing multiple sclerosis is safe but without signals of beneficial effect

A Voldsgaard, P Bager, E Garde, P Åkeson, AM Leffers, CG Madsen, C Kapel, A Roepstorff, SM Thamsborg, M Melbye, H Siebner, HB Søndergaard, F Sellebjerg and P Soelberg Sørensen

Multiple Sclerosis Journal

1–7

DOI: 10.1177/1352458514568173

Malaria and autoimmune diseases

- The presence of a spatial and temporal cluster of MS occurred after malaria eradication
- Correlation between A30-B18-DR3 HLA haplotype, MS and high malaria prevalence areas
- Some TNF polymorphisms in the TNF-promoter region already associated with both malaria and MS are up to 10 times elevated amongst Sardinians as compared to Sicilians and any other population worldwide

Pugliatti et al. Neurology 2002
Wirz et al. 2004
Fernandez-Arquero et al. Neurology 1999
Knight et al. Nat Genet 1999
McGuire et al. J Infect Dis 1999

J Neurol
DOI 10.1007/s00415-016-8263-4

REVIEW

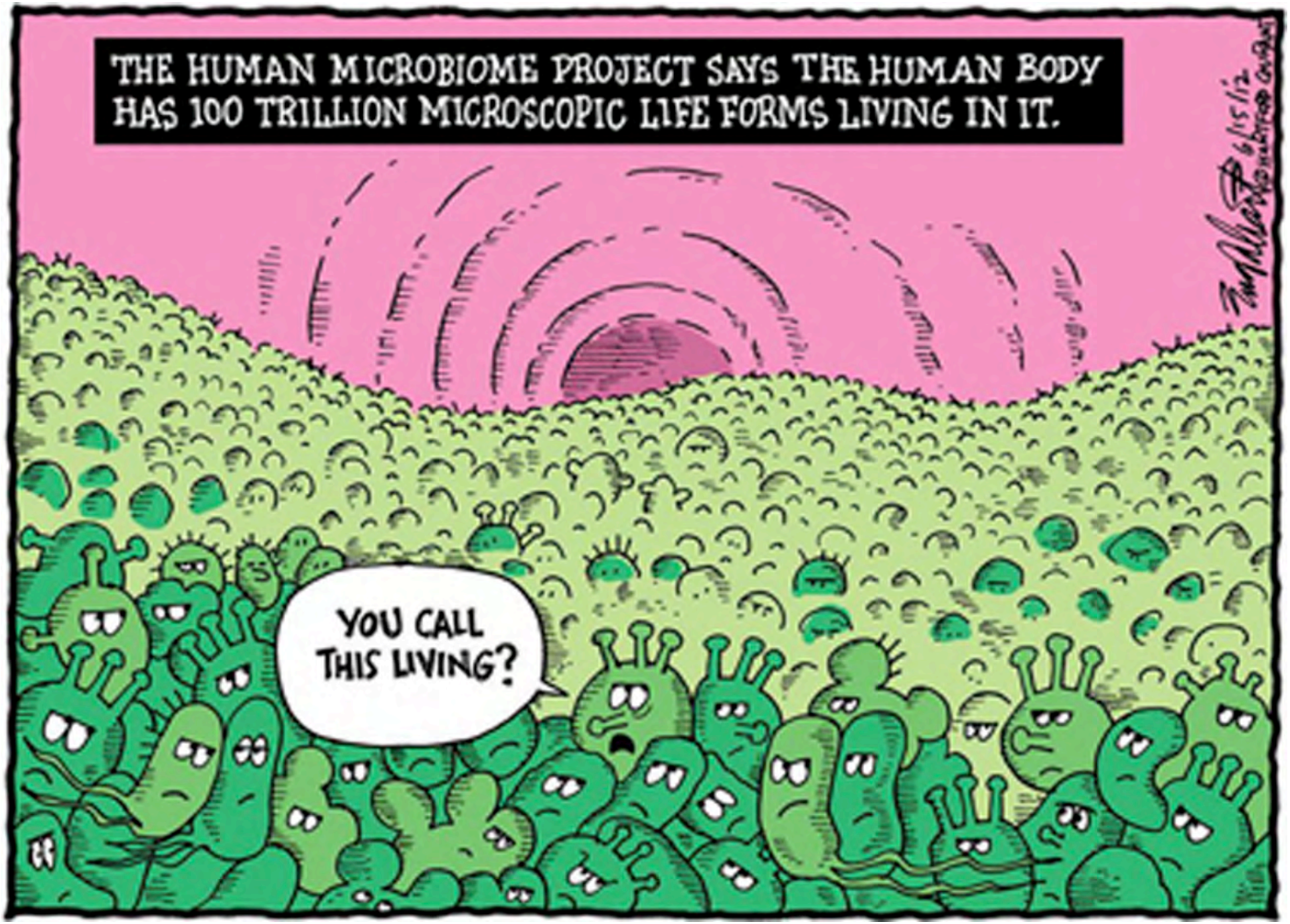
Vaccines and multiple sclerosis: a systematic review

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

Received: 20 July 2016 / Revised: 6 August 2016 / Accepted: 8 August 2016

Abstract Vaccinations are often the most effective tool against some disease known to mankind. This study offers a literature review on the role of vaccines regarding the risk of developing multiple sclerosis (MS) and MS relapse. The method used in this study is a systematic literature review on the database PubMed. The study found no change in risk of developing multiple sclerosis (MS) after vaccination against hepatitis B virus, human papillomavirus, seasonal influenza, measles–mumps–rubella, variola, tetanus, Bacillus Calmette-Guérin (BCG), polio, or diphtheria. No following vaccination and infections give rise to the speculation of a possible causal relationship. The public attitude towards vaccination has a great impact on compliance as illustrated by the drop in HBV (hepatitis B) vaccine coverage following a temporal association of the vaccine and MS onset [1]. This underlines the importance of making and summarizing results of epidemiological studies not to confuse temporal and causal association.

The knowledge of vaccine safety in patients with MS is of great importance, as this provides clear instructions for


THE HUMAN MICROBIOME PROJECT SAYS THE HUMAN BODY HAS 100 TRILLION MICROSCOPIC LIFE FORMS LIVING IN IT.
YOU CALL THIS LIVING?

Ho rubato slides a:
Maura Pugliatti
Michel Brahic
Priyanka Sharma
Roberto Benigni