Vaccines

How They Work, Their History and Their Impact

By

AJ Russo

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Introduction

Vaccines are biological preparations that provide active acquired immunity to infectious diseases. They are considered one of the most effective tools for preventing illness and have had a profound impact on global health. The process of vaccine manufacturing is complex and involves several stages, each critical to ensuring the safety, efficacy, and quality of the final product. Key Points on Vaccine Manufacturing Processes

Selection and Cultivation of Antigens

The vaccine manufacturing process begins with the careful selection of target pathogens or antigens (1). These antigens are the components that will stimulate the immune system to recognize and fight the disease-causing organism (2). Once the target antigens are determined, they undergo a cultivation process to grow the necessary quantities (3).

Purification and Formulation

Following cultivation, antigens are purified to remove impurities and unwanted substances (4). This step is crucial to ensure that the vaccine is safe for human use. After purification, the antigens are combined with other components necessary for the vaccine formulation, such as adjuvants, stabilizers, and preservatives (5,6).

Testing and Regulatory Approval

Vaccines undergo rigorous testing to ensure their safety and effectiveness. Preclinical studies using animal models assess immunogenicity and potential side effects (8). Clinical trials involving human volunteers are then conducted to evaluate the vaccine's effectiveness, opti-

mal dosage, and safety profile (8). Regulatory approval is required before vaccines can be distributed and administered (9).

Types of Vaccines and Their Manufacturing Methods

Live-Attenuated Vaccines

Live-attenuated vaccines contain weakened forms of the virus or bacteria that are capable of replication but do not cause disease in healthy individuals (10,11). Examples include the MMR and varicella vaccines (12).

Inactivated Vaccines

Inactivated vaccines are made from pathogens that have been killed or inactivated, often using chemical treatments (13-15). The inactivated polio vaccine is an example of this type (16).

Subunit and Toxoid Vaccines

Subunit vaccines include only parts of the virus or bacteria, such as proteins or sugars, rather than the entire organism (17-18). Toxoid vaccines, on the other hand, use inactivated toxins produced by the bacteria (19).

Viral Vector and mRNA Vaccines

Viral vector vaccines use a harmless virus to deliver genetic material into host cells, prompting an immune response against the target antigen (20,21). mRNA vaccines, which have gained prominence during the COVID-19 pandemic, use the pathogen's genetic code to instruct cells to produce a protein that will trigger an immune response (22,23).

Recombinant Vaccine Technologies

Recombinant vaccine manufacturing involves cloning and producing single virus components, allowing for immunization against purified components (24). This method is used for vaccines like those against HPV and hepatitis B.

Evolution and Future of Vaccine Manufacturing

Cell Culture and Combination Vaccines

Vaccine manufacturing is evolving with cultured mammalian cells expected to become increasingly important, replacing conventional methods like chicken egg cultures (25). Combination vaccines aim to reduce antigen quantities and decrease undesirable interactions (26).

Regulatory and Economic Considerations

Vaccine manufacturing is subject to stringent regulatory oversight, with authorities licensing both the biological entity and the manufacturing processes (27). Cost pressures and the emphasis on efficient process development are significant factors in the vaccine industry (28).

Safety and Ingredients

Vaccine ingredients undergo thorough testing for safety and effectiveness (29,30). Each ingredient serves a specific purpose, such as stabilizing the vaccine or enhancing the immune response (6).

Conclusion

Vaccine manufacturing is a complex, multi-step process that is essential to produce safe and effective vaccines. The process involves the selection and cultivation of antigens, purification, formulation, and

extensive testing. There are several types of vaccines, each made using different technologies, and the field continues to evolve with advancements in science and technology. Collaboration among manufacturers, governments, and healthcare providers is crucial to ensure equitable access to vaccines worldwide (31). The ongoing research and development in immunology and infectious diseases drive the vaccine manufacturing process, ultimately contributing to the prevention of diseases and the promotion of public health.

Chapter 1

Selection and Cultivation of Antigens for Vaccines

Vaccines are a critical tool in preventing infectious diseases by stimulating the immune system to recognize and combat pathogens. The selection and cultivation of antigens are central to the development of effective vaccines. Here is a comprehensive look at how antigens are chosen and prepared for use in vaccines.

Selection of Antigens

Identifying the Active Component

All vaccines contain an active component known as the antigen, which is responsible for eliciting an immune response. The antigen can either be the actual pathogen, a part of it, or a blueprint for producing the antigen (1-3). The selection process involves extensive screenings and evaluations to determine the most effective antigen to invoke the desired immune response (4).

Types of Antigens Used

The antigens in vaccines can be live but attenuated (weakened), inactivated (killed), or subunit (only a portion of the pathogen) (5). Live vaccines mimic a natural infection closely and can generate a strong immune response (6). In contrast, inactivated vaccines contain pathogens that have been killed and cannot replicate, ensuring they cannot cause disease (7).

Antigen Cultivation

Once the antigen is selected, it is cultivated using cell culture materials such as eggs or other growth mediums to increase the quantity of the antigen (8). This process may involve weakening or killing the pathogen with inactivating ingredients like formaldehyde (9).

Types of Vaccines and Their Antigens

Live Attenuated Vaccines

These vaccines use a weakened form of the virus or bacteria, which is achieved by repeated culturing in a laboratory setting (10). The attenuation process ensures that the pathogen can still activate the immune system without causing the full-blown disease.

Inactivated Vaccines

Inactivated vaccines contain pathogens that have been killed through physical or chemical processes. They are safe for use in immunocompromised individuals as they cannot cause the disease (7).

Subunit and Recombinant Vaccines

Subunit vaccines include only the necessary parts of the virus or bacteria needed to elicit a protective immune response (11). Recombinant vaccines are created using DNA technology to produce protein antigens (12).

Toxoid Vaccines

These vaccines are made from inactivated toxins produced by bacteria. They are designed to induce immunity against the harmful effects of the toxins rather than the bacteria itself (13).

Immune Response and Vaccine Efficacy

Activation of the Immune System

Vaccines stimulate the immune system to produce an immune response similar to that produced by a natural infection (14). This includes the development of antibodies and the activation of T cells, which are crucial for long-lasting immunity (15).

Immune Memory

A key feature of vaccines is the induction of immune memory, which ensures that the body can quickly and effectively respond to future exposures to the pathogen (16).

Herd Immunity

While vaccines may not directly protect every individual due to various reasons such as non-vaccination or non-response to vaccination, they contribute to herd immunity, which can offer indirect protection to those who cannot be vaccinated (17,18).

Special Considerations for Cancer Vaccines

Tumor Antigens

Cancer vaccines aim to stimulate anti-tumor immunity using tumor antigens. These antigens can be tumor-associated antigens (TAAs) or tumor-specific antigens (TSAs), which are recognized by T lymphocytes (19).

Personalized Neoantigens

Advancements in next-generation sequencing technology have enabled the identification of personalized neoantigens, which can be used to create more targeted and effective cancer vaccines (20).

Immune Activation and Escape

Antigen-presenting cells (APCs), such as dendritic cells (DCs), play a crucial role in immune activation induced by tumor antigens (21). However, tumors can develop mechanisms to escape immune detection, which poses challenges for cancer vaccine efficacy (22).

Types of Cancer Vaccines

Cancer vaccines can be categorized into cell-based, peptide-based, viral-based, and nucleic acid-based vaccines, each with its own approach to targeting tumor cells (23).

In conclusion, the selection and cultivation of antigens in vaccines are complex processes that require careful consideration of the type of immune response desired, the nature of the pathogen, and the safety of the vaccine. Through these methods, vaccines have become a cornerstone of public health, providing protection against a wide array of infectious diseases and, more recently, offering new strategies in the fight against cancer.

Chapter 2

Vaccine Purification

Introduction

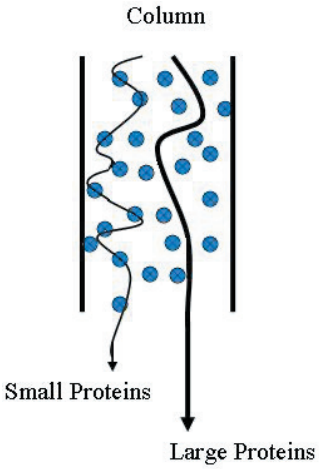
Vaccine purification is a critical step in the production of vaccines, ensuring that the final product is safe, potent, and free from contaminants. This chapter synthesizes information from various sources to provide an overview of the methods and technologies used in the purification of vaccines.

Vaccine Purification Techniques

Chromatography Methods

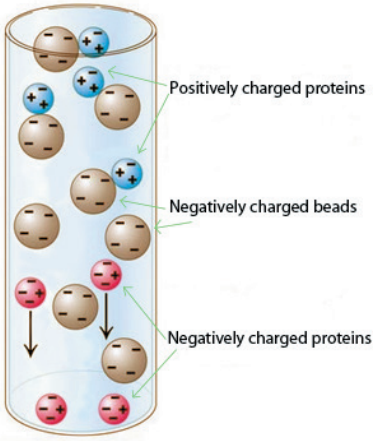
Chromatography is a cornerstone in vaccine purification, with various techniques being employed based on the type of vaccine and the specific requirements of the purification process.

- Size Exclusion Chromatography (SEC): SEC is particularly useful for purifying vaccines and viruses due to its gentle separation process, which preserves the activity and integrity of sensitive biomolecules (1). This method separates components based on their size, with WorkBeads SEC resins being highlighted for their high yield and activity in virus purification (2).



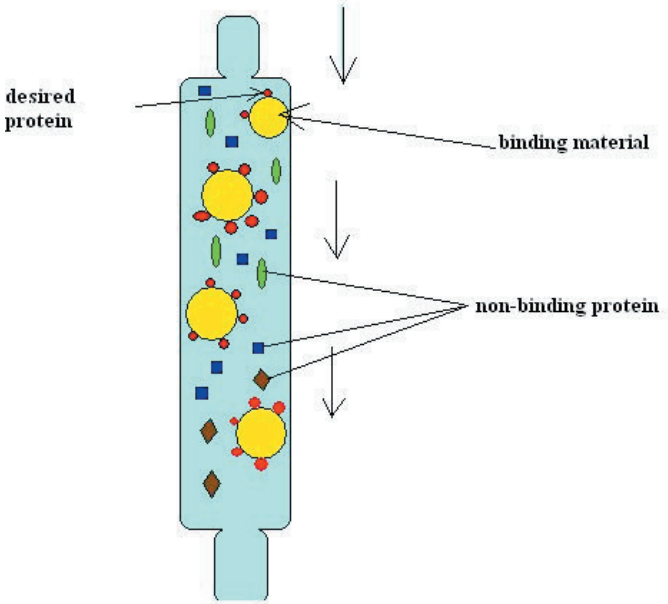
Chapter 2 Fig 1 *Molecular exclusion chromatography. Molecules are separated by size as they run through the column.* Jamit *at* English Wikibooks *(Creative Commons).*

- Ion Exchange Chromatography (IEX): IEX is another chromatographic method that separates molecules based on their charge (3).



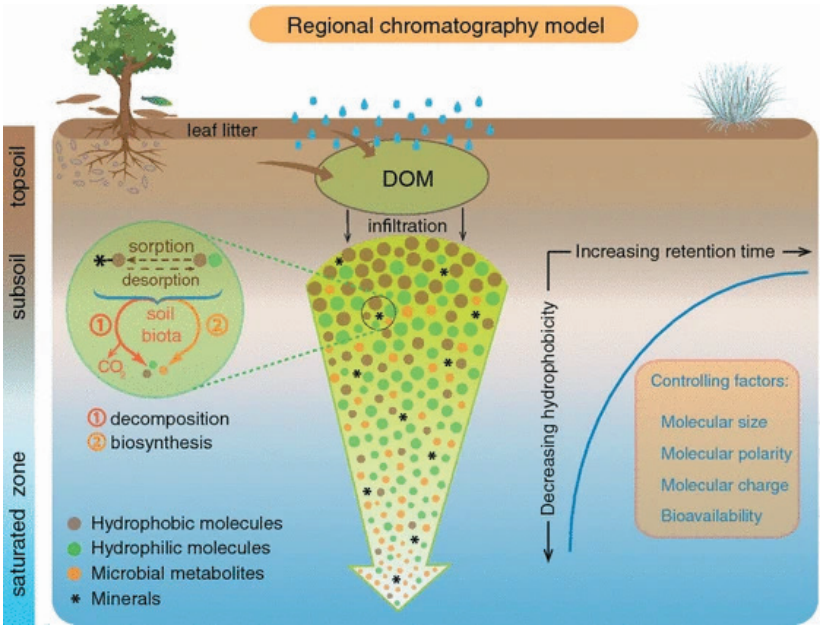
Chapter 2 Fig 2 *In ion exchange chromatography, molecules are attracted to charged beads as they move through the column. The get separated by charge. Jspiteri at English Wikibooks (Creative Commons)*

- Affinity Chromatography: This technique utilizes the specific interactions between biomolecules and ligands to achieve purification (4,5).



Chapter 2 Fig 3 *In Affinity Chromatography the molecules bind specifically to binding materials on beads as they move through column. They then are washed off the beads and collected in purified form. (public domain)*

- Hydrophobic Interaction Chromatography (HIC): HIC separates molecules based on their hydrophobicity (6).



Chapter 2 Fig 4 *Origins and bioavailability of dissolved organic matter in groundwater Regional Chromatography Model—precipitation and surface water leaches dissolved organic matter (DOM) from vegetation and plant litter and percolates through the soil column to the saturated zone. The concentration, composition, and bioavailability of DOM are altered during transport through the soil column by various physico-chemical and biological processes, including sorption, desorption, biodegradation and biosynthesis. Hydrophobic molecules are preferentially partitioned onto soil minerals and have a longer retention time in soils than hydrophilic molecules. The hydrophobicity and retention time of colloids and dissolved molecules in soils are controlled by their size, polarity, charge, and bioavailability. Bioavailable DOM is subjected to microbial decomposition, resulting in a reduction in size and molecular weight. Novel molecules are synthesized by soil microbes, and some of these metabolites enter the DOM reservoir in groundwater. Shen, Y., Chapelle, F.H., Strom, E.W. et al. Origins and bioavailability of dissolved organic matter in groundwater. Biogeochemistry 122, 61–78 (2015). https://doi.org/10.1007/s10533-014-0029-4 (Creative Commons)*

Other Chromatographic Techniques: Additional methods such as reversed-phase chromatography (RP), fast protein liquid chroma-

tography (FPLC), and multimodal chromatography are also used in vaccine purification (7,8).

Centrifugation Methods

Centrifugation is a physical separation process that can be used in vaccine purification.

- Ultracentrifugation: This method relies on high-speed centrifugal forces to separate components based on their density and is a common technique in current vaccine purification processes (9,10).
- Rate Zonal Centrifugation: This technique separates molecules based on their size and shape during centrifugation (11).
- Isopycnic Centrifugation: This method separates particles based on their buoyant density (12).

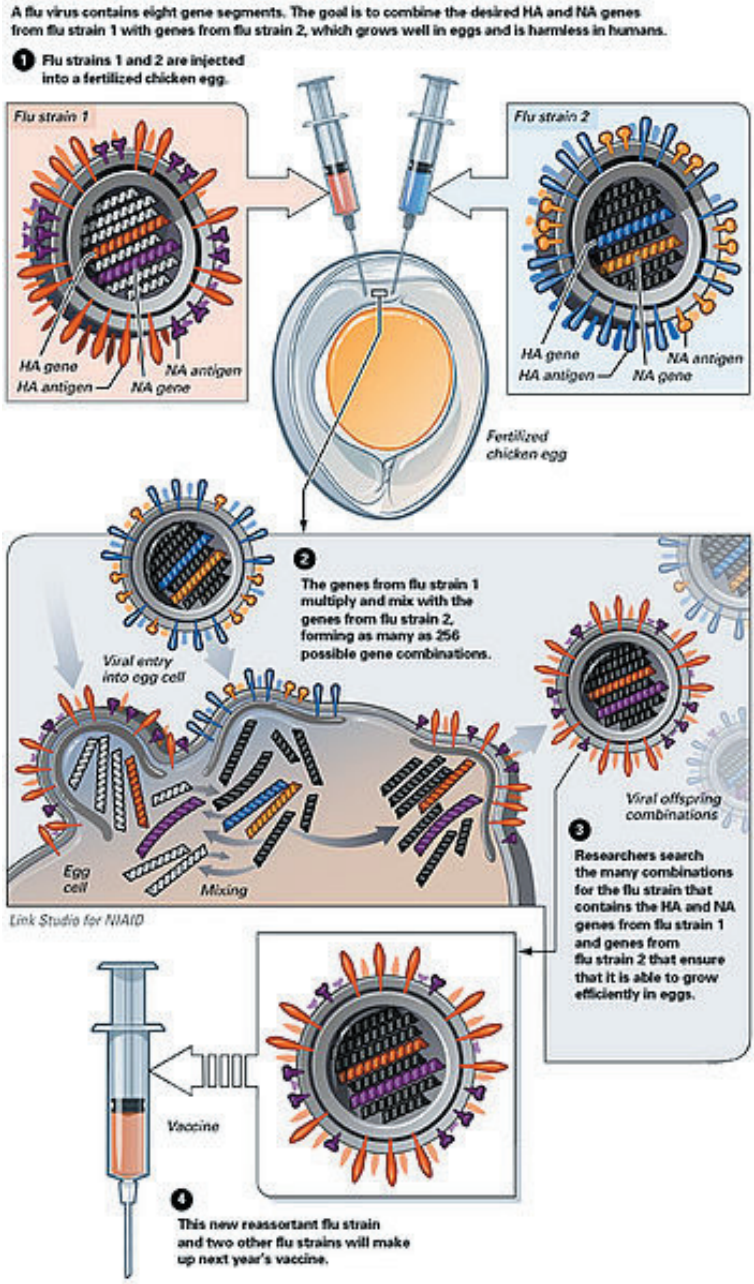
Filtration and Other Techniques

- Filtration: Various filtration techniques, including single-pass tangential flow filtration (SPTFF), are used to remove contaminants from vaccine preparations (13).
- Aqueous Two-Phase Extraction: This technique is being refined for its potential to purify viral vaccines quickly and cost-effectively (13,14).

Vaccine Types and Their Purification

Egg-Based Flu Vaccines

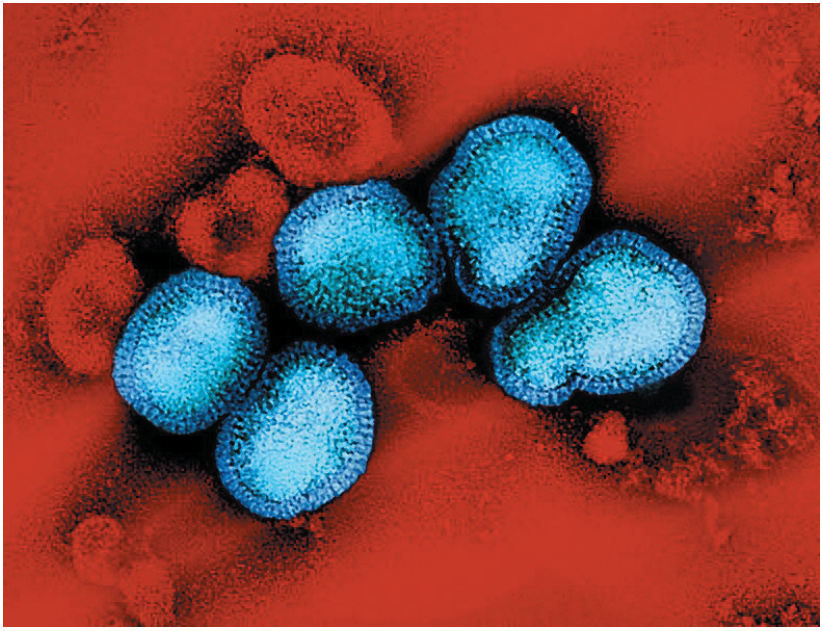
Egg-based vaccines are traditional flu vaccines where the virus is grown in eggs and then harvested for purification (15).


A flu virus contains eight gene segments. The goal is to combine the desired HA and NA genes from flu strain 1 with genes from flu strain 2, which grows well in eggs and is harmless in humans.
1 Flu strains 1 and 2 are injected into a fertilized chicken egg.
Flu strain 1
HA gene
HA antigen
NA antigen
NA gene
Flu strain 2
HA gene
HA antigen
NA antigen
NA gene
Fertilized chicken egg
2 The genes from flu strain 1 multiply and mix with the genes from flu strain 2, forming as many as 256 possible gene combinations.
Viral entry into egg cell
Egg cell
Mixing
Viral offspring combinations
3 Researchers search the many combinations for the flu strain that contains the HA and NA genes from flu strain 1 and genes from flu strain 2 that ensure that it is able to grow efficiently in eggs.
Link Studio for NIAID
Vaccine
4 This new reassortant flu strain and two other flu strains will make up next year's vaccine.

Chapter 2 Fig 5 *The goal of reassortment is to combine the desired HA and NA antigens from the target strain (flu strain 1) with genes from a harmless strain that grows well in an egg (flu strain 2). Illustration showing the flu virus containing eight gene segments. One of the gene segments codes for the surface antigen hemagglutinin (HA), and another codes for the surface antigen neuraminidase (NA). Credit: NIAID (Creative Commons)*

Cell Culture-Based Flu Vaccines

These vaccines are produced by growing the virus in cell cultures, which are then purified using techniques like ultracentrifugation or chromatography (16,17).



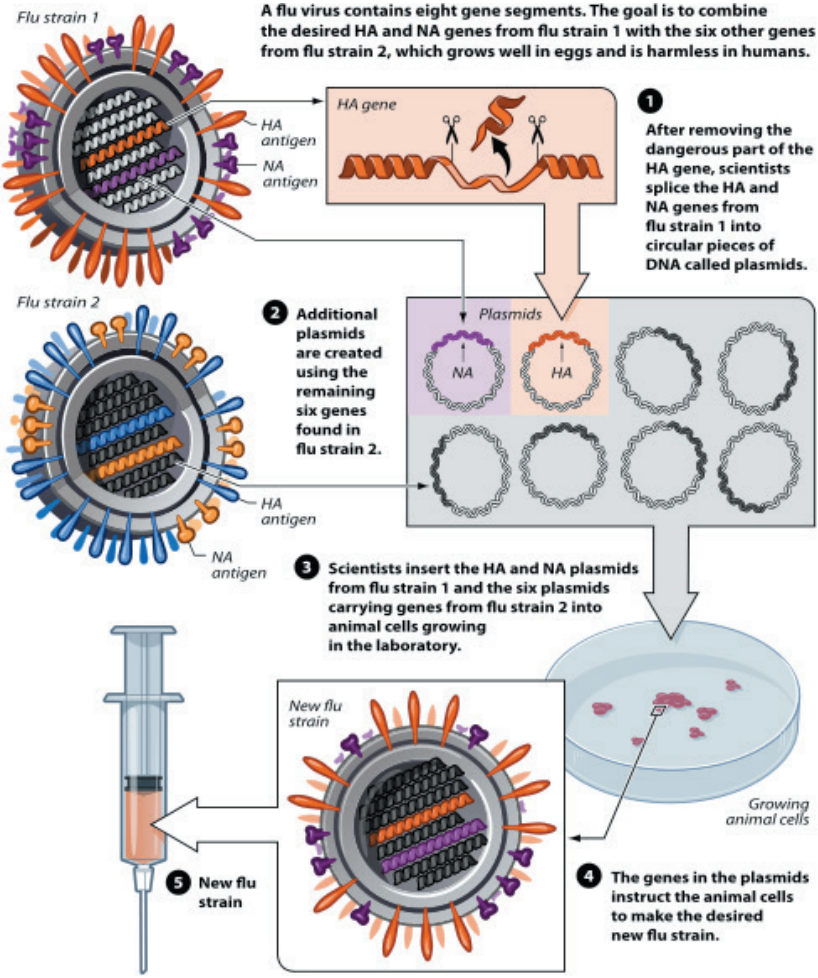
Chapter 2 Fig 6 *Colorized transmission electron micrograph of influenza A virus particles, colorized blue, isolated from a patient sample and then propagated in cell culture. Influenza A can infect both humans and animals, including birds and pigs.*

More specifically, this image features the H3N2 influenza strain, isolated from a patient in Victoria, Australia, in 1975. Notable for

forming both spherical particles/virions (pictured) and filamentous virions, this historical strain can be employed to study the breadth of the immune response elicited by universal flu vaccine candidates. Microscopy by John Gallagher and Audray Harris, NIAID Laboratory of Infectious Diseases. Credit: NIAID (Creative Commons)

Recombinant Flu Vaccines

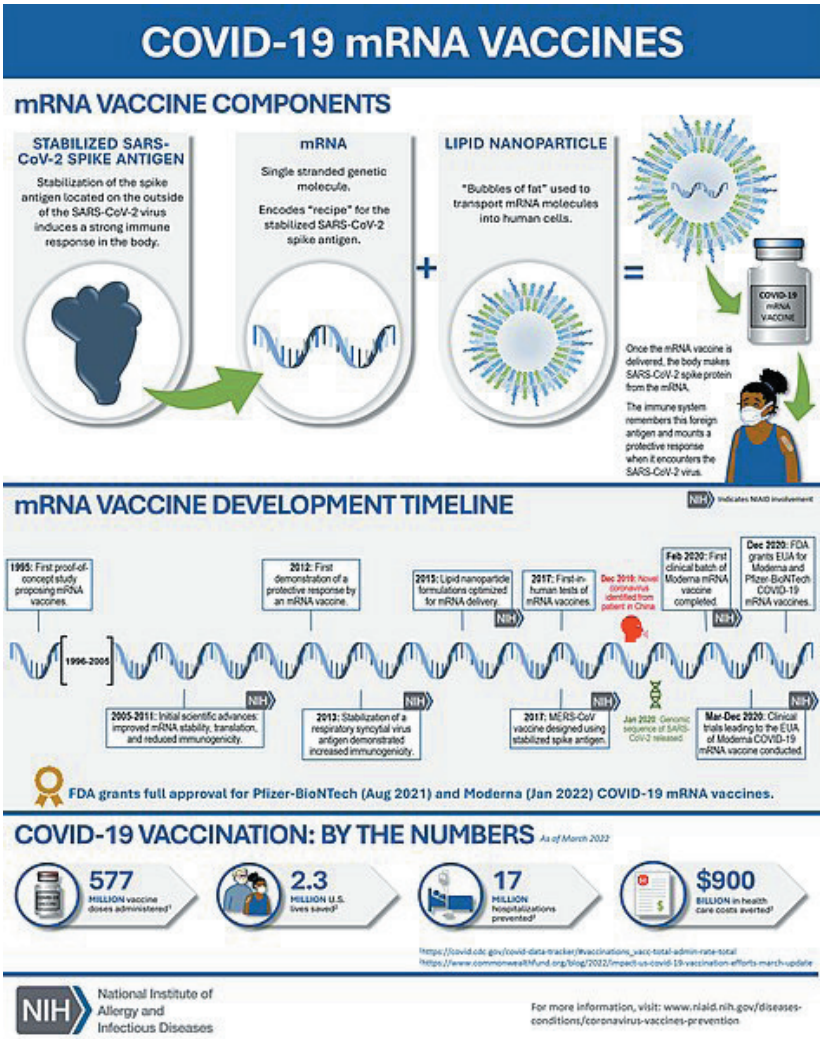
Recombinant vaccines involve expressing vaccine candidate proteins with tags such as the 6xHis-tag for downstream purification using resins or membrane-based technologies (18,19).



Chapter 2 Fig 7 *Avian flu vaccine development by reverse genetics technique. (public domain)*

mRNA Vaccines

mRNA vaccines require highly pure and concentrated mRNA material, with purification methods including chromatography techniques like ion exchange and affinity chromatography (20,21).



Chapter 2 Fig 8 *NIAID has participated in COVID-19 mRNA vaccine research and development. This infographic shows the mRNA vaccine components, development timeline, and an overview of the numbers of doses administered, lives saved, hospitalizations prevented and costs averted. https://www.flickr.com/photos/niaid/52200595641/ NIAID (Creative Commons)*

Technological Advances and Innovations

Single-Use Technologies

The introduction of single-use disposable technology has simplified the establishment of new production lines and increased flexibility in vaccine process development and manufacturing (22).

High-Throughput Systems

High-throughput liquid handling systems for purification development have significantly saved time and resources (23).

In Silico Models and AI

Artificial intelligence and in silico models are being used to accelerate chromatographic purification processes for vaccines (24).

Collaborative Efforts

Collaborations, such as those between Michigan Tech, Johns Hopkins, and Mount Sinai Hospital, are underway to develop improved vaccine manufacturing processes (25).

Conclusion

Vaccine purification is a multifaceted process that employs a variety of techniques to ensure the safety and efficacy of vaccines. Chromatography, centrifugation, and filtration are among the main methods used, with ongoing technological advancements and collaborations aiming to optimize and accelerate the purification process. The choice of purification method depends on the type of vaccine and the specific requirements of the production process.

Chapter 3

Testing and Regulatory Approval for Vaccines

The development and approval of vaccines are critical processes that ensure the safety and efficacy of these vital medical countermeasures. Here is a comprehensive overview of how vaccines are tested and regulated before they reach the public.

Vaccine Development and Clinical Trials

Vaccine development typically follows a multi-phase clinical trial process, starting with preclinical tests and advancing through several phases of human trials (1). Each phase of clinical trials must be completed before moving on to the next, ensuring a step-by-step evaluation of the vaccine's safety and effectiveness (2).

- Phase 1: Involves a small group of participants to assess the vaccine's safety and dosage (3).
- Phase 2: Expands to hundreds of participants with similar characteristics to the intended vaccine recipients to further evaluate safety and immune response (4).
- Phase 3: Involves thousands of participants to confirm efficacy, monitor side effects, and collect comprehensive safety data (5).
- Phase 4: Post-approval studies that continue to monitor the vaccine's safety and effectiveness in the general population (6).

The entire process from research and development to approval can take anywhere from 5 to 15 years, depending on various factors, including the urgency of need (7,8).

Regulatory Approval Process

In the United States, the Food and Drug Administration (FDA) is the regulatory body responsible for overseeing the safety, effectiveness, and quality of vaccines (9,10). The FDA's Center for Biologics Evaluation and Research (CBER) regulates vaccine use, and before a vaccine can be approved, a company must submit a Biological License Application (BLA) for review (11). The FDA's evaluation process is among the most robust in the world, ensuring that vaccines meet high standards for safety and efficacy (12). Decisions are made based on a thorough analysis of the benefits and risks for the intended population (13).

Even after approval, the FDA, along with other agencies like the Centers for Disease Control and Prevention (CDC), continues to monitor vaccine safety through various surveillance systems (14,15).

Emergency Use Authorization (EUA)

In response to public health emergencies, such as the COVID-19 pandemic, the FDA can issue an Emergency Use Authorization (EUA) to facilitate the availability of vaccines. An EUA allows the use of unapproved medical products when there are no adequate, approved, and available alternatives, and the potential benefits outweigh the risks (16-18).

For an EUA, the FDA requires substantial evidence of safety and effectiveness, including data from phases 1 and 2 of clinical trials (19). Manufacturers must also provide a plan for active follow-up on safety (20). Recipients of a vaccine under an EUA must be informed about

the authorization, the known and potential benefits and risks, and their right to accept or refuse the vaccine (21).

Manufacturing and Distribution

Scaling up vaccine manufacturing is a significant step that usually occurs near the end of the regulatory process due to the substantial financial investment required (22). Manufacturers must comply with Good Manufacturing Practices and ensure that the vaccine is produced by approved procedures in approved facilities (23). Each batch of the vaccine, or "lot," is subject to release by CBER, ensuring continuous monitoring of product quality (24,25).

Global Perspective

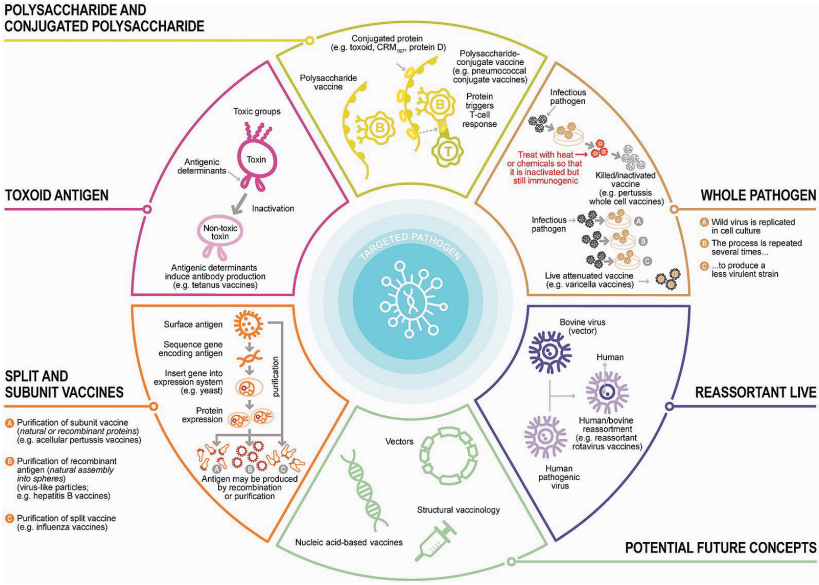
While the FDA regulates vaccines in the United States, other countries have their regulatory bodies, such as the European Medicines Agency (EMA) in the European Union, which has a similar process to the FDA (26). Regardless of the location, the goal of these regulatory agencies is to ensure that vaccines are safe and effective for public use.

Conclusion

The journey of a vaccine from the research lab to the public's arm is a complex and rigorous process that involves multiple stages of testing and stringent regulatory oversight. The FDA and other regulatory agencies worldwide work to ensure that vaccines meet the highest standards of safety and efficacy before they are approved for use. Even after approval, ongoing surveillance is critical to monitor for any adverse events or long-term complications (27-29).

Chapter 4

Types of Vaccines – Live Attenuated



Chapter 4 Fig 1 *Different types of vaccines. Vaccines can be produced using different processes. Vaccines may contain live attenuated pathogens (usually viruses), inactivated whole pathogens, toxoids (an inactivated form of the toxin produced by bacteria that causes the disease), or parts of the pathogens (e.g. natural or recombinant proteins, polysaccharides, conjugated polysaccharide or virus-like particles). Volker Vetter, Gülhan Denizer, Leonard R. Friedland, Jyothsna Krishnan, Marla Shapiro https://www.tandfonline.com/doi/full/10.1080/07853890.2017.1407035 (Creative Commons)*

Live-attenuated vaccines are a type of immunization that uses a weakened form of the pathogen that causes a disease. These vaccines are designed to trigger protective immunity without causing the illness itself (1,2). The process involves weakening the virus so that it can