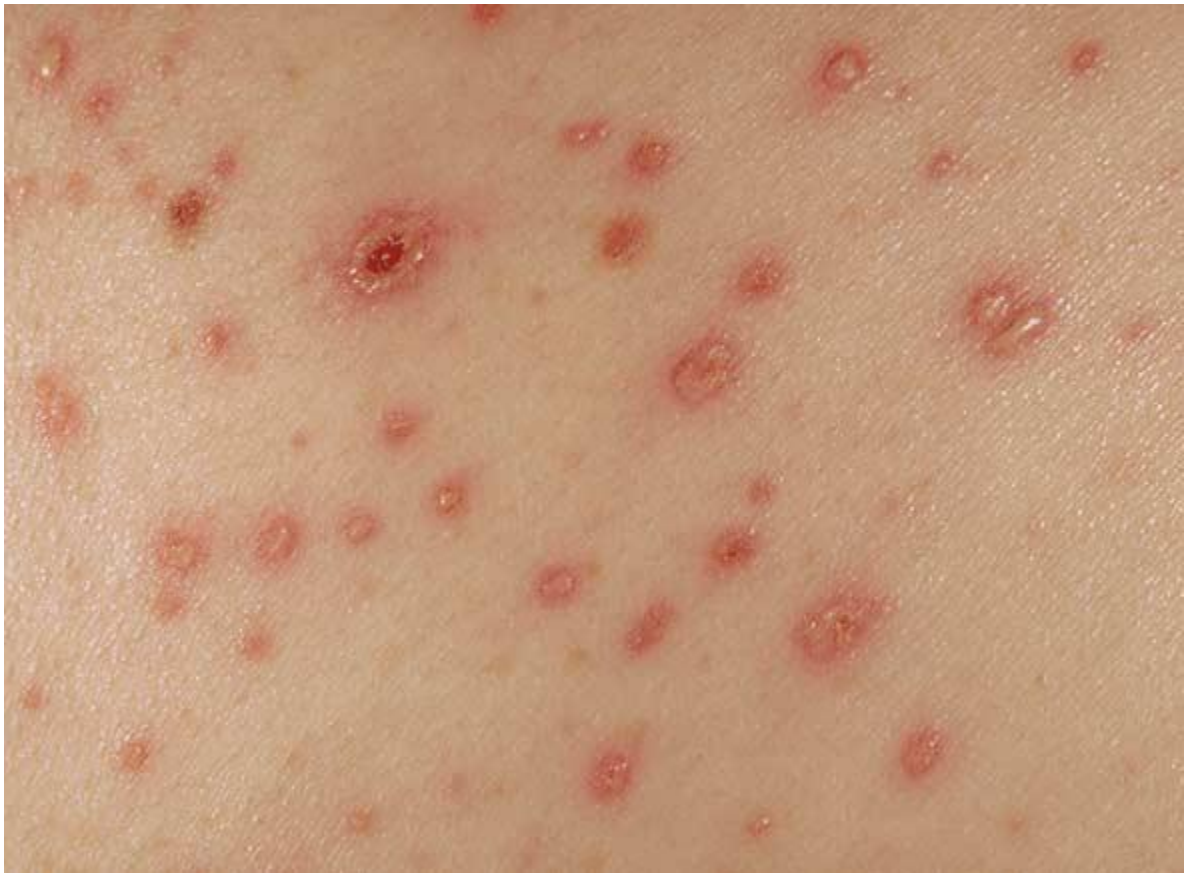
Correlates

Andrew J Pollard

Professor of Paediatric Infection and Immunity, Oxford University

Correlates of what?
What correlates?



Estimated case fatality by age group per 100,000 1995-7

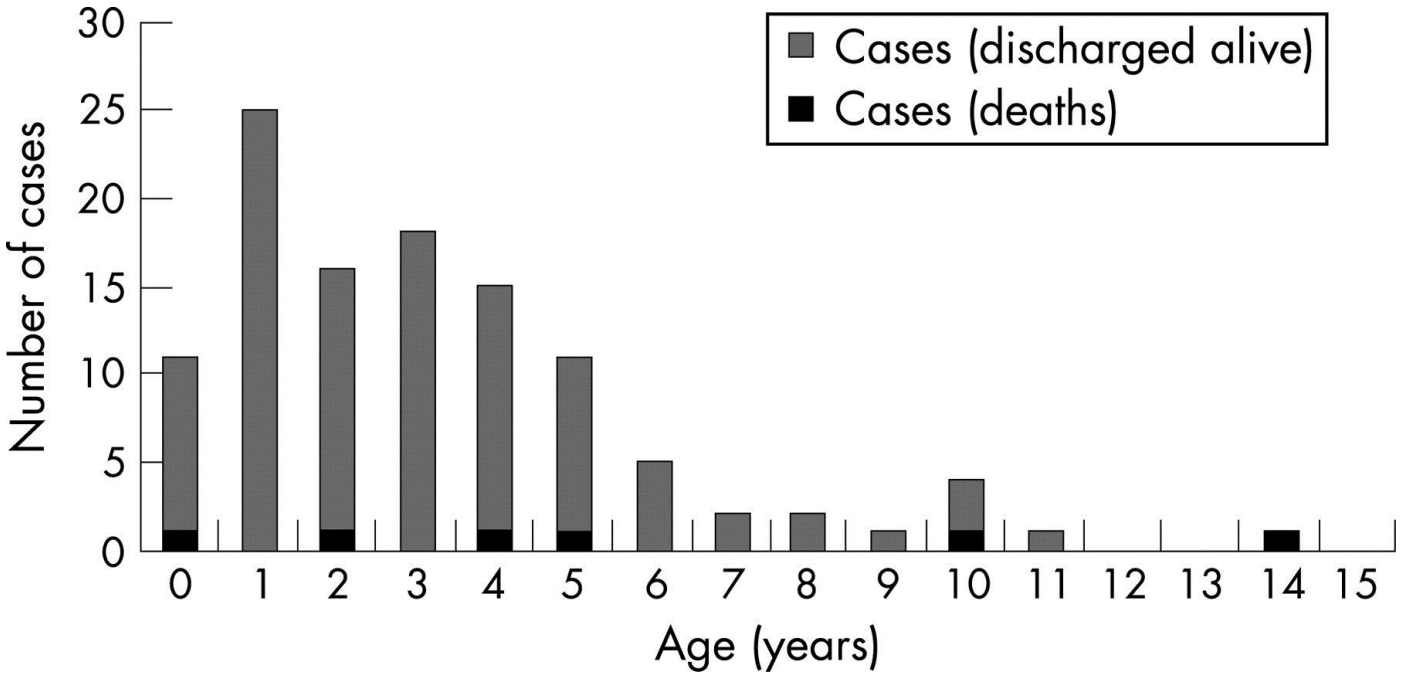
	0-4 years	5-14 years	15-44 years	45-64 years	65 years	Total
Deaths (confirmed)	12	2	29	11	21	75
No of cases*	456 444	211 930	144 597	11 056	2854	826 881
Rate per 100 000 (95% CI)	2.63 (1.36 to 4.60)	0.94 (0.11 to 3.41)	20.06 (13.43 to 28.80)	99.49 (49.67 to 178.02)	735.8 (455.5 to 1124.8)	9.07 (7.13 to 11.37)

Correlate of what?

*Cases based on consultation rates for 1995-7, Royal College of General Practitioners.

Rawson et al

Figure 2 Confirmed cases of severe varicella by age (n = 112).



Cameron, J C et al. Arch Dis Child 2007;92:1062-1066

Correlate of what?

Copyright ©2007 BMJ Publishing Group Ltd.

ADC ONLINE

Varicella

- Viral infection
  - Protection mediated by ?

Child with AIDS – Disseminated VZV

X-linked agammaglobulinaemia

- No antibody
- Course of illness with primary VZV is the same as individual who is not immunodeficient

Perinatal VZV

- Postnatal exposure VZV unlikely or very mild if mother immune
- Maternal VZV 5 days before to 2 days after delivery
- ZIG is not detectable in blood after im injection – very small amount needed for protection
- With VZIG still 30-40% develop disease
- VZIG reduces severity in perinatal exposure
- Reduction in complications and mortality

Reviewed in Isaacs 2007

Vaccine Immunogenicity

- One dose
- > 5 gpELISA units in 92-98%
- Lower seroconversion in adolescents
- 4-fold rise in antibody in 78-87%
- 98-100% persistence for 6 years

Shinefield 2002

Vaccine Efficacy

- 5 years = 90%
- 97% effective against severe and moderately severe disease
- Breakthrough cases 5-7% over 5 years

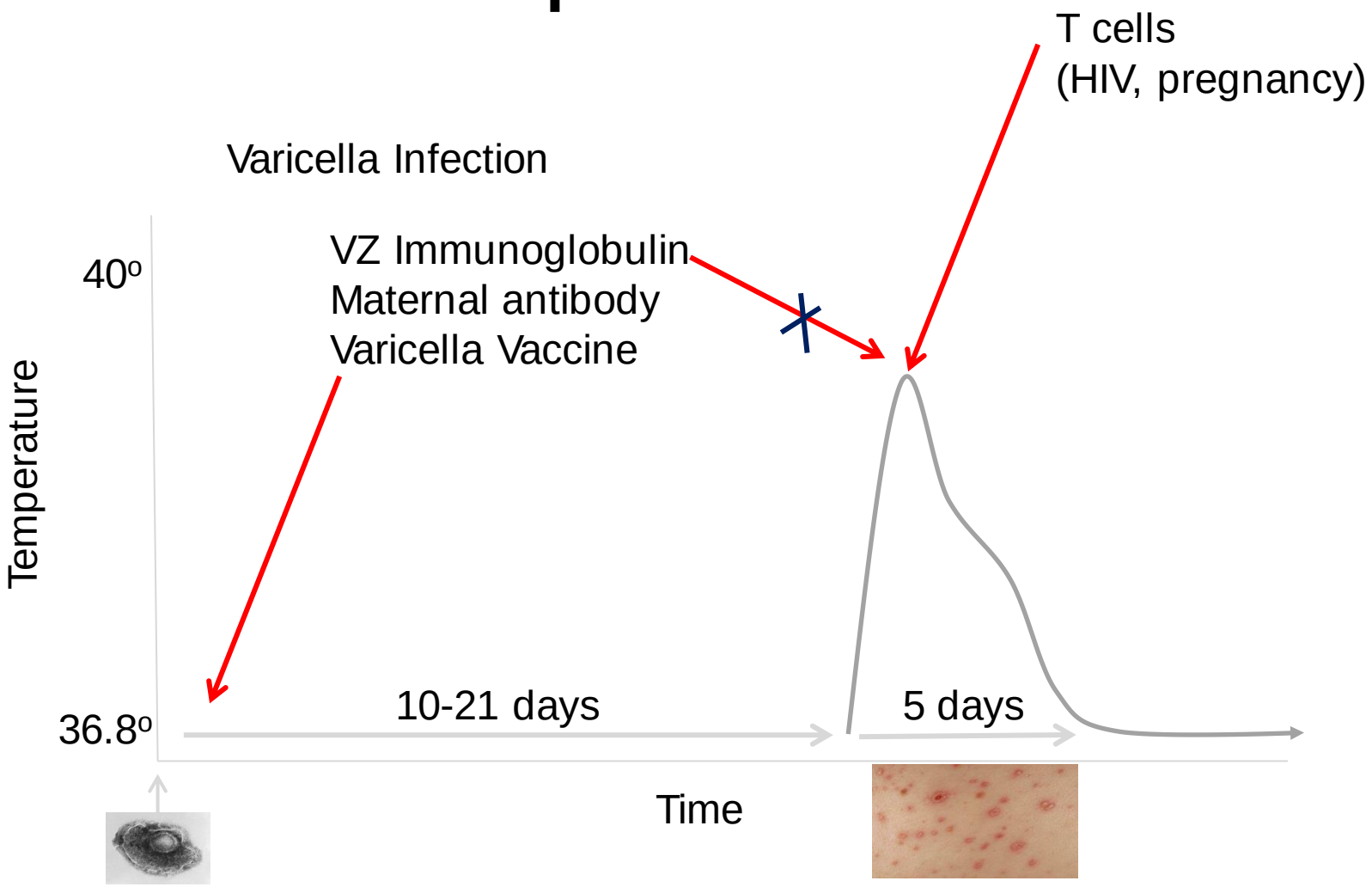
Shinefield 2002, Vazquez 2001, Chaves 2007

Correlate of protection

- Level and type of T cells required to limit disease in an individual is unknown
- Passive antibody provides protection but we don’t know the quality of IgG or absolute level for protection
- gpELISA correlates
- FAMA correlates better

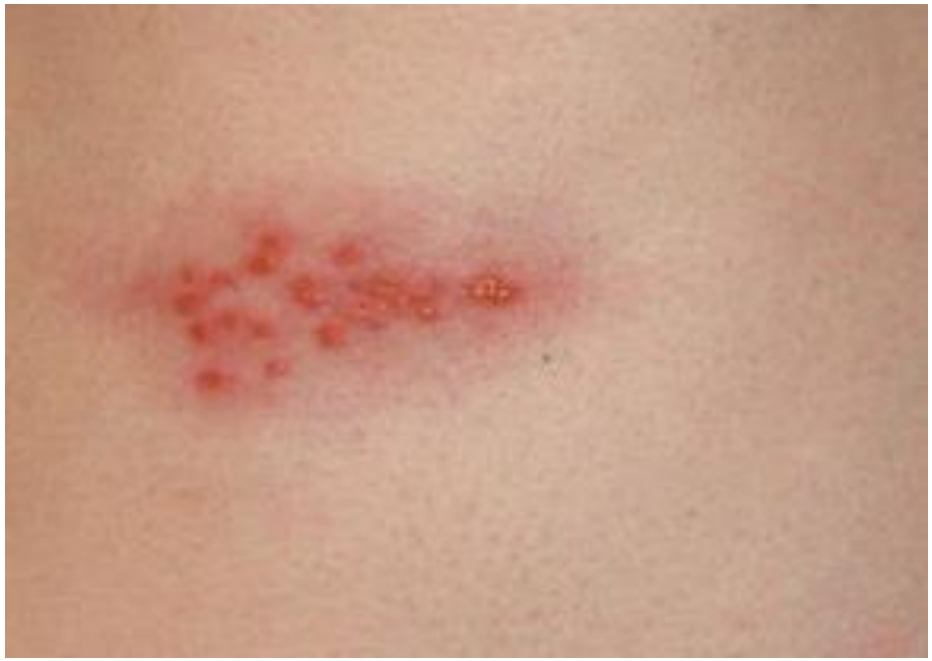
Fluorescent antibody to membrane antigen

Why are T cells not correlates of protection?



Zoster (Shingles)

- Need T cells
- Role of antibody?



Zoster vaccine efficacy

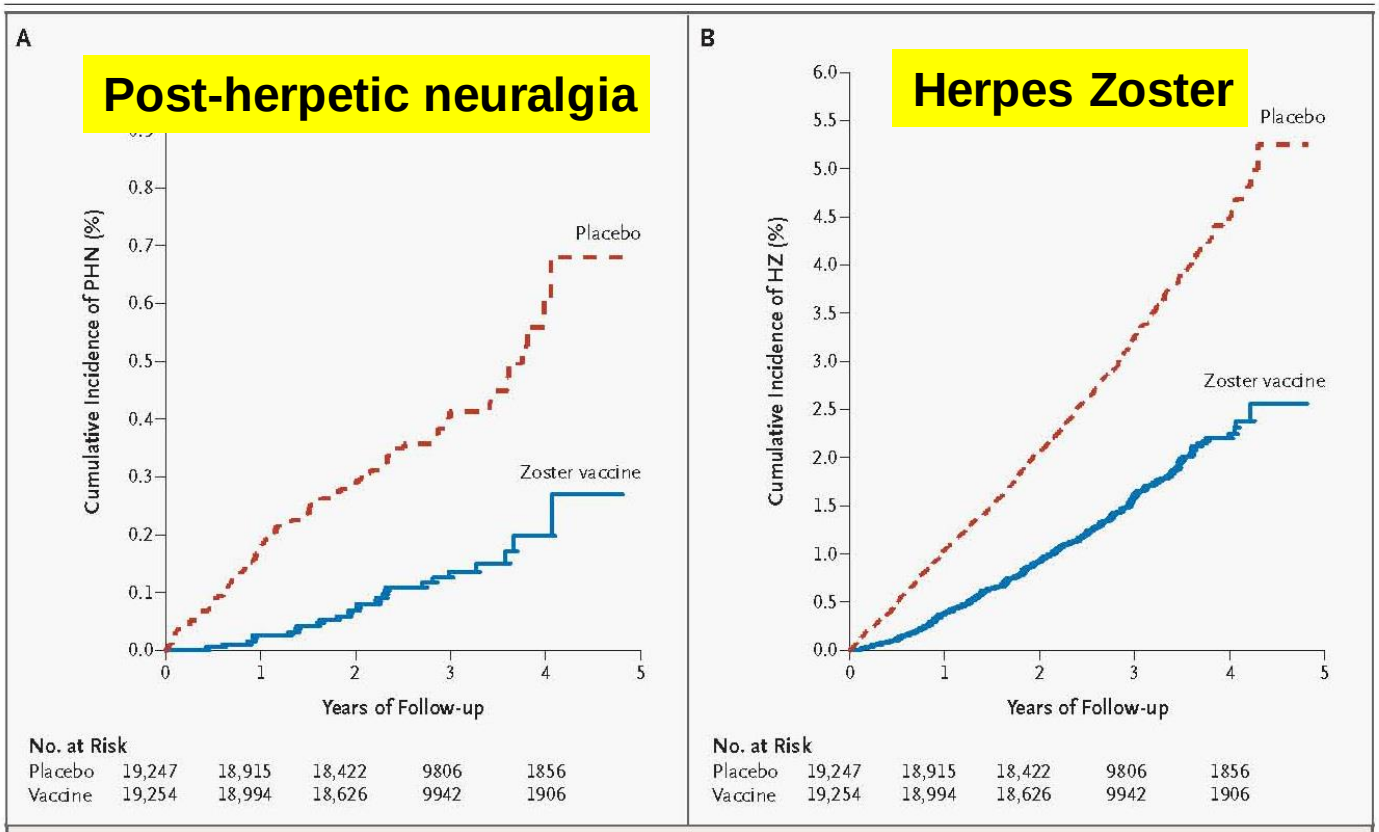


Figure 2. Kaplan–Meier Estimates of the Effect of Zoster Vaccine on the Cumulative Incidence of Postherpetic Neuralgia (Panel A) and Herpes Zoster (Panel B) in the Modified Intention-to-Treat Population.

Incidence rates of postherpetic neuralgia (PHN) and herpes zoster (HZ) were significantly lower in the vaccine group than in the placebo group ($P<0.001$, by a stratified log-rank test that pooled the results of the log-rank test from the two age groups). Cumulative incidence, expressed as a percentage of the subjects at risk, is the probability of the development of the disease during the period from 30 days after vaccination to the follow-up time.

Oxman 2005

Zoster Vaccine

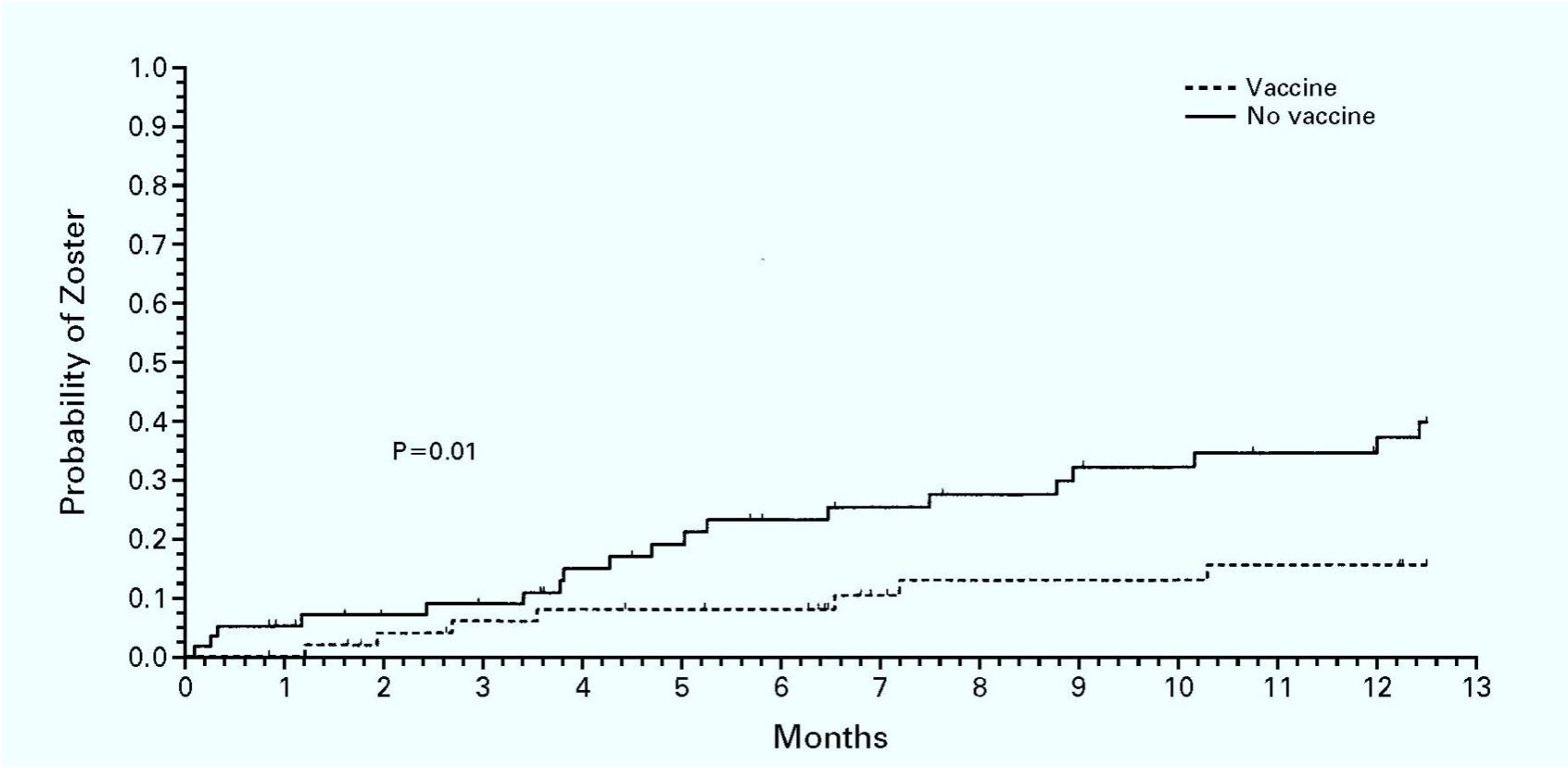
- Vaccine contains large amounts of infectious and non-infectious varicella virus

- VZ antigen stimulates flagging cellular immunity in the elderly

- Correlate of protection is VZ-specific CD4+ lymphocyte proliferation stimulation index

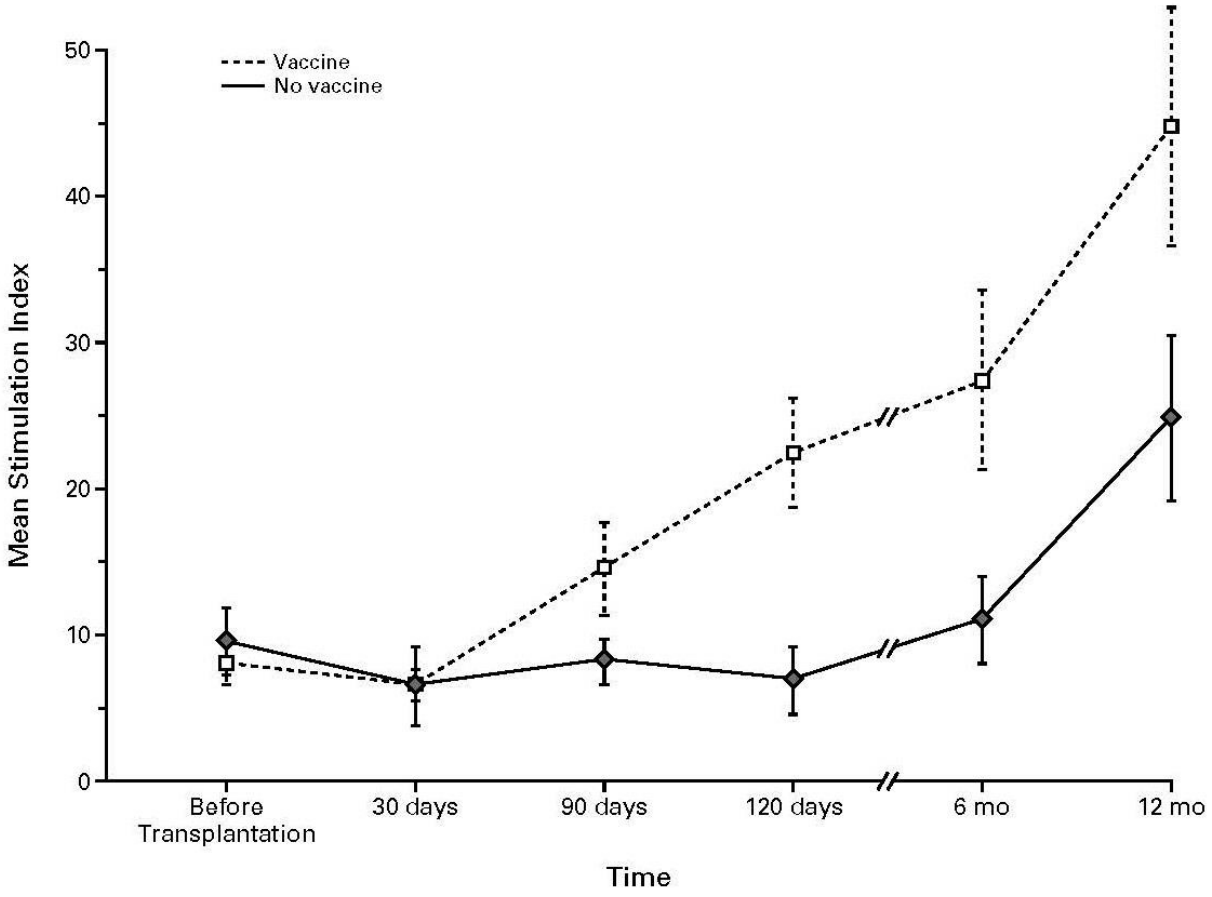
Hata et al. NEJM 2002

Zoster vaccine in transplanted adults



Hata et al. NEJM 2002

CD4 T cell Stimulation index



No. Tested						
Vaccine	53	49	42	39	34	33
No vaccine	58	50	43	34	30	27

Hata et al. NEJM 2002

CD4 T cell SI and reduction in Zoster

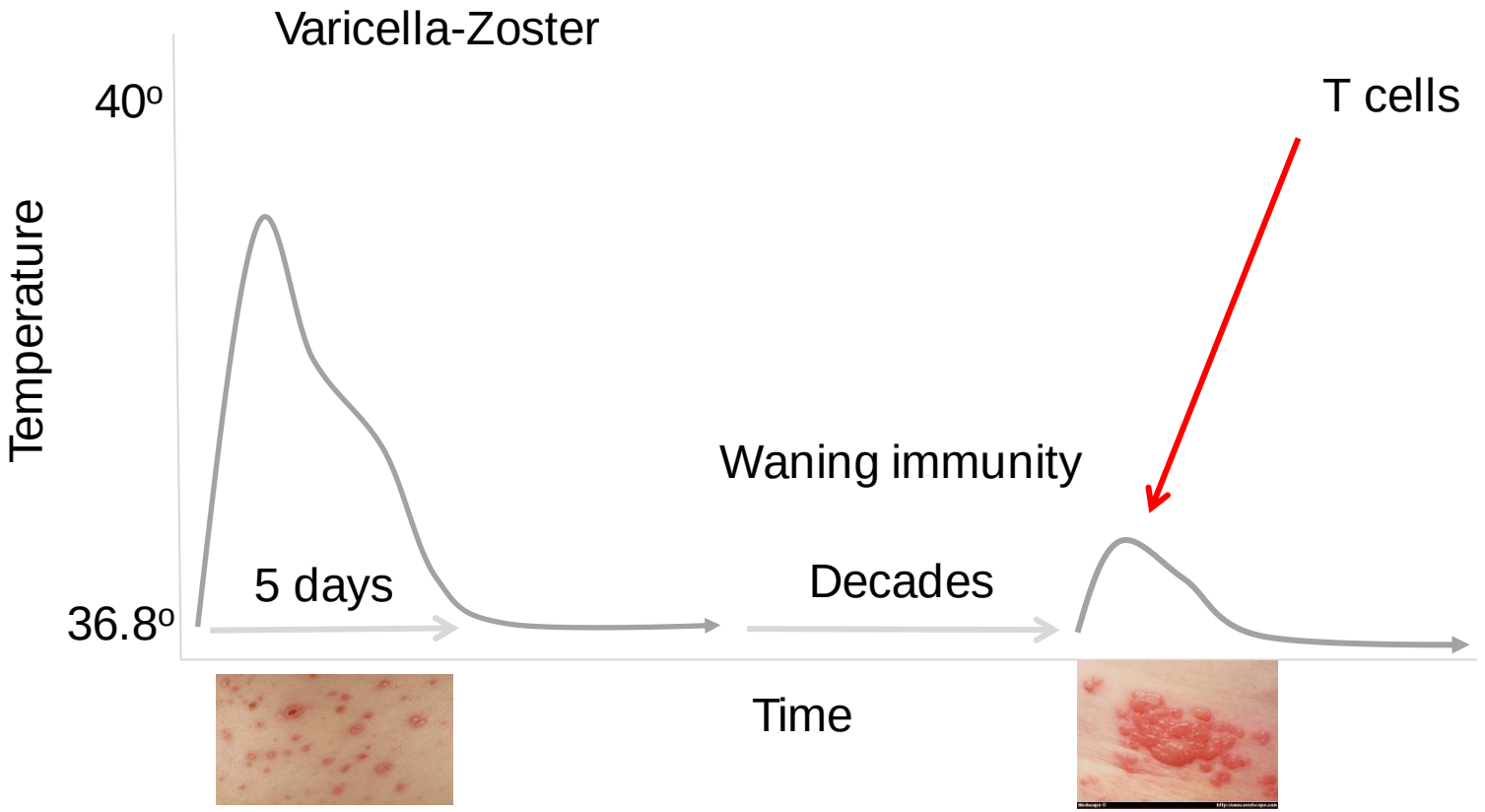
Stimulation Index	Reduction in risk (%)
1.6	68
3.0	76
4.0	83
5.0	93

Hata et al. NEJM 2002

Comparison of varicella-zoster virus (VZV)-specific immune responses in immunology substudy subjects who developed herpes zoster (HZ) and those who did not

Time immune assay	Clinical endpoint	Vaccine	Placebo	
		Observed geometric mean (95%) CI	Observed geometric mean (95%) CI	*p*
Before rash onset				
Responder Cell Frequency	HZ	2.3 (2.1–6.9)	2.4 (1.3–4.4)	.006
	Matched control	6.5 (5.3–8.0)	5.6 (4.8–6.5)	
ELISPOT	HZ	28.6 (7.1–114.2)	28.8 (17.2–48.2)	<.001
	Matched control	99.8 (80.8–123.2)	56.7 (47.3–68.0)	
gpELISA	HZ	252.4 (126.1–504.9)	181.3 (122.3–268.8)	.030
	Matched	331.9	346.6	

T cells as effectors and correlates



Stanley's Definitions Page:

Correlate: An immune response that is ***responsible*** for and statistically interrelated with protection

Absolute Correlate: A specific level of response highly correlated with protection: a threshold

Relative Correlate: Level of response variably correlated with protection

Co-Correlate: One of two or more factors that correlate with protection in alternative, additive, or synergistic ways.

Surrogate: An immune response that substitutes for the true immunologic correlate of protection, which may be unknown or not easily measurable

Principle 1

Must Define Protection

Against

Infection ? (Local or Disseminated or even colonisation/carriage)

Disease ? (Mild or severe)

Cost to the health system

Hospitalisation

Varicella

- Define as short-term protection against clinical (severe) disease

Rotavirus

- Define as prevention of hospitalisation or severe disease

What are used to look for a correlate

Serum Antibody

- Neutralizing
- Non-neutralizing
- Functionality (opsonsphagocytosis)
- Avidity (cytotoxicity, etc.)

CD4+ T cells

- B cell help (Th2)
- T cell help (Th1)
- Help to inflammation (Th17)
- Cytokines
- Lysis

Mucosal Antibody

- IgA locally produced
- IgG diffused from serum

CD8+ T cells

- Lysis
- Avidity

How Correlates Are Determined

1. **Levels of passively administered or maternal antibody that protect**

2. **Analysis of immune responses in protected and susceptible individuals in efficacy trials**

3. **Analysis of immune responses in protected cohorts in effectiveness studies**

4. **Observations made on vaccine failures, e.g. immunosuppressed individuals**

5. **Human challenge studies**

6. **Extrapolation from animal challenge studies**

Principle 2

The Mechanism of Protection by Vaccination is *NOT* Necessarily the Same Mechanism as Recovery From Infection

Varicella

- Antibody neutralises the virus and prevents disease

- T cells kill viral infected cells and limit disease

Mechanism of Disease Prevented by the Vaccine

Viral	**Viraemia:**	**Smallpox, Yellow Fever, Measles Mumps, Rubella, Polio, Varicella, Hepatitis A, Hepatitis B Japanese Encephalitis, Tick-Borne Encephalitis**
	Mucosal replication:	**Influenza, Rotavirus, HPV**
	Neuronal Invasion:	**Rabies**
	Neuronal reactivation	**Zoster**
Bacterial	**Bacteremia:**	***Haemophilus influenzae* type b Meningococcal, Pneumococcal, Typhoid (Vi)**
	Colonisation	***Haemophilus influenzae* type b Meningococcal, Pneumococcal,**
	Mucosal Replication:	**Pertussis, Typhoid (Ty 21a)**
	Toxin Production:	**Diphtheria, Tetanus, (Pertussis) Cholera, Anthrax**
	Macrophage Replication:	**Tuberculosis**

Adapted from Plotkin S. *C.R. Acad. Sci*. 1999;322:943-951.

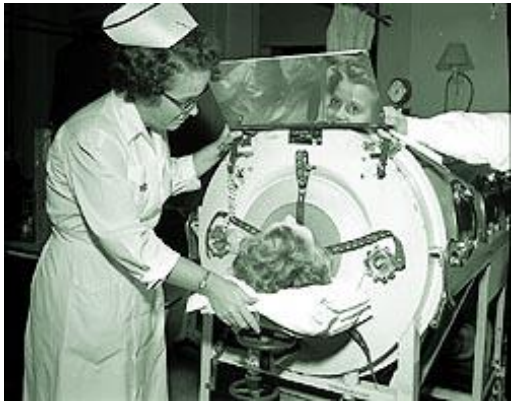
Principle 3

A Large Challenge Dose Can Overcome Immunity

Well recognised for viral infections – severity is associated with dose

This is a caution to those working in vaccine development using challenge studies to guide clinical development programmes

“Challenge” of Poliovaccine by OPV



% Infected 7 days after challenge

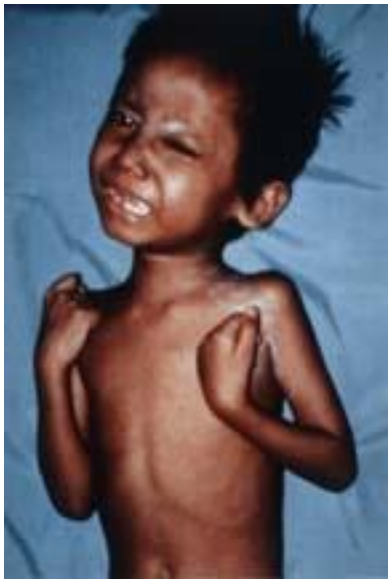
	Low dose	High Dose
OPV Vaccinees	**3%**	**15%**
IPV Vaccinees	**30%**	**70%**

Principle 4

Current Vaccines were ~~almost~~ exclusively developed to

Protect Through Antibodies

(Be suspicious of anyone who believes in T cells)

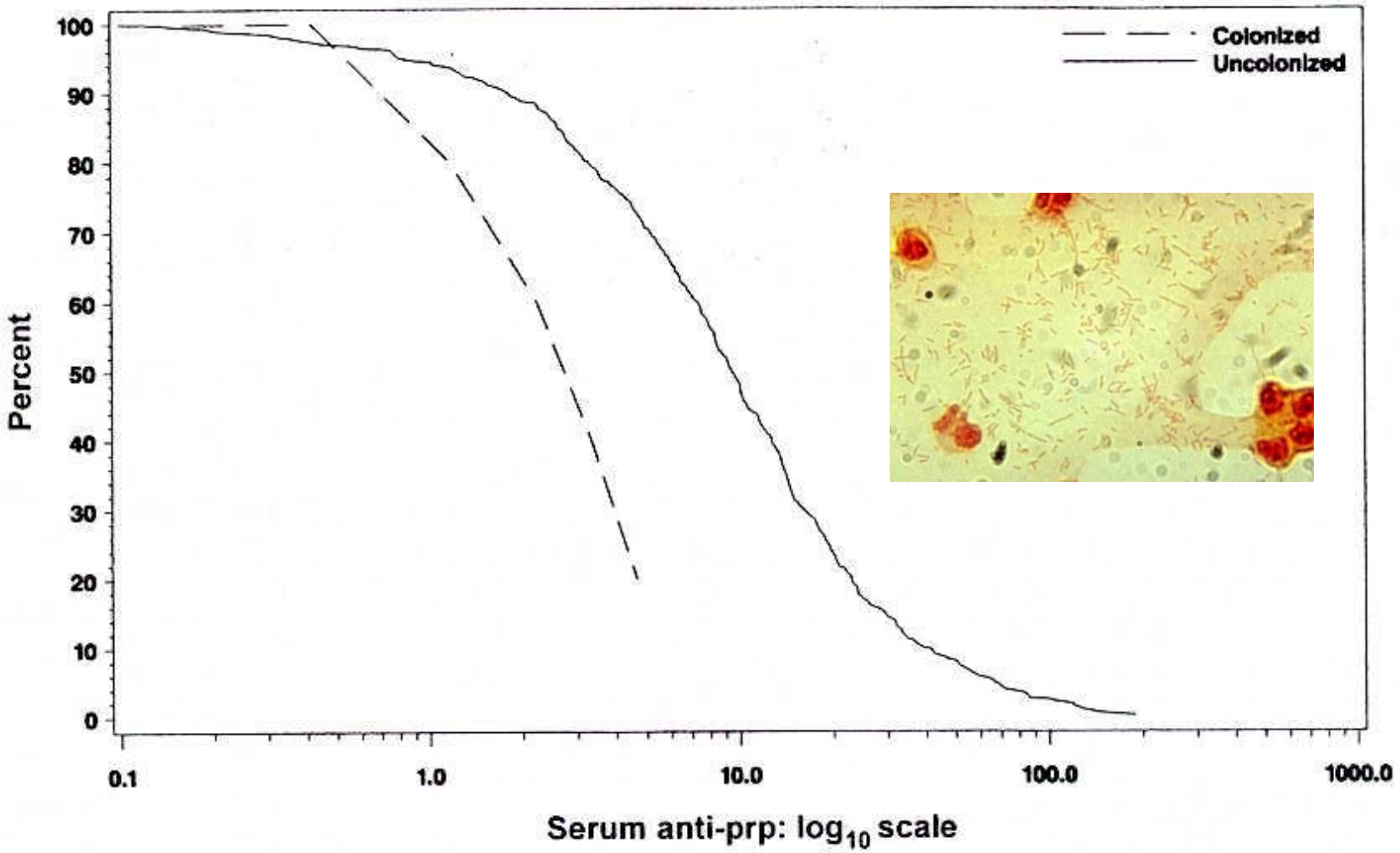


Infections for which Passive Immunity is Clearly Useful

Diphtheria
Pertussis
Tetanus
Staph
Group B Strep
Hib
Pneumo

Hepatitis A
Hepatitis B
RSV
CMV
VZV
Parvovirus B19
Enteroviruses (polio)
Measles
Rubella
Vaccinia

Anti-PRP Antibody and Hib Colonization



Fernandez J, et al. JID 2000;182:1553-6

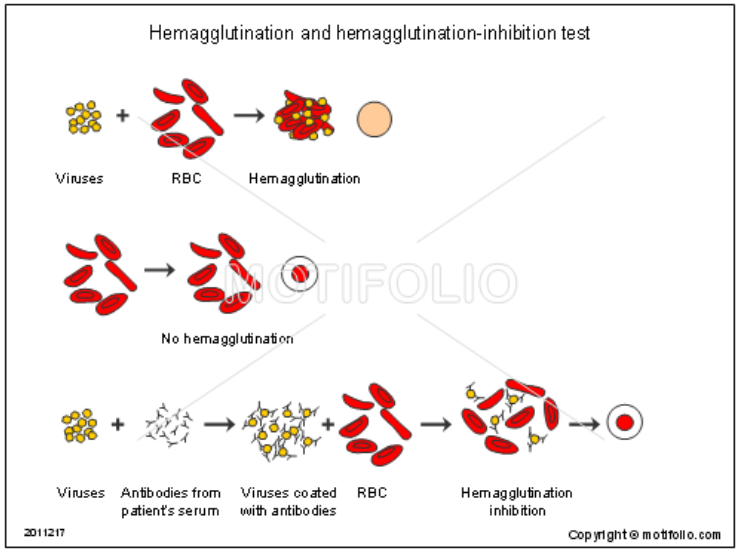
Antibody is used to derive quantitative correlates

Table 4. Some quantitative correlates of protection after vaccination.

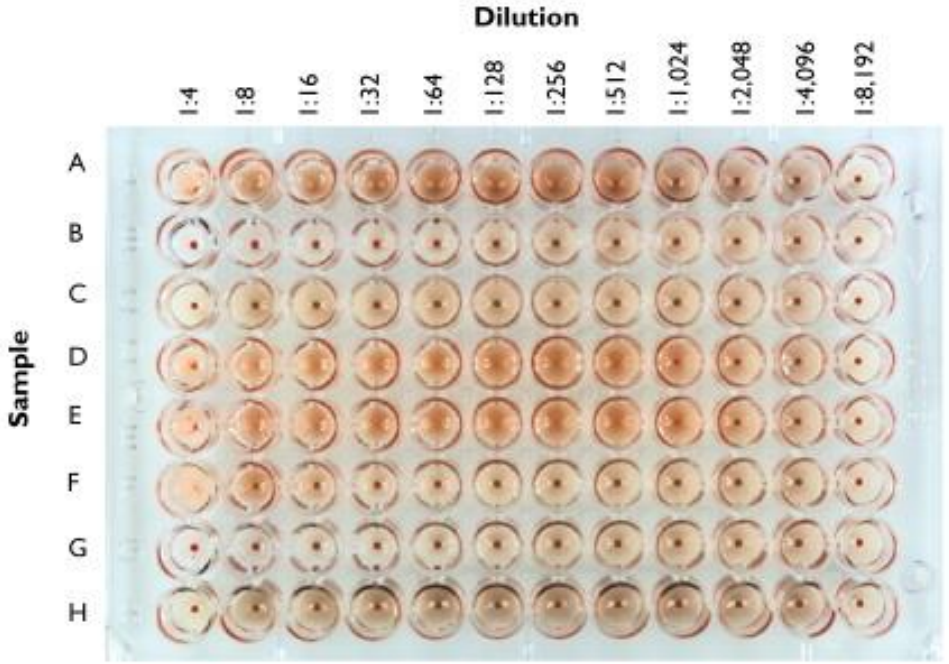
Vaccine	Test	Correlate of protection	Reference(s)
Diphtheria	Toxin neutralization	0.01–0.1 IU/mL	[14]
Hepatitis A	ELISA	10 mIU/mL	[15]
Hepatitis B	ELISA	10 mIU/mL	[16]
Hib polysaccharides	ELISA	1 mcg/mL	[17]
Hib conjugate	ELISA	0.15 mcg/mL	[18]
Influenza	HAI	1/40 dilution	[19]
Lyme	ELISA	1100 EIA U/mL	[20]
Measles	Microneutralization	120 mIU/mL	[7]
Pneumococcus	ELISA; opsonophagocytosis	0.20–0.35 mcg/mL (for children); 1/8 dilution	[21, 22]
Polio	SN	1/4–1/8 dilution	[23]
Rabies	SN	0.5 IU/mL	[24]
Rubella	Immunoprecipitation	10–15 mIU/mL	[25, 26]
Tetanus	Toxin neutralization	0.1 IU/mL	[27]
Varicella	SN; gpELISA	≥1/64 dilution; ≥5 IU/mL	[28, 29]

NOTE. gp, glycoprotein; HAI, hemagglutination inhibition; Hib, *Haemophilus influenzae* type b; SN, serum neutralization.

Plotkin CID 2008


Hemagglutination and hemagglutination-inhibition test
Viruses
RBC
Hemagglutination
No hemagglutination
Viruses
Antibodies from patient's serum
Viruses coated with antibodies
RBC
Hemagglutination inhibition
2011217
Copyright © motifolio.com

HAI


Dilution
1:4
1:8
1:16
1:32
1:64
1:128
1:256
1:512
1:1,024
1:2,048
1:4,096
1:8,192
Sample
A
B
C
D
E
F
G
H

1/40

HAI

- Factors affecting correlation with immunity
  - Age
  - Strain H3N2, H1N1, H5N1, H7N9
  - Virus Match
  - Co-morbidity
  - Previous exposure

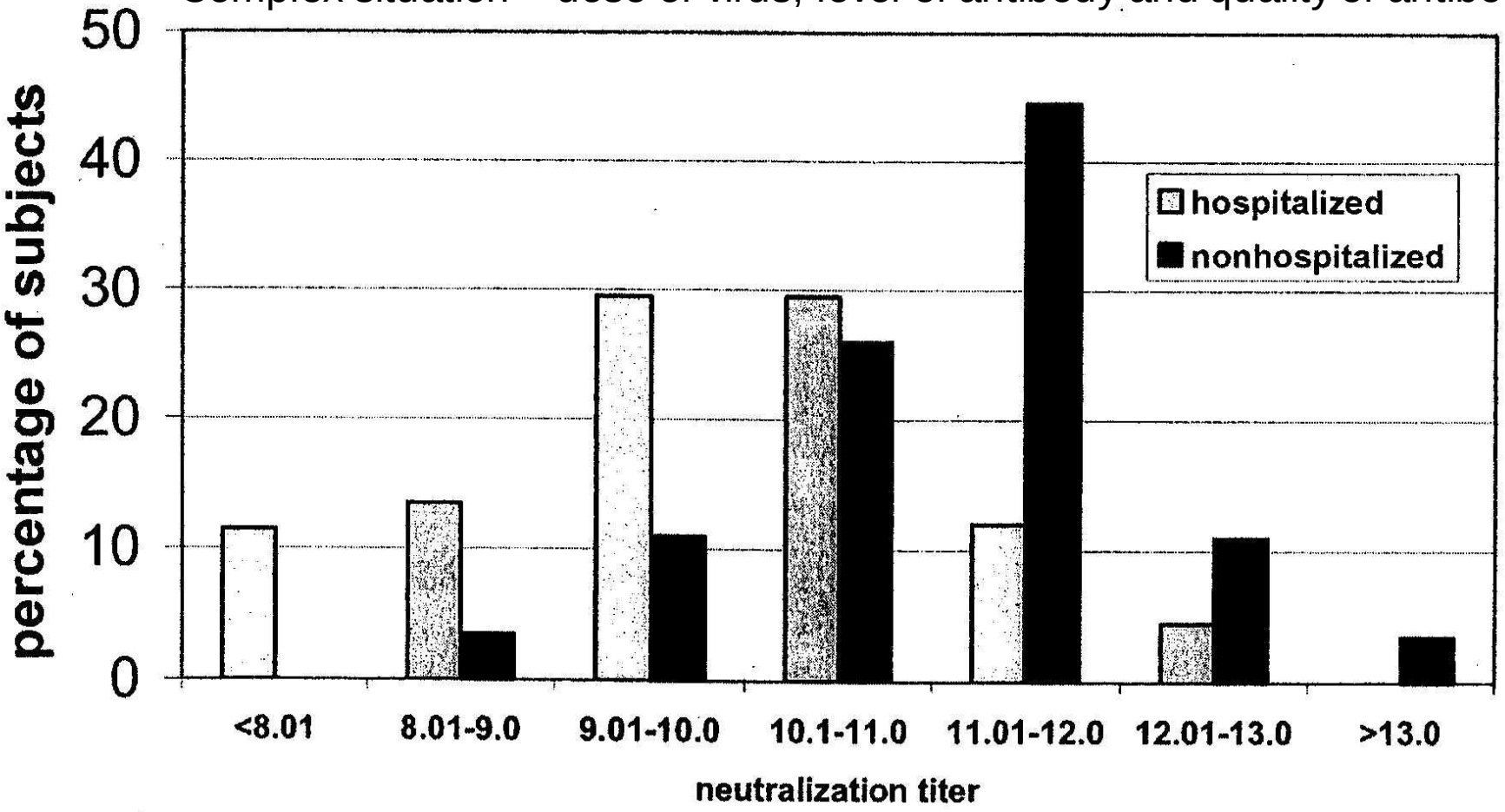
Principle 5

Correlates may be relative

Which means that the situation is more complex

Distribution of serum neutralizing titers in hospitalized and non-hospitalized adult subjects with RSV

Complex situation – dose of virus, level of antibody and quality of antibody



Walsh EE. JID 2004;189:233.

Elderly?

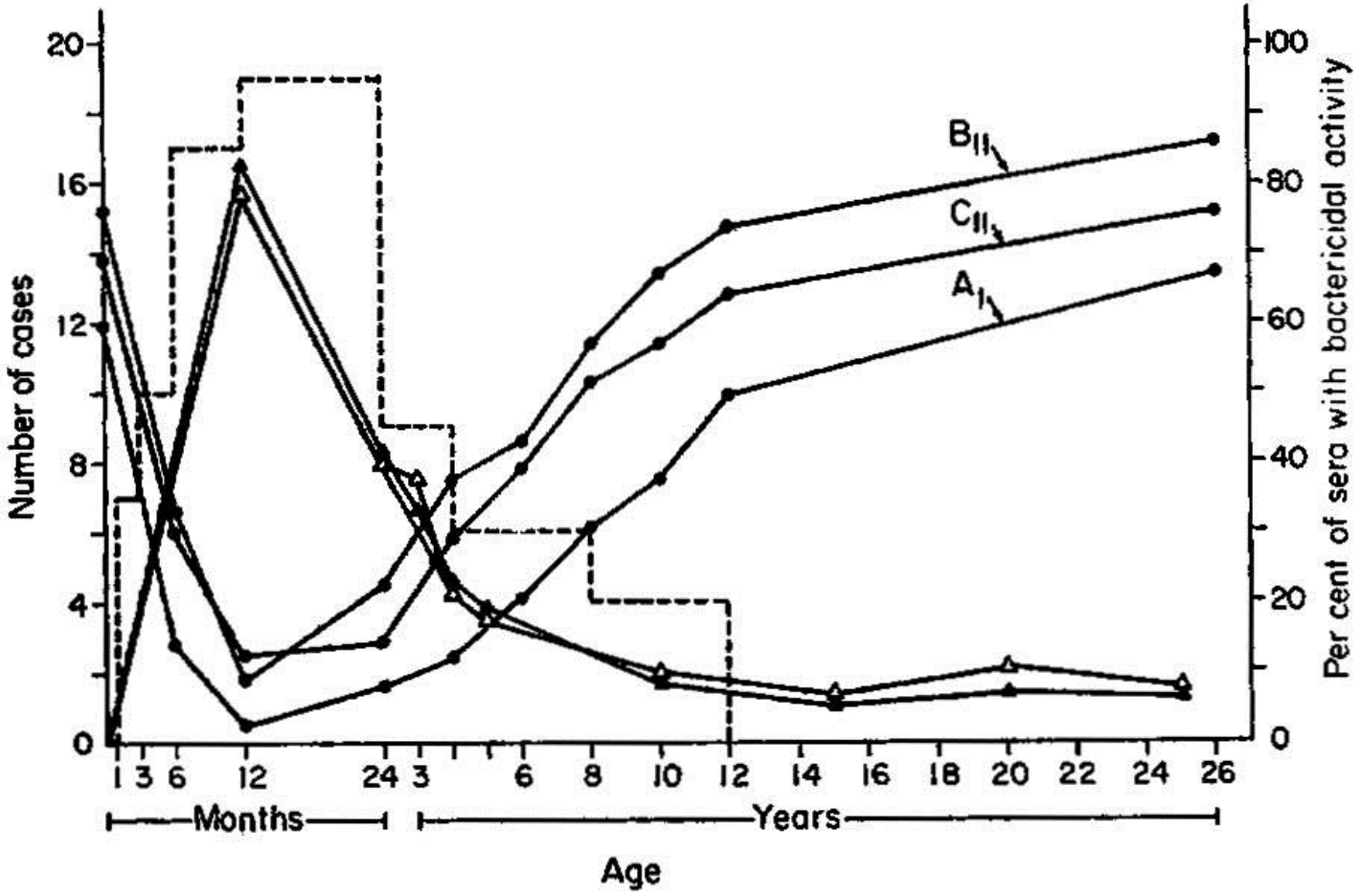
Principle 6

Antibodies must be

FUNCTIONAL

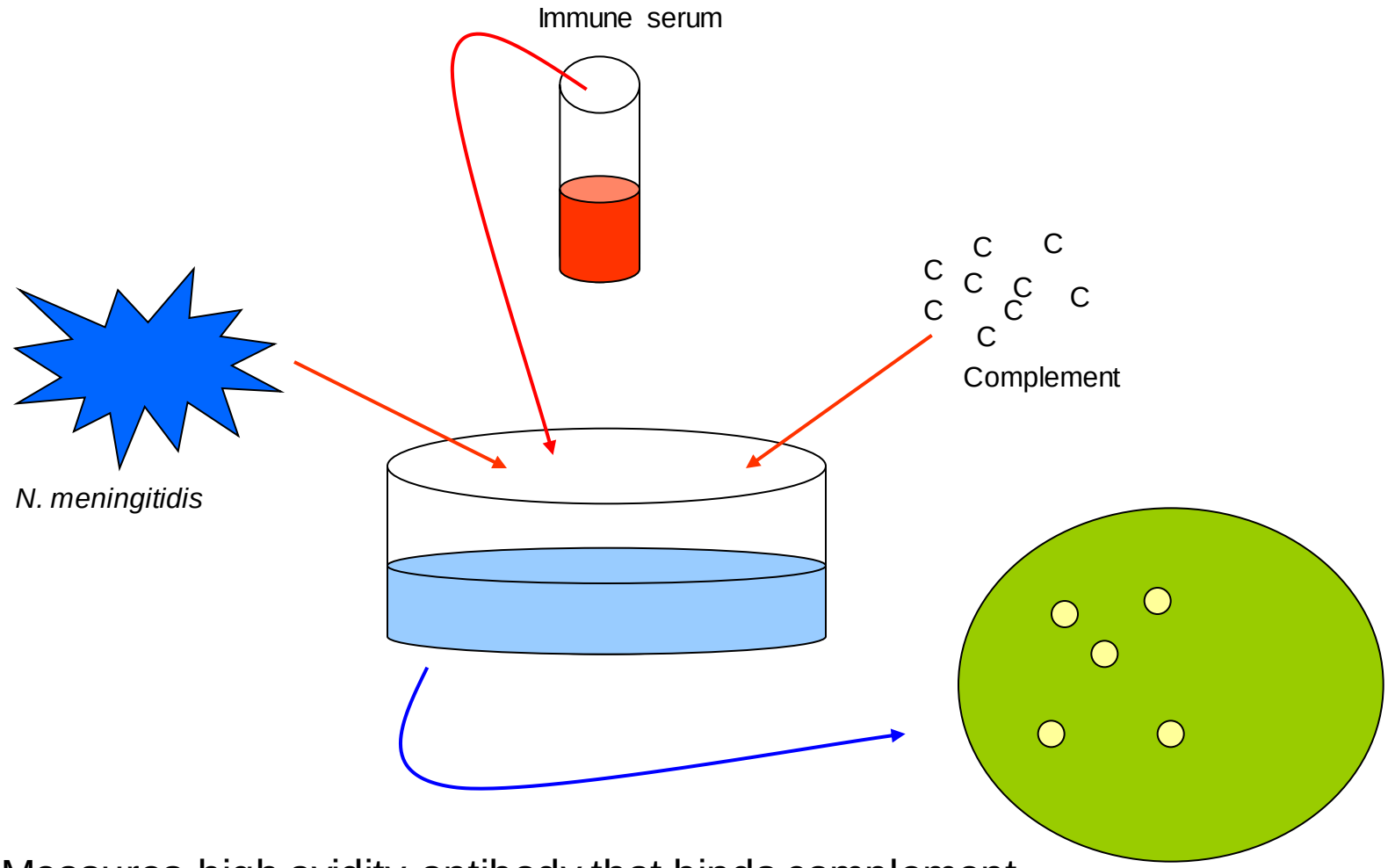
Do we need to measure them and are we are measuring the right thing ?

Meningococcal Disease



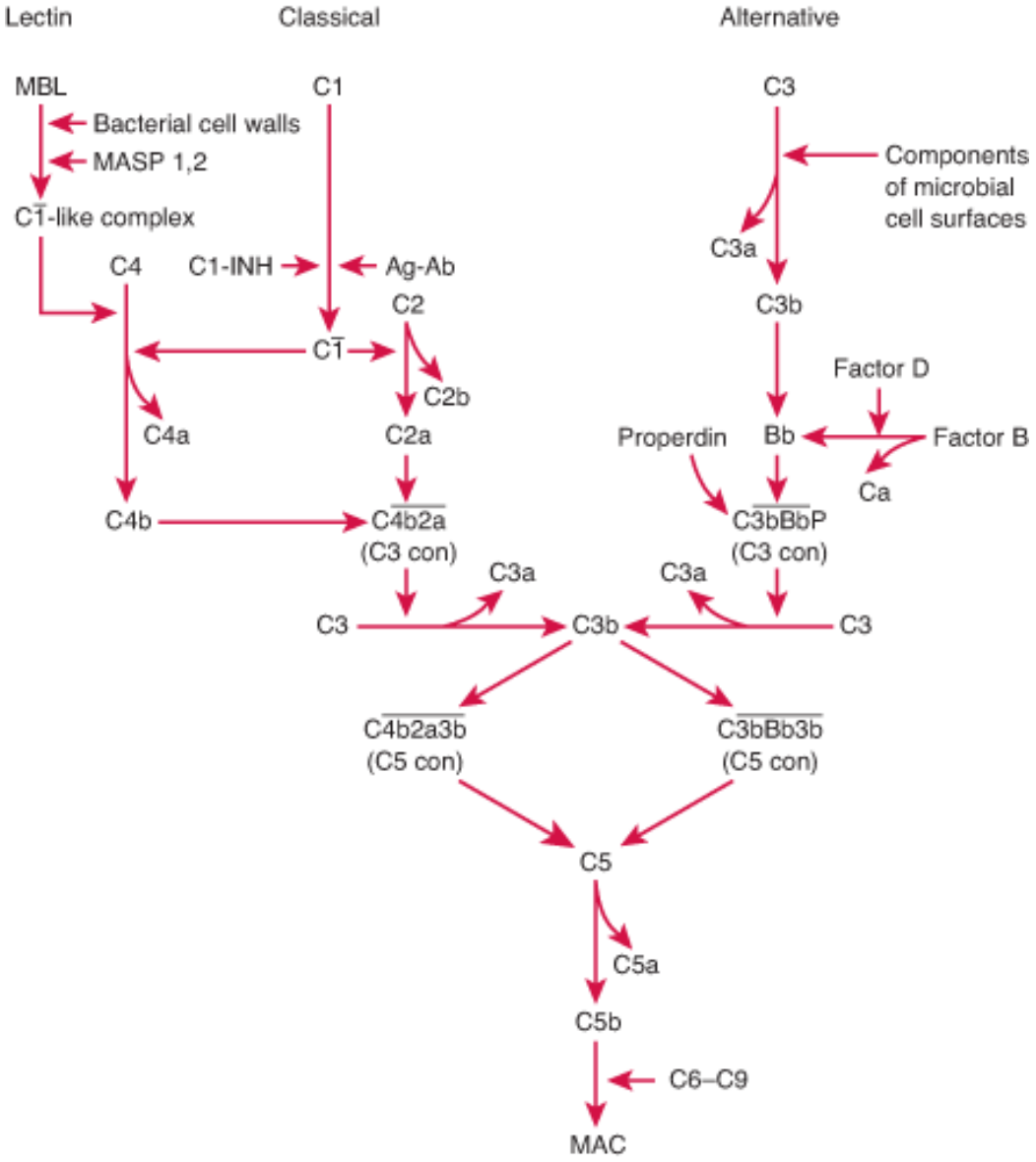
Goldschneider 1969

Measuring immunity against meningococcus – bactericidal assay



Measures high avidity antibody that binds complement

The complement system



ELISA and Bactericidal Antibodies After Group C Meningococcal Polysaccharide Vaccination

Age (Yrs)	ELISA % Pos.*	Bactericidal % Pos.#	Efficacy in Canada
1	93	18	0%
2	94	35	
3	92	56	41%
4	94	75	
5	84	68	
Adult	100	100	83%

*≥ 2 mcg/ml # ≥ 1/8

Maslanka SE, et al. *Infect Immun*, 1998, 66:2453-59
DeWals P, et al. JAMA 2001

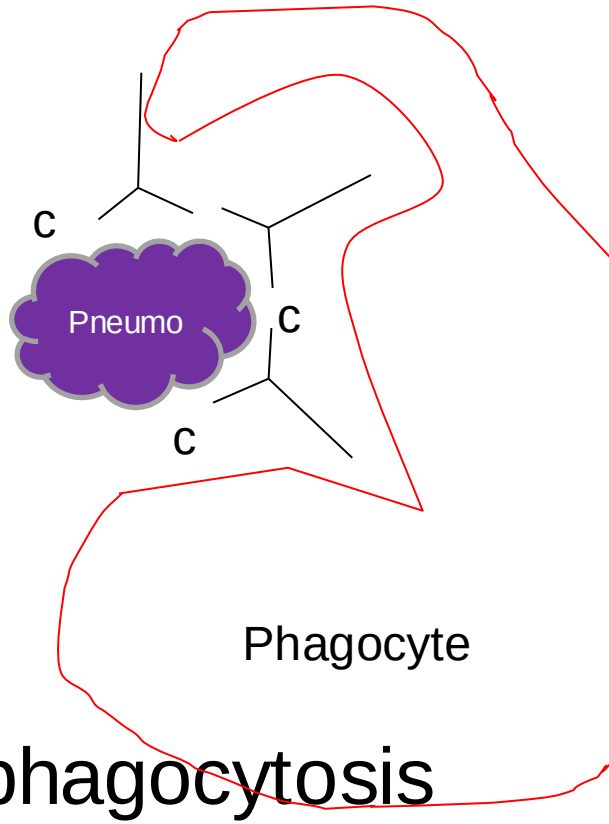
Complement deficiency

- 0.3% of those with meningococcal disease have complement deficiency
- After B and C disease complement deficiency very very rarely reported

- Rare serogroups:
  - W 135: 54 people (56%): 16/54 (30%) with complement deficiency
  - X: 9 people (9%) of whom 3 (33%) with complement deficiency
  - Y: 23 people (24%) of whom 11 (48%) had complement deficiency
  - Z: 1 person (1%) — no one had complement deficiency
  - 29E: 2 people (2%) — no one had complement deficiency
  - non-groupable; 8 people (8 %) of whom 2 (25%) had complement deficiency

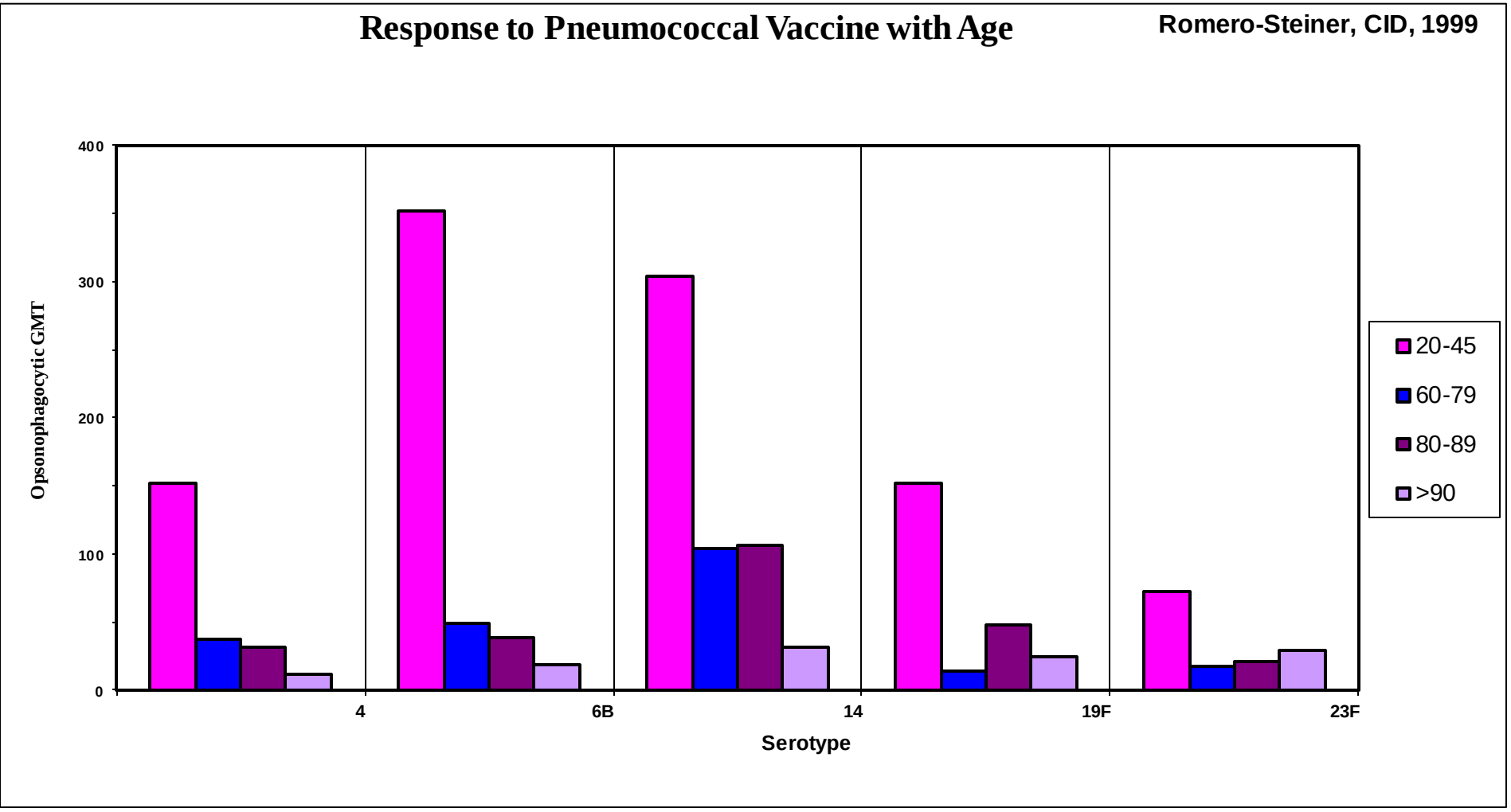
Pneumococcal Disease

- Increase risk in asplenia
- T cell deficiency (HIV)
- Antibody deficiency
- Complement deficiency



- Protection mediated by opsonophagocytosis
- Licensure based on measurement of ELISA antibody
  - Contains both high and low avidity antibody

Opsonophagocytic Antibodies



What are you actually measuring in the laboratory?

Cell line
Exogenous complement
Serum

Principle 7

More than One Factor May Protect Co-Correlates

For example: Mucosal Antibodies

Correlates of Immune Protection After Live Influenza Vaccine or Natural Infection

(Artificial Challenge in Children)

Serum HAI	Nasal lgA	Shedding
-	-	63%
-	+	19%
+	-	15%
+	+	3%

Belshe, JID, 2000

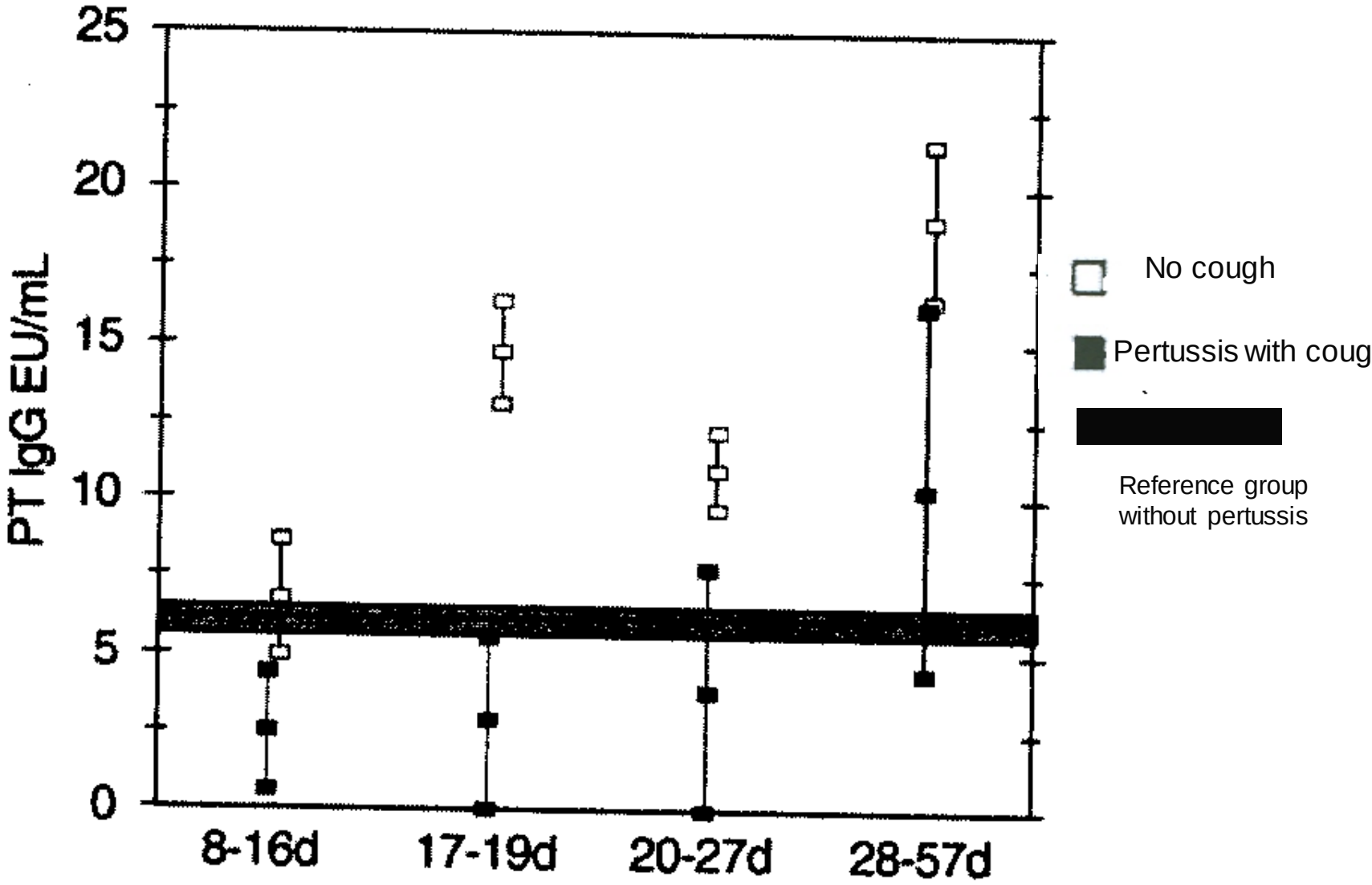
- **HAI antibodies in serum and on mucosa correlate with protection**

- **However, in the elderly antibody responses are poor. CD8+ responses, rather than CD4+ responses correlate with antibody rises, and CD8+ CTL independently correlates with protection**

Goronay, J Virol, 2001

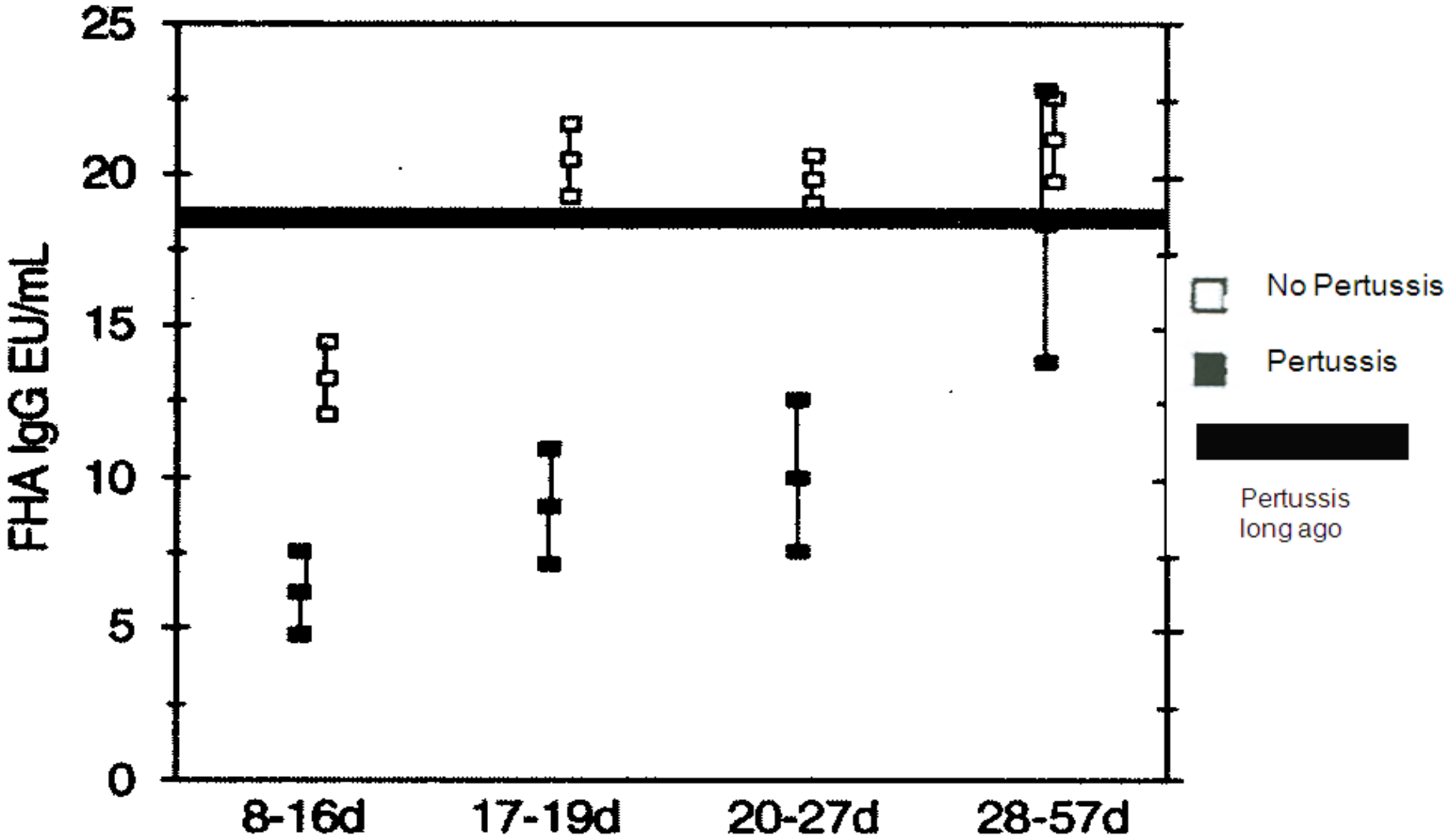
Pertussis co-correlates

Exposure to Pertussis and PT



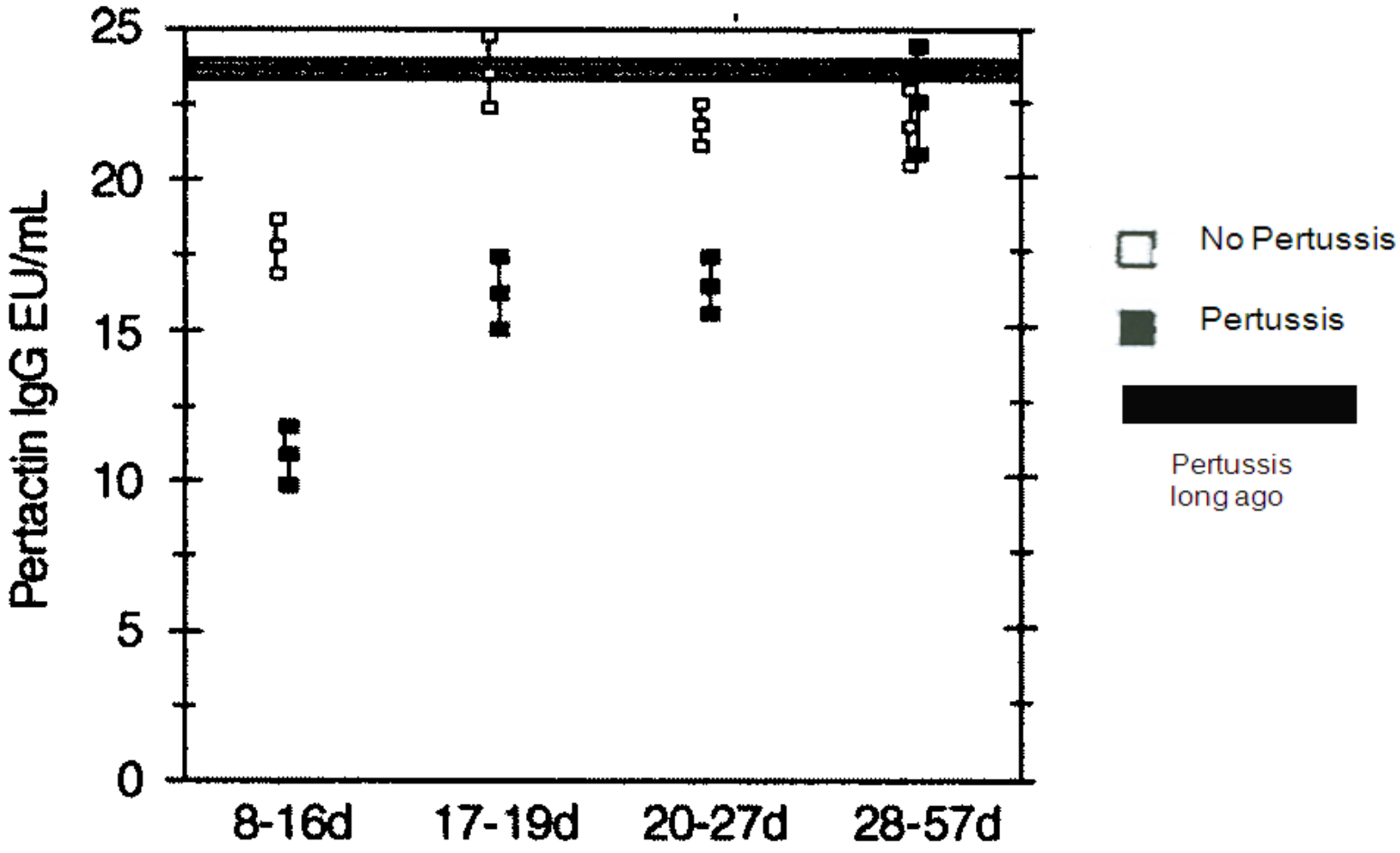
Storsaeter J, et al. Vaccine 21:3542-3549, 2003

Exposure to Pertussis and FHA



Storsaeter J, et al. Vaccine 21:3542-3549, 2003

Exposure to Pertussis and Pertactin



Storsaeter J, et al. Vaccine 21:3542-3549, 2003

Do Vaccines Elicit “Sterile” Immunity ?

Yes	Depends on Ab on Mucosa	No
Dengue	Hib	Rota
Diphtheria	HPV	
Hepatitis A	Influenza	
Lyme	Measles	
Rabies	Pertussis	
(Tetanus)	Polio	
Yellow Fever	Rubella	
	Varicella	

Principle 8

Memory may be a Surrogate

(but not always)

Anti-HBs response to a 1-μg booster dose of recombinant-derived vaccine administered to persons vaccinated with plasma-derived vaccine 5-7 years earlier

Percentage with <10 S/N at time of booster dose	**46% (24/52)**
Percentage with anamnestic response	**90% (47-52)**

West DJ, *Am J Inf Contr* 17:172-180, 1989.

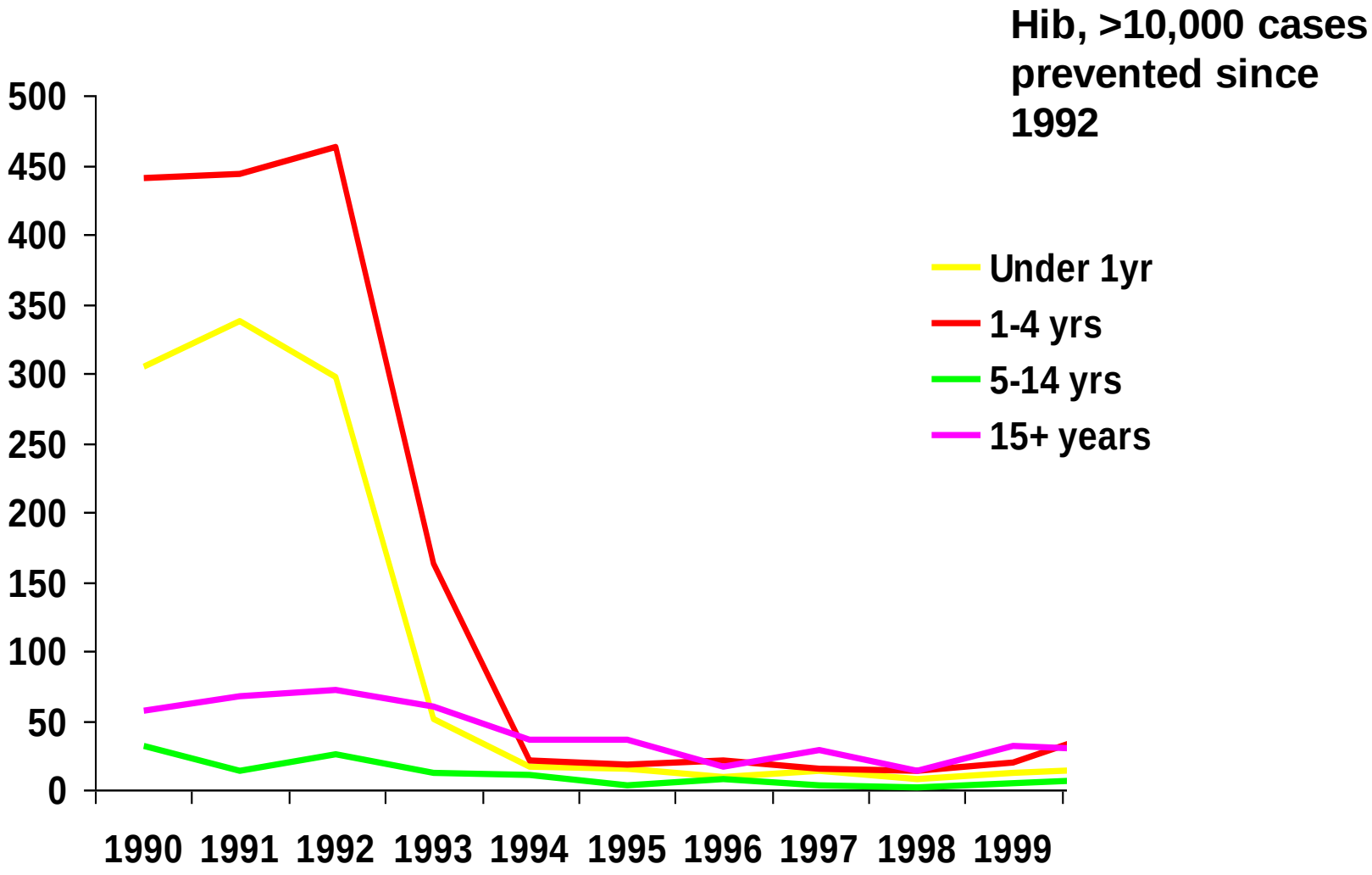
Long Term Efficacy of Hepatitis B Vaccine Despite Antibody Loss

(Chinese infants assessed 15 yrs. after vaccination)

	Anti-HBs	HBs Ag+	Efficacy
Vaccine	**50%**	**1.9%**	**89%**
Controls	**33%**	**16.7%**	

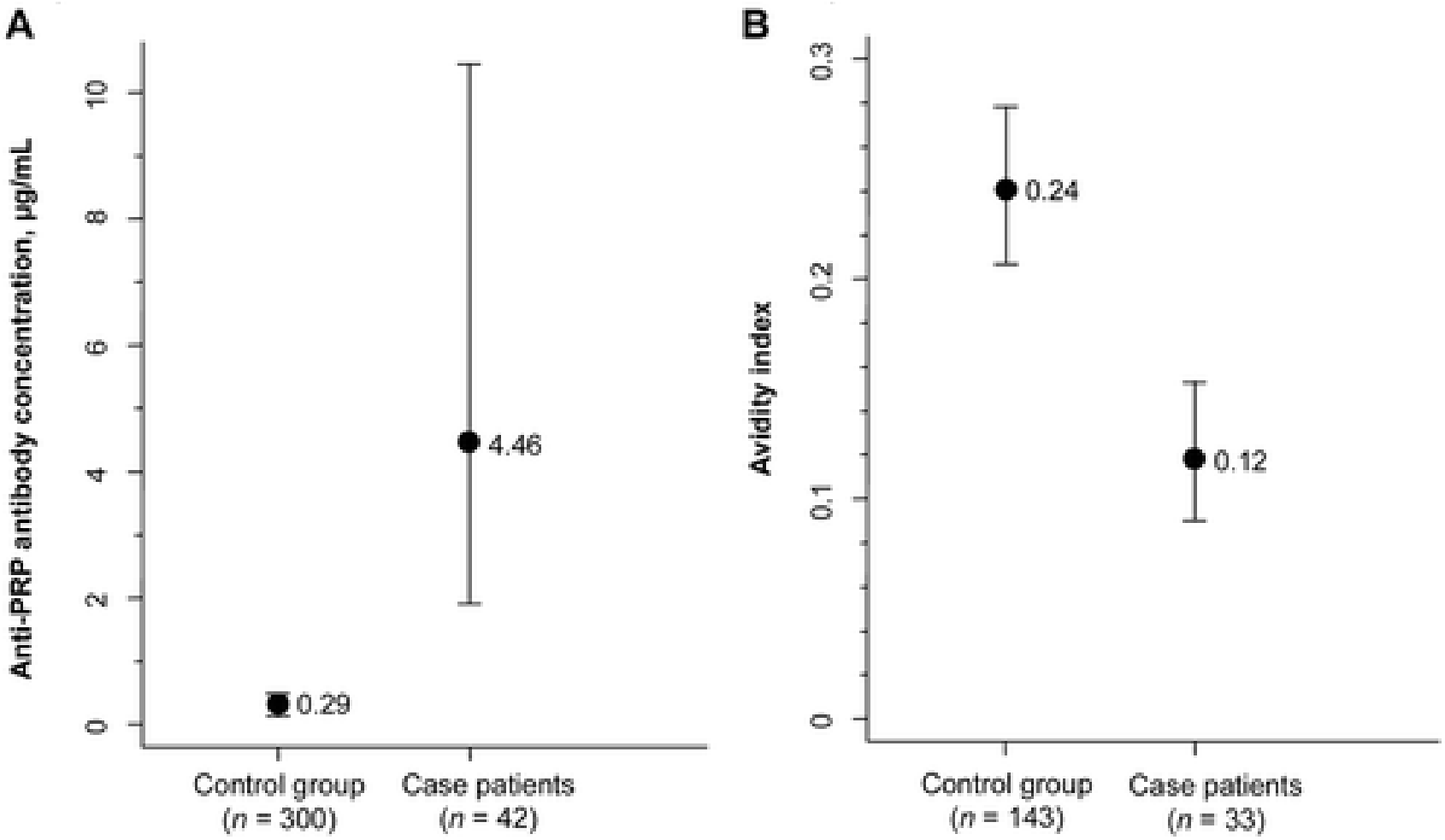
Liao SS Vaccine, 1999

Invasive Hib infections by age group, 1990-2002



Source: Dr M Ramsay, Health Protection Agency CDSC, Colindale

Comparison of the concentration & avidity of anti-PRP antibody in serum samples from children who experienced true vaccine failure and controls 1992–2003.



Lee et al, 2007

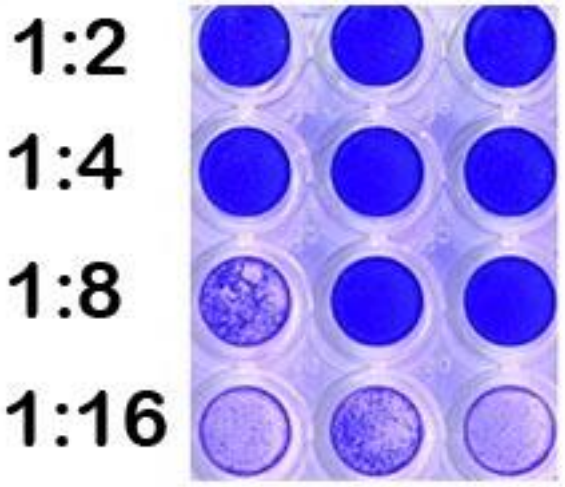
Principle 9
Its probably more complicated than you think

Principle 9a
Antibody "correlates" should contain the absolute correlate but may measure something more, or less

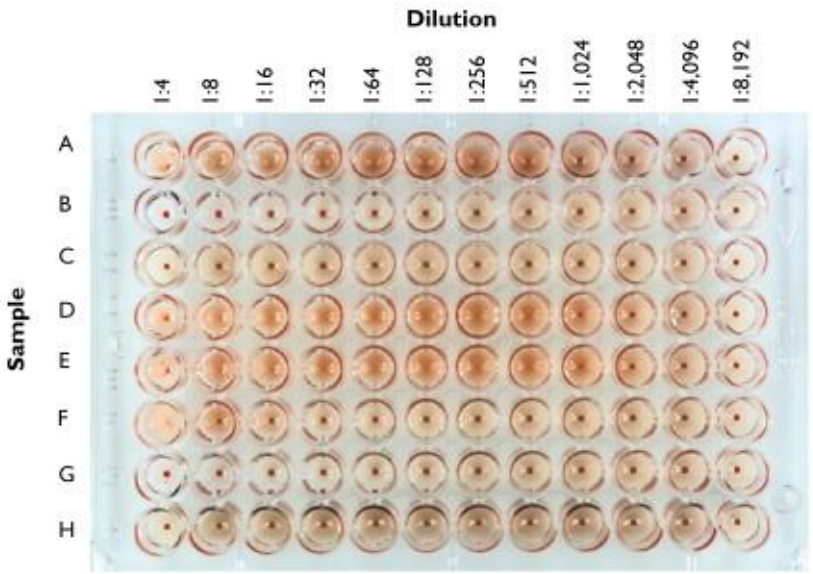
- Hib antibody level >0.15mcg/ml correlates with protection

- AJP
  - 100mcg/ml
  - Avidity very low
  - Complement binding antibody probably important

2 examples of ways to measure immune responses to influenza vaccines



MN (microneutralisation)



HAI (haemaglutination inhibtion assay)

OXFORD VACCINE GROUP

Principle 9b
Don’t be fooled, correlates may be about population protection more than individual protection

CLINICAL AND VACCINE IMMUNOLOGY, May 2010, p. 840–847 Vol. 17, No. 5
1556-6811/10/$12.00 doi:10.1128/CVI.00529-09
Copyright © 2010, American Society for Microbiology. All Rights Reserved.

Updated Postlicensure Surveillance of the Meningococcal C Conjugate Vaccine in England and Wales: Effectiveness, Validation of Serological Correlates of Protection, and Modeling Predictions of the Duration of Herd Immunity▽

Helen Campbell,[1]* Nick Andrews,[2] Ray Borrow,[3] Caroline Trotter,[4] and Elizabeth Miller[1]

Immunisation, Hepatitis and Blood Safety Department, Health Protection Agency Centre for Infections, 61 Colindale Avenue, London NW9 5EQ, United Kingdom[1]; Statistics, Modelling & Bioinformatics, Health Protection Agency, Centre for Infections, 61 Colindale Avenue, London NW9 5EQ, United Kingdom[2]; Meningococcal Reference Unit, Health Protection Agency North West, Manchester Royal Infirmary, Manchester, United Kingdom[3]; and Department of Social Medicine, University of Bristol, Canynge Hall, Whatley Road, Bristol BS8 2PS, United Kingdom[4]

Received 23 December 2009/Returned for modification 2 February 2010/Accepted 1 March 2010

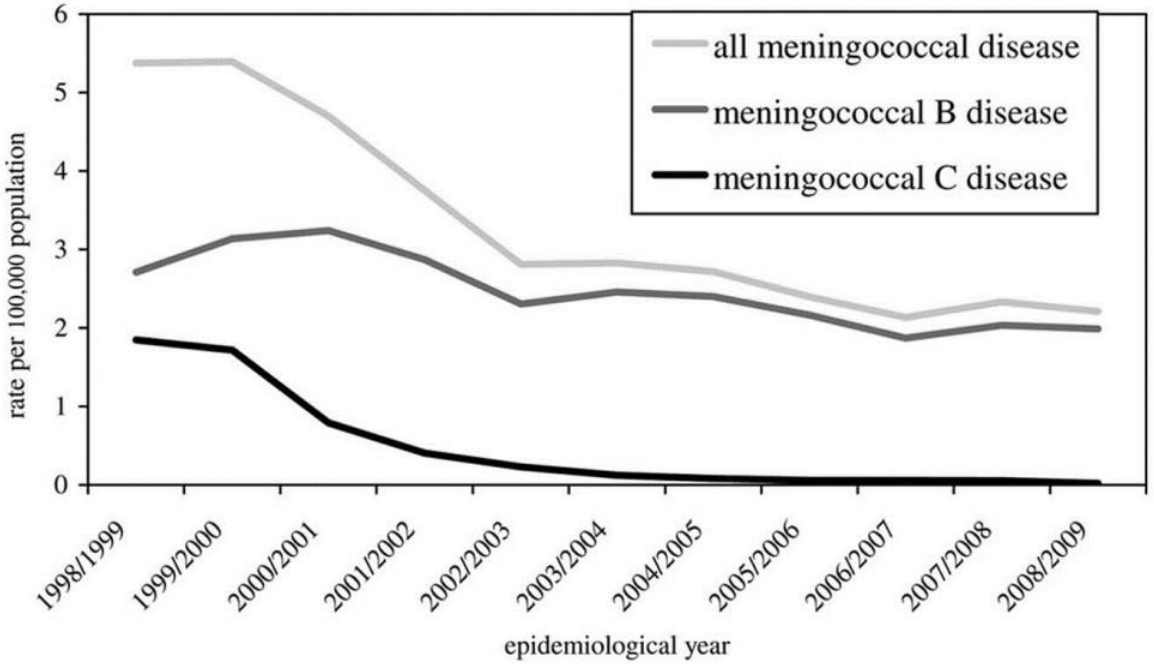


FIG. 1. Incidence of meningococcal disease in England and Wales by epidemiological year between 1998–1999 and 2008–2009.

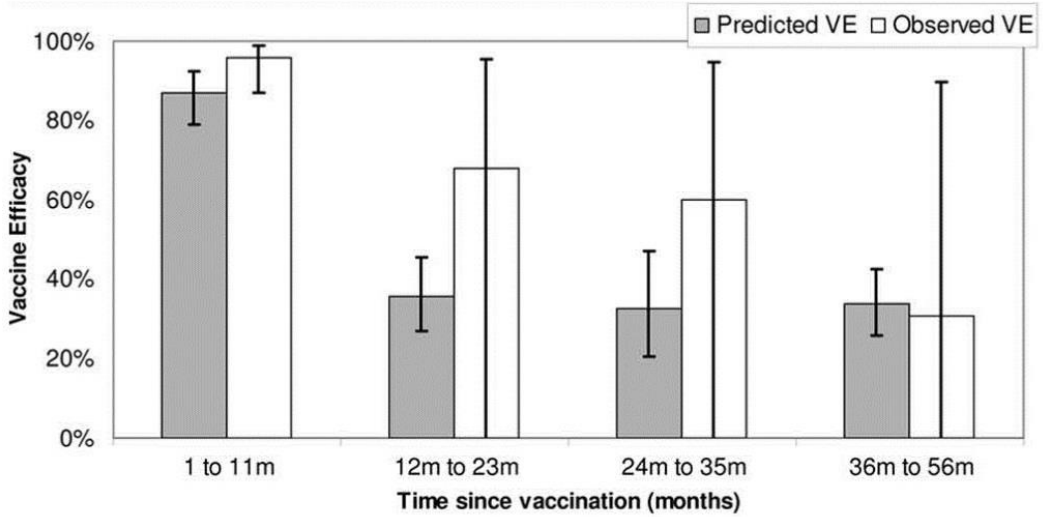


FIG. 3. Predicted MCC vaccine effectiveness (VE) and observed MCC vaccine effectiveness, using a 1:8 cutoff, by months (m) since vaccination, with a 95% CI.

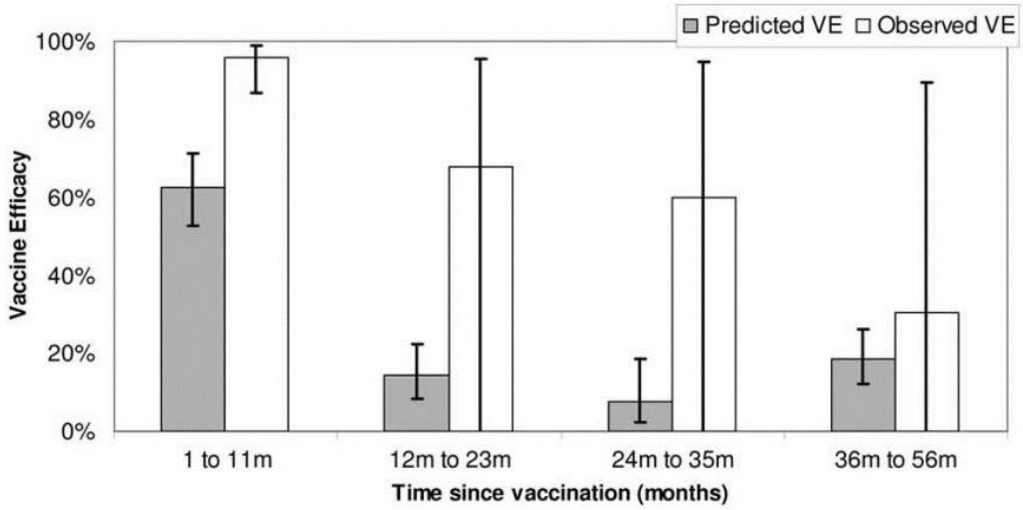


FIG. 4. Predicted MCC vaccine effectiveness (VE) and observed MCC vaccine effectiveness, using a 1:128 cutoff, by months (m) since vaccination, with a 95% CI.

PCV13 introduced in the UK 1/4/10

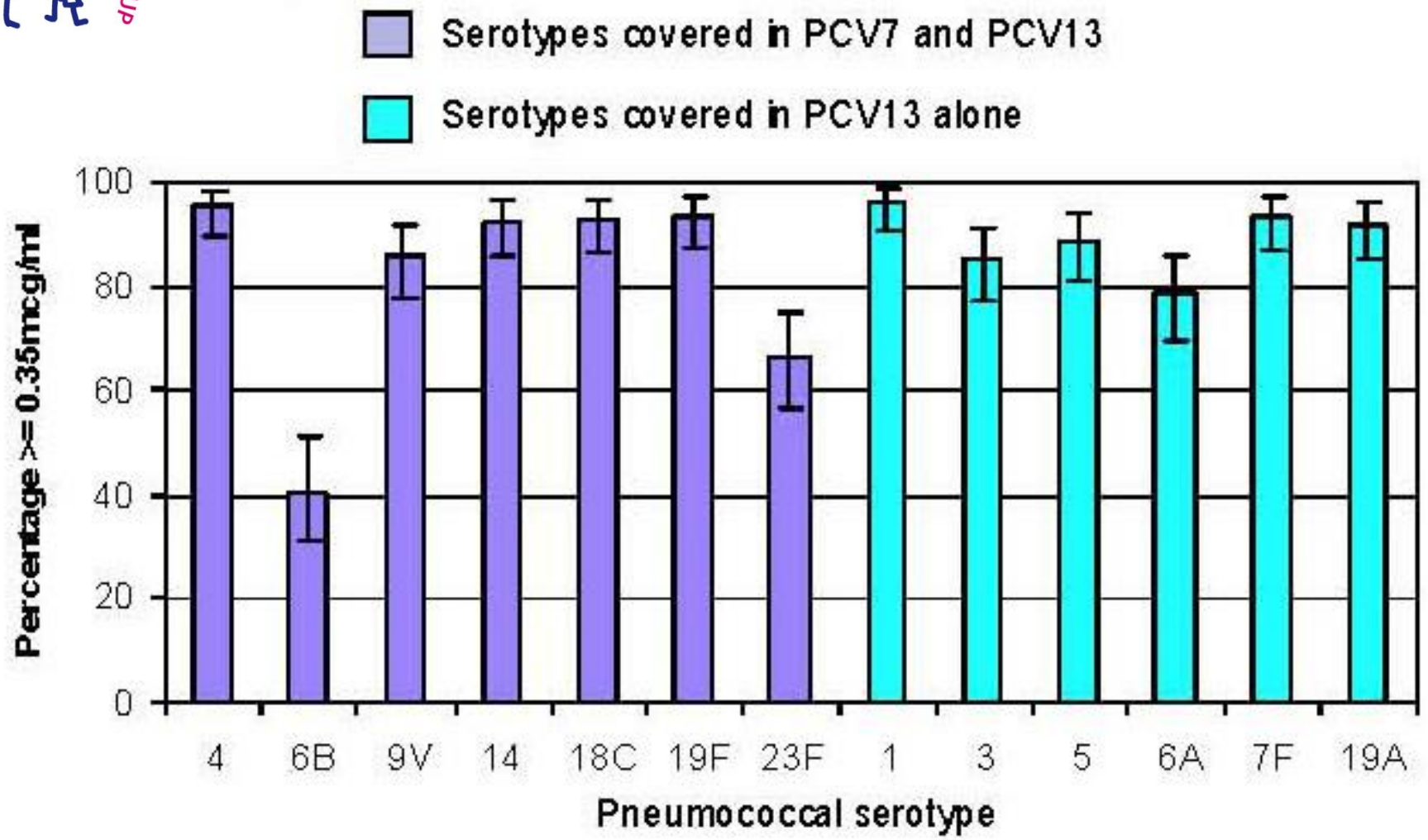


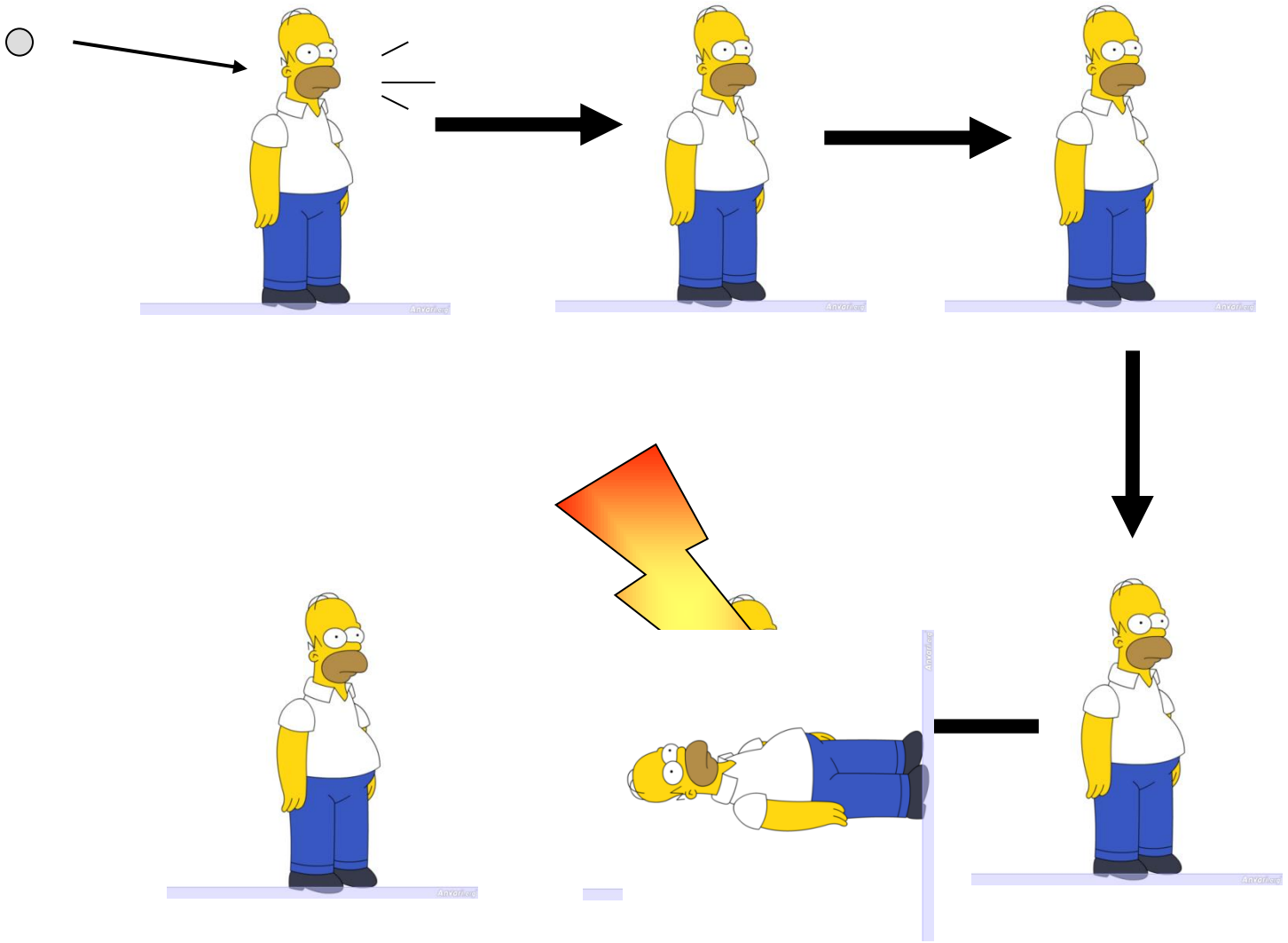
Figure 3: Percentage of participants in the PCV13 group achieving IgG ≥ 0.35 mcg/ml for each pneumococcal serotype

Snape et al, CID 2010

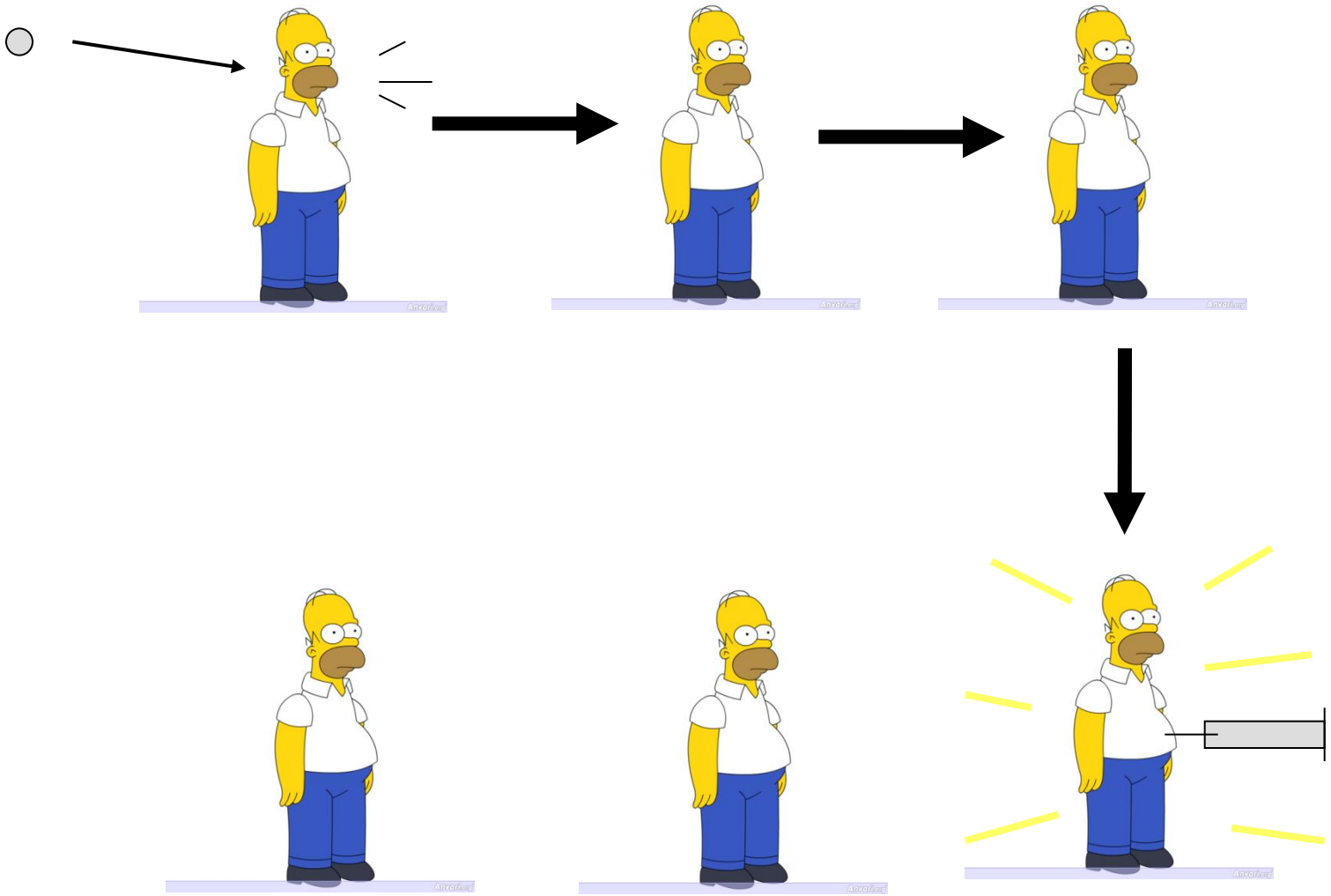
Principle 10
Main correlate for protecting susceptibles may be herd immunity rather than a direct correlate in the individual

- Is herd immunity a measurable correlate?

Herd Immunity



Herd Immunity



Herd Immunity might be the most important correlate for your protection – measure through carriage studies?

Research Letters

Effectiveness of meningococcal serogroup C conjugate vaccine 4 years after introduction

Caroline L Trotter, Nick J Andrews, Edward B Kaczmarski, Elizabeth Miller, Mary E Ramsay

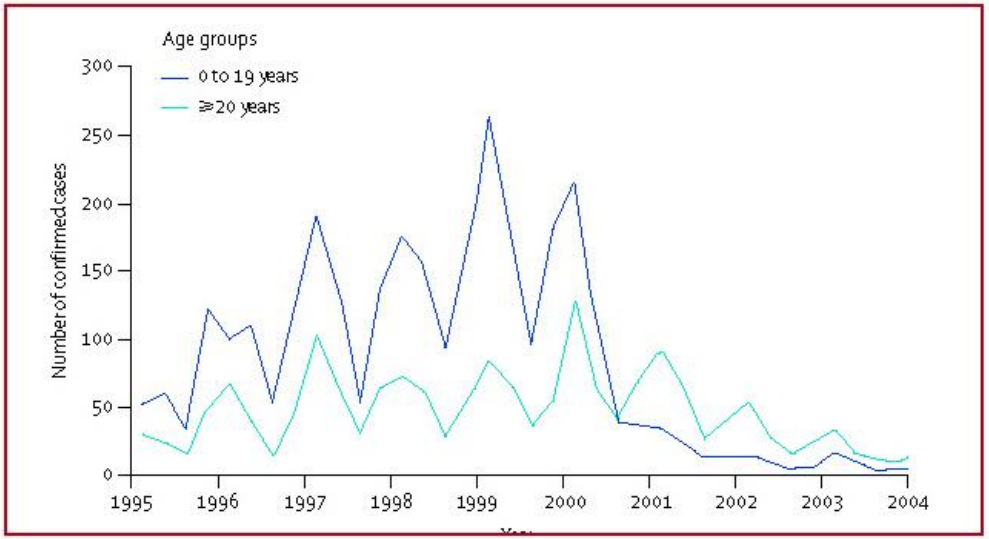


Figure: Cases of laboratory-confirmed meningococcal serogroup C disease by age group and quarter, 1995–2004

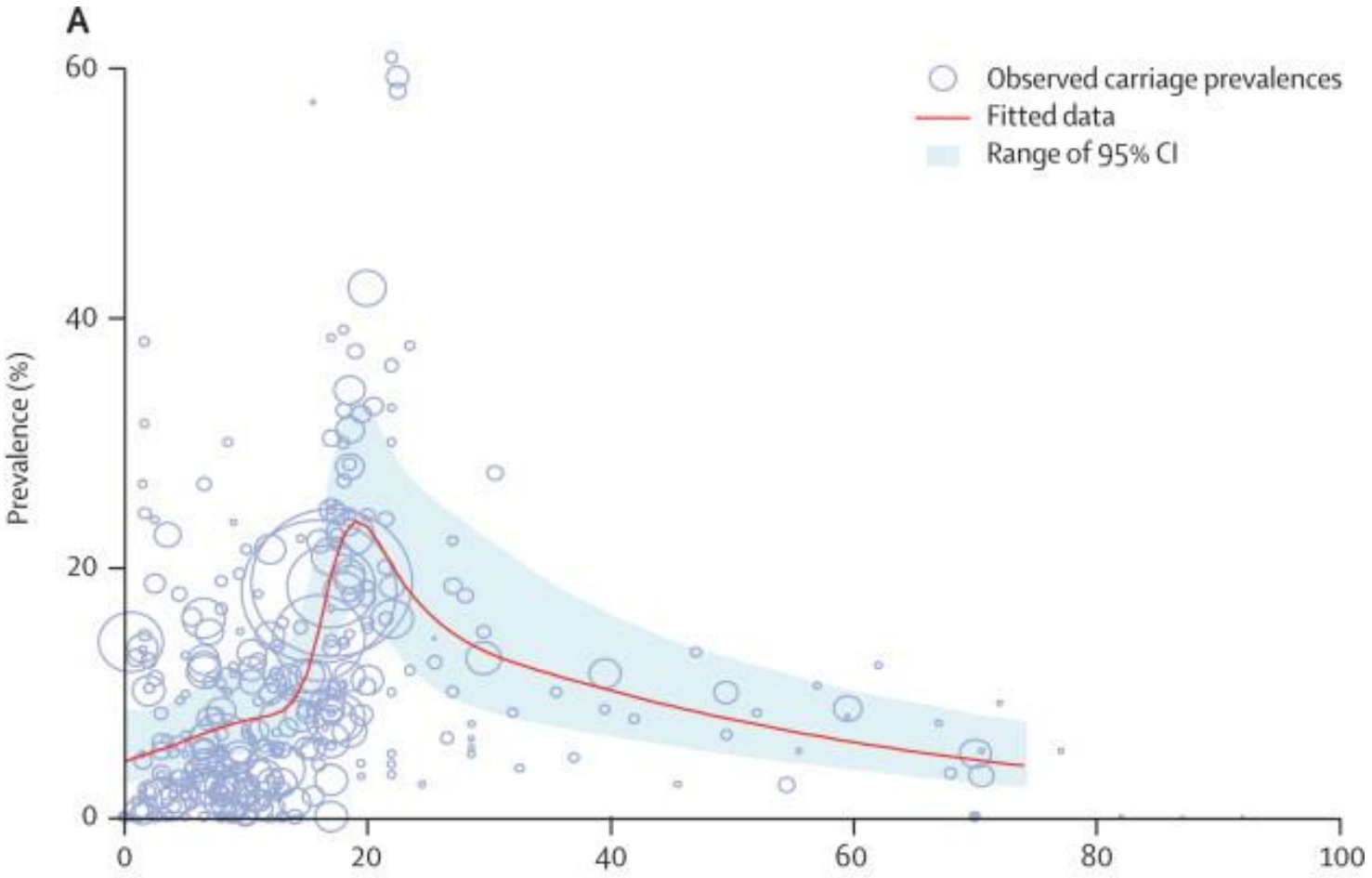
Lancet 2004; 364: 365–67

See Comment page 309

Statistics, Economics, and Modelling Department (C L Trotter PhD, N J Andrews MSc) and Immunisation Department (E Miller FRCPath, M E Ramsay FFPHM), Health Protection Agency Communicable Disease Surveillance Centre, 61 Colindale Avenue, London NW9 5EQ, UK; and Health Protection Agency Meningococcal Reference Unit, Manchester Royal Infirmary, Manchester, UK (E B Kaczmarski FRCPath)

Correspondence to:
Dr Mary Ramsay
mary.ramsay@hpa.org.uk

Carriage of meningococci



Christensen 2010

Principle 11

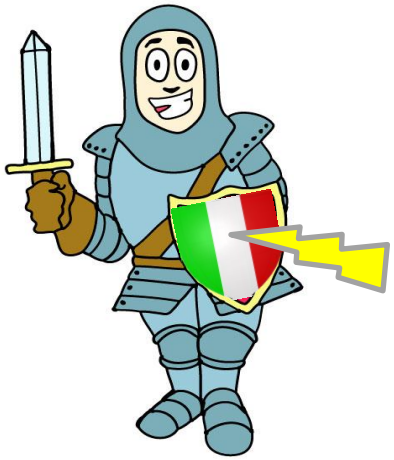
We might have to use Surrogates

Definition

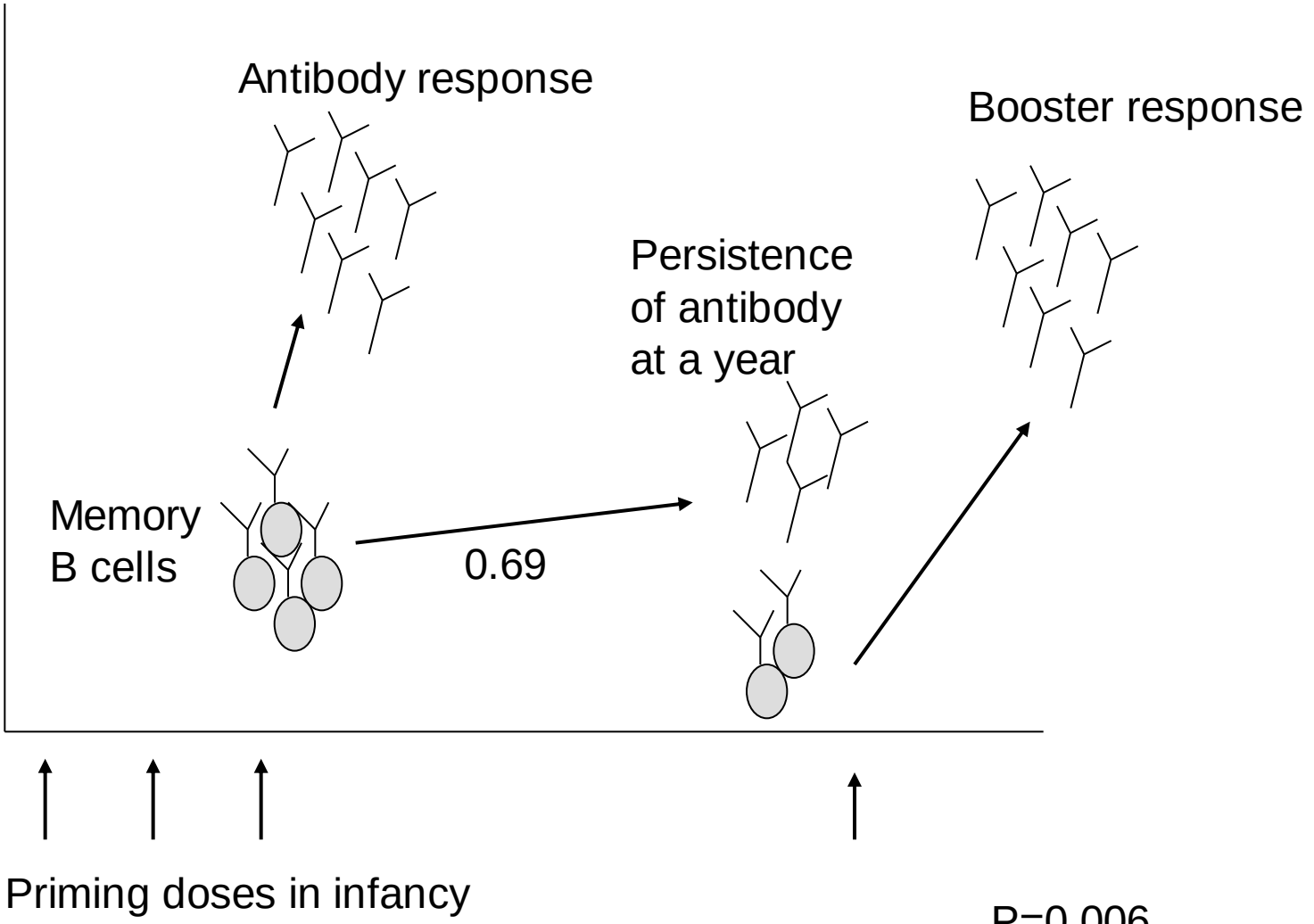
Definition of a “surrogate”:

“A biomarker that is closely correlated to another marker, that is in turn statistically related to and responsible for protection from a disease”

i.e. a surrogate is one step removed from the correlate



Magnitude of primary B cell responses may determine persistence of antibody



Blanchard-Rohner et al (J Immunol 2008)

What about T cells?

Correlates for paediatric vaccines

Antibody correlates	Cell mediated correlates (T cell)
Diphtheria, antibody (toxin neutralisation)	
Tetanus, antibody (toxin neutralisation)	
Hib, antibody (ELISA)	
MenC, antibody (serum bactericidal assay)	
Pneumococcus, antibody (ELISA)	
Hepatitis A, antibody (ELISA)	
Hepatitis B, antibody (ELISA)	
Measles, antibody (microneutralisation)	
Rubella, antibody (immunoprecipitation)	
Varicella, antibody (serum neutralisation or gp ELISA)	
Influenza, antibody (HAI)	
Polio antibody (serum neutralisation)	
Rabies, antibody (serum neutralisation)	

Conclusion

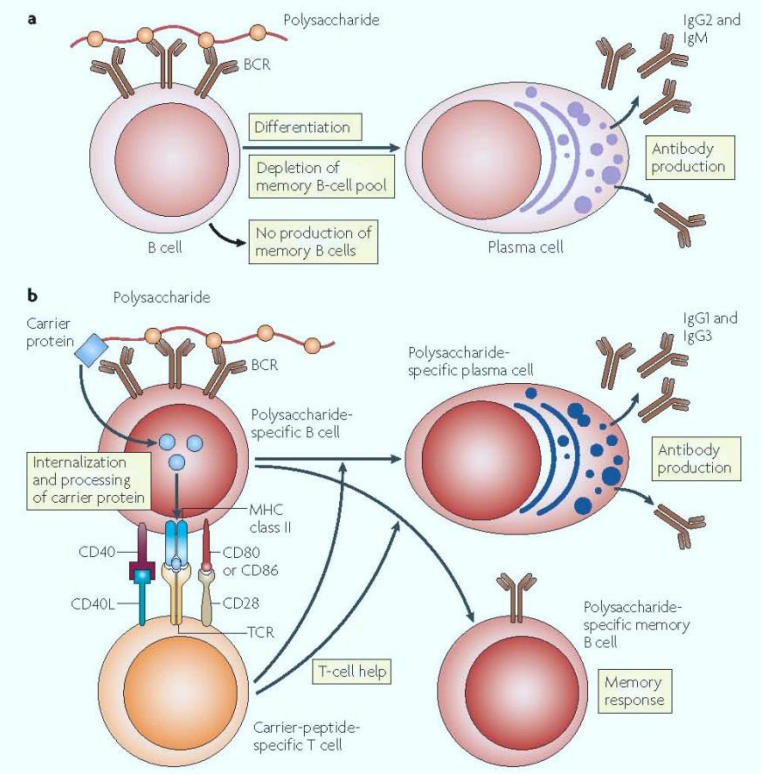
- There are no paediatric T cell correlates of protection

T cells

- Needed to recover from disease after viral infections
- Measurement probably not sophisticated enough yet
- CD4 T cells necessary to help B cells
- CD4 T cells producing IL-23 probably important in response to BCG
- CD8 T cells maintain latency in TB
- CD4 frequency T cells correlate with Zoster protection
- CD4 T cells correlate long term immunity (mice and pigs)

B cell help

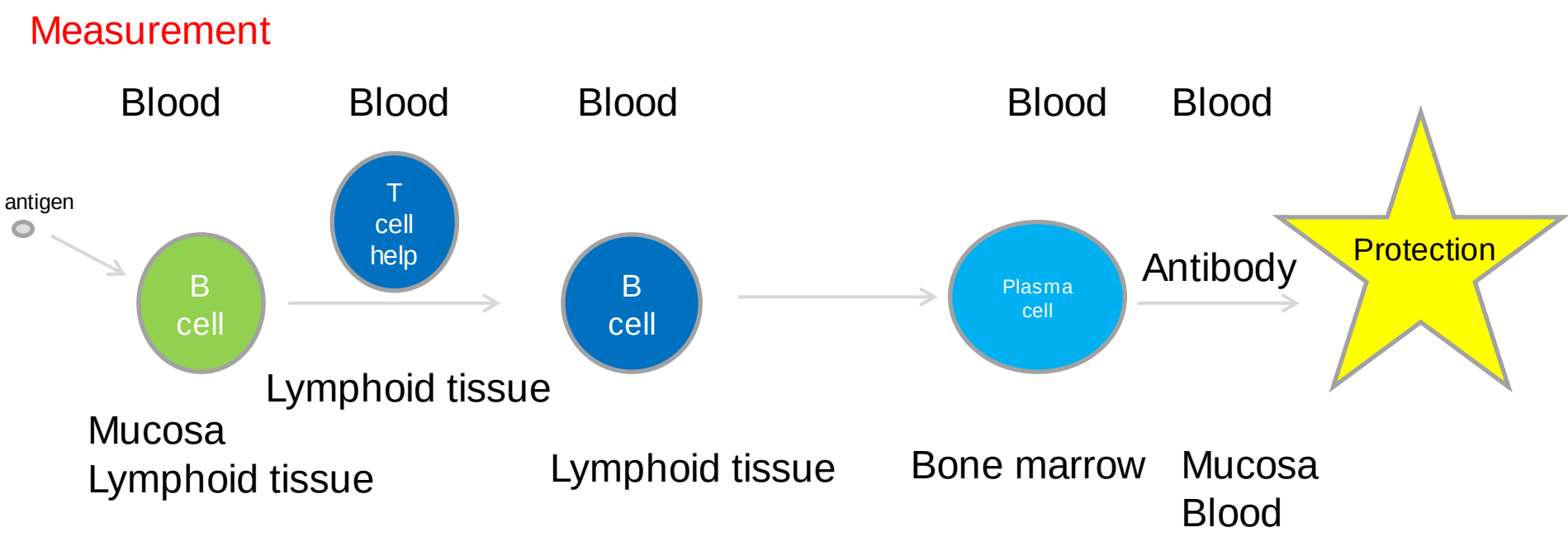
Vaccine	T cell involvement?
Diphtheria, tetanus antitoxin, pertussis	B cell help
Hib, MenC, PCV antibody	B cell help
Measles, Rubella, Mumps, Polio, Varicella	B cell help



So why don't we have T cell surrogates?

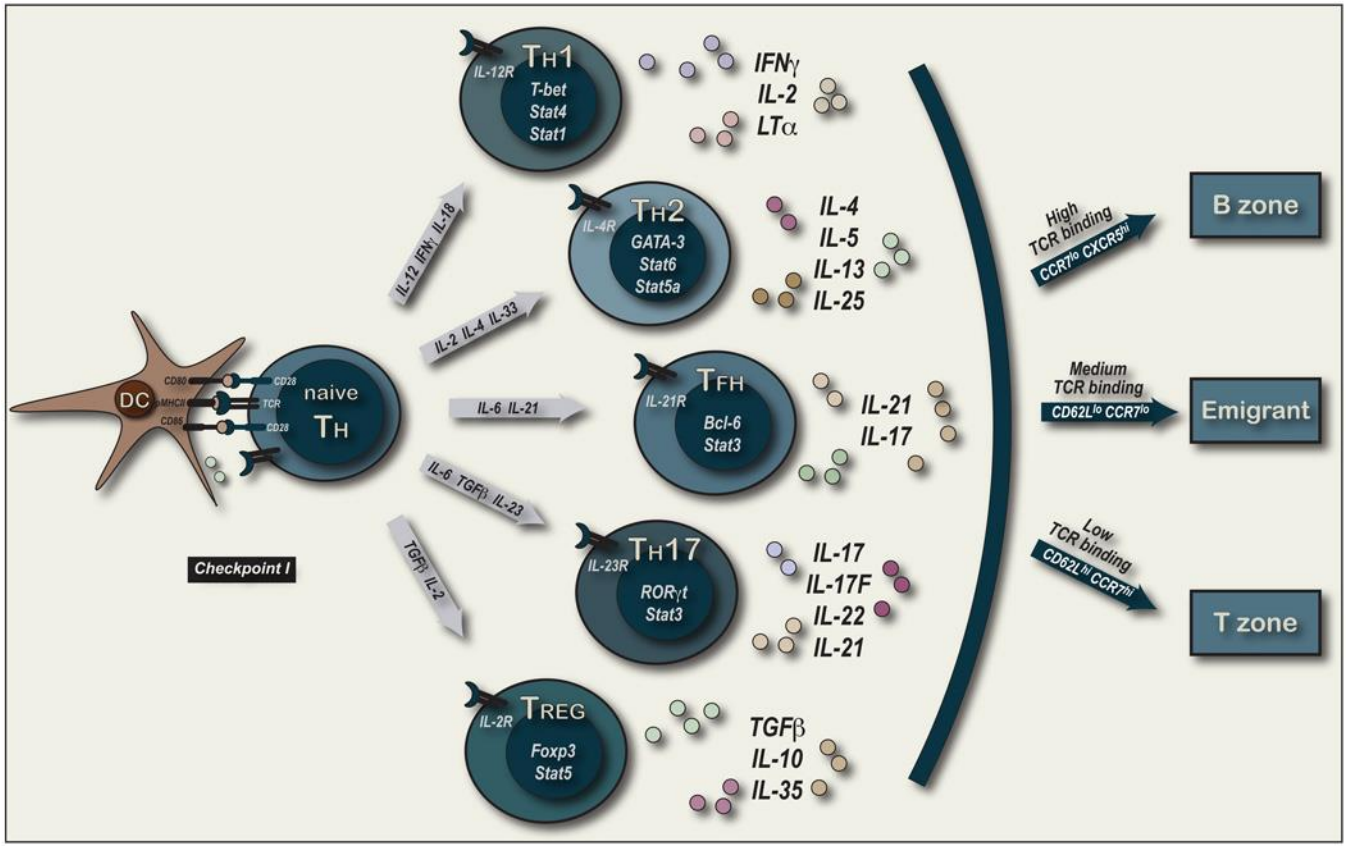
Pollard, Perrett, Beverley. *Nature Rev Immunol.* 2009.

Immune response



It’s a bit more complicated

T cell help



Immunity. 2009 March 20; 30(3): 324–335.

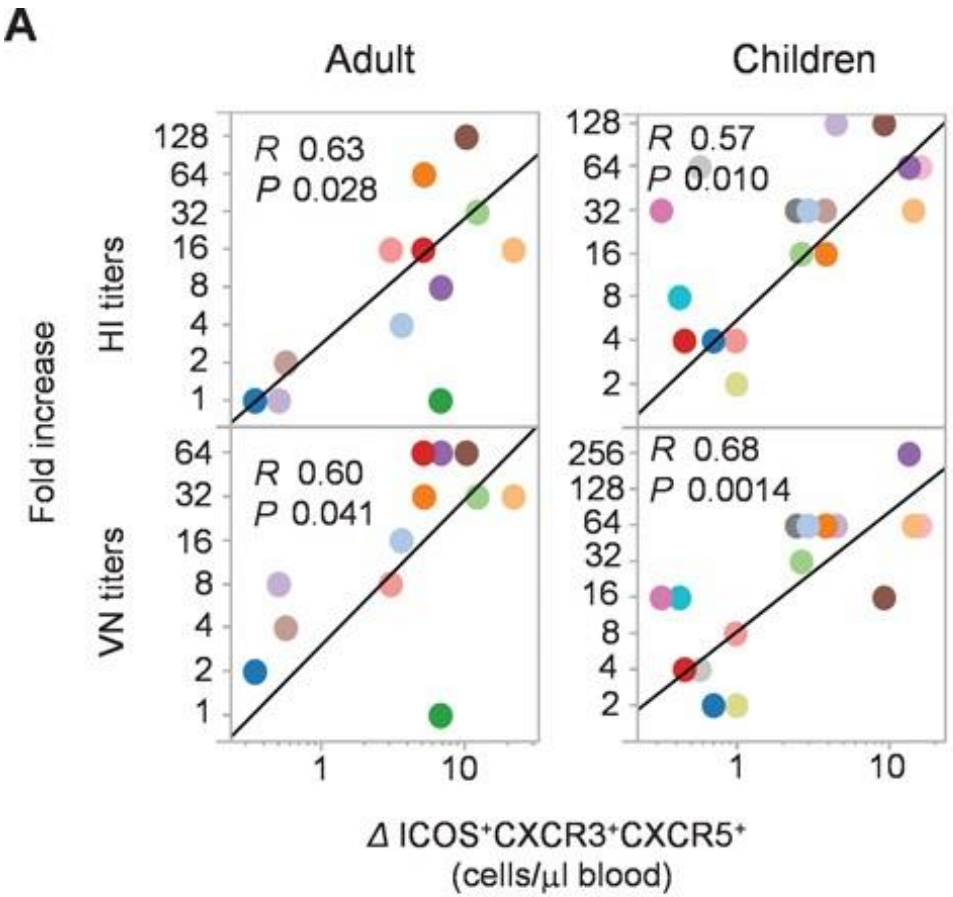
Measuring B cell help

- T cells which provide B cell help likely correlate with protection

- BUT difficult to measure
  - Access to the location of relevant cells
  - Definition of the right subset of cells
  - Standardised assay not available that specifically measures B cell help (assays for proliferation etc)
  - Relevant testing has not been done in efficacy trials to define T cell, B helper responses as a surrogate

FhT cells correlate with antibody response

Induction of ICOS+CXCR3+CXCR 5+ TH cells correlates with antibody responses to influenza vaccination at 7 days



Science Translational Medicine, 2013

More T cells

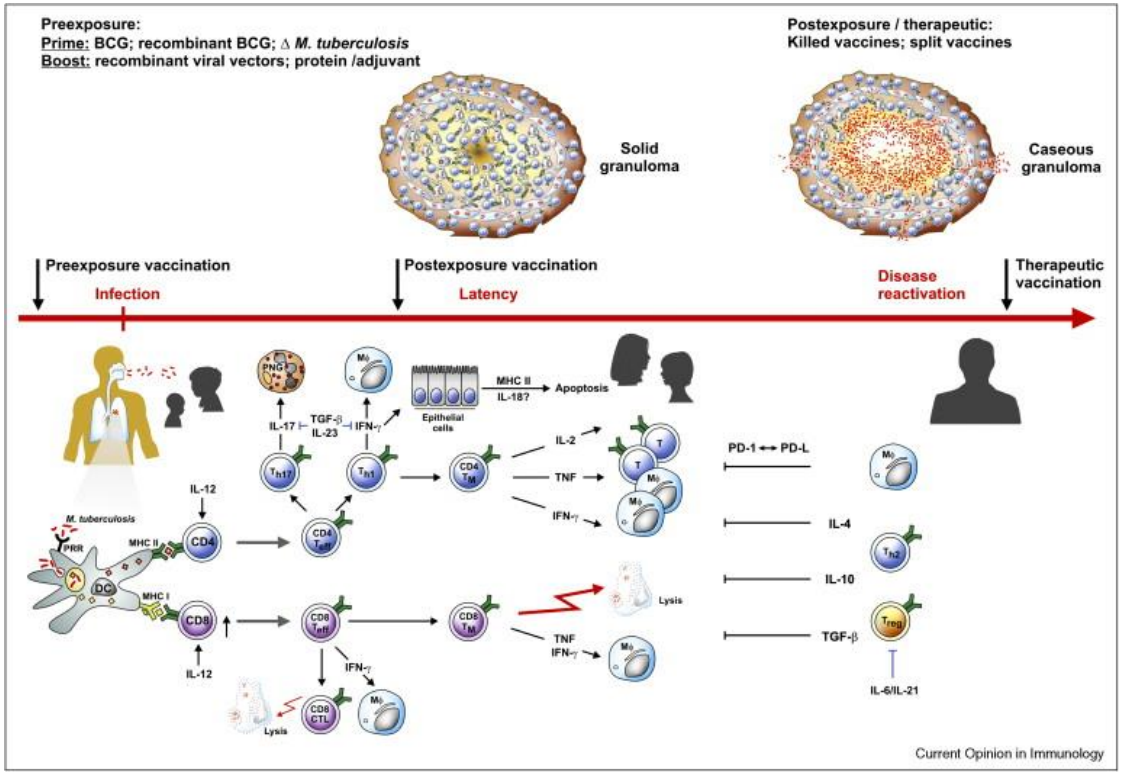
- CD4 T cell responses correlate with protection against Zoster
- Standardisation of assays needed

But what about other infections…….

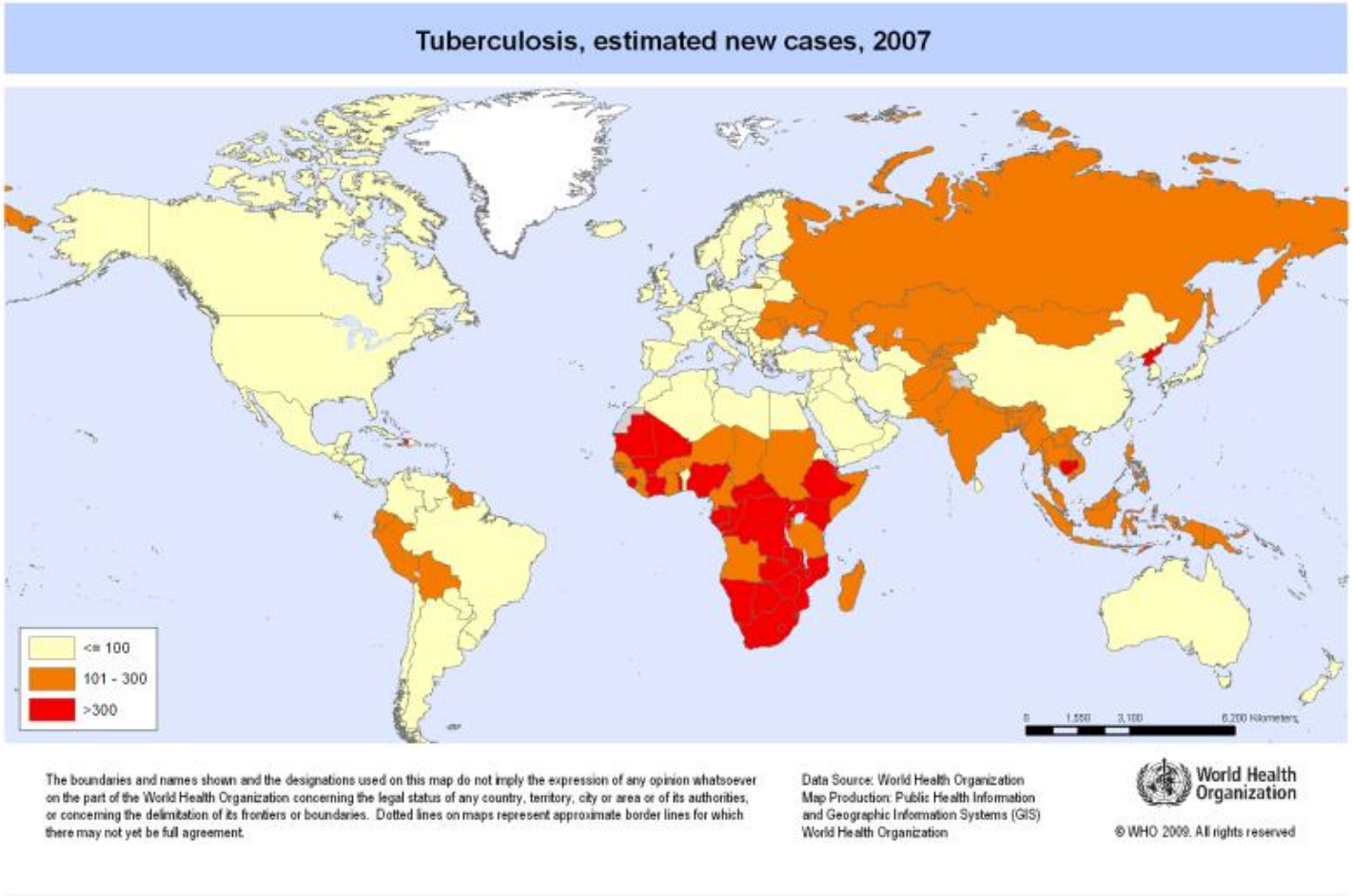
TB, malaria?

TB – T cells should be the correlate

- No established correlate.
- Need efficacy trials to establish the correlate.
- Last trial in infants in 1968



TB

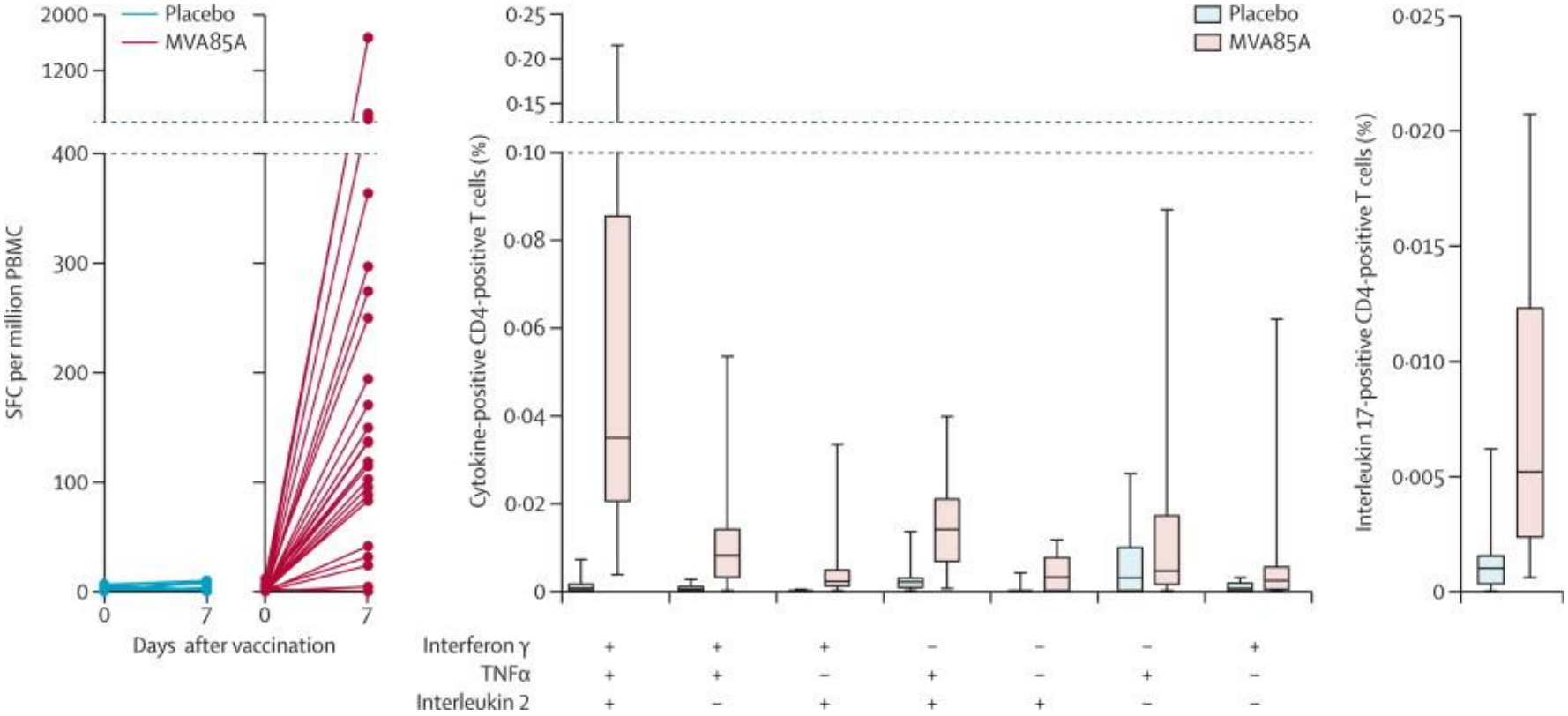

Tuberculosis, estimated new cases, 2007
<= 100
101 - 300
>300
0
1,550
3,100
6,200 Kilometers
The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.
Data Source: World Health Organization
Map Production: Public Health Information and Geographic Information Systems (GIS)
World Health Organization
World Health Organization
© WHO 2009. All rights reserved

MVA85A

- Boosting BCG with MVA85A
  - improves BCG-induced protection against mycobacterial challenge in animals.
  - induces antigen-specific Th1 and Th17 cells in infants (thought to be important in protection)

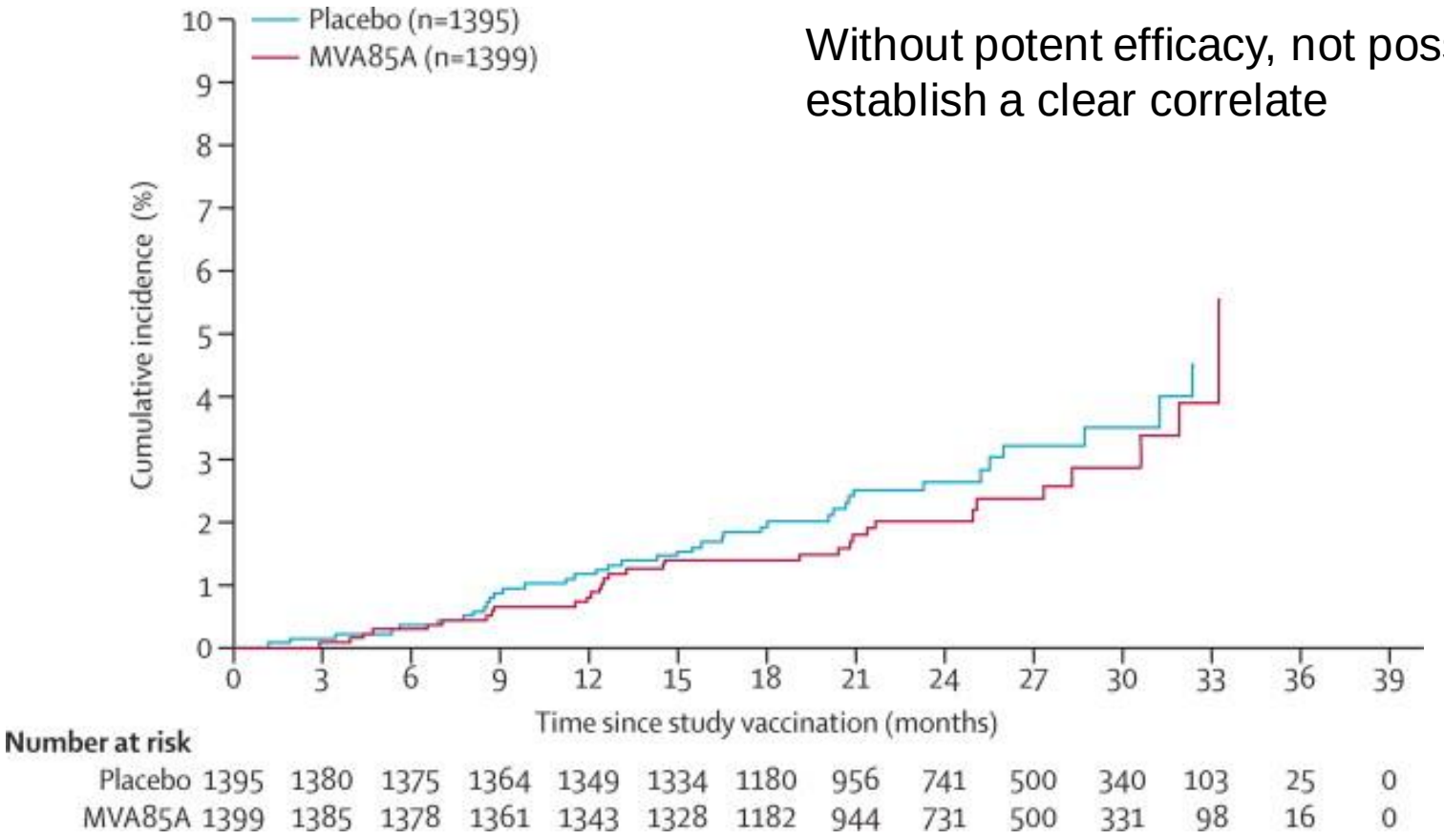
MVA85A

1st infant TB trial since 1968



2797 infants enrolled
BCG or BCG+ MVA85A

Tameris et al, The Lancet 2013

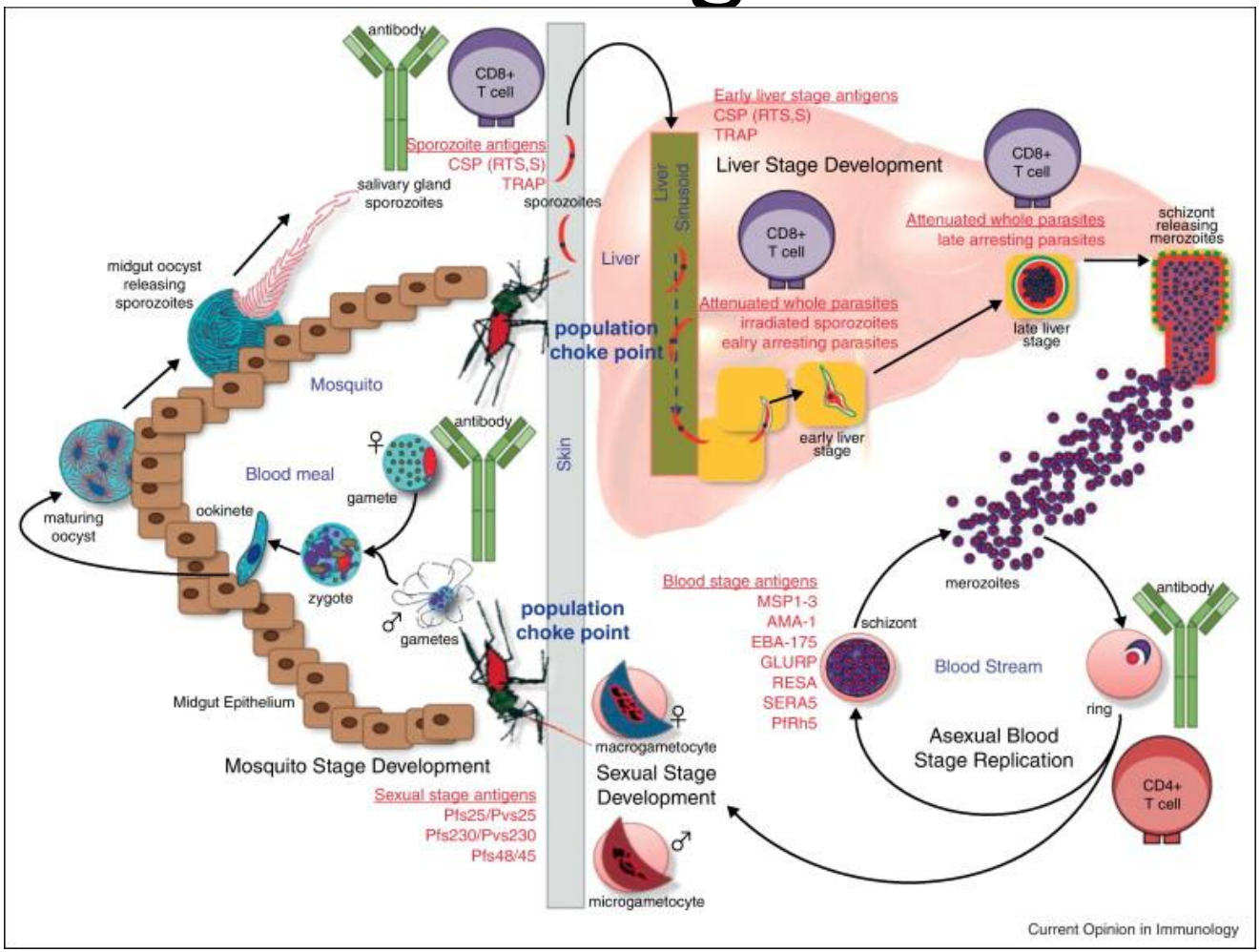


Without potent efficacy, not possible to establish a clear correlate

Tameris et al, The Lancet 2013

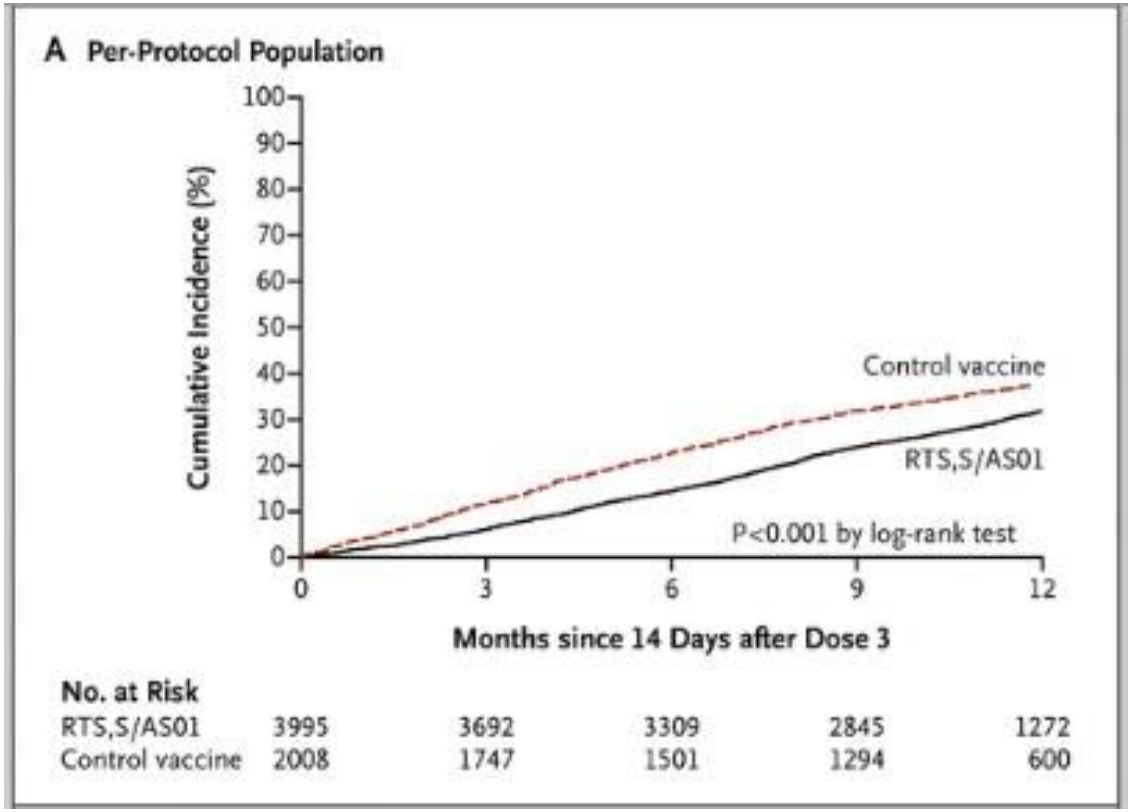
Malaria – establishing a correlate or a surrogate

Difficult to pin down protective responses without potent vaccines but T cells and antibodies should be candidates



RTS,S

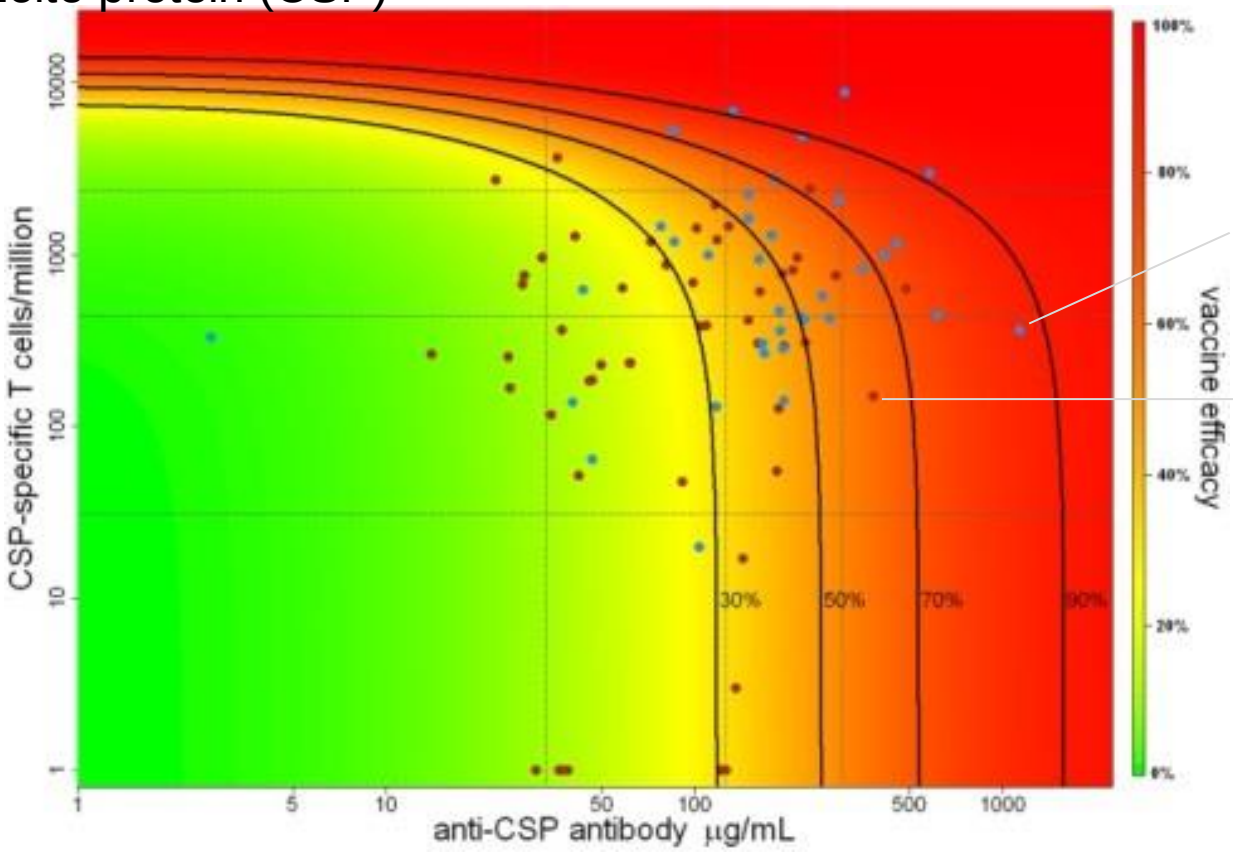
vaccine efficacy of 30.1%
(95% confidence interval, 23.6 to 36.1)



NEJM 2012

RTS,S malaria vaccine in a challenge model

circumsporozoite protein (CSP)



CSP antibody

CSP CD4 T cel

Both antibody and CD4 T cells are surrogates

White et al, Plos One 2013

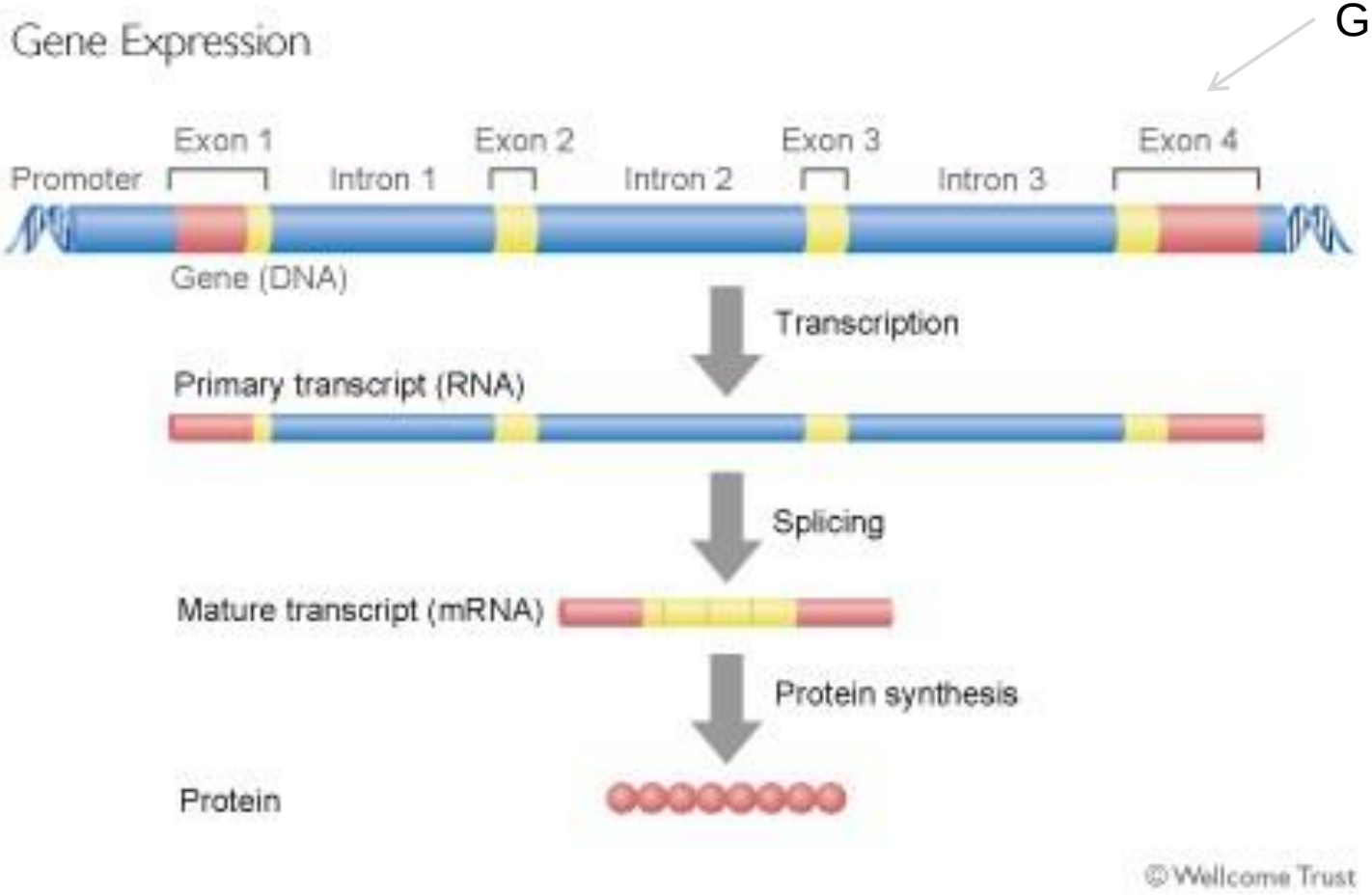
T cells in TB and Malaria

- The hunt for T cells for TB and malaria correlates continues…….
- TB
  - We can measure T cell responses in a sophisticated way
  - but without efficacy data we cant identify a correlate
- Malaria
  - Both T cells and antibodies may be surrogates or correlates
- Other approaches?

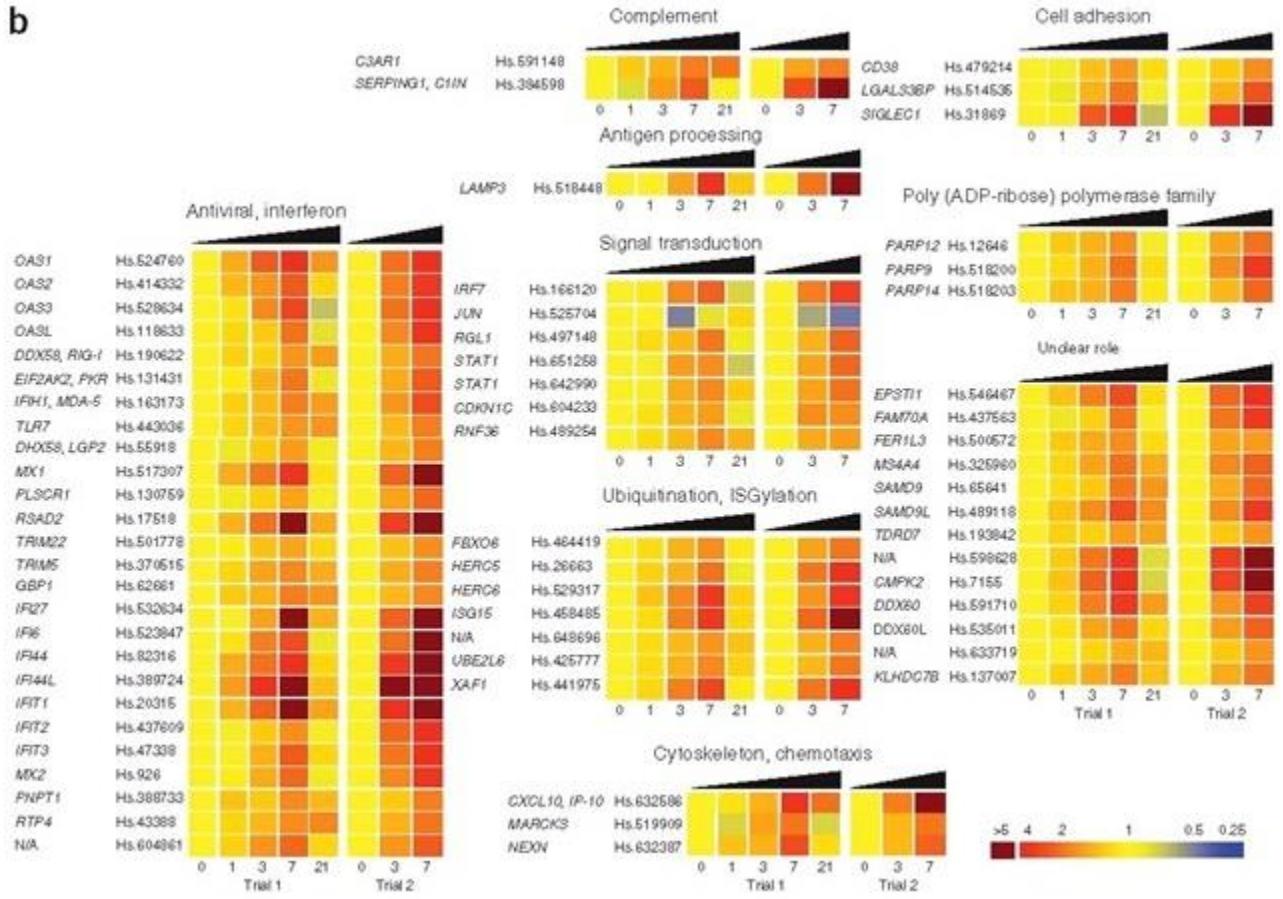
Principle 12
Look harder and the correlates may be out there

Increase sophistication

Gene regulation



Yellow fever vaccine



Querec et al, Nature Immunology 2009

Predicting neutralising antibody titres

Table 5 RT-PCR validation of genes in the DAMIP models for signatures that predict neutralizing antibody titers

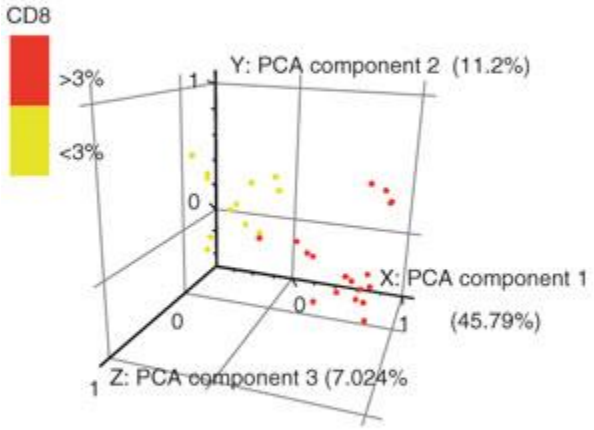
Symbol	UniGene	Day	Pearson *r*	*P*-value
BEND4	Hs.120591	7	0.764	0.00002
KBTBD7	Hs.63841	7	0.543	0.02510
TNFRSF17	Hs.2556	7	0.784	0.000001
TPD52	Hs.368433	7	0.530	0.00667

Querec et al, Nature Immunology 2009

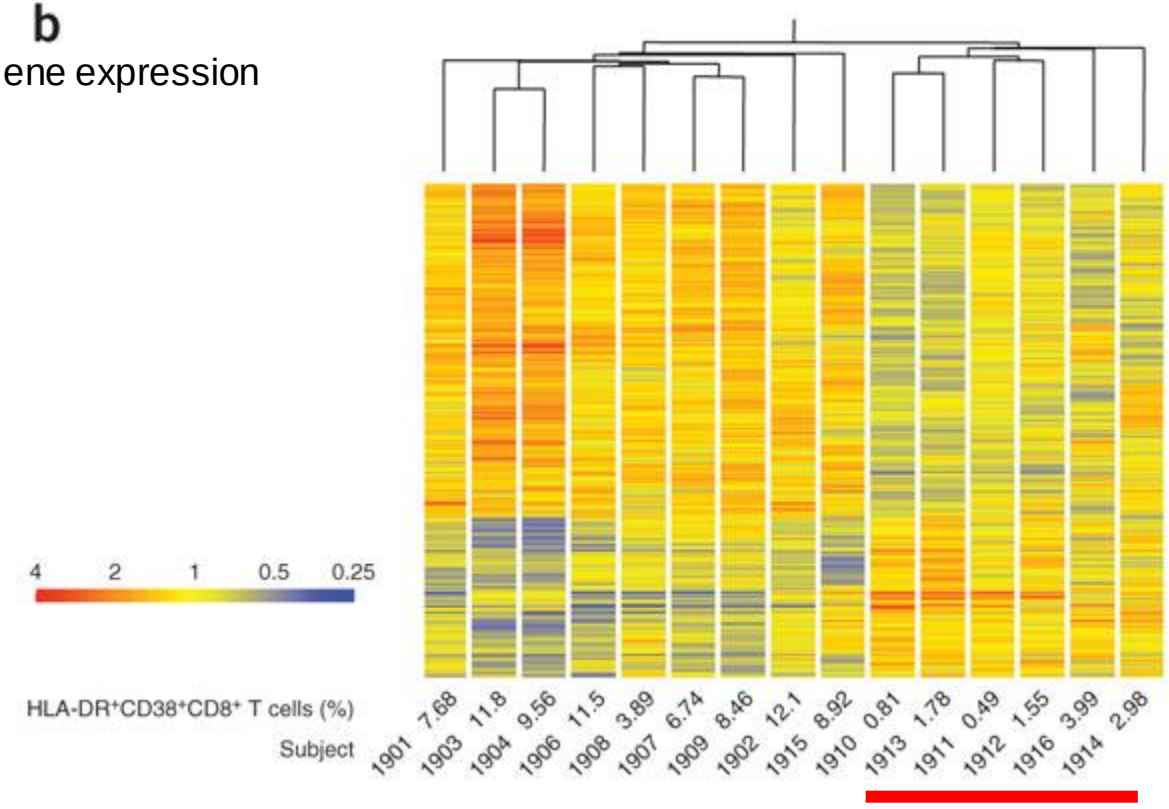
Genomic signatures that correlate with the magnitude of the CD8$^+$ T cell response

a

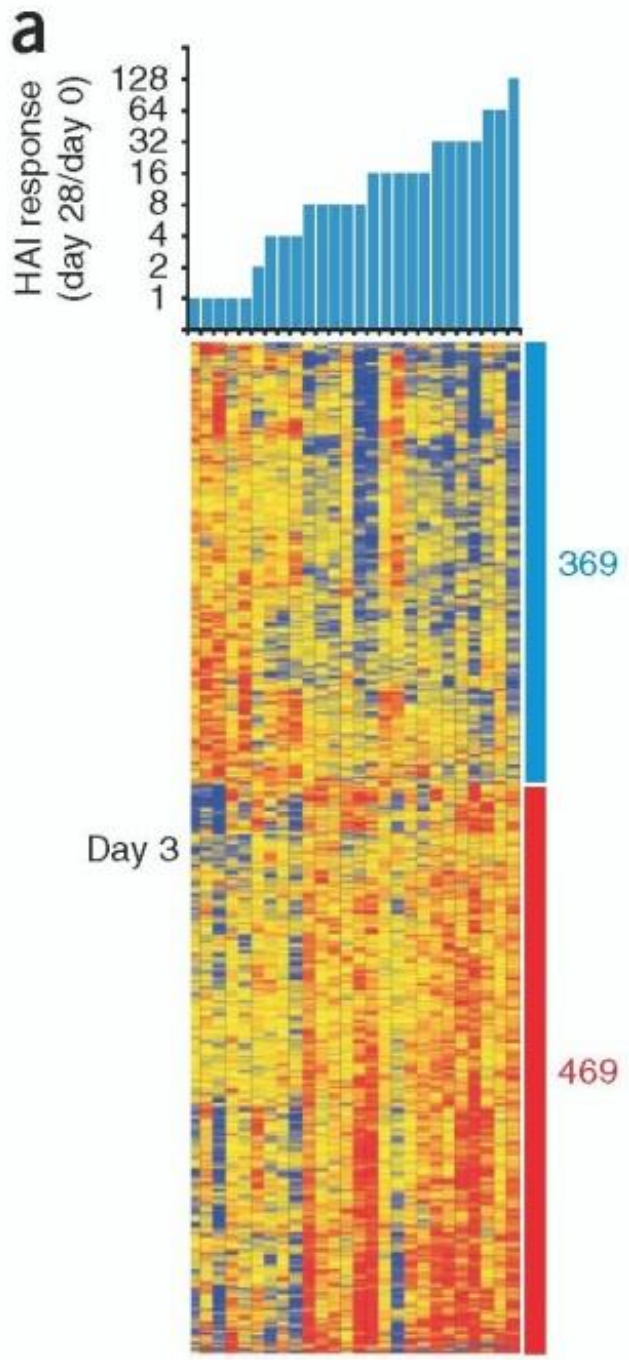
Separate high and low responders on gene expression



b



Querec et al, Nature Immunology 2009



Influenza

Nakaya et al, Nature Immunology 2011

Gene expression signatures correlate with influenza antibody (HAI)

Future studies – will gene expression on day 1 be predictive of protection 1 year later?

Conclusions

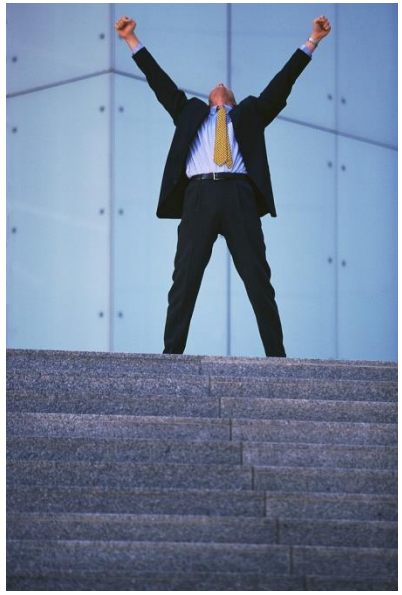
How to make a correlate – Step 1

- Choose a disease and decide what your vaccine will protect against (infection, disease, severe disease, hospitalisation, death)
- Use observations from disease, (immuno)deficiency, passive immunity, challenge studies and clinical study evidence to determine what mediates protection

Step 2

- If the answer is T cells, employ an army of immunologists, as the road ahead is uncertain or choose a new disease/change jobs

- If the answer is antibody (celebrate and), find a lab test that is easy to measure that is related to protection and can be justified



- Call it a correlate so everyone knows you are serious even though it might be a relative correlate, contain the correlate or even be just a surrogate

- While functionality is critical, If you have a simple correlate, take care not to be distracted by complex in vitro assays of functionality unless the regulator asks as this risks holding up vaccine development
- Consider memory and persistence of immunity and colonisation (mucosal bacteria) as a surrogate for diseases for which risk continues for a long time after vaccination (possibly in addition to a short term correlate)

- Whatever you do, make sure you find a correlate or surrogate as it will save you much time and money during development of your vaccine

If you have no correlate you need a lot of self belief (and then efficacy trials)