Development and Formulation of Vaccines

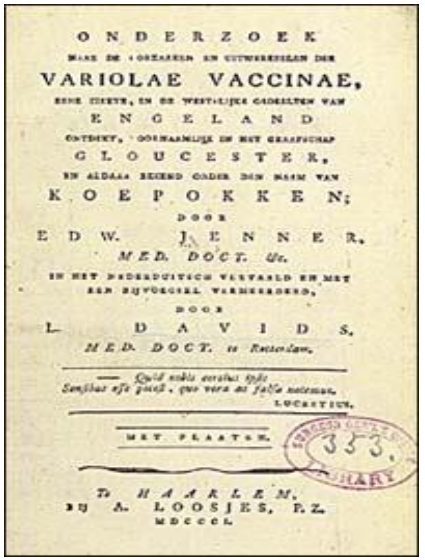
Dr. Omar Sarheed, PhD
Department of Pharmaceutics
RAK College of Pharmaceutical Sciences

Learning Objectives

- Define vaccines
- Classify different types of vaccines
- Describe vaccines development and production
- Explain the importance of vaccine safety
- Describe adverse effects associated with vaccines
- Describe some formulation aspects of vaccines

What is a Vaccine?

- **A vaccine is an antigenic material that stimulate adaptive immunity to a disease.**
- **The word “vaccine” originates from the Latin Variolae vaccinae (cowpox), which Edward Jenner demonstrated in 1798 could prevent smallpox in humans.**


ONDERZOEK
VARIOLAE VACCINAE,
ENGELAND
GLOUCESTER,
KOEPOKKEN;
DOOR
EDW. JENNER,
M.E.D. DOCT. &c.
DOOR
L. DAVIDS,
M.E.D. DOCT. te Rotterdam.
MET PLAATEN.
TE HAARLEM,
BIJ A. LOOSJES, P.Z.
MDCCCI.

Types of Vaccination

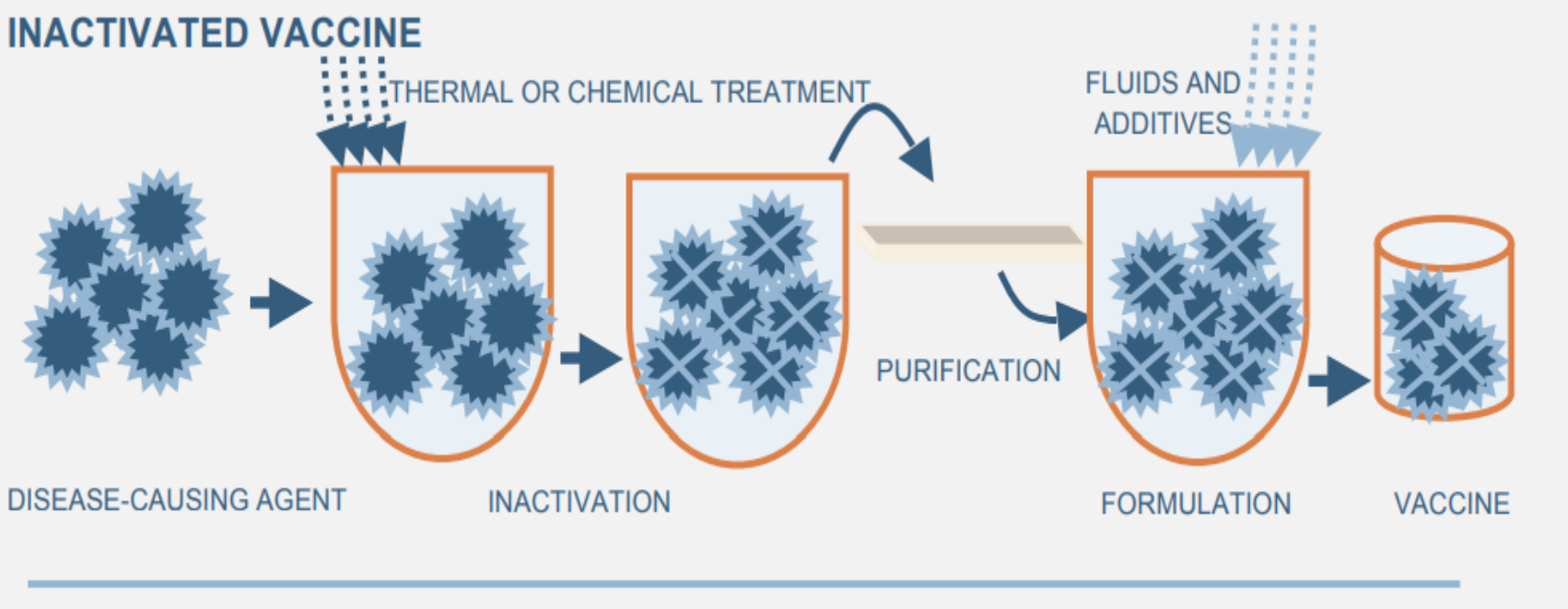
- **Main types that are currently in clinical use are:**

Type of vaccine	Examples
Live-attenuated	Measles, Mumps, Rubella, Varicella zoster
Inactivated	Hepatitis A, Influenza, Pneumococcal polysaccharide
Recombinant sub-unit	Hepatitis B
Toxoid	Tetanus, Diphtheria
Conjugate polysaccharide-protein	Pneumococcal, meningococcal, *Haemophilius influenzea* type b (Hib)

http://www.phrma-jp.org/wordpress/wp-ontent/uploads/old/library/vaccine-factbook_e/1_Basic_Concept_of_Vaccination.pdf

Inactivated Vaccine

- **An inactivated vaccine consists of virus particles which are grown in culture and then killed using a method such as heat or formaldehyde.**



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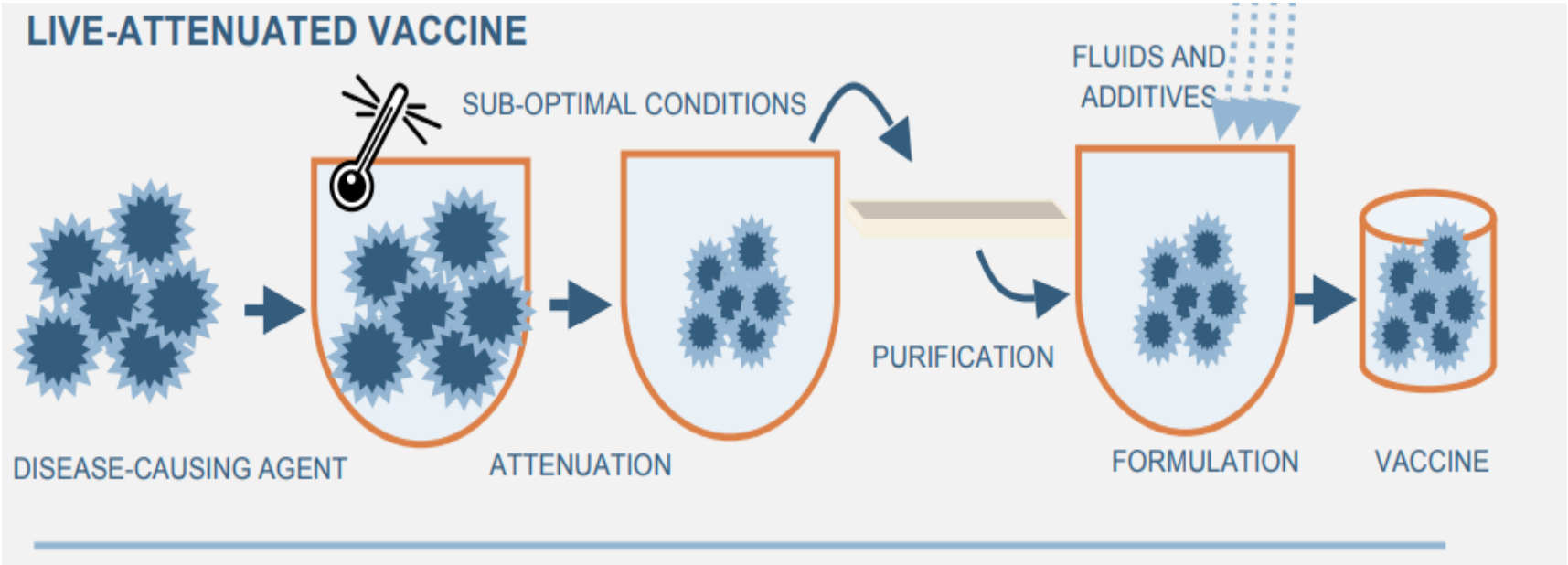
Attenuated Vaccine

- **Live virus particles with very low virulence are administered. They will reproduce, but very slowly. Since they do reproduce and continue to present antigen beyond the initial vaccination, boosters are required less often. There is a small risk of reversion to virulence**



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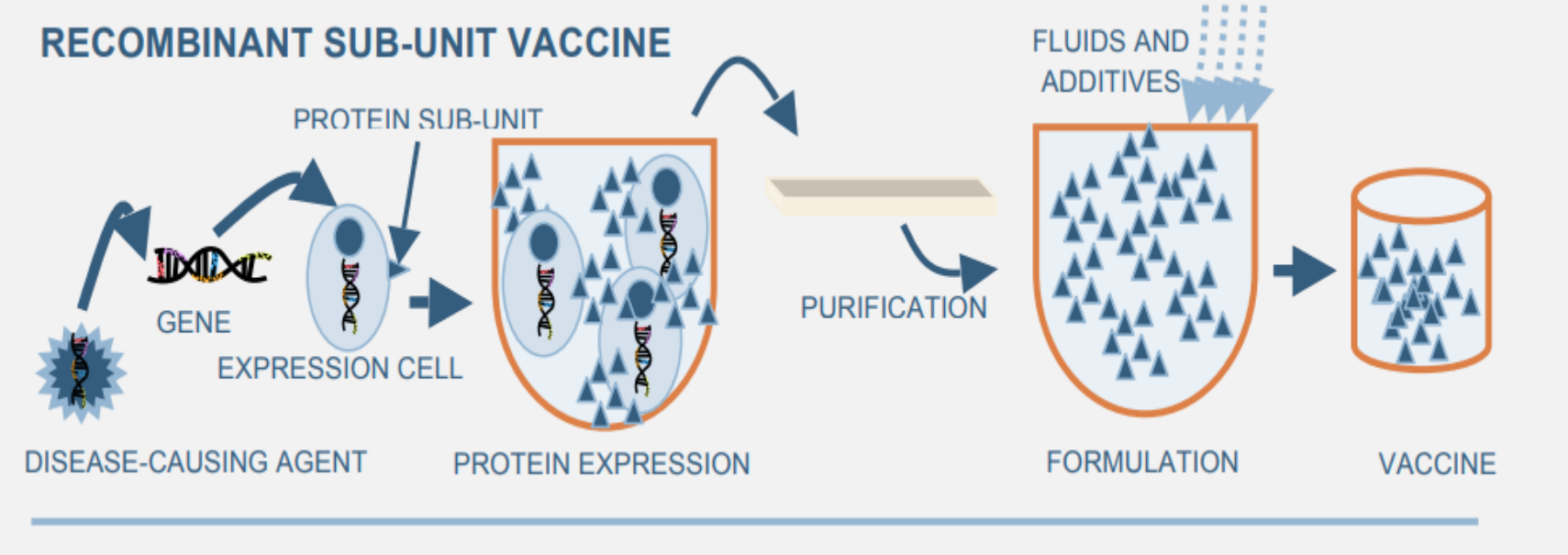
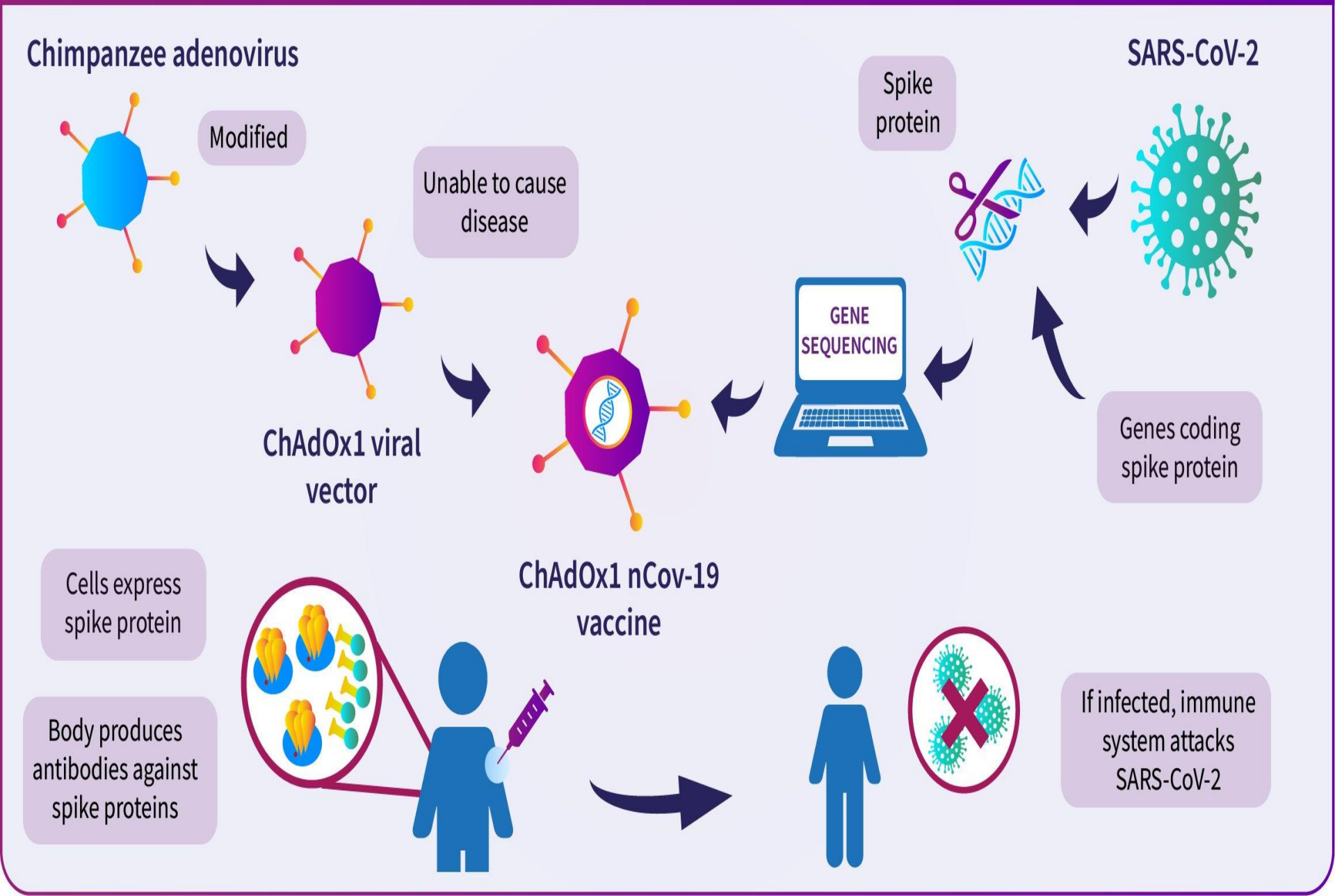
Subunit Vaccine

- **A subunit vaccine presents an antigen to the immune system without introducing viral particles, whole or otherwise. A weakness of this technique is that isolated proteins may have a different three dimensional structure than the protein in its normal context, and will induce antibodies that may not recognize the infectious organism.**



http://www.phrma-jp.org/wordpress/wp-ontent/uploads/old/library/vaccine-factbook_e/1_Basic_Concept_of_Vaccination.pdf

COVID-19 OXFORD VACCINE TRIAL

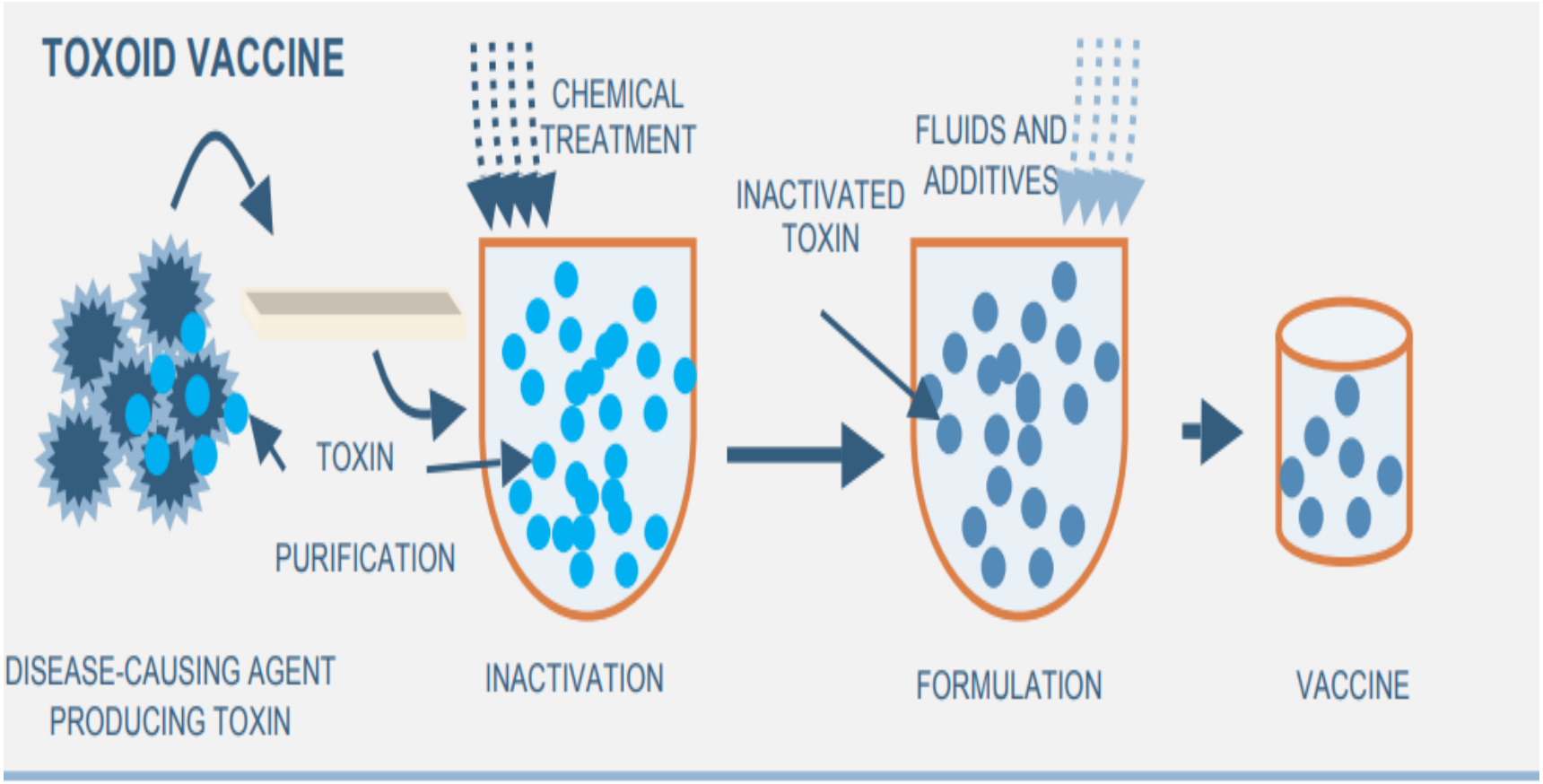


How the Oxford COVID-19 vaccine works

- The ChAdOx1 vaccine is a chimpanzee adenovirus vaccine vector. This is a harmless, weakened adenovirus that usually causes the common cold in chimpanzees.
- ChAdOx1 was chosen as the most suitable vaccine technology for a SARS-CoV-2 vaccine as it has been shown to generate a strong immune response from one dose in other vaccines.
- It has been genetically changed so that it is impossible for it to grow in humans.
- Chimpanzee adenoviral vectors are a very well-studied vaccine type, having been used safely in thousands of subjects.

https://www.research.ox.ac.uk/Article/2020-07-19-the-oxford-covid-19-vaccine

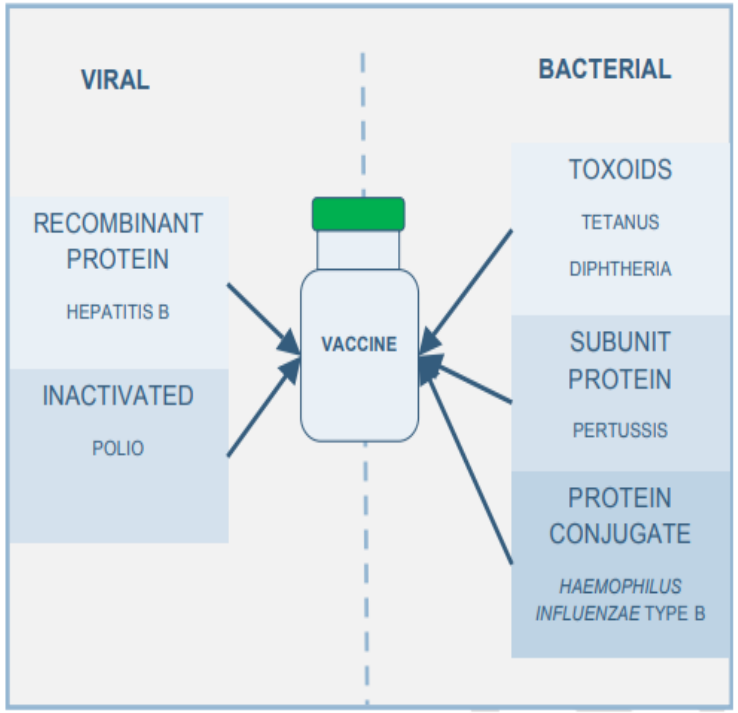
Toxoid Vaccine



http://www.phrma-jp.org/wordpress/wp-ontent/uploads/old/library/vaccine-factbook_e/1_Basic_Concept_of_Vaccination.pdf

Common Combination Pediatric Vaccine

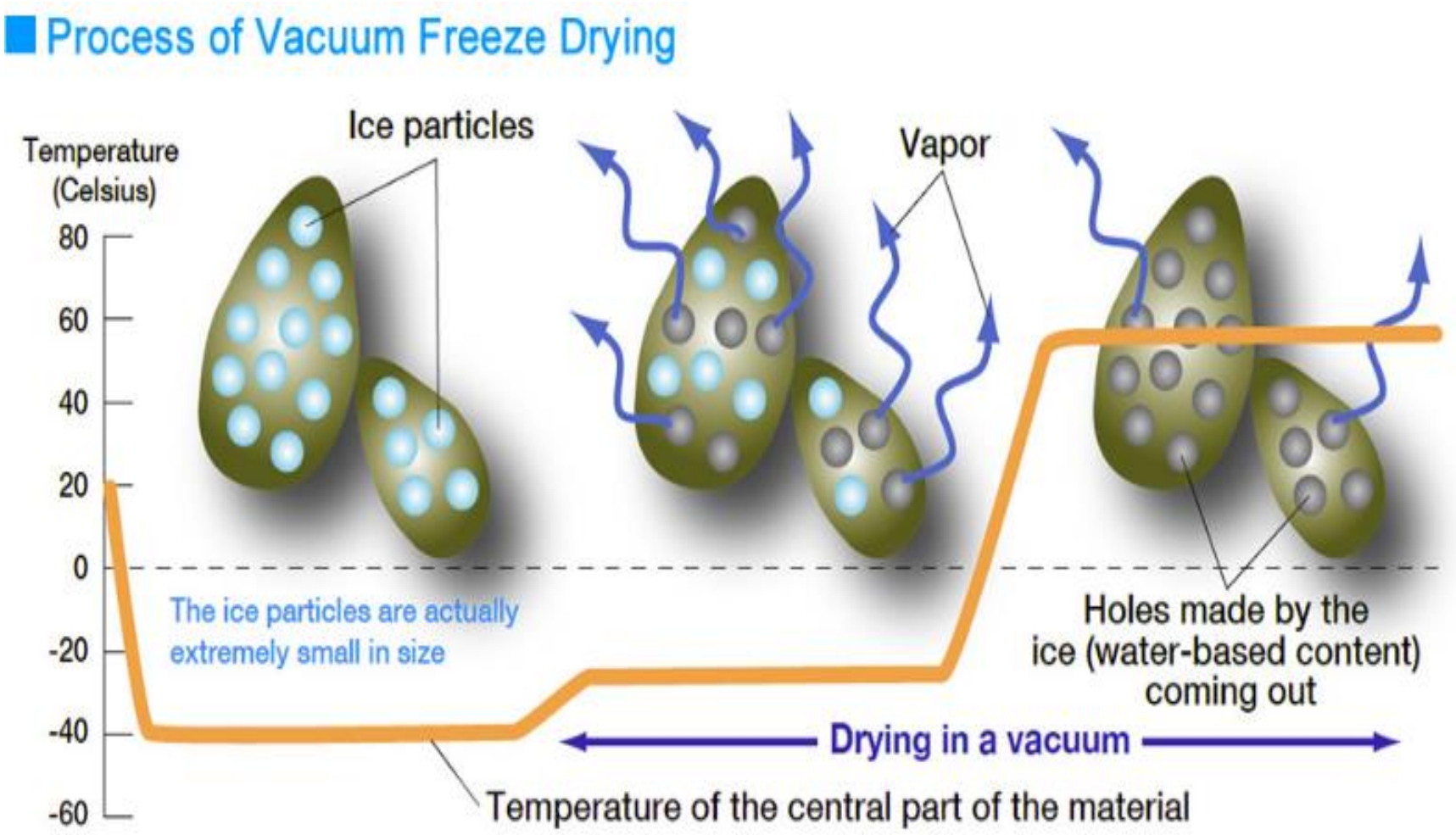
- **Vaccines incorporate both viral and bacterial vaccines and contain toxoids, purified protein sub-unit vaccine, conjugated polysaccharide vaccine, recombinant protein vaccine, and inactivated viral vaccine respectively.**



What Does a Vaccine Contain?

- Vaccines are formulated (mixed) with other fluids (such as water or saline), additives or preservatives, and sometimes adjuvants.
- These ingredients are known as the excipients.
- These ensure the quality and potency of the vaccine over its shelf-life.
- Vaccines are usually formulated as liquids, but may be freeze-dried (lyophilized) for reconstitution immediately prior to the time of injection.

Freeze-drying (Lyophilization)



www.ulvac.com.sg

Preservatives

- **Ensure the sterility of the vaccine over the period of its shelf-life.**
- **Preservatives may be used to prevent contamination of multi-dose containers.**

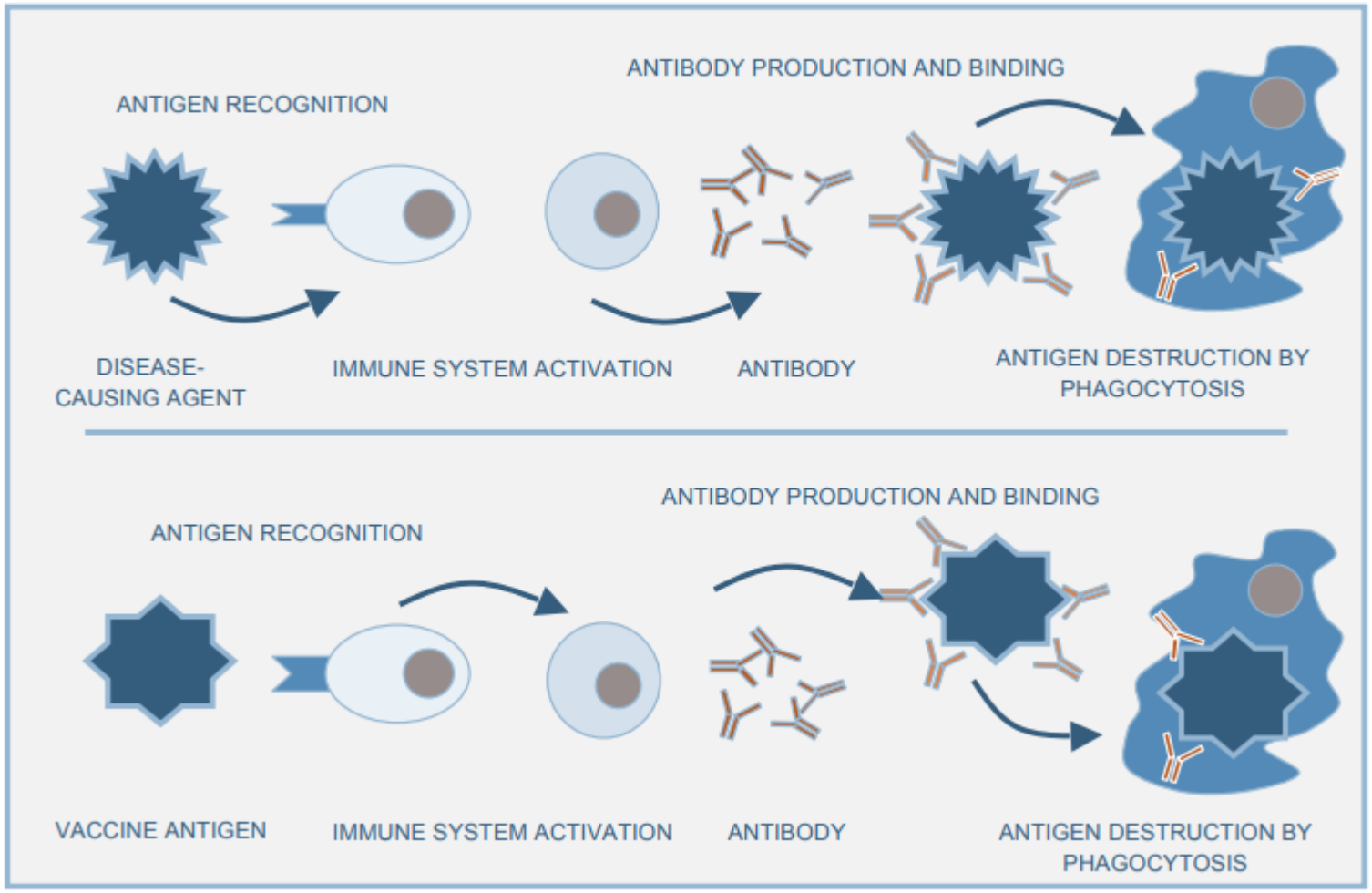
Preservative	Vaccines
Phenol	Typhoid, pneumococcal polysaccharide
Benzethonium chloride	Anthrax
2-phenoxyethanol	Inactivated polio
Thimerosal	Multi-dose influenza

US Department of Health and Human Services. US Food and Drug Administration. Thimerosal in vaccines. http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/VaccineSafety/UCM096228#t2
US Centers for Disease Control and Prevention. Vaccine safety. Frequently asked questions about adjuvants. http://www.cdc.gov/vaccinesafety/Concerns/adjuvants.html. [Accessed on March 7, 2019]

Adjuvants

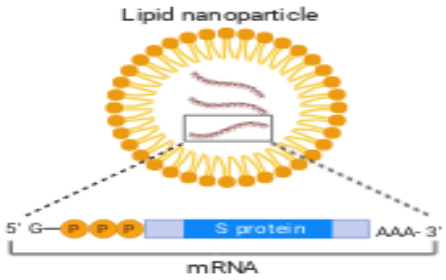
- **Adjuvants enhance the immune effect of the vaccine antigen, but do not themselves act as antigens.**
- **Aluminum salts are the most commonly used adjuvant for vaccines.**
- **Adjuvanted vaccines may have a slightly higher rate of adverse reactions, including pain at the injection site, malaise and fever.**

How Do Vaccines Work?



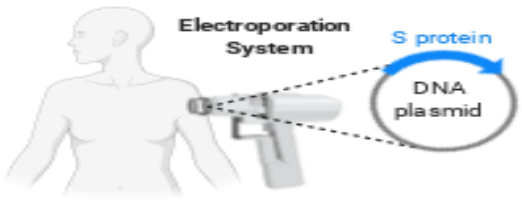
Clinical Phase Vaccine Candidates for COVID-19*

Moderna (mRNA-1273)



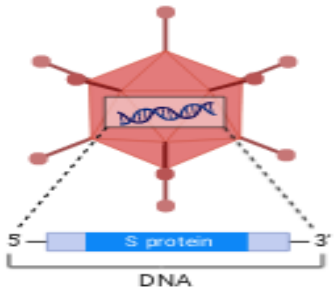
Platform: LNP-encapsulated mRNA encoding S protein.

Inovio Pharma (INO-4800)



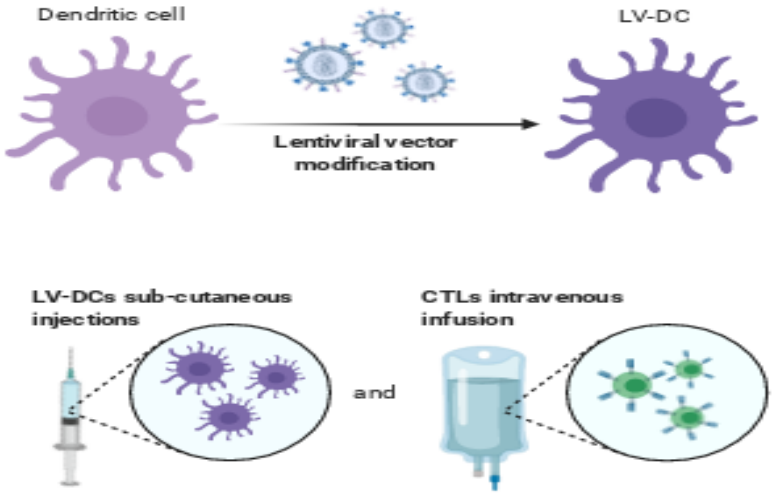
Platform: Electroporation of DNA plasmid encoding S protein.

CanSino Biologics (Ad5-nCoV)



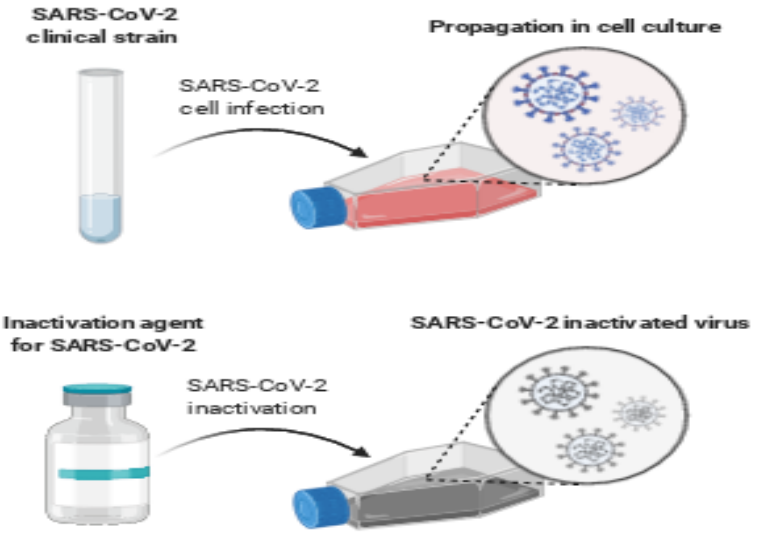
Platform: Adenovirus type 5 vector that expresses S protein.

Shenzhen Medical Institute (LV-SMENP-DC)



Platform: Lentiviral vector modification of dendritic cells (LV-DCs) and antigen-specific cytotoxic T lymphocytes (CTLs).

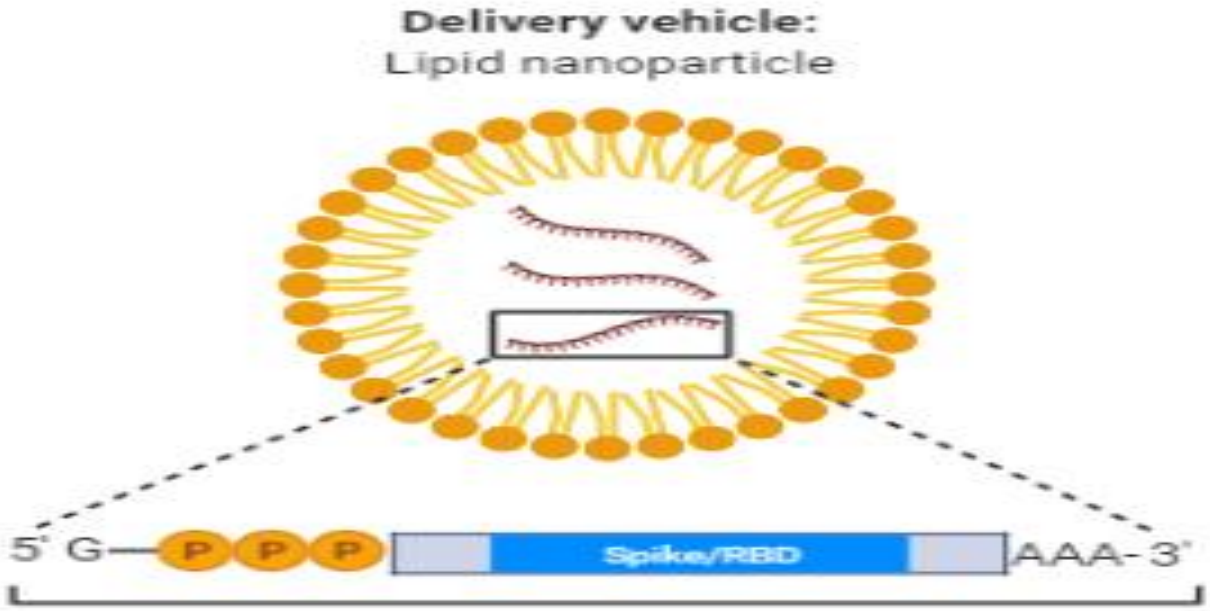
Sinovac Biotech (unnamed)



Platform: Inactivated virus vaccine produced from viral propagation in cells infected with a SARS-CoV-2 clinical strain.

*As of April 2020

BioNTech (BNT162: a1, b1, b2, c2)



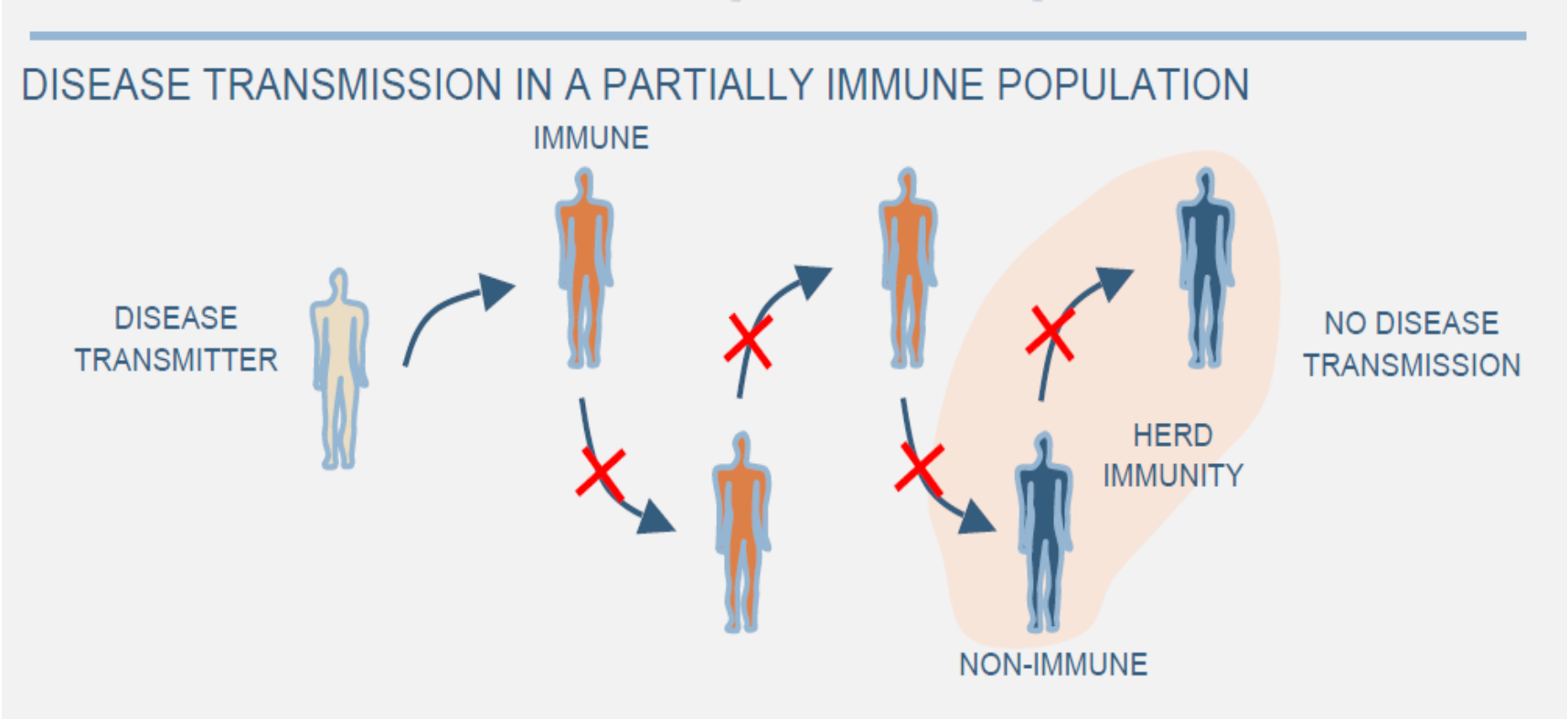
Platform: Four individual LNP-encapsulated mRNA vaccines (2 modRNA, 1uRNA, 1 saRNA) encoding Spike protein or Receptor Binding Domain (RBD).

Vaccine Efficacy

- Is the reduction in incidence of a disease amongst those who have been vaccinated relative to the incidence in the unvaccinated.
- Most effective vaccines induce a protective immune response in > 95% of individuals.
- When disease transmission is interrupted, even those individuals who were not vaccinated, or who were vaccinated and did not develop immunity, will be protected from disease. This effect is known as **HERD immunity.**

Vaccine Efficacy

- Smallpox was eradicated by achieving sufficient immunization coverage to prevent transmission of disease to unvaccinated non-immunes (susceptible).



Officials at the European Medicine Agency (EMA) said that even if the efficacy rate of a vaccine was below 50%, they could give it the green light as long it was safe, per the Wall Street Journal.

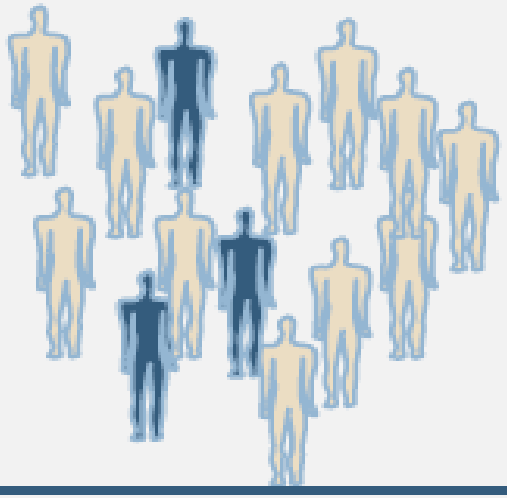
The guidance also discusses the importance of ensuring that the sizes of clinical trials are large enough to demonstrate the safety and effectiveness of a vaccine. It conveys that the FDA would expect that a COVID-19 vaccine would prevent disease or decrease its severity in at least 50% of people who are vaccinated.

https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-takes-action-help-facilitate-timely-development-safe-effective-covid

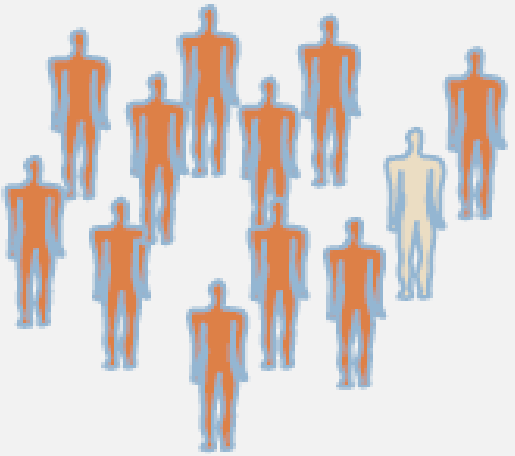
Vaccine Efficiency

- **It measures the decrease in incidence of a disease in the vaccinated population compared to the incidence of the disease in the unvaccinated population.**
- **In epidemiological terms, it is defined as the difference between the Attack Rate of the disease in the Unvaccinated and the Vaccinated relative to the Attack Rate in the Unvaccinated.**

PROPORTION INFECTED IN THE UNVACCINATED



PROPORTION INFECTED IN THEVACCINATED



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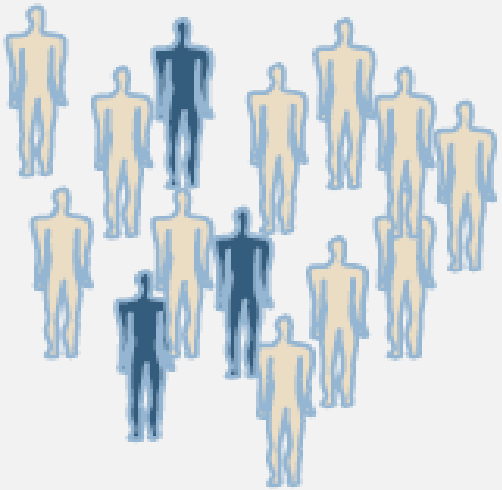
PROPORTION INFECTED IIN THE UNVACCINATED



= INFECTED

= NOT INFECTED UNVACCINATED

= NOT INFECTED VACCINATED

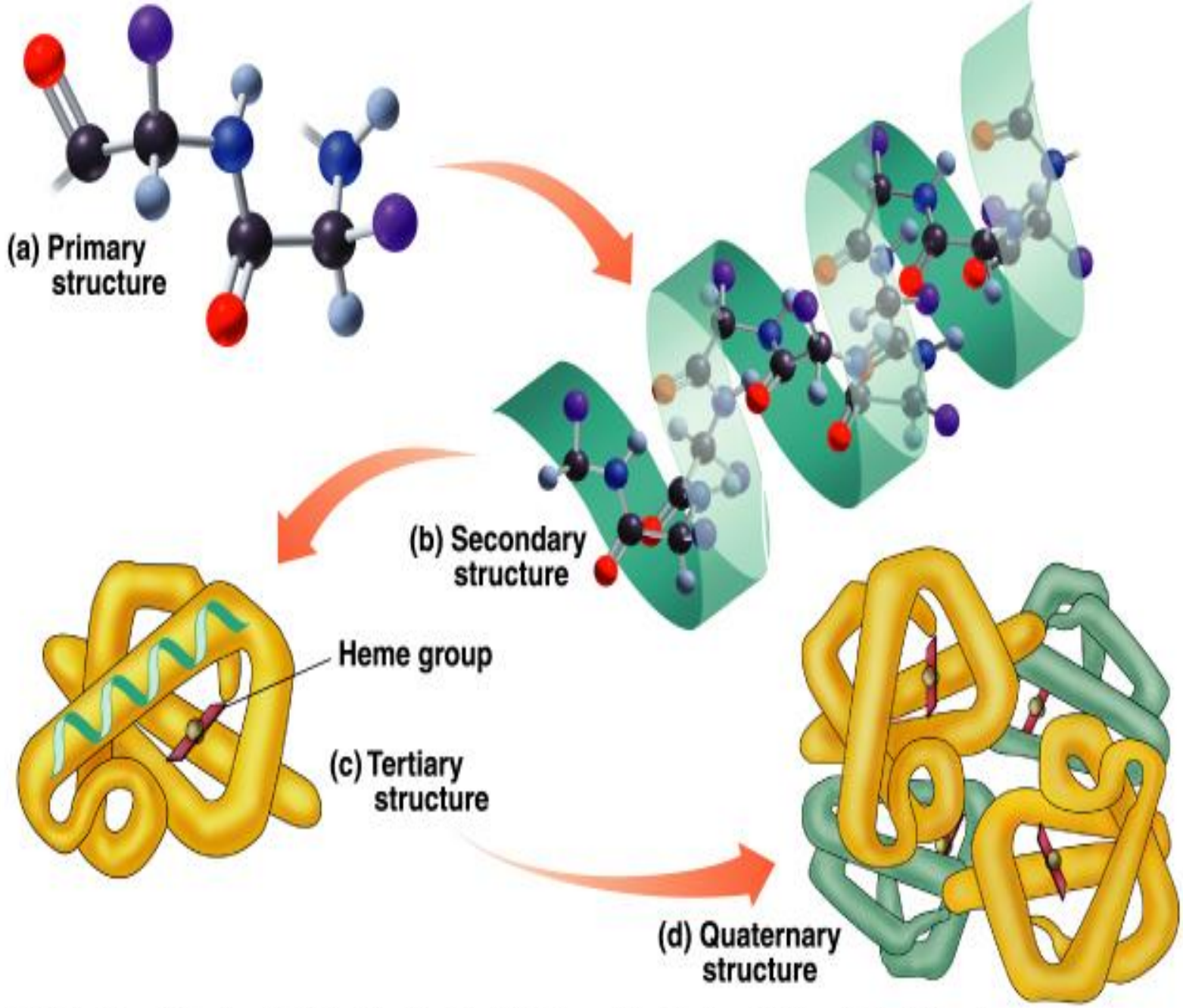
Vaccine Safety

- The vast majority of adverse events associated with vaccines are minor and transient. These are typically pain at the injection site, or mild fever.
- More serious adverse events occur rarely. Some serious adverse events may be so rare that they occur only once in millions of vaccine doses delivered*.
- Some individuals may be sensitive to some components or trace elements in some vaccines, such as eggs, antibiotics, or gelatin.

Australian government. The Australian immunization handbook 9th edition. 1.5. post-vaccination procedures. http://www.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook-adverse

Adverse Event Classification

- Vaccine-induced
- Vaccine-potentiated
- Programmatic error
- Coincidental



Chemical degradation of proteins

- The mechanisms by which proteins and peptides degrade include
  - deamidation,
  - racemination,
  - hydrolysis,
  - oxidation, and
  - disulphide exchange,
- deamidation and oxidation being the most common degradation pathways

Dave A. Parkins and Ulla T. Lashmar, (2000). The formulation of biopharmaceutical Products. PSTT

Primary structure and stability

Table 1. Amino acids or sequences susceptible to chemical degradation, together with formulation strategies to reduce degradation.

Amino acid or sequence	Mechanism of degradation	Formulation strategy
Cysteine–cysteine	Aggregation	Addition of surfactants, polyalcohols and other excipients
Glutamine, asparagine	Deamidation	pH 3–5
Tryptophan, methionine, cysteine, tyrosine, histidine	Oxidation	pH <7
Methionine	Oxidation	Protect from oxygen
Tryptophan	Photo decomposition	Protect from light
Lysine–threonine	Copper induced cleavage	Chelating agents
Asparagine–proline, asparagine–tyrosine	Hydrolysis	pH >7

Dave A. Parkins and Ulla T. Lashmar, (2000). The formulation of biopharmaceutical Products. PSTT

Formulation strategies for macromolecules

- **Exclusion of water**
  - The stability of many macromolecules can be enhanced by the exclusion of water from the product.
  - Freeze-drying is most often employed for this purpose.

Formulation strategies for macromolecules

- **Sugars**
  - Sugars have been shown to protect macromolecules against denaturation and are particularly used as cryoprotectants.
  - The presence of a sugar creates a thermodynamically unfavourable condition, because the chemical potential – the partial molar free energy for both the macromolecule and the sugar – is increased.
  - Preferential exclusion of the sugar from the surface of the macromolecule minimizes thermodynamic activity, which in turn preserves the preferred conformation.

Formulation strategies for macromolecules

- **Amino acids**
  - Amino acids have been added to biopharmaceuticals for a variety of reasons; dicarboxylic amino acids such as aspartic and glutamic acid have been used to reduce aggregation.
  - In addition, amino acids have been found to be useful as chelating agents, and may reduce surface adsorption.

Formulation strategies for macromolecules

- **Ionic compounds**
  - Ionic compounds such as salts and buffers interact with macromolecules via non-specific or specific binding.
  - Depending on the type of interaction, a salt may increase thermal stability, increase the solubility and reduce the extent of aggregation.

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- **Poster and plug stickers available to order from DH publications orderline (www.dh.gov.uk)**
- **CDC Vaccine Storage and Handling Toolkit http://www2a.cdc.gov/vaccines/ed/shtoolkit/**
- **WHO. Temperature sensitivity of vaccines. August 2006. http://www.who.int/vaccines-documents/DocsPDF06/847.pdf**


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