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VACCINE DELIVERY SYSTEMS: A REVIEW

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ABSTRACT

Vaccines are among the most effective public health interventions for the prevention and control of infectious diseases. They induce immunologically mediated protection by stimulating the body's immune system through the administration of inactivated or live-attenuated pathogens, purified antigenic subunits, nucleic acids (DNA or mRNA), or viral vectors encoding specific antigens. The success of vaccination depends not only on the antigen but also on the efficiency of the vaccine delivery system and the use of suitable adjuvants. Delivery platforms such as emulsions, liposomes, microparticles, nanoparticles, and polymer-based carriers enhance antigen stability, improve targeted delivery, promote sustained release, and strengthen immune responses. Likewise, adjuvants including aluminum salts (alum), CpG oligodeoxynucleotides, and other immunostimulatory molecules further enhance vaccine efficacy by activating innate and adaptive immunity. This review highlights the different types of vaccines, their delivery systems, mechanisms of immune activation, recent technological advances, and future perspectives in vaccine development.

KEYWORDS: Vaccine delivery systems; Vaccines; Adjuvants; Nanoparticles; Liposomes; mRNA vaccines; Viral vector vaccines; Immune response.

INTRODUCTION

Vaccines are biological preparations that induce immunologically mediated protection against infectious diseases by stimulating the body's immune system to recognize and eliminate specific pathogens. They are formulated using inactivated or live-attenuated microorganisms, purified antigenic subunits, toxoids, nucleic acids (DNA or mRNA), or viral vectors encoding antigenic proteins. While subunit vaccines offer excellent safety, specificity, and reduced risk of adverse reactions, they are often poorly immunogenic and therefore require effective delivery systems and adjuvants to elicit robust and long-lasting immune responses.

Vaccine delivery systems, including emulsions, liposomes, microparticles, nanoparticles, immune-stimulating complexes (ISCOMs), and polymer-based carriers, play a critical role in protecting antigens from degradation, improving their stability, enhancing targeted delivery to antigen-presenting cells, and promoting sustained antigen release. In addition, immunostimulatory adjuvants such as aluminum salts (alum), unmethylated CpG oligodeoxynucleotides, and other pathogen-associated molecular patterns (PAMPs) activate innate immunity through pattern recognition receptors (PRRs), particularly Toll-like receptors (TLRs) expressed on dendritic cells, macrophages, and B cells. This activation enhances both humoral and cellular immune responses, thereby increasing vaccine efficacy.

Conventional vaccine platforms include live-attenuated and inactivated vaccines. Live-attenuated vaccines contain weakened pathogens capable of limited replication, producing a mild infection that closely mimics natural disease and induces strong, durable immune responses. Examples include vaccines against varicella (chickenpox), influenza (FluMist), and rotavirus (Rotarix). More recently, inactivated whole-virus vaccines such as Covaxin (developed by Bharat Biotech) and CoronaVac (developed by Sinovac) have been successfully used for the prevention of COVID-19.

Advances in biotechnology have led to the development of next-generation vaccine platforms, including DNA, mRNA, and viral vector vaccines. DNA vaccines, such as INO-4800, encode the SARS-CoV-2 spike protein and have demonstrated the ability to induce antigen expression in host cells, resulting in both T-cell activation and neutralizing antibody production against SARS-CoV-2. Viral vector vaccines utilize genetically engineered viruses to deliver antigen-encoding genes into host cells, thereby eliciting strong cellular and humoral immune responses. Commonly used viral vectors include adenoviral vectors, adeno-associated viral (AAV) vectors, and retroviral vectors. These advanced vaccine technologies have expanded the possibilities for rapid vaccine development and have shown significant promise in combating emerging infectious diseases.

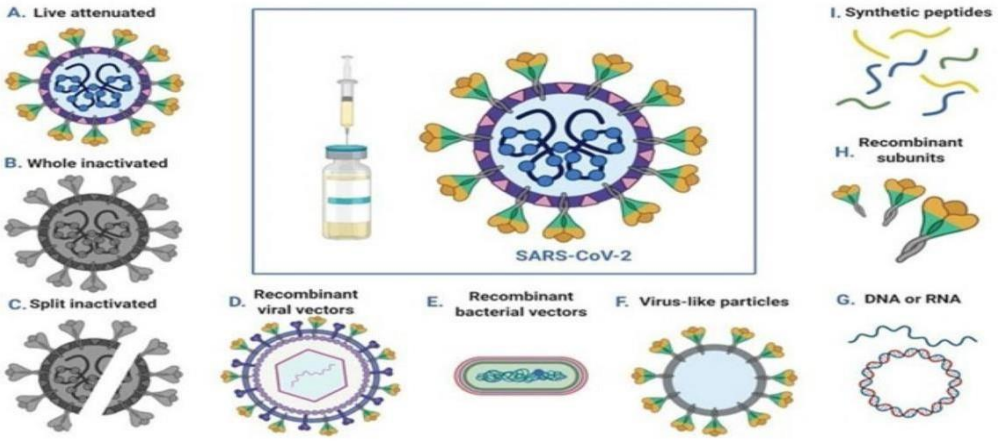
Delivery of Antigens

Efficient antigen delivery is a key determinant of vaccine efficacy, as it influences the magnitude and duration of the immune response. Traditionally, oil-based adjuvants such as Freund's adjuvant have been used to enhance antigen presentation and reduce the number of vaccine doses required. However, their clinical application is limited because of safety concerns, including severe local inflammation, granuloma formation, and tissue irritation at the injection site. Consequently, these adjuvants are not approved for routine use in humans.

Currently, the U.S. Food and Drug Administration (FDA) has approved aluminum-based adjuvants, including aluminum hydroxide and aluminum phosphate (collectively known as alum), for use in several human vaccines. Although alum effectively enhances antibody-mediated immune responses, it has limited ability to induce strong cellular immunity. This limitation has driven the development of safer and more effective antigen delivery systems capable of improving both humoral and cell-mediated immune responses.

Modern vaccine formulations increasingly incorporate antigens into particulate delivery systems rather than administering them in soluble form. Microparticles, nanoparticles, liposomes, and polymer-based carriers protect antigens from enzymatic degradation, improve their stability, facilitate targeted uptake by antigen-presenting cells, and enable controlled and sustained antigen release. Studies employing techniques such as light microscopy, confocal microscopy, electron microscopy, flow cytometry, and gel permeation chromatography have demonstrated that microparticles smaller than 10 μm can rapidly penetrate the gut-associated lymphoid tissue (GALT) within approximately one hour after oral administration. These particles are efficiently internalized by specialized M cells and dendritic cells, making them promising carriers for oral vaccine delivery and controlled-release immunization strategies. Such advanced antigen delivery systems have the potential to enhance vaccine efficacy, reduce the need for booster doses, and improve patient compliance.

Types Of Vaccines



Based on a number of these factors, scientists decide which type of vaccine they will make. There are several types of vaccines, including:

- ✓ Inactivated vaccines
- ✓ Live-attenuated vaccines
- ✓ Messenger RNA (mRNA) vaccines Subunit,
- ✓ recombinant,
- ✓ polysaccharide, and
- ✓ conjugate vaccines
- ✓ Toxoid vaccines
- ✓ Viral vector vaccine

Inactivated Vaccines
Inactivated vaccines are prepared by using disease-causing microorganisms (viruses or bacteria) that have been killed or inactivated through physical or chemical methods, such as heat, formaldehyde, or β-propiolactone. Since the pathogen is no longer capable of replication, these vaccines cannot cause the disease they are designed to prevent, making them safer for immunocompromised individuals and people with weakened immune systems.

These vaccines stimulate the immune system to produce protective antibodies against the pathogen. However, because they do not replicate within the host, the immune response is generally weaker than that produced by live-attenuated vaccines. Consequently, multiple doses and periodic booster vaccinations are often required to maintain long-term immunity.

Examples of diseases prevented by inactivated vaccines include
Hepatitis A
Influenza (inactivated injectable influenza vaccine)
Poliomyelitis (Inactivated Polio Vaccine, IPV)

Rabies
Inactivated vaccines are widely used because of their excellent safety profile, ease of storage, and suitability for large-scale immunization programs. They play a crucial role in preventing infectious diseases and reducing disease-related morbidity and mortality worldwide.

Live-Attenuated Vaccines
Live-attenuated vaccines contain weakened forms of viruses or bacteria that are capable of limited replication in the host without causing disease in healthy individuals. These vaccines closely mimic natural infection, thereby stimulating strong and long-lasting humoral and cellular immune responses. In many cases, one or two doses are sufficient to provide durable immunity.

Live-attenuated vaccines are used to protect against the following diseases:
Measles, Mumps, and Rubella (MMR) – administered as a combined vaccine.
Rotavirus infection – protects infants against severe gastroenteritis and diarrhea.
Varicella (Chickenpox) – prevents chickenpox and its associated complications.

Yellow Fever – provides protection against yellow fever virus, particularly for individuals traveling to endemic regions.
Smallpox – historically used to eradicate smallpox worldwide and currently reserved for specific high-risk populations.
Although live-attenuated vaccines are highly effective, they are generally contraindicated in individuals with severe immunodeficiency and in pregnant women because the weakened pathogen may pose a risk in these populations.

mRNA Vaccines
mRNA (messenger RNA) vaccines contain a synthetic mRNA sequence that encodes a specific antigen, which is translated into protein by the host cells after vaccination. The expressed antigen stimulates both humoral and cellular immune responses without using a live pathogen. mRNA vaccines are highly effective, can be rapidly developed, and have played a significant role in controlling emerging infectious diseases.

mRNA vaccines are currently used to protect against
- **Coronavirus disease 2019 (COVID-19)**

Subunit, Recombinant, Polysaccharide, and Conjugate Vaccines
These vaccines contain purified antigenic components of a pathogen, such as proteins or polysaccharides, rather than the whole microorganism. Because they do not contain live pathogens, they are considered safe and well tolerated. However, they often require adjuvants and booster doses to produce long-lasting immunity.

These vaccines are used to protect against
- **Haemophilus influenzae type b (Hib) disease**
- **Hepatitis B**
- **Human papillomavirus (HPV) infection**
- **Whooping cough (Pertussis)** – included in the **DTaP** combined vaccine
- **Pneumococcal disease**
- **Meningococcal disease**
- **Herpes zoster (Shingles)**

Subunit and conjugate vaccines are widely used because they provide effective protection while minimizing the risk of adverse reactions associated with whole-pathogen vaccines.

Toxoid Vaccines
Toxoid vaccines are developed using inactivated bacterial toxins (toxoids) that have been chemically modified to eliminate their toxicity while retaining their ability to stimulate an immune response. Instead of targeting the bacteria themselves, these vaccines induce the production of antibodies that neutralize the toxins responsible for disease. Toxoid vaccines are safe, effective, and often require booster doses to maintain long-term immunity.

Toxoid vaccines are used to protect against
- **Diphtheria**
- **Tetanus**

These vaccines are commonly administered as part of combination immunization schedules, such as the **DTaP**, **Td**, and **Tdap** vaccines, which provide protection against diphtheria, tetanus, and pertussis (whooping cough).

Mechanism of Single-Shot Vaccines

Single-shot vaccines are designed to provide long-lasting immunity with a single administration by utilizing advanced vaccine delivery technologies. These vaccines employ delivery systems such as biodegradable polymer-based carriers, nanoparticles, microneedle patches, and viral vectors to achieve controlled and sustained release of antigens. The gradual release of antigens over time mimics the effect of multiple booster doses, resulting in prolonged stimulation of the immune system.

Following administration, the released antigens are captured by antigen-presenting cells (APCs), such as dendritic cells, which process and present them to T lymphocytes. This activates both cellular and humoral immune responses, leading to the production of antigen-specific antibodies and the generation of long-lived memory B and T cells. Consequently, single-shot vaccines can provide durable immune protection, reduce the need for repeated booster vaccinations, improve patient compliance, and facilitate large-scale immunization programs.

Mucosal Delivery System

Mucosal vaccine delivery is an emerging and effective strategy for inducing both local and systemic immune responses by targeting mucosal surfaces, which serve as the primary entry points for many infectious pathogens. The successful design of mucosal vaccines depends on the appropriate selection of antigens, efficient delivery systems, and safe, effective mucosal adjuvants that enhance antigen uptake and stimulate protective immunity. Advanced delivery platforms such as nanoparticles, liposomes, microspheres, and mucoadhesive polymers protect antigens from degradation, improve their residence time on mucosal surfaces, and facilitate uptake by specialized antigen-presenting cells. The incorporation of suitable adjuvants further enhances mucosal immune responses by activating innate and adaptive immunity.

Mucosal Immune System

The mucosal immune system represents the largest immune compartment in the human body, covering an estimated surface area of approximately 400 m^2. It lines the respiratory, gastrointestinal, urogenital, and ocular tracts, where it acts as the first line of defense against invading pathogens. The mucosal epithelium is thin and highly permeable to support essential physiological functions, including gas exchange in the lungs, nutrient absorption in the gastrointestinal tract, sensory perception in the eyes, nose, mouth, and throat, and reproductive functions in the uterus and vagina. However, this permeability also increases susceptibility to microbial invasion, necessitating a highly efficient immune defense system.

The mucosal immune system consists of an integrated network of lymphoid tissues, immune cells, and soluble immune mediators. It includes organized mucosa-associated lymphoid tissues (MALT), such as gut-associated lymphoid tissue (GALT) and nasopharynx-associated lymphoid tissue (NALT), along with dendritic cells, macrophages, B lymphocytes, T lymphocytes, epithelial cells, and specialized microfold (M) cells. These components work together with effector molecules, including secretory immunoglobulin A (sIgA), cytokines, and chemokines, to coordinate innate and adaptive immune responses. Following mucosal vaccination, antigens are captured by antigen-presenting cells, leading to the activation of B and T lymphocytes and the generation of long-lasting immune memory. As a result, mucosal vaccine delivery offers significant potential for preventing infections at their primary sites of entry while also providing systemic immune protection.

Transdermal Delivery System

Transdermal vaccine delivery is an innovative approach that administers vaccines through the skin, providing a painless, minimally invasive, and patient-friendly alternative to conventional hypodermic needle injections. Among the various transdermal delivery technologies, microneedle (MN) patches have gained considerable attention because they can efficiently deliver vaccine antigens directly into the epidermis and dermis, which are rich in antigen-presenting cells such as dendritic cells and Langerhans cells.

Microneedle patches create microscopic channels in the skin without reaching nerve endings, making the vaccination process virtually painless and reducing needle-related anxiety (needle phobia). These systems enhance antigen uptake by immune cells, resulting in improved immunogenicity and, in many cases, allowing dose sparing while maintaining strong immune responses. In addition, transdermal vaccine delivery offers several practical advantages, including ease of self-administration, reduced risk of needle-stick injuries, improved patient compliance, and simplified storage and transportation. These benefits are particularly valuable during large-scale immunization campaigns and in resource-limited settings.

Recent research has demonstrated the potential of microneedle-based transdermal delivery for vaccines against influenza, COVID-19 (including mRNA vaccines), and several other infectious diseases. Owing to their effectiveness, safety, and logistical advantages, transdermal vaccine delivery systems are considered a promising next-generation platform for improving global vaccination strategies.

CONCLUSION

Vaccine delivery systems play a crucial role in determining the safety, efficacy, and long-term success of immunization strategies. Conventional vaccine formulations have significantly reduced the global burden of infectious diseases; however, advances in delivery technologies have further improved antigen

stability, targeted delivery, and immune responses. Novel delivery platforms, including nanoparticles, liposomes, biodegradable polymeric carriers, microneedle patches, viral vectors, and mucosal delivery systems, enable controlled and sustained antigen release, enhance both humoral and cellular immunity, reduce the need for multiple booster doses, and improve patient compliance.

In addition, the development of safer and more effective adjuvants has strengthened vaccine-induced immune responses while minimizing adverse effects. Emerging technologies such as mRNA vaccines, transdermal delivery systems, and single-shot vaccine platforms have demonstrated immense potential for rapid vaccine development and large-scale immunization against emerging infectious diseases.

Despite these advances, challenges related to formulation stability, large-scale manufacturing, storage, regulatory approval, and global accessibility remain. Continued research focusing on innovative delivery systems, targeted antigen delivery, and next-generation adjuvants is expected to further enhance vaccine performance, improve immunization coverage, and contribute to the prevention and control of both existing and emerging infectious diseases worldwide.

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