Influenza virus evolution and vaccine development

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Abstract. Although the effectiveness of universal influenza vaccines may vary from year to year, getting vaccinated against the influenza virus remains the optimal strategy for preventing influenza virus infection. As a result, recent research has focused on improving the protective efficacy and potency of influenza vaccines. This paper explores two theories: antigenic drift and antigenic imprinting. Antigenic drift refers to the gradual changes and evolution of antigens within influenza viruses. However, epidemiological data suggest that a single strain dominates each flu season. The theory of antigenic imprinting helps explain this phenomenon. Population immunity targets epitopes of limited variables (ELVs). Influenza vaccines can target ELVs to enhance vaccine effectiveness specifically.

**Keywords:** influenza virus, antigenic drift, antigenic thrift, vaccination, vaccine efficacy.

1. Introduction

Influenza viruses severely threaten human health and can infect many hosts. Seasonal influenza is estimated to cause 3 to 5 million cases of severe illness and 290,000 to 650,000 deaths yearly [1]. Despite decades of extensive surveillance and pharmacological and non-pharmaceutical interventions, seasonal influenza viruses cause annual epidemics worldwide. A significant factor contributing to these epidemics' resurgence is the virus's ability to evolve and evade immunity from previous infections or vaccination [2]. The prevailing view is that influenza viruses evolve mainly through antigenic drift, that is, the gradual mutation of their surface protein (Hemagglutinin, HA), enabling them to evade herd immunity. As strains carrying favorable escape mutations circulate among hosts, they become the dominant seasonal strains [3]. This pattern of evolution is also the basis for designing flu vaccines. However, epidemiological data show that only a single or limited number of strains predominate in the epidemic [4].

Furthermore, Paules and Subbarao claim that vaccines designed based on the antigenic drift theory may not be effective against emerging virus strains [5]. The antigen-thrifty idea has received widespread attention from scholars as a potential vaccine development theory in recent years. Antigenic thrift suggests that immune selection favors epitopes with low variability, which reduces the virus's diversity in contrast to antigenic drift. This paper will delve into the current theories of influenza virus evolution and summaries the vaccines developed based on these theories. A comparison of the strengths and weaknesses of each model will be presented to offer insights for future influenza virus research.

2. Influenza virus surface antigen (hemagglutinin and neuraminidase)

Influenza A virus is an enveloped single negative-sense RNA virus [6], and its genome consists of 8 independent gene segments with a total length of about 13kb. It encodes up to 16 proteins (Figure 1).
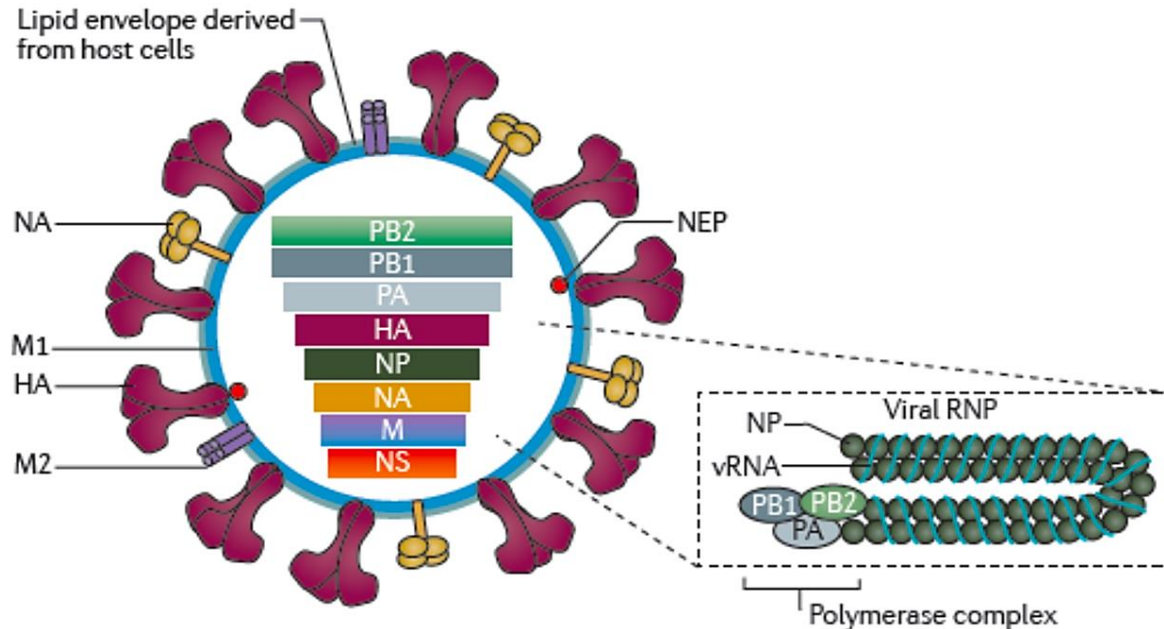
Figure 1. Structural diagram of influenza A virus. Figure adapted from Medina and García-Sastre [7]. The figure shows the genome structure of the influenza A virus, which contains 8 RNA gene segments. Polymerase Basic Protein 2, Polymerase Basic Protein 1, Neuraminidase, Nucleoprotein, Neuraminidase, Matrix, Nonstructural.

Hemagglutinin (HA) protein serves as the major surface antigen of the influenza virus and is the primary target of the host immune response [8]. It consists of two main domains, the head and the stem. The head domain, which is exposed to the immune system, contains the receptor binding site (RBS) that interacts with the sialic acid receptor on target cells, initiating the process of endocytosis [9]. The head domain partially conceals the stem domain from the immune system due to steric hindrance [10]. Compared to the head domain, the stem domain exhibits less flexibility [11].

The neuraminidase segment encodes the neuraminidase (NA), which cleaves the sialic acid (SA) residues from glycoproteins or glycolipids on the cell surface. This releases the virus from host cells, facilitating further spread and dissemination [12]. Similar to HA, NA protein is another surface antigen of the influenza virus.

3. Evolution of influenza viruses

Due to the lack of a correction mechanism of RNA polymerase, the influenza virus can produce many mutations. Each gene of the influenza virus has diversity through modification, but the surface glycoproteins HA and NA are mainly evolved due to immune selection, among which HA protein exists. Many antigenic epitopes bear the most positive selection pressure [13].

3.1. Antigenic drift

Antigenic drift refers to the influenza virus changing its antigenic properties by continuously accumulating amino acid substitutions on its surface glycoproteins (HA and NA), especially on antigenic epitopes. First, the influenza virus can constantly change its antigenicity and evade the host immune system. Second, strains with favorable escape mutations spread among host populations, becoming the most prevalent seasonal strains. Phylogenetic trees can confirm this. However, due to the significant number of samples, the evolutionary tree cannot form a clear group, which makes it impossible for

people to understand the evolution of the influenza virus. The evolutionary panorama has been improved on this basis [14].

3.2. Antigenic thrift

Although many people think that the tremendous variability of influenza viruses is brought on by the ongoing accumulation of mutations on their surface antigens, there is a paradox in their diversity. However, according to Zinder et al., many antigenically and genetically different strains predominate during the seasonal influenza season [15]. The antigen thrift model proposed as a result of ongoing research by academics like Raymond can be used to explain why just one strain predominates [16]. This is since limited variety epitopes (ELVs) in the head are targeted by herd immunity rather than highly variable epitopes.

Overall, the antigenic thrift theory offers a verifiable method for comprehending the development of dominant strains of influenza (Table 1).

**Table 1.** Antigenic thrift and antigenic drift contrast in influenza viruses.

	Antigenic drift	Antigenic thrift
Definition	- Influenza is highly variable - Escapes population immunity through the accumulation of incremental mutations over time	Population immunity is directed against epitopes of limited variability (ELV)
Influence	- Influenza vaccine needs to be updated every year - Trivalent and quadrivalent vaccines(TIV/QIV)	- Provides a mechanism by which universal influenza vaccines couldbe created - Also have the potential to protect against emerging influenza strains

4. Vaccines for influenza viruses

Influenza vaccines are one of the main strategies for preventing influenza virus infection. It stimulates the immune system to produce antibodies and cellular responses, protecting against the virus [17]. The widely administered vaccines are Trivalent and Quadrivalent (TIV/QIV) [18]. However, the effectiveness of influenza vaccines, known as vaccine effectiveness (VE), remains suboptimal. A study conducted in the United States between 2004 and 2018 showed that the VE of influenza vaccines ranged from 10% to 60% [19]. This can be attributed to the following factors:

- Influenza vaccines target antibodies to highly variable regions of the virus.
- Vaccination only provides approximately 33% protection.
- Though the strains that become common during the actual flu season do not always match those used in the vaccination, there is still a need to research and manufacture the corresponding influenza vaccines six months before the flu season.

Review the history of influenza vaccine development (Figure 2). In the future, it is expected to improve the protection of influenza vaccines. Some scholars have proposed alternatives based on the antigen thrift theory [20].
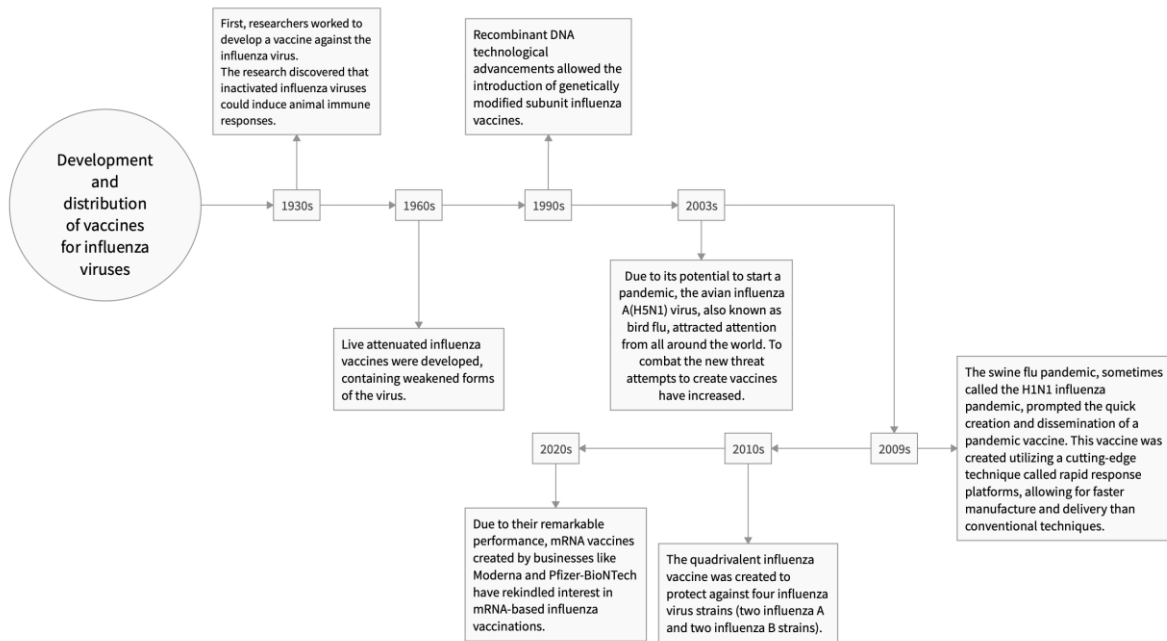
Figure 2. Influenza vaccine development and distribution from 1930 to 2020. Sources adapted from [21-25].

4.1. Trivalent and quadrivalent vaccines (TIV/ QIV)

Trivalent vaccine (TIV) and quadrivalent vaccine (QIV) are commonly used types of influenza vaccine for the prevention of seasonal influenza [26]. Trivalent and quadrivalent vaccines (TIV/QIV) consist of one strain of influenza A (H1N1), one strain of influenza A (H3N2) and one or two strains of influenza B (Victorian and Yamagata lineage) [27].

According to the antigenic drift model, the head region of the influenza virus is prone to mutations due to its interaction with the host immune system and immune pressure. This leads to the emergence of different strains and subtypes of influenza viruses [28]. In contrast, the stem region is relatively stable and undergoes fewer mutations. Therefore, TIV and QIV vaccines are designed to target the stem region, which allows them to provide broad protection against multiple strains of influenza viruses due to the higher sequence conservation in this region [28].

However, limitations are associated with targeting the conserved stem region in vaccine design. Antigens in the stem region may not induce as strong of an immune response as those in the head region because the stem region is relatively hidden and has less direct interaction with the host immune system [29]. The immune system may require additional stimulation to generate a sufficient immune response and provide protection against the stem region. Moreover, vaccines targeting the conserved stem region may offer protection only against specific subtypes of influenza viruses and may not provide broad protection against other subtypes or variants. Although the stem region is relatively stable, there are still some differences in the stem sequences among different influenza virus subtypes, necessitating the development of subtype-specific vaccines [30]. Further research and innovation are needed to address these limitations and enhance the effectiveness and coverage of influenza vaccines.

Different countries have also compared the cost-effectiveness of TIV and QIV. Firstly, a research team in Italy conducted a statistical analysis using a decision tree on elderly individuals aged 65 and above who received the vaccine. The results indicated that QIV has higher cost-effectiveness [31]. Additionally, a Markov model was used in the UK to assess cost-effectiveness, and the results showed that most simulations (96%) demonstrated the economic viability of QIV, with an Incremental Cost-Effectiveness Ratio (ICER) below the £20,000 per Quality-Adjusted Life Year (QALY) cutoff [32]. Research conducted in China also supported these findings [33].

4.2. Targeting restricted immunogenic epitopes

TIV and QIV inhibit viral variation by targeting conserved regions, but they do not consider the evolution of influenza viruses. Thompson et al. suggested targeting highly immunogenic epitopes with limited variability and may serve as natural foci for humoral immunity [19]. Restricted variability epitopes offer a novel strategy for creating universal influenza vaccines that may protect from recently discovered influenza strains. The variability of influenza viruses poses an ongoing challenge, with new strains constantly emerging. Traditional vaccine designs often require frequent updates to accommodate newly emerging influenza strains [34]. However, by targeting epitopes with limited variability, vaccines can partially overcome this challenge [35]. Vaccines can still rely on conservative and relatively stable epitopes to induce an immune response against these strains, even if newly emerging influenza strains undergo variation in other regions.

According to the antigen-thrifty model, although new influenza virus strains continue to emerge, they can often not cause large-scale infection in hosts with immune memory against limited variation. The evolutionary mechanism of antigenic thrift drives influenza viruses to maintain a relatively stable antigenic profile while limiting the ability of new strains to spread in host populations [36].

5. Conclusion

In conclusion, this study investigated the antigenic drift and thrift models in influenza virus evolution and their impact on vaccine development. The findings suggest that targeting limited variable epitopes could enhance vaccine effectiveness. However, further research is needed to validate these findings, including experimental studies and clinical trials. Additionally, continuously monitoring influenza virus evolution and exploring innovative approaches are necessary to improve vaccine strategies. Despite the limitations of this study, the insights gained contribute to the ongoing efforts to reduce the global burden of influenza-related illnesses.

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