World Health Organization

Global Advisory Committee
on Vaccine Safety
6 - 7 June 2006

Potential immunogenic overload resulting from concomitant vaccination with too many antigens

David Goldblatt
Professor of Vaccinology and Immunology/
Consultant Paediatric Immunologist
Director of Clinical R&D

Institute of Child Health, UCL
And Great Ormond Street Children's Hospital

Director, WHO Pneumococcal Serology Reference Laboratory

Daily Mail

LIFESAVER JAB FOR ALL BABIES

A VACCINE against meningitis should soon be available to every child in Britain.

By Jenny Hope
Medical Correspondent

Daily Mail

FEMAIL MAGAZINE

Three new jabs are on the way... before the age of 14 months

BABIES TO GET 25 VACCINES

BABIES are to have 25 vaccinations in a year in a move that raised concern of 'immunisation overload'.

By Emily Cook
Health Reporter

Injection 'overload'?

By the age of 13 months, babies will have been given 25 vaccines, against ten diseases in ten different injections

Two months
- Five-in-one jab protects against diphtheria, tetanus, whooping cough, polio and Hib (Hib is an infection causing bacterial meningitis)
- Pneumococcal vaccine.

Three months
- Five-in-one jab
- Meningitis C vaccine.

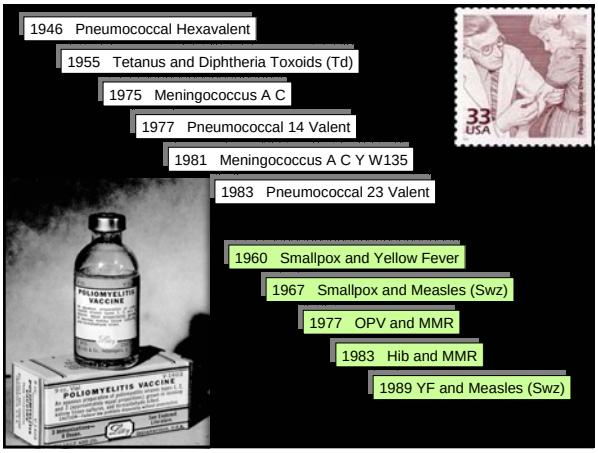
Four months
- Five-in-one jab
- Meningitis C vaccine
- Pneumococcal vaccine.

12 months
- Combined Hib/meningitis C vaccine.

13 months
- MMR (protects against measles, mumps and rubella)
- Pneumococcal vaccine.

Is there a scientific question to answer?

- What is "injection overload" or "immune overload"?
- How is it identified?
- What would the symptoms of overload be?
  - reduced responses to multiple vaccines given at the same time?
  - increased risk of other infections after vaccination?



Live Viral Vaccines

Multi-component Combination Vaccines

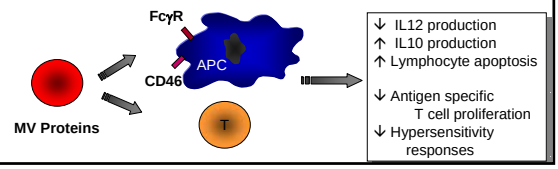
Simultaneous Administration Of Childhood Vaccines

Immunity, Vol. 14, 69–79, January, 2001, Copyright ©2001 by Cell Press

Mechanism of Measles Virus–Induced Suppression of Inflammatory Immune Responses

Julien C. Marie,*§ Jeanne Kehren,* Marie-Claude Trescol-Biemont,* Alexey Evlashev,* Hélène Valentin,* Thierry Walzer,* Rosine Tedone,* Bruce Loveland,† Jean-François Nicolas,* Chantal Rabourdin-Combe,* and Branka Horvat*‖¶
*INSERM U503, CERVI Immunobiologie Fondamentale et Clinique Lyon, 69365 France
†The Austin Research Institute Heidelberg, VIC 3084 Australia

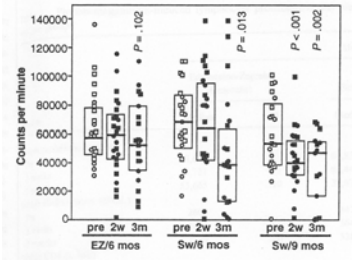
Although MV was the first pathogen reported to induce immunosuppression, documented nearly 100 years ago (Von Pirquet, 1908), the lack of a suitable small animal model has impeded progress in understanding the mechanisms of MV-induced immune abnormalities. Monkeys have been used (Auwaerter et al., 1999), but their utilization is extremely restricted by limited supply and high cost. SCID mice grafted with human PBL showed a reduced production of human IgG after MV infection (Tishon et al., 1996); nevertheless, this model is not convenient for an accurate analysis of antigen-specific responses due to the lack of MHC compatibility between murine stromal tissue and human PBL.



The Effect of Edmonston-Zagreb and Schwarz Measles Vaccines on Immune Responses in Infants

Gregory D. Hussey, Elizabeth A. Goddard, Jane Hughes, Judith J. Ryon,* Mustaphah Kerran, Edgar Carelse, Peter M. Strebel, Lauri E. Markowitz, John Moodie, Peter Barron, Zainub Latief, Rauoff Sayed, David Beatty, and Diane E. Griffin

Departments of Paediatrics and Child Health, Immunology, Community Health, and Medical Virology, University of Cape Town, Western Cape Regional Services Council, Cape Town, South Africa; Department of Medicine and Neurology, Johns Hopkins University School of Medicine, Department of Molecular Microbiology and Immunology, Johns Hopkins University School of Hygiene and Public Health, Baltimore, Maryland; National Immunization Program, Centers for Disease Control and Prevention, Atlanta, Georgia



J Infect Dis 1996

CDC
MMWR
Weekly

Simultaneous Administration of Varicella Vaccine and Other Recommended Childhood Vaccines --- United States, 1995--1999

TABLE 2. Relative risk (RR) of infection with breakthrough varicella in children aged ≥12 months associated with receiving another vaccine <30 days preceding varicella vaccine (Var) or simultaneously compared with receiving Var ≥30 days before or after another vaccine, by vaccine — California and Oregon, 1995–1999

Vaccine*	Simultaneous with Var RR	Simultaneous with Var (CI†)	Var <30 days later RR	Var <30 days later (CI)
MMR	1.1	(0.9–1.4)	2.5	(1.2–4.9)
DTP	1.1	(0.9–1.3)	1.0	(0.4–2.5)
Hib	1.1	(0.8–1.3)	0.4	(0.1–2.6)
OPV	1.1	(0.8–1.5)	1.6	(0.5–5.1)
IPV	2.1	(0.5–8.4)	—¶	
HepB	1.2	(0.7–1.9)	2.3	(0.8–6.7)

* MMR: combined measles-mumps-rubella vaccine; DTP: diphtheria and tetanus toxoids and pertussis vaccine; Hib: *Haemophilus influenzae* type B vaccine; OPV: oral poliovirus vaccine; IPV: inactivated poliovirus vaccine; HepB: hepatitis B vaccine.
† Confidence interval.
§ RR significant.
¶ Numbers were too small for meaningful analysis.

Return to top.

Does MMR "overwhelm" the immune system?

Clinical and Serologic Evaluation of Measles, Mumps, and Rubella (HPV-77:DE-5 and RA 27/3) Virus Vaccines, Singly and in Combination

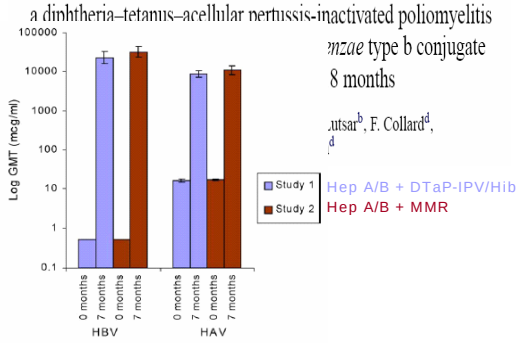
Stephen J. Lerman, MD, Mitzi Bollinger, RN, and Jan M. Brunken, RN

From the Departments of Pediatrics and Medical Microbiology, College of Medicine, University of Nebraska, Omaha

% seroconversion	Measles	Mumps	Rubella
Single Measles	100	--	--
Single Mumps	--	92	--
Single Rubella	--	--	100
MMR Vaccine	96	90	100

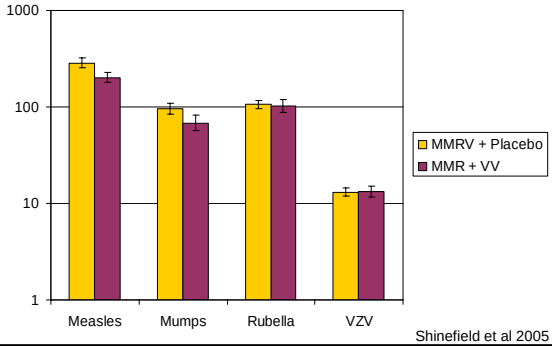
Pediatrics 1981

Immunogenicity and safety of a combined hepatitis A and B vaccine administered concomitantly with either a measles–mumps–rubella or a diphtheria–tetanus–acellular pertussis-inactivated poliomyelitis
nzae type b conjugate
8 months
.utsar[b], F. Collard[d],
[d]



Vaccine 2005

Response of 12-23 month old children receiving MMR and VZV vaccines alone or in combination



Shinefield et al 2005

SHORT REPORT

Bacterial infections, immune overload, and MMR vaccine

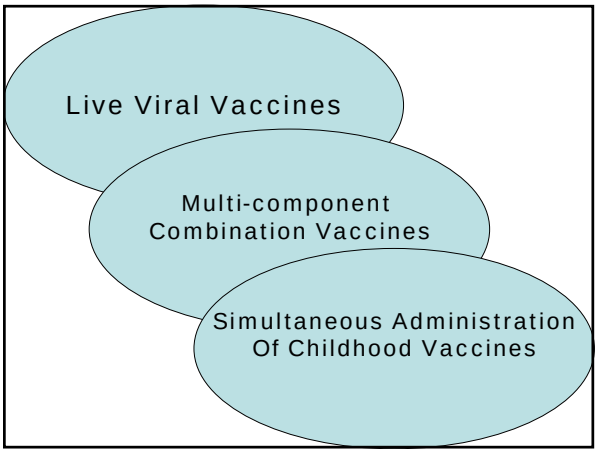
E Miller, N Andrews, P Waight, B Taylor

Arch Dis Child 2003;**88**:222–223

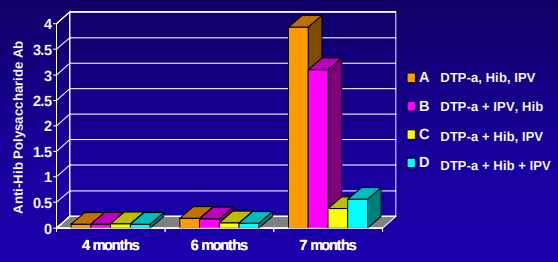
Combined measles, mumps, and rubella (MMR) vaccine did not increase the risk of hospitalisation with invasive bacterial infection in the three months after vaccination; rather there was a protective effect. These results provide no support for the concept of "immunological overload" induced by multiple antigen vaccinations, nor calls for single antigen vaccines.

Table 1 Relative incidence, 95% CI [total cases in the risk periods]

Risk period (days)	Lobar pneumonia code	Invasive bacterial infection code	Both codes
−14 to −1	0.26 (0.09 to 0.79) [3]	0.19 (0.03 to 1.37) [1]	0.25 (0.09 to 0.64) [4]
0 to 30	0.77 (0.48 to 1.23) [23]	1.00 (0.52 to 1.94) [12]	0.81 (0.56 to 1.19) [35]
31 to 60	0.80 (0.50 to 1.28) [24]	1.17 (0.62 to 2.20) [14]	0.90 (0.62 to 1.31) [38]
61 to 90	0.52 (0.30 to 0.90) [16]	0.62 (0.27 to 1.40) [7]	0.56 (0.36 to 0.89) [23]
0 to 90	0.70 (0.50 to 0.97) [63]	0.93 (0.58 to 1.49) [33]	0.76 (0.58 to 0.99) [96]



Co-administration of DTaP and Hib conjugate vaccine at 4 and 6 m of age following DTaP at 2 m.



Eskola et. al. 1996 *Lancet*;**348**:1688-92

What is the mechanism?

Is this immune overload?

Table II. Serum *Haemophilus influenzae* type b capsular polysaccharide antibodies, measured by radioimmunoassay, in 18- to 23-month-old children injected with Hib CPS, Hib-TT, or Hib-TT ads

Vaccine	n	GM μg Ab/mL (25th to 75th percentiles) Before immunization	After immunization	GM-rise	%With ≥4-fold rise	%With ≥1.0 μg Ab/mL
Hib CPS	28	0.18 (0.03-0.74)	2.80* (0.39-20.7)	15.6-fold	71.4	75.0
Hib-TT	28	0.16 (0.06-0.34)	26.8† (9.67-76.5)	168-fold	96.4	100.0
Hib-TT ads	27	0.17 (0.05-0.56)	0.55 (0.13-1.65)	3.2-fold	40.7	40.7

*P < 0.001 versus preimmunization titer.
†P < 0.001 versus preimmunization titer; P < 0.001 versus postimmunization titer for Hib CPS and Hib-TT ads.

Claesson et al J Pediatr 1988

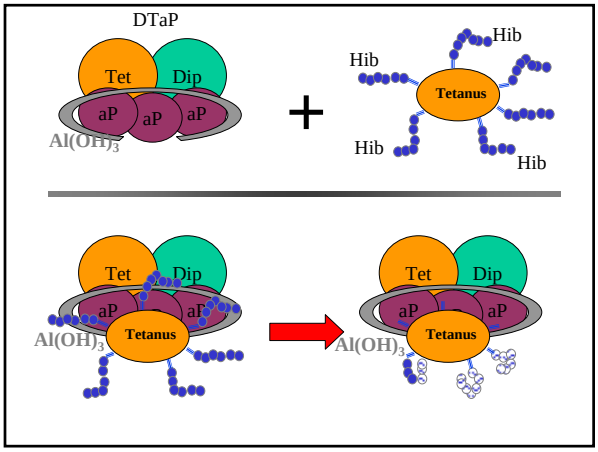
ELSEVIER

Vaccine 17 (1999) 1169–1178

Vaccine

Haemophilus influenzae type b conjugate vaccine stability: catalytic depolymerization of PRP in the presence of aluminum hydroxide

Annie W. Sturgess[a], Kay Rush[a], Ronald J. Charbonneau[a], James I. Lee[a], David J. West[b], Robert D. Sitrin[a], John P. Hennessey Jr.[a,*]



INFECTION AND IMMUNITY, May 1998, p. 2093–2098
0019-9567/98/$04.00+0
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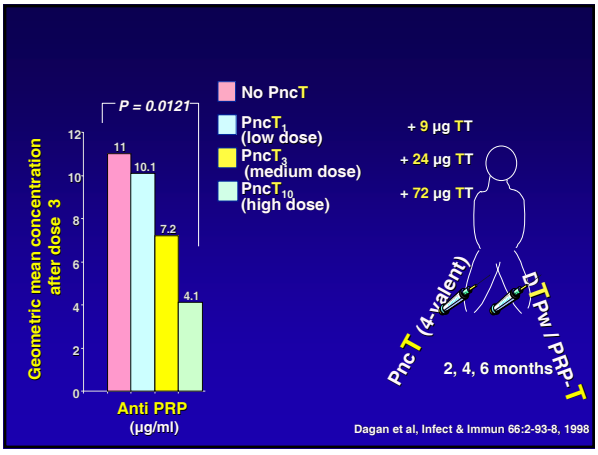
Vol. 66, No. 5

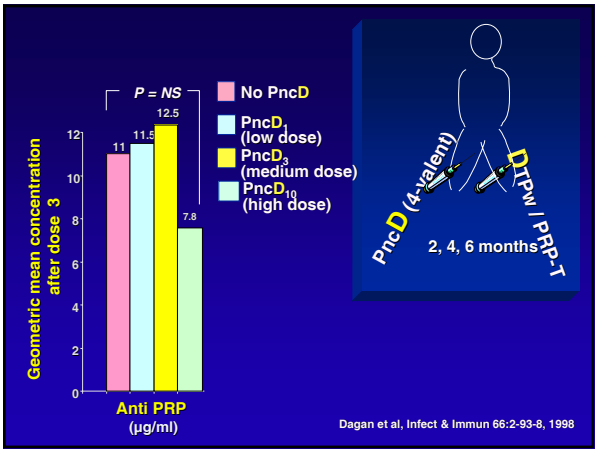
Reduced Response to Multiple Vaccines Sharing Common Protein Epitopes That Are Administered Simultaneously to Infants

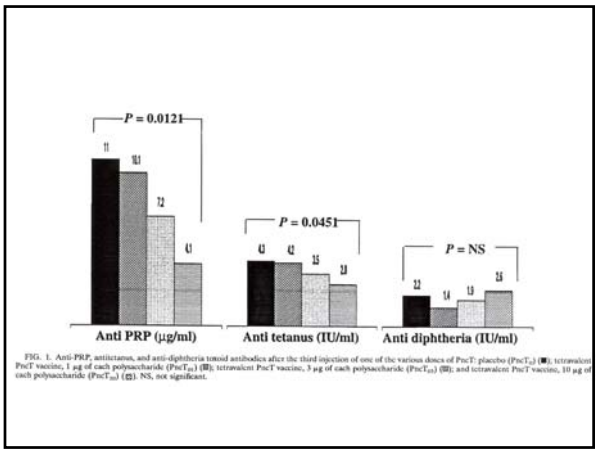
RON DAGAN,[1,2]* JUHANI ESKOLA,[3] CLAUDE LECLERC,[4] AND ODILE LEROY[5]

Pediatric Infectious Disease Unit, Soroka University Medical Center,[1] and Faculty of Health Sciences, Ben-Gurion University of the Negev,[2] Beer-Sheva, Israel; National Public Health Institute, Helsinki, Finland[3]; and Department of Immunology, Institut Pasteur, Paris,[4] and Pasteur Mérieux Connaught, Marnes la Coquette,[5] France

Received 13 October 1997/Returned for modification 21 November 1997/Accepted 5 February 1998







Biologicals (1999) 27, 167–176
Article No. bicl.1999.0204, available online at http://www.idealibrary.com on IDEAL®

Evaluation of a Guinea Pig Model to Assess Interference in the Immunogenicity of Different Components of a Combination Vaccine Comprising Diphtheria, Tetanus and Acellular Pertussis (DTaP) Vaccine and *Haemophilus influenzae* type b Capsular Polysaccharide Conjugate Vaccine

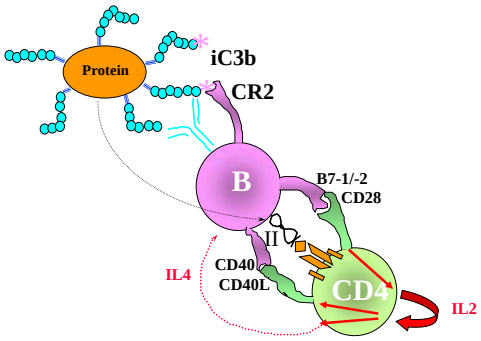
Rajesh K. Gupta*†, Roger Anderson, Douglas Cecchini, Bradford Rost, Jin Xu, Katherine Gendreau, Denise L Saroff, Colin Marchant and George R Siber*
Massachusetts Public Health Biologic Laboratories, 305 South St, Boston, MA 02130, U.S.A.

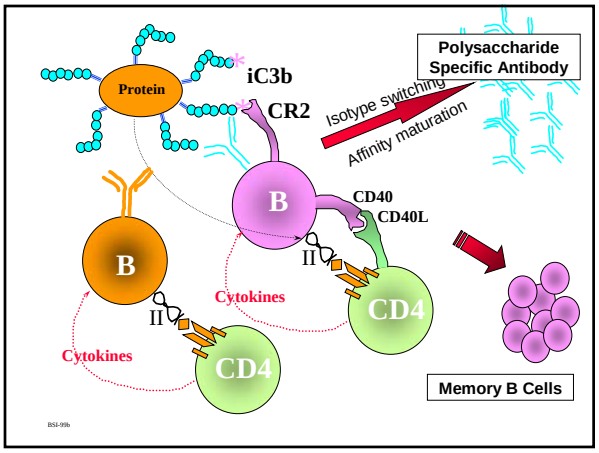
MAJOR ARTICLE

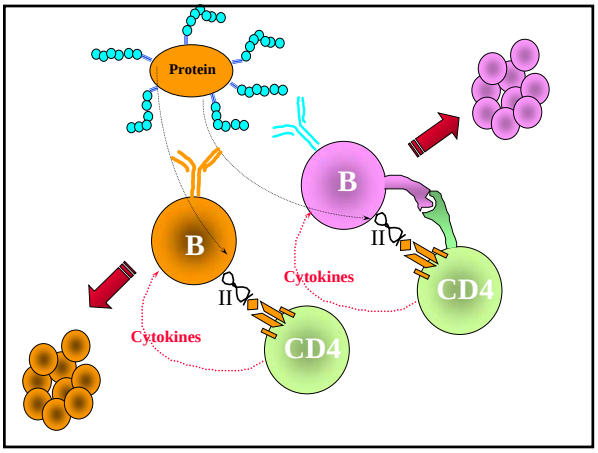
Suppression and Modulation of Cellular and Humoral Immune Responses to *Haemophilus influenzae* Type B (Hib) Conjugate Vaccine in Hib–Diphtheria-Tetanus Toxoids–Acellular Pertussis Combination Vaccines: A Study in a Rat Model

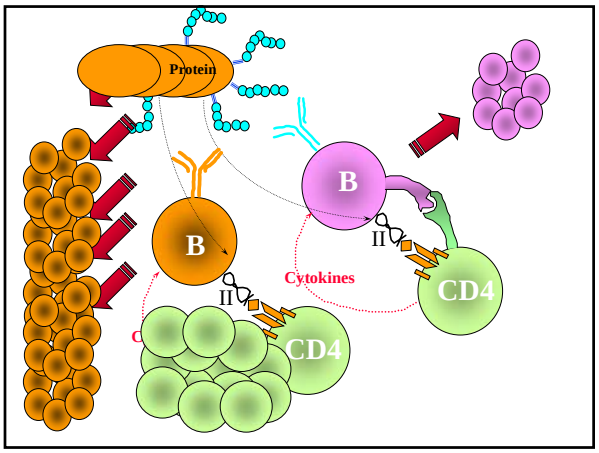
Fatme Mawas, Gareth Newman, Samantha Burns, and Michael J. Corbel
Division of Bacteriology, National Institute for Biological Standards and Control, Hertfordshire United Kingdom

Journal of Infectious Diseases 2005









INFECTION AND IMMUNITY, Sept. 2004, p. 5383–5391
0019-9567/04/$08.00+0 DOI: 10.1128/IAI.72.9.5383–5391.2004

Vol. 72, No. 9

Reduction of Antibody Response to an 11-Valent Pneumococcal Vaccine Coadministered with a Vaccine Containing Acellular Pertussis Components

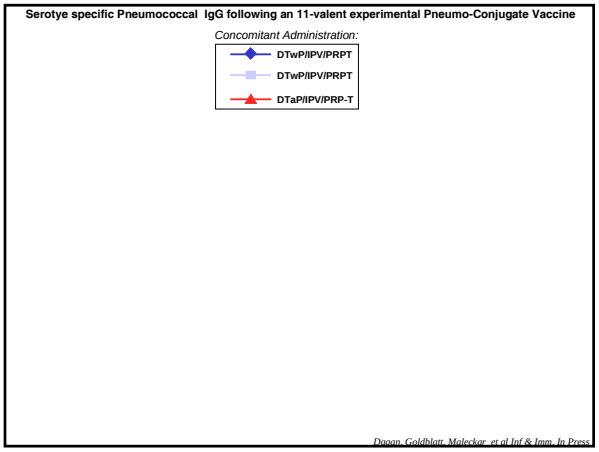
Ron Dagan,[1]* David Goldblatt,[2] James R. Maleckar,[3] Mansour Yaïch,[4] and Juhani Eskola[4]†

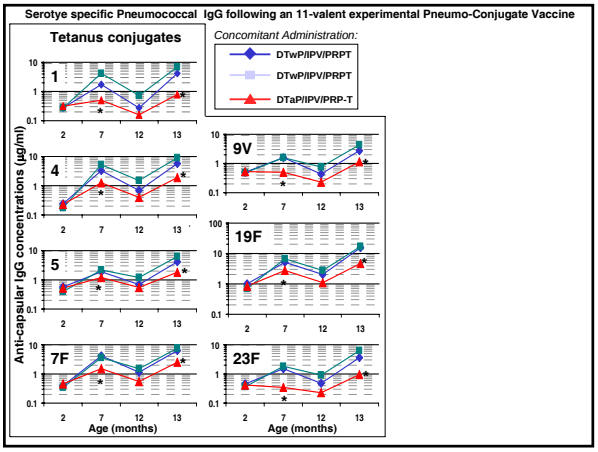
Pediatric Infectious Disease Unit, Soroka University Medical Center and the Faculty of Health Sciences, Ben Gurion University, Beer Sheva, Israel[1]; Immunobiology Unit, Institute of Child Health, University College London, London, United Kingdom[2]; Aventis Pasteur, Inc., Swiftwater, Pennsylvania[3]; and Aventis Pasteur, Lyon, France[4]

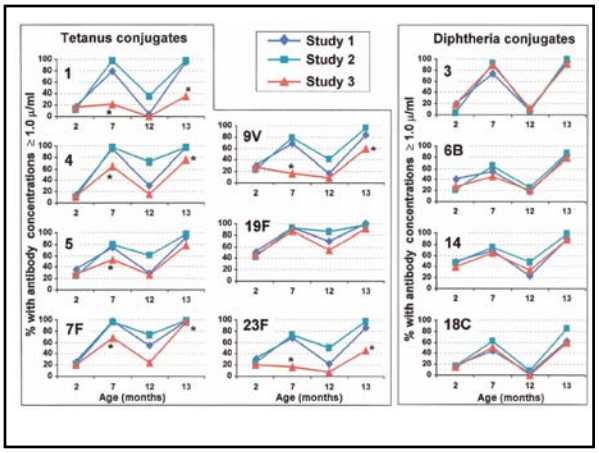
TABLE 1. Design of studies 1 to 3[a]

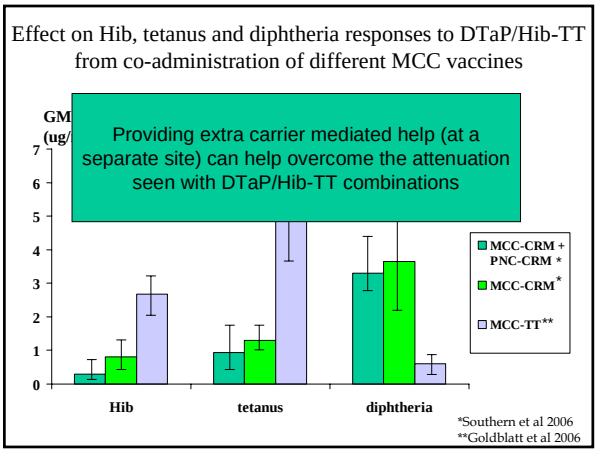
Age (mo)	Study vaccine (PncD/T11)	Blood sample	Concomitant vaccine		
			Study 1	Study 2	Study 3
2	+	+	DTwP/IPV/PRP-T	DTwP/IPV/PRP-T	DTaP/IPV/PRP-T
4	+		DTwP/IPV/PRP-T	DTwP/IPV/PRP-T, OPV	DTaP/IPV/PRP-T, OPV
6	+		DTwP/IPV/PRP-T	DTwP/PRP-T, OPV	DTaP/PRP-T, OPV
7		+	OPV		
12	+	+	DTwP/IPV/PRP-T	DTwP/IPV/PRP-T, OPV, MMR	DTaP/IPV/PRP-T, OPV
13		+	OPV, MMR		MMR

[a] See the text for detailed explanation. Study 1 was conducted in 1998 to 1999, study 2 was conducted in 1999 to 2000, and study 3 was conducted in 2000 to 2001.









- Responses to Measles, Mumps and Rubella are similar irrespective if given singly or in combination
- MMR does not interfere with responses to concomitant vaccines
- MMR does not lead to susceptibility to infections in the 90 days post infection
- Combined vaccines may display reduced responses due to individual components
- These are due to physical degrading of vaccine components or skewing of the immune response to those components present in high dosage

DAILY MIRROR
12/3/98

My girl was happy and healthy till she had a routine jab ..now she is autistic

AT 13 months old, Melissa Mackay was a happy, healthy baby. She could speak a few words, walk a few steps, and loved laughing and playing with her elder sister Vanessa.

ings will worry millions of parents currently being targeted by Government campaigns to ensure that their babies are vaccinated against childhood illnesses.

In a bid to allay anxieties, the Health Department has commissioned the Medical Research Council to investigate any possible link. Its findings are expected to be announced by the end of this month.

Despite controversy over its safety since the MMR vaccine was introduced in October 1988, the Government's medical advisers say that all children should be vaccinated, and that there is no evidence of any risk. Experts stress that symptoms of autism do not usually appear until a child is two — often the time of the MMR vaccination — so there may be no association. And there have been millions of doses given with no adverse side-effects.

Risks

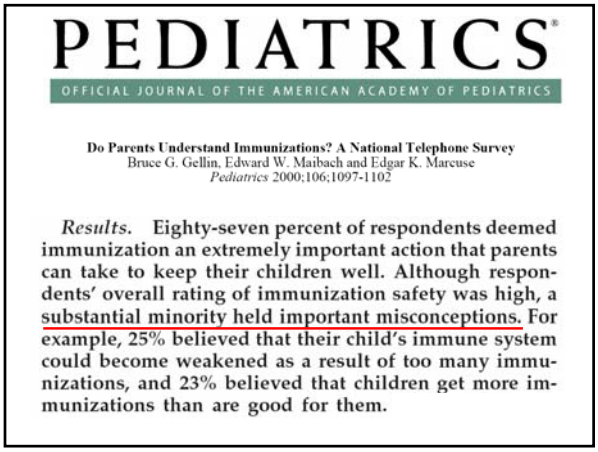
"The risks of not using this vaccine far outweigh any possible side-effects," says Dr Jeremy Metters, deputy chief medical officer. "Our advice to parents is to continue to vaccinate your children."

But Clare and thousands of other mothers are not so confident. "I was not in the least worried when Melissa had her vaccination," says Clare, 31, from Great Yarmouth, Norfolk. "I was always a strong believer in children being vaccinated.

"Now I am not so sure. It all seems too much of a coincidence — especially as there are so many children who were previously well and are now suffering these awful problems.

"Melissa had hardly a day's illness before the MMR. Now she is a sick little girl. Yet the Government still insists there is no connection.

"I want to know the truth. I want proof whether this vaccination is safe

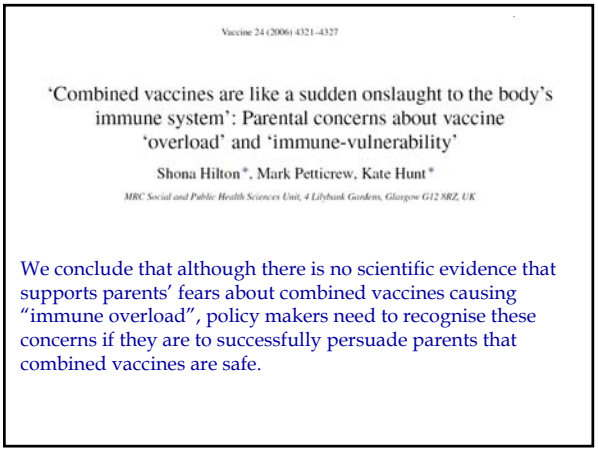


PEDIATRICS

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Do Parents Understand Immunizations? A National Telephone Survey
Bruce G. Gellin, Edward W. Maibach and Edgar K. Marcuse
Pediatrics 2000;106;1097-1102

Results. Eighty-seven percent of respondents deemed immunization an extremely important action that parents can take to keep their children well. Although respondents' overall rating of immunization safety was high, a substantial minority held important misconceptions. For example, 25% believed that their child's immune system could become weakened as a result of too many immunizations, and 23% believed that children get more immunizations than are good for them.



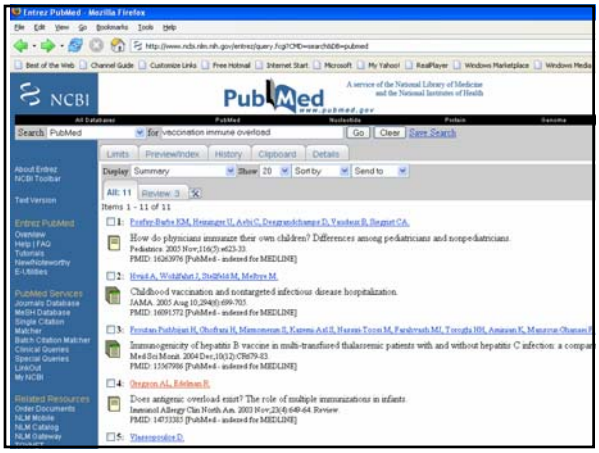
Vaccine 24 (2006) 4321–4327

'Combined vaccines are like a sudden onslaught to the body's immune system': Parental concerns about vaccine 'overload' and 'immune-vulnerability'

Shona Hilton*, Mark Petticrew, Kate Hunt*

MRC Social and Public Health Sciences Unit, 4 Lilybank Gardens, Glasgow G12 8RZ, UK

We conclude that although there is no scientific evidence that supports parents' fears about combined vaccines causing "immune overload", policy makers need to recognise these concerns if they are to successfully persuade parents that combined vaccines are safe.



Among physicians in Switzerland interested in immunization, a significant proportion of nonpediatricians decline or delay the immunization of their own children with the recommended MMR- or DTP-based combination vaccines, which indicates that clarification of misconceptions such as fear of "immune overload" has not yet reached important targets among health care providers who thus are unlikely to answer parental concerns adequately. *Pediatrics* 2005;116:e623–e633.