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Approaches to Traditional Vaccines and the Development of New Person-Centered Vaccines

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ABSTRACT

According to the World Health Organization, immunizations save between two and three million lives every year by avoiding illness. In addition to these immunizations, eradicating human smallpox was possible and is close to eradicating polio. In addition, vaccines have a significant economic impact because they prevent hospitalization of patients and other care costs. A vaccine is a biological product that specifically leads to acquired immunity against a pathogenic pathogen and prevents the disease in the face of the main pathogen in a person. Therefore, vaccines are an important tool for maintaining health in the global community. Traditional vaccines have been used against a wide range of pathogenic pathogens, both viral and bacterial, and have been successful. However, these vaccines do not work and are ineffective against pathogens that change rapidly in terms of genetic material and surface epitopes.

During the last decade, vaccines based on nucleic acids, viral vectors and biomaterials have shown promising results. This study has discussed an overview of traditional vaccines, mRNA-based vaccines, viral vector-based vaccines, and biomaterials.

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INTRODUCTION

According to the World Health Organization, immunizations save between two and three million lives every year by avoiding illness. In addition to these immunizations, eradicating human smallpox was possible and is close to eradicating polio. In addition, vaccines have a significant economic impact because they prevent hospitalization of patients and other care costs (1-3).

Traditional vaccines have been effective against many diseases. Still, there are infectious diseases for which no effective vaccine has been definitively developed, such as human immunodeficiency virus (HIV), tuberculosis (TB), and respiratory syncytial virus. (RSV), cytomegalovirus (CMV), herpes simplex virus (HSV), and Epstein Barr (EBV) (4). In addition, other infectious agents such as the Ebola virus, Zika virus, and acute respiratory syndrome virus have become major threats to global health (3).

Vaccine development began in 1791 by Edward Jenner, who noticed that people who received cowpox had a much milder illness than the original disease (5).

Since then, safer and engineered vaccines have been developed, for example, inactivated/live-attenuated pathogen vaccines (6), subunit vaccines (7), immune epitopes (8), and various classes of adjuvants have significantly increased long-term immunogenicity (9). Newer vaccines produce higher antibody titers and also have fewer side effects (10). After three hundred years since the first vaccination, there are still

many challenges in the development of new vaccines, including low stability, inefficient delivery, and lack of translation in human cells (11, 12).

Fighting the spread of such diseases requires making vaccines with a new method, which is usually not possible with traditional vaccines. These challenges have led to the development of research related to new vaccine manufacturing technologies. Table 1 lists some of the challenges in vaccine development.

The human body has different defense barriers that protect the human body against pathogenic agents. Innate immune systems and acquired immunity are the two components that make up the immune system of an individual. The first barrier of the innate immune system is the skin, mucus and stomach acid, which prevents the entry of pathogenic pathogens (13). After the first barrier of the innate immune system, there are macrophage cells, dendritic cells, monocytes, complement proteins, natural killer cells, mast cells, neutrophils, basophils and eosinophils (14).

The next barrier of the acquired immune system includes B and T lymphocytes. If the innate immune system fails to control the infection, the acquired immune system comes into action. The innate immune system acts non-specifically against all pathogens, but the acquired immune system specifically recognizes and targets the type of pathogen. Also, due to having memory B and T cells, it can create permanent immunity to that pathogen. Therefore, in vaccine production, the goal is to stimulate the acquired immune system to prevent the re-infection of the disease by creating memory cells and appropriate and quick responses و to the pathogen (14).

In general, vaccines work by exposing a person to the whole or part of the pathogen, and as a result, it leads to the activation of the person's immune system.

Traditional vaccines

There are different types of vaccines. Traditional vaccines are live attenuated, killed pathogens, as well as subunit and conjugate vaccines (Fig 1) (15). Live attenuated vaccines consist of a weakened form of a pathogen and can induce a strong immune response. Live attenuated vaccines targeting smallpox, measles, mumps, rubella, and yellow fever are among those that have received clinical approval (16). Although the injection of live weakened pathogens leads to a strong immune response, it can be a risk factor for people with a weak immune system or with underlying diseases. Therefore, an alternative approach such as a completely inactivated pathogen is needed to reduce the risk of disease. Inactivated vaccines are such as hepatitis B virus, poliovirus and rabies vaccines, the development of live attenuated and inactivated vaccines requires the growth of pathogens on a large scale, which is associated with biosafety risk (3).

Subsequently, a pathogen component makes up subunit vaccinations. Subunit vaccines are better in terms of immunogenicity and eliminate the need for pathogen culture. But they often need a booster to create effective immunity (17). The limitations of traditional vaccines have led to the discovery and development of new technologies in the production of vaccines, which include carrier vaccines, nucleic acid-based vaccines, and materials science approaches to vaccination Fig1.

Virus-like Particle Vaccines (VLP vaccine)

One of the unique features of viruses is that viral structural proteins and envelope proteins can self-assemble to form virus-like particles (VLPs) without the viral genetic material. Therefore, this feature can be used to make viral particles without pathogenicity. VIIPs have many applications in medical sciences such as therapy, drug delivery, some diagnostic tests and the development of vaccines (18).

Unlike conventional vaccines, VIPs have many features that make them attractive platforms for vaccine design. They are 20-200 nm in size and also have special geometric structures with multivalent epitopes (19-22) and have the ability to activate helper T cells.

In addition, VLPs are considered harmless because they do not contain the genetic material of the virus and therefore cannot replicate. However, VLPs, like any other vaccine, can cause side effects such as pain and swelling at the injection site. VLP-based vaccines have been developed using viruses that infect humans.

Table 1. Challenges in vaccine development

host variability	Pathogen Variability	Environmental factors
Individual variability	Pathogen diversity	Pollution
Non-responder populations	Hypervariable viruses	Co-infection
Age, Race, Sex, Ethnicity	Antigenic drift	Poor nutrition
	Interactions of Host-pathogen	Obesity
	Immune response evasion	Prior immunity

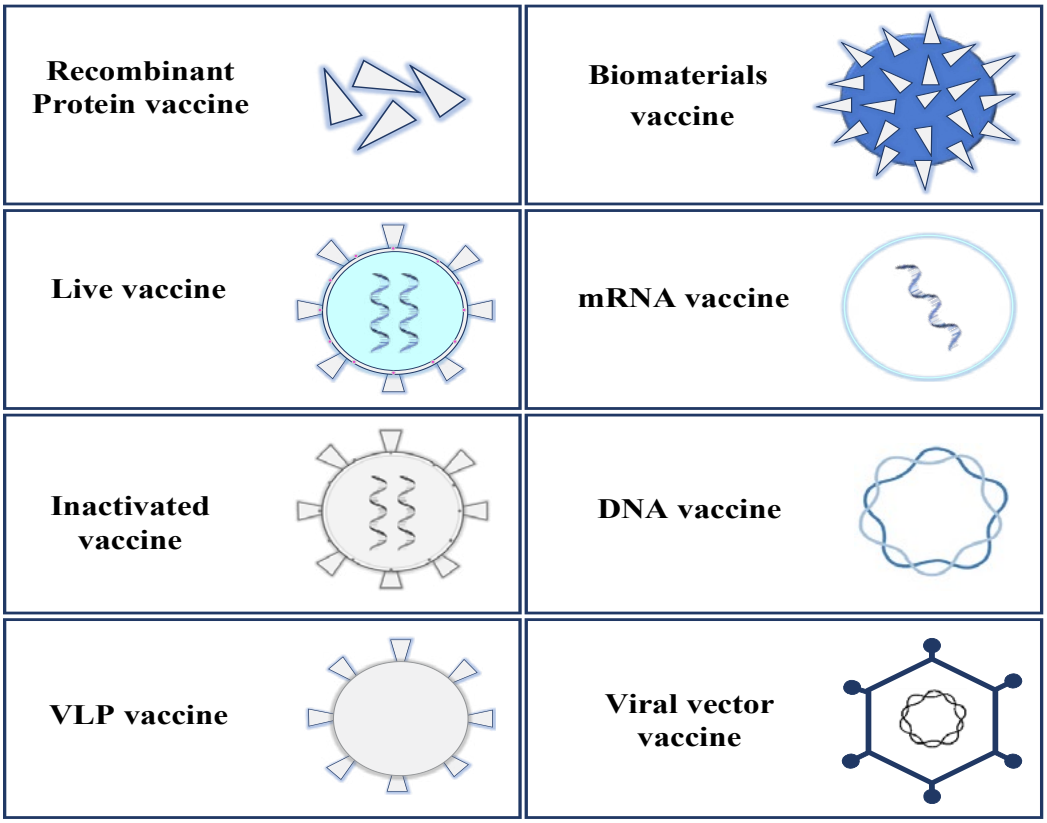

Fig1. All types of vaccines show this figure.

These vaccines are approved against three human viral infections, hepatitis B virus, human papilloma virus and hepatitis E (18).

mRNA vaccine

The concept of vaccines based on DNA and RNA nucleic acids was proposed in the past decades with the hope of being able to develop a flexible, easy-to-produce and safe vaccine. Until the late 2000s, DNA-based vaccines were emphasized due to the stability of RNAs (23). Also, efficient in vivo delivery as well as stimulation of excessive inflammatory responses were obstacles to nucleic acid-based vaccines (Fig1) (24). The production of transcribed mRNA in vitro is a relatively simple process (25-27), but the production of therapeutic, non-infectious and high-quality mRNA that can be well translated and cause serious inflammatory responses has been one of the main limitations in this field. In the early 2010s, the problems facing mRNA by optimizing the coding sequence, and purification of mRNA in the laboratory environment by HPLC to remove possible contaminants in the synthesized mRNA led to the reduction of toxicity and improvement of mRNA performance (28). However, there was still a problem with mRNA stability and efficient cytoplasmic delivery (29, 30). Various approaches have been developed to transfer mRNA into the cell, such as the use of gene guns and electroporation (31). These approaches are complex and expensive, and on the other hand, it is difficult to use them in humans, so the most ideal method is to use a substance that prevents mRNA degradation. In the past few years, many materials have been developed for the efficient delivery of nucleic acids, which have brought significant results (32).

mRNA vaccines work by delivering a fragment of mRNA that corresponds to a protein from a virus or other pathogen. People who receive the mRNA vaccine are not directly exposed to the virus, so they cannot be infected by the vaccine. Using this mRNA, cells can produce viral proteins, and as a natural immune response, the immune system identifies pathogen proteins and secretes antibodies against them (33).

The mRNA in these vaccines is not uniform and is rapidly degraded shortly after injection and after the target protein is made, reducing the risk of toxicity and long-term complications. mRNA vaccines enable the precise design of antigenic proteins and on the other hand, by delivering multiple mRNAs to a cell, it enables the production of multi-protein complexes or protein antigens from different pathogens, and thus a single vaccine It can act against several pathogens (34, 35).

Mechanisms that may affect the response of these types of vaccines by B and T lymphocytes include the half-life of antigen availability, the extent of antigen

presentation by MHC Class I/II, the participation of other components of the innate immune system, and the cytokine-induced environment. by the mRNA molecule itself as well as its delivery substance (23).

Viral vector vaccines

Adenovirus vectors were initially used as a promising strategy for gene therapy for gene transfer and gene therapy and basic studies to analyze gene function (36). Because these vectors have high transfer efficiency, and relatively large capacity (37), and on the other hand, they can infect a wide range of cells, including liver cells, myoblasts, epithelial and endothelial cells, and also induce a moderate level of innate immunity, have high thermal stability (37) Fig1. Therefore, adenovirus vectors are a suitable option for making vaccines. These types of vaccines can be effective in preventing infectious diseases such as the Ebola virus and HIV.

Adenoviruses are non-enveloped viruses that contain linear double-stranded DNA enclosed in a protein capsid.

This group of viruses cause 70 types of diseases in humans and is classified into 7 types (A-G) (38). Infection in humans causes symptoms of cold, sore throat, diarrhoea and vomiting.

Viral vector vaccines use a harmless virus to transfer a piece of genetic sequence to our cells, allowing them to produce pathogenic proteins. The harmless virus acts as a vector to transfer the genetic sequence. Our cells then make the viral protein that was transferred to our cells by the vector and present it to the immune system (39).

However, viral transmission itself plays an important role by enhancing the immune response. Which leads to a more severe reaction to the presentation of the pathogen's genetic sequence to the cell.

Biomaterials vaccine

However three centuries following the initial vaccination, there are still a lot of obstacles to overcome in the creation of novel vaccines, such as poor strength, ineffective administration, and a failure to penetrate human cells (40). To increase the effectiveness, long-term safety, and durability of vaccines, biomaterials including lipids, microneedles, scaffolds, and other material transporters, as well as natural and artificial polymers, have been created within the last three decades(Fig1) (41, 42).

Biomaterials offer a unique strategy for safe cargo delivery, protection, modification and management for targeted delivery, minimizing the number of injections and reducing systemic toxicity (43-45).

Biocompatibility, adjustable immunity, minimal inflammatory reactions, and comparatively high stability across various vaccine administration classes are just a few of the numerous benefits that biomaterials provide. Several types of biomaterials have been developed in micron and nano sizes, there are a large number of biomaterials, few of which offer sustained release properties (40).

Synthetic biodegradable polymers, including polylactic acid (PLA), polylactic-glycolic acid (PLGA), polyurethane (PU), and poly ε-caprolactone (PCL), are the most widely used biodegradable polymers in medicine (46-48).

Meanwhile, PLGA copolymers have been recognized as safe by the FDA and are suitable as a carrier for the sustained release of antigens and vaccine adjuvants due to their safety profile (49, 50).

Another type of biomaterials is polysaccharides, which are composed of carbohydrate polymers and are made of monosaccharide subunits. Polysaccharides form a very wide category of compounds found in plants, bacteria, fungi and even mammals (40). There are different types of polysaccharides, such as alginate (51, 52), cellulose (53), chitosan (54), hyaluronic acid (55), and starch (56), which have been evaluated in vaccines.

Approaches that combine immunogens with biomaterials have emerged as a promising approach for various types of vaccines (57, 58).

DISCUSSION

In the past decade, significant progress has been made in the field of making new vaccines, including mRNA-based vaccines. These vaccines, by optimizing the design of mRNA and its manufacturing processes, have led to the creation of vaccines that are effective in humans. They can be expressed well and have a higher immunogenicity. Another important feature of mRNA vaccines is targeting multiple pathogens simultaneously. They have also been found in some studies to be able to produce strong and long-lasting responses (57, 58).

Viral vector-based vaccines are also a promising field for developing new vaccines. The design of vaccines based on adenoviruses is based on most of the uncommon and non-pathogenic viruses. The structural components of viruses can be modified and optimized to increase tropism to body cells and tissues to optimally bind to body cells and tissues and express antigens efficiently. Adenovirus-based vaccines can be rapidly developed and produced on a commercial scale. Adenovirus vaccines mentioned suitable features such as stability, no need for cold chain transfer and targeted selection. Also, their use against various pathogens and the flexibility of these vaccines have made them suitable candidates for vaccine production (59, 60).

The use of biomaterials due to their wide spectrum and capabilities such as increased control in the

release of pathogens, targeted delivery, minimizing the number of injections and reducing systemic toxicity has turned them into a promising approach for the production of new vaccines. Also, biomaterials are biocompatible and produce low inflammatory responses and stable immunogenicity. In general, for any pathogenic pathogen, especially diseases such as HIV, TB, RSV, CMV, and Ebola virus that cannot be prevented with traditional vaccines, it is necessary to develop vaccines with a new method. However, it still requires specialized research in the field of each emerging disease (60-63).

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Availability of data and materials

The author who supplied the data may provide the raw data used in this work upon an appropriate request.

Ethics approval and consent to participate

Not applicable.

Consent to publication

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