
Fly Emirates
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THE FA CUP

Understanding Responses to Polysaccharide and Conjugate Vaccines in infants and adults

David Goldblatt
Institute of Child Health,
University College London
London

- Biology of encapsulated bacteria and the role of the capsule
- Polysaccharides as vaccine antigens and the development of conjugates
- Pneumococci in the nasopharynx: impact of vaccines on carriage and the influence of exposure to capsule on subsequent vaccine responses
- Pneumococcal disease in the elderly: Biology and Prevention – Conjugate or polysaccharide?

PAEDIATRIC HANDBOOK

14 MENINGITIS

A J G THOMSON

The commonest causes are bacterial and viral; rarely fungal, rickettsial or protozoal. Acute bacterial meningitis occurs more often in the paediatric age group than any other.

ORGANISMS

Children over 3 months of age Haemoph, Meningo, Pneumo, TB 6-24

The overwhelming majority of cases of bacterial meningitis are due to haemophilus influenzae (less so after the age of 3 years), meningococci, and pneumococci. Tuberculous meningitis is not uncommon in South Africa. Its highest incidence is between 6 and 24 months.

Babies under 3 months of age G-ve's, Strept (B haem Grp B)

Here coliforms and other enteric bacteria are the commonest organisms as well as streptococci.

DIAGNOSIS

Early clinical recognition is essential.

Neonate: Specific signs and symptoms are commonly absent and therefore there should be liberal indications for lumbar puncture. Noteworthy features may be poor sucking, hypothermia, apathy, failure to gain weight and apnoeic attacks.

Infants: Fretfulness, high pitched cry, convulsions, vomiting, pyrexia, full or tense fontanelle.

Children: Headache, fever, vomiting, photophobia, neck stiffness, positive Kernig and/or Brudzinski signs.

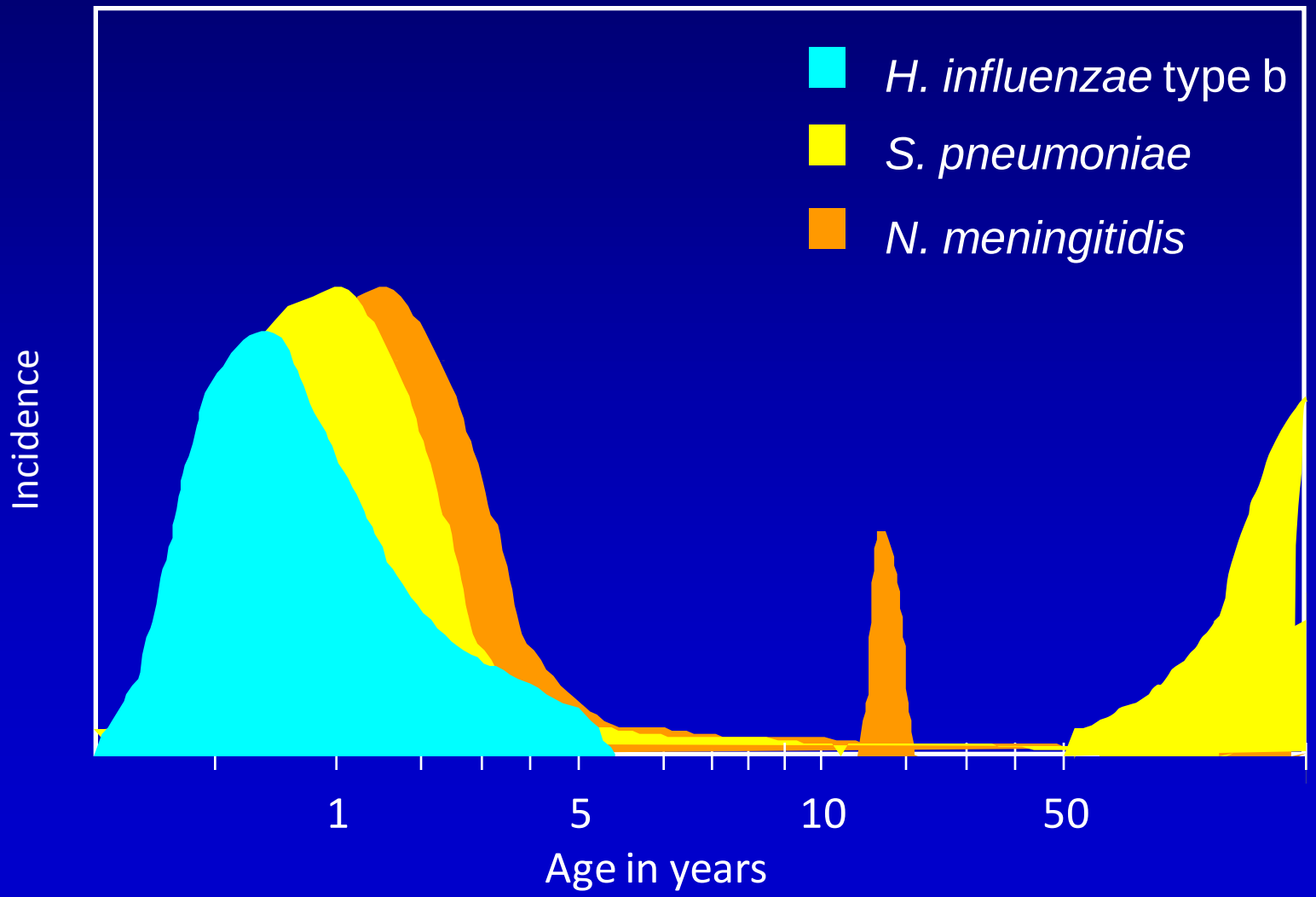
Specific laboratory diagnosis

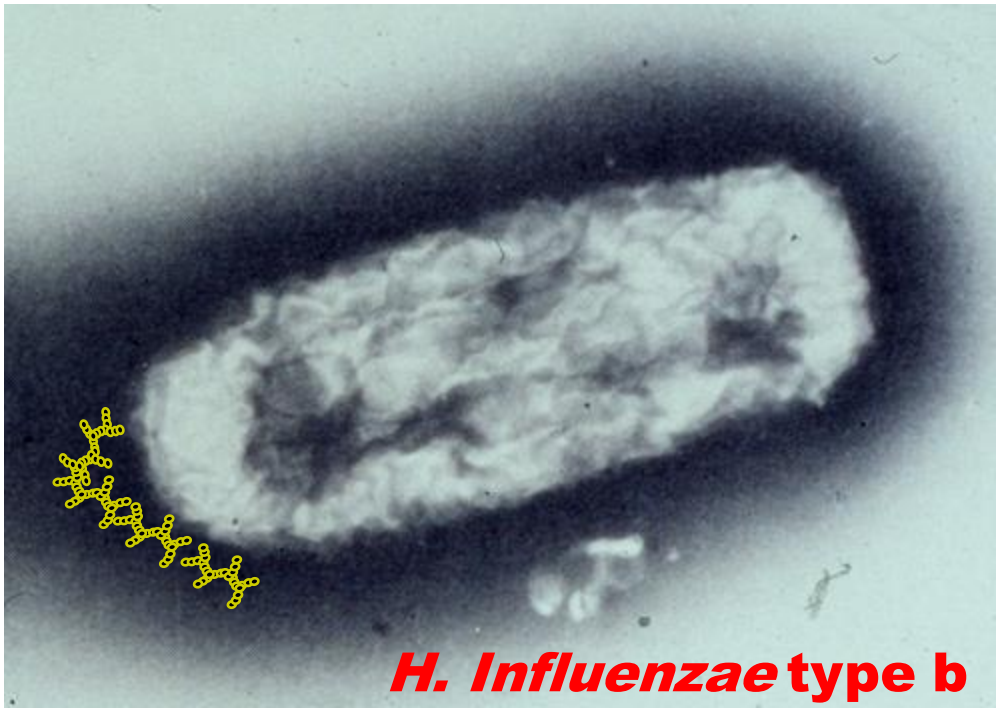
By lumbar puncture, with thorough examination of CSF, including culture and sensitivity of organisms.

Disturbed consciousness is due to *cerebral oedema* and must be treated at once by reducing the raised intracranial pressure. Use Mannitol and Steroids (see Chapter 15), do blood culture, start antibiotics. No LP for 12 hours. Early death may be from cerebral oedema, not meningitis.

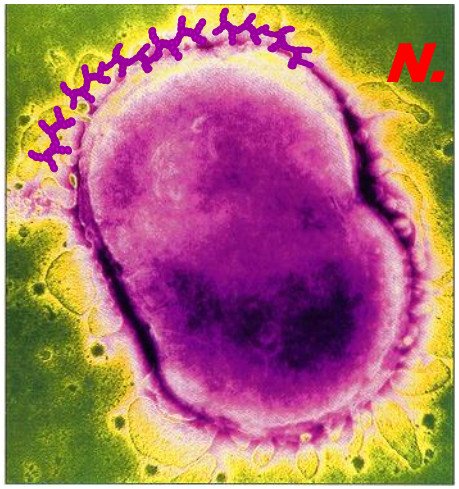
CSF ADA → TB meningitis

Epidemiology of invasive infection due to *H. influenzae* type b, *N. meningitidis* and *S. pneumoniae*.

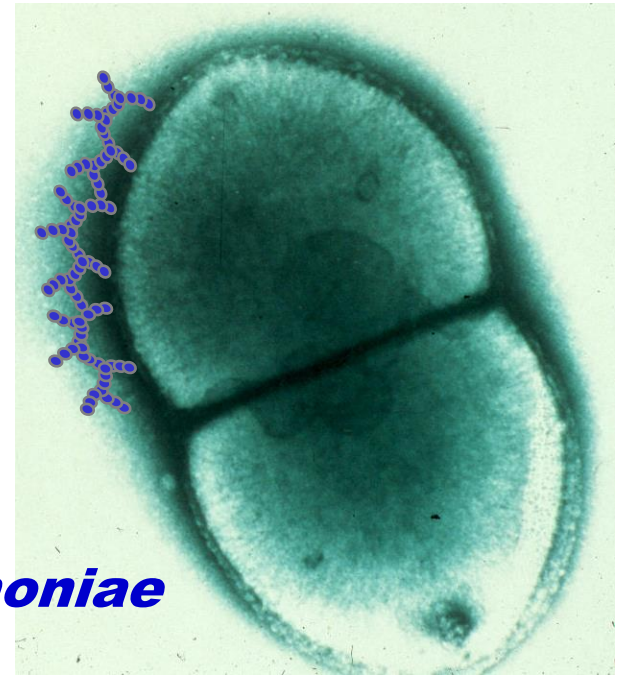




H. Influenzae type b

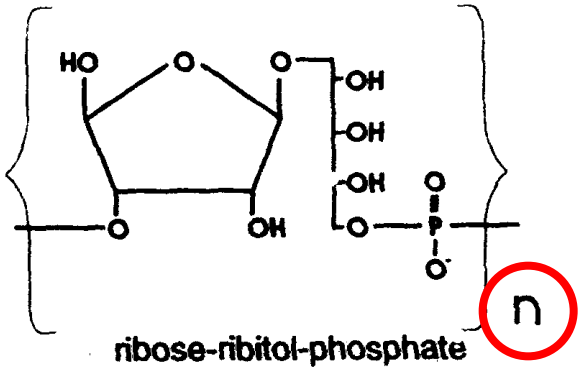


N. meningitidis



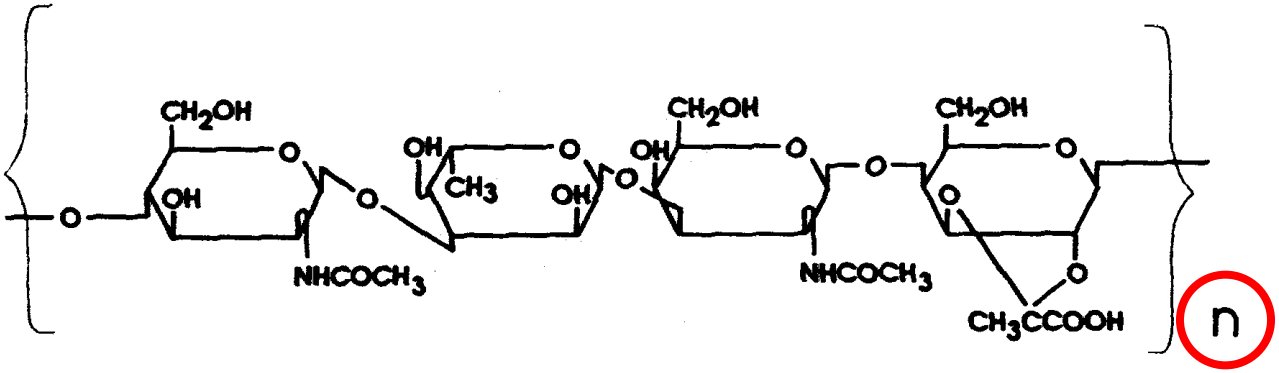
S. pneumoniae

Haemophilus influenzae type b

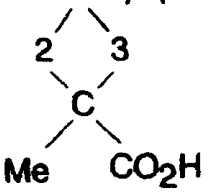


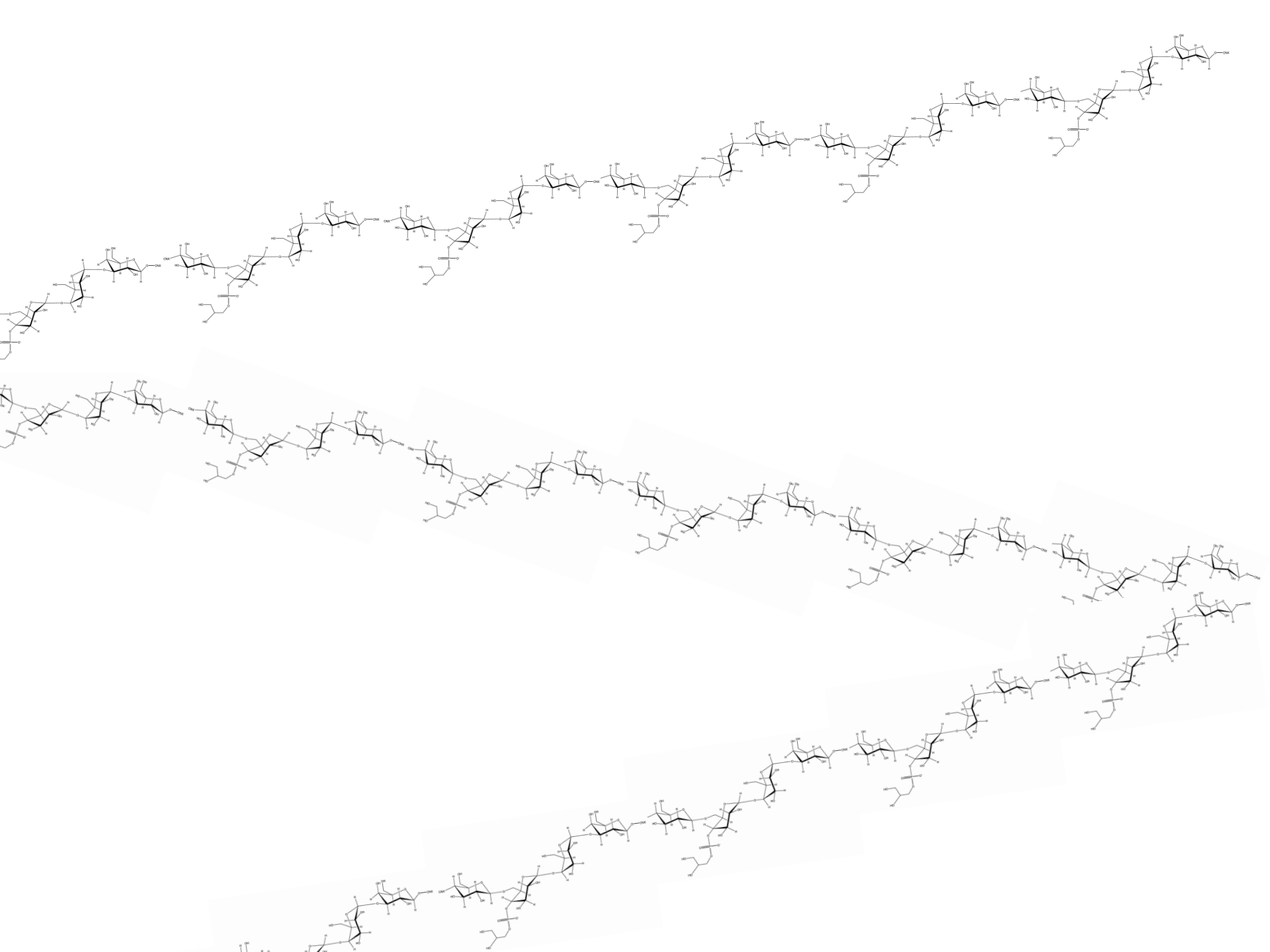
ribose-ribitol-phosphate

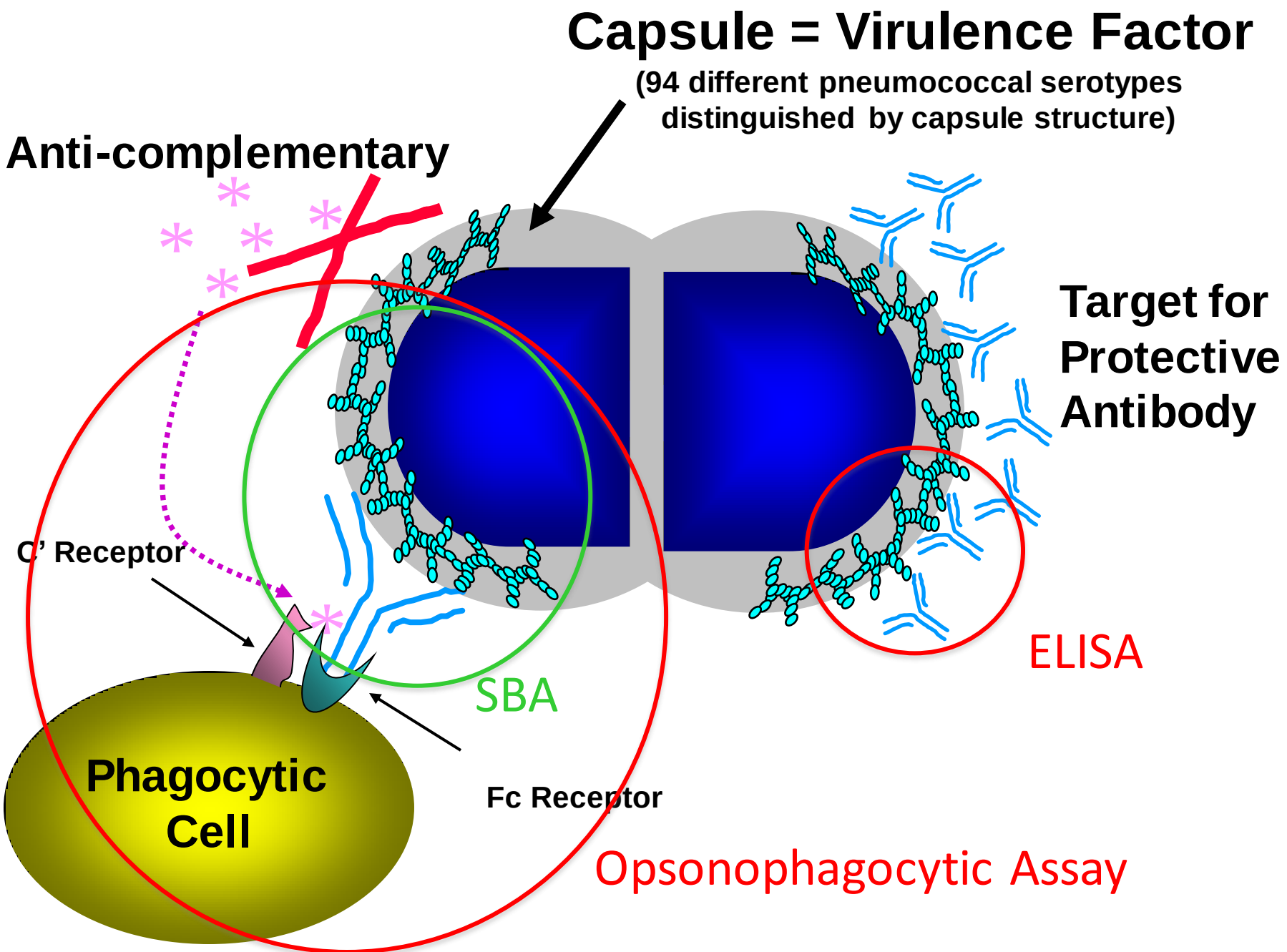
Streptococcus pneumoniae type 4



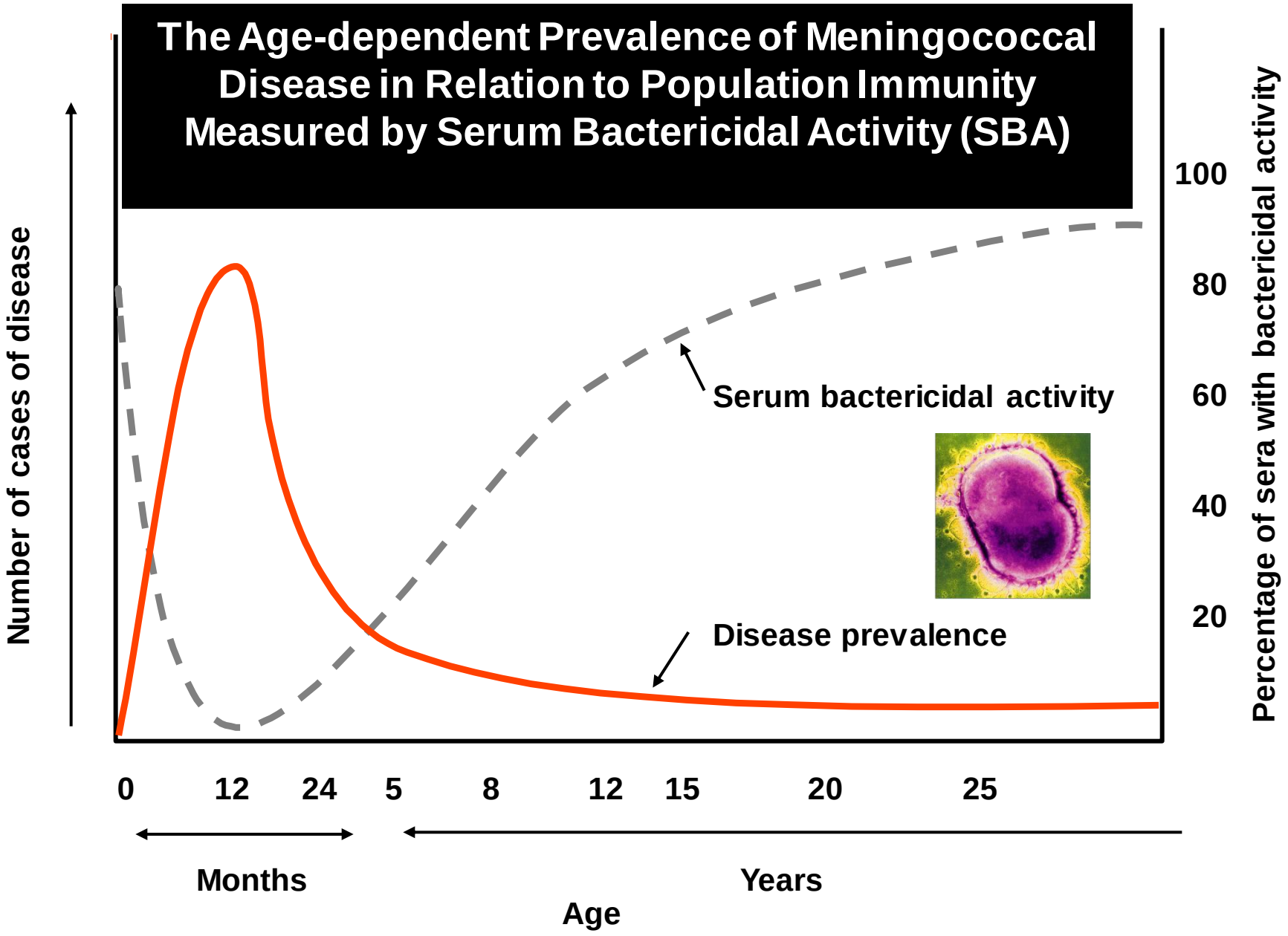
→4)-β-D-Man*p*NAc-(1→3)-α-L-Fuc*p*NAc-(1→3)-α-D-Gal*p*NAc-(1→4)-α-D-Gal*p*-(1→






Capsule = Virulence Factor
(94 different pneumococcal serotypes distinguished by capsule structure)
Anti-complementary
Target for Protective Antibody
C' Receptor
SBA
ELISA
Phagocytic Cell
Fc Receptor
Opsonophagocytic Assay

The Age-dependent Prevalence of Meningococcal Disease in Relation to Population Immunity Measured by Serum Bactericidal Activity (SBA)



Goldschneider II, et al. *J Exp Med.* 1969;129:1307-1326.

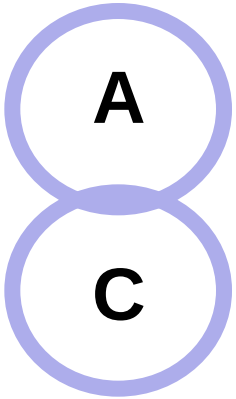
Effectiveness of Serogroup C Meningococcal Polysaccharide Vaccine: Results from a Case-Control Study in Quebec

Philippe De Wals,[1,2] Geneviève Deceuninck,[3] Gaston De Serres,[1,2] Jean-François Boivin,[4,5] Bernard Duval,[2] Robert Remis,[6] and Richard Massé[2,4]

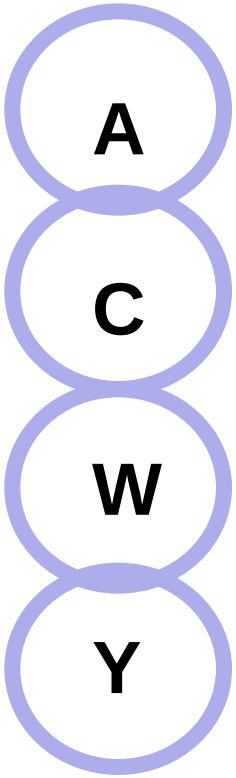
[1]Department of Social and Preventive Medicine, Laval University, [2]Quebec National Public Health Institute, and [3]Public Health Research Unit, Quebec University Hospital Centre, Quebec City, [4]Department of Epidemiology and Biostatistics, McGill University, and [5]Centre for Clinical Epidemiology, Jewish General Hospital, Montreal, and [6]Department of Public Health Sciences, University of Toronto, Toronto, Canada

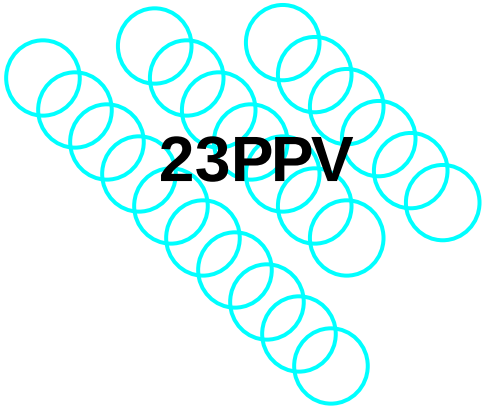
	Vaccine Effectiveness (95% CI)	
	After 0-2 years	After 3-5 years
6 years		
2-5 years		
< 2		

JID 2005



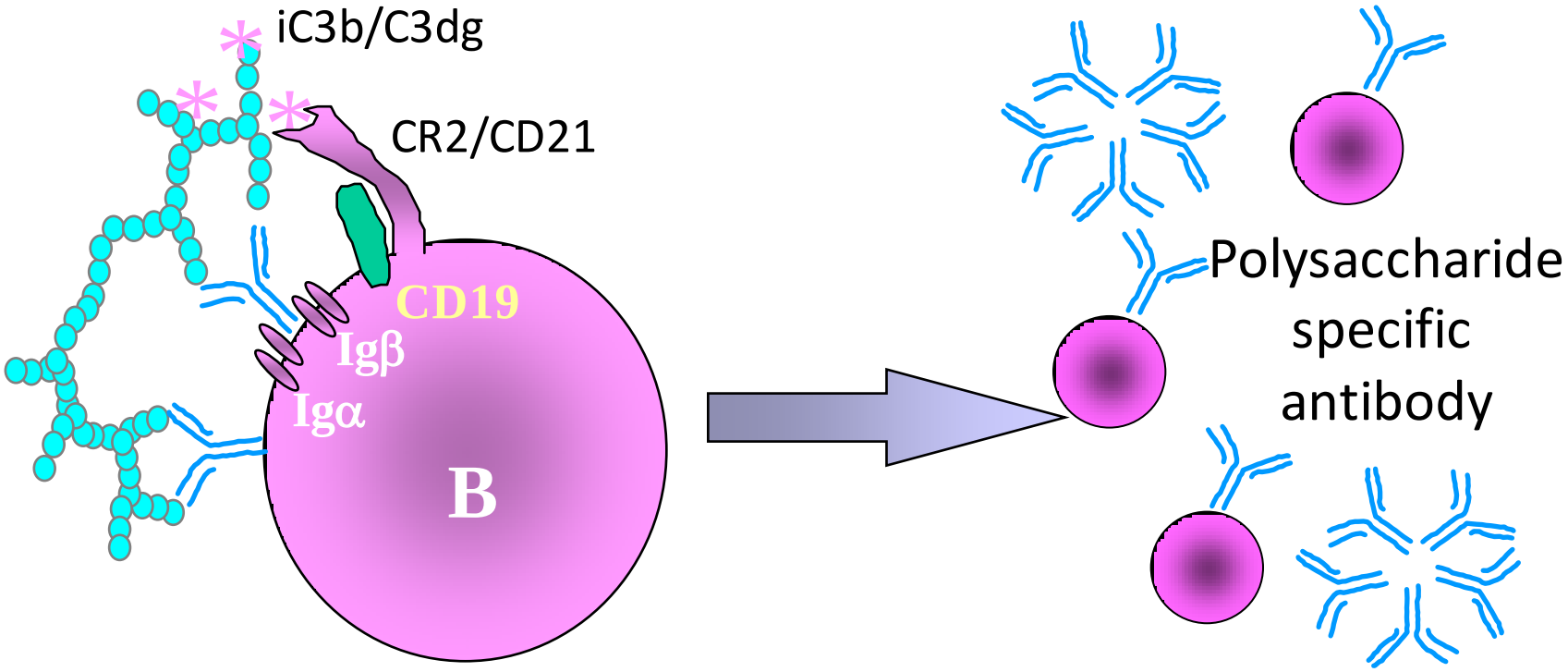
Licensed Capsular Polysaccharide Vaccines





LIMITATIONS

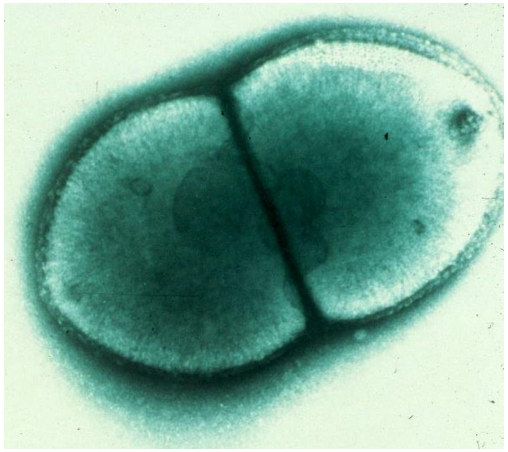
- Generally Poor Ab response <2 years of age
- Short Duration of Protection



Purified Polysaccharides (T independent antigens):

- Poor B cell response below 2yrs of age
  (absent/poorly developed marginal zones?)
- Isotype restricted at any age (IgG2)
- No evidence of B cell memory in humans
- Possible depletion/inhibition of reactive B cell pool

Limited immune response to capsule



- Protective Immunity present
- Natural exposure
- Maturing Immune System

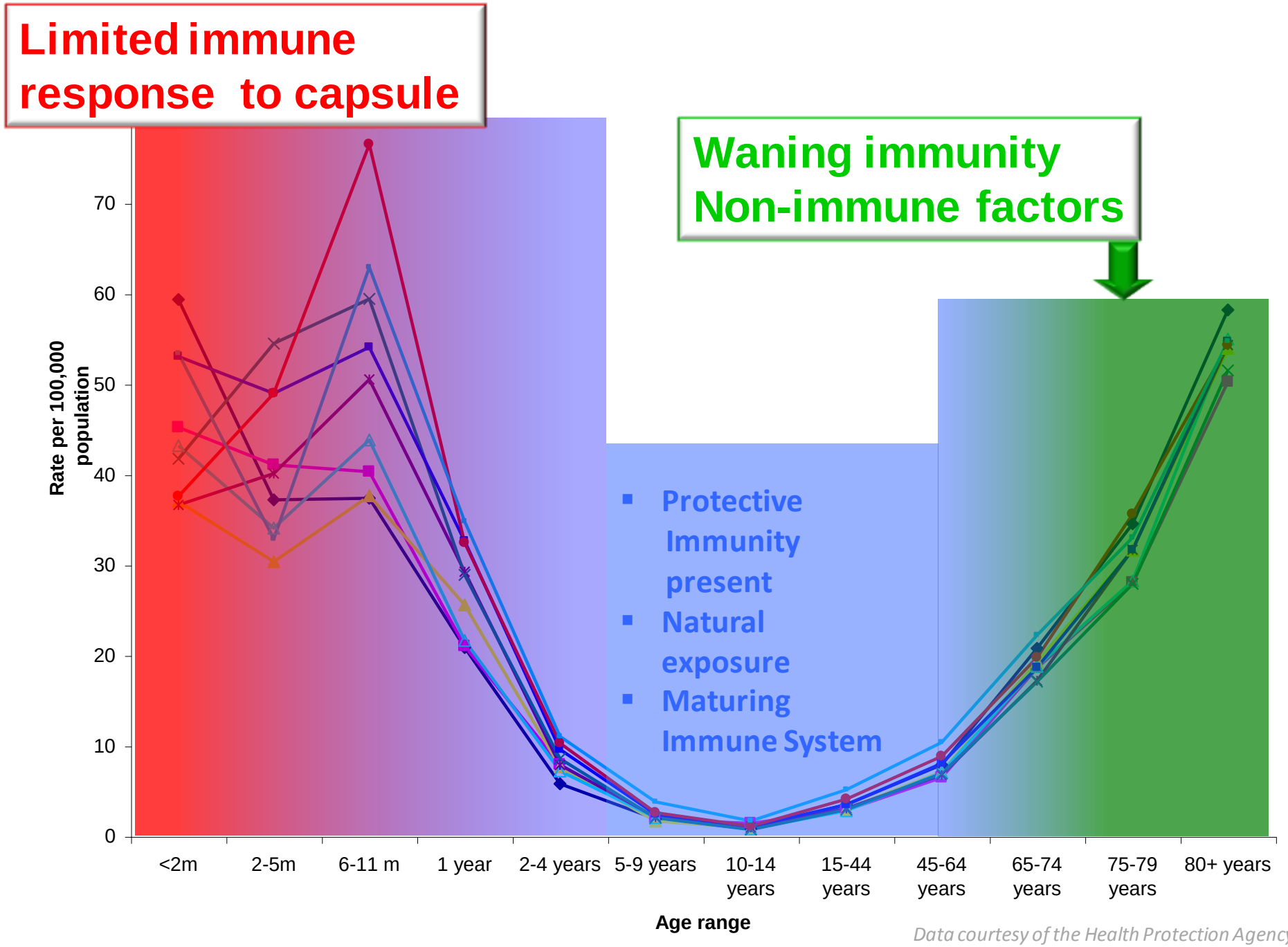
Rate per 100,000 population

0
10
20
30
40
50
60
70

<2m | 2-5m | 6-11 m | 1 year | 2-4 years | 5-9 years | 10-14 years | 15-44 years | 45-64 years | 65-74 years | 75-79 years | 80+ years

Age range

Data courtesy of the Health Protection Agency


Limited immune response to capsule
Waning immunity
Non-immune factors
Protective Immunity present
Natural exposure
Maturing Immune System
Rate per 100,000 population
0
10
20
30
40
50
60
70
<2m
2-5m
6-11 m
1 year
2-4 years
5-9 years
10-14 years
15-44 years
45-64 years
65-74 years
75-79 years
80+ years
Age range
Data courtesy of the Health Protection Agency

THE JOURNAL
OF
EXPERIMENTAL MEDICINE

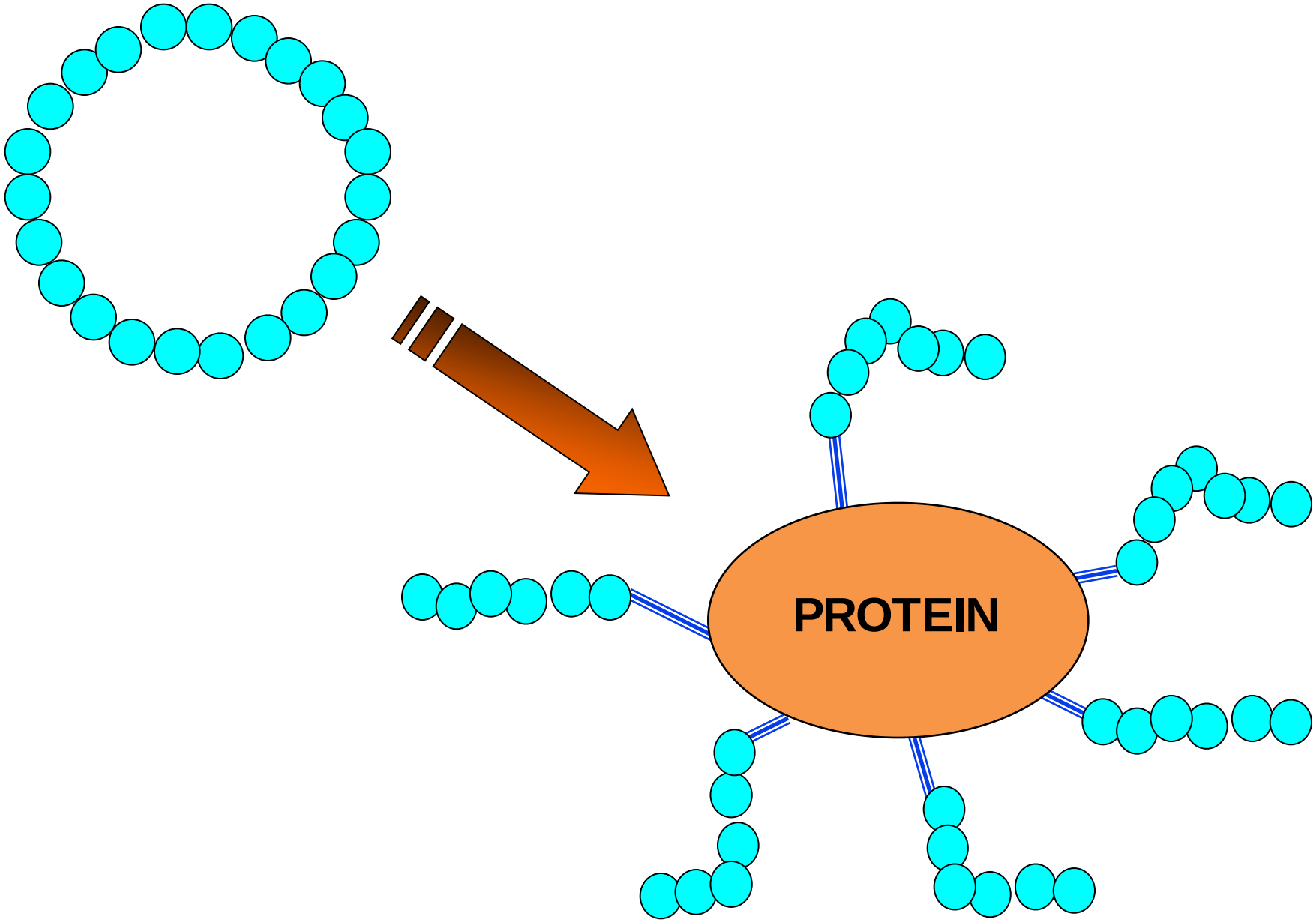
CHEMO-IMMUNOLOGICAL STUDIES ON CONJUGATED CARBOHYDRATE-PROTEINS

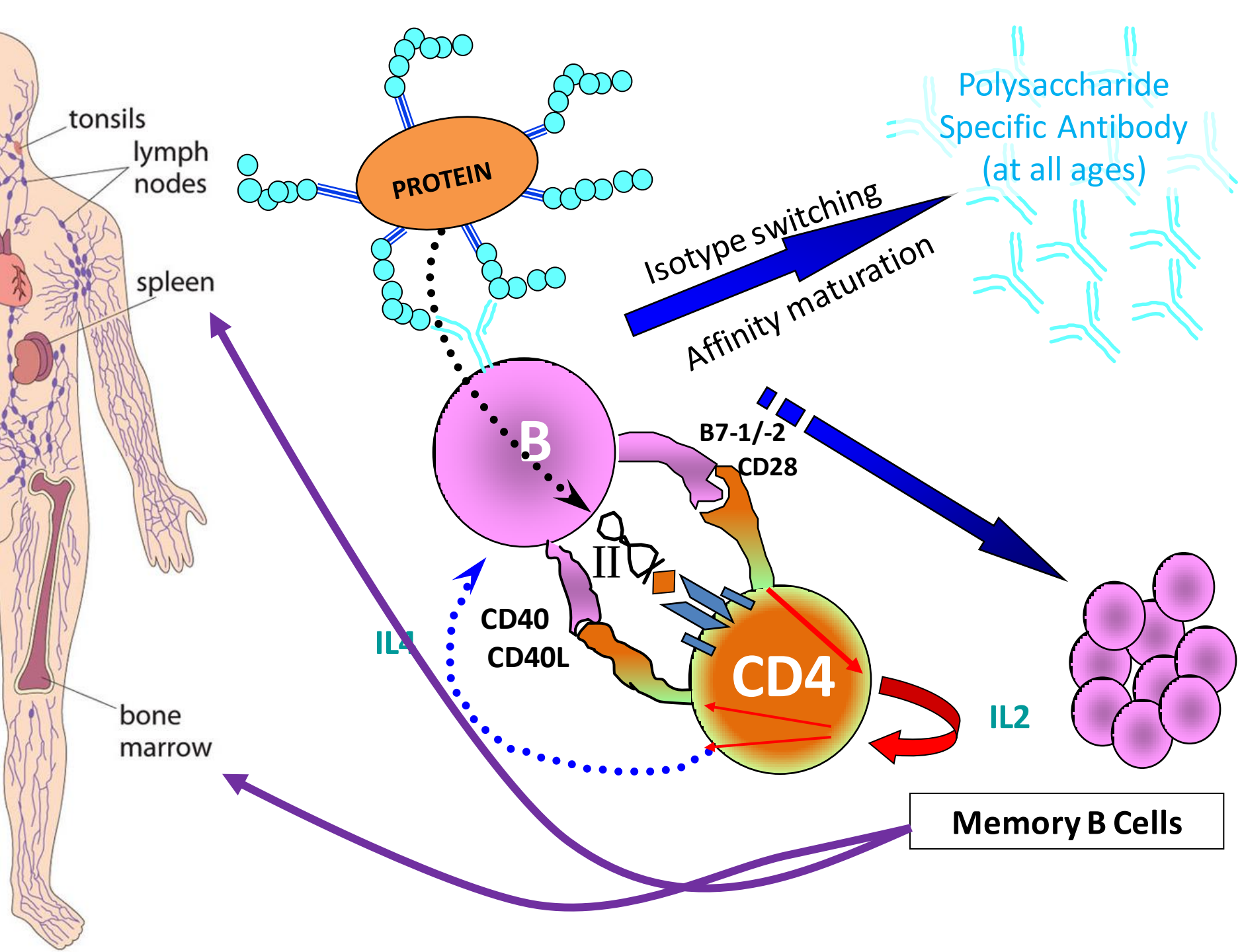
I. The Synthesis of *p*-Aminophenol β-Glucoside, *p*-Aminophenol β-Galactoside, and Their Coupling with Serum Globulin

By WALTHER F. GOEBEL, Ph.D., and OSWALD T. AVERY, M.D.

(*From the Hospital of The Rockefeller Institute for Medical Research*)

(Received for publication, June 24, 1929)


PROTEIN


tonsils
lymph nodes
spleen
bone marrow
PROTEIN
B
II
CD4
CD40
CD40L
IL4
B7-1/-2
CD28
IL2
Isotype switching
Affinity maturation
Polysaccharide Specific Antibody (at all ages)
Memory B Cells

Clinical Infectious Diseases Advance Access published August 23, 2011

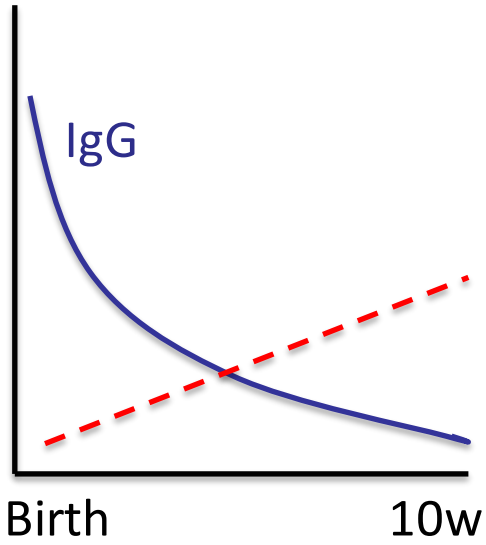
MAJOR ARTICLE

Pneumococcal Conjugate Vaccine Given Shortly After Birth Stimulates Effective Antibody Concentrations and Primes Immunological Memory for Sustained Infant Protection

J. Anthony G. Scott,[1,2] John Ojal,[1] Lindsey Ashton,[3] Anne Muhoro,[1] Polly Burbidge,[3] and David Goldblatt[3]

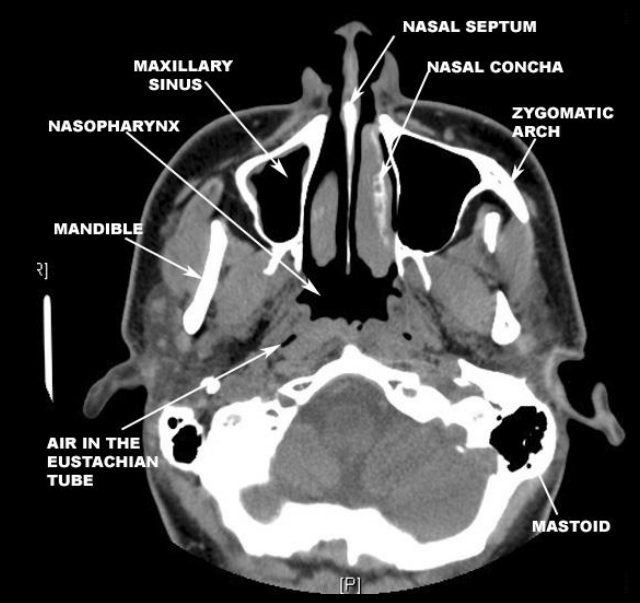
[1]Kenya Medical Research Institute–Wellcome Trust Research Programme, Kilifi, Kenya; [2]Nuffield Department of Clinical Medicine, University of Oxford, Oxford, United Kingdom; and [3]University College London Institute of Child Health, London, United Kingdom

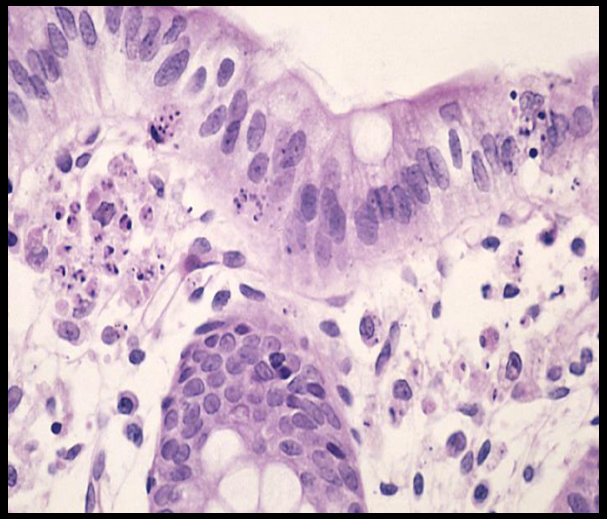
Vaccine groups:
0/ 10/14w
6/10/14w

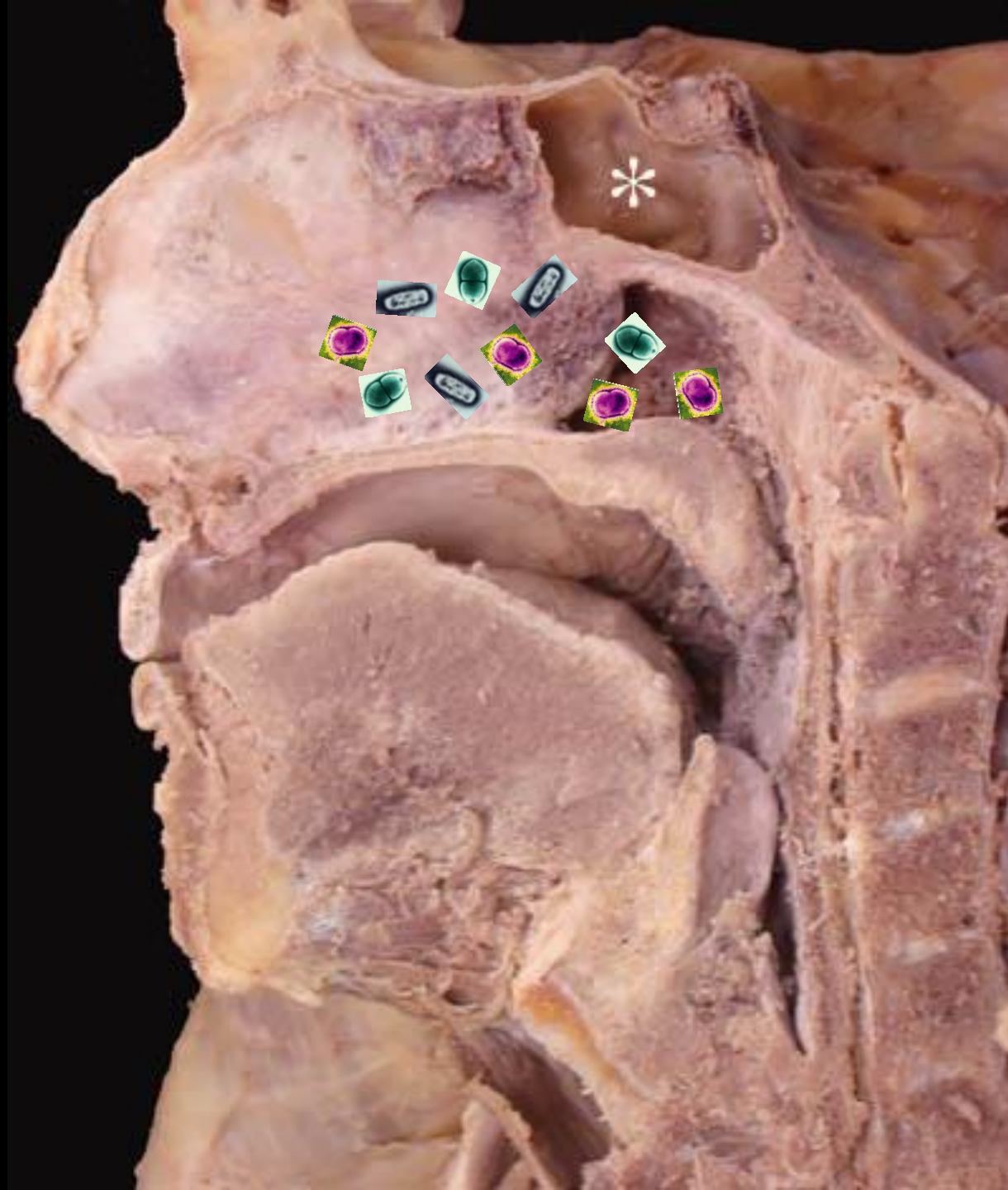


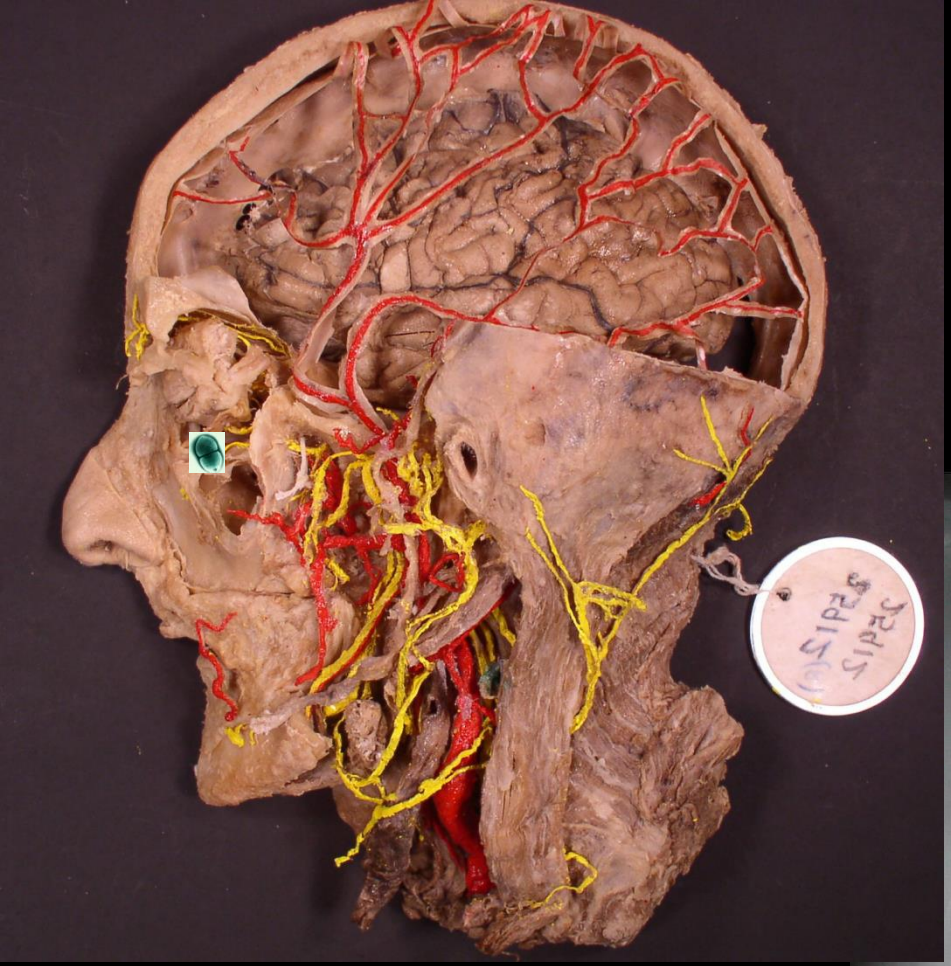
Serotype	Decay rate in µg/mL/week (EPI group)
4	0.176
6B	0.170
9V	0.157
14	0.142
18C	0.182
19F	0.185
23F	0.153

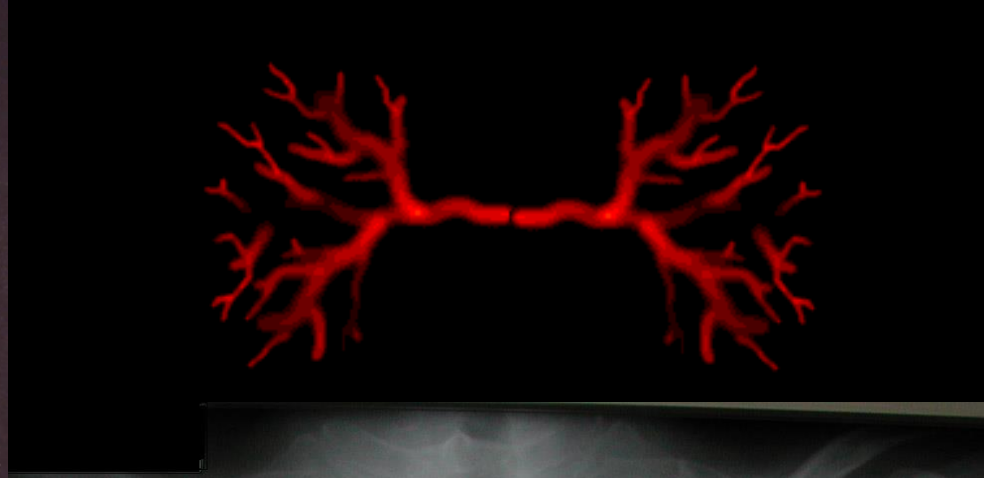
Observed concentration at 10 weeks versus concentration predicted from cord blood (newborn group), geometric mean ratio (95% CI)

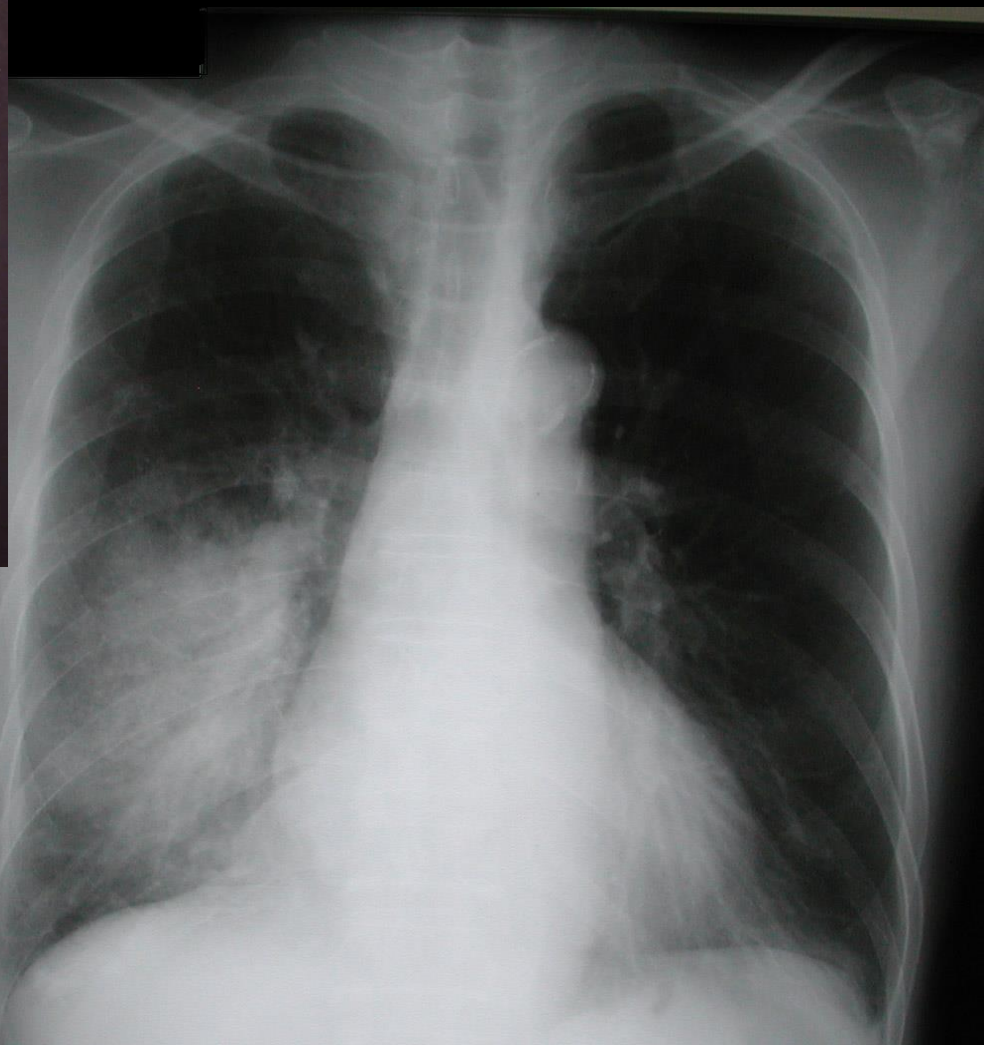

NASAL SEPTUM
MAXILLARY SINUS
NASAL CONCHA
NASOPHARYNX
ZYGOMATIC ARCH
MANDIBLE
AIR IN THE EUSTACHIAN TUBE
MASTOID
[P]

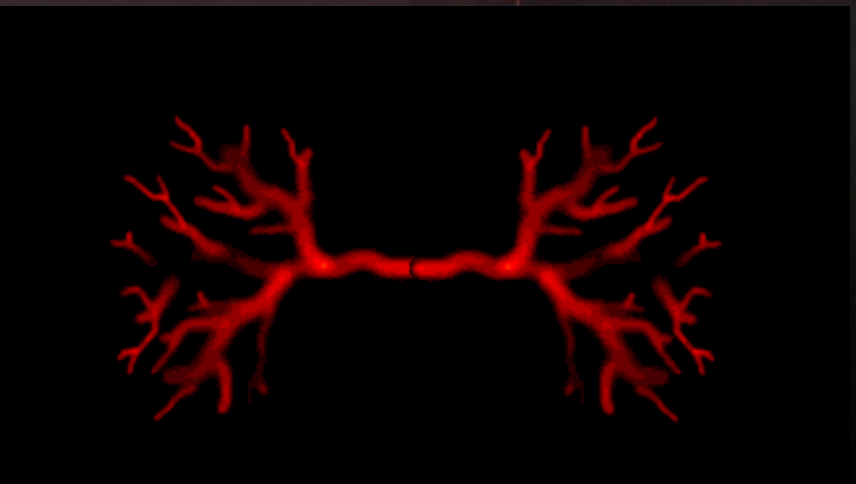




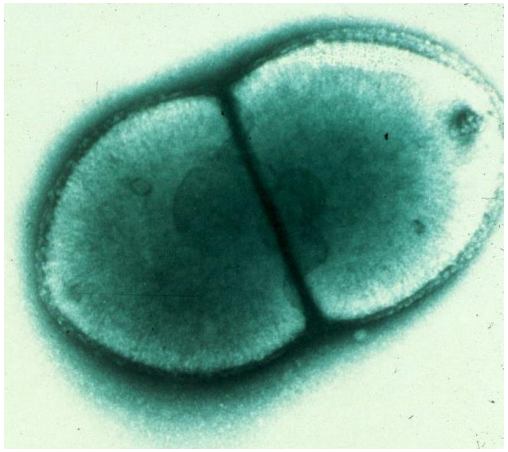








Invasive pneumococcal disease incidence rate per 100,000 population by age grouping England and Wales, 1996-2005



Rate per 100,000 population

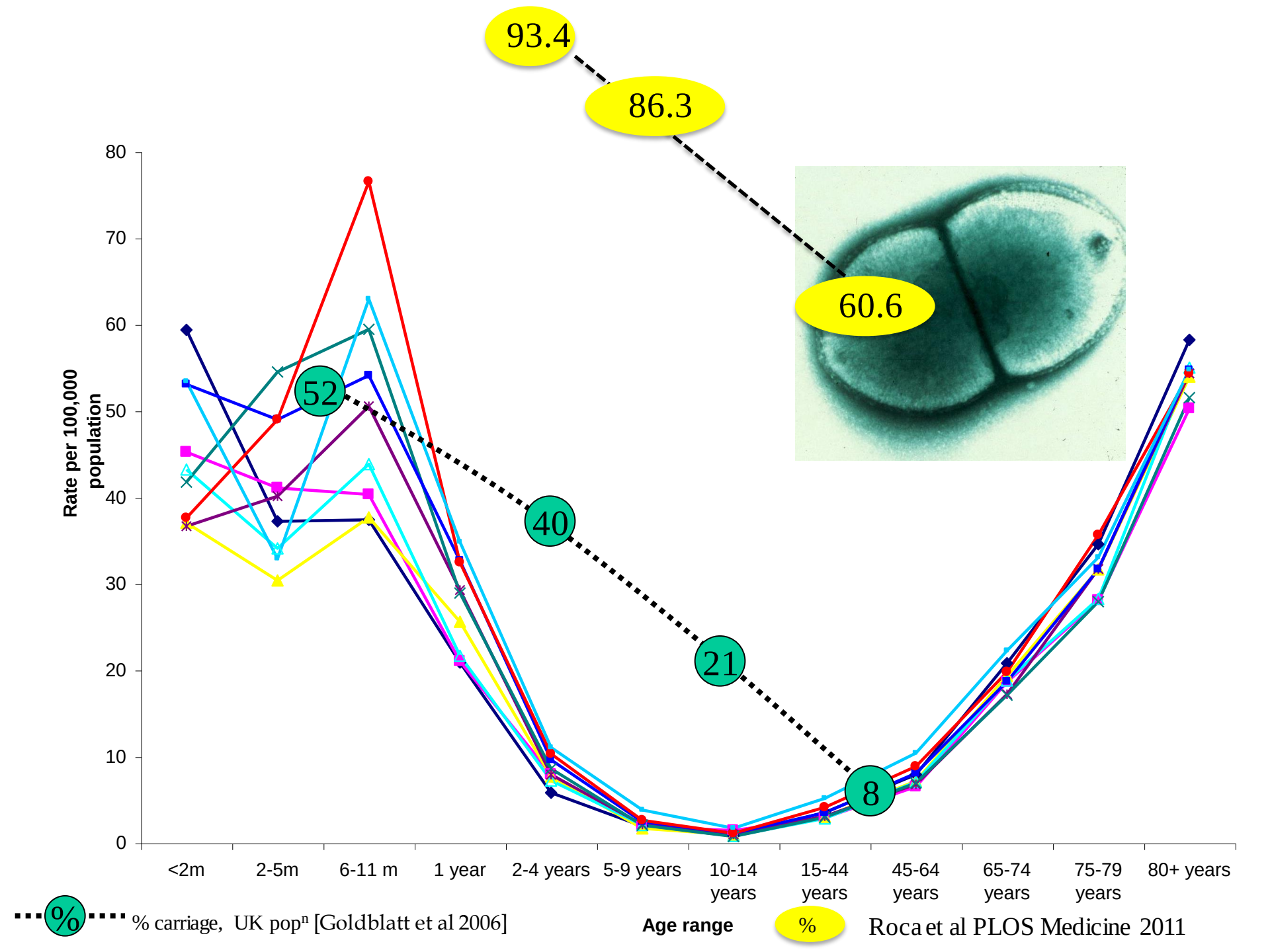
80
70
60
50
40
30
20
10
0

52
40
21
8

<2m | 2-5m | 6-11 m | 1 year | 2-4 years | 5-9 years | 10-14 years | 15-44 years | 45-64 years | 65-74 years | 75-79 years | 80+ years

Age range

% % carriage, UK popⁿ [Goldblatt et al 2006]

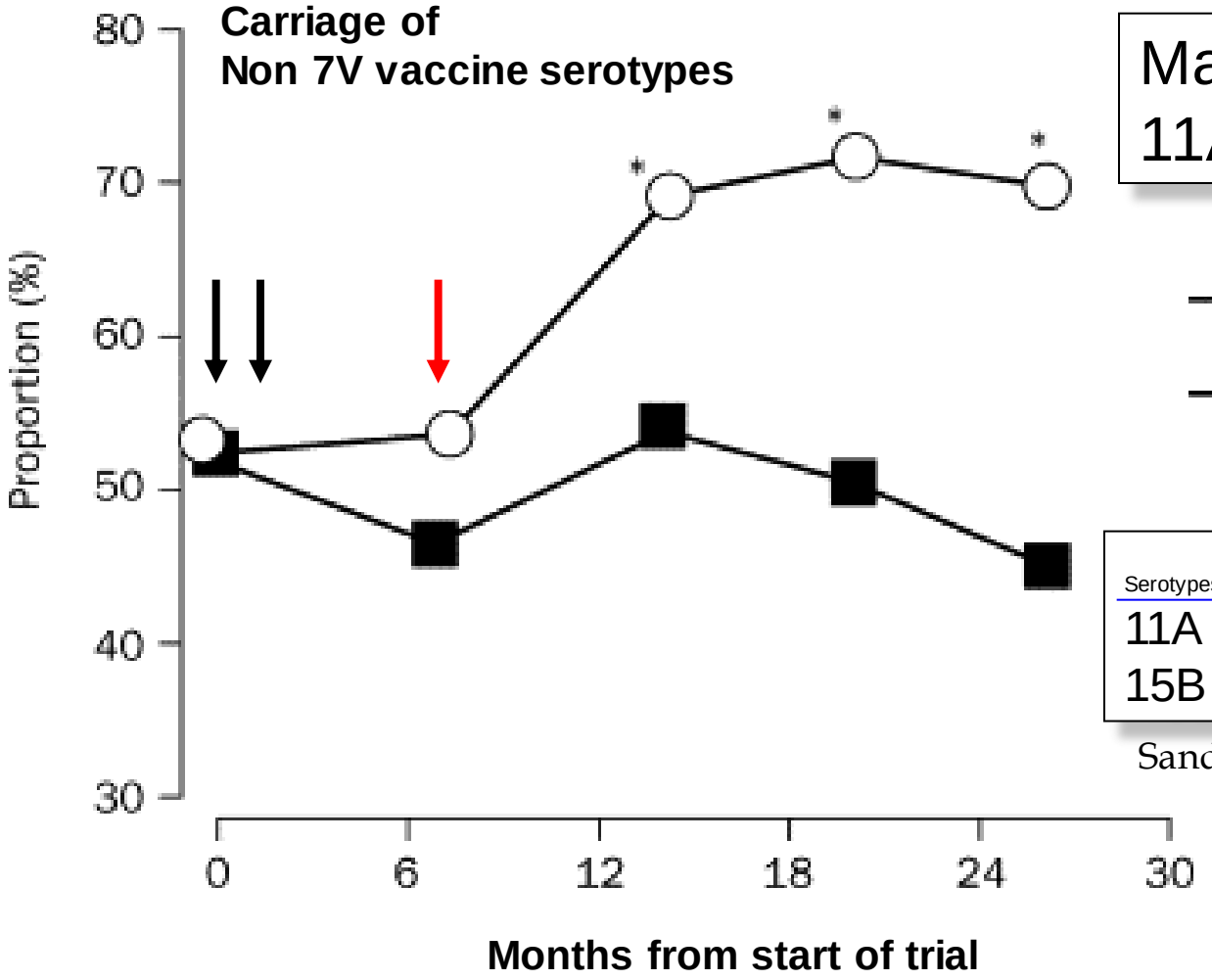

93.4
86.3
60.6
52
40
21
8
Rate per 100,000 population
80
70
60
50
40
30
20
10
0
<2m
2-5m
6-11 m
1 year
2-4 years
5-9 years
10-14 years
15-44 years
45-64 years
65-74 years
75-79 years
80+ years
% carriage, UK popⁿ [Goldblatt et al 2006]
Age range
%
Roca et al PLOS Medicine 2011

= conjugate vaccine

= 23V polysaccharide vaccine

Effect of conjugate pneumococcal vaccine followed by polysaccharide pneumococcal vaccine on recurrent acute otitis media: a randomised study

Reinier Veenhoven, Debby Bogaert, Cuno Uiterwaal, Carole Brouwer, Herma Kiezebrink, Jacob Bruin, Ed IJzerman, Peter Hermans, Ronald de Groot, Ben Zegers, Wietse Kuis, Ger Rijkers, Anne Schilder, Elisabeth Sanders



Mainly serotypes 11A, 15B and 16

Serotypes \ age	12-24m	>24m
11A	45.3	41 µg/ml
15B	11.83	23 µg/ml

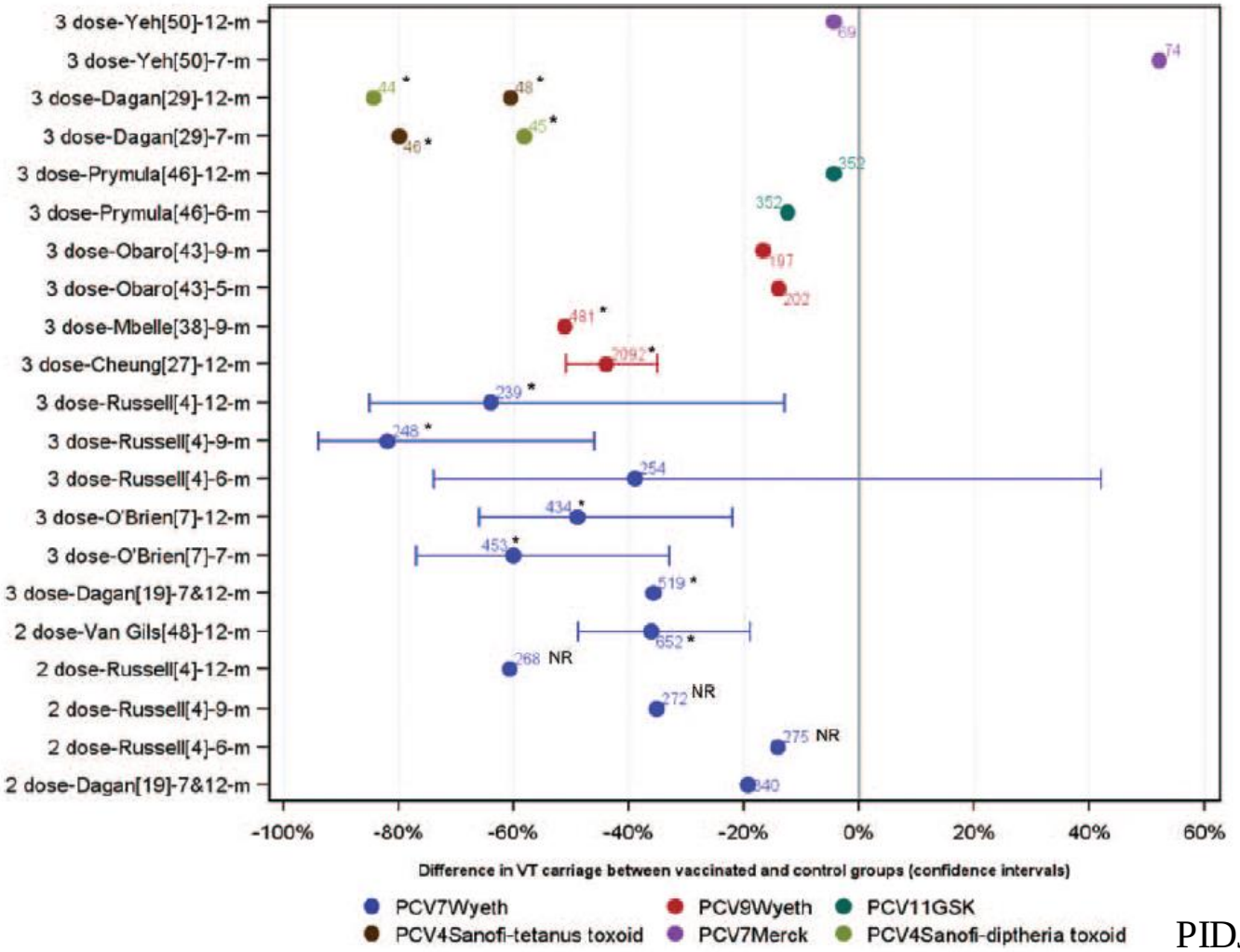
Sanders & Veenhoven (Personal Comm)

Lancet 2003

Systematic Review of the Effect of Pneumococcal Conjugate Vaccine Dosing Schedules on Vaccine-type Nasopharyngeal Carriage

Katherine E. Fleming-Dutra, MD,† Laura Conklin, MD,† Jennifer D. Loo, MPH,† Maria Deloria Knoll, PhD,‡ Daniel E. Park, MSPH,‡ Jennifer Kirk, MSc,§ David Goldblatt, MBChB, PhD,¶ Cynthia G. Whitney, MD, MPH,† and Katherine L. O'Brien, MD, MPH‡*

Difference in VT Carriage Prevalence: Vaccinated vs Unvaccinated/ Placebo for Carriage in 1st year of life

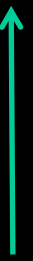


PIDJ 2014

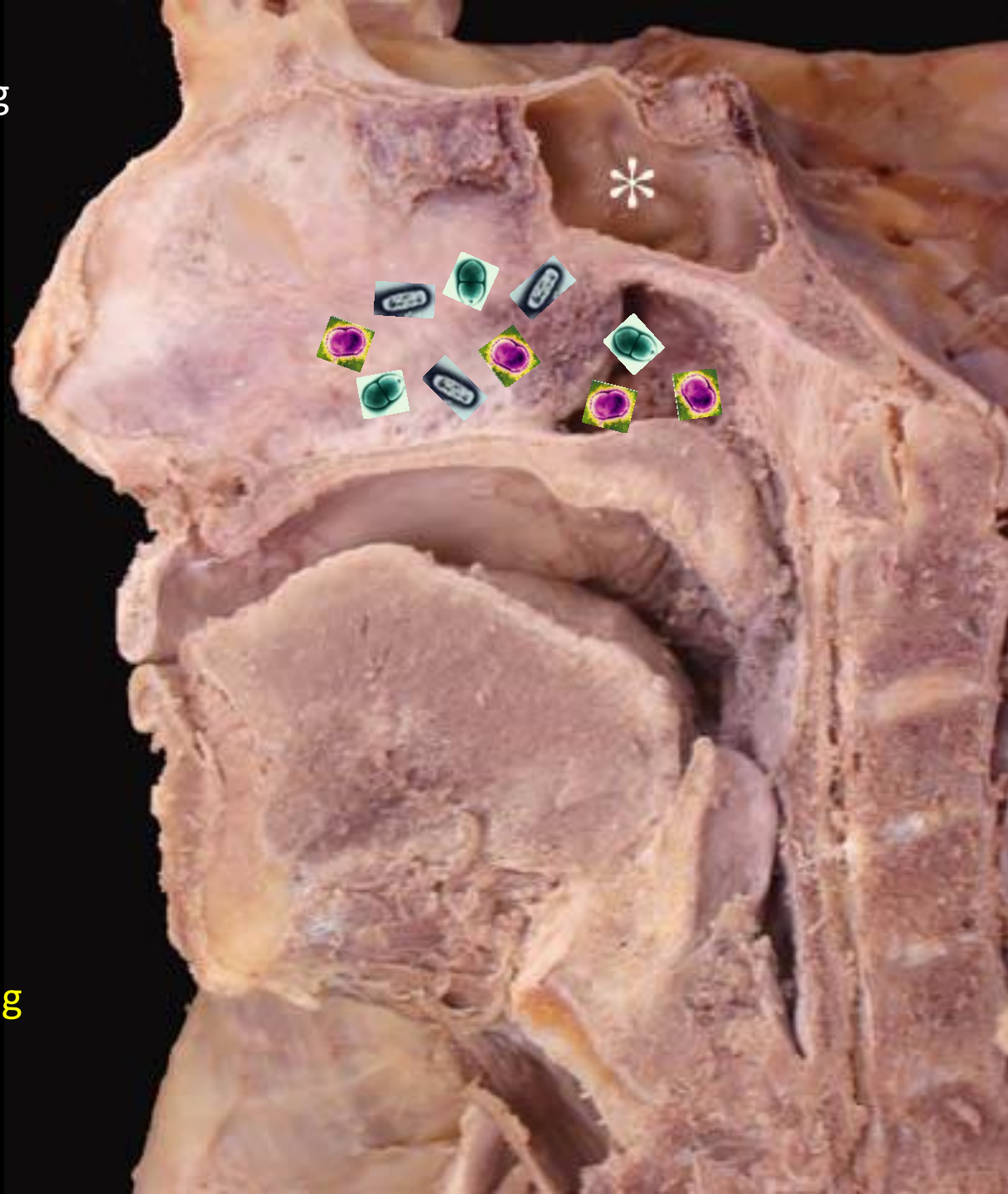
High Circulating IgG following Polysaccharide Vaccine

No Impact on Carriage

Carriage reduced

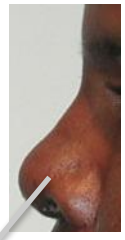


High Circulating IgG following Conjugate Vaccine

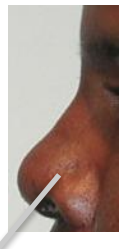


Vakevainen et al J Paeds 2010

6B, 19F and 23F GMC sig reduced @ 18w and 9m if homologous serotype carried at 6w



Impact of Carriage on Vaccine Responses



6B, 19F and 23F GMC sig reduced to 1º and boost if homologous serotypes detected

Dagan et al JID 2010

INFECTION AND IMMUNITY, Nov. 2008, p. 5305–5309 Vol. 76, No. 11
0019-9567/08/$08.00+0 doi:10.1128/IAI.00796-08

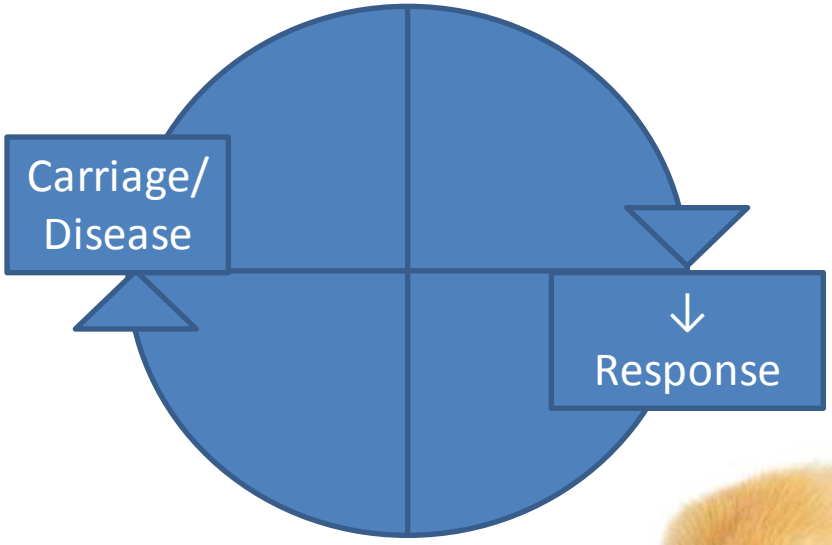
Serotype-Specific Immune Unresponsiveness to Pneumococcal Conjugate Vaccine following Invasive Pneumococcal Disease▽

Ray Borrow,[1]* Elaine Stanford,[1] Pauline Waight,[2] Matthew Helbert,[3] Paul Balmer,[1] Rosalind Warrington,[1] Mary Slack,[4] Robert George,[4] and Elizabeth Miller[2]

TABLE 4. Vaccination, infection, and specific IgG characteristics of children who were immunologically unresponsive to a particular serotype

Case	Age (mo) when IPD occurred	Ages (mo) at which PCV7 administered	Time (days) from last dose of PCV7 to blood sample	Infecting serotype	Serotype-specific IgG concn (μg/ml) following last dose of PCV7[a]						
					4	6B	9V	14	18C	19F	23F
1	13.2	15, 17, and 19	78	18C	20.09	8.66	3.82	0.93	**0.02**	5.18	5.94
2	13.2	15, 19, and 25	28	18C	25.45	12.29	7.86	6.11	**0.03**	4.93	61.54
3	8.9	10, 14, 16, and 19	30	19F	6.64	6.27	1.63	6.47	5.65	**0.29**	6.85
4	7.0	8, 10, 12, and 14	28	6B	18.41	**0.34**	5.95	22.73	19.96	14.06	182.74
5	3.1	2, 5, 8, 14, and 17	60	6B	6.53	**0.05**	6.65	3.95	8.18	5.15	58.29
6	16.3	13, 20, and 23	45	6B	3.27	**0.01**	1.95	6.89	2.92	3.10	12.16
7	12.7	8, 11, 14, and 21	28	6B	100.24	**0.01**	56.24	115.36	83.37	31.29	39.14
8	12.5	14, 17, and 19	29	14	2.16	1.71	5.19	**0.25**	4.45	1.17	4.18
9	9.4	12, 14, and 17	36	14	19.41	**0.08**	6.17	7.35	20.15	9.18	15.84
10	13.7	13, 16, 20, and 26	49	7F	1.85	**0.08**	3.14	22.66	28.21	15.15	7.37

[a] The value for the serotype to which each child was immunologically unresponsive is in bold font.


Carriage/
Disease
↓
Response

Vaccine 28 (2010) 3341–3349

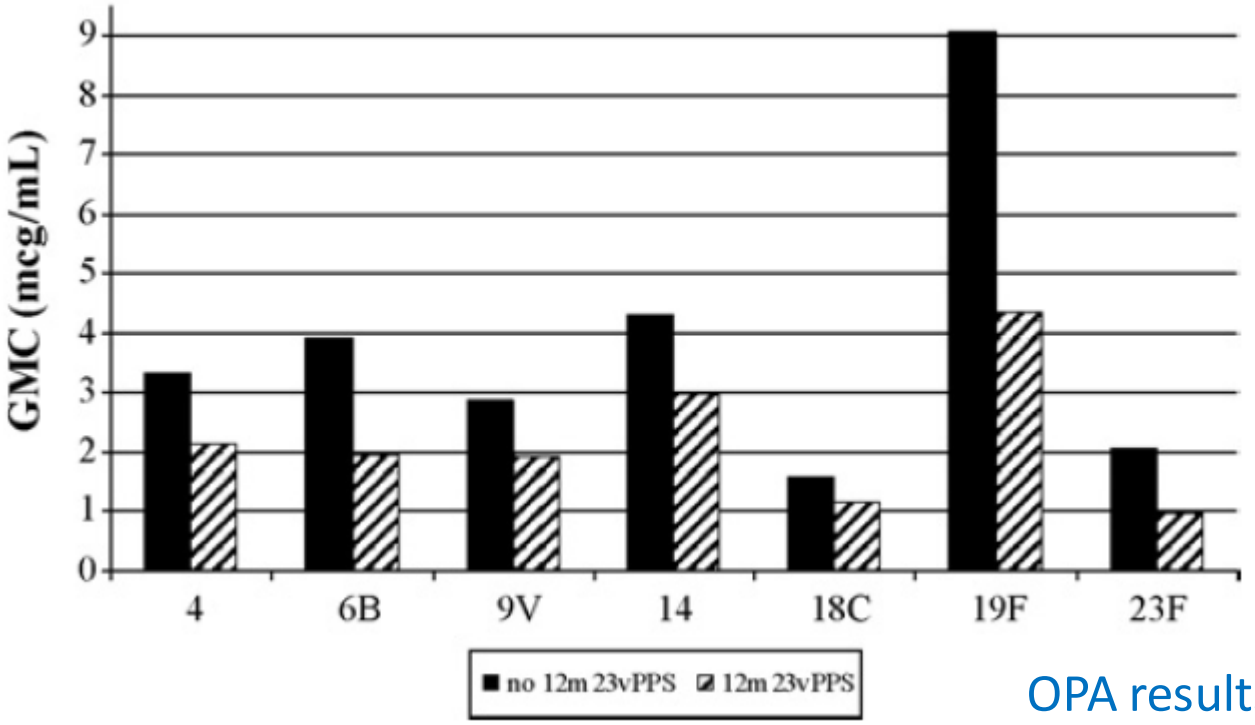
Contents lists available at ScienceDirect

Vaccine

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

Hyporesponsiveness to re-challenge dose following pneumococcal polysaccharide vaccine at 12 months of age, a randomized controlled trial

F.M. Russell[a,*], J.R. Carapetis[b], A. Balloch[c], P.V. Licciardi[c], A.W.J. Jenney[a], L. Tikoduadua[d], L. Waqatakirewa[d], J. Pryor[e], J. Nelson[b], G.B. Byrnes[f], Y.B. Cheung[g,h], M.L.K. Tang[c,i,j], E.K. Mulholland[b,k]



Infant PCV7 Prime
2/3/4m of age

⇩

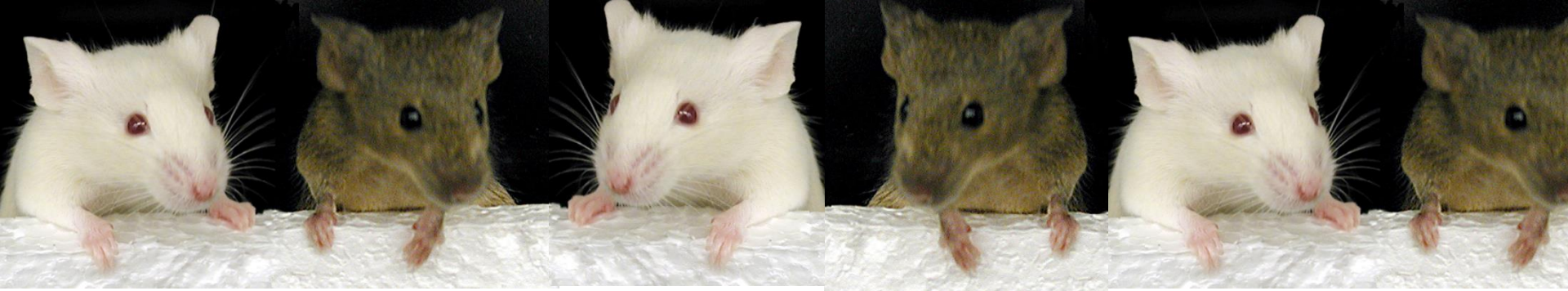
Half received
PPV23 Boost @12m

⇩

All received
0.1ml (20%) PPV23
(@17m)

OPA results similar

Russell at al Vaccine 2011



Pneumococcal Polysaccharide Abrogates Conjugate-Induced Germinal Center Reaction and Depletes Antibody Secreting Cell Pool, Causing Hyporesponsiveness

Stefania P. Bjarnarson[1,2], Hreinn Benonisson[1,2], Giuseppe Del Giudice[3], Ingileif Jonsdottir[1,2,4]*

1 Landspitali, The National University Hospital of Iceland, Department of Immunology, Reykjavik, Iceland, **2** University of Iceland, Faculty of Medicine, Reykjavik, Iceland, **3** Novartis Vaccines and Diagnostics, Siena, Italy, **4** deCODE Genetics, Reykjavik, Iceland

Neonatal Mice

Primed with
Pnc1-TT +LT-K63
in or sc
1, 2 or 3 doses

→

Boosted with
PPS1+LT-K63,
PPS1-TT or
saline

→

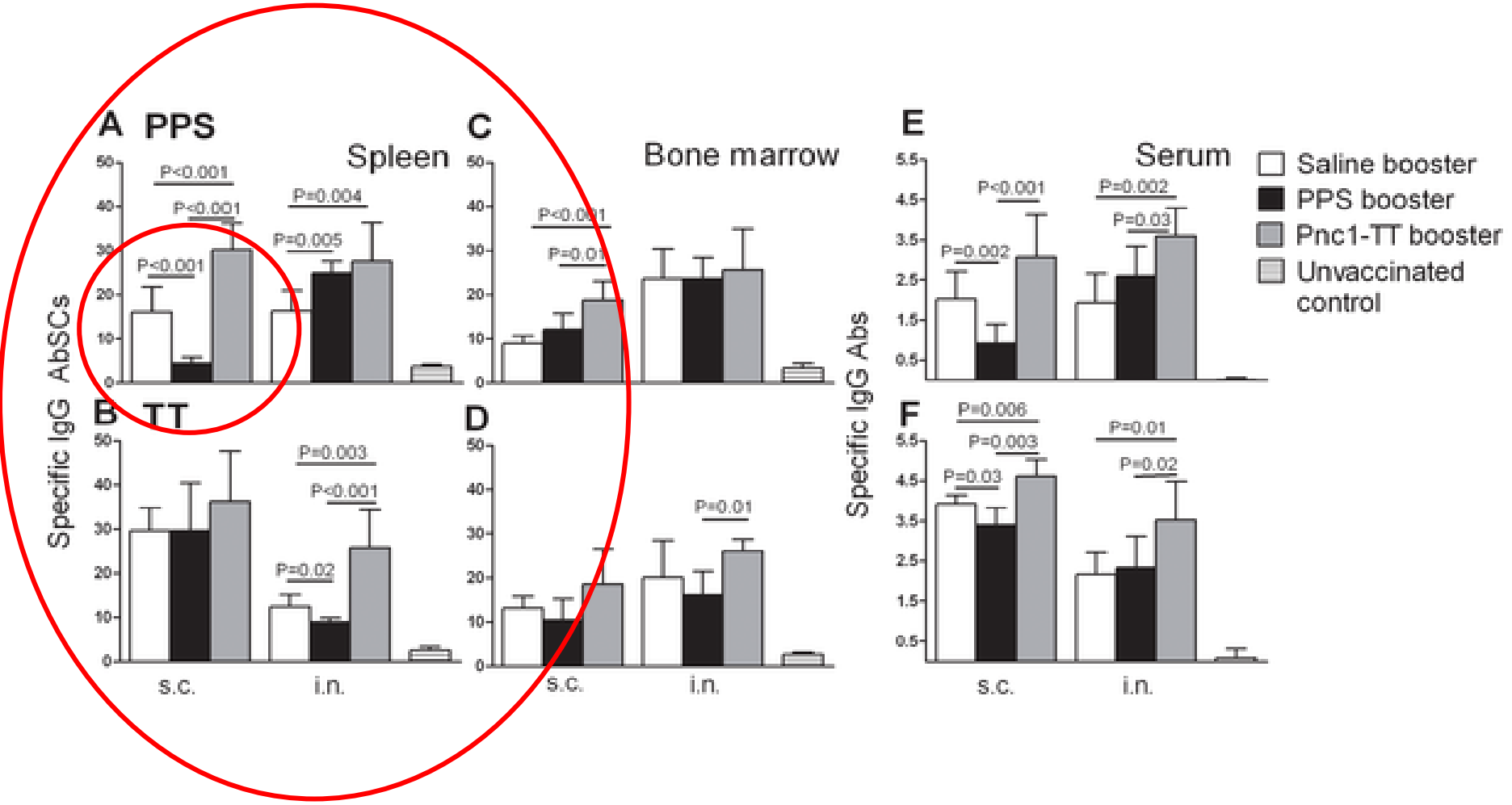
PPS1
Specific
Memory
B Cells

→ Spleen
(+GC formation)

→ Bone Marrow

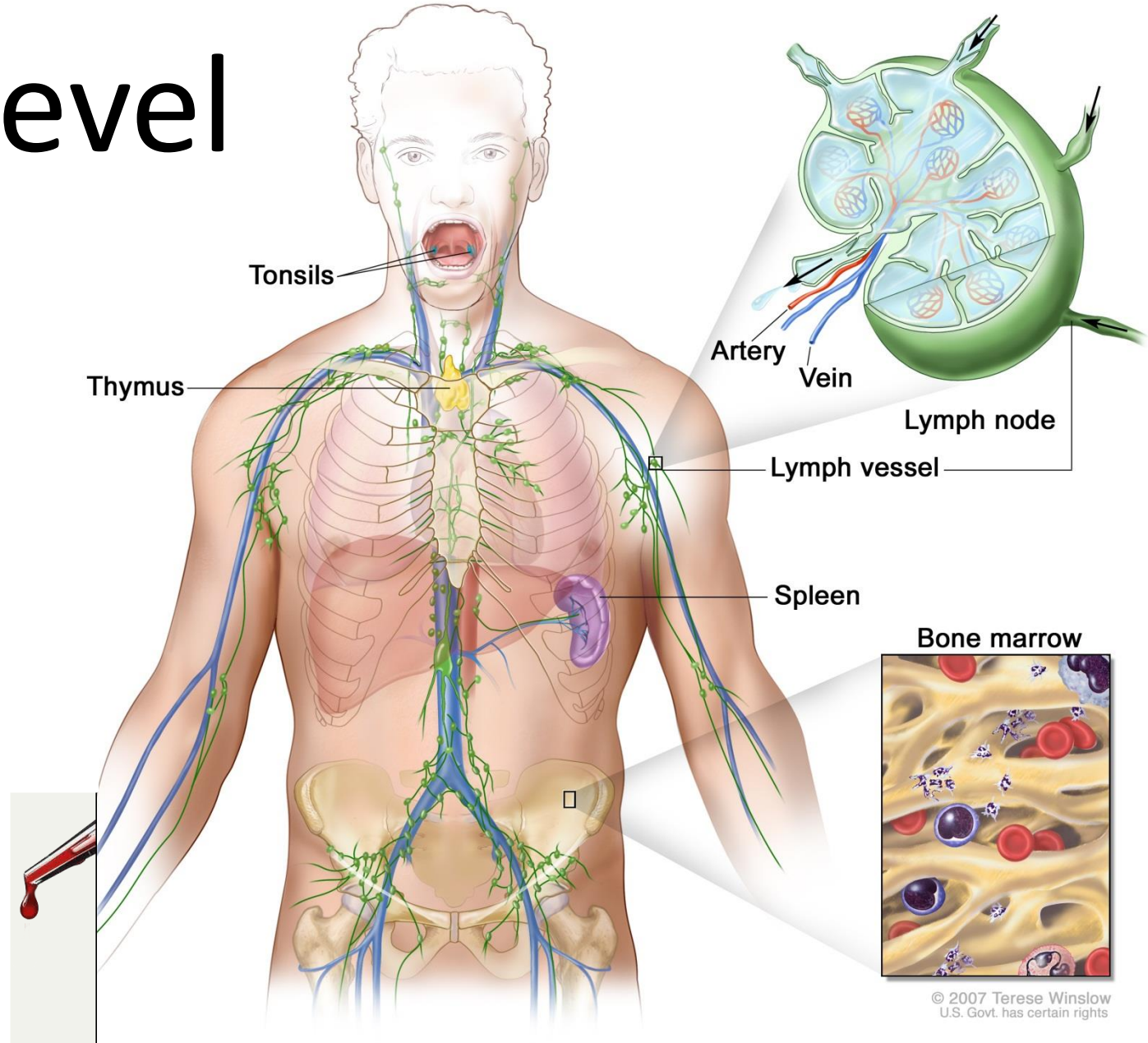
PLOS One 2013

Figure 1. Subcutaneous administration of PPS-1 booster depletes Pnc1-TT-induced PPS-1-specific AbSC pool in the spleen.



Bjarnarson SP, Benonisson H, Del Giudice G, Jonsdottir I (2013) Pneumococcal Polysaccharide Abrogates Conjugate-Induced Germinal Center Reaction and Depletes Antibody Secreting Cell Pool, Causing Hyporesponsiveness. PLoS ONE 8(9): e72588. doi:10.1371/journal.pone.0072588
http://www.plosone.org/article/info:doi/10.1371/journal.pone.0072588

Responses at the B Cell level

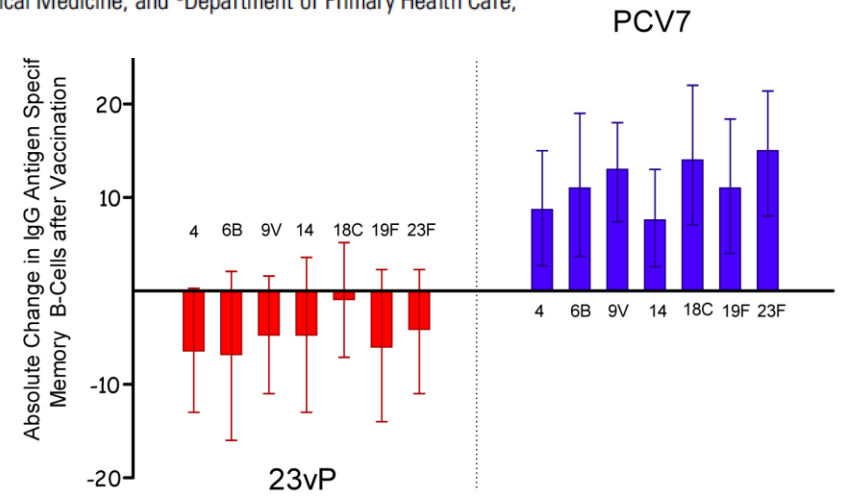


Pneumococcal Conjugate and Plain Polysaccharide Vaccines Have Divergent Effects on Antigen-Specific B Cells

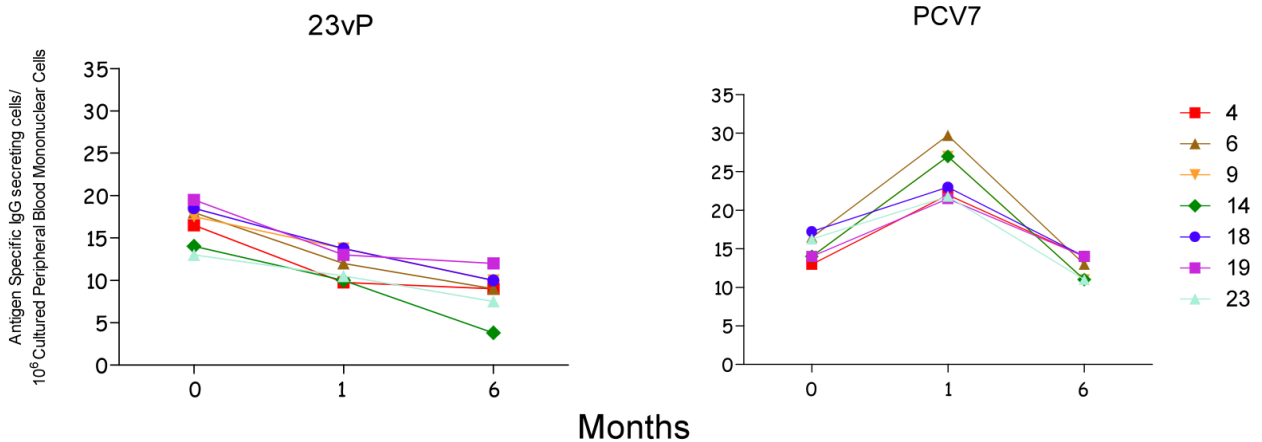
Elizabeth A. Clutterbuck,[1,a] Rajeka Lazarus,[1,a] Ly-Mee Yu,[2] Jaclyn Bowman,[1] Elizabeth A. L. Bateman,[1,b] Linda Diggle,[1,c] Brian Angus,[3] Tim E. Peto,[3] Peter C. Beverley,[4] David Mant,[5] and Andrew J. Pollard[1]

[1]Oxford Vaccine Group, Department of Paediatrics, University of Oxford; [2]The Centre for Statistics in Medicine, Oxford; [3]Nuffield Department of Clinical Medicine, [4]The Peter Medawar Building for Pathogen Research, Nuffield Department of Clinical Medicine, and [5]Department of Primary Health Care, University of Oxford, United Kingdom

Over 1 month



Over 6 months



J Infect Dis 2012

Pneumococcal Polysaccharide or Conjugate Vaccines In Adults?

Vaccines for preventing pneumococcal infection in adults (Review)

Moberley S, Holden J, Tatham DP, Andrews RM

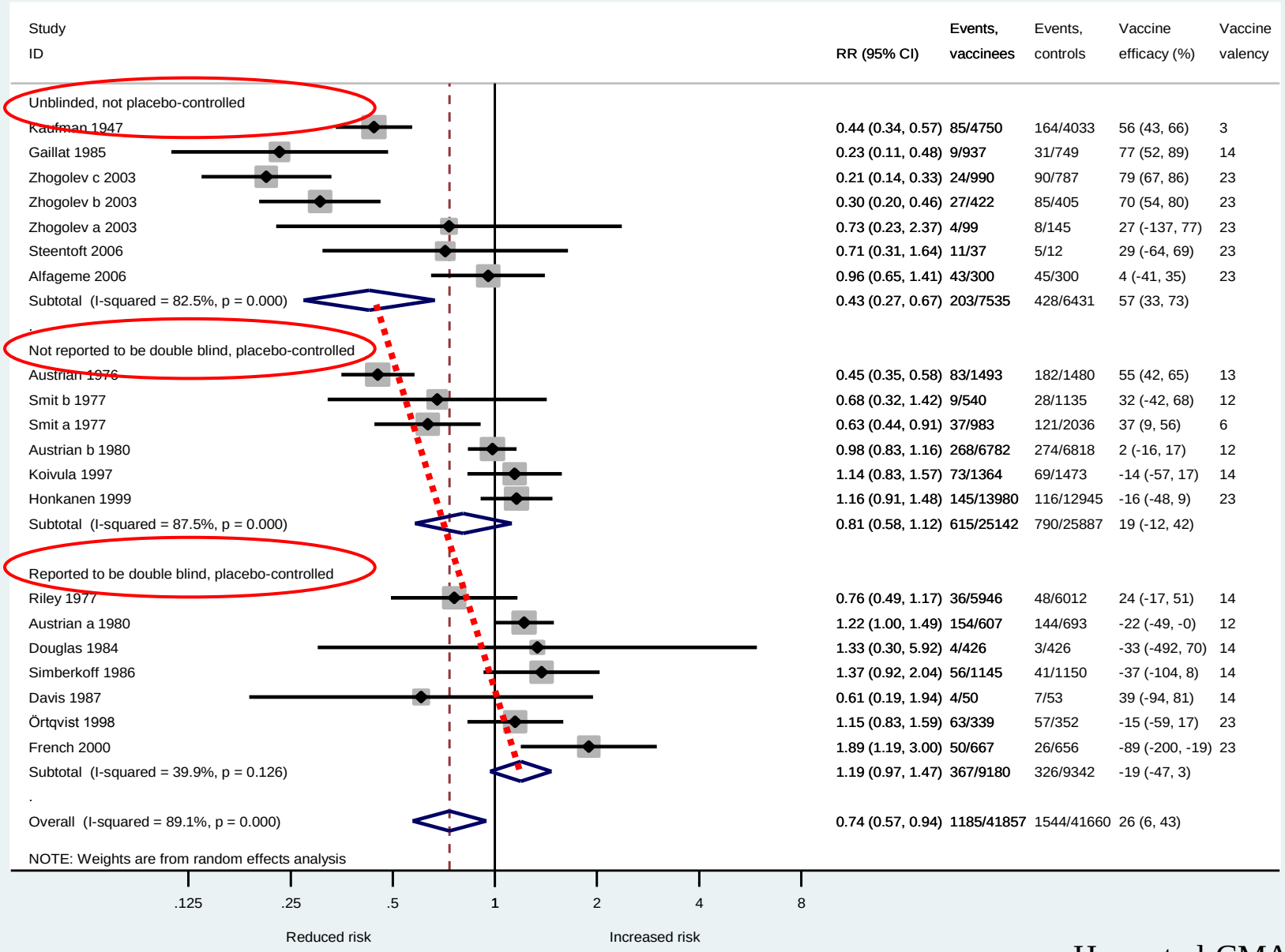
THE COCHRANE COLLABORATION®

2008

- PPV prevents IPD in healthy adults
- RCT's less clear in chronic illness
- No evidence for pneumonia prevention or mortality reduction

All cause pneumonia, cases/episodes combined

By blinding



Huss et al CMAJ 2009

PNEUMOCOCCAL VACCINATION POLICY IN EUROPE

RG Pebody[1], T Leino[2], H Nohynek[2], W Hellenbrand[3], S Salmaso[4], P Ruutu[2]

TABLE 2

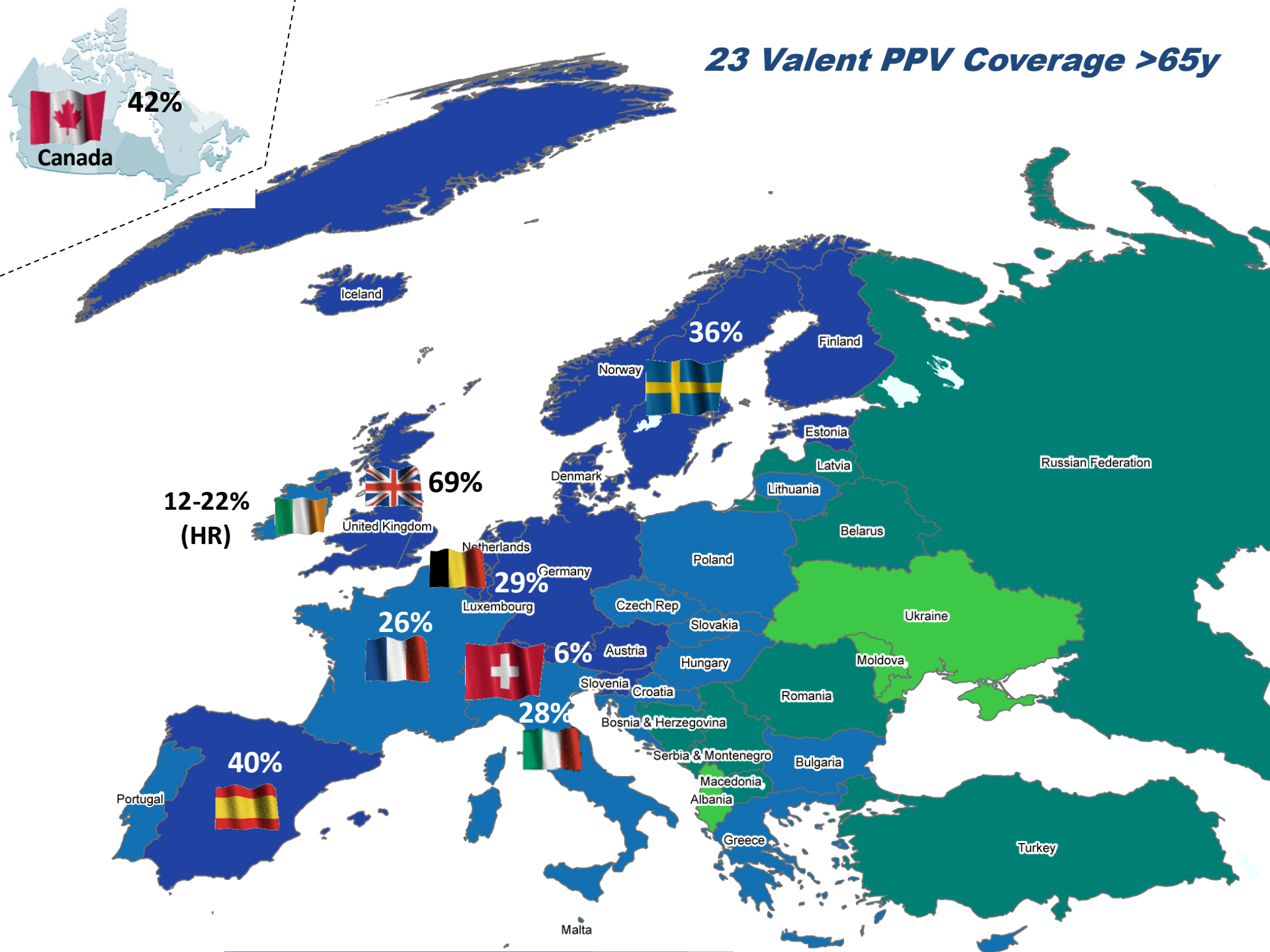
Country-specific recommendations for use of pneumococcal polysaccharide vaccine by risk group in 19 European countries

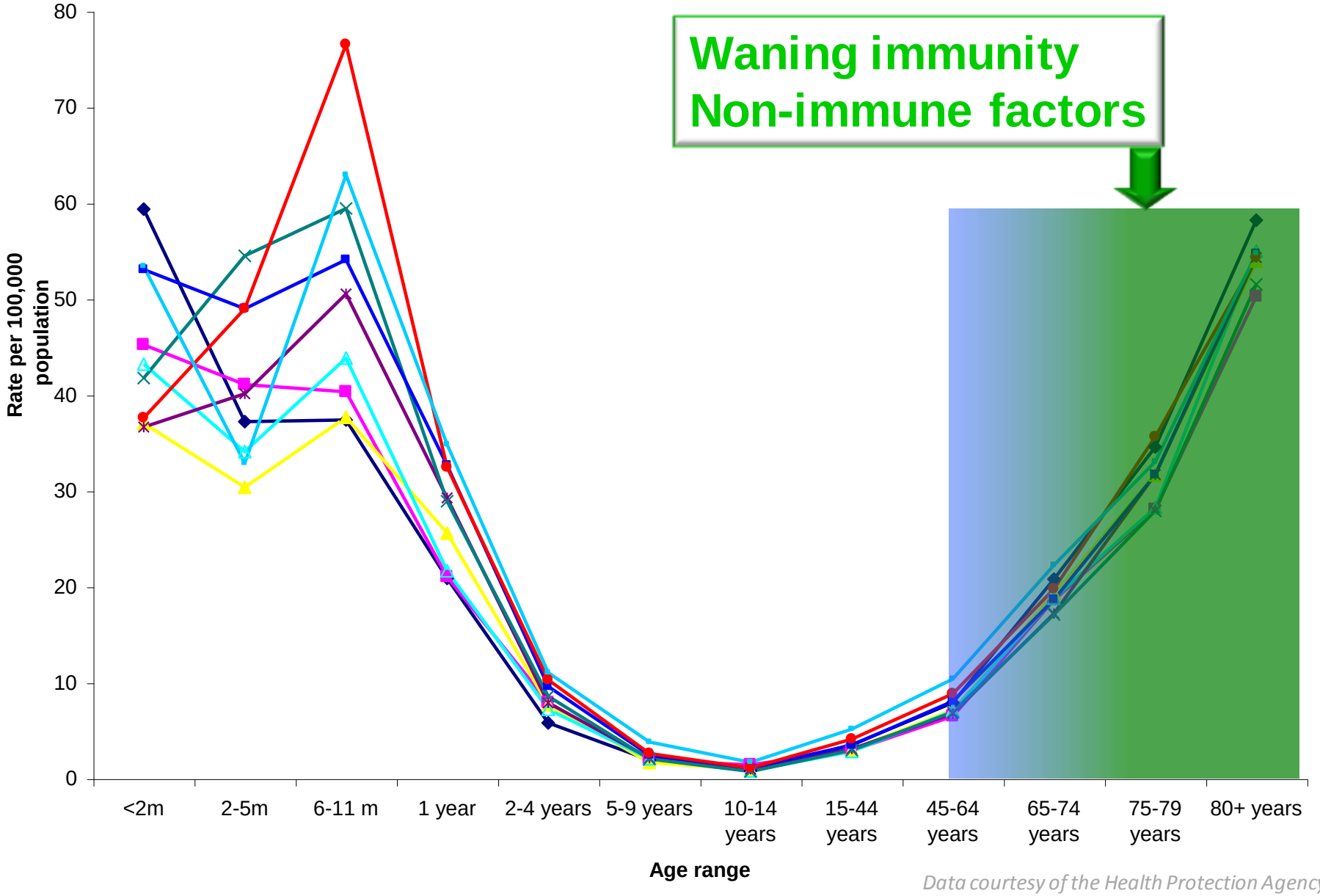
	AUS	BEL	CZE	CYP	DEN	ENG	EST	FIN	FRA	GER	IRE	LAT	LIT	LUX	NET	NOR	SLO	SWE	SWI
Splenic dysfunction	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes[1]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Chronic cardiovascular disease	Yes	Yes[2]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Chronic pulmonary disease	Yes	Yes[2]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Diabetes mellitus	Yes	Yes[2]	No	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	No	No	Yes	Yes	Yes
Alcoholism	Yes	Yes[2]	No	Yes	No	No	No	Yes	Yes	No	Yes	No	na	Yes	No	No	No	Yes	No
Chronic liver disease	Yes	Yes[2]	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes
CSF fluid leak	Yes	No	No	Yes	Yes	No	No	Yes	No	Yes	Yes	No	na	Yes	No	Yes	Yes	Yes	Yes
Immunodeficiency	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
HIV infected	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes
> 65 years of age	Yes[4]	Yes[4]	Yes[3]	Yes	Yes	Yes[5]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes[4]	No	Yes	Yes	Yes[3]	Yes
In nursing home	No	Yes	Yes	Yes	No	No	Yes	Yes	No	No	No	No	na	Yes	No	Yes	Yes	No	No

1 Children only
2 >45 years old
3 In some regions
4 >60 years old
5 Phased introduction from 2003 onwards
6 Under consideration
na= not available
Information not available for Slovak Republic

Eurosurveillance 2005;10(9):174-8

23 Valent PPV Coverage >65y





Data courtesy of the Health Protection Agency

Vaccine 28 (2010) 4763–4770

Contents lists available at ScienceDirect

Vaccine

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

The early kinetics of circulating pneumococcal-specific memory B cells following pneumococcal conjugate and plain polysaccharide vaccines in the elderly

Helen E. Baxendale[a,b,*], Sheila M. Keating[b], Marina Johnson[b], Jo Southern[c], Elizabeth Miller[c], David Goldblatt[b]

[a] Department of Immunology, University College London Medical School, Royal Free Hospital Campus, London NW3 2PF, UK
[b] UCL Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK
[c] Health Protection Age

Vaccine 28 (2010) 6915–6922

Contents lists available at ScienceDirect

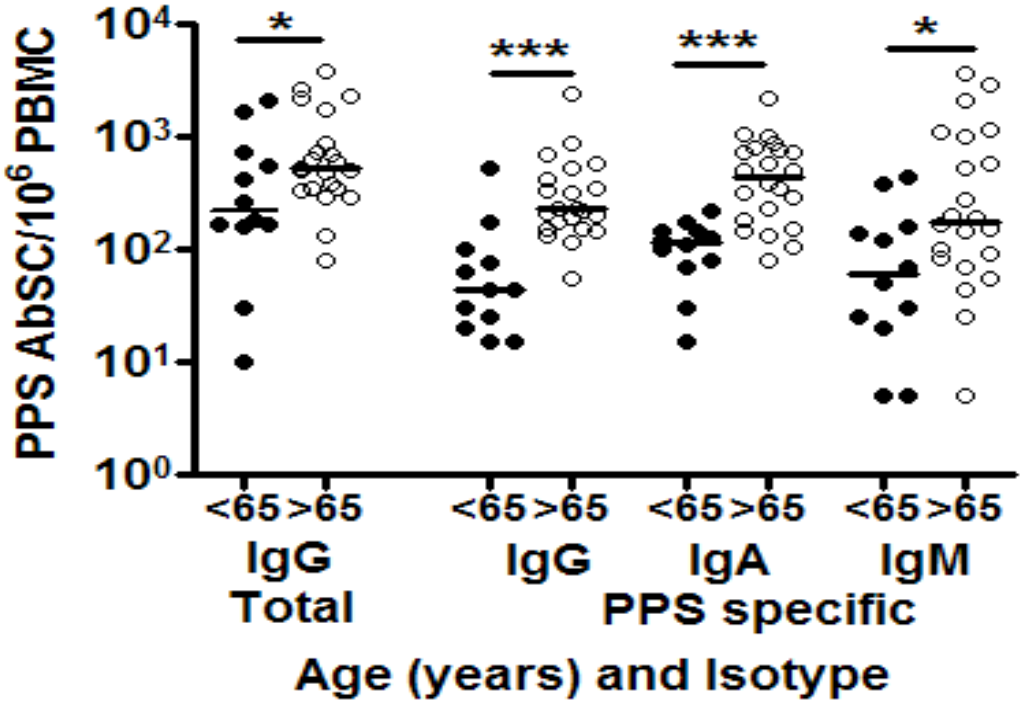
Vaccine

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

Circulating pneumococcal specific plasma and memory B cells in the elderly two years after pneumococcal conjugate versus polysaccharide vaccination

Helen E. Baxendale[a,b,*], Marina Johnson[b], Sheila M. Keating[b], Lindsey Ashton[b], Polly Burbidge[b], Sarah Woodgate[b], Jo Southern[c], Elizabeth Miller[c], David Goldblatt[b]

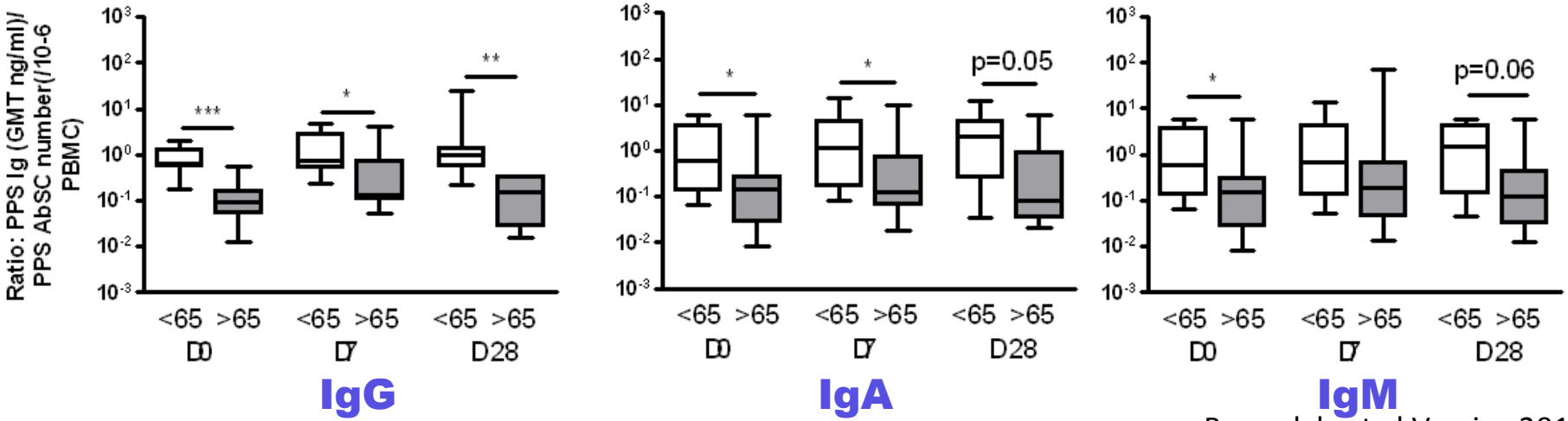
[a] Department of Immunology, University College London Medical School, Royal Free Hospital Campus, London NW3 2PF, UK
[b] UCL Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK
[c] Health Protection Agency, Centre for Infections, 61 Colindale Avenue, London NW9 5EQ, UK



Increase in Polysaccharide Specific Plasma Cells with age

(n=12 and 23)

Reduction in Polysaccharide Specific Ab produced per Plasma cell with age



Baxendale et al Vaccine 2010

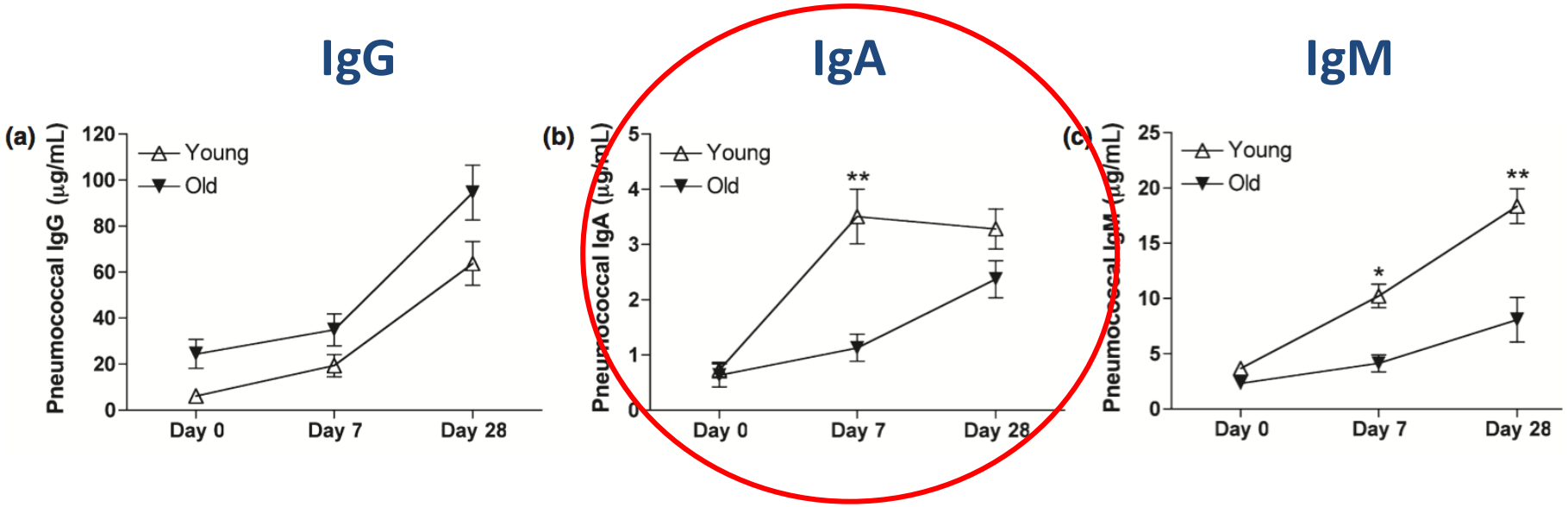
Increasing age but reduced function

Aging Cell (2011) **10,** pp922–930 Doi: 10.1111/j.1474-9726.2011.00732.x

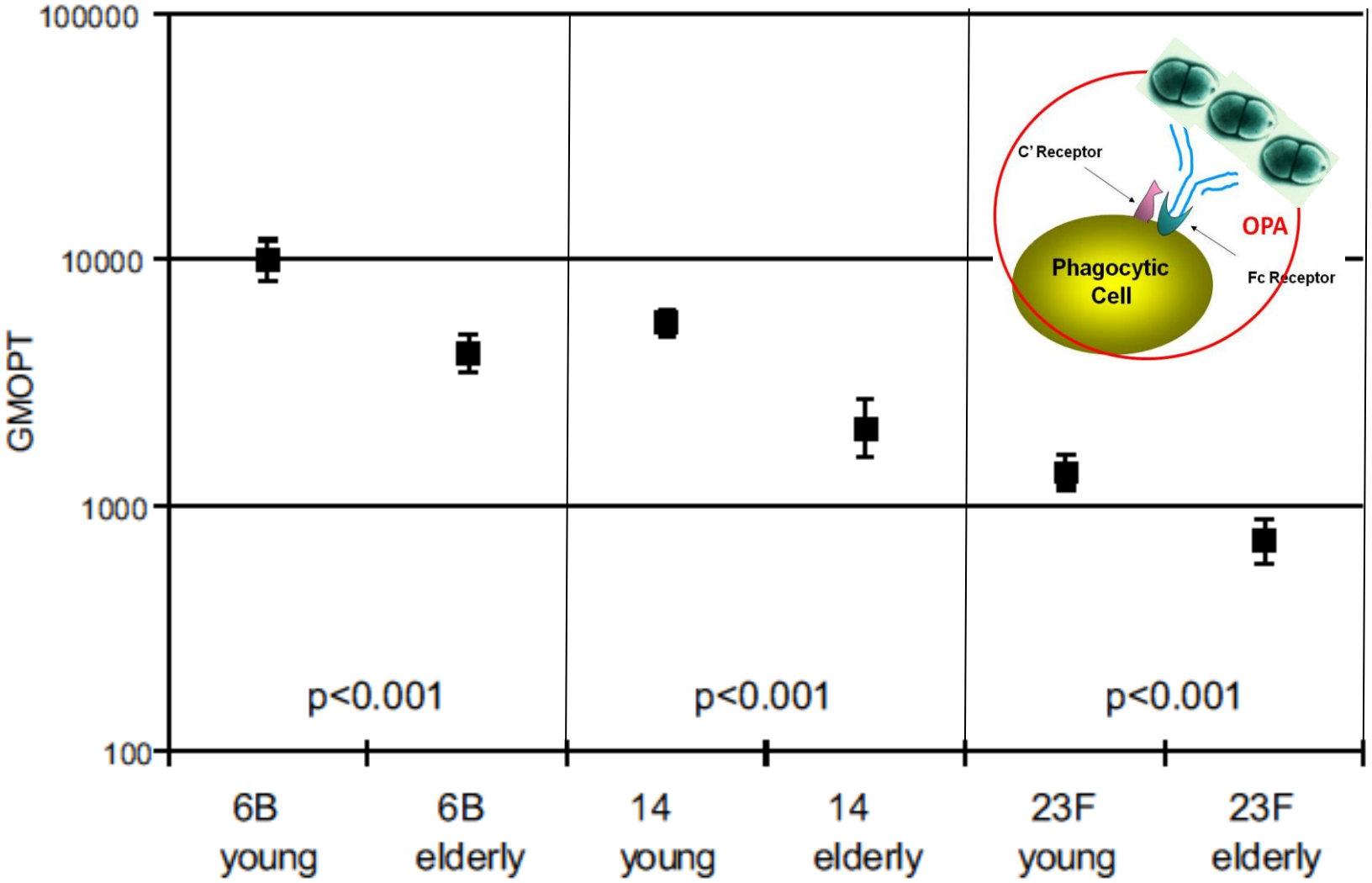
Vaccination-induced changes in human B-cell repertoire and pneumococcal IgM and IgA antibody at different ages

Alexander Ademokun,[1] Yu-Chang Wu,[1] Victoria Martin,[1] Rajive Mitra,[2] Ulrich Sack,[3] Helen Baxendale,[4] David Kipling[5] and Deborah K. Dunn-Walters[1]

2 groups of adults: 18-49y (n=39), 65-89y (n=27)
Pneumovax 23™ (Sanofi Pasteur MSD) , bled day 7 and 28



Phagocytes from the young (mean age 34y) & elderly (mean age 74y) differ in their capacity to kill pneumococci



Simell et al Vaccine 2011

Summary of Head to Head PCV vs PPV immunogenicity studies in healthy adults

Netherlands
The Journal of Medicine

ORIGINAL ARTICLE

Rationale and design of a RCT of 13-valent conjug mococcal vaccine efficacy a er adults

E. Hak[1,2*], D.E. Grobbee[1], E.A.M. Sand . Bolkenbaas[1], S.M. Huijts[1], W.C. Gruber[3], S. Tansey[3], A. McDonough[3] on[3], A.J. van Alphen[4], M.J.M. Bonten[1,5]

[1]Julius Center for Health Care, Departments of [2]Pediatric Immunology and Infectious Diseases, a gy, University Medical Center Utrecht, the Netherlands, [3]Wyeth Vaccines Res er New York, USA, [4]Netherlands Vaccine Institute, Bilthoven, the Neth g author: tel.: +31 (0)88-756 82 14, fax: +31 (0)88-76 80 99,

Results announced at the 9th International Symposium on Pneumococci and Pneumococcal disease, Hyderabad, India, March 2014

October 2008, Vol 66, No 9

- 84,496 Dutch volunteers ≥ 65yrs old
- Randomised to PCV13 or control
- Primary Endpoint: Accrual of Vaccine Type Community Acquired Pneumonia (CAP)
- Other endpoints:
  - VT non bacteraemic/non invasive pneumococcal CAP
  - VT invasive Pneumococcal Disease
- Vaccine type pneumonia confirmed by Serotype Specific Urinary Antigen Detection

Data Presented ISPPD9, March 2014

Primary and Secondary Objectives: Per Protocol

Efficacy Endpoint	Vaccine Group		VE (%)	95.2% CI	p-Value
	PCV13 (n=42,240)	Placebo (n=42,256)			
First episode of confirmed VT pneumococcal CAP	49	90	45.56	(21.82,62.49)	0.0006
First episode of confirmed NB/NI VT pneumococcal CAP	33	60	45.00	(14.21, 65.31)	0.0067
First episode of VT-IPD	7	28	75.00	(41.43, 90.78)*	0.0005

* 95% Confidence Intervals

Data Presented ISPPD9, March 2014

- Vaccine was safe
- Most prominent effects were on serotypes 3, 7F and 19A

  {Holland introduced PCV7 into the NIP in 2008 and PCV10 in March 2011, all 13 serotypes were circulating during the study}
- Effectiveness was stable over the period of observation (mean 3.97 years)
- No effect on mortality

Data Presented ISPPD9, March 2014

Summary

1. Polysaccharides remain interesting!
2. They are limited as pure vaccine antigens
3. Conjugated to proteins they make powerful vaccines
4. Exposure to pure polysaccharides as
   i. vaccine antigens
   ii. through infection or
   iii. NP carriage

   interferes with the immune system and effects subsequent responses.
5. This may be related to B cell apoptosis
6. There may be an as yet unrecognised role for T cells in polysaccharide immunity
7. In healthy adults PCV can prevent pneumonia, this will intensify the debate about PCV use in adults.