CORRELATES OF VACCINE-INDUCED IMMUNITY

by

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Why are Correlates of Immunity Important ?

1. Basic immunology
2. Enables correct choice of vaccine antigen
3. To permit consistency of potency
4. To determine susceptibility of an individual or a population
5. If efficacy trial not feasible or ethical, immunological data enable licensure of vaccine
6. Enables bridging from first-generation vaccine to second generation

My Definitions:

Correlate of Protection (CoP): An immune response that is 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.

mCoP – Mechanistic
Correlate of Protection

An immune response
that is responsible for protection

nCoP – non-mechanistic

Correlate of Protection

Formerly called:

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

How Correlates Are Determined

1. Levels of passively administered or maternal antibody that protect
2. Analysis of immune responses in protected and unprotected subjects in efficacy trials
3. Observations made on vaccine failures, e.g. immunosuppressed individuals
4. Human challenge studies
5. Extrapolation from animal challenge studies, including immunodeficiency

Potential Protective Adaptive Immune Mechanisms Induced by Vaccination

Serum Antibody

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

CD4+ T cells

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

Mucosal Antibody

- IgA locally produced
- IgG diffused from serum

CD8+ T cells

- Lysis
- Avidity

Principle 1

Must Define Protection

Against what ?

Infection ? (Local or Disseminated)

Disease ? (Mild or severe)

Polio

Protection against disease
IgG serum antibodies

Protection against infection
IgA- IgG mucosal antibodies

Correlates of Protection Against Pneumococcal Disease

	ELISA Units
Bacteremia	0.2 – 0.35
Pneumonia	2.5
Otitis	2.0 – 3.5
NP Carriage	5.0

Goldblatt D, WHO Bamako meeting

Principle 2

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

Results of Exposure to Measles in Relation to Preexisting Neutralizing Antibodies

Titer (mIU/ml)	Clinical Measles	Seroconversion
≤120	100%	100%
200-1000	0%	63%
≥1000	0%	0%

Chen R et al. JID 162:1036, 1990

However, B cell deficient humans do recover from measles, whereas

- T cell deficient humans suffer serious and fatal measles.
- Monkeys vaccinated with measles HA alone (low CD4+ T cell response) are protected against rash, but remain chronically viremic.
- Monkeys depleted of CD8+ T cells have increased viremia

Pan CH, PNAS, 2005

Immunity Against Poxviruses

- Primary Infection and recovery from Vaccination: Both B cells and T cells necessary for survival
- Secondary Exposure to Infection in previously vaccinated: Only B cells necessary for protection, although T cells may give partial protection.
- Neutralizing antibodies (ca. 1/20- 1/32) are protective
- However, titers decline and susceptibility to nonfatal smallpox returns at about 20 years postvaccination

Panchanathan, J. Virol. 2006, Sarkas J, Bull WHO, 1975
Liu, Nat Med, 2000

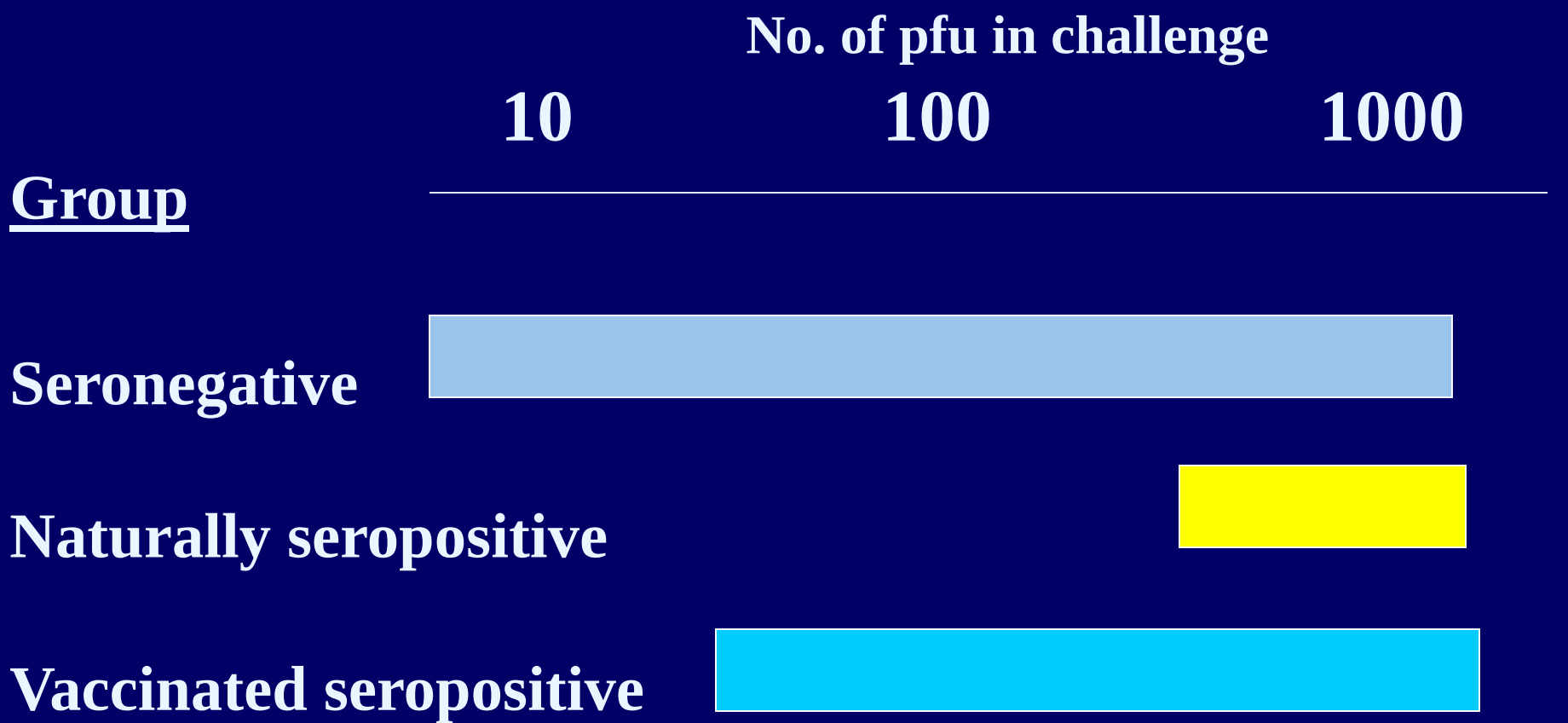
Principle 3

A Large Challenge Dose Can Overcome Immunity

“Challenge” of Poliovaccine by OPV

	% Infected 7 days after challenge	
	Low dose	**High Dose**
OPV Vaccinees	**3%**	**15%**
IPV Vaccinees	**30%**	**70%**

Challenge dose of subcutaneously administered Toledo strain (low passage) CMV that infects at least 50% of subjects in different groups



Plotkin,S.A. et al. *J Infect Dis* 1989;159: 860-865.

Principle 4

Most Current Vaccines Protect Through Antibodies

Major Licensed Viral and Bacterial Vaccines for Humans According to the Mechanism of Disease Prevented by the Vaccine

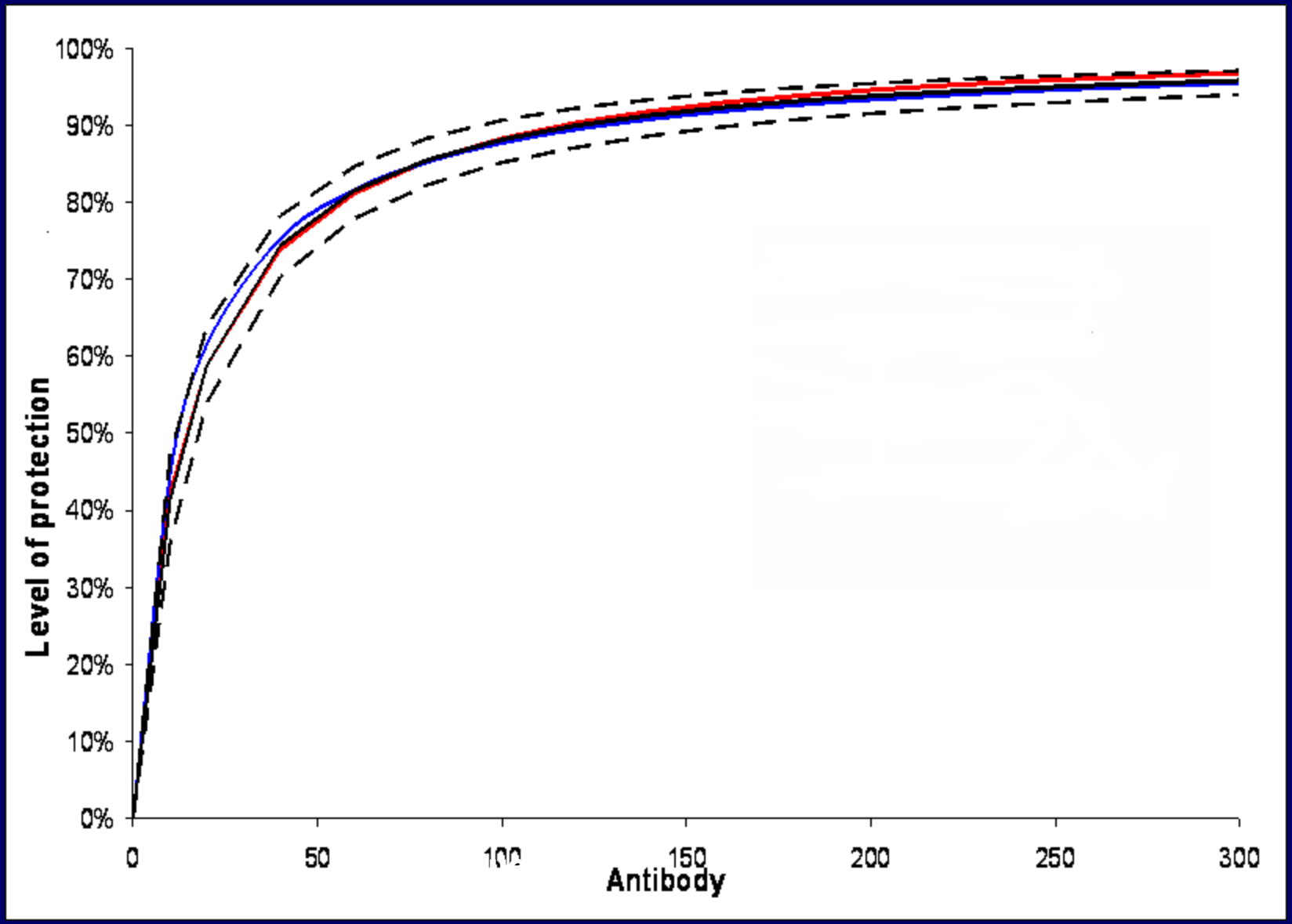
Viral	Viremia:	Smallpox, Yellow Fever, Measles Mumps, Rubella, Polio, Varicella, Hepatitis A, Hepatitis B Japanese Encephalitis, Tick-Borne Encephalitis
	Mucosal replication:	Influenza, Rotavirus, HPV
	Neuronal Invasion:	Rabies
	Neuronal reactivation	Zoster
Bacterial	Bacteremia:	Hemophilus influenzae,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

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

Principle 5

Correlates may be relative

Protection Against Influenza and Anti-HA Antibodies



Coudeville, L Personal communication

Pertussis Toxin Antibody as Correlate of Protection Against Pertussis Disease

Modsan Titers

Symptoms	Exposure	
Severe	Household 79 U/ml	Non-household 99 U/ml
Mild	156	124
None	246	155

Taranger, JID, 2000

Principle 6

Antibodies must be FUNCTIONAL

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%

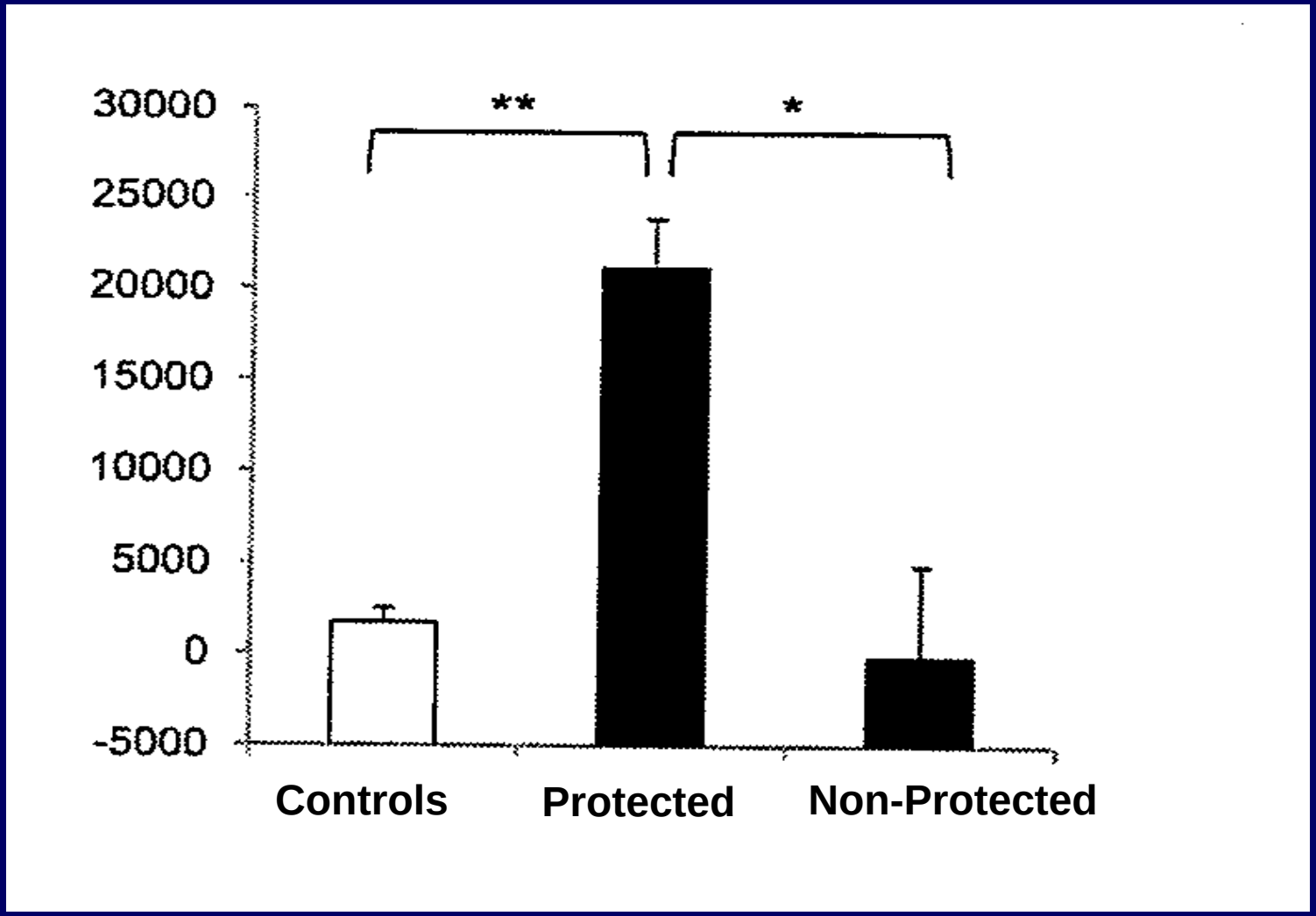
*≥ 2 mcg/ml # ≥ 1/8

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

Principle 7

T Cell Responses as Correlates

The Frequency of TB Antigen-specific IFN-y-secreting T Lymphocyte Correlates with Protective Immunity in cows



Hope JC, et al. Clin Vacc Immunol 2001;18(3),373-379.
Bhaff, CVI, 2015

mCoPs for Malaria Vaccines

RTS, S/AS01

Combination of anti circumsporozoite protein antibodies and TNFα producing CD4+ T cells

IV killed sporozoites

CD8+ T cells producing interferon in liver best correlate

White, et al, PLoS One 2013; Epstein et al, Science 2011

Principle 8

More than One Factor May Protect as Co-Correlates

Correlates of Immune Protection After Live Influenza Vaccine or Natural Infection

(Artificial Challenge in Children)

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

Belshe, JID, 2000

Inactivated Influenza

- HAI and neutralizing antibodies in serum correlate with protection although Nt antibodies are best correlate.
- Stimulation of Tfh cells correlates with increase in preexisting antibody
- 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, particularly granzyme production

Goronay, J Virol, 2001

Principle 9

Memory may be
An mCoP

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

Effector vs. Central Memory as mCoP

- Effector Memory important in short incubation infections like *H. influenzae* type b + meningococcus
- Also can abort HIV infection in rhesus model, given 24-72 hr incubation period for dissemination of HIV
- Central Memory important for long incubation infections and long-term memory (long-lived plasma cells)

Hansen et al Nature, 2011

Principle 10

Non-Mechanistic Correlates of Protection nCoP

Zoster Vaccine

- Vaccine contains large amounts of infectious and non-infectious varicella virus
- Inactivated virus also protects, as does gE glycoprotein and TLR agonist adjuvant
- VZ antigen stimulates flagging cellular immunity in the elderly
- Correlate of protection is VZ-specific CD4+ lymphocyte proliferation stimulation index ≥ 5.0, but VZ antibody response is used as an nCop

Hata et al. NEJM 2002

Additional Protective Immune Mechanisms Besides Neutralization and CTL

- Binding antibodies that prevent attachment (Ebola)
- Th17 that attract PMN's and prevent carriage (pneumococcal, TB?)
- Antibody Dependent Cellular Cytotoxic antibody (HIV)
- Stimulation of CD4+ T helper cells that secrete cytokines (pertussis)

Correlates of Protection Against Intestinal Pathogens

- Mucus
- Innate immune responses
- Barrier to vascular entry
- Mucosal lgA Antibody
- Mucosal lgG Antibody
- Serum lgG Antibody
- T cell responses

Protection against Rotavirus Disease (1)

- Heterotypic responses are more important than homotypic
- Responses to VP4 (VP8), VP6 and VP7 are all involved in protection
- Both non-neutralizing and neutralizing responses may be important
- Intestinal IgA induction measured directly in gut or indirectly in serum (Secretory IgA) are key
- However, maternal IgG and possibly IgG induced by prior infection can modify disease

Protection against Rotavirus Disease (2)

- Intestinal bacterial flora may increase or decrease protection by vaccination
- T cell produced interferon plays a role in heterotype protection
- Responses to NSP1 and NSP4 probably contribute to protection
- No single immune response provides an absolute CoP, but several responses provide a relative CoP
- Role of memory B cells should be elucidated

Conclusion

With respect to Correlates of Protection induced by rotavirus vaccination

POLYTHEISM IS PREFERABLE TO MONOTHEISM

(which may be also true for other vaccines)

Conclusions

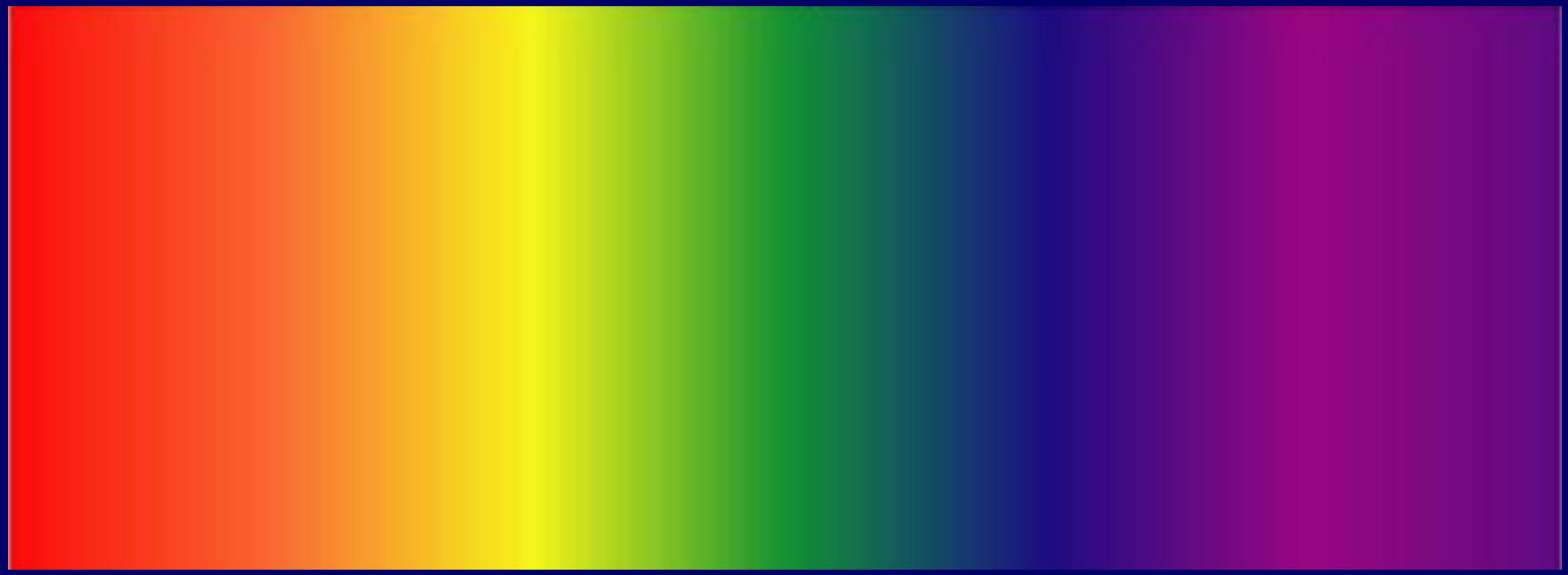
1. The immune system is redundant.
2. However, almost all current vaccines work through antibodies in serum or on mucosa that block infection or bacteremia/viremia and thus provide a mechanistic correlate of protection
3. The functional characteristics of antibodies as well as quantity are important.
4. Antibody may be highly correlated with protection or synergistic with other functions

Conclusions

5. Immune memory is a critical correlate:
   Effector memory for short incubation diseases,
   Central memory for long incubation diseases.
6. Cellular immunity acts to kill or suppress intracellular pathogens and may also synergize with antibody.
7. For some vaccines we have no true mCoP but only useful nCoP for an unknown protective response.
8. There may be multiple synergistic, additive or subtractive correlates of protection.

Correlates of Protection

Anthrax **Zoster**



Antibody Response **Cellular Response**