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REVIEW ARTICLE **OPEN ACCESS**

Drug Delivery Systems for Augmenting Immune Response Through Vaccination

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ABSTRACT
Prophylactic vaccines are biological preparations that triggers the immune responses in both humans and animals, resulting in the creation of antibodies or cell-mediated responses that will combat infectious organisms or non-infectious illnesses like cancer. Alarming safety profiles of live vaccines, sub-unit vaccine immunogenicity, and immunization failure due to poor patient compliance to booster doses that should potentiate prime doses are just a few of the compelling reasons that have necessitated the development of a new generation of prophylactic and therapeutic vaccines to promote effective immunization. This paper reviews various types of vaccines such as Live attenuated vaccine, Inactivated vaccine, Replicating Viral Vector vaccine, Non-Replicating Viral Vector vaccine, DNA vaccine, Sub unit vaccine, RNA vaccine, Recombinant vaccine and Edible vaccine. This review also enlightens various routes for administration of vaccine into the human body such as transdermal, mucosal, oral, intranasal and also reviews different delivery systems such as colloidal, liposomes, sonophoresis, microneedle, electroporation, virosomes which are now being examined and developed as vaccine delivery methods.
Keywords: Vaccine, live attenuated vaccine, microneedles, needle-free delivery, transdermal, vaccine delivery systems.

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INTRODUCTION

A vaccine is a biological preparation that stimulates the body's immunological response to illnesses. Vaccines are conventionally administered through needle injection, but few can be delivered oral route or nasal route.

An immunologically mediated resistance to a disease, but not necessarily an infection, is what a vaccine induces. Typically, vaccines contain DNA encoding antigenic proteins from diseases, live, attenuated or killed organisms, or subunits of organisms. Although extremely selective and specific when responding with antibodies, subunit vaccines typically fail to show these reactions in scenarios such as alterations in an antibody's antigenic identification center and are not very immunogenic. However, by exposing them to the immune system in such a way that a specific and powerful immune response is elicited, the selectivity and specificity of the pathogenic organism's subunits, such as proteins and carbohydrates, can be used to elicit strong and long-lasting immunological responses. These epitopes may potentially enable the development of vaccinations against chronic conditions like cancer and hepatitis-C in addition to infectious diseases.(1)

Vaccines with the similar efficacy as the original live-attenuated or inactivated type has been created using next-generation technologies, but without the drawbacks and hazards. The development process has clearly shifted away from Pasteur's three Is paradigm (isolate, inactivate, inject) to strategy based on rational design. This is made possible by advances in our understanding of the pathogen-host interaction and immune system mechanisms. In order to fix dosing regimens to the timing of immune system stimulation and the reality of healthcare delivery in dispersed communities, these innovative vaccines have

investigated strategies for targeted delivery of antigenic material as well as for the regulation of release profiles.(2)

Vaccines having high affinity for producing virus-neutralizing antibodies have been reported to be the best protection against covid-19. Over 120 innovative vaccination candidates are undergoing preclinical and clinical testing worldwide. These candidates include live-attenuated, inactivated, viral-vectored nonreplicating and replicating, peptide or protein-based and nucleic acid-based techniques. For vaccine studies, accurate clinical management is just as crucial as extensive safety analyses and immunological responses. The current appearance of many SARS-CoV-2 variants is posing a fresh threat to the global community and making it difficult for researchers to develop the most effective COVID-19 vaccine. The need for developing next-generation vaccinations combats current and potential variants, is driven by the prospect of natural and vaccine-induced immunity in variants.(3) Typically, there are multiple vaccine options available for various diseases (such as cancer). They include whole cell vaccines (dendritic cell-based and tumor cell-based vaccines), viral-like particles (VLP) vaccines, recombinant live vector vaccines (viral and/or bacterial vector vaccines), nucleic acid vaccines (DNA and/or RNA replicon vaccines), protein and peptide vaccines, and combined approaches.(4)

TYPES OF VACCINES:

Diagrammatic representation of different types of vaccines are as shown in figure 1.

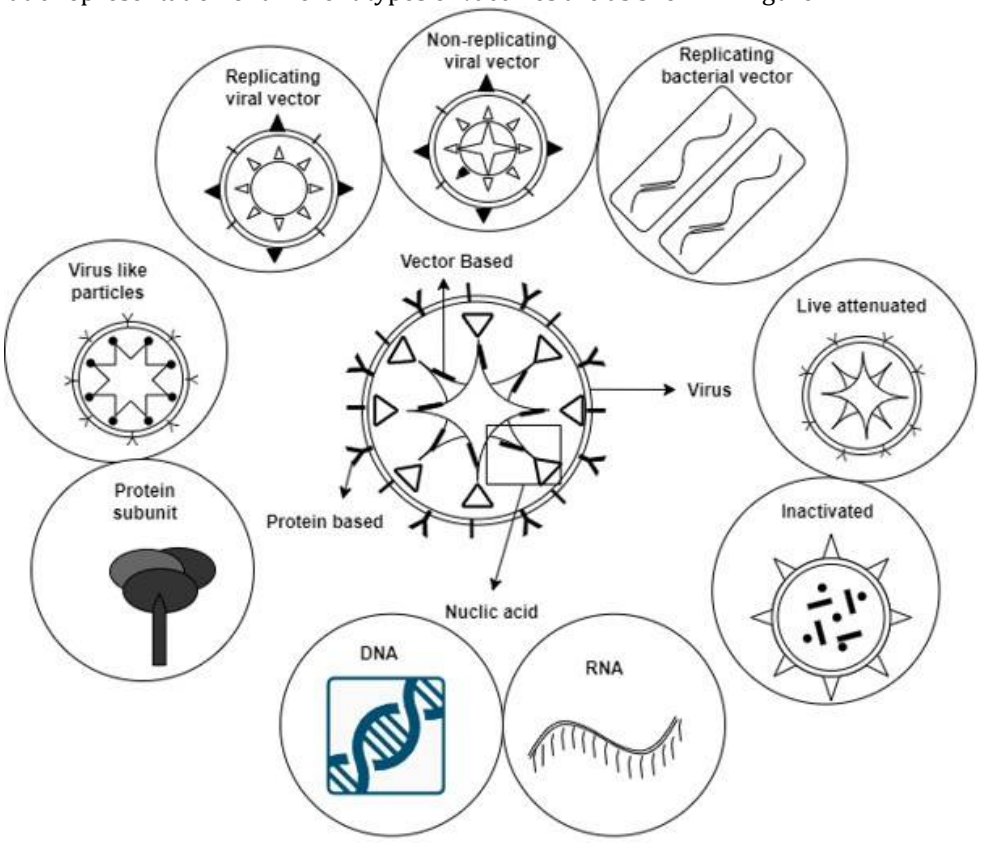

Figure 1: Diagrammatic representation of different types of vaccines

Live attenuated vaccine:

To prevent them from spreading disease, these vaccines include live virus particles that have been weakened. Some live attenuated vaccines may not be suitable for those with weakened immune systems because they induce a significant immunological response.(5)

Inactivated Vaccine:

To prevent them from spreading disease, these vaccines contain entire virus particles that have been destroyed or inactivated. Since the virus is already dead, they are safer. The protection offered by these vaccines are milder than that of live vaccines. Inactivated vaccines require booster doses.(5)

Replicating Viral Vector Vaccine:

These vaccines transform less-pathogenic viruses, which are mostly safe, into viral vectors that produce some of the same proteins as the disease-causing virus. This stimulates the immune system, however it may not work for persons who are already immune to the low pathogenic virus. In the current scenario, vaccines built on viral vectors have emerged as the top contenders for creating a COVID-19 pandemic vaccine that is efficient, secure, and scalable. Replicating and non-replicating viral vectors are used in this vaccine platform. Viral vectors offer an intriguing platform for the creation of the COVID-19 vaccine, as demonstrated by the success of the smallpox vaccine and other potential vaccines against several infectious diseases.(5,6)

Non-Replicating Viral Vector Vaccine:

These vaccines are identical to replicating viral vector vaccines in that the critical viral replication genes are eliminated from the low pathogenic vector virus, but they cannot replicate inside the body. These are more effective and safer, but require high dosages to confer immunity.(5)

DNA Vaccine:

These vaccines make use of DNA plasmids that contain a gene as well as other genetic components that produce some of the similar antigenic proteins as the disease-causing virus. They are simple to create and manufacture. There is no risk of infection, but it is possible that the immune system will fail to combat the antigen. DNA vaccines have been extensively studied. In animal models, these vaccines produce antibodies against particular proteins implicated in immunity to infection have showed promise. The negative charge and content of DNA often reduce the stability and trapping effectiveness of vaccine formulations. For the purpose of intranasal administration, several researchers have employed cationic components like chitosan and polyethyleneimine (PEI) to combine with DNA antigens. Other cationic polymers were successfully used to transport the plasmid DNA for the SARS DNA vaccine in order to stimulate humoral and cellular immune responses specific for the antigen.(7)

Subunit Vaccine:

These vaccines don't include any genetic material and instead use antigenic proteins from the disease-causing virus. Since they lack genetic material and cannot reproduce inside the body, they are comparatively harmless. Multiple doses of these vaccinations are necessary for long-lasting immunity. They need adjuvants, which are substances that boost the immune response. Adjuvants may be used to increase the immunogenicity of the subunit vaccine. In case of SARS-CoV-2 S-protein is in charge of receptor binding and membrane fusion, making it an ideal target for the creation of subunit vaccines, most subunit vaccines have concentrated on it.(5,8)

RNA Vaccine:

The messenger RNA (mRNA) used in these vaccines mimics some of the antigenic proteins found in the disease-causing virus. The RNA molecules avoid the risk of integrating into the host genome, but occasionally they can cause an unexpected immunological reaction in the body. Cancer vaccines based on mRNA have recently and thoroughly been studied. Immunotherapies, such as cancer vaccines, are intriguing alternatives to conventional cancer treatments. Cancer vaccines can be developed to specifically target tumor-associated antigens such as growth hormones or antigens particular to cancer cells as a result of somatic mutation. As mRNA vaccine targets in humans, these neoantigens or the neoepitopes within them have been used. Most cancer vaccines aim to stimulate cell-mediated reactions, hence are capable of lowering tumor burden. They are therapeutic rather than preventative.(5,9)

Recombinant vaccine:

Recombinant vaccines are typically created using yeast, mammalian, insect, and bacterial cells. The DNA region that codes for the antigen must be inserted into the target cell and transferred. Bacterial expression is the most widely used type of unaltered cell among those described, unlike cells found in mammals and insects. Recombinant protein vaccines consist of the majority among the recombinant vaccines created in recent years. Recombinant protein vaccines have drawbacks, including high price and restricted availability. However, this type's safety record is notably better than others.(10) The example for the use of recombinant vaccine in humans is the vaccine against hepatitis B. The hepatitis B surface antigen (HBsAg) is expressed in yeast cells to create this vaccination. The human papillomavirus (HPV) vaccine is a modern example of a recombinant vaccine. Infection with HPV is one of the most commonly encountered sexually transmitted infection which has been linked to a variety of mucocutaneous disorders in human beings, including genital warts, cervical, vulvar, and vaginal tumors. There are now two HPV vaccines in use, both of which were created using VLPs obtained from HPV-6, -11, -16, and/or -18 subtypes.(11)

Edible vaccine:

An edible vaccine for a disease is typically a plant that generates vitamins, proteins, or other nutrients. When a plant, fruit, or product made from plants is consumed orally, the immune system is stimulated.

Traditional vaccines have several limitations, which are overcome by edible vaccines. Traditional vaccines may be too expensive or difficult to produce and develop in some nations. On the other hand, it is easy to create, purify, sterilize and distribute edible vaccinations. Due to the fact that they only require healthy soil and no expensive production machinery, the cost of developing vaccines is significantly lowered. Additionally, edible vaccines do not require the sterilized manufacturing facilities or the expensive biosafety standards that are required to be adopted and maintained to create specific pathogenic agents for conventional vaccines.(12) Several plant-based vaccines for human use are place in market, but the first commercial plant-based vaccine is most likely going to be a veterinary vaccine. There are at least 30 of these compounds that have been expressed in plants, some of which offer defense against threats from disease causing pathogens. In a prodiGene Inc. study, it was shown for the first time that a plant-based oral immunization could protect livestock from virulence challenge. The initial product launched in the market is a poultry vaccine developed by Dow AgroSciences in 2006.(13) Table 1 shows some of the examples of vaccines and the challenges during manufacturing (14).

Table 1:Examples of vaccines and the challenges during manufacturing(14).

Examples	Type of vaccine	Challenges during manufacturing
Polio vaccine (Oral route)	Live-attenuated viruses	Maintaining the survivability of each of the three strains' phenotypic and genetic stability throughout production and the supply cold-chain.
Rabies	Inactivated virus	Ensuring total suppression while preserving immunogenicity and preventing reactogenicity. Suitable BSL containment procedures for live viruses.
Pertussis (whooping cough)	Purified proteins of Bordetella pertussis	Stability, quality assurance, component detoxification, and consistent production.
Pneumococcal polysaccharide vaccine	Glycoconjugates of polysaccharides on a suitable carrier protein	The yields, formulation to prevent immunological interferences between valencies, QC on complicated combinations, use of sophisticated chemical conjugation chemistries customized and done independently for each specific valency
Hepatitis B vaccine	Recombinant protein	Production consistency, reproducible immunogenicity, and low levels of host protein contaminant profiles

ROUTES OF ADMINISTRATION:

Transdermal administration:

Since the skin contains a significant number of immune cells, it serves as a hub for immunological activity and is therefore a good candidate for vaccines. Studies are focused on the transdermal administration of vaccines using passive delivery techniques. These initiatives have concentrated on a number of medications that are already approved for transdermal administration, including testosterone and nicotine. However, vaccine molecules need to be extremely potent, have a low molecular weight, and be somewhat lipophilic in order to be susceptible to good passive delivery (as the percentage of dose delivered is so low). One study that revealed a prolonged exposure of 16 hours to antigen on the skin was required to elicit a robust antigen-specific response illustrated the fundamental disadvantage of passive delivery as the lengthy lag time to induce a response. Because it may be simple and painless to access a vibrant immunological environment, transdermal administration is a desirable goal. The enormous inter- and intra-person heterogeneity in stratum corneum thickness, moisture levels, and hair follicle density present a general difficulty that must be solved. Additionally, all of the possible techniques will need to match the outstanding needle-and-syringe price point in order to displace them as the chosen administration method.

Mucosal administration:

Most of the infections occur through mucosal surfaces of the digestive, respiratory, or reproductive tracts. These surfaces provide a first site of contact for opportunistic infections since they are in direct contact with the air, water, and food from our surrounding environment. Despite this, only five pathogens—cholera, typhoid, rotavirus, poliomyelitis, and influenza—have mucosal vaccines approved for their treatment at the moment. In general, it is believed that traditional systemic vaccination techniques involving a needle and syringe are insufficient to stimulate potent mucosal immune responses. However, the administration of vaccinations through mucosal surfaces has the ability to elicit such reactions, neutralizing invasive bacteria before they may transmit an infection widely. The ability of mucosal

vaccination to produce systemic immunity on level with immunization with a needle and syringe has also been demonstrated. However, there are various obstacles to mucosal vaccination, from the stomach's severe acidic environment to the mucus layer that covers all mucosal surfaces. Despite these obstacles, a variety of mucosal vaccine delivery systems are being investigated. The two most popular are oral and intranasal; other options include ocular, intravaginal, and intrarectal(15).

Oral vaccination:

Research has shown the opportunity for a range of therapies that can be used to alter the immune system's defences against a variety of illnesses like cancer and autoimmune diseases. Intravenous treatment typically results in direct distribution to the systemic circulation; however, noninvasive routes of administration, particularly oral formulations, are particularly desirable in that they are economical and effective means of drug delivery for more patient compliance(16).

Intranasal Route:

The most effective form of mass immunization during pandemics is nasal nano vaccines administered via the intranasal route, which is convenient for eliciting mucosal and systemic immune responses. Nasal delivery enhances transport over the nasal membrane by promoting the transfer of small polar molecules, peptides, and proteins utilized in vaccines, which include DNA vaccines. Over the past few decades, intranasal drug delivery research has received a lot of interest and is seen as an attractive alternative route of pharmaceutical administration(17).

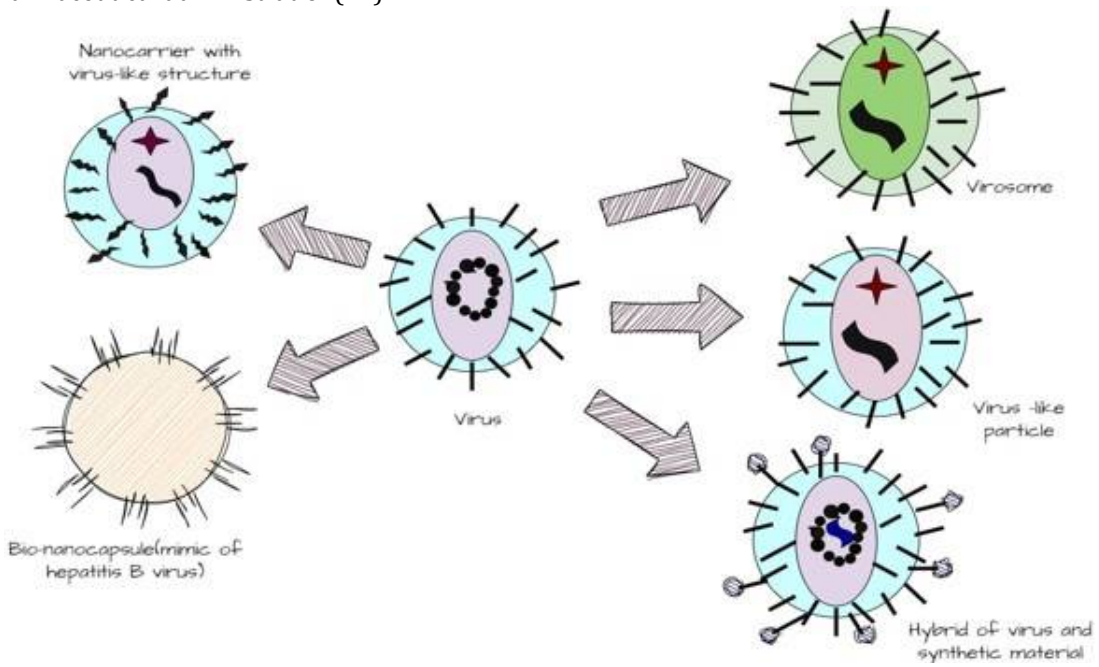

Figure 2: Virus mimicking nanocarriers

DIFFERENT DELIVERY SYSTEM OF VACCINE:

Colloidal Drug Delivery Systems:

Colloidal drug delivery systems for the secure and efficient administration of vaccines have been listed in numerous publications. The production of parenteral, oral, transmucosal, and/or transcutaneous immunization is possible using such methods.

Liposomal drug delivery system:

Liposomes being phospholipid and cholesterol-based bilayer lipid vesicles with lamellar architecture that function as a fluidity buffer to produce a densely packed structure and impart vesicle integrity. These have a higher acceptance in the delivery of vaccines because of their increased biocompatibility and biodegradable nature(18). Antibodies, antibody fragments, antigens, and other targeting molecules coated on polymerized liposomes have the ability to attach to particular cell surface receptors present in the mucosal tissues(1).

Sonophoresis:

To enhance transdermal medication and vaccine administration, ultrasonography is used. Cavitation is the primary mechanism underlying the improved sonophoresis delivery. Focused ultrasound is utilized in this procedure to cause the expansion and breakdown of gas bubbles, which results in shockwaves and

microstreaming. Sonophoresis has been used to either make the skin more permeable before administering the vaccine topically or as a way to apply the vaccine and cavitation at the same time, actively driving the vaccine particles into the skin(15).

Microneedle:

A hypodermic needle is used to inject the majority of vaccines. Injecting any chemical into the body is a simple, quick, and straightforward process. However, because hypodermic needles are difficult for individuals to use on their own, they are typically used in clinics or at their residence by patients who have undergone specific training on proper injecting technique, secure needle disposal, and others. Microneedles, on the other hand, can be manufactured as a inexpensive patch that is comfortable for patients to apply for delivery of biomacromolecules. Microneedle-targeted vaccine administration to skin's antigen-presenting cells is also of great interest(19).

Electroporation:

The distribution of vaccines in laboratories over the years has been made possible by electroporation (EP) technology. With the use of brief electrical pulses, this method allows big molecules like DNA or RNA to pass through the cell membrane and into the cytoplasm. These pores would immediately shut after the electrical field was turned off, trapping the molecules in the cytoplasm without leading to cell death. For electroporation, typically milli- and microsecond pulses are employed. EP may increase immunological responses in addition to increasing target cell permeability by increasing protein expression, secreting inflammatory chemokines and cytokines, and attracting antigen-presenting cells (such as macrophages and dendritic cells) to the EP site. EP mediated distribution of plasmid increases both antigen-specific humoral and cellular immune responses(4).

Virosomes:

The majority of virus-like particles, which have an average diameter of 50 nm and are produced in biological systems, are basically non-infectious particles devoid of (infectious) genetic material. Virosomes, on the other hand, are VLPs created in-vitro, in this a virus's envelope is exploited as a platform for the attachment or insertion of additional viral components. VLP formulations give a chance to display the target immunogen in its natural shape. The immune system is triggered by VLPs and virosomes using the host's natural process and structural principles(20). A virosome vaccine that incorporates the influenza virus hemagglutinin(HA) protein into liposomes has been created as a seasonal influenza vaccine(21). Virus mimicking nanocarriers are shown in figure 2.

VACCINE STABILITY AND INFLUENCING FACTORS:

Vaccine must have an sustainable shelf life, which is essential for eliciting strong immune reactions, and to be stable. The physical and chemical factors influencing the vaccine stability are, Physical stability factors like particle size, crystal structure, emulsion stability, whereas chemical stability factors like temperature- or pH-related vaccine degradation. In order to improve their thermal stability, vaccines must be maintained in accordance with the WHO Expanded Program of Immunization(20).

Effect of pH on vaccine stability:

For stability and effectiveness, vaccines are maintained at controlled pH using buffer. It is generally known that chemical degradation, which includes acid-catalyzed events like the hydrolysis of the peptide link in proteins and the deamidation of asparagine and glutamine residues, is most frequently brought on by an acidic pH. Additionally, it results in the hydrolysis of glycosidic linkage, which has an impact on DNA vaccines, vaccines based on polysaccharides, and vaccines based on glycoprotein-based subunits. In general, the majority of vaccines are stable at neutral pH or at pH 6–8 and do not cause local responses or discomfort that is mediated by pH when administered. On occasion, the pH of the formulation buffer may also be influenced by the physiochemical characteristics of a particular vaccine. Therefore, in these circumstances, using a powerful buffer to keep the pH at a suitable level is crucial(22).

Effect of ionic strength on vaccine stability:

The weakening of electrostatic interactions by charge shielding, the enrichment of polar contacts, or secondary effects on aqueous solvent are the mechanisms through which ionic strength has an impact. Through a chaotropic action that influences intermolecular solubility, anions and cations can increase molecular solubility. For the vaccine to be as stable as possible, the formulation buffer must be optimized with the proper ionic strength. Surfactants are used in the formulation of protein-based drugs and vaccines as excipients/stabilizers primarily to prevent or minimize protein aggregation and maintain the active ingredients in their maximum functioning state. These work by regulating interactions between proteins and other surfaces' (hydrophilic and hydrophobic forces such as glass vials). Gelatin and albumin are two common proteins that have been used to stabilize vaccine components and avoid or reduce the interaction of the vaccine with the surface of the vial or container(23).

Effects of Adjuvants:
It looks more unlikely than ever that innovative adjuvants will prove powerful enough to enable the development of therapeutic vaccinations. Therapeutic vaccines would be developed to treat existing illnesses rather than prevent them, such as chronic infectious diseases (such as those brought on by HIV, HSV, HCV, HBV, human papillomavirus, or H. pylori); cancers; autoimmune diseases and allergic or autoimmune disorders. Particularly if the vaccine is intended to treat cancer or the life-threatening effects of an infectious disease are greater than the potential risk of a prophylactic vaccine intended for use in healthy individuals, the level of toxicity acceptable for an adjuvant to be used in a therapeutic situation is likely to be higher. As a therapeutic cancer vaccine, PLG microparticles containing DNA encapsulation have recently been tested in people and have showed clinical promise(24).

METHOD FOR DETERMINING VACCINE STABILITY:

These methods are classified into two types(25)**:**

Chemical method:
High-resolution mass spectrometry is frequently employed in conjunction with a number of techniques, including reverse-phase high-performance liquid chromatography, hydrophobic interaction, ion-exchange, and size-exclusion chromatography.

Physical method:
Some of the widely used techniques include X-ray crystallography, NMR, static and dynamic light scattering, gel filtration, light diffraction spectroscopy, tryptophan fluorescence, extrinsic fluorescence probe, and the use of lipophilic dyes like 1-annilino naphthalene sulfonate, DNA intercalating dye, and circular dichroism spectroscopy.

SIDE EFFECTS OF VACCINES:
A new vaccine must often undergo safety tests involving 3,000–10,000 people in order to be licensed. As a result, the regulator makes extensive disclosures of common side effects at the time of licensing. Numerous vaccines frequently cause injection site discomfort, redness, and swelling in addition to certain systemic side effects like fever, malaise, and headache. The inflammatory and immunological reactions that result in the successful development of vaccine-induced safety are reflected in the first 1-2 days after immunization. A moderate viraemia, which can cause a fever, rashes, and occasionally feverish convulsions, develops in around 10% of one year old infants about a week after receiving the measles, mumps, and rubella vaccine(26).

CONCLUSION:
The research field of vaccinology continues to evolve at a rapid pace, with more efficient and acceptable new vectors of methods making their way into clinical practice. Vaccines are the most effective life-saving medical therapy available today. Vaccine drug delivery systems are relatively new and have shown to be patient-friendly, as they eliminate the need for booster doses and give long-term therapy in modest doses. Vaccines have safely reduced the diseases like polio, measles and small pox helping children grow up healthy and happy. Vaccines must be effective at significantly reducing the spread of the virus from them to be successful.
Immunization is a cost-effective tool for decreasing the high child Mortality. Vaccines are also critical for the prevention and control of infectious disease outbreak. Vaccines prevent the risk of developing a disease by enhancing the body's natural defences.

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Conflict of Interest
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