Vaccines

Passive immunization
=transfer of antibodies

Vaccines are usually
active immunizations

TABLE 18-1 Acquisition of passive and active immunity

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§

*An antibody-containing solution derived from human blood, obtained by cold ethanol fractionation of large pools of plasma; available in intramuscular and intravenous preparations.

†An antibody derived from the serum of animals that have been stimulated with specific antigens.

‡A suspension of attenuated live or killed microorganisms, or antigenic portions of them, presented to a potential host to induce immunity and prevent disease.

§A bacterial toxin that has been modified to be nontoxic but retains the capacity to stimulate the formation of antitoxin.

Passive Immunization

Passive immunization is the transfer of antibodies, and any immune protection lasts as long as the antibodies are present. Transfer of antibodies does not transfer or establish memory.

Best examples of passive immunization are

1. Antitoxins= antibodies from horses immunized with bacterial toxins (e.g. diphtheria, tetanus or botulinum toxins).
2. Antivenom consists of antibodies from horses immunized with snake venom. https://www.who.int/activities/addressing-antivenoms-issues
3. Human gammaglobulin shots which are pooled human IgG collected from many donors with a broad array of antibodies to many pathogens.

Most vaccines are active immunizations

- Active immunizations seek to induce an adaptive immune response that is **similar to** immunity (immune memory) provided by a "**natural infection**".
- These **active** vaccines seek to provide protection <u>from disease</u> by establishing **memory T and B cells**.

***Most vaccines prevent disease but not infection.

Preventive vs Therapeutic vaccines

Preventive vaccines

Given to naïve individuals in order to provide protection from primary infection or prevent disease.

Therapeutic vaccines

Given to infected individuals to prevent disease, reduce disease or stimulate anti-tumor response.

Smallpox eradication is the example case of vaccine success

<u>But why was eradication possible for smallpox?</u>

- No animal reservoir.
- Lifelong immunity.
- One serotype meant little antigenic variation and no repeat infections.
- Effective attenuated vaccine provided long-term (lifelong?) immunity.

Routes for vaccinations

- Many vaccines are given intramuscular (injection in arm) or subcutaneous. Live polio virus and rotavirus vaccine given orally.
- Immunization site will influence where immune responses are elicited but most vaccines are tested in easy to administer route and assessed for protection.

CDC recommended route for US vaccines

- Oral route: administered by mouth
- Subcutaneous route: injected into the area just beneath the skin into the fatty, connective tissue
- Intramuscular route: injected into muscle tissue
- Intradermal route: injected into layers of the skin
- Intranasal route: administered into the nose

VACCINES	ROUTE
Rotavirus (RV1, RV5)	Oral
DTaP, DT, HepA, HepB, Hib, HPV, IIV3, IIV4, RIV3, ccIIV3, IPV,* MenACWY, MenB, PCV13, PPSV23,* Td, Tdap, TT	Intramuscular injection
HZV, IPV,* MMR, PPSV23,* VAR	Subcutaneous injection
Fluzone ID	Intradermal injection
COMBINATION VACCINES	**ROUTE**
DTaP-IPV, DTaP-IPV-HepB, DTaP-IPV/Hib, HepA-HepB	Intramuscular injection
MMRV	Subcutaneous injection

Routes of immunization

FluMist vaccine is quadrivalent, which means it contains 4 different live influenza viruses.

This live-attenuated intranasal vaccine for influenza was designed so that it will replicate only in nasal passages.

This flu vaccine was withdrawn in 2016 for lack of efficacy for H1N1 2009 but CDC returned the vaccine to market for 2018/2019 flu season.

Routes of immunization

Monkeypox vaccine is given subcutaneous (under the skin) or intradermal (between layers of the skin).

Monkeypox vaccine is a non-replicating attenuated version of the smallpox vaccine (Modified Vaccinia Ankara).
Injection into the skin may be more challenging than usual intramuscular.
Why this different route? How will the immune system view the antigens differently?

Vaccines often need adjuvants

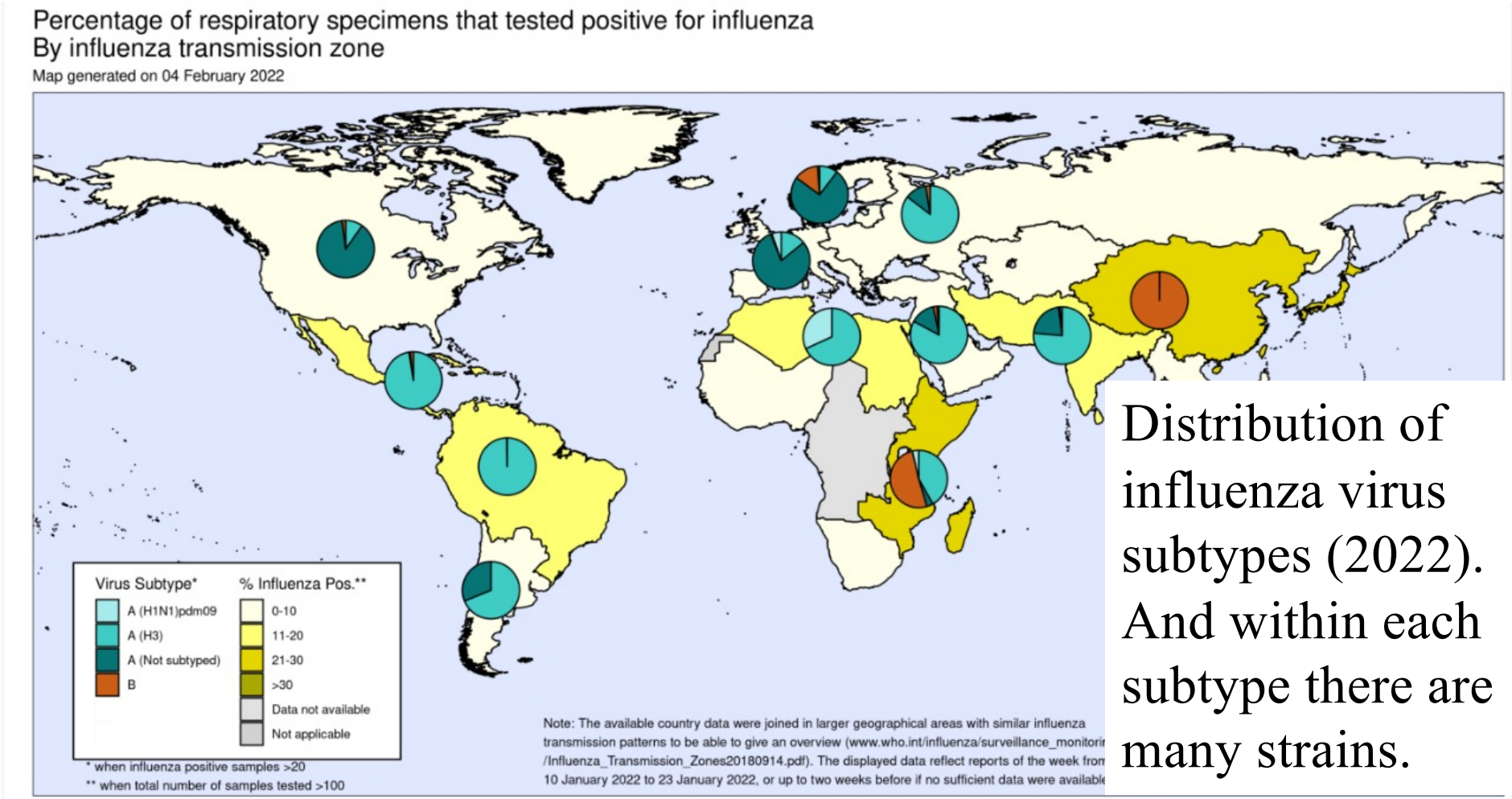
Adjuvants are added to vaccines in order to enhance immunogenicity. Adjuvants usually activate macrophages and DCs to increase inflammation at the site of antigen exposure.

- Old adjuvants were inorganic salts, such as aluminum hydroxide or aluminum phosphate or Calcium phosphate
- Newer adjuvants provide ligands to bind TLRs

  AS01-AS06 are oil in water emulsions with Lipid A or saponin (a detergent) or CpG (DNA). These adjuvants contain PAMPs that activate inflammation via TLRs.

Vaccines must deal with antigenic variation

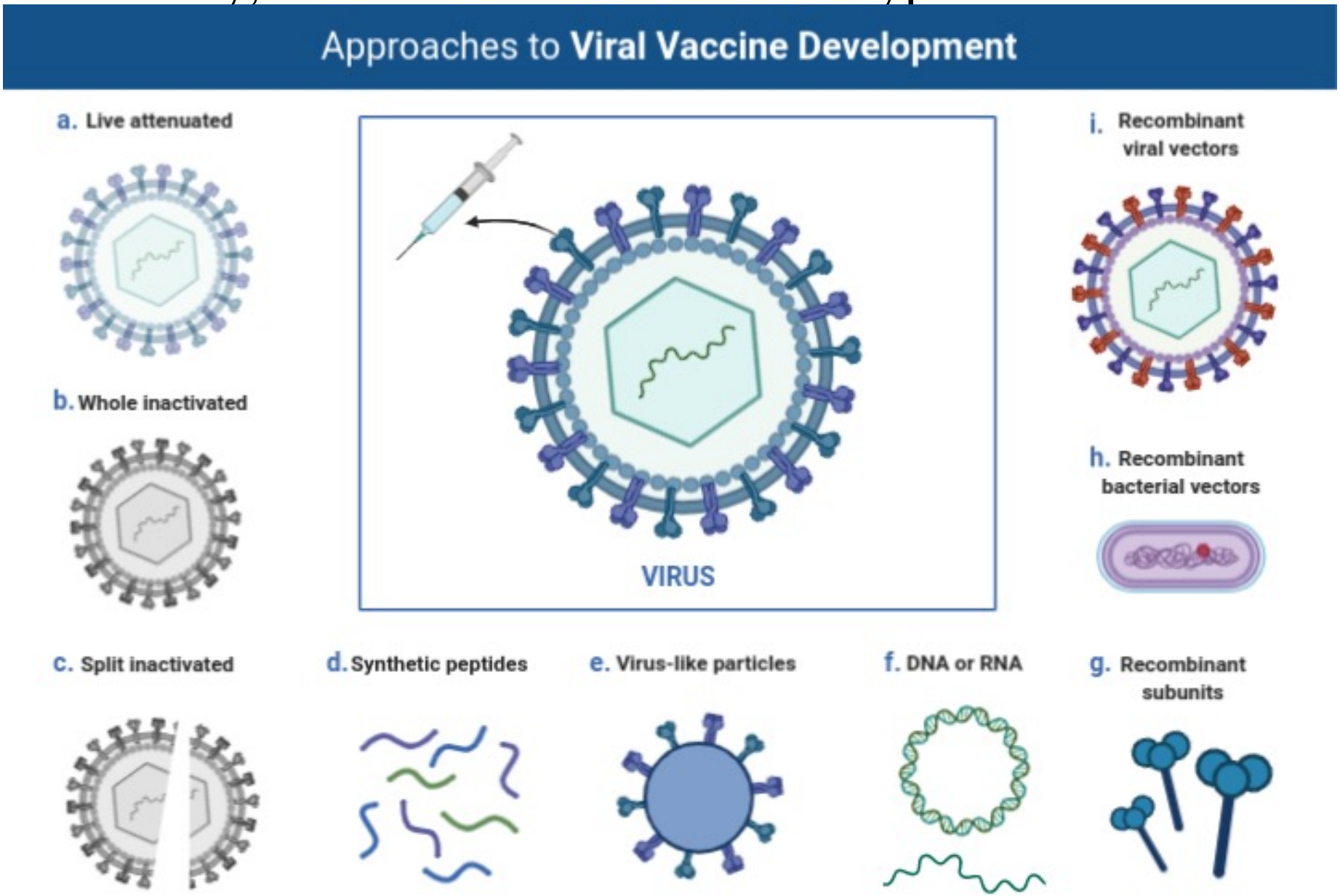
Some viruses have many different antigenic subtypes and high mutation rates.



Distribution of influenza virus subtypes (2022). And within each subtype there are many strains.

Viral vaccine approaches

Basically, these are all the different types of vaccines



Types of Vaccines

Attenuated vaccines

"Live Vaccines"

A Pakistani health worker gives polio vaccine drops to a child as part of current polio eradication efforts.

Attenuated vaccines were made by growing pathogen in non-human cell culture system until the pathogen is less virulent in humans. Now attenuated vaccines can be made using recombinant DNA technology.

- Examples Sabin Oral polio vaccine (OPV). Measles. Mumps. Rubella. Varicella zoster virus (VZV).

Types of Vaccines

Attenuated vaccines

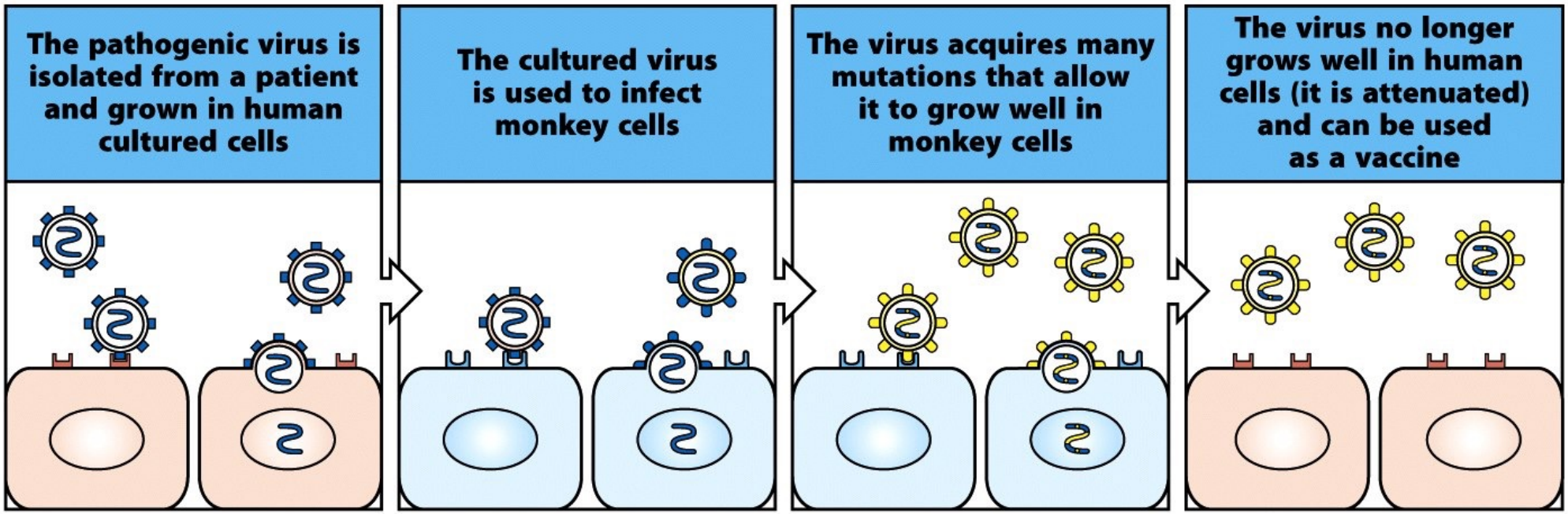
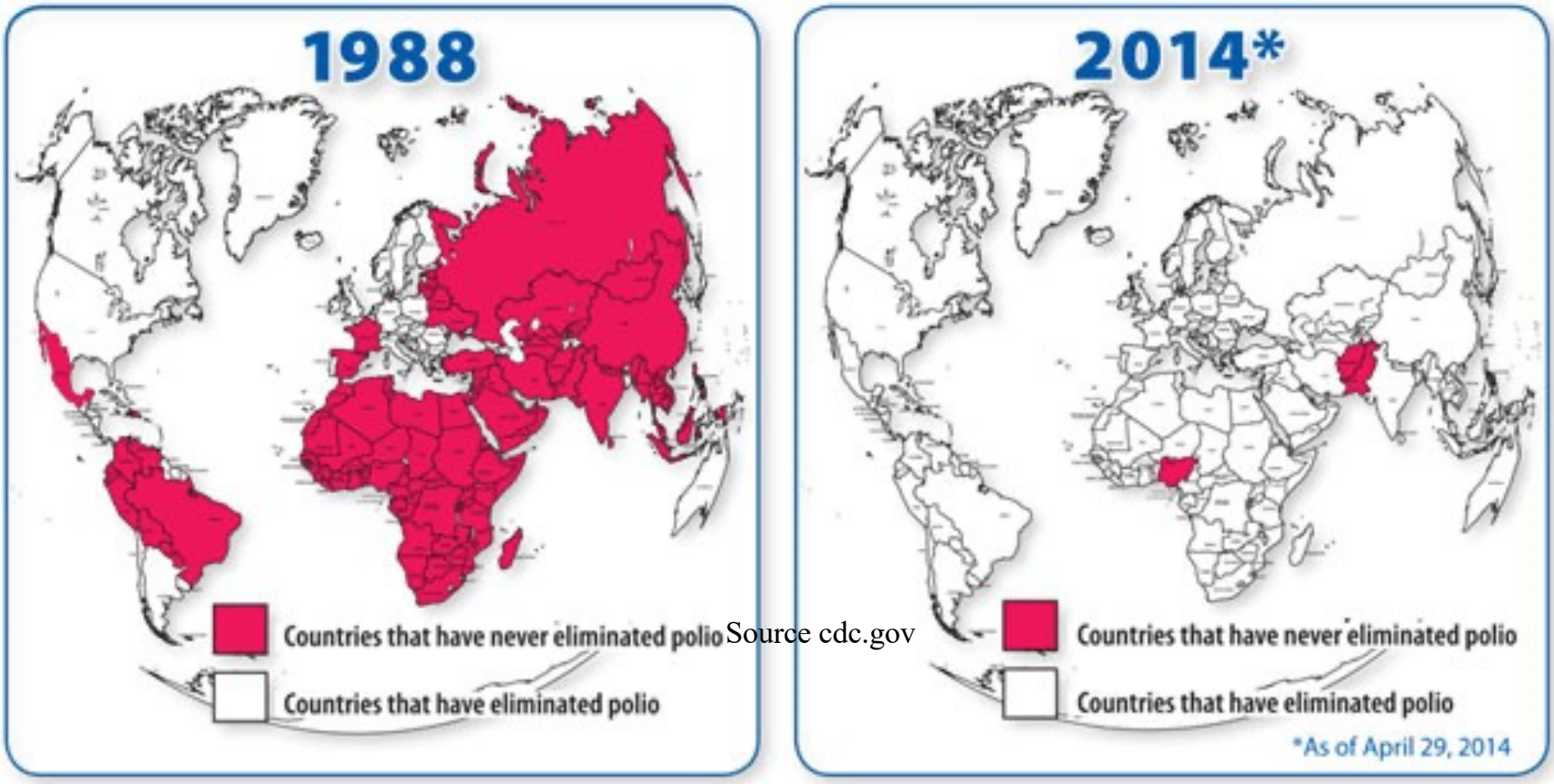


Figure 15-29 Immunobiology, 7ed. (© Garland Science 2008)

Pathogen is passaged in non-human cell culture until it has low replication in human cells.

Success with attenuated polio vaccine



Source cdc.gov

Polio Eradication efforts using better surveillance and strategic vaccination have reduced incidence to less than 50 cases/year worldwide.

Paid for by Bill & Melinda Gates Foundation and Jeffrey Modell Foundation

http://polioeradication.org/polio-today/polio-now/

Types of Vaccines
Attenuated vaccines

- Advantages:
  - Self-replicating can use low dose and no adjuvant
  - Authentic antigen presentation
  - More effective at eliciting CTLs
- Disadvantages:
  - If vaccine replicates, the vaccine could infect other people and mutate to return to virulent (reverse the attenuation).
  - Does not deal with strain variability/antigenic variation

Types of Vaccines
Inactivated Vaccines

Killed (inactivated) whole organism OR inactivated toxin. These vaccines are inactivated by heat, chemicals, or irradiation

Examples; Influenza, Hepatitis A virus, Pertussis bacteria, Salk inactivated polio vaccine (IPV), tetanus toxin, diphtheria toxin

- Advantages: No revirulence (higher safety).
- Disadvantages: No replication of pathogen, poor antigen presentation for CTLs.

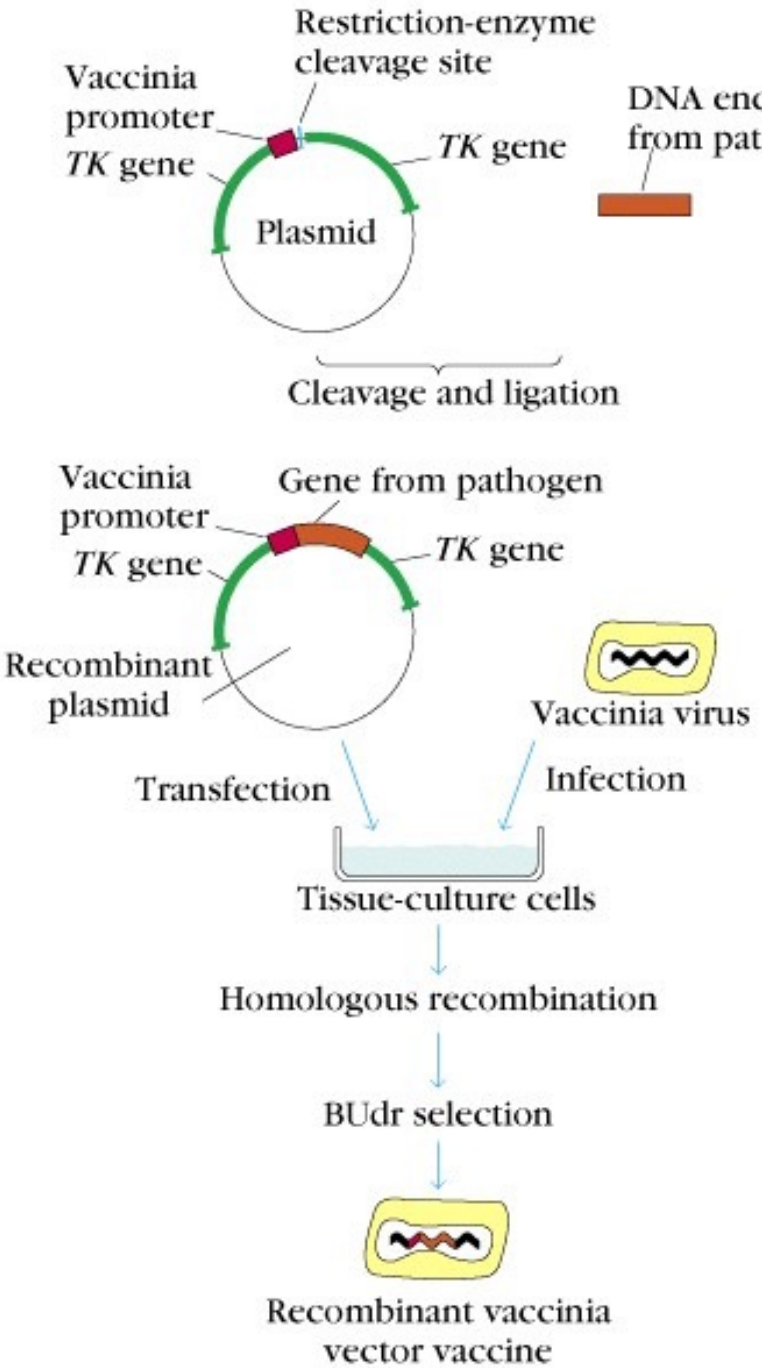
Flu Vaccines

- Standard Inactivated vaccine– the “flu shot”

Given intramuscular in arm.100 million doses available each year. Usually **trivalent with 3 different viral strains.**

- Traditional approach: Identify target "new virulent" strains, recombine and grow in **eggs**.

Subunits in live vector vaccines



Insert genes from pathogen into a well characterized vaccine vector.
(Common vectors: Vaccinia, adenovirus, salmonella, vesicular stomatitis virus).

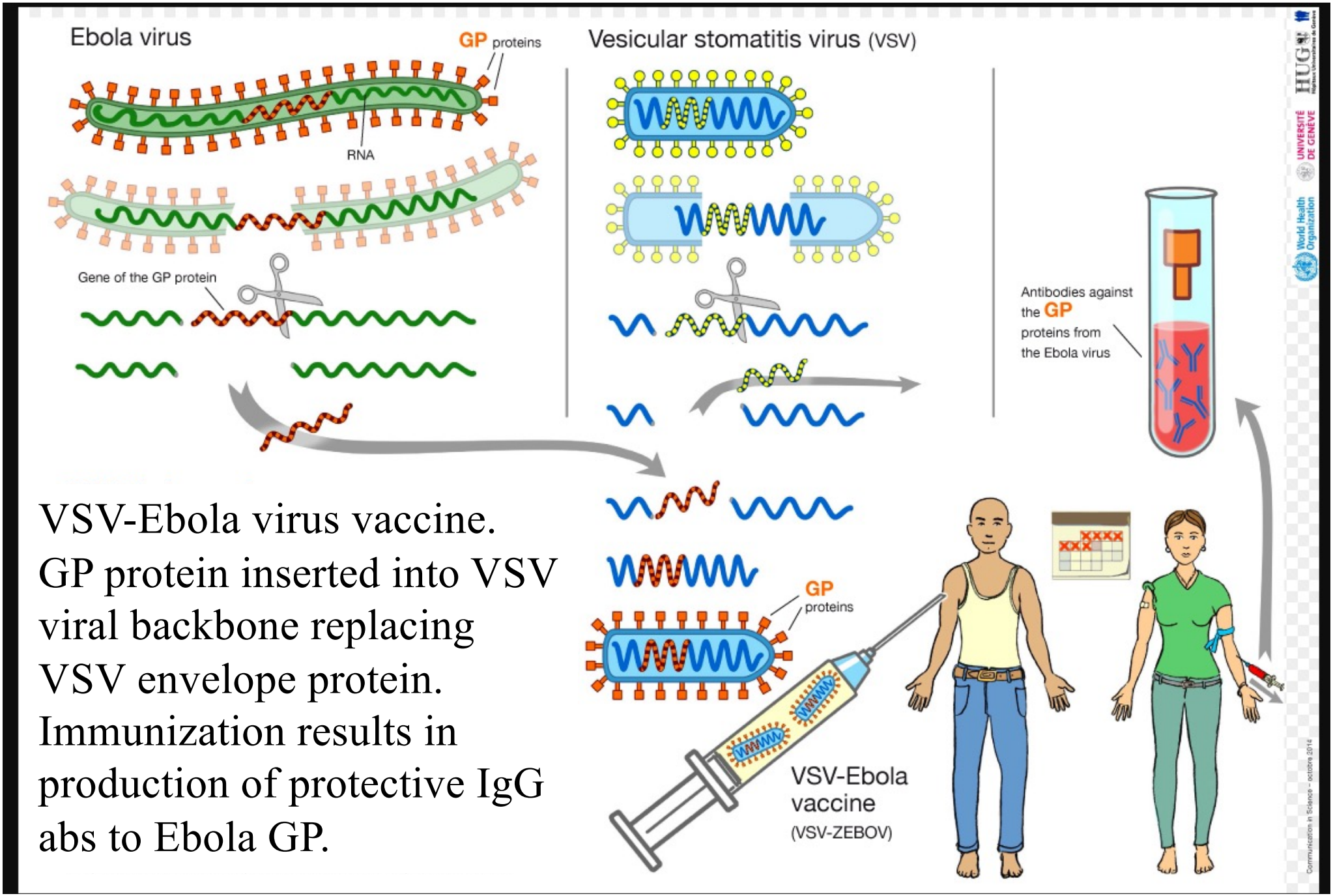
Advantages

Live vaccines are self-replicating.
No adjuvant needed.

Disadvantages

Live vector could be an issue with possible pathogenesis.

Live vector vaccine for Ebola



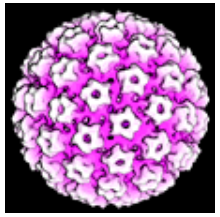
VSV-Ebola virus vaccine.
GP protein inserted into VSV viral backbone replacing VSV envelope protein.
Immunization results in production of protective IgG abs to Ebola GP.

Types of Vaccines

Recombinant protein vaccines

- Identify immunogenic proteins.
  - Usually, envelope or outer membrane proteins.
  - Produce large quantities for immunization.
  - Examples: Hepatitis B virus, HPV, new malaria vaccine.
- Advantages:
  - Potentially less expensive production. Very safe.
- Disadvantages:
  - Protein alone= no replication of pathogen, need adjuvant and boosters. May not elicit long-term memory as well.

Human Papilloma virus (HPV) vaccine
Recombinant protein vaccine



Vaccinia is used to express HPV capsid proteins that create "virus-like particles" (VLPs) that mimic structure of virus. VLPs contain no HPV viral DNA.

People are immunized 3 times with VLPs + adjuvant

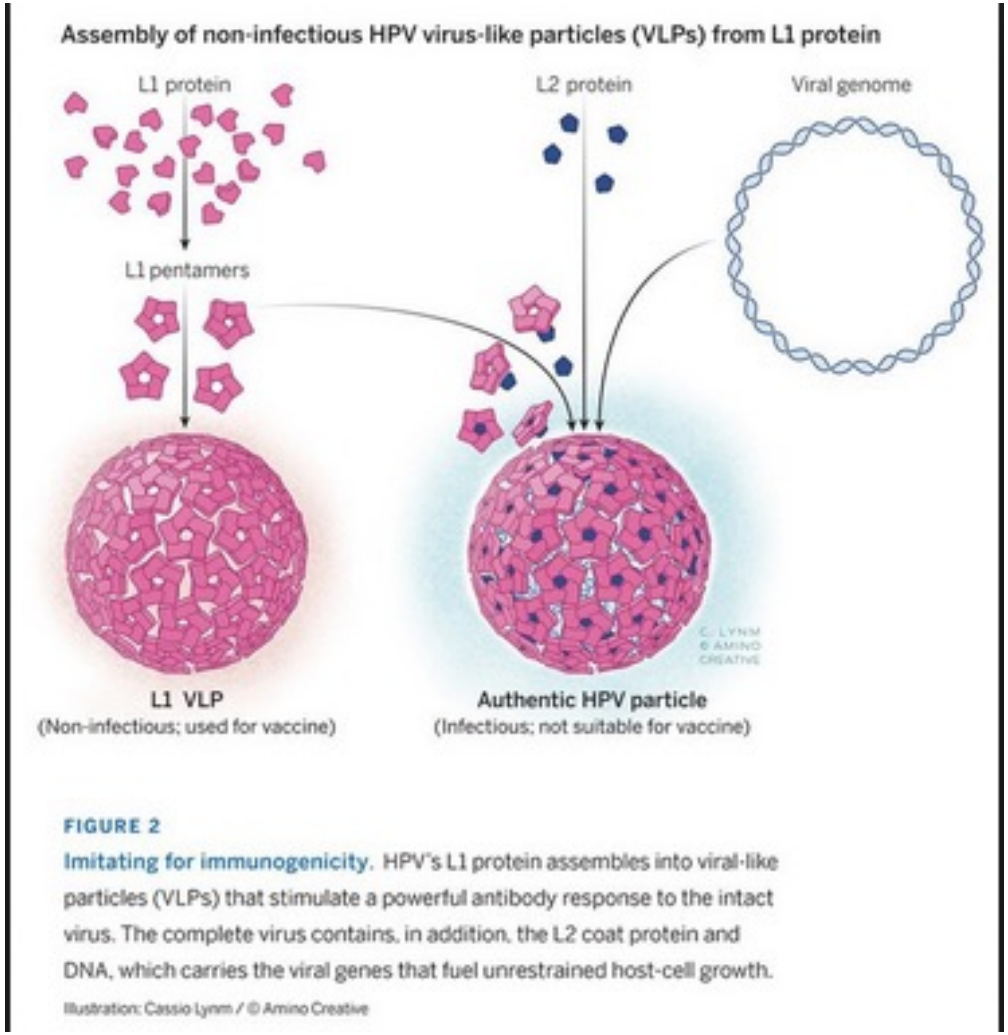
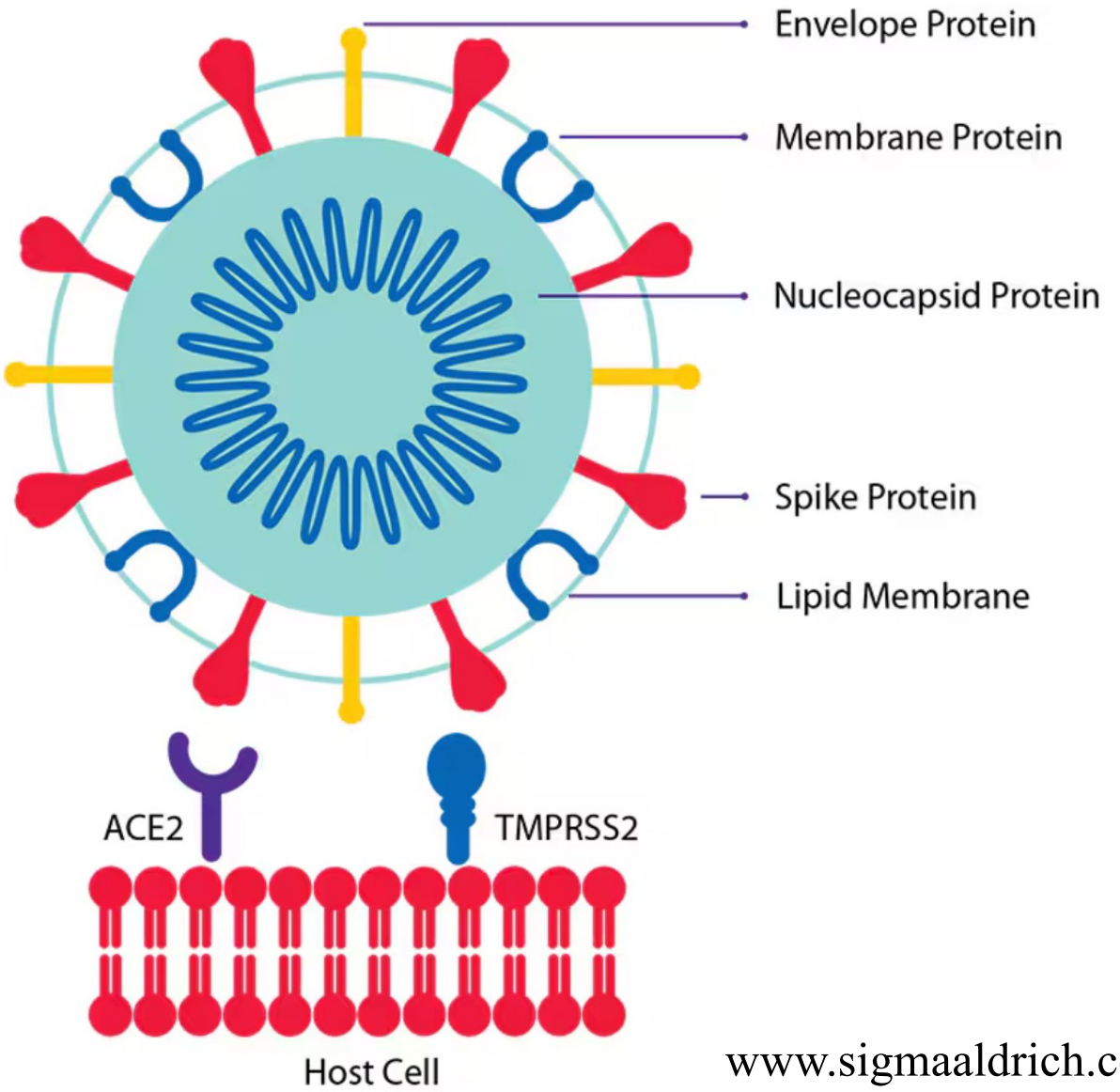


FIGURE 2

Imitating for immunogenicity. HPV's L1 protein assembles into viral-like particles (VLPs) that stimulate a powerful antibody response to the intact virus. The complete virus contains, in addition, the L2 coat protein and DNA, which carries the viral genes that fuel unrestrained host-cell growth.

Illustration: Cassio Lynm / © Amino Creative

Spike protein makes up the distinctive crown structure on surface of SARS CoV-2.
Spike is key target of neutralizing antibodies

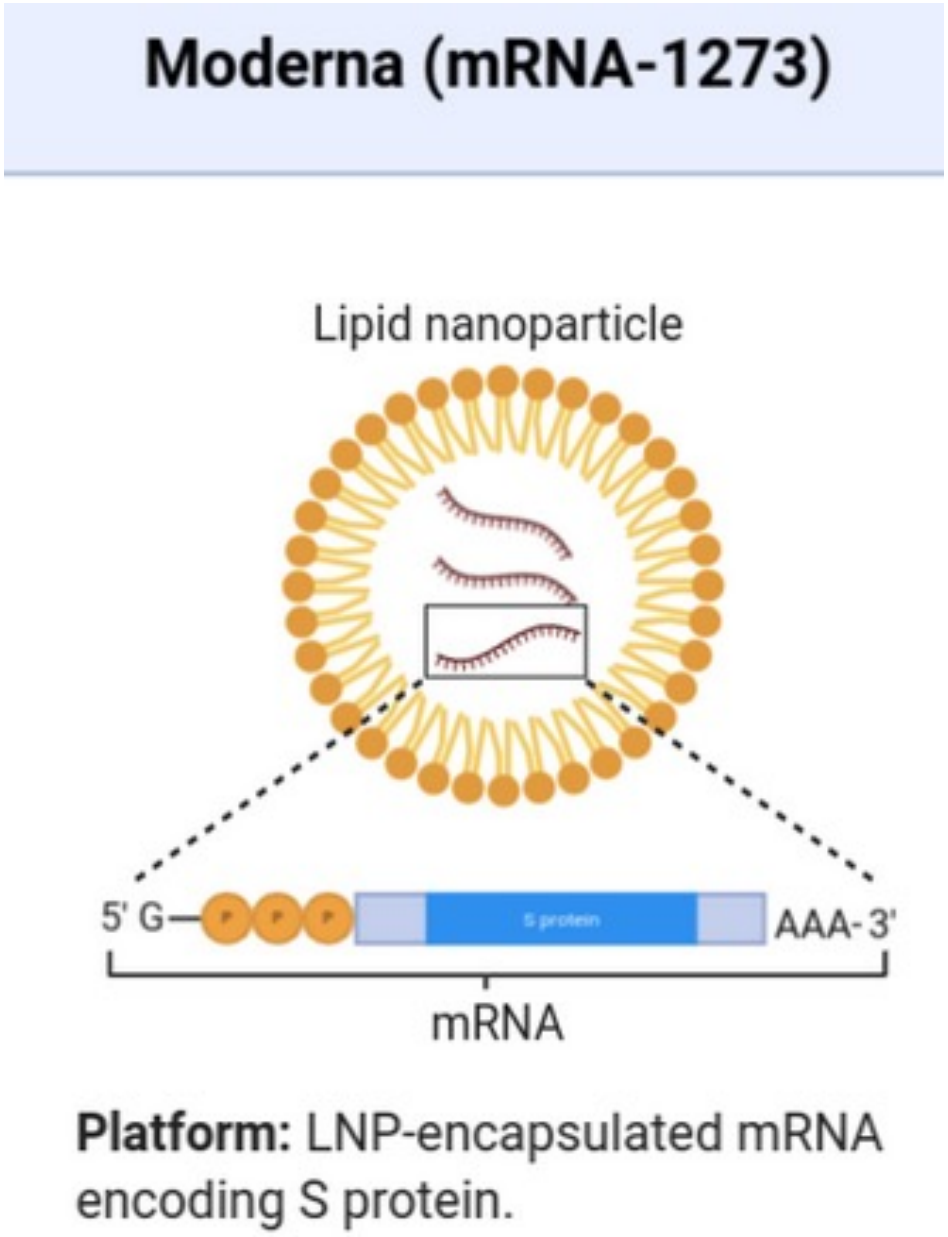


www.sigmaaldrich.com

Most SARS vaccines use SARS CoV-2 spike protein as main antigen! Few have whole virus.

Moderna's SARS CoV-2 mRNA Vaccine

Moderna vaccine is mRNA for spike protein inside lipid nanoparticle (various lipids with PEG2000).
Host cells "uptake" the spike mRNA and generate the spike protein.
Protein must get released from cell to generate Th and antibody response.



mRNA Vaccines Pros and Cons

PROS

- Fast production and ease for inserting new viral strain/variant into same mRNA vector.
- Mimics aspects of infection- gets inside cells, makes proteins, lipid nanoparticle activates TLRs.
- Safer than most vaccine types.

CONS

- Must be encapsulated in lipids or sugars.
- Must be kept frozen until use.
- Not very stable once thawed for use.

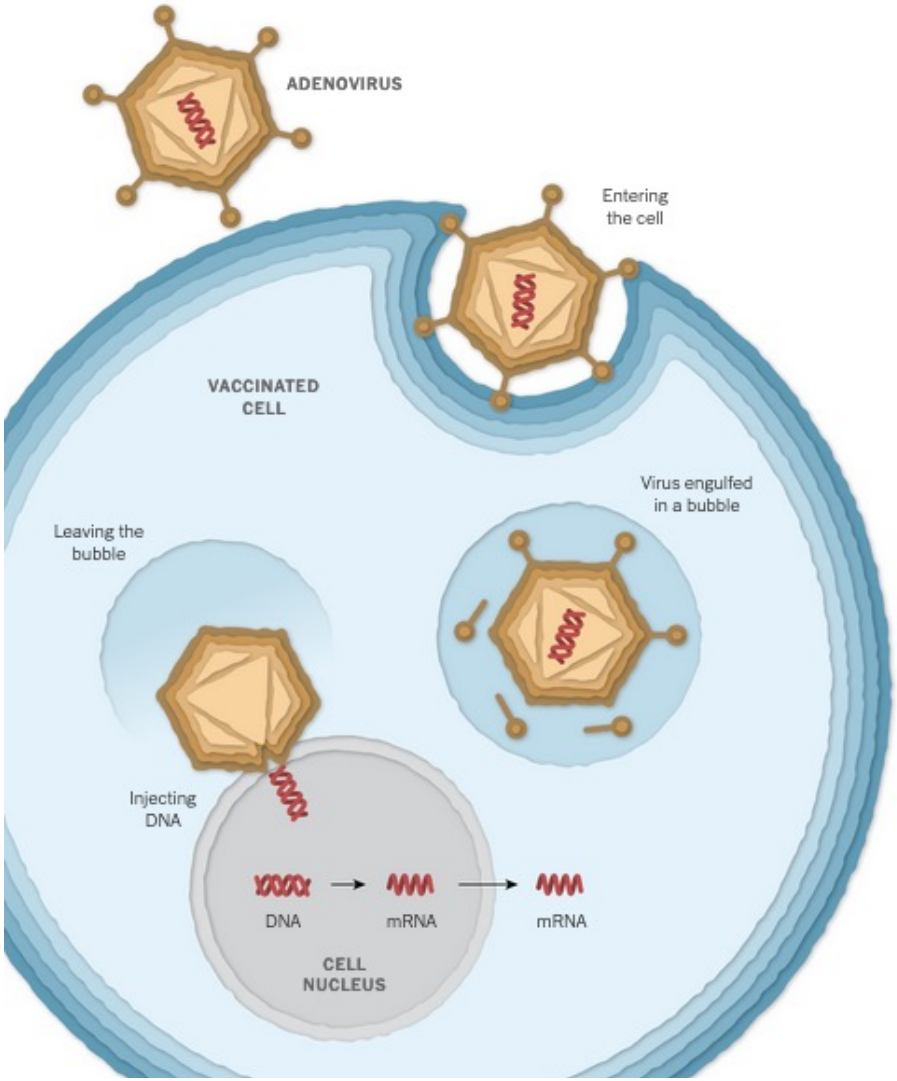
Johnson and Johnson Adeno/Spike vaccine

JNJ-78436735/Ad26.COV2.S. Adenovirus 26/spike given as a single dose had efficacy of 66-72%.

Spike gene added to Adenovirus 26 (a modified adenovirus that can enter cells, but virus can not replicate).
Only makes spike protein!

Adenoviruses are common viruses that typically cause colds or flu-like symptoms.

https://www.nytimes.com/interactive/2020/health/johnson-johnson-covid-19-vaccine.html



Issues in Vaccine Development

Efficacy. How well the vaccine protects the immunized population. Most common human vaccines are >90% protective but influenza virus vaccine is 20-70% protective.

- How efficacious (protective) does a vaccine need to be for general use?
- There might be different efficacy in adults versus children OR in immunocompetent versus immunocompromised individuals.

Issues in Vaccine Development

Cost. Number of people vaccinated versus cost to manufacture.

Most original attenuated vaccines were incredibly cheap.

- The WHO BIG SIX: diphtheria toxoid, tetanus toxoid and acellular pertussis (DTaP), polio, measles, and BCG cost <$1/person. WHO has vaccinated >80% of the world population with these vaccines.
- New vaccines usually have incredibly high development costs that result in a high initial cost and can take years before costs come down depending on volume of production.