How Vaccines are Made

And What's In them

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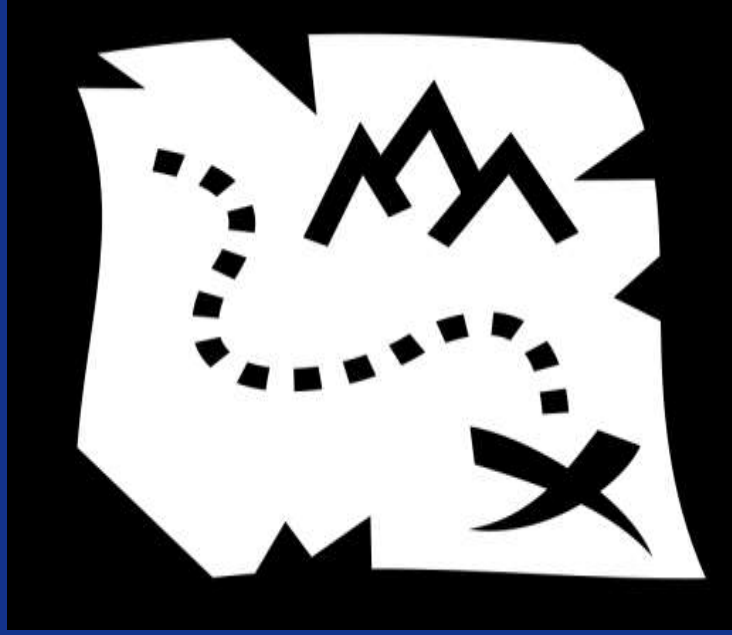
Road map



- What's in that Vaccine there?
  - Antigens / epitopes
  - Maybe adjuvant
  - Minimal preservative use
  - Excipients, solubilizers
- Processes for development and safety monitoring
  - 4 Phase to get FDA approval
  - Vaccine safety
    - During 4 phases
    - Post marketing surveillance
    - VAERS, CISA
- Local Vaccine Uptake Tidbit

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Pertussis Containing Combo Vaccine 1

Pediarix® (GlaxoSmithKline)

- Diphtheria toxoid 15 Lf , tetanus toxoid 5 Lf
- IPV - 40DU Type 1, 8 DU Type 2, and 32DU Type 3
- aP antigens = 10 µg detoxified PT, 5 µg FHA, 3 µg pertactin, and 5 µg FIM 2 and 3
- **10 µg HBsAg**
- Aluminum salt adjuvant (≤ 0.85 mg aluminum)
- Neomycin (≤0.05 ng) and polymyxin B (≤0.01 ng) – IPV manufacturing process
- Residual formaldehyde ≤100 µg; solubilizer ≤100 µg
- NaCl 4.5 mg
- ≤5% yeast protein - HBsAg manufacturing

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Pertussis Containing Combo Vaccine 2

Pentacel® (Sanofi Pasteur)

- Diphtheria toxoid 15 Lf, tetanus toxoid 5 Lf
- IPV- 40DU Type 1, 8 DU Type 2, and 32DU Type 3
- aP Ags - 20µg detoxed PT, 20µg FHA, 3µg pertactin, 5µg FIM
- **PRP-T = Hib PRP 10µg covalent to tetanus toxoid 24µg**

- $AlPO_4$ adjuvant (0.33 mg aluminum)
- Neomycin <4 pg, and polymyxin B <4 pg
- Residual formaldehyde ≤5 µg, glutaraldehyde <50 ng, and bovine serum albumin ≤50 ng

- Sucrose 42.5 mg and solubilizer ~ 10 PPM
- 2-phenoxyethanol (non-preservative) 3.3 mg (0.6% v/v)

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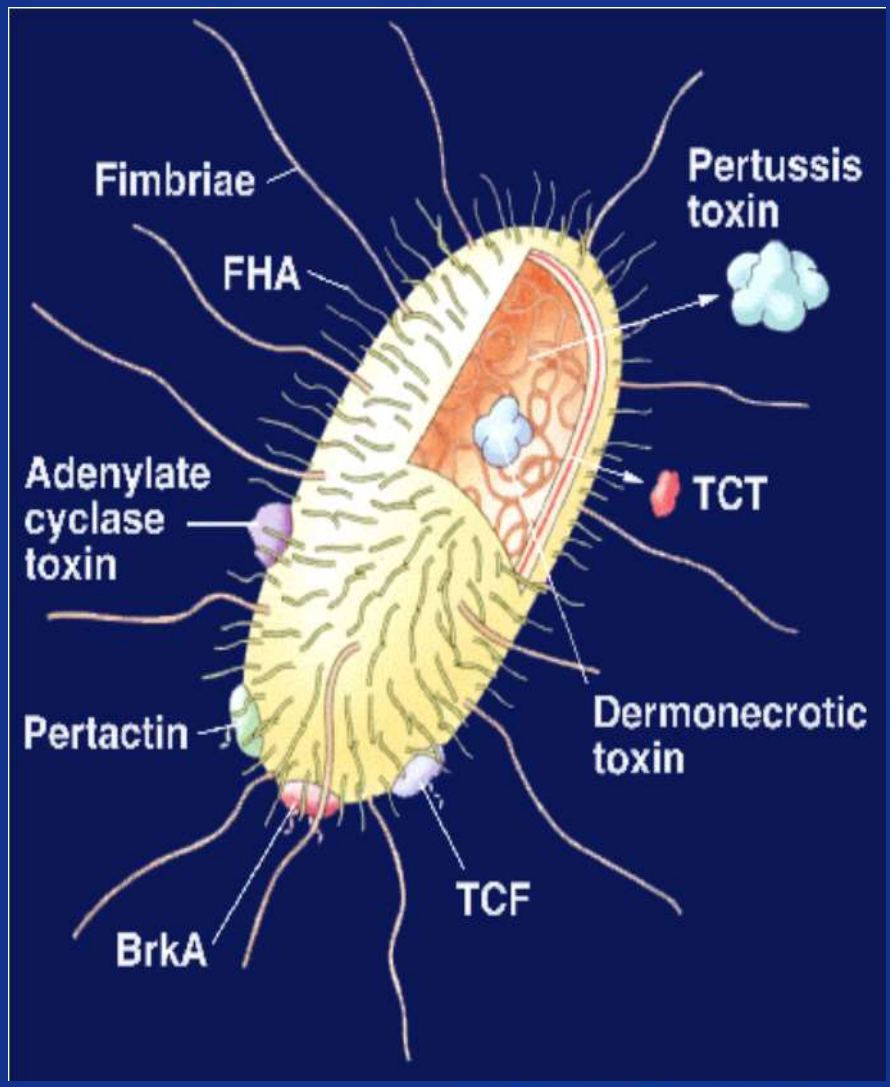
Pertussis and Antigen Targets

- Pertussis toxin (PT), also known as lymphocytosis- promoting factor (LPF)
- Filamentous hemagglutinin (FHA)
- Pertactin (PRN)
- Fimbrial agglutinogens (FIM)



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Antigens are “Active ingredients”

- Direct targets of immune response
- Goal
  - Induce protective immune response similar to post-disease without vaccine getting disease
- Epidemiology and immunology studies
  - To suggest best pathogen component
  - Best at inducing protective responses
- Screened in vitro and in animals
  - Minimize reactogenicity
- New processes
  - Computer predicted structures
  - Computer modelling immune responses

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Sources of Vaccine Antigens

1. Whole weakened live or inactivated viruses
   - MMR and varicella vaccines, IPV
   - Current influenza vaccines – LAIV and IPV
2. Detoxified toxins
   - Diphtheria and tetanus toxoids
3. Purified parts of wild type viruses or bacteria
   - Polysaccharide pneumococcal capsule (PPV23 or PCV13)
   - Pertussis component vaccines
4. Virus like particles (VLP)
   - HPV vaccines
5. Vector produced components
   - Baculovirus produced influenza vaccine
6. Genetically modified viruses
   - Experimental RSV and influenza vaccines

- New – assembled epitopes, 3D printing

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Inactivated Virus or Detoxified Toxin

- Examples: IPV, Hep A, IIV, and rabies vaccines
- Usually modified via chemical treatment
- Antigens still recognized and presented by immune system nearly the same as if on living virus or native toxins by the body
- Pros:
  - Killed viruses or toxoids cannot possibly cause infection
  - Viable options for those with weakened immune systems
- Cons:
  - Usually need multiple doses for reasonably durable protection

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Weakened vs Wild Type Virus

- In disease, wild type viruses multiply 1000s times
- Weakened viruses reproduce poorly once in host
  - Measles, mumps, rubella, rotavirus, VZV vaccines
- Vaccine strains usually multiply < 20 times
  - Sufficient to induce responses
  - Cell-mediated and antibody
- Whole virus more likely decades of immunity
  - Longer than most killed or sub-unit vaccines
  - Caveat for live vaccines :
    - Usually not for those with weakened immune systems

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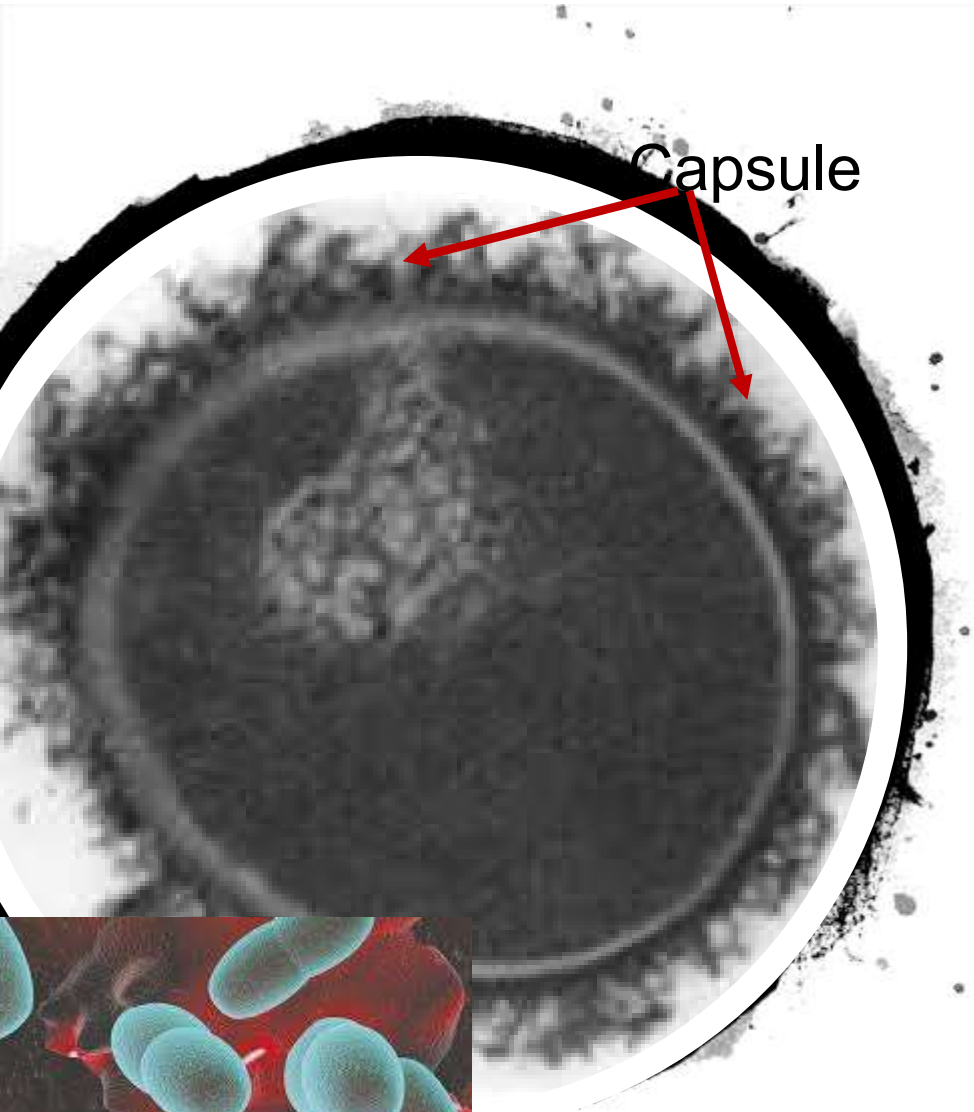
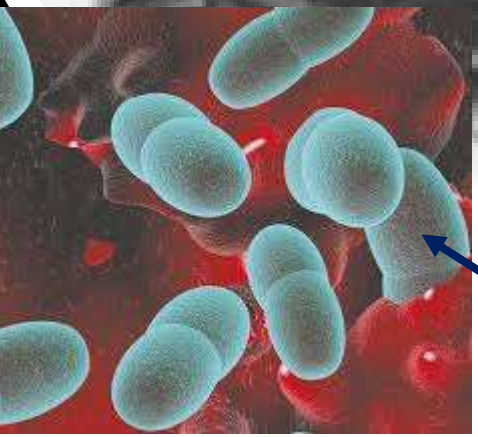
Polysaccharide Capsule of Pneumococcus





Diplococcal form

- Bulk cultures
  - Billions of organisms
  - Each serotype of interest
- Capsule stripped
  - Each serotype
- Purified – unconjugated capsular antigen is B-cell dependent
  - Not boostable – short lived
  - PPsP23
- Conjugated - protein/peptide
  - Makes it T-cell dependent antigen
  - Boostable – more durable
  - PCV7, PCV13, PCV20

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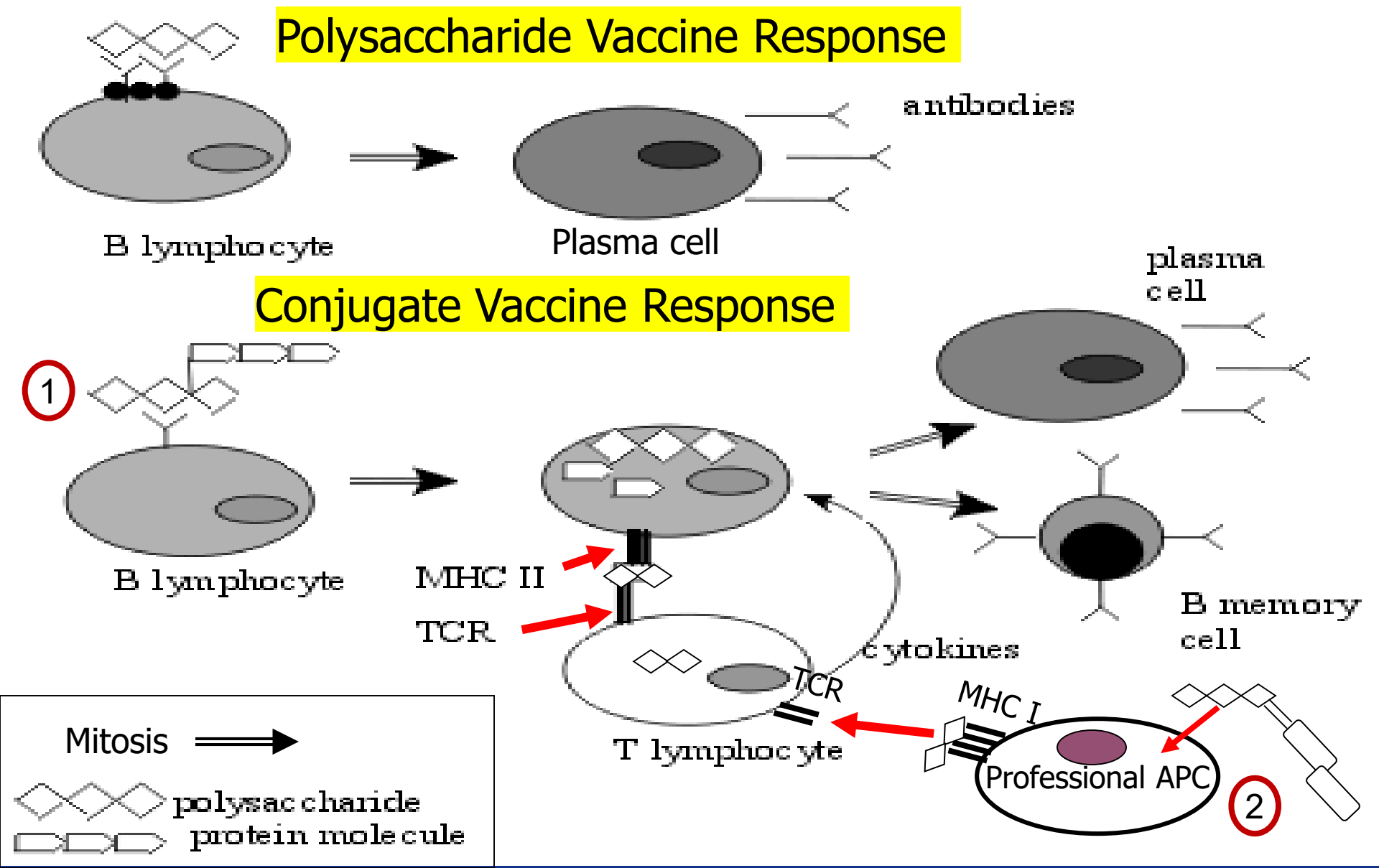
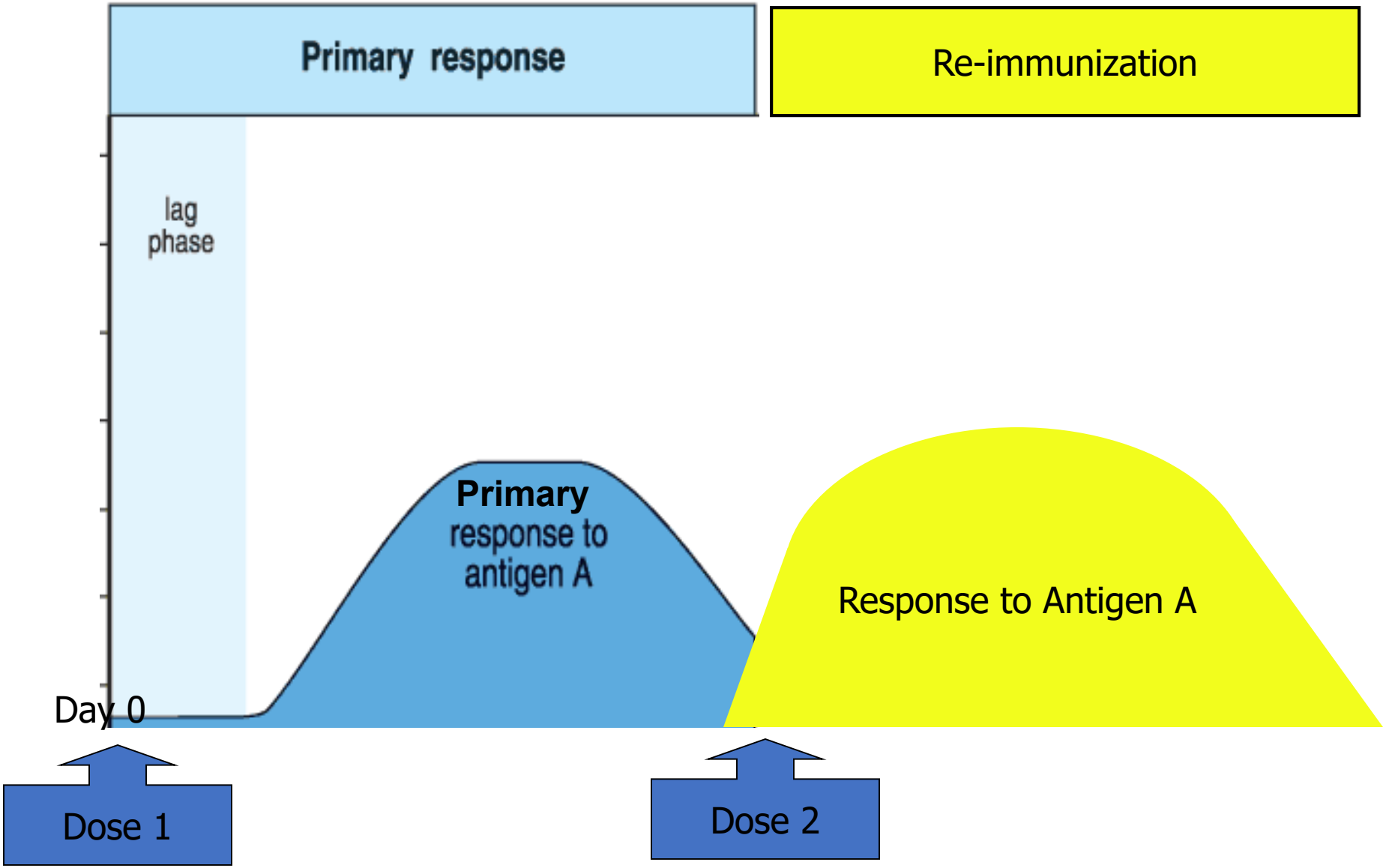
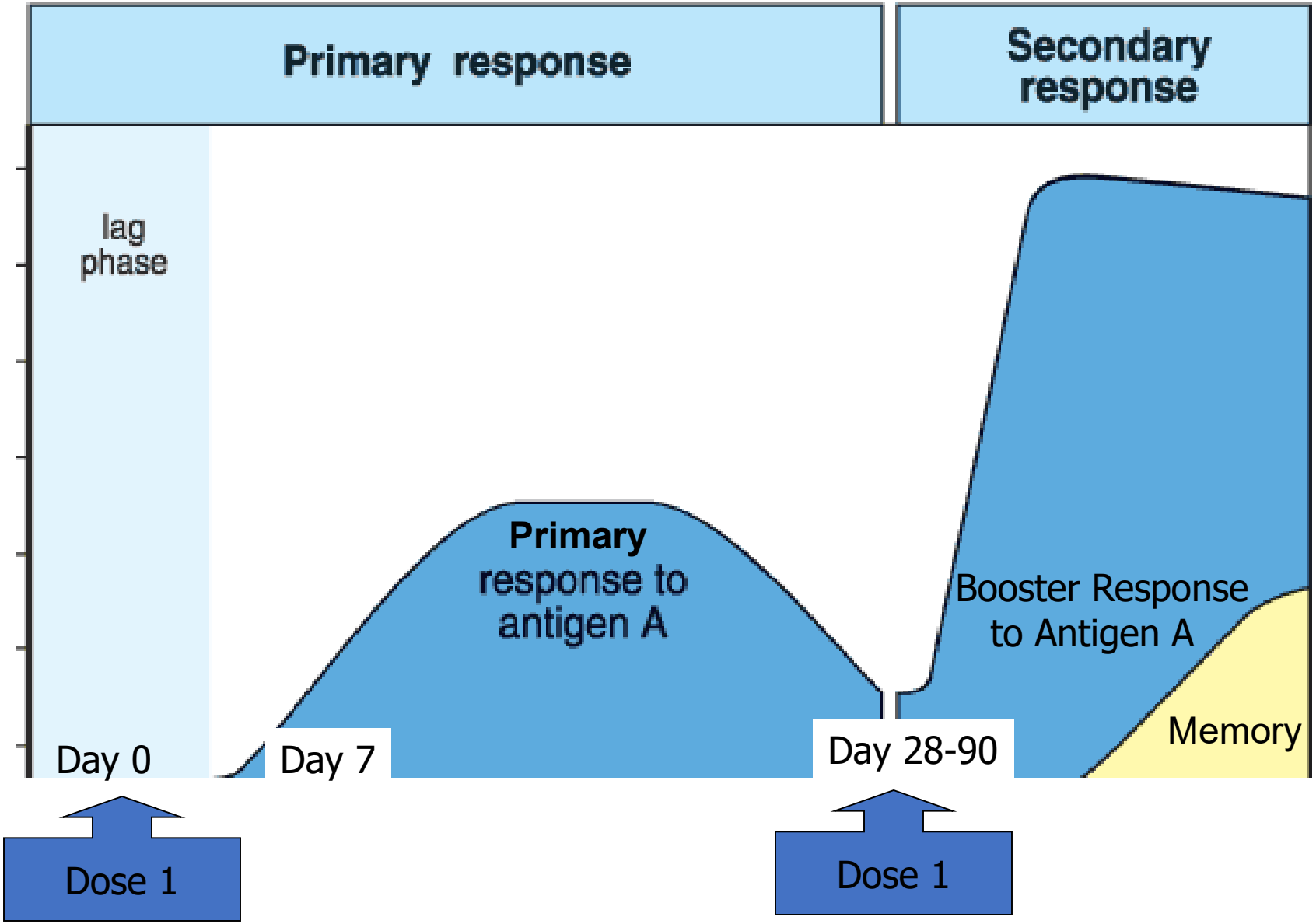
Why Conjugate an Antigen?



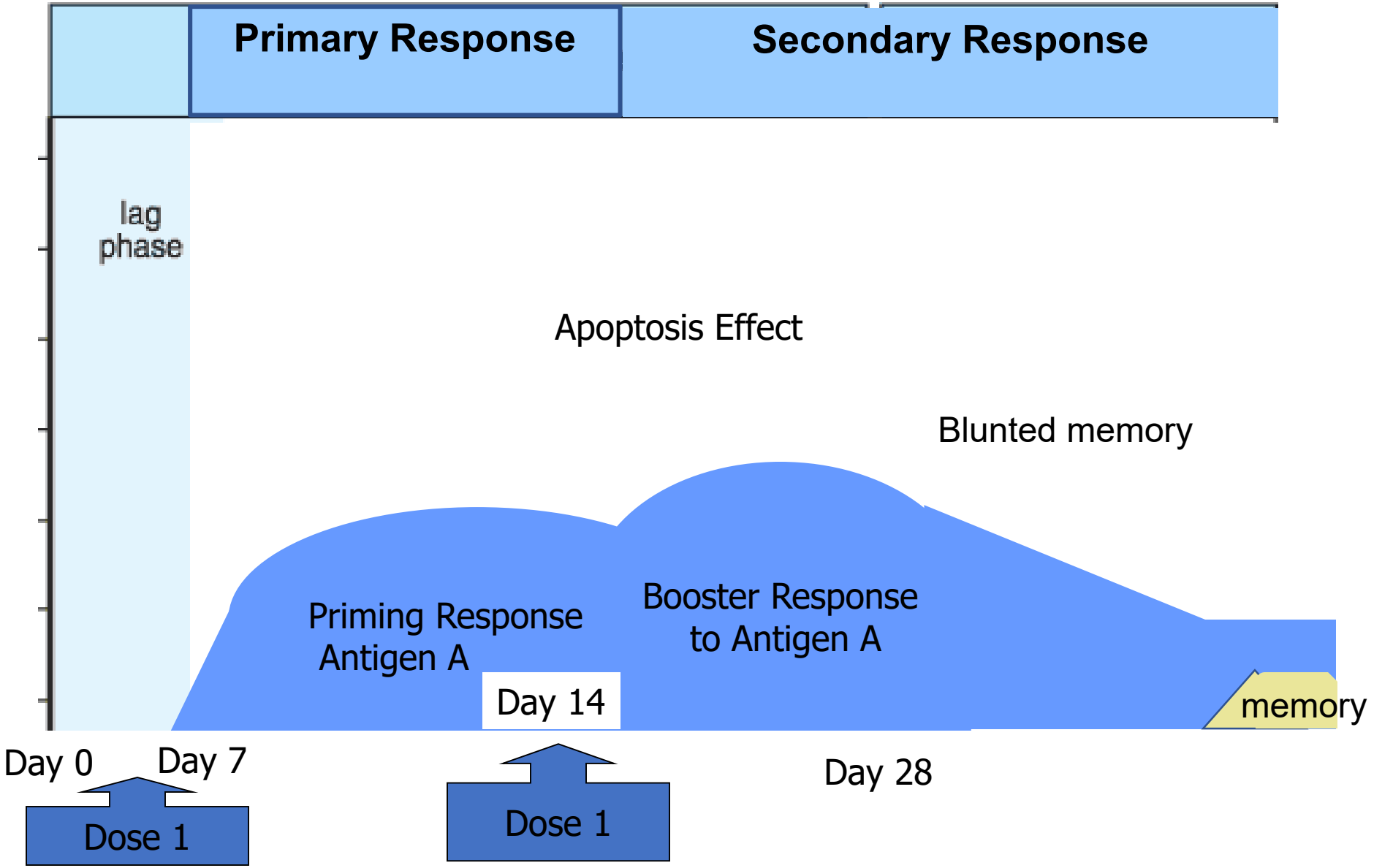
Antibody response After Re-Immunization
T-cell Independent Response (Polysaccharide)



Antibody Response to Booster Vaccine: T-cell Dependent Response (Peptide)

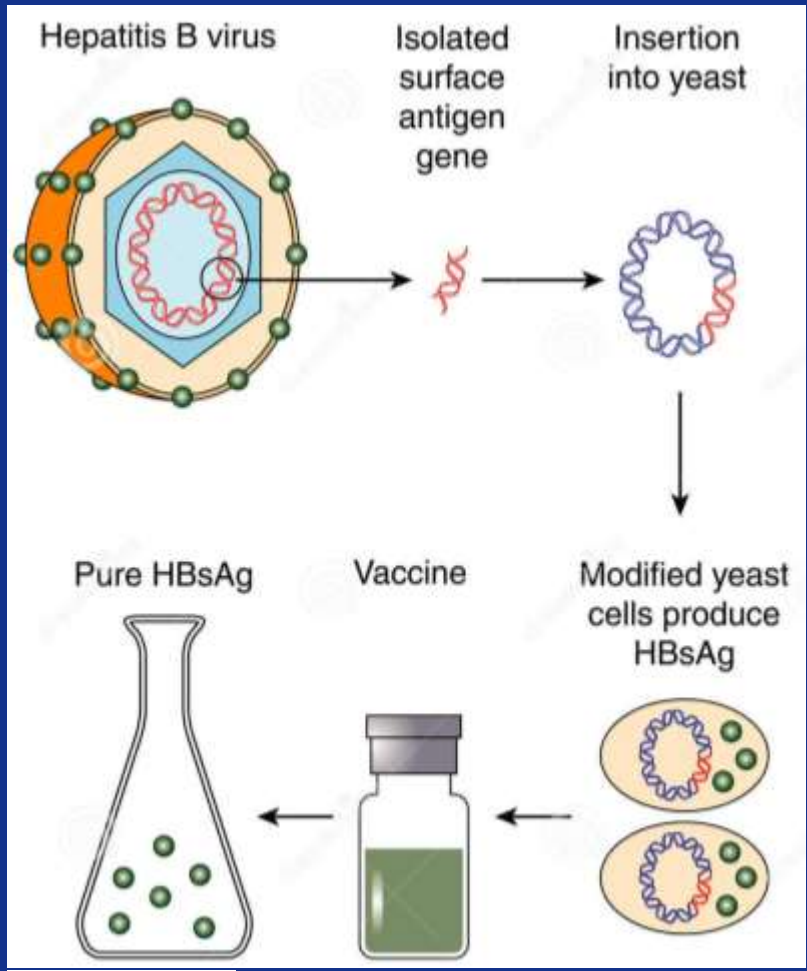


Caution: Antibody Response to Too Early Booster Dose: T-cell mediated Response (Peptide)



Purified or Genetically Engineered Ag

- Pathogen component or sub-components
- Examples: Hep B, pertussis, or HPV
- Response to a particular antigen is known target of protective immune responses
- Pros:
  - Generally less reactogenic
  - No chance to cause targeted infection
  - OK with weakened immunity
- Cons:
  - Need multiple doses
  - Often need adjuvants for durable protection
  - Extra steps in production adds expense



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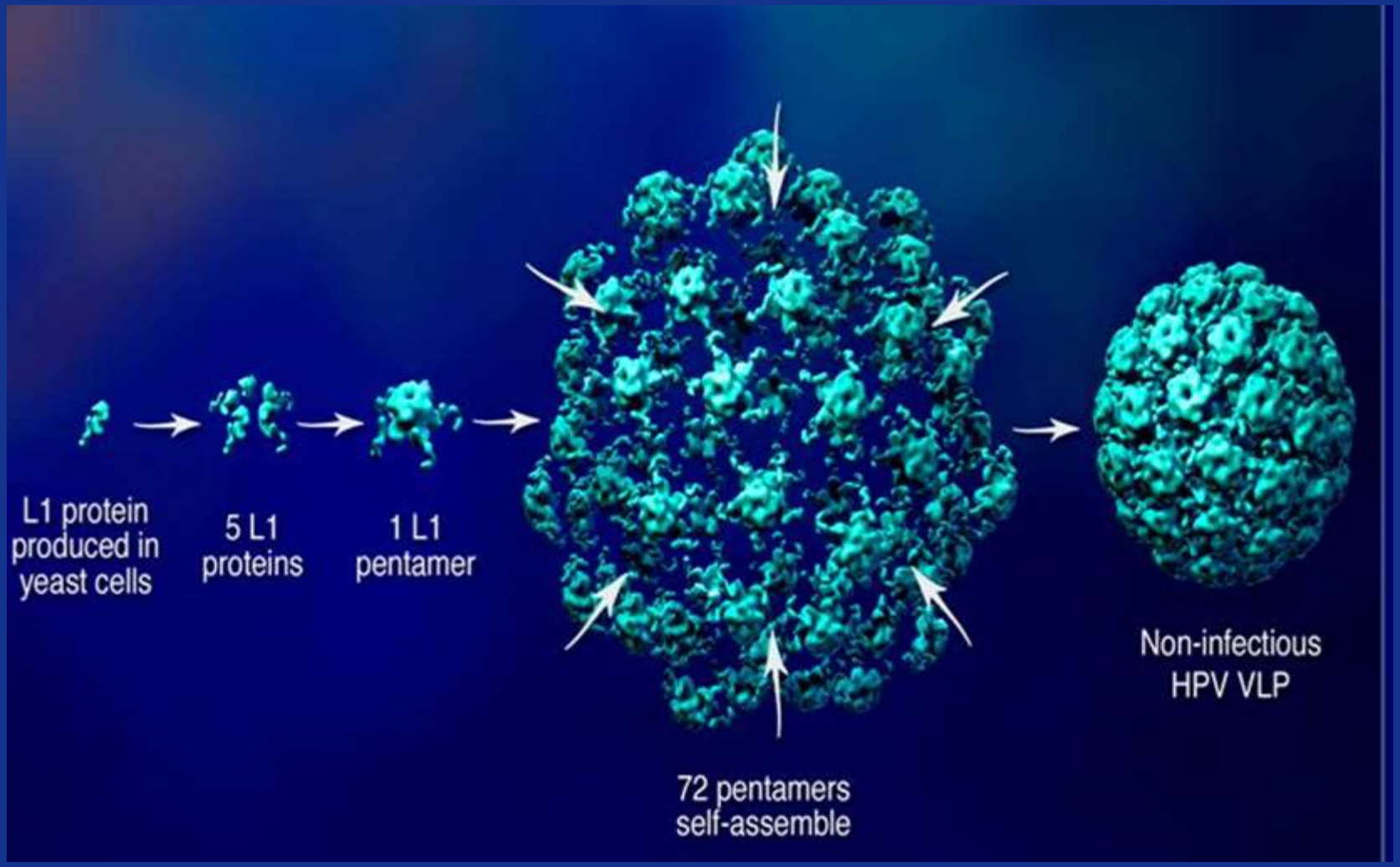
HPV Vaccine Imitates Infectious Virion



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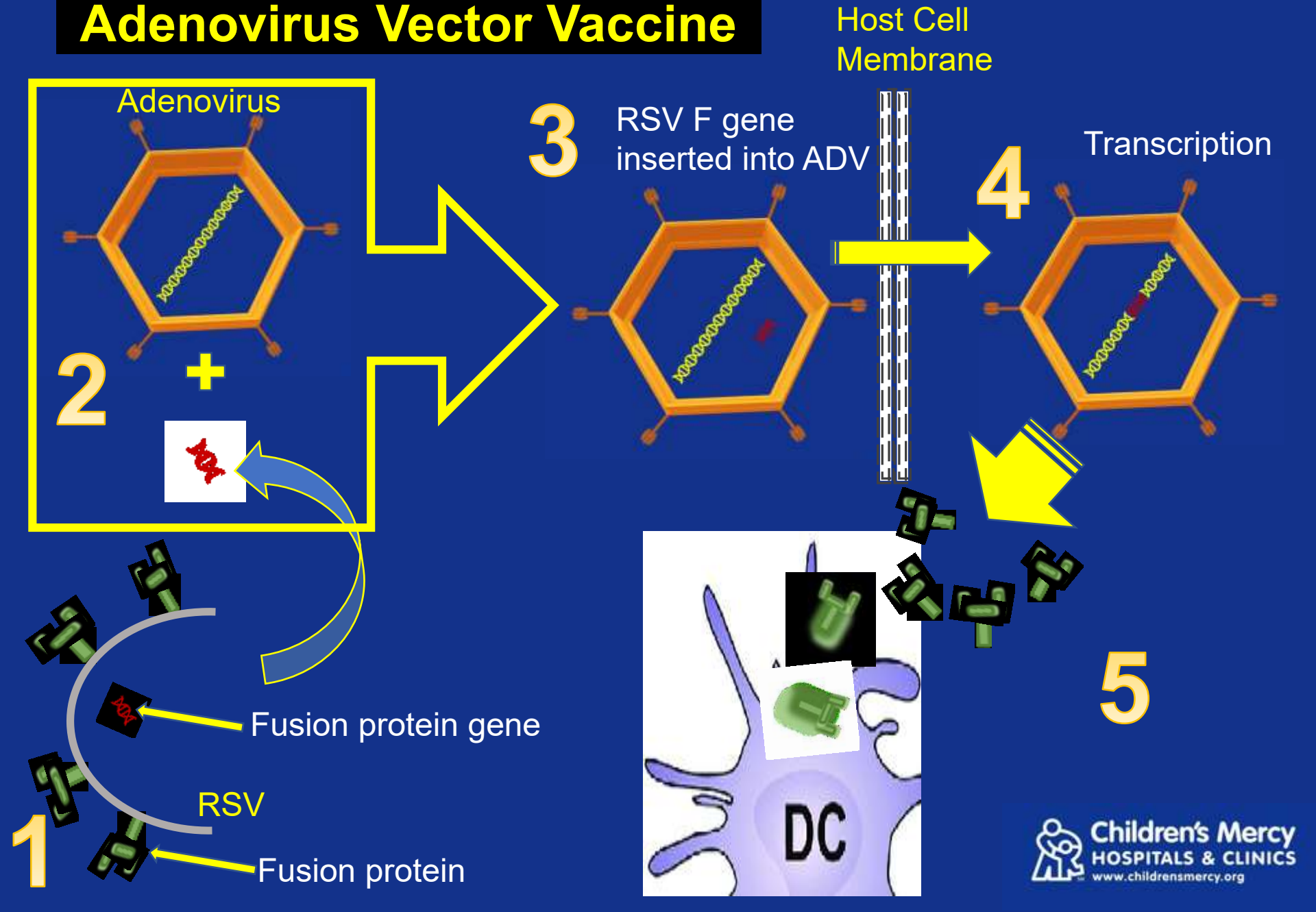
RSV Fusion Protein Adenovirus Vector Vaccine



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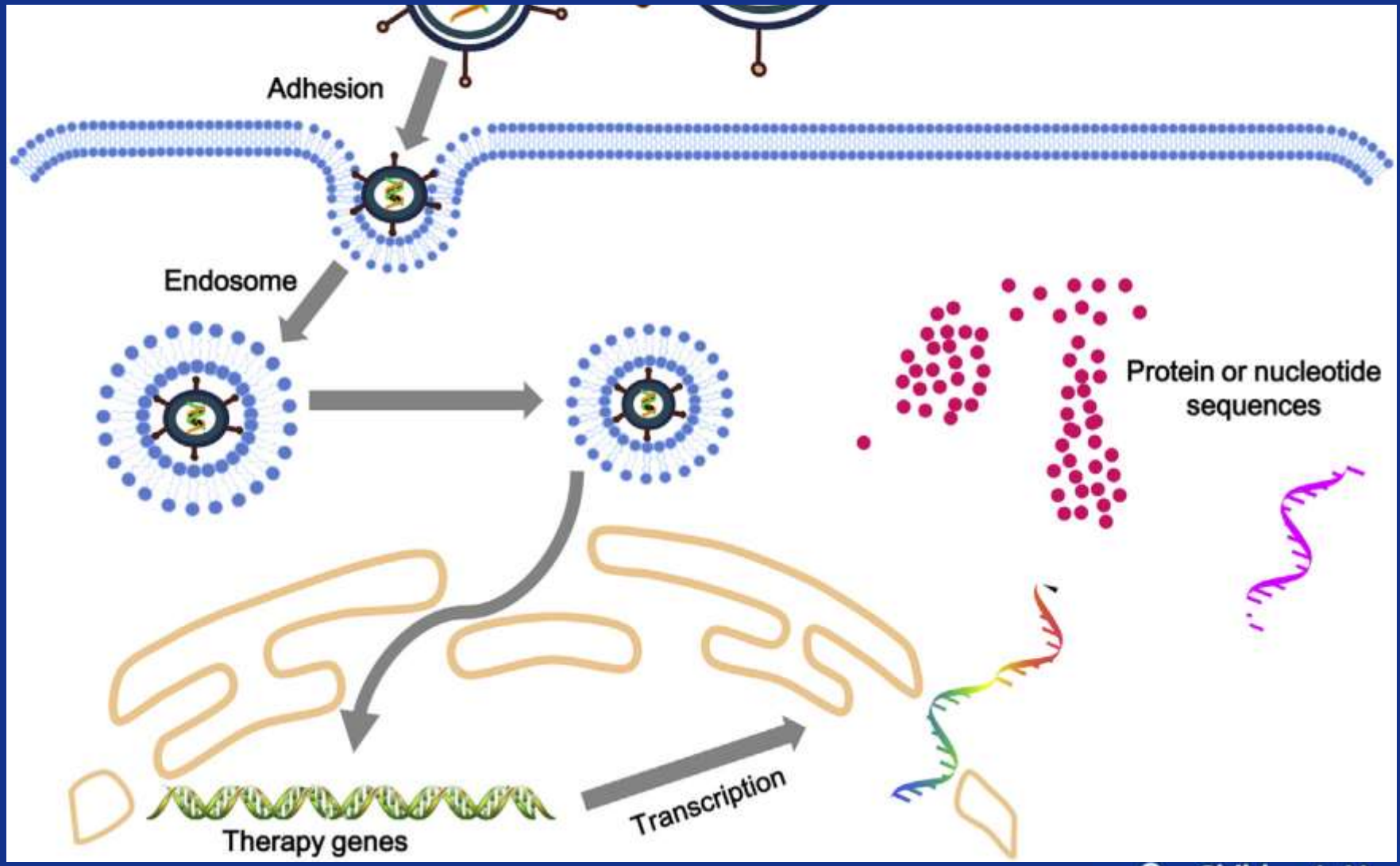
Viral vector Vaccine Post Administration



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What's an Epitope?

- Ideally vaccine-induced immune responses :
  - Targeted to be as selective and specific as possible
  - Less non-targeted material means less likely to induce damaging responses
- Epitope is the small precise sequence within an antigen that is the specific target of immune response
  - Sometimes as little as 5 amino acids
  - Antibody may have different targets than T-cells
  - Different antibodies induced by same antigen may target different epitopes - some neutralizing and some not
- Immune "geography"
  - Pathogen is a city block
  - Antigen is a building
  - Epitope is a section of the building

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Job of Immune System: Deconstruct pathogen to get the Correct Target

- Break city block into buildings
  - May use non-immune body functions
    - Apoptosis – rupture infected cells
    - Enzymes digest proteins, lipids and polysaccharides
- Antigen presenting cells (APC)
  - Ingest pathogen or pathogen parts - antigens
  - Shuttle pathogen parts to correct intracellular compartment
- Break building into parts (epitopes)
  - Lysosomes, endosomes, etc
  - Like micro septic tanks
  - Make ready for adaptive immune recognition

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Epitope Simile – mutation effect

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Adjuvants

- Non antigen substances purposefully added to vaccines
- Possible benefits
  - Increase host responses
  - Decrease amount of antigen needed
  - Decrease number of doses
- Possible detriments
  - May increase reactogenicity
  - May trigger unwanted immune response
  - Mya reduce public acceptance of vaccine

Wack A, Rappuoli R. *Curr. Opin. Immunol.*17(4), 411–418 (2005).
O'Hagan DT, Valiante NM. *Nat. Rev. Drug Discov.* 2(9), 727–735 (2003).
https://www.fda.gov/syn/html/ucm187810

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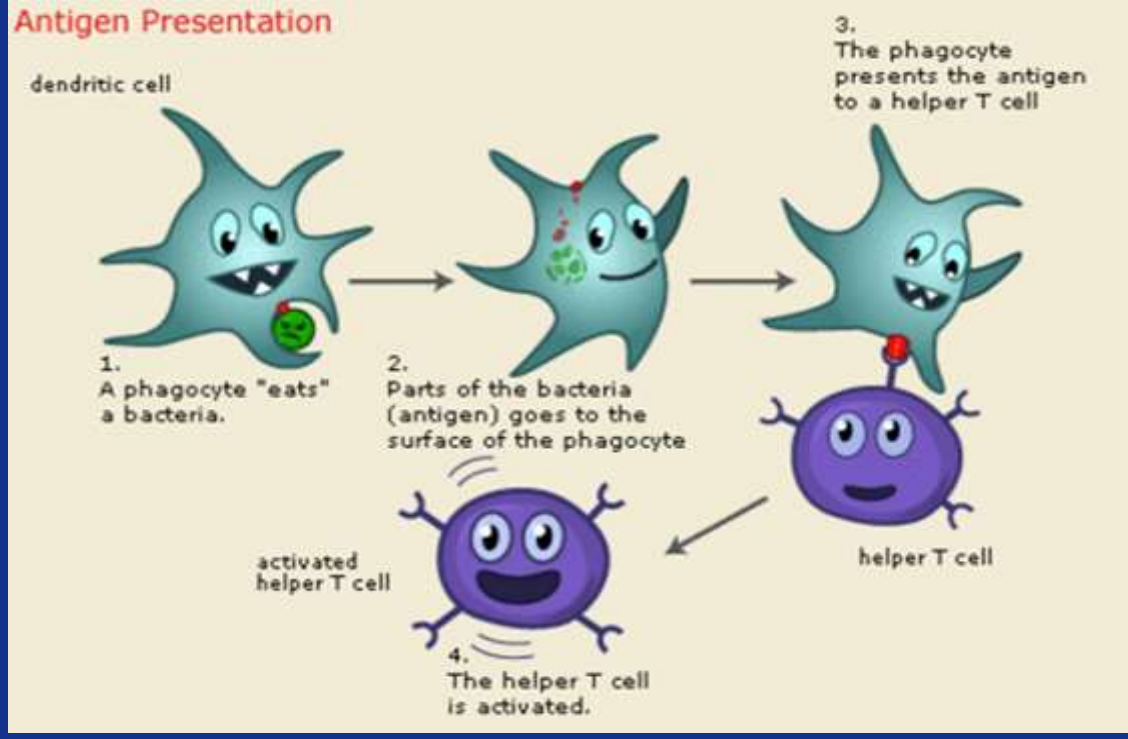
Adjuvants

Kono H, Rock KL. *Nat. Rev. Immunol.*8(4), 279–289 (2008).
McKee AS, et al *BMC Biol.* 8, 37 (2010).



- Persistent antigen depots

OR

- Trigger innate immune responses that groom adaptive immune responses
  - Engage pathogen-recognition receptors, TLRs
    - Increase antigen presentation efficiency
  - Accelerate and amplify
    - $CD4^+$ T-helper (Th) lymphocyte responses (Th1 or Th2)
    - $CD8^+$ CTL responses
  - Can alter type of antibody that is produced

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FDA Approved Adjuvant Types

- Aluminum salts e.g. Hydroxide
- Liposomes – micro bags of fatty molecules
  - Imitate cell membranes – present antigen
  1. Monophoshoryl lipid A (MPL)
  2. Squalene oil-in-water emulsion
     - MF59 (Fluad® - vaccine > 65yo)
  3. QS-21 (Shingrix® with AS01B)
  4. ASO4 (Cervarix® w MPL + Al-OH)
     - No longer marketed
- Toll like receptor (TLR) agonists
  - Engage TLRs specifically to boost Ag presentation
  - Induce cytokines that facilitate T-cell “learning”
  - CpG 1018 in adjuvanted recombinant Hep B vaccine
    - (Heplisave-B®)

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Aluminum – Normal Origins?

- 3rd most common element in nature
  - 0.1-0.4% absorbed from GI tract
  - Citrate in diet increased absorption
  - Concentrated in tea, grasses, antacids
  - Cereals, nuts, dairy products, baby formulas, honey
- Air
  - 0.005–0.18 μg/m^3 (rural); 0.4–8.0 μg/m^3 (urban)
  - 2% absorption rate
  - Child averages 2 cubic meter air exchange /day
- Soil - 7-100 g/kg
- Surface Water - <0.1 mg/L

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Normal Levels of Aluminum

- Total body burden in healthy person = 30–50 mg
  - ~50% in skeleton and 25% in lungs
  - Levels in bone tissue = 5-10 mg/kg
    - Healthy 10 kg child has ~75mg in whole body
  - Serum normally has 1 to 3 µg/L
    - Healthy 10 kg child has ~100ug in serum
- Daily intake ave = 7-9 mg/day
- Daily absorption = 7-12 mcg absorbed
- Renal excretion ~95%
  - ½ life ~100 days

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Adjuvanted vs Non-Adjuvanted Influenza Vaccine: Antibody in Peds

- Vaccine #1 adjuvanted, N=464
  - 1.875 µg HA in GSK AS03B split-virus
- Vaccine #2 non-adjuvanted, N=469
  - 7.5 µg HA in Baxter whole-virus vaccine
- After 2 doses

	% Seroconversion	
	< 3YO	>3YO
#1 Vaccine	98.2	99.1
#2 Vaccine	80.1	95.9
	P<0.001	P=0.03

Rates of 1:40 HAI antibody were similarly superior in #1 vs #2, P<0.001

Waddington C, et al. BMJ 2010. DOI: 10.1136/bmj.c2649

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Aluminum- Infant Vaccines vs Diet

- In 1st 6mos of life
  - Vaccine burden* 4.4mg
  - Breast-feeding ~7 mg
  - Cow milk based formulas - ~38 mg
  - Soy formula = ~117 mg
  - Absorbed from regular diet ~ 2 mg
- Aluminum in any given dose of vaccine
  - No rise in base level in blood
  - Even immediately after an injection

* Hep A, Hep B, DT-containing, Hib, and PCV vaccines

1. Keith et al. Aluminum toxicokinetics regarding infant diet and vaccinations. Vaccine. 2002;20:S13-S17.
2. https://www.publichealth.org/public-awareness/understanding-vaccines/goes-vaccine/

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Preservatives - In some vaccines

- Prevent bacterial or fungal contamination
- History:
  - FDA required since 1930s after incidents in early 20th century
  - Multi-dose vials inadvertently contaminated
  - 1916 - contaminated typhoid vaccine
    - 4 children died, 26 local abscesses, and 68 severe systemic *S aureus* infections
- Thimerosal, a mercury-containing preservative
  - Intense scrutiny by U.S. Congress, media and anti-vacciners
  - No longer (since 2001) in any routine pediatric vaccine
  - Exception - multi-dose IIV vials
- No evidence that thimerosal ever caused long term sequelae in humans
  - Other than acute hypersensitivity

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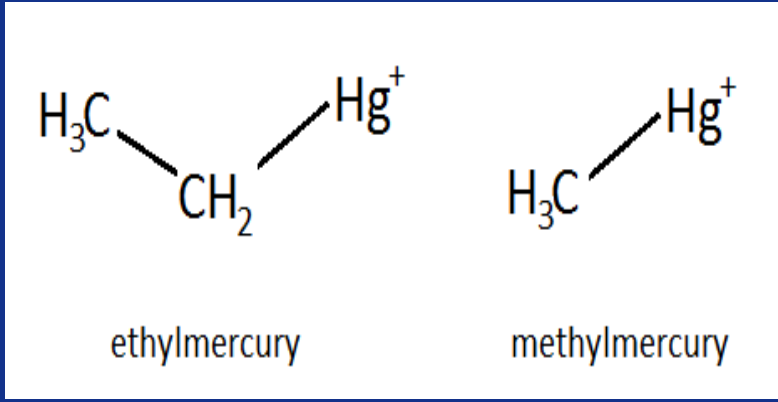
Forms of Mercury

- Elemental – “Quicksilver”
  - Liquid mercury
  - Old thermometers, fulminate, special lights button cell batteries
- Inorganic mercury
  - Hg salts, e.g. O_2 or sulfur
  - Manufacturing other chemicals (antiseptics, fungicides, disinfectants
- Organic mercury
  - Hg combines with carbon forms
  - Mainly 2 forms
    - Methyl mercury - fish and diet mostly
    - Ethyl mercury - thimerosal



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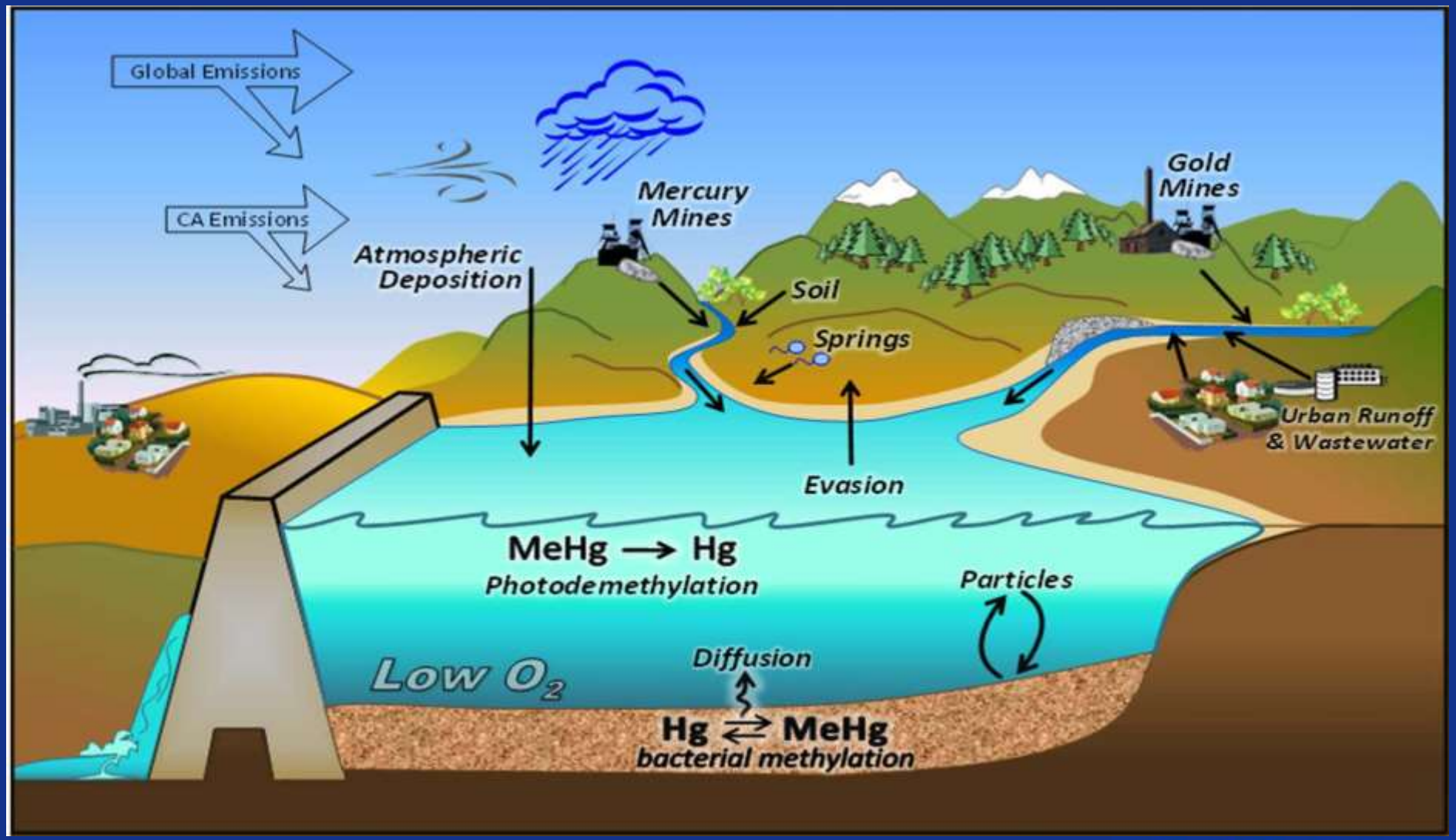
Many Sources of Methyl Mercury



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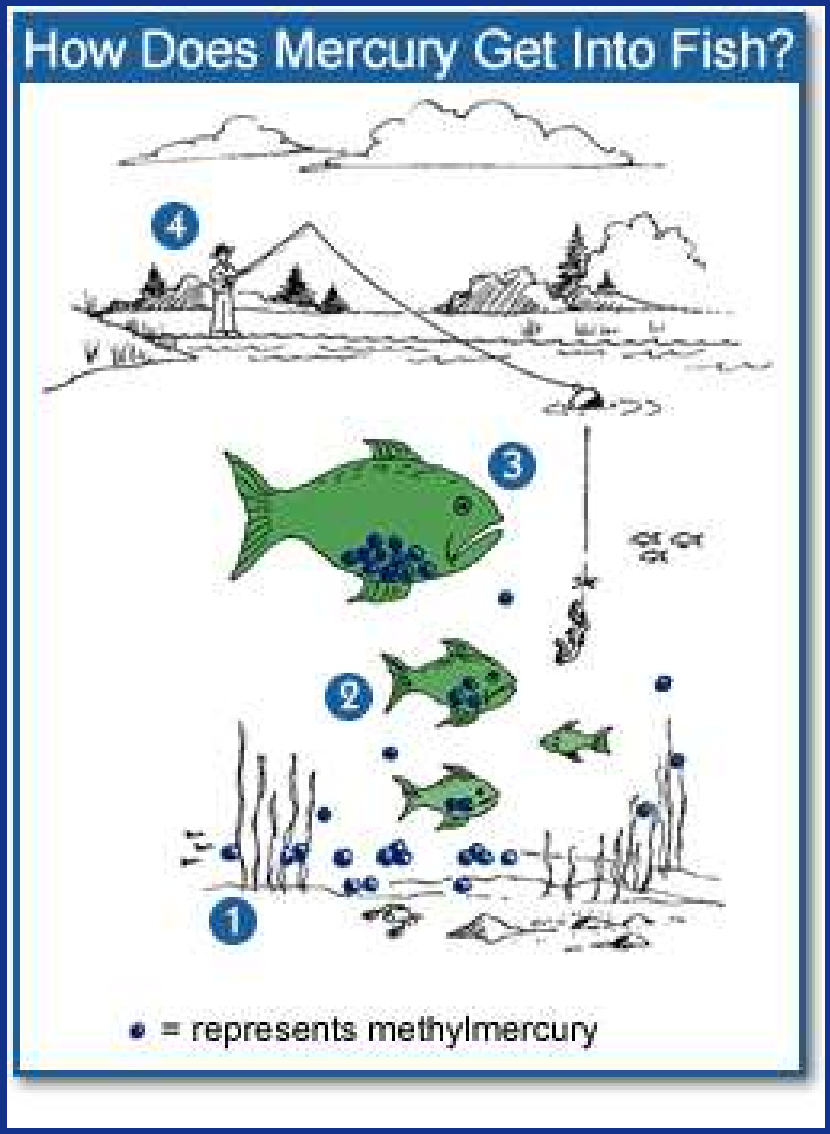
Methyl Mercury

- When elemental mercury interacts carbon in environment
  - High levels can be very toxic
  - Fetus highly susceptible
  - Body has limited ability to break down or eliminate methyl form
  - Natural source - fish/shellfish and fish eating animals, but can be in air
  - Pregnant women advised to limit Hg containing fish and shellfish
  - Tuna 5.6 oz can = 0.115 mcg/gm methylmercury
  - Breast milk: = 0.015 mcg/L methylmercury even with normal diet



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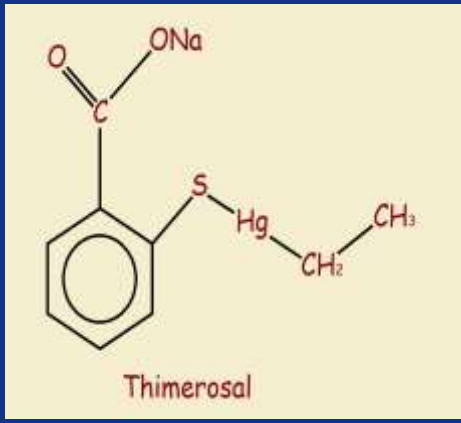
Ethyl Mercury from Thimerosal

- Byproduct in body of thimerosal – not methyl form
- Broken down and excreted from body much more rapidly
  - Much less likely to accumulate to toxic Hg levels or cause harm
- Multidose flu vaccine thimerosal =
  - 0.025 ethyl mercury mcg/gm
- 1990s
  - AAP suggested manufacturers make “safe vaccines safer”
  - Was and still is no evidence that thimerosal caused any harm
  - AAP wanted to be cautious and reduce even unwarranted concerns
- Over 1st 6 months of life, exclusively breastfed infants exposure
  - Even in 1980s breast milk had >2X mercury in all vaccines
  - Now, 15X mercury in breast milk vs 1 influenza multi-dose vaccine dose



Thimerosal

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Excipients

- Fillers
- Extenders
- Diluents
- Wetting agents
- Solvents
- Emulsifiers
- Flavors
- Coloring agents

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Excipients: Many Are Manufacturing By-products

- Antigen sources
  - Laboratory grown viruses or bacteria
  - Some by-products (chemicals and cell components) may remain in the final preps in minute quantities
- Some examples include
  - Antibiotics
  - DNA
  - egg proteins
  - Fetal tissues
  - Formaldehyde
  - Human proteins
  - Yeast proteins

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Formaldehyde: Other Side of Story

- Isn't formaldehyde used to embalm bodies? - eek!
- Produced naturally in body during
  - Energy related processes
  - Making amino acids
- Other sources
  - Ground water, meat, fish, plants
  - Building materials
  - Preservative in labs
  - Production of many household products
- By-product of vaccine production
  - Inactivate polio virus or detoxify diphtheria toxin
- Most removed during later vaccine production steps
  - Minute quantities remain in some vaccines
- Amount of formaldehyde naturally in body
  - 10X that in any vaccine
  - Not a safety concern

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Polyethylene glycol – Antifreeze?

- Antifreeze typically made of ethylene glycol
  - Ethylene glycol is unsafe
- Polyethylene glycol (PEG)
  - Used in personal care products
  - EXAMPLES: skin creams, toothpaste
  - Amount and form in vaccines is safe
    - <0.02%
- Used to inactivate influenza virus in some influenza vaccines
- Also used during antigen purification in some other vaccines

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Stabilizers

- Protect integrity of the active ingredients during manufacture, storage and transport
- Most common are:
  - Gelatin
  - Polysorbate 80 in HPV vaccine
    - Some claim it may cause infertility
  - Note:
    - Polysorbate 80 in use for decades
    - Emulsifier to make ice cream smooth and slow melting
    - 4oz ice cream has ~170,000 mcg polysorbate 80
    - HPV vaccine dose has 50 micrograms

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Safe Can Mean Different Things

- Is safe an absolute or relative term?
  - Safe = always harmless vs. safer than alternative
- No vaccine 100% effective or 100% safe
- Vaccine risks and side effects
  - Serious side effects are mostly rare
  - Mild side effects more common but self-limited
- Safety standard higher for vaccines vs drugs
  - Vaccines generally given to many, most of whom are healthy
  - Less risk tolerated from Hib vaccine than Abx that treat the disease

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Vaccine Licensure Process

- Years to decades before pharmaceutical companies can actually start providing the vaccine
  - Gaining FDA approval is longest step
  - VZV vaccine took ~11 years after IND granted to be licensed
    - Jokingly called “Never-vax”
- 1st step – 1-2 years
  - Show safety and effectiveness in animals
- 2nd step – 6 month – 2 years
  - Obtain Investigational New Drug (IND) license
  - Allows further study in adults and eventually, children
- 3rd step – 5-10 years
  - Conduct clinical trials to document safety and efficacy
  - Phase I through IV trials

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But Before That, Vaccine Development Often not at Pharmaceutical Company

- University/small biotech company's research labs
  - Grant funding by government or private foundations
  - Develop reagents and tests to measure success
- Multiple scientists/groups often work separately on similar vaccines
- Accomplishments evaluated by other scientists
  - Presentations at scientific meetings
  - Peer-reviewed papers in journals
- Progress also followed by pharmaceutical company scientists
  - Look for leads on newer or better vaccines
  - Approach those showing progress about expanding research toward product development
- Alternative:
  - University scientist may form company to develop/market vaccine

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Phase I -Usually <100 Subjects

- Inform FDA of intentions to conduct human trials
- Two scientific goals:
  1. Safety
     - 1st adults; then step down in age if appropriate
  2. Protective immune response
- Other goals
  - Confirm a test that measures immune correlates of protection/response
    - Consistently (+) in vaccinees and (-) in known vulnerables
  - Manufacturing
    - Are large vaccine batches possible? (Phase II and III)
    - Preservatives or stabilizers needed for reasonable shelf life?
    - Is an adjuvant needed?
- Often takes 1-2 years

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Phase II – Multiple 100s of Subjects

- Scientific goals
  - Determine proper vaccine dose
  - Continue to study safety
    - Age stepdown process again if appropriate
  - Confirm assays needed for Phase III trials
  - Keep FDA up on progress/results
- Manufacturing Goals
  - Confirm factory building in which all product will subsequently be produced
  - Confirm methods for manufacturing, stabilizing, and packaging vaccine
  - Confirm lot consistency
- Takes 2-5 years if things go well

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Phase III: 1,000s of Subjects

- Last phase before product licensing request
  - Confirm shelf-life
- Study protocol
  - Power calculation
    - Statistical differences can be detected
    - Rotavirus vaccines needed ~130,000 to R/O rare intussusception
  - Subjects = population as intended for real use
    - Infants for a new infant product
  - Blinded randomization needed
  - FDA endpoints must be reached
- Post- clinical study (1-3 yr)
  - Sponsor data review and product license request
- FDA - site visits throughout
  - Added 10-12 mos for further data review
  - Grant licensure
- Ramp up production
- Takes 3-5 years overall - usually

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Phase IV studies

- After release to public
  - Seek rare side effects not detected in Phase III trials
  - Safety is continually monitored by CDC at least 4 ways
- Safety questions arising from any source may generate a Phase IV study
- Powered to answer questions that arise
  - 1,000s to 100,000s of subjects
- Sometimes funded by pharmaceutical companies and sometimes federal government
  - Examples – MMR and autism, HPV and infertility

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Why Post-Marketing Safety Surveillance?

- Rapidly identify new or rare adverse events of clinical importance
- Monitor changes in patterns for known adverse events
- Assess safety in special populations (e.g., pregnant women and children)
- Determine patient risk factors for particular adverse events
- Assess safety of vaccine lots (FDA)

Example of changing practice: Rotashield®

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CDC: Vaccine Safety Monitoring

1. Selected health departments monitor every vaccinee and report to CDC regularly
2. CDC monitors every health department for disease
   - Abnormal disease occurrences after vaccine implemented
   - Are vaccine and abnormal events events?
3. Vaccine Adverse Event Reporting System (VAERS)
   - Anyone perceives significant negative AE of vaccine can report
   - CDC continuously monitors for trends in data
   - Generates questions – not able to determine causality
4. Vaccine Safety DataLink (VSD)
   - 6 million in 6 large HMOs (West Coast)
   - Vaccinees vs non-vaccinees testing safety concerns

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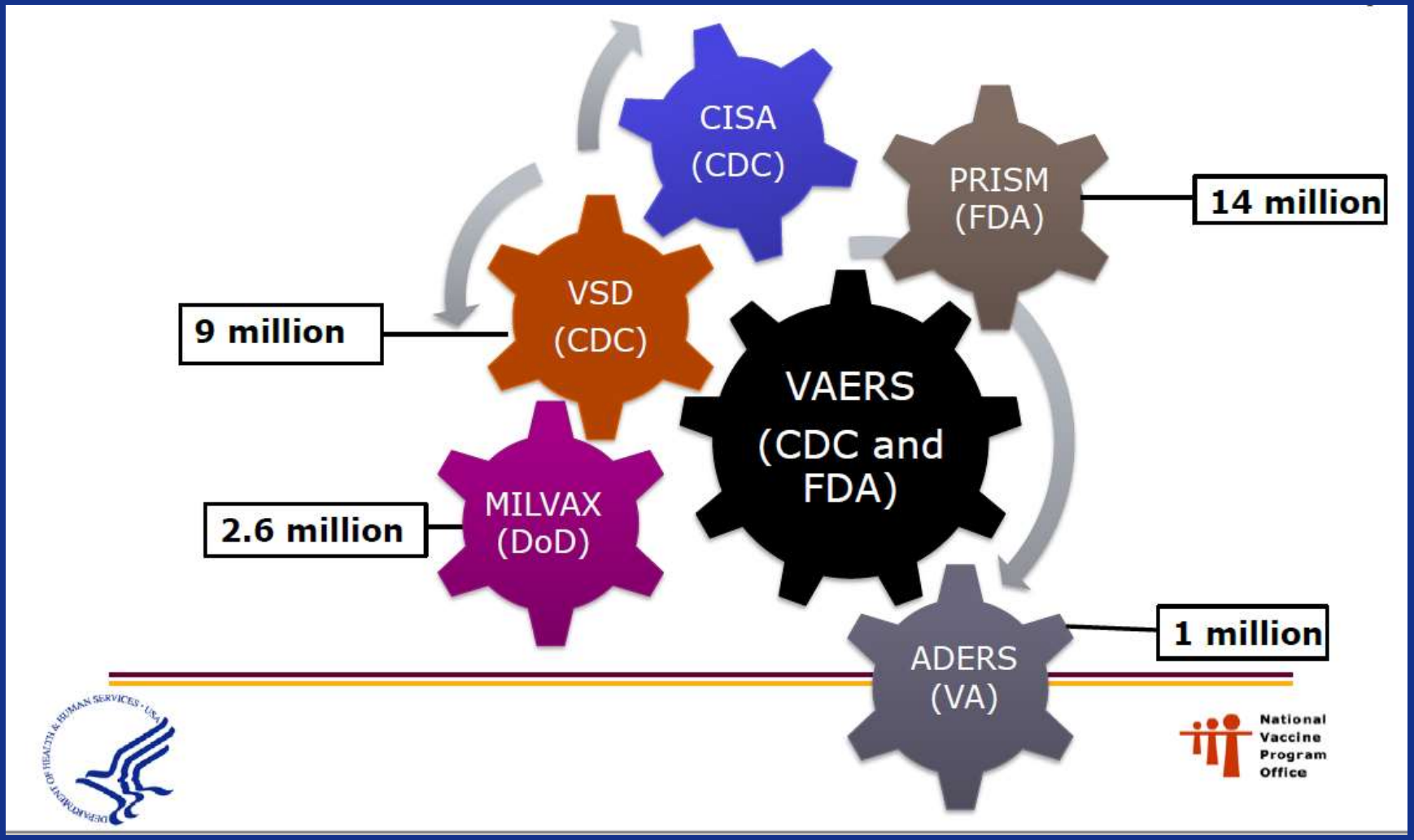
Vaccine Safety Surveillance Systems



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Vaccine Adverse Event Reporting System (VAERS)

- National spontaneous reporting system for adverse events after US-licensed vaccines
  - In recent years, received around 30,000 U.S. reports annually
  - Accepts reports from healthcare providers, manufacturers and the public
  - Signs/symptoms of adverse event coded and entered into database
- Jointly administered by CDC and FDA
- Authorized by National Childhood Vaccine Injury Act of 1986

Passive system no verification required

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VAERS

Strengths	Limitations
• National data; accepts reports from anyone	• Reporting bias
• Rapid signal detection; rare adverse events	• Inconsistent data quality and completeness
• Collects information about vaccine, characteristics of vaccine	• Generally cannot assess if vaccine caused an adverse event
• Data available to public	• Lack of unvaccinated comparison group
	• Pregnancy inconsistently reported

1. **VAERS website: http://vaers.hhs.gov**
2. **Some reports have no adverse event**

National Vaccine Program Office

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Establishing cause requires information in all four boxes

A hypothetical story

Vaccination	Illness or Syndrome: Yes	Illness or Syndrome: No
Yes	"95% of kids with autism received MMR"	95% of "normal" kids received MMR
No	"Only 5% of kids with autism did not receive MMR"	Only 5% of "normal" kids did not receive MMR

VAERS

- Post-marketing surveillance system
- "Mandatory" reporting by HC providers
  - Events listed as contraindications
  - Events listed in the Reportable Events Table
- Voluntary reporting:
  - Any event by any one
  - Intent:

    hypothesis generation not *hypothesis testing*

Offit, in Marshall. The Vaccine Handbook. Lippincott Williams & Wilkins, 2017

VAERS Only Contains Box "a"

		Outcome: Yes	Outcome: No
Exposure	Yes	a	b
	No	c	d

87% of all thimerosal-related VAERS reports in 2002 were made by lawyers

Clinical Immunization Safety Assessment (CISA) Project

- Collaboration between CDC and 7 medical research centers
- Established by CDC to:
  - Serve as a vaccine safety resource for consultation on clinical vaccine safety issues
  - Develop strategies to assess individuals who may be at increased risk for adverse events following immunization (AEFI)
  - Conduct studies to identify risk factors and preventive strategies for AEFI, particularly in special populations

Active; investigations often when unusual event reported directly to CISA or signal in VAERS

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2012 Kindergarten Vaccine Data

Goal is 95% for each metric

	Kindergarten population	No. (%) surveyed	Type of survey	MMR	DTaP	Varicella
				2 doses (%)	4 or 5 doses (%)	2 doses (%)
Kansas	38,484	8,728 (22.7)	Stratified 2-stage cluster sample	89.1	89.5	88.3
Missouri	73,113	73,113 (100.0)	Census	95.2	95.3	95.0

	Medical N= (%)	Nonmedical exemptions		Any exemption				Grace period or prov enroll N= (%)
		Religious	Total N= (%)	Period 1 2017–2018, N=	Period 1 2017–2018 %	Period 2 2016–2017 %	% diff period 1 to period 2	
Kansas	125 (0.3)	N= 544	544 (1.4)	669	1.7	1.8	-0.1	NR
MO	0.2%	2.1%	2.3%	669	1.7	1.8	-0.1	NR

https://www.cdc.gov/mmwr/volumes/67/wr/mm6740a3.htm?s_cid=mm6740a3_e

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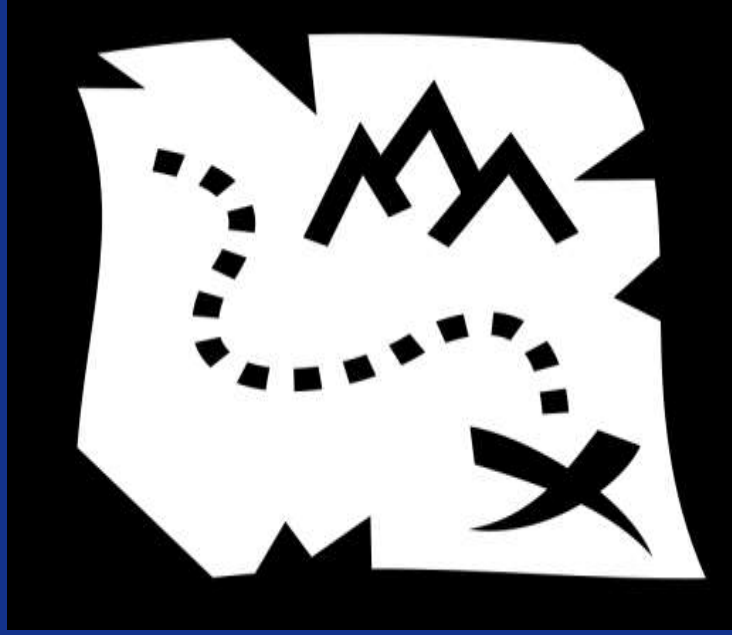
Road map



- What's in that Vaccine there?
  - Antigens / epitopes
  - Maybe adjuvant
    - Aluminum
  - Minimal preservative use
    - Multi-dose vials IIV
  - Excipients, solubilizers
    - Formaldehyde, polyethylene glycol
- Processes for development and safety monitoring
  - 4 Phase to get FDA approval
  - Vaccine safety
    - During 4 phases
    - Post marketing surveillance
    - VAERS, VSDL, CISA
- Local Vaccine Uptake Tidbit

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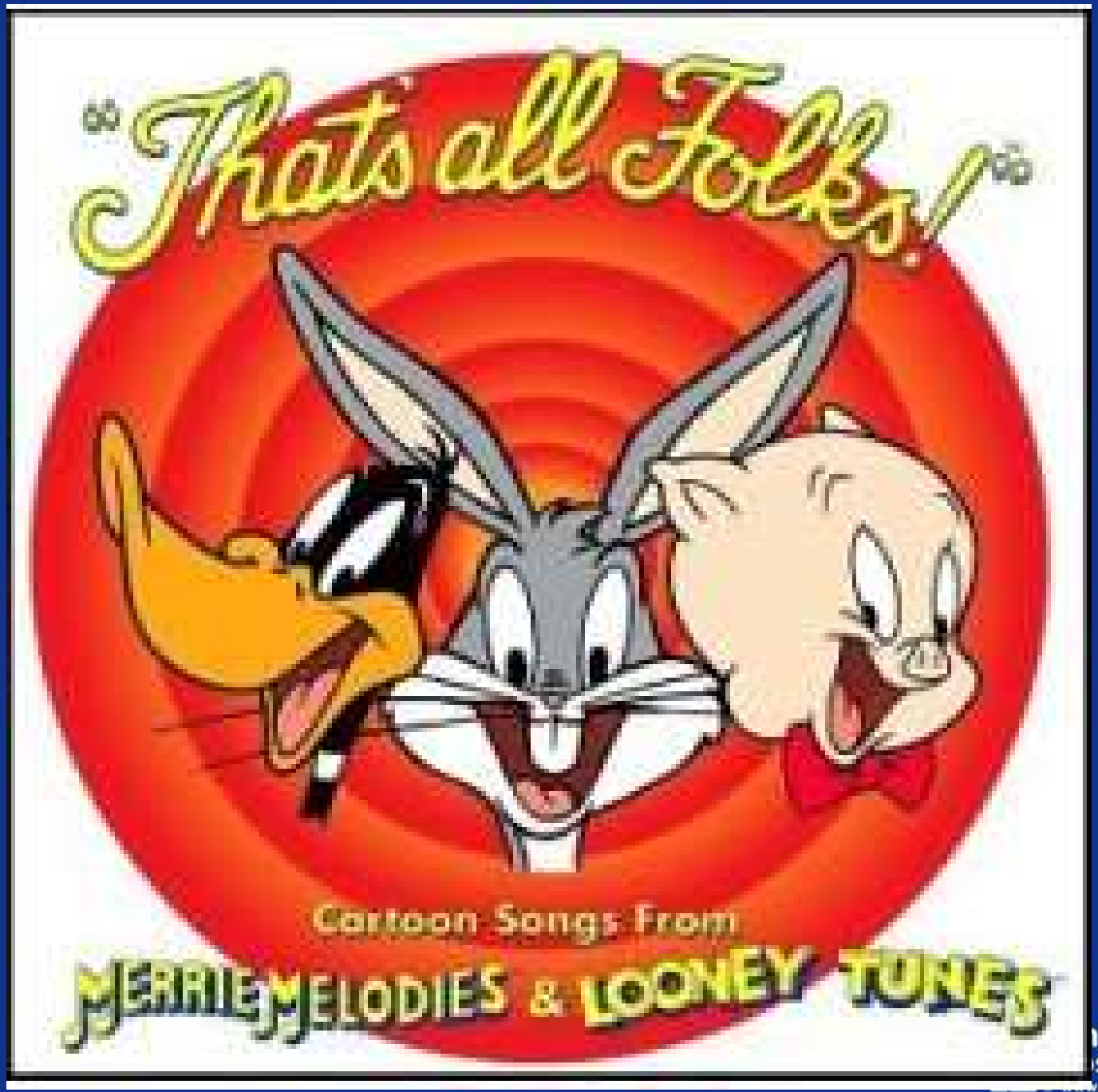

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