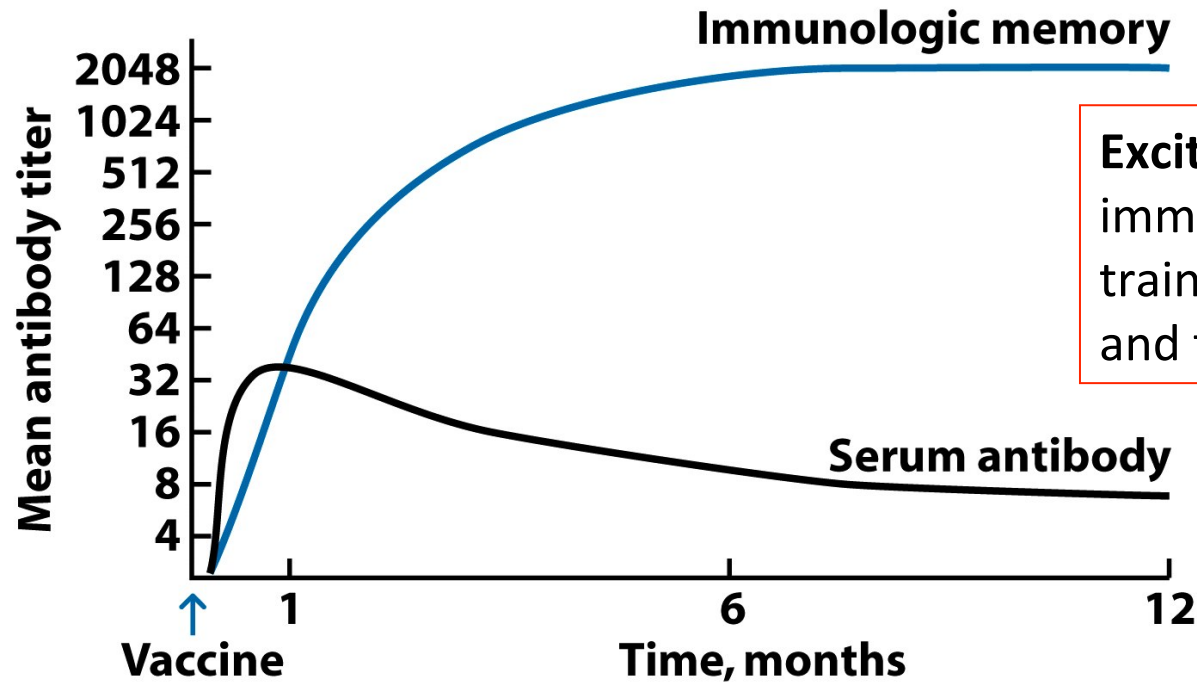




Exciting news - our immune system can be trained to remember and fight off pathogens!

Vaccines and the Immune Response

Aimee Pugh-Bernard, PhD

October 10, 2013

Outline of Talk

- Innate vs. Adaptive Immunity
- B cells, T cells, and Immunologic Memory
- Passive vs. Active Immunity
- Immune System Capacity
- Vaccines – immune response to different forms
 - live, attenuated (nasal flu)
 - inactivated (shot form of flu)
 - conjugate (Hib)
 - subunit (acellular pertussis)
- Concept of Herd Immunity
- Efficacy vs. Risks of Vaccination (immune specific)

Learning Objectives

- **Compare** and **contrast** innate and adaptive immunity
- **Describe** the role of B cells and T cells in the adaptive immune system
- **Describe** the adaptive immune system characteristics of specificity, memory, and diversity
- **Compare** and **contrast** passive and active immunity
- **Explain** the capacity of the immune system in the context of the number of antigens that can be combated at any given time
- **List** the 4 different forms of vaccines discussed – be sure to include the example pathogen for each
- **Describe** the immune response to each type of vaccine
- **Explain** the concept of herd immunity
- **Compare** and **contrast** the efficacy and risks of vaccination

Two basic types of immunity

	Innate	Adaptive
Response time	Hours	Days
Specificity	Limited and fixed	Highly diverse; improves during the course of immune response
Response to repeat infection	Identical to primary response	Much more rapid than primary response
Major components	Barriers (e.g., skin); phagocytes; pattern recognition molecules	Lymphocytes; antigen-specific receptors; antibodies

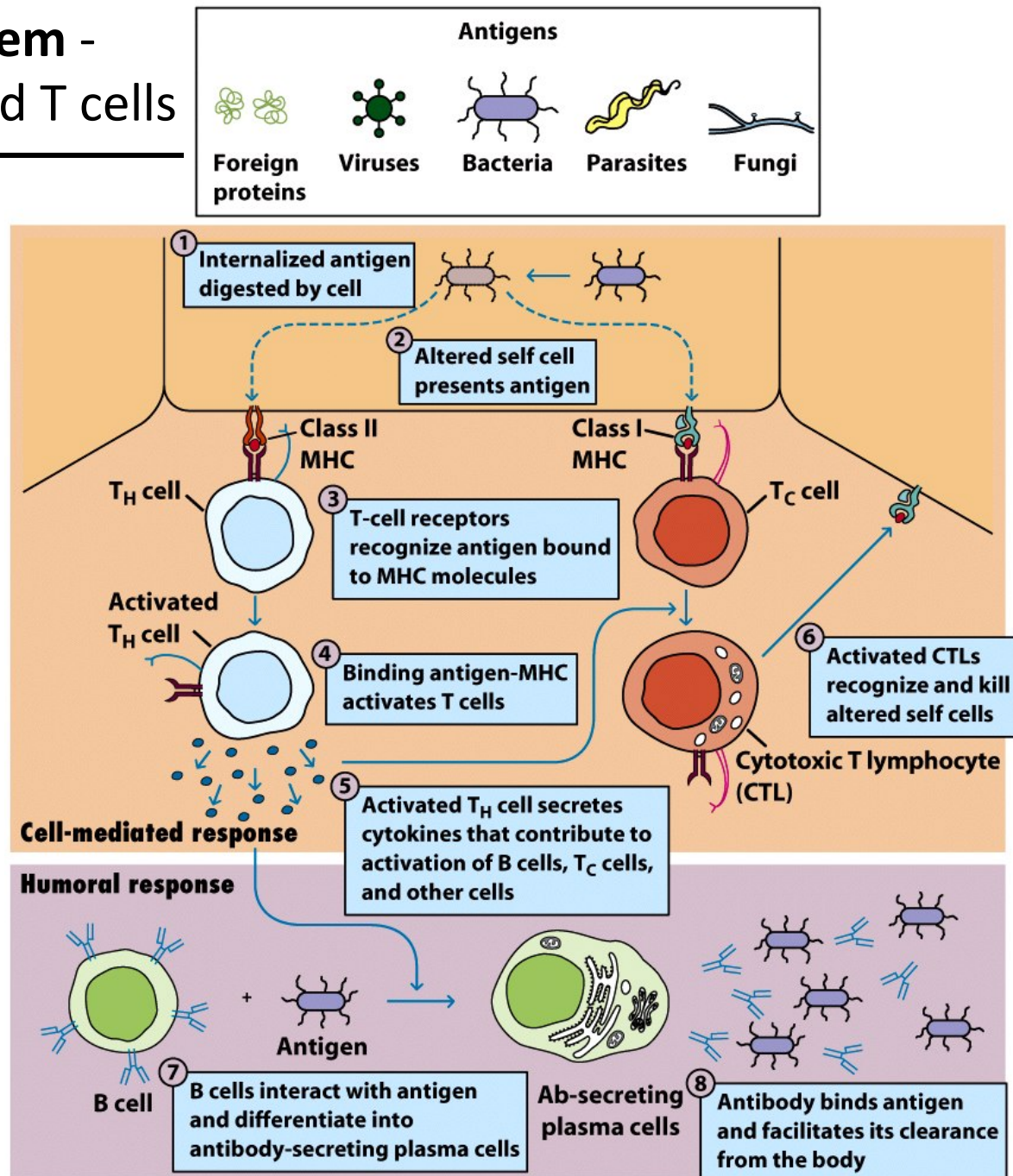
Kuby Immunology 6e WH Freeman

- **Innate** immunity is **non-specific** – first line of defense - cellular and molecular components that recognize classes of molecules unique to frequently encountered pathogens
- **Adaptive** immunity is **specific** in response to each pathogen - occurs within 7-10 days after the initial recognition of pathogen

- Adaptive Immune System -

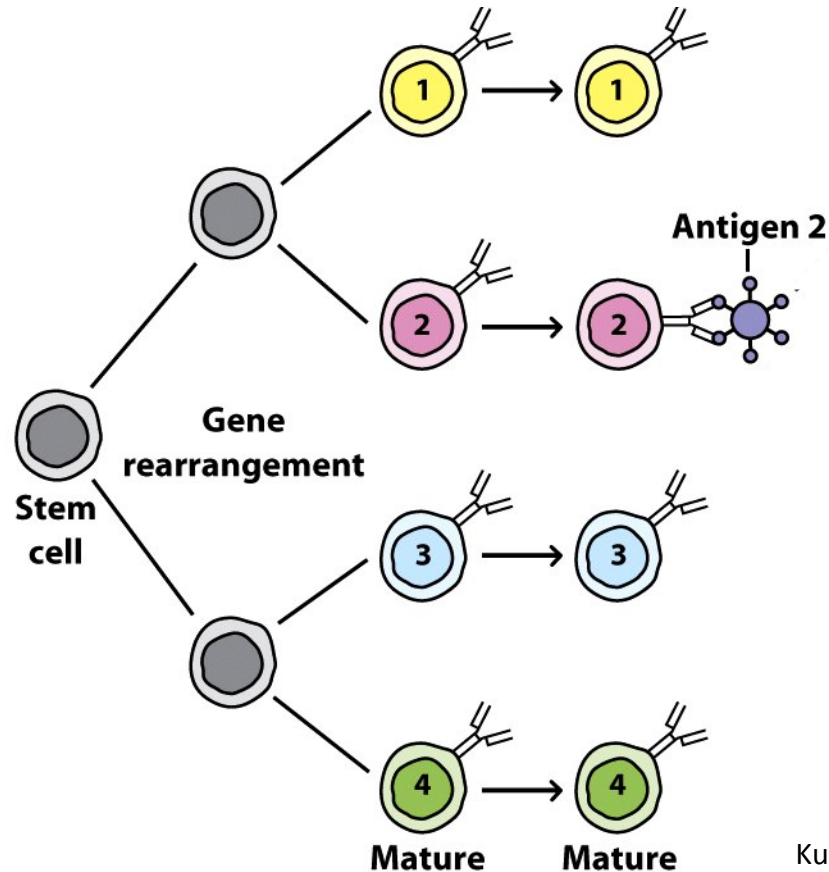
major players are B cells and T cells

- T cells recognize antigens presented on self cells in the context of MHC molecules
- T_H cells respond to antigen by producing cytokines and 'helping' B cells become activated
- T_C cells respond to antigen by becoming cytotoxic T cells (CTLs) that kill infected cells
- B cells interact with free antigen and differentiate into antibody-secreting plasma cells
- Antibody binds to antigen to facilitate clearance



Specificity

a characteristic of cells of the adaptive immune system



BCR = B Cell Receptor
- also called membrane-bound immunoglobulin or membrane-bound antibody

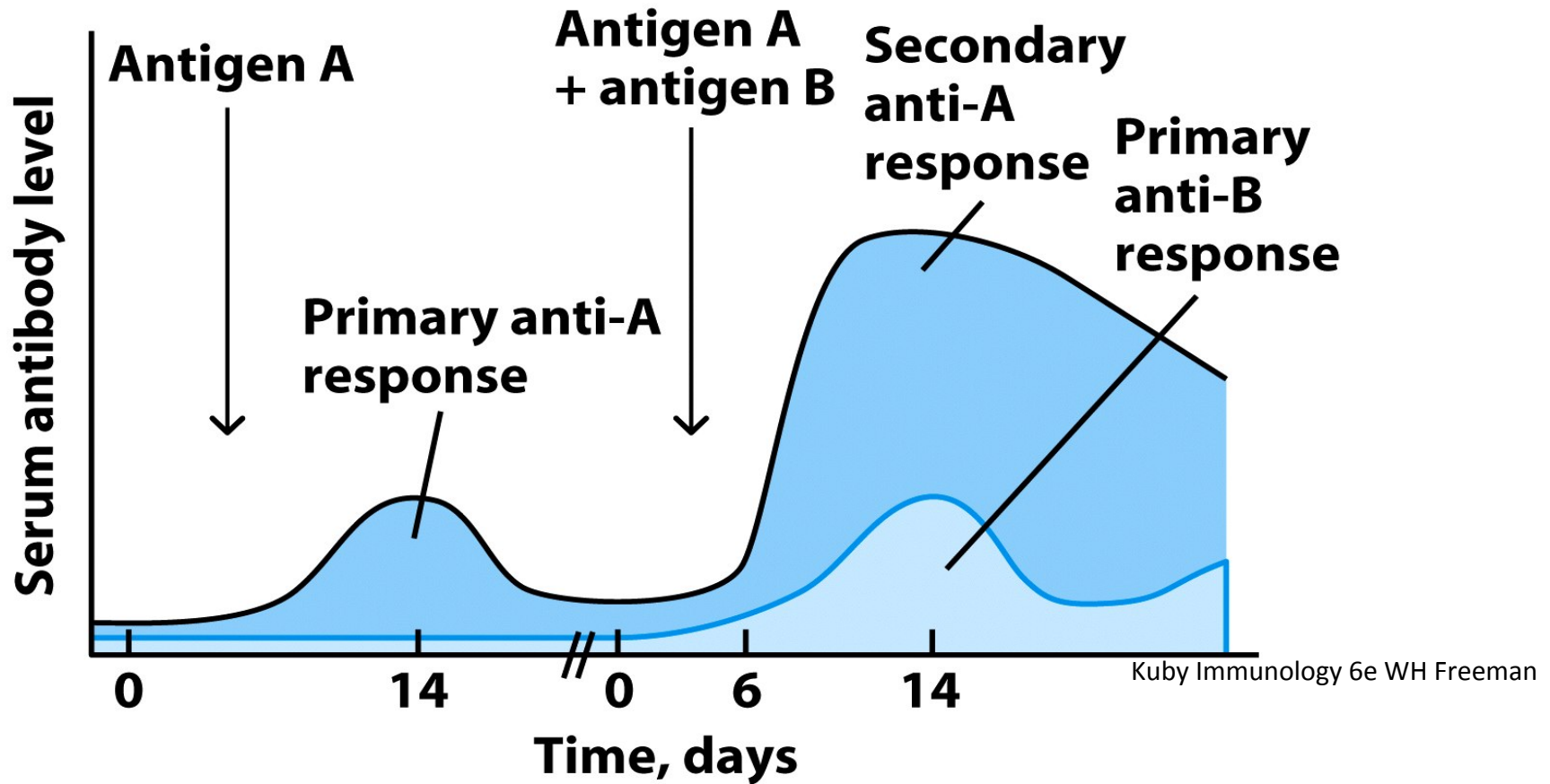
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Specificity – all BCR on each B cell and all TCR on each T cell is specific for a distinct antigenic determinant

– compare one B cell to another *or* one T cell to another

Memory

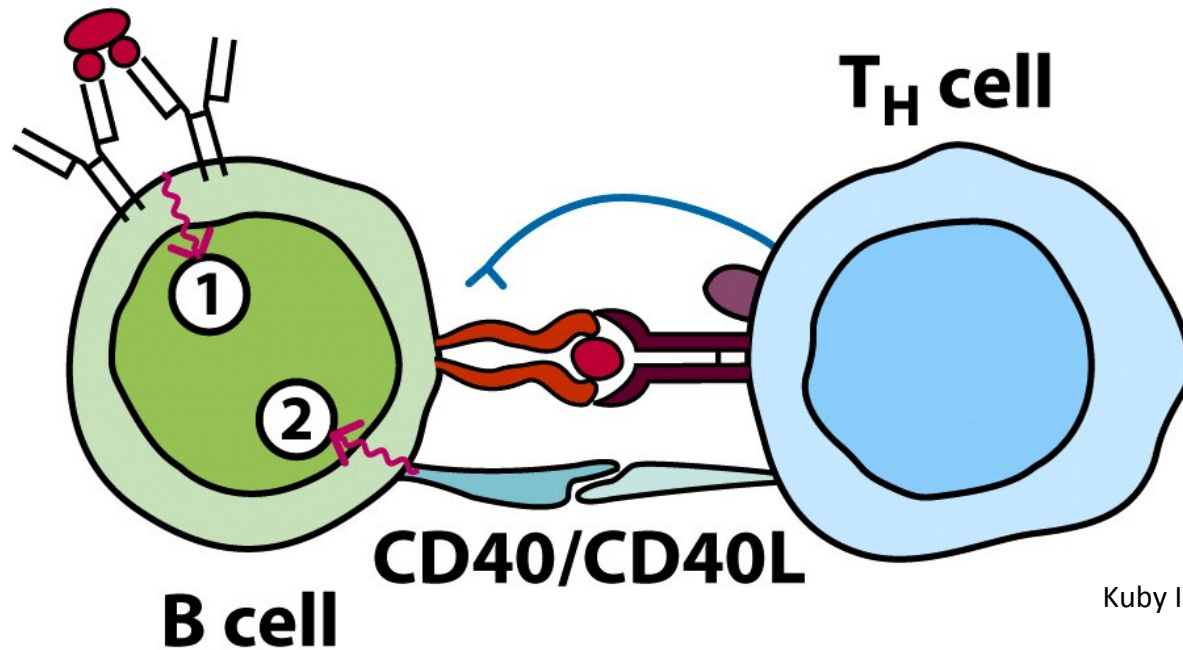
a characteristic of cells of the adaptive immune system



Memory – a second encounter with the same antigen induces a quick and robust immune response

– compare primary response to secondary response

Differences in activation of **Naïve** vs. **Memory** B cells



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Signal 1 – recognition of specific antigen via the BCR

Signal 2 – ligation of CD40 (B cell) via CD40L (TH cell) – the ‘help’

- The activation of a **naïve B cell** requires two signaling events – signal 1 and signal 2
- The activation of a **memory B cells** only requires signal 1

TABLE 19-1**Acquisition of passive and active immunity****Two major forms of Immunization**

Type	Acquired through
Passive immunity	Natural maternal antibody Immune globulin* Humanized monoclonal antibody Antitoxin [†]
Active immunity	Natural infection Vaccines [‡] Attenuated organisms Inactivated organisms Purified microbial macromolecules Cloned microbial antigens Expressed as recombinant protein As cloned DNA alone or in virus vectors Multivalent complexes Toxoid [§]

- **Passive:** transfer of antibodies from one person to another (maternal or pooled from donated samples)

- **Active:** pathogen exposure that generates an effective immune response and leads to memory of the pathogen (natural infection or vaccines)

Active immunization

produces memory and long-term protection

- The goal of **passive immunization** is **transient protection** or alleviation of an existing condition
- The goal of **active immunization** is to produce **immunologic memory** and result in **long-term protective immunity**
- Active immunization is achieved by natural infection or through the administration of a vaccine
- The adaptive immune system plays an active role - **T and B cells are activated, proliferate, and form long-lasting memory cells**
- When active immunization is successful, subsequent exposure to the pathogen elicits a heightened immune response that successfully eliminates the pathogen and/or prevents disease (chickenpox 'concept check')

Immune Capacity vs. Antigens Encountered

The Ocean Analogy - Dr. Paul Offit

“When an infant is in the mother’s womb, they’re in a sterile environment. When they enter the birth canal and are born, they’re no longer in a sterile environment. Bacteria quickly begin to live on the baby’s skin, their nose, their throat. The average person has trillions of bacteria living on the surface of their body. We are able to make an immune response to these bacteria. If we didn’t, they would invade the bloodstream and cause death. Each bacterium has 2,000 to 6,000 proteins that our immune system is able to handle. If you consider all 14 vaccines given to children, it’s probably 150 immunological components or proteins. That’s literally just a drop in the ocean.”

- Dr. Paul A. Offit, Children’s Hospital of Philadelphia, Division Chief, Infectious Disease Section
- borrowed from Dr. Rachel Herlihy’s talk “Delayed, Selective and Alternative Vaccine Schedules” September 10, 2012

'History' of Shots and Antigens

1900		1960		1980		2000	
Vaccine	Proteins	Vaccine	Proteins	Vaccine	Proteins	Vaccine	Proteins/ Polysacc
Smallpox	~200	Smallpox	~200	Diphtheria	1	Diphtheria	1
Total	~200	Diphtheria	1	Tetanus	1	Tetanus	1
		Tetanus	1	WC-Pertussis	~3000	AC-Pertussis	2–5
		WC-Pertussis	~3000	Polio	15	Polio	15
		Polio	15	Measles	10	Measles	10
		Total	~3217	Mumps	9	Mumps	9
				Rubella	5	Rubella	5
				Total	~3041	Hib	2
						Varicella	69
						Pneumococcus	8
						Hepatitis B	1
						Total	123–126

- Offit et al., Pediatrics, January 2002

- borrowed from Dr. Rachel Herlihy's talk "Delayed, Selective and Alternative Vaccine Schedules" September 10, 2012

Diversity

a characteristic of cells of the adaptive immune system

- 10^9 to 10^{11} different antibody specificities in our body at any given time
- Can handle $\sim 10,000$ antigens at one time (limited by blood volume)
- Due to the tremendous capacity of the immune system and the specificity of an immune response to each pathogen there is no physiologic reason to design an alternative immunization schedule due to limited capacity or for fear of overwhelming the immune system

immune system capacity is tremendous

Vaccines and the Immune Response

Type	Vaccine
Live, Attenuated	influenza (intranasal)
Inactivated	influenza (shot form)
Conjugate	<i>Haemophilus influenza type b</i> (Hib)
Subunit	acellular pertussis (<i>Bordetella pertussis</i>)

<http://www.cdc.gov/vaccines/pinkbook>

Live, attenuated virus vaccines

example: nasal form of flu vaccine

- Contains a weakened strain of a virus that has been derived from a wild-type (WT) virulent strain – LAIV is cold-adapted and replicates effectively in the mucosa of the nasopharynx
- To be effective, live, attenuated virus must possess the following properties:
 1. The surface antigens must be identical or very similar to the wild-type virus so that the immune response to the vaccine virus provides protection from the wild-type virus (i.e. it molecularly resembles the WT virus and will be recognized by the memory cells created)
 2. The wild-type virus used to make the vaccine must be attenuated and have little or no virulence

Immune Response to Attenuated Vaccines

- Because the virus is live and replicates effectively in the mucosa of the nasopharynx, the amount of **virus antigen** in the body **increases as the virus replicates** – this gives the immune system more viral material to work with and respond to

- As a result, the **immune response is typically wide-ranging** and includes B cells, CD4, and CD8 T cells, which is an ideal outcome as all the major players of the adaptive immune system have been called to action

Inactivated virus vaccines

example: injection form of flu vaccine

- Inactivated or killed virus vaccines are made by mass producing the virulent or WT virus and then inactivating it via treatment with a chemical like formaldehyde
- There are challenges in determining the correct concentration of chemical and the proper reaction time that inactivates all the virus but leaves the antigens unchanged so that they remain immunogenic

Vaccine biologists need to inactivate the virus but do not want to destroy it beyond recognition. It must molecularly resemble the wild-type virus so that the memory cells created recognize the native pathogen when they encounter it.

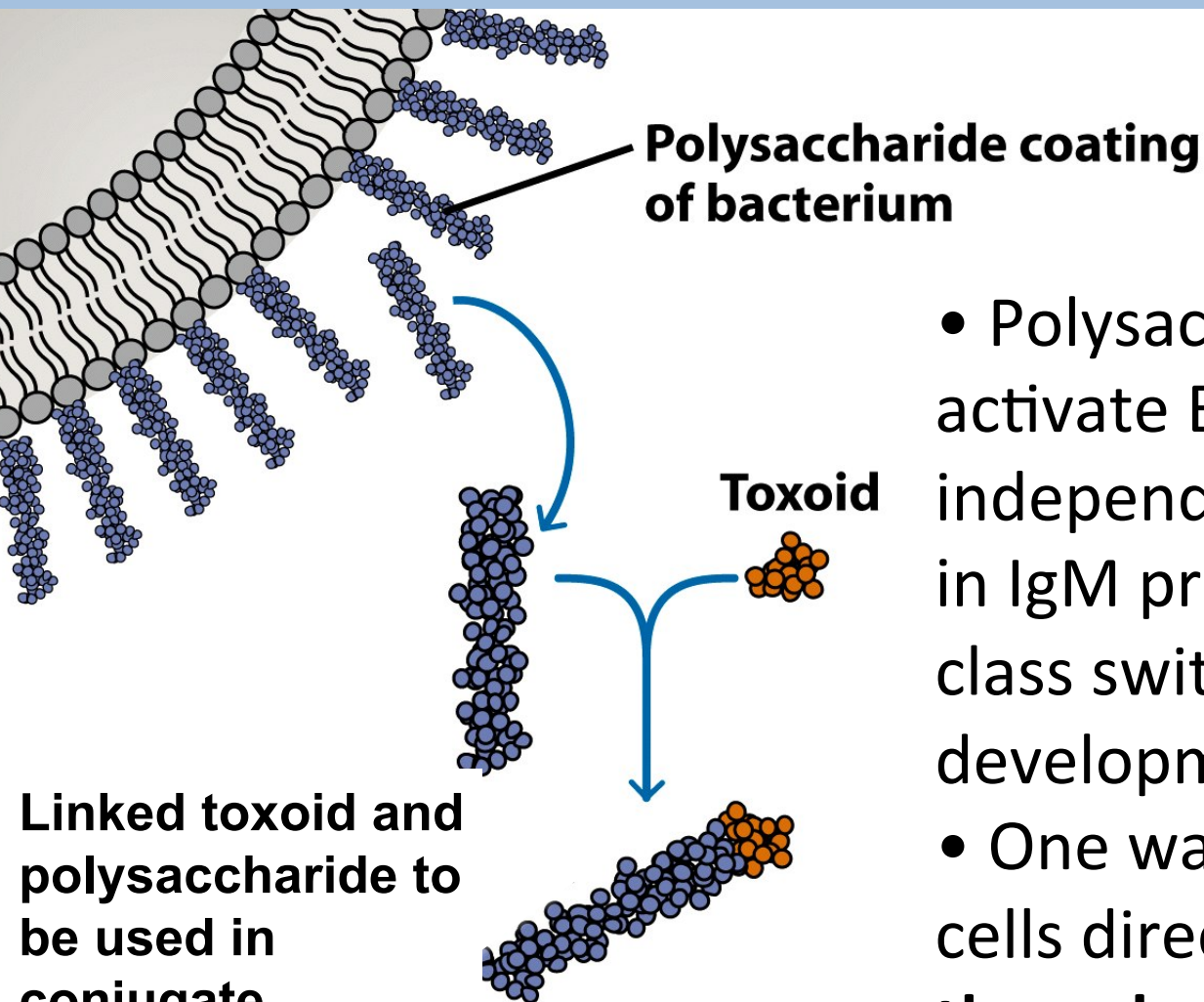
Immune Response to Inactivated Vaccines

- Because the virus is inactivated or killed it is incapable of replicating (making more virus) and the amount of **virus antigen** in the body **remains the same** – the immune system has to work with the antigen in the single dose administered
- As a result, **inactivated vaccines induce a predominantly humoral* antibody response**; they are less effective than attenuated vaccines at inducing cell-mediated immunity

* Immunologists use the term 'humoral-immunity' to refer to the activation of B cells and 'cell-mediated immunity' to refer to the activation of T cells

Conjugate vaccines

example: Hib (*Haemophilus influenzae* type b)



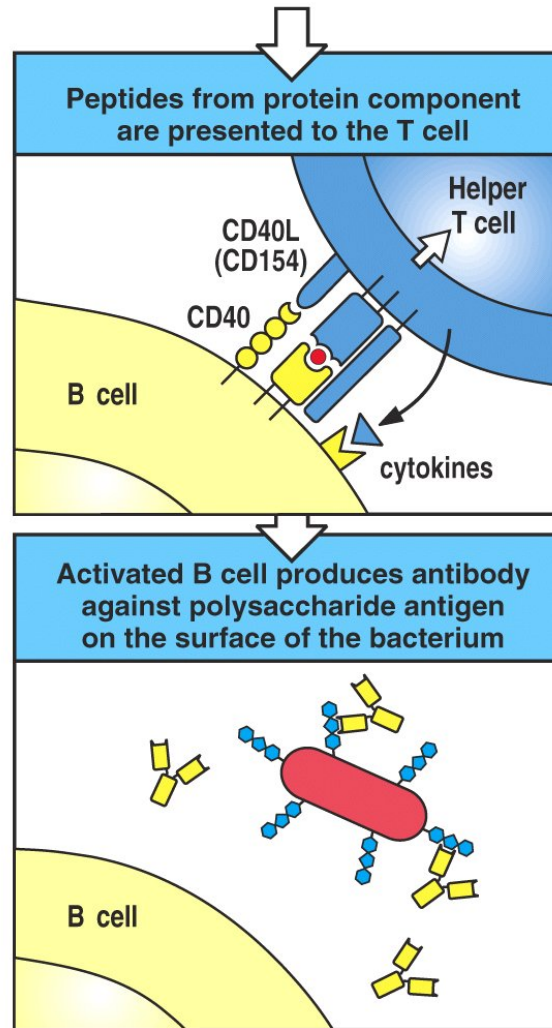
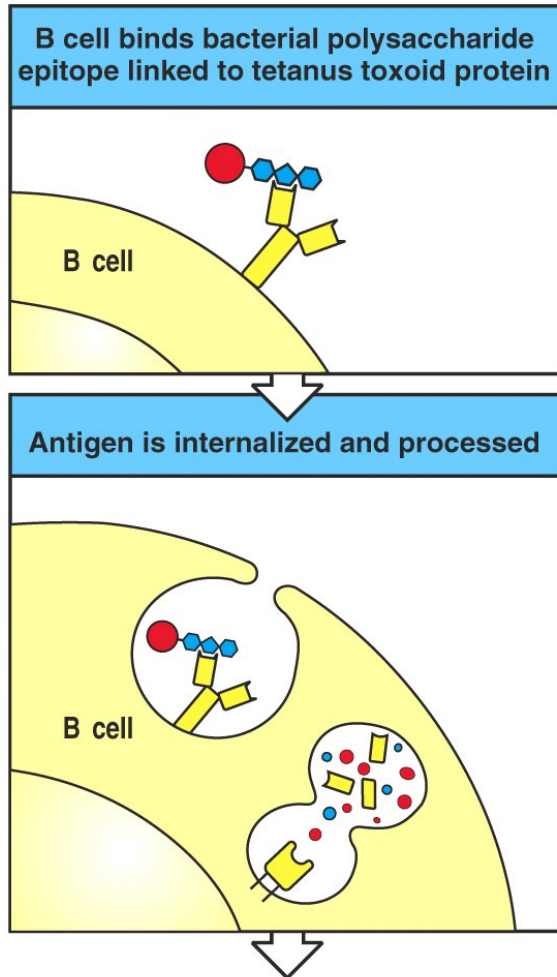
- Polysaccharides alone will activate B cells in a thymus-independent manner resulting in IgM production, little/no class switching, and little/no development of memory cells
- One way to involve CD4+ TH cells directly is to **conjugate the polysaccharide antigen to a protein carrier**

Immune Response to Conjugate Vaccines

- **B cells** can recognize all types of antigens in native configuration – proteins, polysaccharides, lipids, etc.
- **T cells** only recognize proteins (that have been processed and presented in the context of MHC molecules)
- **B cells need to T cell help** to become activated and produce antibody
- Additionally, B cells and T_H cells must recognize epitopes from the **same molecular complex** to interact (called 'linked recognition')
- **B cells and T cells work together**

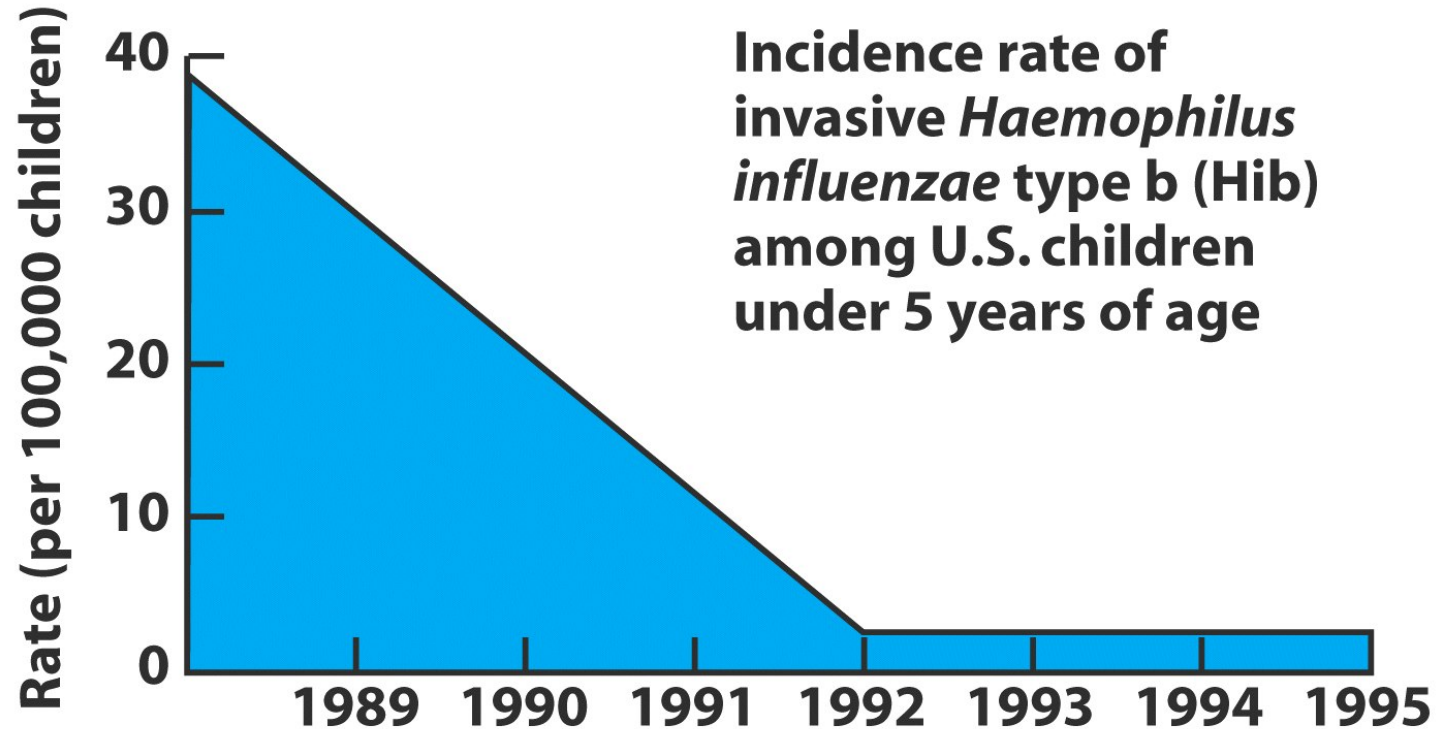
Immune Response to Conjugate Vaccines

- Linked recognition is important for the **regulation** and **manipulation** of the humoral immune response – polysaccharide epitope + protein



- Protein antigens attached to polysaccharide antigens allow T cells to help polysaccharide-specific B cells

Conjugate vaccines activate both B cells and T cells



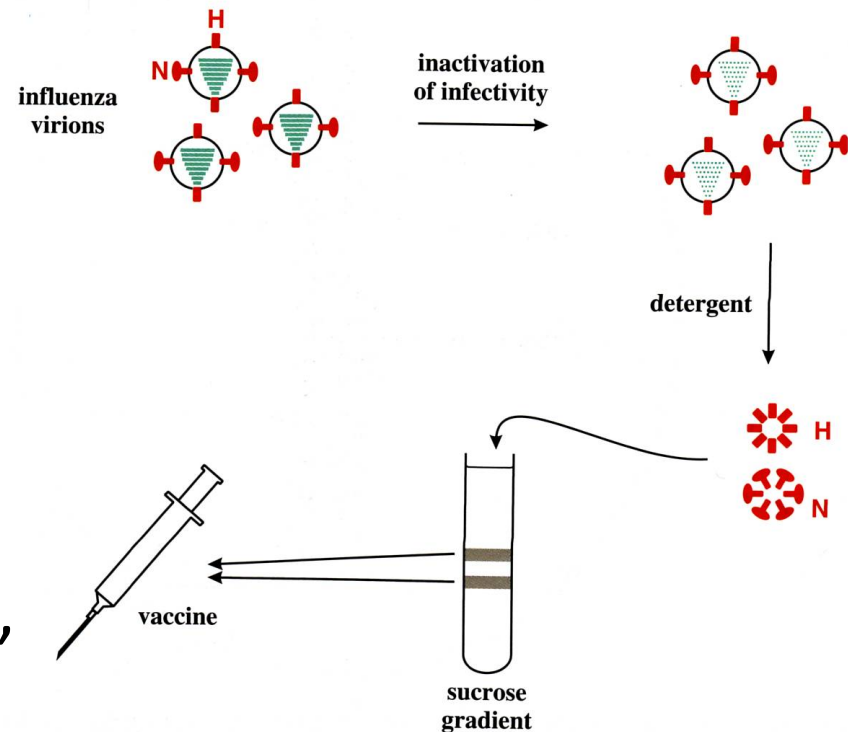
Kuby Immunology 6e WH Freeman

- The vaccine for *Haemophilus influenza* type b (Hib) consists of type b capsular **polysaccharide covalently linked to a protein carrier**, tetanus toxoid
- The tetanus toxoid proteins activates TH cells, enables class switching, and induces the formation of memory B cells

Subunit vaccines

example: acellular pertussis vaccine

- Rather than giving a whole pathogen, fragments of the pathogen can be used to trigger specific immune responses
- Subunit vaccines contain purified components of pathogens that are combined to form the vaccine
- Only the outer 'surface antigens' are used for subunit vaccines – this is the portion of the pathogen the immune cells would encounter
- DtaP (ped) and Tdap (adult) vaccines contain the following antigens depending on manufacturer; pertussis toxin (PT)*, filamentous hemagglutinin (FHA)*, pertactin, fimbriae types 2 & 3



Carter & Saunders Virology, Wiley – basic strategy for a subunit vaccine. Example here is the subunit formulation of the annual influenza vaccine.

Immune Response to Subunit Vaccines

- Because subunits (or pieces of pathogen) are administered these types of vaccines are **typically not as immunogenic as whole pathogens** – **booster doses are often needed** to be completely effective
- The immunogenicity is often determined early in vaccine design studies and the most highly immunogenic are chosen
- However, **choice of antigen is limited to antigens expressed on the outer surface of the pathogen**
- DtaP/Tdap is also an example of a combination vaccine that contains purified toxoid components from tetanus and diphtheria

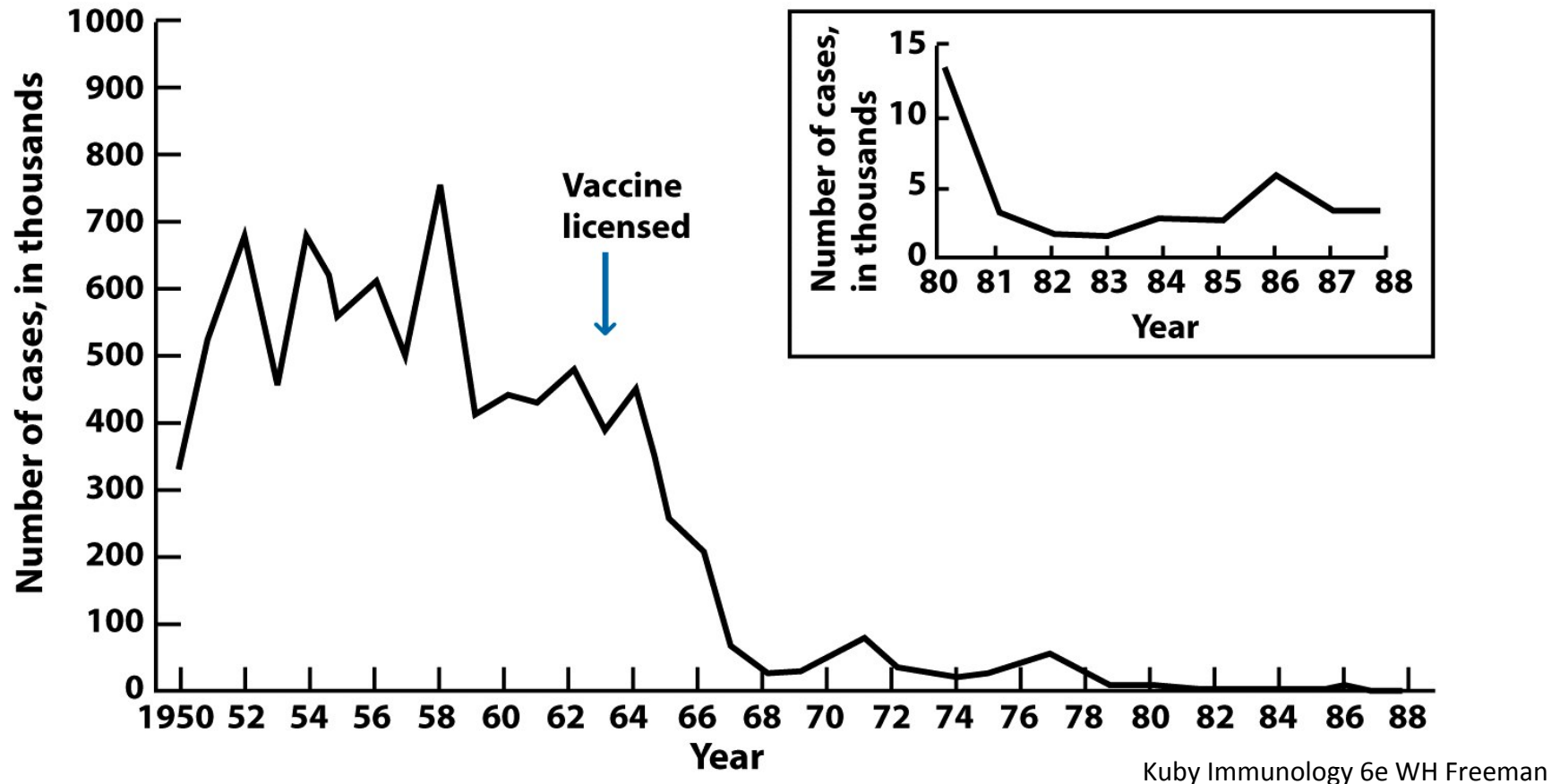
Herd Immunity

If the majority of the population is immune to an infectious agent, the chance of a susceptible (unvaccinated) individual contacting an infected individual is so low that the susceptible person is not likely to become infected

Those that are vaccinated ‘protect’ those that are not vaccinated* by not becoming sick and not spreading the disease

*infants too young for a particular vaccine or immunocompromised individuals (HIV+, undergoing chemotherapy, immunodeficiency, transplant patients) that can't safely be exposed to a vaccine

Introduction of measles vaccine in 1962 led to a dramatic decrease in the annual incidence of measles in the US



- Occasional outbreaks have been observed - in the 1980s measles epidemics appeared as a result of unvaccinated preschool age children – a breakdown in ‘herd immunity’

Potential Risks of Vaccination

- **Any vaccine can cause side effects** – most are minor (e.g. soreness at injection site or low-grade fever) and go away within a few days
- A vaccine, like any medicine, could cause a serious reaction but the risk of a vaccine causing serious harm, or death, is extremely small
- For a complete list of potential risks associated with each vaccine visit the **CDC website** on 'Vaccinations & Immunizations' under 'Possible Side-effects from Vaccines'

In the context of the immune response:

- **swelling, redness and soreness at the injection site** are due to the influx of monocytes and lymphocytes recruited to the site of vaccination, which is part of a normal immune response
- **fever** is most likely due to the activation of immune cells and the subsequent release of pro-inflammatory cytokines that aid in the inflammatory response

Guillain-Barre' Syndrome (GBS)

- **A rare autoimmune disorder** in which a person's own immune system damages the nerves causing muscle weakness and sometimes paralysis
- **Most people recover fully from GBS** - symptoms can last for a few weeks or several months
- Although the causes of GBS are not fully understood, it is known that ~2/3 of people who develop GBS have been sick with diarrhea or an illness of the lungs or sinuses
- An infection with the bacteria *Campylobacter jejuni*, which can cause diarrhea, is one of the most common illnesses linked to GBS
- In very rare cases GBS may develop in the days or weeks after getting a vaccination – in 1976 there was a small increased chance of GBS after the flu vaccine (1 more case per 100,000)
- **It is more likely to develop GBS after a natural infection than after receiving a vaccine**

Vaccination is the most cost-effective ‘weapon’ for disease prevention

Colorado needs a ‘shot of education’ about vaccines

Aimee Bernard - Colorado Health Foundation Health Relay blog in April 2012
written in response to ‘Prevention: Strong Investment in Colorado’s Health’ the
supplement to the ‘2011 Colorado Health Report Card’

“Oddly, vaccines are a victim of their own success. In this day and age in the United States, we rarely see the diseases that vaccines prevent, which may actually be part of the problem – **the general public hasn’t seen these horrific diseases (e.g. polio, smallpox) in quite some time because vaccines work.**”

Colorado Children's Immunization Coalition

'Team Vaccine' blog

www.teamvaccine.com

'Immunology 101 Series'

- Understanding the Immune System & How Vaccines Protect Us
- 5 Ways Vaccines are Made
- The Process of Making Safe & Effective Vaccines
- Herd Immunity
- What's the Deal with Combination Vaccines and Booster Shots
- Do Too Many Vaccines Too Soon Overwhelm the Immune System? No!
- Why Mild Side Effects (after vaccination) are a Good Thing

References

- Kuby Immunology. WH Freeman.
- Janeway Immunobiology. Garland Sciences.
- Dr. Rachel Herlihy “Delayed, Selective and Alternative Vaccine Schedules” talk given on September 10, 2012
- CDC Pink Book ‘Epidemiology and Prevention of Vaccine-Preventable Diseases’ 12e
- CDC website ‘Vaccines & Immunizations’ and ‘Possible Side-Effects from Vaccines’
- CDC website ‘Fact Sheet: Guillain-Barre’ Syndrome’

Thank you!

Aimee.Bernard@ucdenver.edu

Why do we need a flu vaccine every year?

- Influenza viruses are constantly changing and it is not unusual for new strains to emerge each season. The circulating influenza viruses are analyzed each year to determine which strains are most common and should be included in the current vaccine.

How does the flu virus change?

- **Antigenic shift** – a major change in one or both surface antigens (H or N) due to genetic recombination – it is a segmented virus that can recombine if 1 cell is infected with two viruses having different H and N antigens
- **Antigenic drift** – a minor change in surface antigens that results from point mutations in a gene segment
- **Both can alter surface antigens and the immune response**