

Are we overloading the neonatal/infant immune system with the current vaccinations?

- Quantitative overload
- Qualitative overload
- Impact

I. Question:

Is the neonatal/infant immune system quantitatively overloaded by the current vaccine schedule?

- 1. How many antigens (Ags) could the immune system **respond to?**
- 2. How many Ags is the neonate/infant **exposed to naturally?**
- 3. How many additional Ags is the neonate/infant **exposed through vaccination?**

Quantitative overload ?

1. How many Ags could the immune system respond to?

- @ birth:
 - more T & B -cells/cc of blood than adult
 - adult-like diverse T-cell receptor (TCR)
& B-cell immunoglobulin (Ig) repertoire

$>10^{16}$

(10,000,000,000,000,000)

different possible TCR or Ig specificities

Quantitative overload ?

How many Ags is the neonate/infant exposed to naturally

- *In utero*: fetus is sterile = no/low exogenous Ag
- @ birth: colonized with maternal
 - genital tract flora (**~18 species**)
 - fecal flora $10^{11}/g$ (**~400 species**)
- breast-milk 10^9 microbes/L (**~8 species**)
- each species $\sim 3-6 \times 10^3$ different proteins

$>10^6$

different proteins

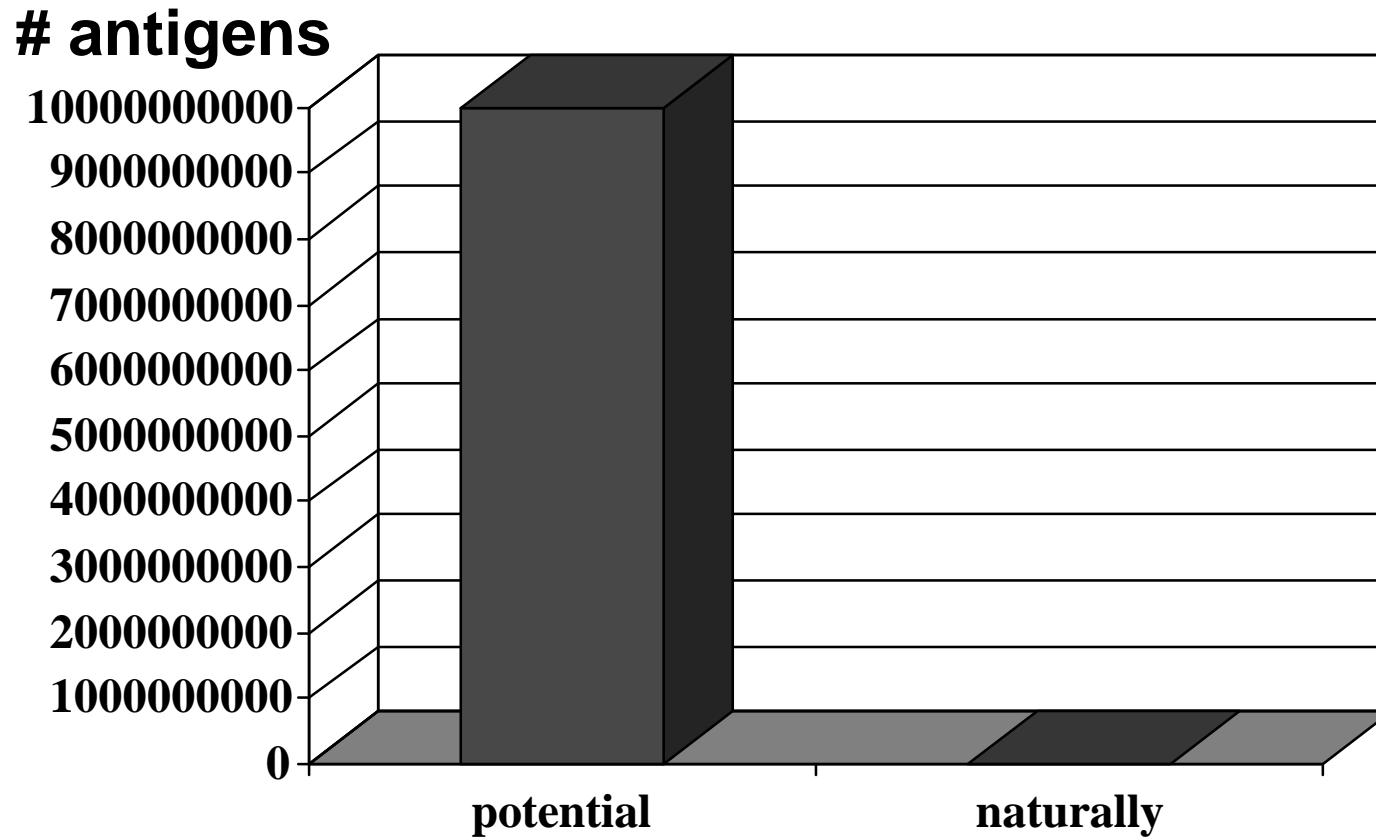
Quantitative overload ?

10^{16} vs. 10^6 ?

- Not all TCR/Ig recombinations produced
- Not all T- and B-cells reactive
- Each protein ~ 0-3 antigenic epitopes
- Some microbial proteins are not antigenic at all

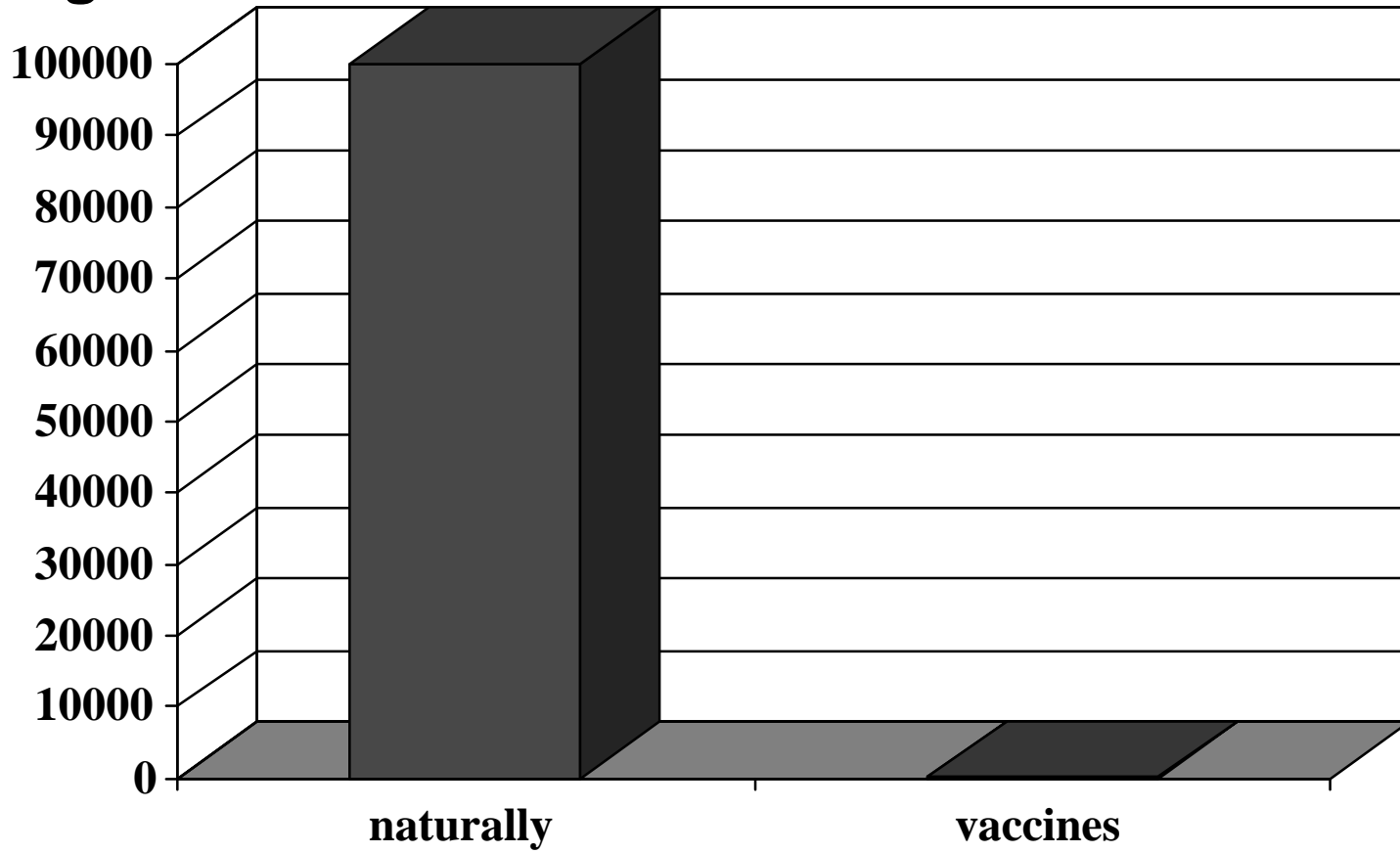
**# of potential T- and B-cell specificities
is several logs in excess over Ag
exposure**

Quantitative overload ?



Quantitative overload ?

antigens

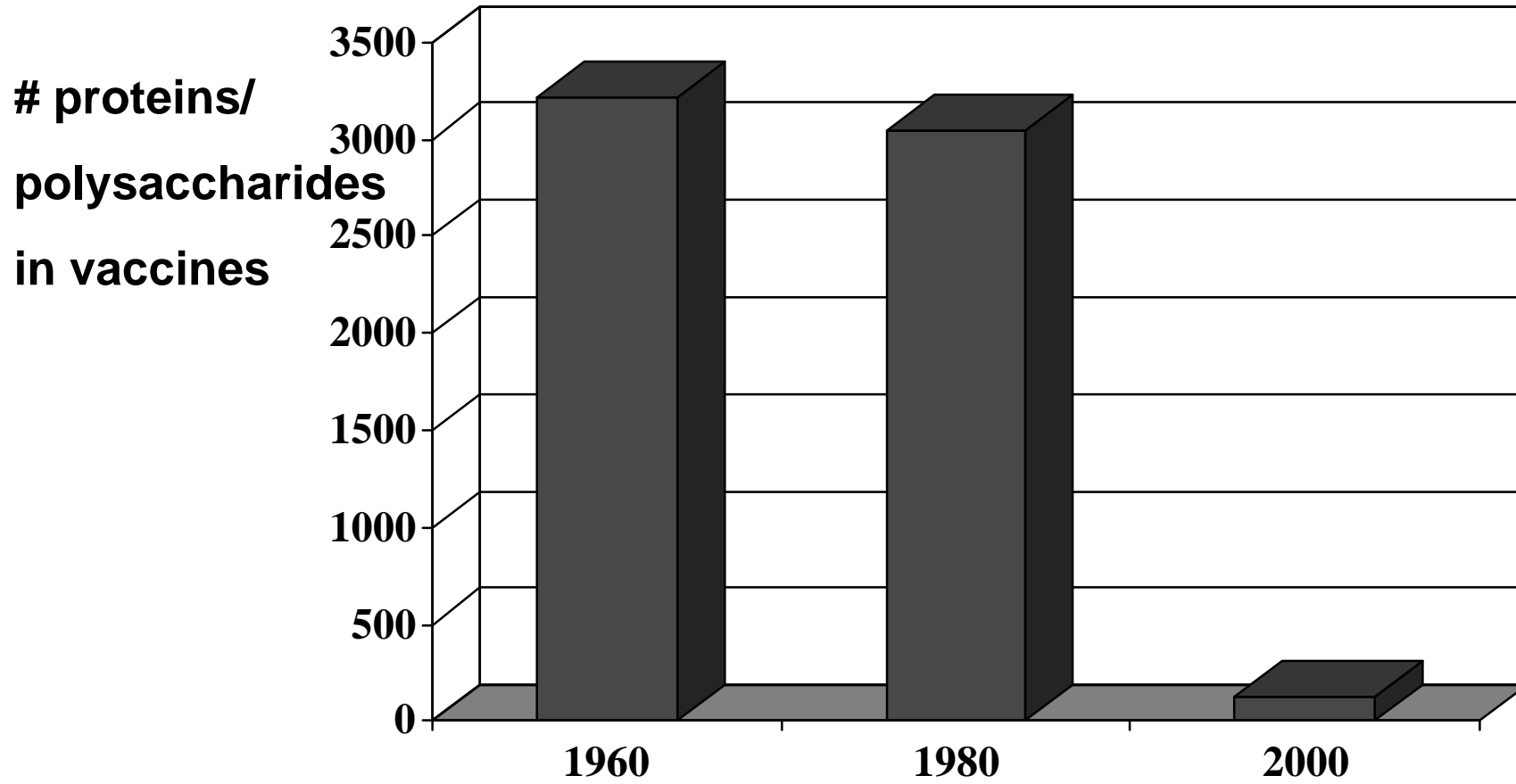


Immunogenic Proteins, Polysaccharides in Vaccines

1900		1960		1980		2000	
<i>Vaccine</i>	<i>Proteins</i>	<i>Vaccine</i>	<i>Proteins</i>	<i>Vaccine</i>	<i>Proteins</i>	<i>Vaccine</i>	<i>Proteins</i>
smallpox	~200	smallpox	~200	diphtheria	1	diphtheria	1
		diphtheria	1	tetanus	1	tetanus	1
		tetanus	1	wc-pertussis	~3000	wc-pertussis	2-5
		wc-pertussis	~3000	polio	15	polio	15
		polio	15	measles	10	measles	10
				mumps	9	mumps	9
				rubella	5	rubella	5
						Hib conj.	2
						varicella	69
						pneumo conj.	8
						hepatitis B	1
Total:	1~200		5~3217		7~3041		11~123 - 120

Modified from Offit PA, et al. Pediatrics 2002 (in press)

Quantitative overload ?



Offit et al., in press

- **I. Question:**
Is the neonatal/infant immune system *quantitatively* overloaded in the current vaccine schedule?

Answer: No!

II. Question:

**Is the neonatal/infant immune system
qualitatively overloaded,
i.e. changed by current vaccines?**

- 1. What determines the quality
of an immune response (IR)?**
- 2. How might vaccines affect this quality?**

Qualitative overload ?

The neonatal/infant immune system

- low antigen exposure in utero:

T-cells = mostly **naïve**

in phenotype & function

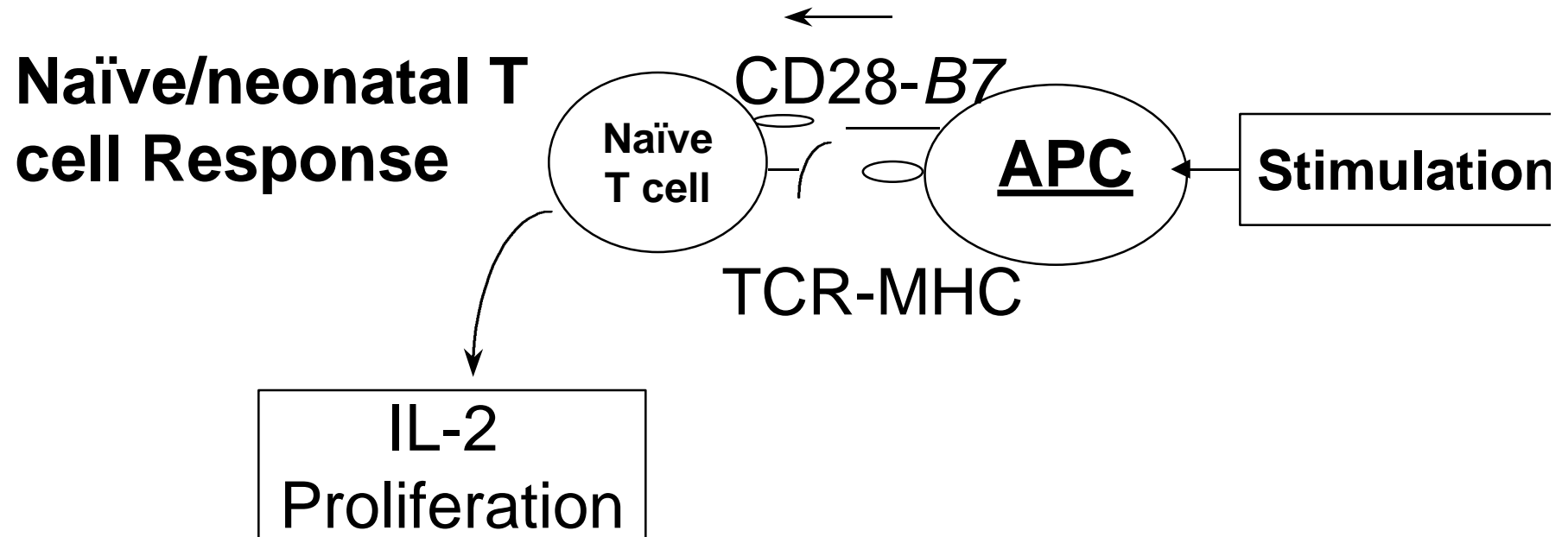
activation **threshold** higher:

= more **costimulus** dependent

= more **context** dependent

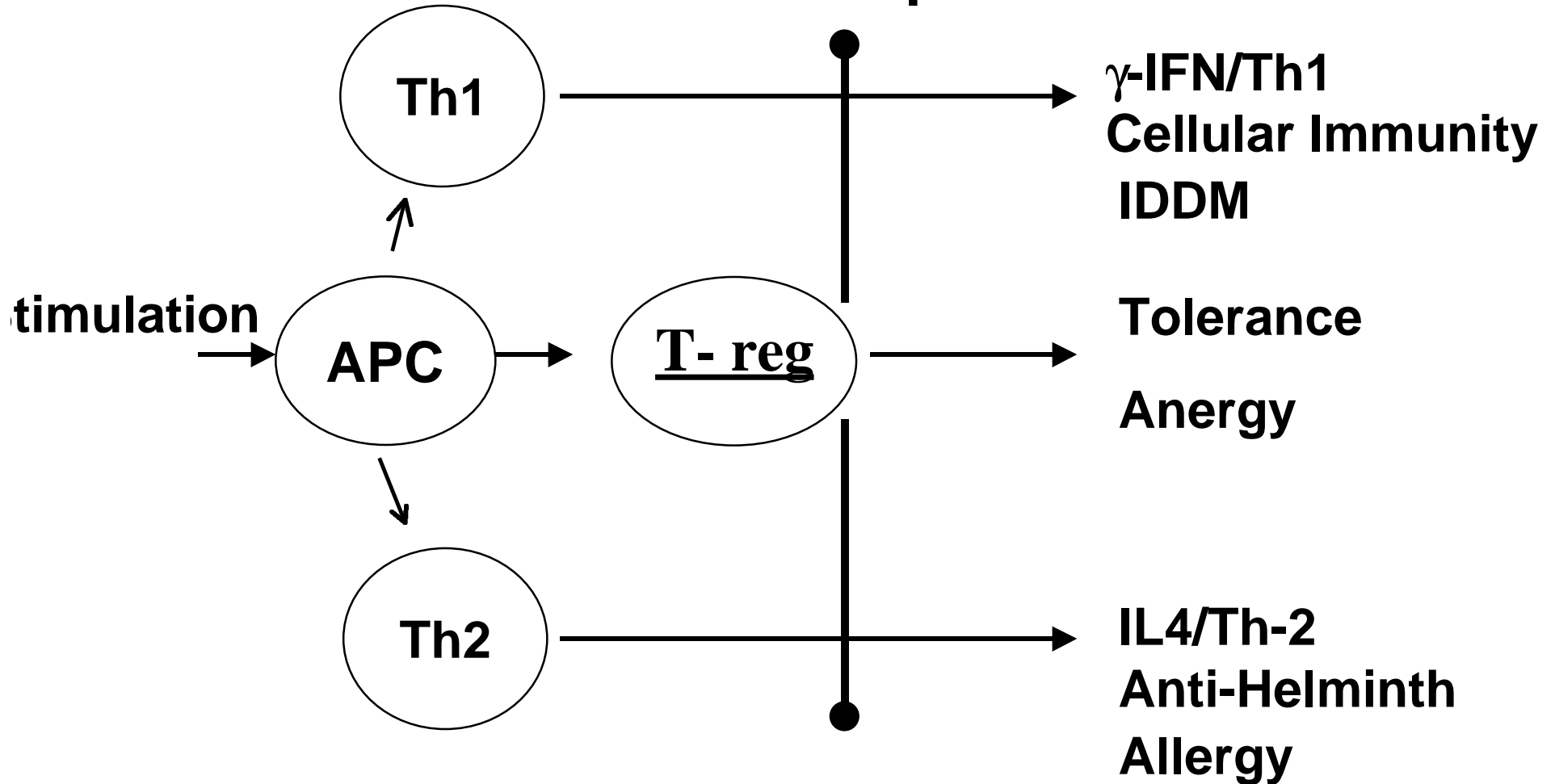
Qualitative overload ?

Naïve T cells Require Both TCR and Costimulation for Efficient Activation



Qualitative overload ?

Context of APC stimulation determines the quality of the immune response



Qualitative overload ?

1. What determines the quality of an IR?

Answer: Context

What determines the context?

- Microbial Stimuli (e.g. concurrent infection)**
- General Health (nutrition etc.)**
- Genetics**
- ...**

Qualitative overload ?

2. Do vaccines affect this quality?

- **BCG induces persistent Th-1 cell-mediated response**
(Marchant group)
- **Measles vaccine induces strong Th-1 response**
(Arvin group)
- **Pertussis induces a robust Th-1 response, but DTaP in alum induces a mixed Th-1/Th-2 response**
(Mill, Ausiello, and Holt groups)

Qualitative overload ?

2. How do vaccines affect this quality?

**Vaccines influence context of the immune response by
nature of the antigens & amount and route of
administration of antigens, as well as adjuvants**

› **II. Question:**

Is the neonatal/infant immune response qualitatively changed by the current vaccine schedule?

Answer:

It might, depending on the circumstance.

If vaccination could influence the quality of neonates/infants IR:

III. Question: What is the overall impact of vaccination on infectious diseases?

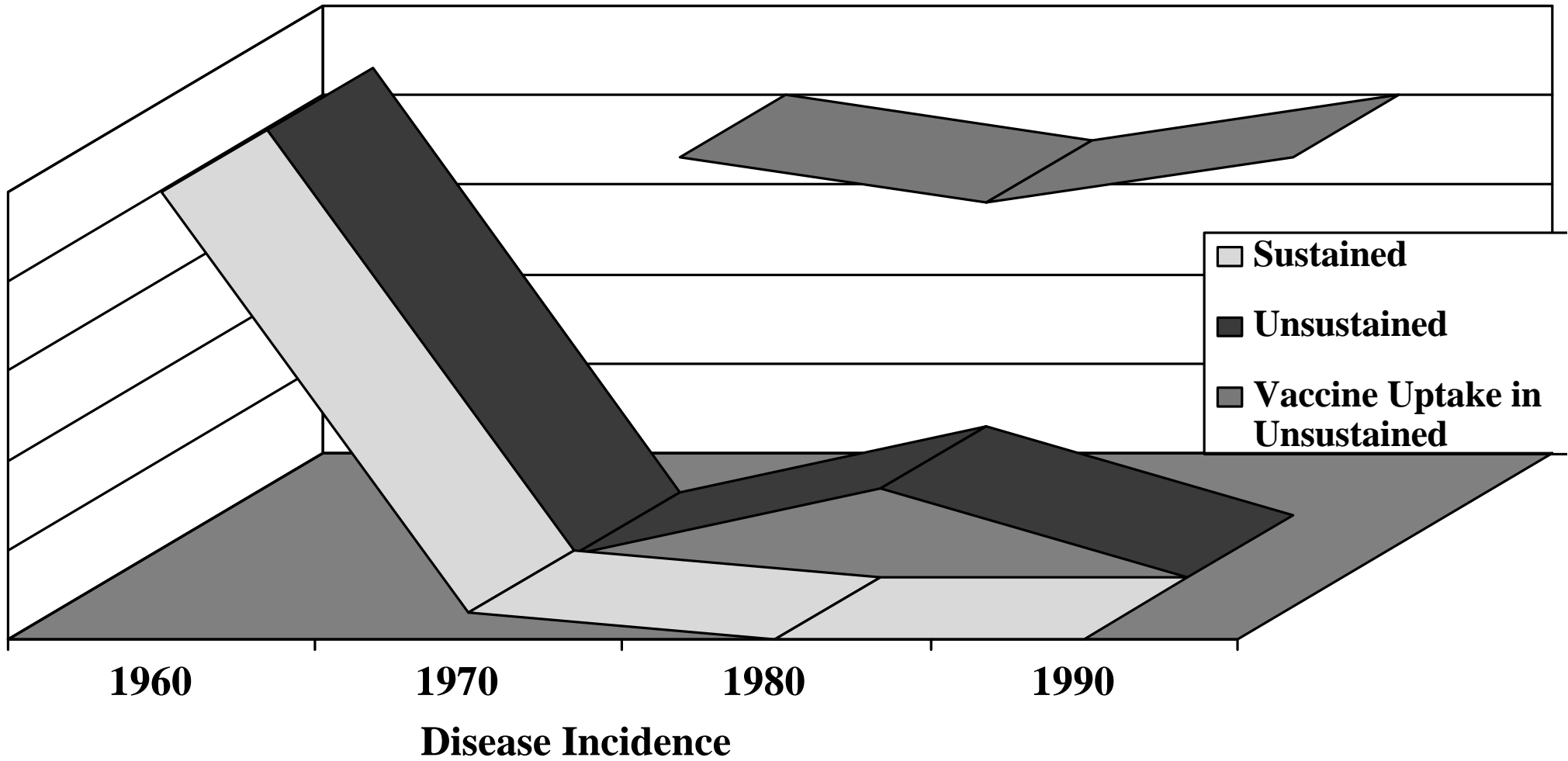
Vaccines & Infection

- 1. Do current vaccines prevent the infections they are targeted to prevent (homologous effect)?**
- 2. Do current vaccines increase or decrease infections they are not targeted to prevent (heterologous effect)?**

Impact

Homologous Effect: e.g. Pertussis

(Gangarosa, 1998)



Homologous Effect: e.g. Tetanus (Mulholland, 1998)

~ 350,000 neonates die every year from neonatal tetanus in countries with low TT vaccination rates, i.e. 98% of these deaths occur in the developing world

- extremely rare case of neonatal tetanus in developed world with high TT vaccination rates

Impact

Do current vaccines prevent the infectious diseases they are targeted to prevent (homologous effect)?

Answer: YES!

mpact

2. Do current vaccines increase or decrease infectious diseases they are *not* targeted to prevent (heterologous effect)?

Several studies, but with different 'read-outs':

- vaccinations impact on defined infections**
- vaccinations impact on overall morbidity**
- vaccinations impact on overall mortality**

Impact

Heterologous effect: specific infections

Prior to introduction of Hib-vaccines, 2 studies compared effect of regular, scheduled vaccinations on invasive Hib disease:

Davidson, et al. 1991:

-DTP no effect on Alaskan Native Americans

Black et al. 1991:

-MMR/DTP/OPV possibly protected from disease in California for 3 months after vaccination

Impact

Heterologous effect: morbidity

Read out: decreased non-specific signs of infectious disease (fever, URI, GI symptoms)

Otto et al., 2000 (Germany)

DTaP/Hib/OPV

reduced morbidity

for 3 months following vaccination

Impact

Heterologous effect: mortality

Read out: decreased mortality 'above the extend attributable to the disease prevented'

Aaby's group (Africa)

Vaccination with BCG, OPV, DTP, Measles

reduced mortality

for up to 6 months following vaccination

Question about effects of DTP on BCG currently under investigation by Global Advisory Committee on Vaccine Safety

Impact

2. Do current vaccines prevent infectious diseases they are not targeted to prevent (heterologous effect)?

Answer: YES!

Impact

- › **III. Question: What is the overall impact of vaccination on infectious diseases?**

Answer: POSITIVE!

Vaccines prevent infectious diseases.

Immune Overload?

Quantitative overload: No!

Qualitative overload: possible.

Impact: Positive!