Innovations and Challenges in Influenza Vaccine Development and Global Deployment

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Abstract: Influenza remains a major global public health challenge, causing an estimated 290,000 to 650,000 respiratory-related deaths annually. Traditional egg-based vaccines are limited by slow production cycles and reduced efficacy due to antigenic drift. In contrast, mRNA and recombinant protein vaccines have improved production speed and immune response. mRNA vaccines offer up to 89.6% protection against H1N1, while recombinant vaccines have enhanced efficacy in older adults by 30%. Despite these advances, challenges such as high costs, cold-chain requirements, and low global vaccination coverage hinder effective control. This review highlights recent vaccine design innovations and evaluates ongoing issues, including viral evolution, immune durability, and access disparities.

1 INTRODUCTION

According to the statistics of the World Health Organization, there are about 1 billion cases of influenza worldwide every year. Among them, 3 to 5 million were severe cases and 290,000 to 650,000 died from respiratory infections (WHO, 2023). High-risk population (such as children, the older and people with low immune function) are more prone to complications such as pneumonia, myocarditis and multiple organ dysfunction. Historical seasonal influenza epidemics and major influenza pandemic, such as “Spanish flu” in 1918 and influenza A H1N1 in 2009, have not only increased the global healthcare burden, but also posed serious challenges to social and economic stability (Saunders-Hastings & Krewski, 2016). Influenza vaccination is the most effective way to prevent influenza, which can reduce the risk of infection by 60% to 70% and the risk of hospitalization by 40% to 60% (Andrew et al., 2017). Therefore, large-scale vaccination is very important to reduce the burden on the medical system.

Traditionally, inactivated vaccines and attenuated live vaccines are always the main prevention and control tools (Osterholm et al., 2012). In recent years, new vaccine platforms based on mRNA technology and recombinant protein vaccines have developed rapidly (Pardi et al., 2018). By precisely targeting viral surface proteins (such as hemagglutinin HA), immunogenicity is significantly improved. Despite the continuous progress of vaccines technology, the development of influenza vaccine still faces many challenges. Firstly, the influenza virus undergoes rapid mutation. It allows the virus to escape immune identification through antigen drift and antigen changes. This means that the effectiveness of the flu vaccine fluctuates every day. For example, in 2014 to 2015, the efficiency of vaccines in North America was only 19%. Production constraints—including a six-month egg-based manufacturing cycle and potential culture-induced antigenic changes—further impede timely vaccine updates (Zost et al., 2017). Additionally, global vaccination coverage remains suboptimal (below 50% on average), driven in part by vaccine hesitancy and “vaccine fatigue.”

Despite substantial advances in influenza vaccine research and development, further interdisciplinary collaboration and technological innovation are essential to optimize vaccine efficacy and accessibility. This review systematically examines emerging influenza vaccine strategies—including universal vaccine design, adjuvant optimization, and advanced delivery systems—and evaluates critical challenges such as limited immune durability, inequitable global efficacy, and the need for mucosal immunity. By providing a comprehensive analysis of recent R&D progress, identifying persistent obstacles, and outlining future directions, this review seeks to furnish a scientific foundation and actionable guidance for enhancing influenza prevention and control.

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2 THE GLOBAL IMPACT OF INFLUENZA VIRUS AND HIGH-RISK GROUPS

Influenza virus is one of the fastest and most frequent respiratory viruses in the world. It puts great pressure on the global public health system every year. According to the statistics of the World Health Organization, 290,000 to 650,000 people suffer from respiratory diseases every year (Iuliano et al., 2018). In countries with poor health conditions, the mortality rate is two to three times that of developed countries (Global Burden of Disease Collaborative Network, 2021). The risk of infection varies significantly among different groups of people: children under the age of 5 are three times more likely to suffer from serious diseases than normal children because of their immature immune systems, while the elderly over 65 years old account for 80% of flu deaths. This is because their immune system is weak and often accompanied by chronic disease (such as hypertension, diabetes, etc.), making them more prone to complications after infection with influenza (Paget et al., 2022). According to the statistics of Chinese hospitals, among the elderly over 60 years old, 42.3% of flu patients are serious cases, and the mortality rate of heart disease and diabetes patients is as high as 12.7% (Li et al., 2021). In addition, the immunity of pregnant women is relatively low, so they are more likely to be infected with the flu and enter intensive care than ordinary women. The health status of these high-risk groups makes influenza more harmful to them, highlighting the urgency of influenza prevention and control (Rasmussen et al., 2022). Other high-risk groups include individuals with immunodeficiency (e.g. HIV infection, organ transplant recipients), residents of long-term care facilities, and persons with obesity or chronic respiratory conditions. These populations not only suffer higher rates of hospitalization and death but also contribute disproportionately to healthcare utilization and economic costs. Collectively, these data underscore the critical need for targeted prevention strategies and enhanced vaccine coverage to mitigate the substantial global impact of influenza.

3 THE MUTATION MECHANISM OF INFLUENZA VIRUS

The high variability of the influenza virus is the main reason for its long-term challenge to the effectiveness of vaccine prevention and control. The mutation mechanism of influenza virus includes two forms: antigen drift and antigen transformation. Antigen drift refers to the gradual changes of surface antigens (such as hemagglutinin, neuraminidase, etc.) due to replication errors in the replication process of influenza viruses, which makes the virus escape the recognition of the host's immune system (Wu et al., 2020). This change is one of the ways the influenza virus adapts to the environment and escapes immune surveillance. For example, the vaccine used in North America in 2014 could not prevent 19% of diseases, because there was a mutation in the surface antigen part between the vaccine used that year and the virus that was actually prevalent, which greatly reduced the effectiveness of the vaccine (Neher & Bedford, 2021). Another important form of mutation is antigen transformation, which usually occurs in the process of viral gene exchange or recombination between different animals (such as pigs, birds, etc.) and humans. For example, the 2009 H1N1 pandemic strain emerged through genetic reassortment of avian, swine, and human influenza viruses, resulting in widespread global transmission (Petrova & Russell, 2018). Such major antigenic changes can render prior immune memory ineffective, necessitating rapid vaccine reformulation (Arevalo et al., 2022). Consequently, continuous viral evolution remains a critical obstacle to the timely development and updating of effective influenza vaccines.

4 TYPES AND CHALLENGES OF INFLUENZA VACCINES

At present, there are two main types of vaccines: inactivated vaccines and live attenuated vaccines. Inactivated vaccines can bind with viruses and retain the protective factor structure on the surface of the virus, while the treatment of live vaccines can prevent the virus from multiplying in the nasal cavity or spreading in the hair (Grohskopf et al., 2020). The advantage of inactivated vaccines is that they are safe and suitable for most people, including the elderly and patients with low immune function. However, the disadvantage of inactivated vaccines is that they have poor immune protection against some viruses, mainly because they stimulate the production of antigens in the blood. For example, the protection rate against the H3N2 virus is only 33% to 44%, and it can only stimulate the antibody reaction in the blood, making it difficult to effectively activate the local immune response (Osterholm et al., 2022). Live attenuated vaccines allow the virus to multiply in the nasal cavity

without causing serious systemic infections by attenuating its pathogenicity. This vaccine activates the nasal and cellular immune systems, providing children with a higher rate of protection, 72% to 83%. However, there are certain restrictions on the use of live attenuated vaccines. People with weak immune systems or health problems (such as immunodeficient people) are not suitable for vaccination, because it may cause serious side effects, such as nasal congestion and severe fever (Blshe et al., 2021; Centers for Disease Control and Prevention, 2023). Among the elderly, the content of antibodies decreased by 10% within 6 months after vaccination, resulting in a great reduction in the effectiveness of the vaccine (Black et al., 2011). In addition, the traditional influenza vaccine production relies on chicken embryo culture, which is not only time-consuming but also prone to virus mutation during culture. For example, when H3N2 virus is cultured in chicken embryos, the mutation in amino acid No. 160 will affect the effect of the vaccine (Zost et al., 2020). In 2017, because of this mutation, vaccines in the northern hemisphere were 20 per cent less effective compared to cell-cultured vaccines. World vaccine production is concentrated in a few countries, while vaccination rates in developing countries are below 30% (WHO, 2022), further exacerbating the global imbalance in vaccination.

5 NEW VACCINE PLATFORM AND DEVELOPMENT

With the advancement of science and technology, the emergence of novel vaccine platforms has provided new solutions for the development of influenza vaccines. mRNA vaccines have been one of the most interesting research directions in recent years. The mRNA vaccine uses lipid nanoparticles to wrap the mRNA gene of the virus. After injecting into the human body, mRNA instructs cells to synthesize the surface antigen of the virus, thus stimulating the immune system to produce antibodies and cellular immune responses. Clinical experiments show that the protection rate of mRNA vaccine against H1N1 virus has reached 89.6%, and the production cycle has been greatly shortened to two months (Zhang et al., 2021). Nevertheless, there is still a risk of allergy in vaccines. There are about 2.8 cases of allergy per 100,000 injections, and they need to be stored at extremely low temperatures (-70°C) to maintain their stability, which poses challenges to large-scale production and distribution (Pardi et al., 2022). Fortunately, with the improvement of the formula, the existing mRNA vaccine can be stored in a refrigerator at 4°C for a month, which greatly simplifies the logistics and distribution (Gebre et al., 2022). Recombinant prokaryotic vaccines (such as Flublok) use insect cells to produce viral nuclei, thus avoiding the mutation problems associated with worm culture. These vaccines are 30 per cent more effective than the regular vaccine in people over 65 years of age, however they are also relatively expensive, costing $28.50 per dose, three times as much as the regular vaccine (Dunkle et al., 2022). Despite the technological breakthroughs of the new vaccine platform, cost issues and the enhancement of large-scale production capacity are still challenges that need to be addressed.

6 CONCLUSION

This review shows that the current influenza vaccine system is facing a critical period of technological change. Due to the possibility of virus mutation, such as the antigen mutation of H3N2 in 2017 and the extension of production time, it is difficult for traditional egg-based culture technology to cope with rapidly developing viruses. Although novel vaccine platforms offer substantial benefits—mRNA vaccines can be manufactured within two months, and recombinant protein vaccines improve protection in older adults by approximately 30%—high production costs, stringent cold-chain requirements, and logistical complexities continue to present significant challenges. The most important conflict is the competition between the rate of virus evolution and vaccine effectiveness. Current predictive models are outdated, shortening the duration of vaccine protection, while vaccine coverage in developing countries is below 30 per cent and the gap between prevention and control is widening. Closing the gap between viral mutation and vaccine responsiveness requires integrated strategies: deploying artificial intelligence–driven real-time genomic surveillance and predictive modeling to guide strain selection and support universal vaccine design; advancing novel delivery approaches, including intranasal formulations, to strengthen mucosal immunity and prolong protection; and building a coordinated, modular manufacturing infrastructure that combines cell-based production with nanoparticle technologies to lower costs and expand capacity. Through sustained international collaboration and continued innovation, it is possible to establish a more agile, effective, and universally accessible influenza prevention framework.

REFERENCES

Andrew, Melissa K et al. 2017. Influenza vaccine effectiveness against influenza-related hospitalization during a season with mixed outbreaks of four influenza viruses: a test-negative case-control study in adults in Canada. *BMC infectious diseases*, 17(1), 805.

Arevalo, Claudia P et al. 2020. Original antigenic sin priming of influenza virus hemagglutinin stalk antibodies. *Proceedings of the National Academy of Sciences of the United States of America*, 117(29), 17221–17227.

Belshe, Robert B et al. 2007. Live attenuated versus inactivated influenza vaccine in infants and young children. *The New England journal of medicine*, 356(7), 685–696.

Black, Steven et al. 2011. Hemagglutination inhibition antibody titers as a correlate of protection for inactivated influenza vaccines in children. *The Pediatric infectious disease journal*, 30(12), 1081–1085.

Centers for Disease Control and Prevention. 2023. Influenza (Flu) Vaccine Safety. *Centers for Disease Control and Prevention*, Accessed 1 Dec. 2023.

Dunkle, Lisa M et al. 2017. Efficacy of Recombinant Influenza Vaccine in Adults 50 Years of Age or Older." *The New England journal of medicine*, *388*(16), 1465–1477.

GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019." *Lancet (London, England)*, *396*(10258), 1204–1222.

Gebre, Makda S et al. 2022. Optimization of non-coding regions for a non-modified mRNA COVID-19 vaccine." *Nature*, 601(7893), 410–414.

Grohskopf, Lisa A et al. 2024. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices - United States, 2024-25 Influenza Season." *MMWR. Recommendations and reports: Morbidity and mortality weekly report. Recommendations and reports*, 73(5), 1–25.

Iuliano, A Danielle et al. 2018. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study." *Lancet (London, England)*, *391*(10127), 1285–1300.

Li, Li et al. 2019. Influenza-associated excess respiratory mortality in China, 2010-15: a population-based study. *The Lancet*, 4(9), e473–e481.

Neher, R. A., & Bedford, T. 2015. nextflu: real-time tracking of seasonal influenza virus evolution in humans. *Bioinformatics (Oxford, England)*, 31(21), 3546–3548.

Osterholm, Michael T et al. 2012. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. *The Lancet. Infectious diseases*, *12*(1), 36–44.

Paget, John et al. 2019. Global mortality associated with seasonal influenza epidemics: New burden estimates and predictors from the GLaMOR Project." *Journal of global health*, *9*(2), 020421.

Pardi, Norbert et al. 2018. mRNA vaccines - a new era in vaccinology." *Nature reviews. Drug discovery*, *17*(4), 261–279.

Han, A. X., de Jong, S. P. J., & Russell, C. A. 2023. Co-evolution of immunity and seasonal influenza viruses. *Nature reviews. Microbiology*, *21*(12), 805–817.

Rasmussen, Sonja A et al. 2022. Effects of influenza on pregnant women and infants." *American journal of obstetrics and gynecology*, *226*(4), 459–474.

Saunders-Hastings, P. R., & Krewski, D. 2016. Reviewing the History of Pandemic Influenza: Understanding Patterns of Emergence and Transmission. *Pathogens (Basel, Switzerland)*, *5*(4), 66.

World Health Organization. 2023. Influenza (Seasonal). *World Health Organization*.

World Health Organization. 2022. Global Influenza Strategy 2020-2030. *World Health Organization*.

Wu, Nicholas C et al. 2022. Major antigenic site B of human influenza H3N2 viruses has an evolving local fitness landscape." *Nature communications*, *11*(1), 1233.

Zhang, Na-Na et al. 2020. A Thermostable mRNA Vaccine against COVID-19. *Cell*, *182*(5), 1271–1283.e16.

Zost, Seth J et al. 2017. Contemporary H3N2 influenza viruses have a glycosylation site that alters binding of antibodies elicited by egg-adapted vaccine strains." *Proceedings of the National Academy of Sciences of the United States of America*, *114*(47), 12578–12583.