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A Comparative Analysis of Traditional and Novel Influenza Vaccine Platforms

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Abstract: Influenza is a highly contagious respiratory disease with a high incidence and mutation rate, which continues to threaten public health. Although traditional vaccines have played an important role in influenza prevention and control, their protective effects are prone to fluctuations due to the drift of viral antigens. In recent years, the rise of new vaccine platforms such as mRNA vaccines and viral vector vaccines has provided new ideas for the rapid update and broad-spectrum protection of influenza vaccines. However, there is currently a lack of systematic comparison and comprehensive analysis of the advantages and disadvantages of different vaccine platforms in influenza prevention and control. This article reviews the mechanism of action, application potential, experimental basis and practical challenges of inactivated vaccines, protein subunit vaccines, mRNA vaccines and viral vector vaccines, systematically sorts out the differences between various vaccines in inducing humoral immunity and cellular immunity, and analyzes their performance in antigen drift response, vaccine broad spectrum and adaptability. By comparison, it can be seen that the new vaccine platform has obvious advantages in broad spectrum and flexibility. This study provides a theoretical basis for the optimal design and platform selection of future influenza vaccines, and also points out that there are still research gaps in the verification of immune persistence and fair accessibility of vaccines. In the future, we can further explore the multi-platform joint strategy and the development direction of broad-spectrum vaccines targeting conservative antigens.

Keywords: Influenza vaccine, mRNA vaccine, Viral vector vaccine.

1. Introduction

Influenza is an acute respiratory infectious disease caused by a virus, which is highly contagious and variable. Every year, seasonal influenza causes millions of infections and hundreds of thousands of deaths worldwide, especially among the elderly, children and patients with underlying diseases. Traditional inactivated vaccines have long been the main means of influenza prevention, reducing the incidence rate and the risk of severe illness to a certain extent. However, due to the high mutability of the influenza virus, traditional inactivated vaccines need to be updated annually or even quarterly, and the immune protection effect is limited by the matching of the virus strain. Therefore, developing a more broad-spectrum and stable influenza vaccine platform has become an important goal.

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In recent years, with the development of molecular biology and vaccine technology, many new vaccine platforms have emerged one after another. For instance, the latest mRNA vaccines have the advantages of rapid design and high controllability, played a significant role during the COVID-19 pandemic, and also provided a new path for the research and development of influenza vaccines [1]. In addition to mRNA vaccines, viral vector vaccines are also one of the current research hotspots, attracting attention because they can more effectively activate T-cell immune responses. Furthermore, other new vaccine platforms, such as protein subunit vaccines and DNA vaccines, have also demonstrated to varying degrees the possibility of the future development of influenza vaccines.

Although these new vaccines have promising prospects for development, there are still some uncertainties at present, such as the unclear mechanism of side effects and the relatively high difficulty in standardizing the production process. More systematic clinical data support is needed.

Therefore, this paper will systematically review the main types and research progress of the current new development platforms for influenza vaccines, focus on analyzing the technical principles, advantages and limitations of each platform, and explore their application potential in the future influenza vaccine strategy. By collating the existing research results and comparing the immune mechanisms and applicability of different strategies, this paper hopes to provide theoretical basis and technical reference for the optimization and promotion of the new generation of influenza vaccines.

2. The mechanism of vaccine works

Influenza vaccines are biological agents that can train the immune system to recognize and fight against influenza viruses before they cause illness. Their working principle is to introduce antigens —such as inactivated influenza virus particles or specific viral proteins like hemagglutinin (HA) and neuraminidase (NA)—into the body. These antigens do not cause disease themselves but mimic key components of circulating flu viruses, stimulating the immune system to respond.

Influenza viruses enter host cells by using their HA protein to bind to sialic acid receptors on the surface of respiratory epithelial cells. After attachment, the virus is taken up by the cell and transported into acidic compartments called endosomes. There, the virus undergoes structural changes that allow it to fuse with the endosomal membrane and release its genetic material into the cytoplasm. The viral genome is then imported into the cell nucleus, where it initiates replication. By targeting the HA protein, flu vaccine-induced antibodies can block this entry process, preventing infection at the earliest stage.

Once the antigen enters the body, the adaptive immune system is activated. Antigen-presenting cells, such as dendritic cells, capture and process the influenza antigens and present them to T cells and B cells. B cells then produce specific antibodies—primarily targeting the HA protein—which bind to the virus and neutralize it before it enters host cells. T cells help eliminate infected cells or coordinate the broader immune response. During this process, the body also generates memory B cells and memory T cells, which can remain in the body long-term and enable a faster and stronger response to future influenza infections [2].

Generally speaking, when the body is exposed to a specific influenza virus strain for the first time, the primary immune response takes five to ten days to be gradually established due to the time required for cell signaling and proliferation [3]. During this period, antibody levels rise slowly, and the virus may cause noticeable clinical symptoms. In contrast, the secondary immune response, triggered by memory cells, can act more rapidly and effectively just as shown in Figure 1. This is why annual influenza vaccination is so important—especially given the virus's frequent antigenic

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drift, which requires regular updates to the vaccine formulation. By preparing the immune system in advance, flu vaccines can significantly reduce the severity of illness and lower hospitalization and death rates, particularly in high-risk populations.

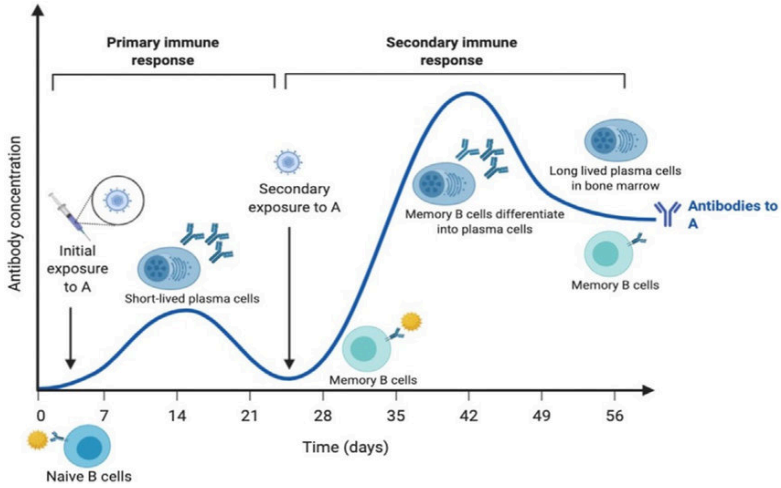

Figure 1. Antibody concentration of primary and secondary immune response [4]

3. Traditional vaccine

3.1. Inactivated vaccine

Inactivated vaccines are also a relatively early type of vaccine. They are produced by multiplying viruses in large quantities in a culture system and then inactivating the viruses through physical methods (such as heating) or chemical methods, preventing them from replicating and infecting cells. However, the virus after such inactivation still retains its structure and antigenicity. Therefore, when this inactivated virus is injected into the body, although it does not cause disease, its antigen can still stimulate T cells and B cells to produce an immune response, thereby establishing immune protection. The advantages of inactivated vaccines are that the technology is relatively mature, the safety is high, and they are suitable for the majority of people to use. However, it usually requires multiple vaccinations and booster shots to establish and maintain a sufficient level of immune protection.

In terms of effectiveness, inactivated influenza vaccines can significantly reduce the risk of severe illness and death, especially providing protection for susceptible groups such as the elderly and children. However, its effectiveness varies each year, mainly depending on the degree of matching between the influenza virus strain and the vaccine. Generally speaking, when the virus and the vaccine are highly matched, the effectiveness of the vaccine can reach 40% to 60%. However, when antigen drift occurs, the effectiveness of the vaccine may decline significantly [4].

One major problem with inactivated influenza vaccines is their weak ability to stimulate cellular immunity, especially the T lymphocyte response. In addition, the immune protective effect of this vaccine usually gradually weakens within 6 to 12 months after vaccination, so it is necessary to get vaccinated annually to maintain immunity.

Not only that, the production cycle of inactivated vaccines is relatively long and mainly relies on eggs for cultivation. This process is affected by multiple factors and may change the antigenicity of the virus, thereby affecting the effectiveness of the vaccine [5]. Despite these limitations, inactivated

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influenza vaccines still play an important role in public health worldwide due to their mature technology and wide coverage.

3.2. Protein subunit vaccine

The main principle of the Protein subunit vaccine is as follows: Firstly, antigen gene of virus is injected into an insect virus (Baculovirus), and then this virus is used to infect a type of moth cell. These Sf9 cells infected by the virus will start to express and produce the S protein of the novel coronavirus in large quantities. In other words, these insect cells have been "reprogrammed" into factories for producing S protein. Next, researchers will collect and purify these S proteins from the culture medium and enhance their immunogenicity by adding a component called PSA (Polysorbate-Adjuvanted Core) to aggregate these proteins into nanoparticles with a virus-like structure.

Finally, adjuvants such as Matrix-M are added to the vaccine formulation to further enhance the effect of the immune response. After being injected into the human body, these nanostructured S proteins can effectively stimulate B cells to produce antibodies and, to a certain extent, activate T cell immune responses, thereby achieving immune protection against the novel coronavirus.

Protein subunit vaccines can effectively induce humoral immune responses. When the virus strain is well matched, its protection rate can reach 50% to 60%, slightly higher than that of traditional inactivated vaccines. In addition, since subunit vaccines do not rely on egg culture, they can reduce some antigenic changes caused by egg production, which to a certain extent helps to improve the matching degree between vaccines and prevalent strains.

However, this type of vaccine also has some shortcomings. Because it does not contain complete viral components, its ability to activate cellular immunity is relatively weak, especially making it difficult to effectively activate T-cell responses. In addition, protein subunit vaccines usually require adjuvants to enhance immunogenicity and may need multiple vaccinations or annual booster shots to maintain immune protection.

4. New type of vaccine

4.1. mRNA vaccine

The mode of action of mRNA vaccines is that they first encapsulate a large number of mRNA fragments encoding viral proteins in a layer of lipid nanoparticles. These mrnas encode the antigen. Because lipid nanoparticles have a similar structure to human cell membranes (also composed of phospholipids), when the vaccine is injected into the body, these lipid particles will fuse with the cell membrane and smoothly release mRNA into the cell. After entering the cell, mRNA is translated in the cytoplasm to produce S protein. These antigen proteins synthesized by human cells themselves are then recognized by the immune system, thereby activating the immune responses of T cells and B cells. Ultimately, the body, like other types of vaccines, will generate memory B cells and memory T cells, providing rapid and effective protection against real viral infections in the future.

Compared with traditional inactivated influenza vaccines, mRNA vaccines have multiple advantages. They can bypass the complex and time-consuming virus amplification process, significantly shorten the research and development cycle, and update vaccines more quickly when facing the frequent antigenic drift of the influenza virus, which is crucial for rapidly mutating influenza.

At present, significant progress has been made in the research and development of mRNA influenza vaccines. The mRNA-1010 developed by Moderna is A quadrivalent vaccine targeting

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four strains, namely A/H1N1, A/H3N2, B/Yamagata and B/Victoria, and has now entered Phase III clinical trials. Pfizer/BioNTech, CureVac, Sanofi and other enterprises have also conducted similar research. moderna has even attempted to design a triple vaccine in combination with COVID-19 and RSV, demonstrating the future potential and possible applications of mrna vaccines [6].

Nevertheless, there are still certain challenges in the promotion of mRNA influenza vaccines. Its storage and transportation usually require a low temperature of -20°C or lower, which increases the difficulty of large-scale global popularization, and the manufacturing cost is higher than that of traditional vaccines, especially with limited accessibility in low - and middle-income countries. The safety of mrna also requires further experimental proof [1]. Despite the limitations of these technical and social factors, mRNA vaccines are still regarded as a key breakthrough direction in the future global influenza prevention and control system due to their advantages of high efficiency, rapid response capability and wide adaptability.

4.2. Viral vector vaccine

Viral vector vaccines involve using adenoviruses as tools and removing their pathogenic genes. At the same time, the genetic information encoding the Spike protein of the novel coronavirus is edited and inserted into the genome of the adenovirus. In this way, adenoviruses can infect normal human cells. However, since their pathogenic parts have been removed, they cannot further replicate or spread after entering the cells and thus do not cause diseases.

However, since its genome carries the coding gene of the Spike protein, when the adenovirus enters the cell, the cell will express this segment of the gene and synthesize the Spike protein. Subsequently, the immune system recognizes these exogenous proteins, activates T cells and triggers a series of subsequent immune responses, including the production of antibodies and memory cells. This process is similar in principle to mRNA vaccines.

The difference is that mRNA vaccines use lipid bubbles to encapsulate mRNA to enter cells. This structure is highly sensitive to temperature and requires ultra-low temperature storage to prevent lipid degeneration. In contrast, viral vector vaccines have lower requirements for stability and storage conditions, and thus are more convenient for transportation and distribution. They are particularly suitable for areas with weak infrastructure.

Compared with traditional inactivated influenza vaccines, viral vector vaccines can quickly skip the virus culture process, induce the host to express antigens, activate potent $CD8^+$ T cells and humoral immunity, thereby effectively dealing with influenza viruses with frequent antigen drift. This gives it the advantage of rapidly updating antigens and responding to new strains [7]. In animal models, the combined use of vector vaccines with conserved hemagglutinin stem antigens (such as cHA+NP+M1) demonstrated a stronger protective effect [8]. Not only that, currently, multiple candidate vaccines on this platform have entered early and mid-stage clinical trials. ChAdOx1 NP+M1 demonstrated good safety and significant T-cell immune response in the Phase I trial [9]. However, it also poses challenges: on the one hand, the pre-existing immunity to the vector in the population may reduce the efficacy of the vaccine, although the use of ape-derived adenovirus partially overcomes this problem 10]. In addition, the deployment of cold chain in resource-limited areas remains a bottleneck, and the public's acceptance of new carrier platforms and concerns about long-term safety also need to be further improved. Viral vector vaccines have the potential for both broad protection and rapid design updates, making them a highly promising platform in the future universal influenza vaccine strategy. However, they still require further optimization and clinical validation.

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5. Conclusion

This article reviews several current major influenza vaccine platforms, including inactivated vaccines, protein subunit vaccines, mRNA vaccines and viral vector vaccines, and makes systematic comparisons respectively from aspects such as immune mechanisms, application advantages and practical challenges. The article highlights that emerging vaccine platforms such as mRNA and viral vectors have demonstrated significant advantages in responding to viral antigenic variations, stimulating broad-spectrum immune responses, and enhancing production flexibility.

Through comparative analysis, it can be seen that the future research and development direction of influenza vaccines is likely to no longer rely on a single technology, but rather tend towards a development trend of multi-platform parallel operation and complementary advantages. This change not only helps to improve the efficiency of influenza prevention and control, but also provides a theoretical basis and technical reserves for facing new virus epidemics in the future. The research results summarized in this article respond to the concerns about the limitations of traditional vaccines in the preface and also provide a reference for constructing a more efficient vaccine system.

However, most new vaccines are still in the early clinical stage or animal experimentation stage. Their long-term protective effects, applicable population range and the feasibility of wide vaccination still need to be further verified. Meanwhile, some technology platforms also face challenges in terms of cold chain requirements, manufacturing costs, and the inherent immunity of the carriers. Therefore, relevant research should focus on enhancing the broad-spectrum efficacy and immune persistence of vaccines, while promoting the integration and translational application of multi-platform strategies. The development of broad-spectrum vaccines targeting conserved antigens and the exploration of combined vaccination regimens, etc., may become the key directions for building a new generation of influenza vaccine systems.

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