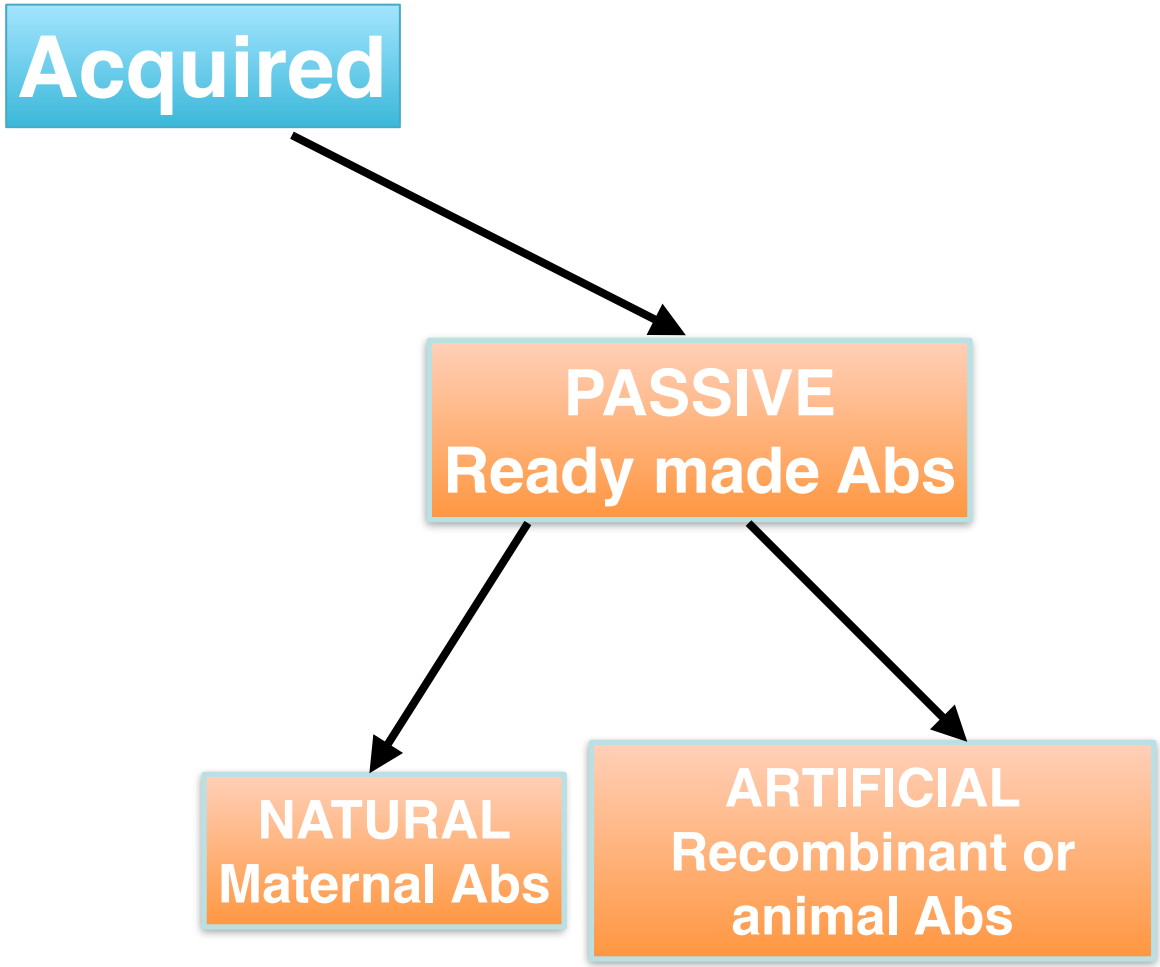
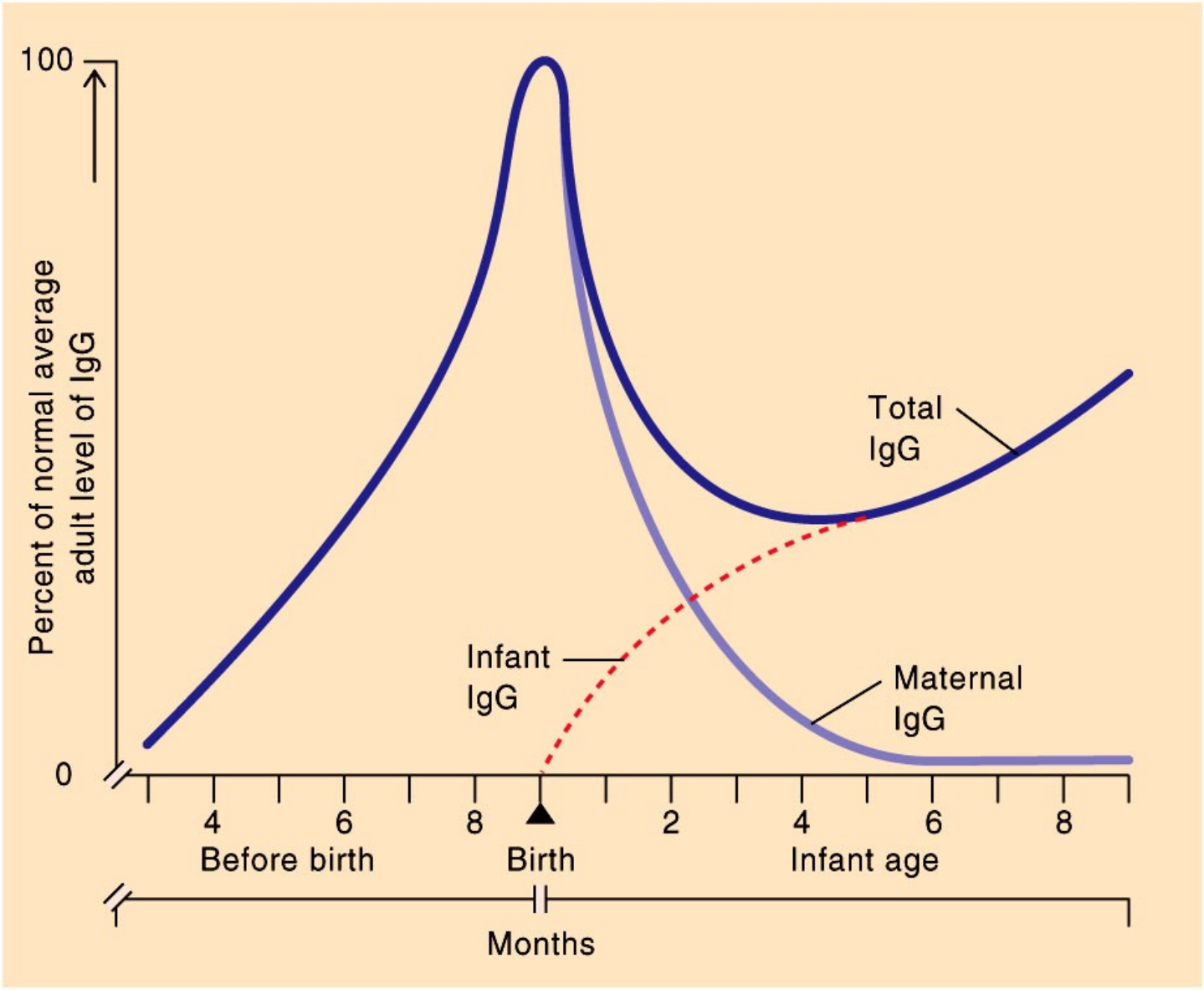
Immunotherapeutic approaches

Passive and Active Immunization for Prevention and Control

How do we acquire immunity?



Passive Immunity in Infants



Artificial Passive Immunity

- Gamma globulin (IgIv)
  - Ig's from pooled blood of at least 1,000 human donors
    - variable content
    - non-specific
- Specific immunoglobulins
  - higher titers of specific antibodies
- Antisera and antitoxins of animal origin (snake and spider bites)

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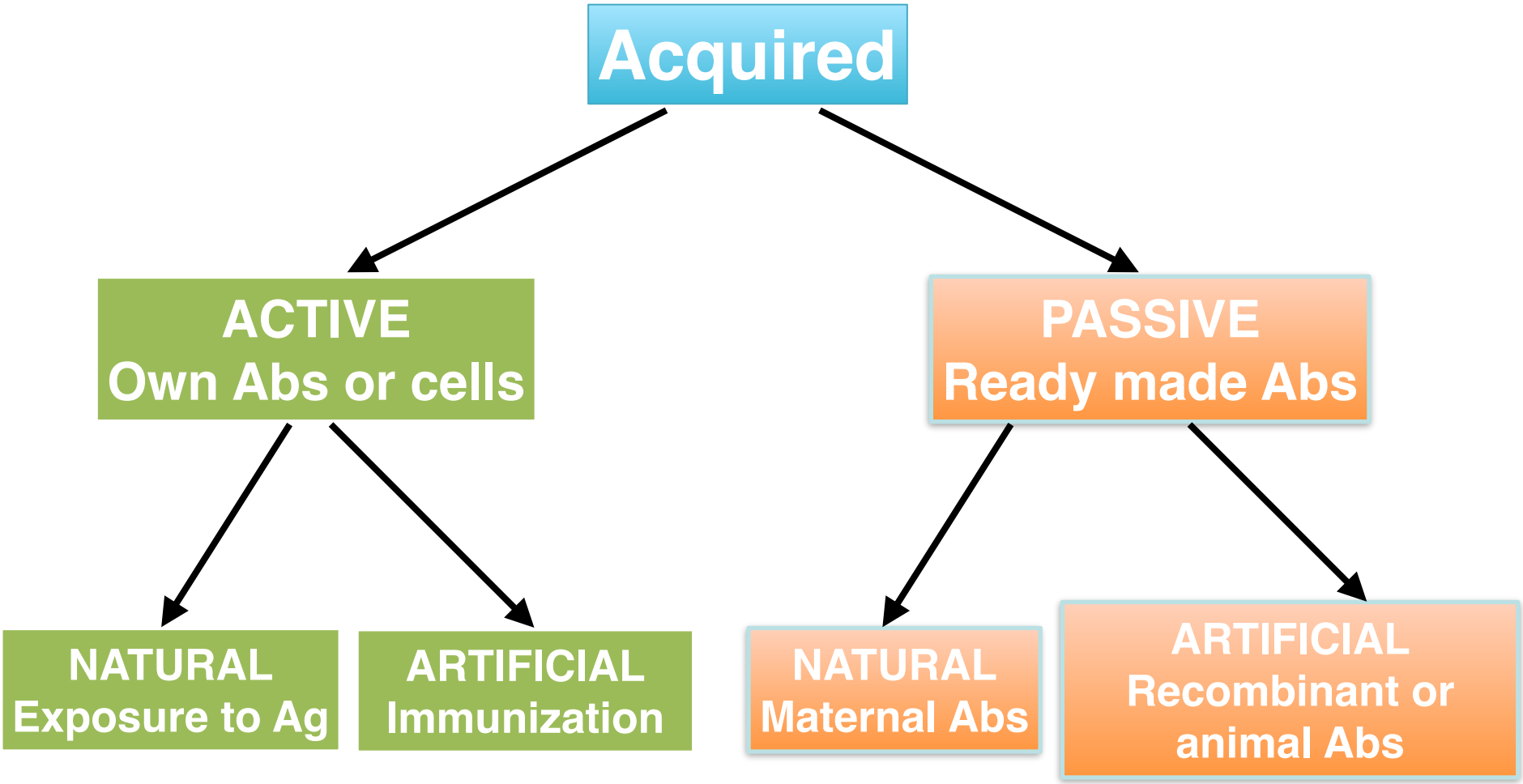
… but also T cell for cancer Immunotherapy)

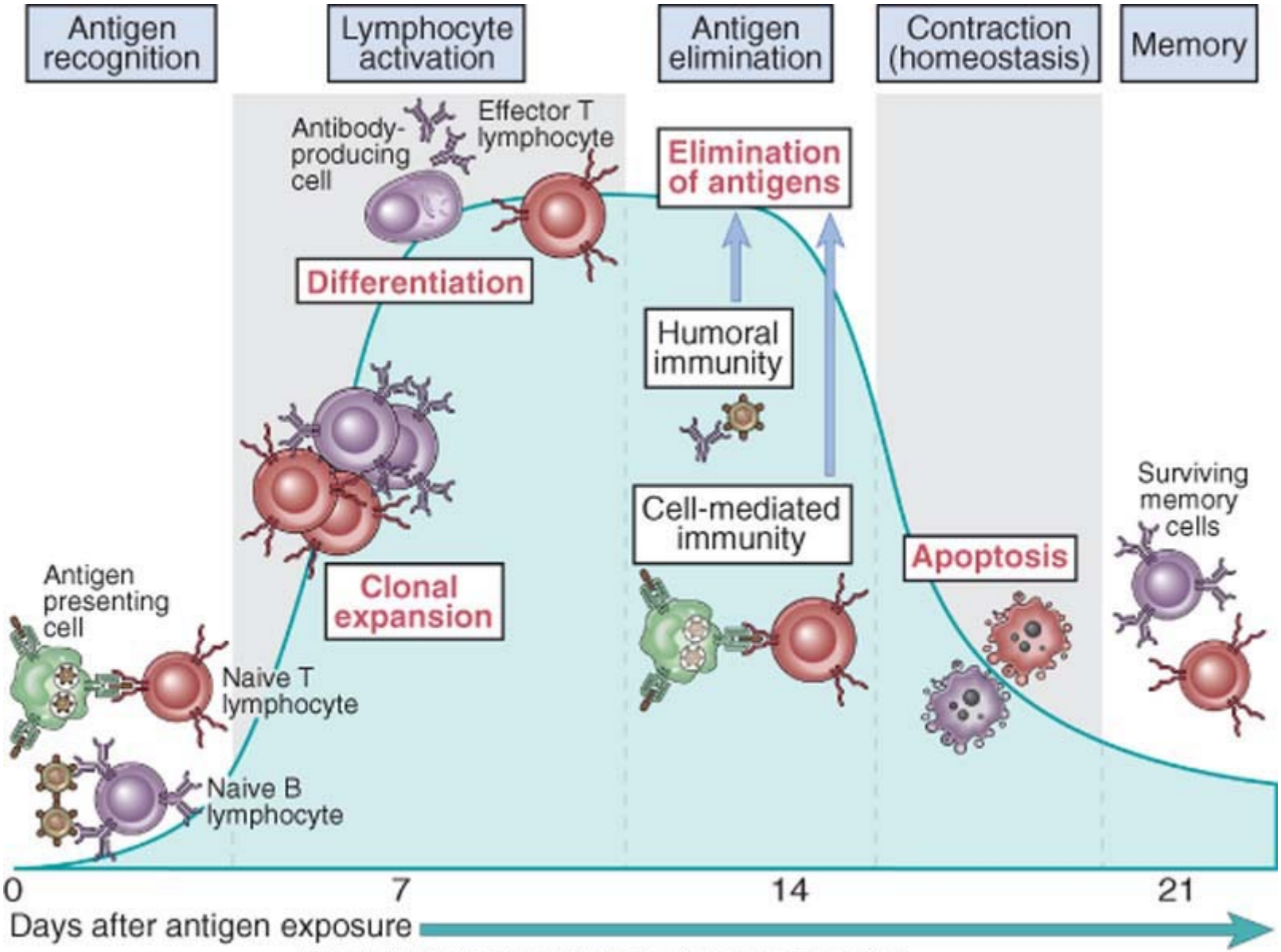
How do we acquire immunity?



Artificial Active Immunity

- Vaccination (Immunization)
  - exposing a person to material that is an antigen but NOT pathogenic.

Phases of immune response



Designing vaccines

Important questions to consider:

1- Which part of the immune system should be activated?

2- Is immunologic memory sufficiently stimulated?

This depends on the disease..

- Influenza has a short incubation (1-2 d); effective immunity against flu depends on maintaining high levels of Ig through repeat immunizations

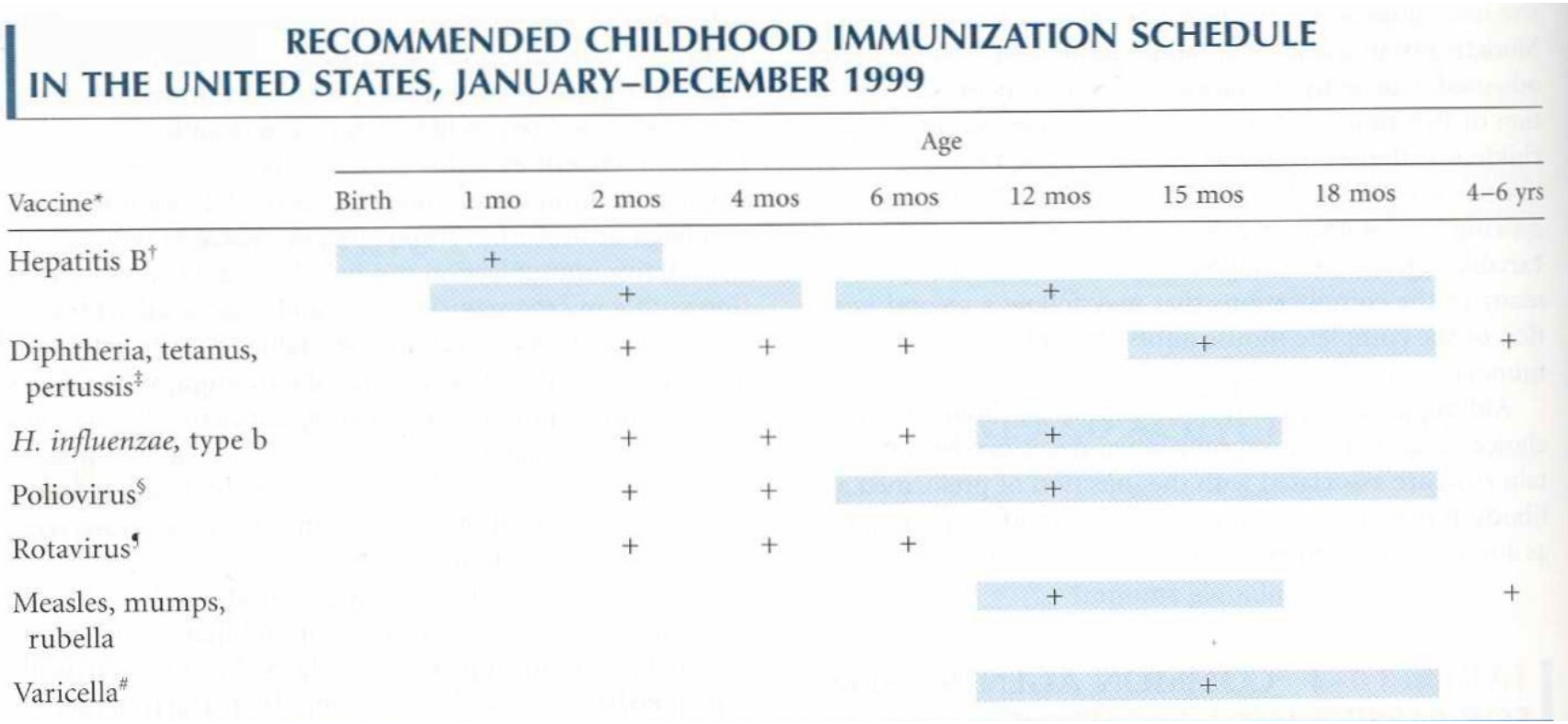
- Polio virus has a longer incubation (>3d) and gives memory cells time to produce ↑serum Ig and activate immune cell effectors

Childhood vaccines

- 7 major vaccines:
  - **HepB**
  - **DTaP (**Diphtheria, Tetanus, Pertussis)
  - **IPV** (smallpox /vaiolo)
  - **MMR (**measles, mumps, and rubella / morbillo, parotite, rosolia)
  - **Hib (**Haemophilus influenzae type B)
  - **Var** (Varicella)
  - **PCV (**Pneumococcal Conjugate Vaccine)

*children require booster shots for most…
(American Academy of Pediatrics, since 2002)

Childhood vaccines



RECOMMENDED CHILDHOOD IMMUNIZATION SCHEDULE IN THE UNITED STATES, JANUARY–DECEMBER 1999

Vaccine*	Age: Birth	1 mo	2 mos	4 mos	6 mos	12 mos	15 mos	18 mos	4–6 yrs
Hepatitis B†	+								
		+				+			
Diphtheria, tetanus, pertussis‡			+	+	+		+		+
H. influenzae, type b			+	+	+	+			
Poliovirus§			+	+		+			
Rotavirus¶			+	+	+				
Measles, mumps, rubella						+			+
Varicella#							+		

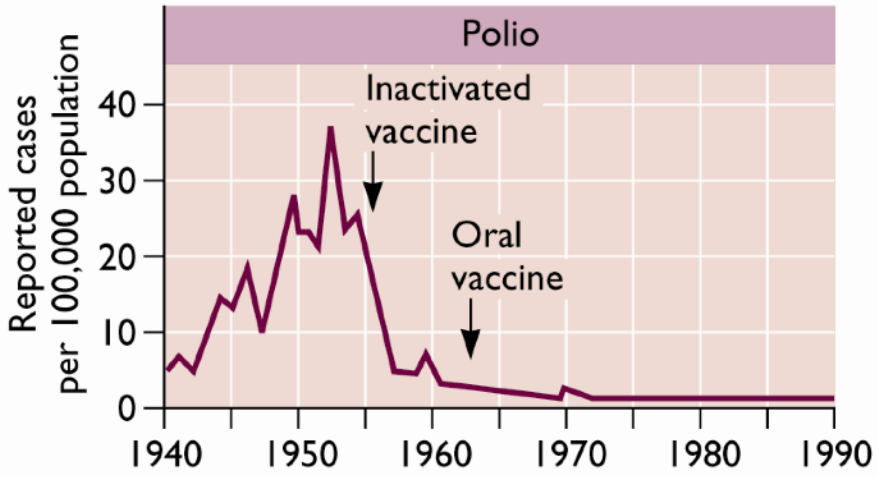
Adult vaccines (dependent on risk group)

- For those living in close quarters
  - Meningitis (Hib)
  - Pneumonia (PCV)
  - Influenza

- For travelers to endemic areas:
  - Cholera
  - Typhus
  - Typhoid
  - Hepatitis
  - Meningits
  - Yellow fever
  - Polio

Large scale vaccination programs

- Dramatic improvements in public health.
- Nobody in this room has had…
  - Smallpox, Polio, Measles, Chickenpox
  - Mumps, Rubella
- …Because of vaccination
- Smallpox is the only human disease to ever be eradicated



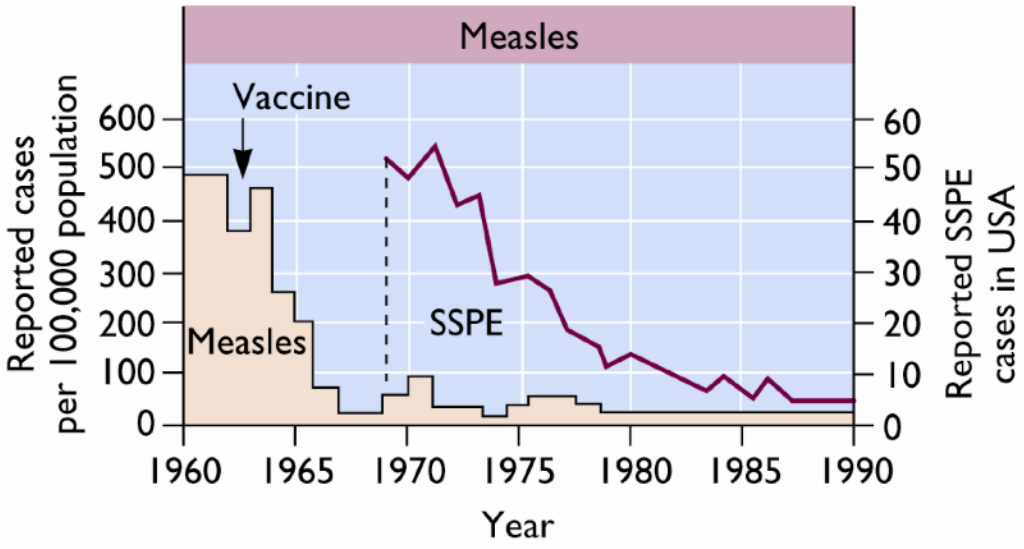


Table 19.1 Features of smallpox that enabled its eradication

Virology and disease aspects
No secondary hosts: this is a human-only virus
Long incubation period
Infectious only after incubation period
Low communicability
No persistent infection
Subclinical infections are not a source of spread
Easily diagnosed

Characteristics of a good vaccine

- **Safe / Few side effects**
- Give long lasting, appropriate protection
- Low in cost
- Stable with long shelf life (no special storage requirements)
- Easy to administer

- Public must see more benefit than risk

Types of vaccines

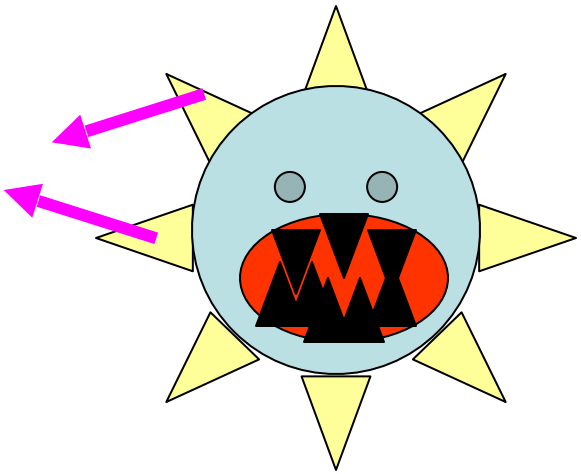
- whole agent

- subunit of the agent
  - recombinant
  - individual parts alone

Whole agent vaccines
Killed using heat or formaldehyde

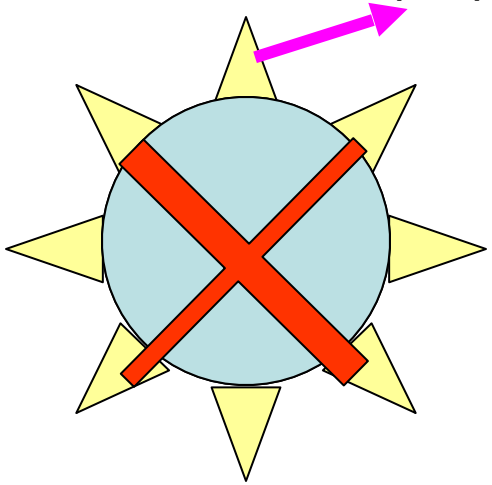
Live virus

epitopes



Killed virus

epitopes

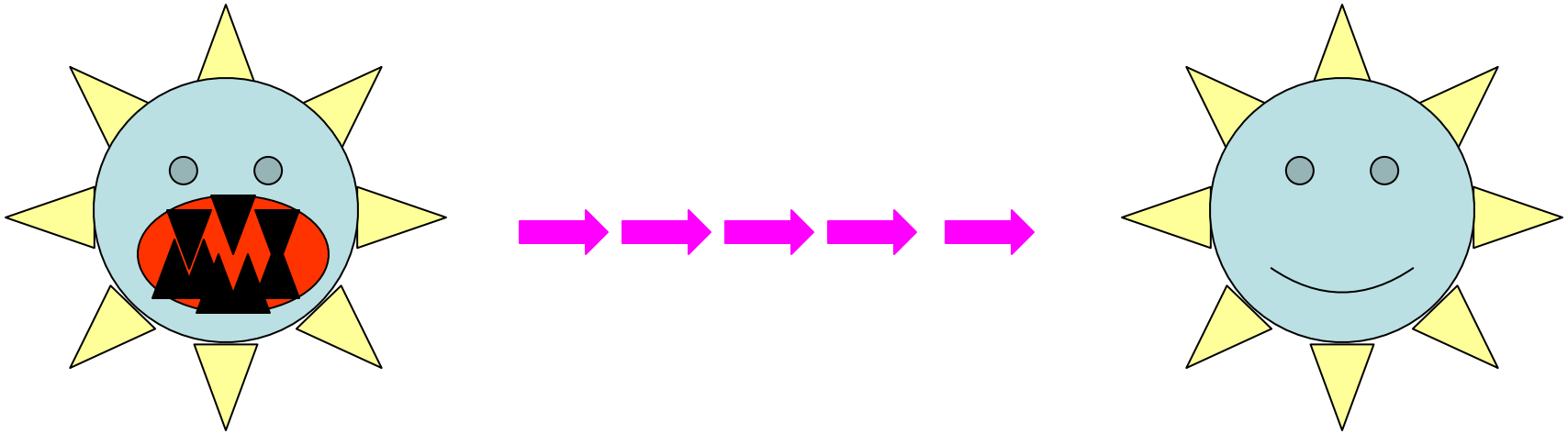


Inactivated polio vaccine (Salk)

Influenza (Classic)

Whole agent - vaccines attenuated

- attenuated - a process that lessens the virulence of a microbe

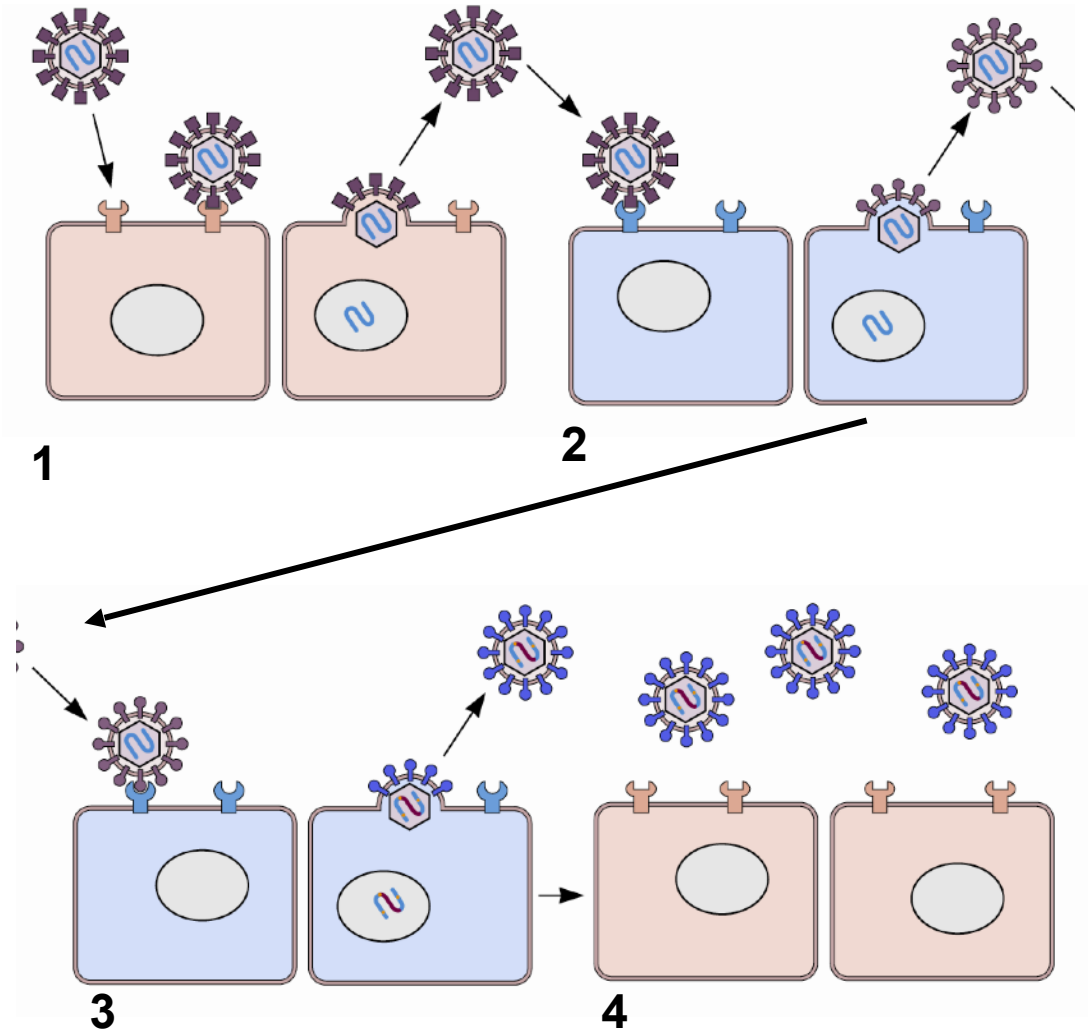


oral polio vaccine (Sabin),

MMR (measles, mumps, rubella)

Influenza -- Flumist

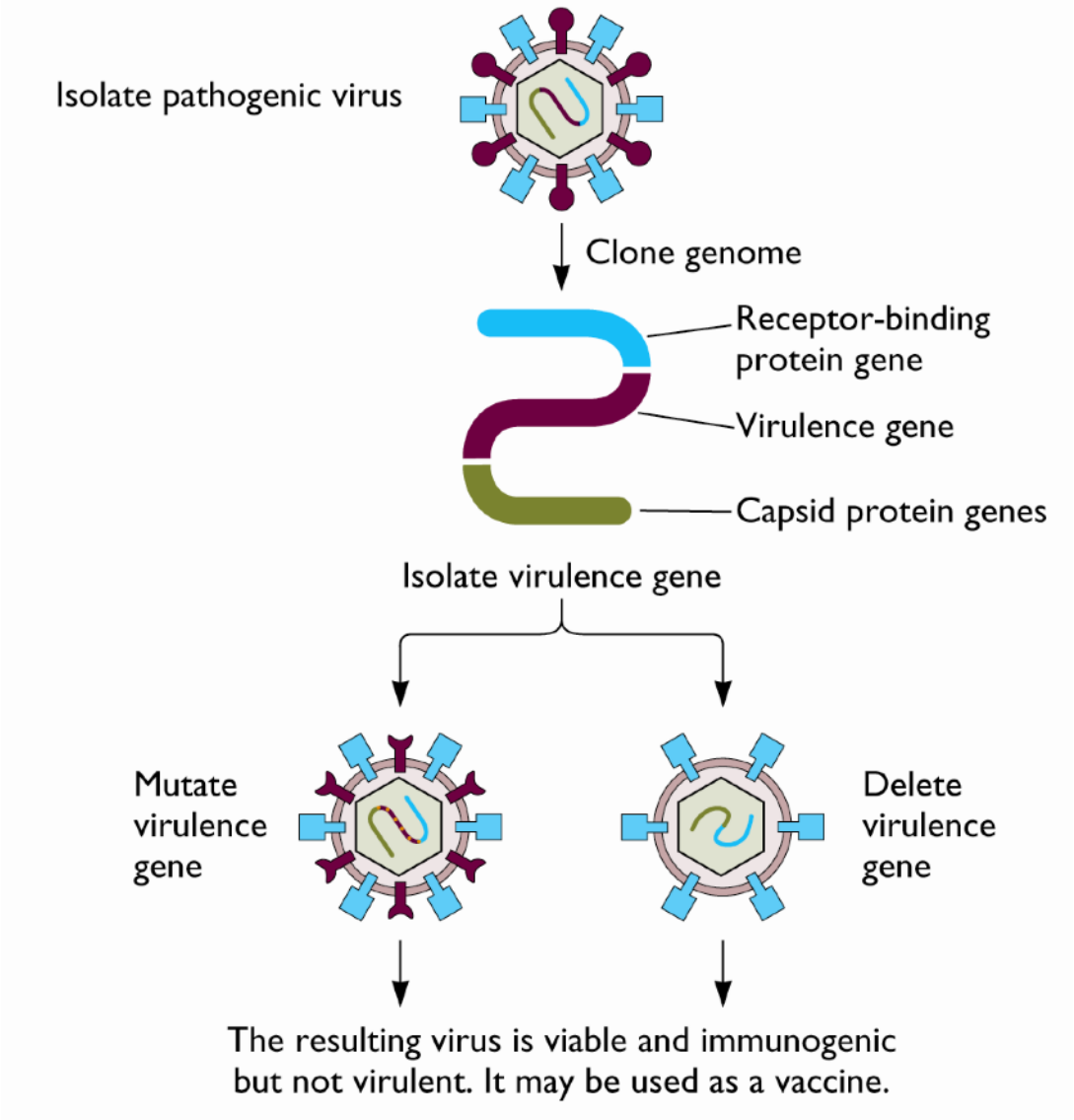
Attenuation of viruses by passage through non-human cells



1. Pathogenic virus isolated from patient, grown in human cells
2. Infect monkey cells with cultured virus
3. Virus acquires many mutations that allow it to grow well in monkey cells
4. Mutations make the virus unable to grow well in human cells

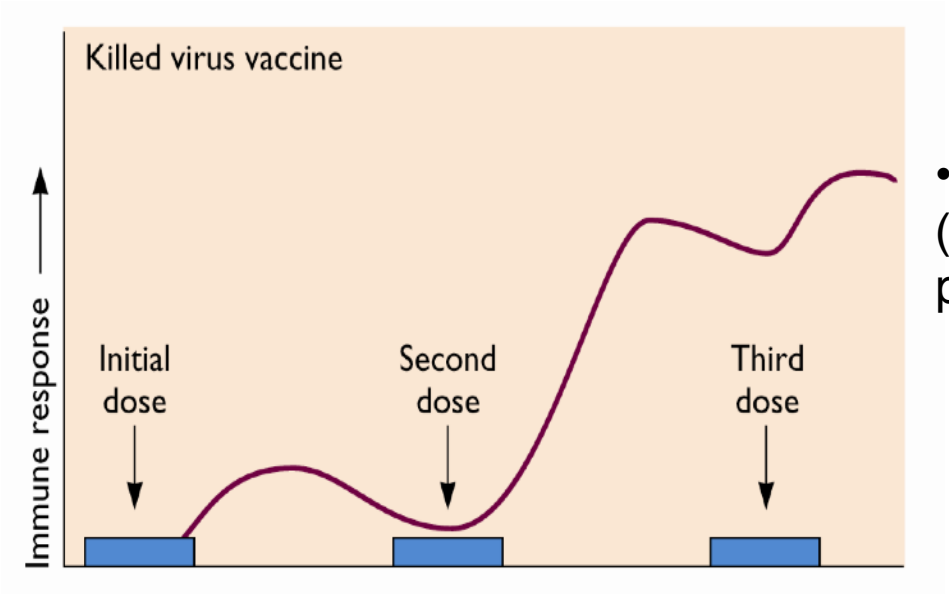
→ Vaccine candidate

Construction of recombinant attenuated virus

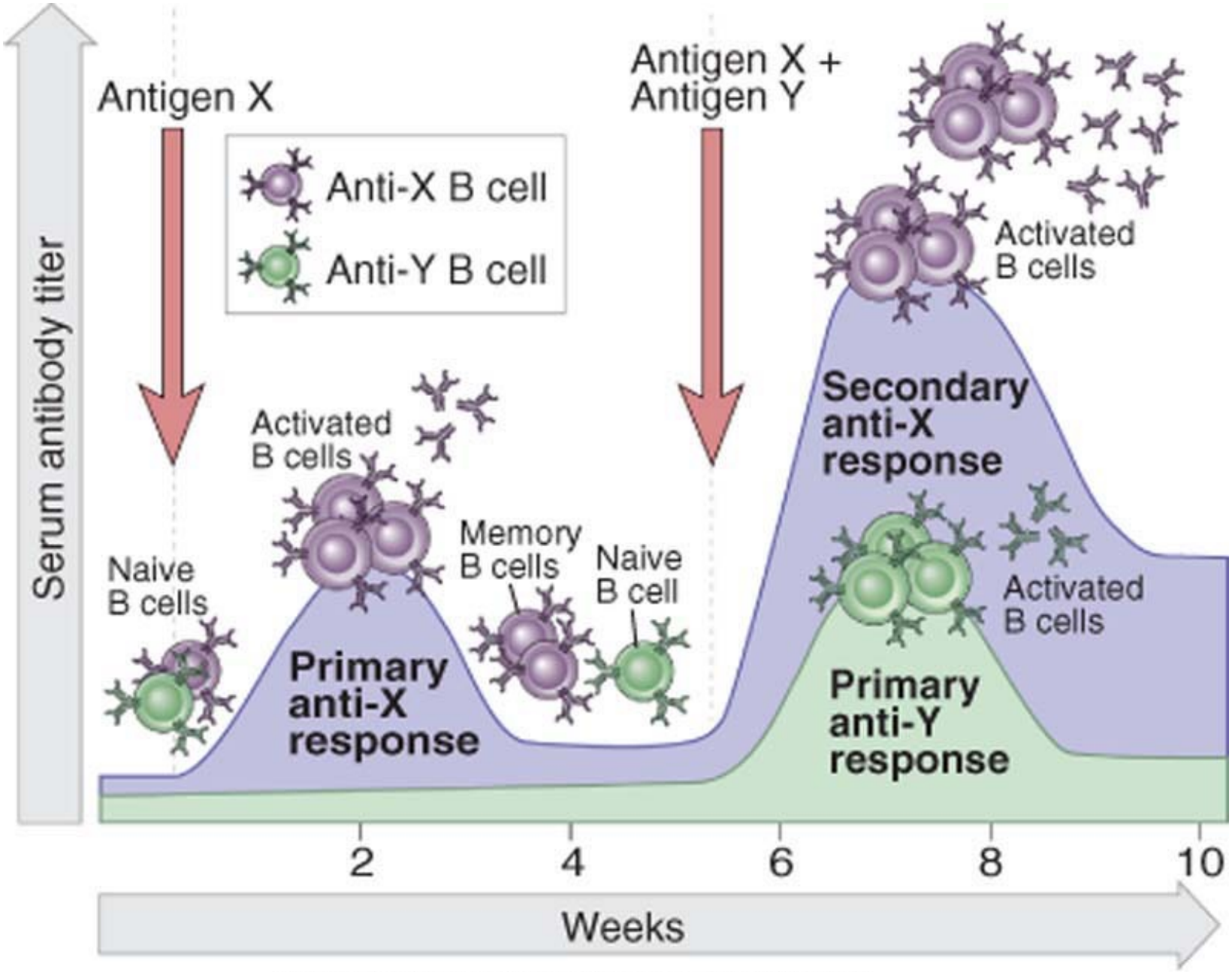


1. **Isolate virus**
2. **Clone genome**
3. **Isolate virulence gene**
4. **Mutate or delete virulence gene**
5. **Resulting virus is**
   - **Viable**
   - **Immunogenic**
   - **Not virulent**
   - **Can be used as a vaccine**

Vaccines stimulate immune memory



•Killed virus vaccine requires multiple doses (booster shots) to adequately stimulate a protective immune response



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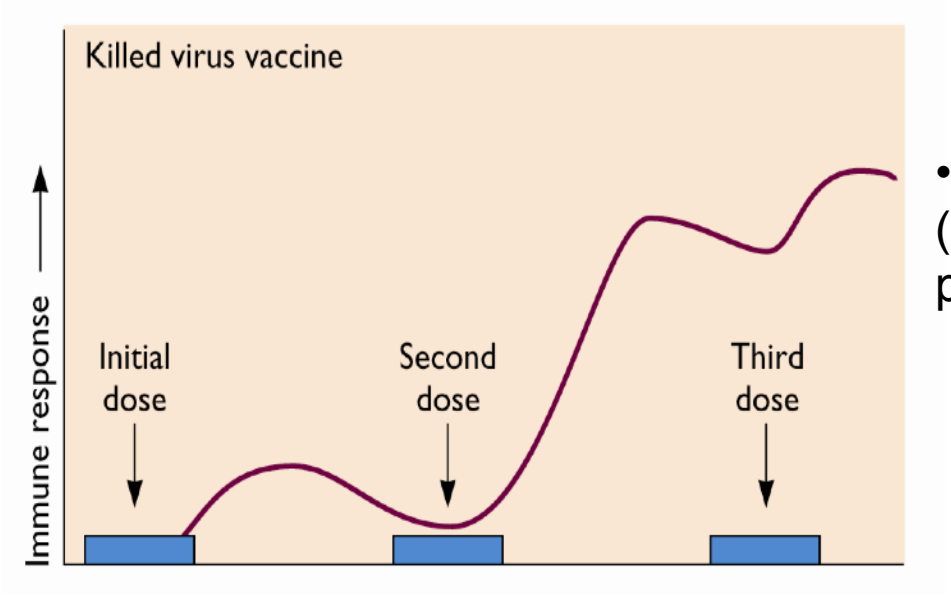

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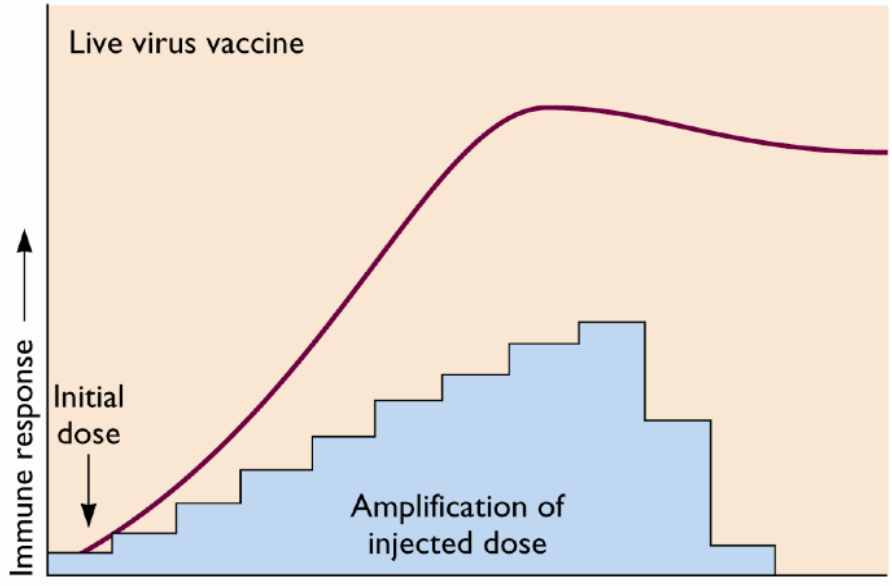


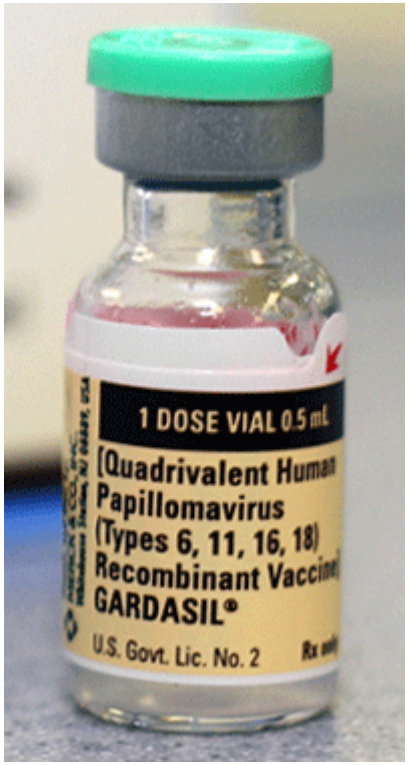
•Live virus vaccines replicate in the host.
•No requirement for boosters.

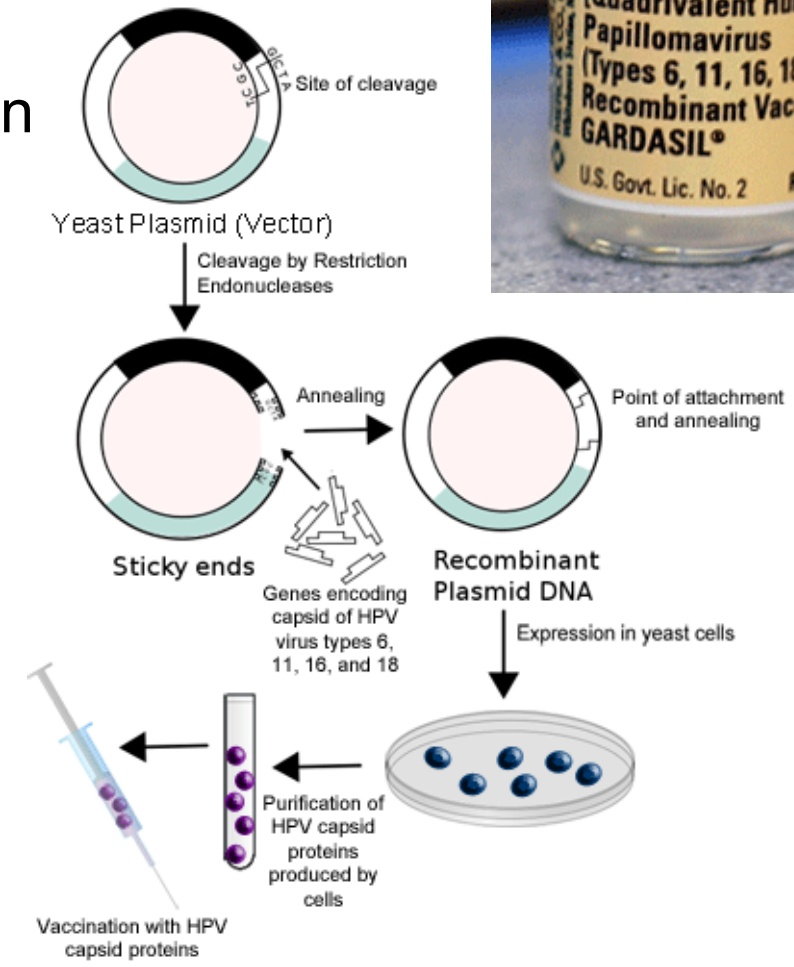
- Advantages for live vaccines
  - multiply like natural organism
  - require fewer doses and boosters
  - long-lasting

- Disadvantages for live vaccines
  - special storage
  - back mutation
  - side effects

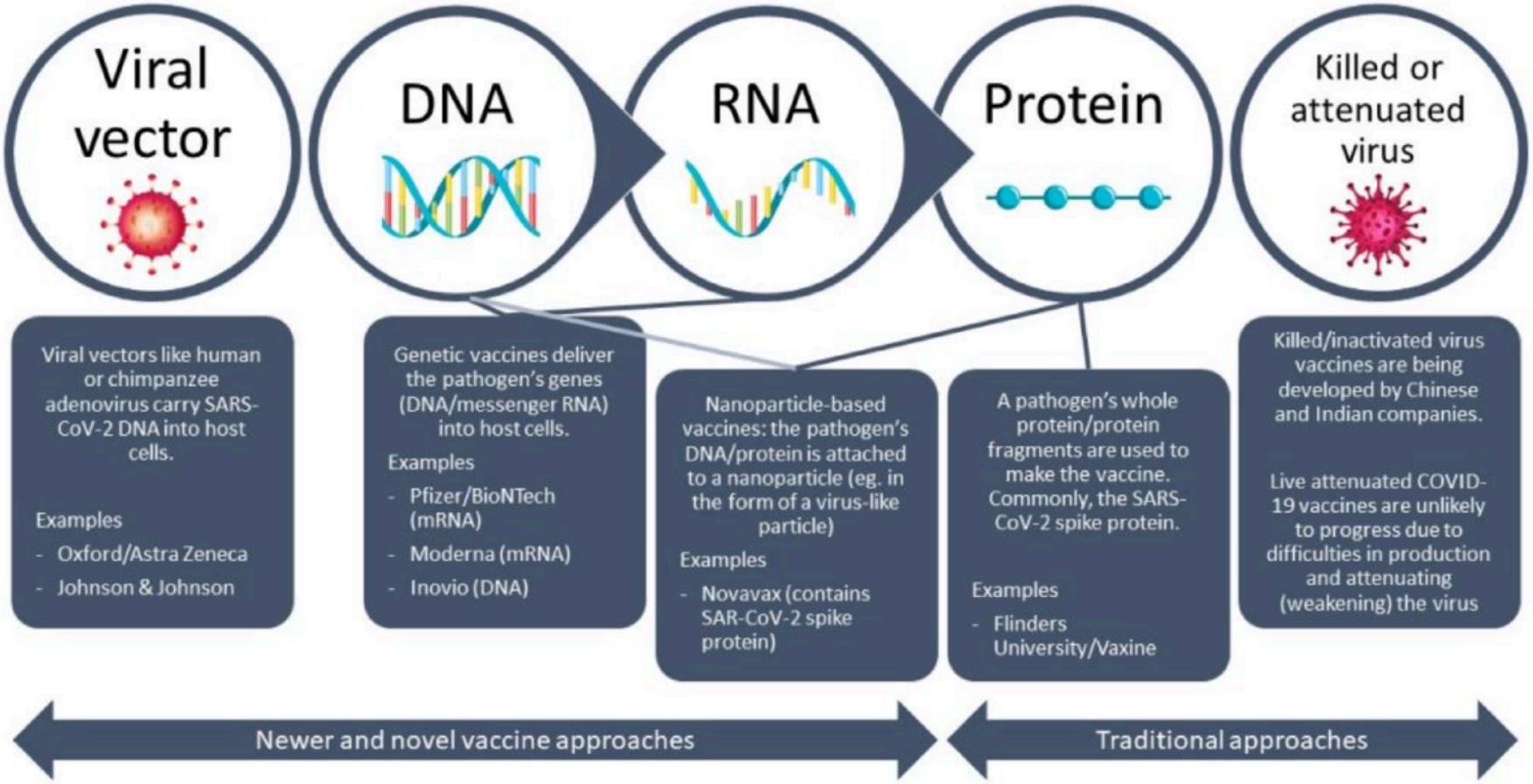
Subunit vaccines

- Single antigen or mixture of antigens
- Safer (cannot reproduce)
- However, often less effective than whole agent vaccines
- Can be costly
- Always require boosters

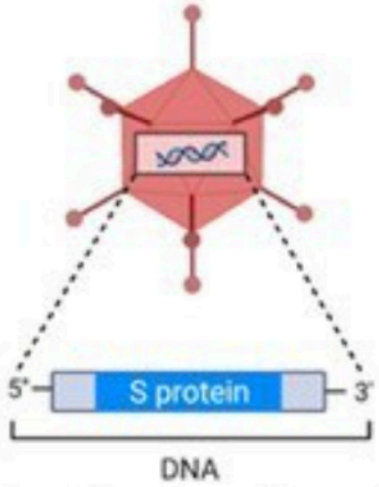




Vaccines approaches for SARS-CoV-2

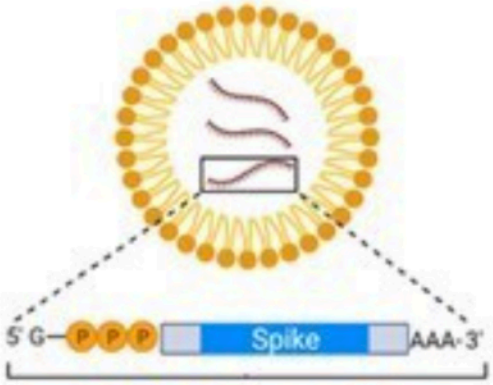


Vaccine: University of Oxford/ AstraZeneca



Platform: Adenovirus with gene for the SARS-CoV-2 spike (S) protein

BioNTech/Pfizer



Platform: lipid nanoparticle-encapsulated mRNA vaccines encoding Spike protein

Novavax

Platform: Synthetic nanoparticle coated with trimer spike protein. Matrix M used an immune-boosting adjuvant

DISADVANTAGES of nucleic acid-based vaccines

- Limited to protein immunogen only
- Extended immunostimulation leads to chronic inflammation
- Some antigen require processing which sometime does not occur

Overcoming Subunit vaccine problems

1. Multiple doses
2. Use adjuvants
   - prolongs stimulation of immune response
   - works by trapping the antigens in a chemical complex and releases them slowly

Vaccine delivery systems and adjuvants

Table 19.4 Vaccine delivery systems and adjuvants[a]

Type of system or adjuvant	Characteristics
Aluminum salt	Aluminum hydroxide or phosphate. Forms precipitates with soluble antigen, making the complexes more immunogenic; antigen "depot" at site of injection; complement activation.
Emulsions	Freund's complete adjuvant: antigen suspended in water-mineral oil emulsion with killed *Mycobacterium tuberculosis* bacteria or muramyl di- or tripeptide to stimulate strong T-cell responses. Freund's incomplete adjuvant: antigen suspended in water-in-mineral oil emulsion.

Summary of adjuvants approved for human use

Adjuvant	Description	Approved vaccine products
Aluminium-based mineral salts (Alum)	E.g. Aluminium phosphate, Calcium phosphate, Aluminium hydroxide	Eg. Anthrax (BioThrax®, Emergent Biosolutions) Hepatitis A (Vaqta®, Merck) DTP (Triple Antigen™, CSL limited)
MF59	Submicron oil-in-water emulsion	Influenza (FLUAD®, Novartis)
Monophosphoryl lipid A (MPL)	Bacteria-derived immunostimulant	Hepatitis B (Fendrix®, GlaxoSmithKline)
Virosomes	Spherical vesicles containing viral membrane proteins in the lipid membrane	Hepatitis A (Epaxal®, Berna Biotech) Influenza (Inflexal®, Berna Biotech)

Types of vaccines

Live vaccines	Live Attenuated vaccines	Killed Inactivated vaccines	Toxoids	Cellular fraction vaccines	Recombinant vaccines
•Small pox variola vaccine	•BCG •Typhoid oral •Plague •Oral polio •Yellow fever •Measles •Mumps •Rubella •Intranasal Influenza •Typhus	•Typhoid •Cholera •Pertussis •Plague •Rabies •Salk polio •Intra-muscular influenza •Japanise encephalitis	•Diphtheria •Tetanus	•Meningococcal polysaccharide vaccine •Pneumococcal polysaccharide vaccine •Hepatitis B polypeptide vaccine	•Hepatitis B vaccine

COMPARISON OF VARIOUS TYPES OF VACCINES

		VACCINE TYPES		
		live, attenuated	killed / subunit	DNA / RNA
TYPE OF IMMUNE RESPONSE				
Antibody mediated	B- cells	+++	+++	+++
cellular	CD4+ T-cells	+/- TH1	+/-TH1*	+++ TH1*
	CD8+ T-cells	+++	-	++
	antigen presentation	MHC I / II	MHC II	MHC I / II
memory	humoral	+++	+++	+++
	cells	+++	+/-	++
production	Difficulty of development	+	++	++++
	price	+	+	+++
	Transportation storage	+	+++	+++
safety		++	++++	+++

Routes of administration

- Deep subcutaneous or intramuscular route (most vaccines)
- Oral route (sabine vaccine, oral BCG vaccine)
- Intradermal route (BCG vaccine)
- Scarification (small pox vaccine)
- Intranasal route (live attenuated influenza vaccine)

Periods of maintained immunity due to vaccines

- Short period (months): cholera vaccine
- Two years: TAB vaccine
- Three to five years: DPT vaccine
- Five or more years: BCG vaccine
- Ten years: yellow fever vaccine
- Solid immunity: measles, mumps, and rubella vaccines.

Levels of effectiveness

- Absolutely protective(100%): yellow fever vaccine
- Almost absolutely protective (99%): Variola, measles, mumps, rubella vaccines, and diphtheria and tetanus toxoids.
- Highly protective (80-95%): polio, BCG, Hepatitis B, and pertussis vaccines.
- Moderately protective (40-60%) TAB, cholera vaccine, and influenza killed vaccine.

Vaccination Coverage

- Vaccination coverage is the percent of at risk or susceptible individuals, or population who have been fully immunized against particular diseases by vaccines or toxoids. To be significantly effective in prevention of disease on mass or community level at least a satisfactory proportion (75% or more) of the “at risk” population must be immunized.

New approaches

- Cancer
- HIV/AIDS
- Malaria
- New infective agents

Vaccines against bioterrorism

- Anthrax
- Small pox
- Plague

Vaccination: It works

REDPEN/
BLACKPEN

Hey guys - I don't even feel any rain. Why are we doing this again? Just put down the stupid umbrellas - they're bad for your arms anyway.