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The Global Burden of Influenza: Challenges and Future Directions

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Abstract: Influenza remains a significant global health challenge, particularly affecting high-risk groups like the the elderly, pregnant woman, young children, and individuals with underlying health conditions. Its unique characteristics, including rapid growth, high variability, and segmented RNA genome, enable the emergence of new viral subtypes that can evade existing immunity and render vaccines less effective. Surface proteins like hemagglutinin (HA) and neuraminidase (NA) further contribute to its ability to infect host cells and undergo frequent changes. Annually, millions of hospitalizations and numerous deaths are attributed to influenza, with complications ranging from mild illnesses to severe conditions like pneumonia. Despite these challenges, vaccines remain a crucial tool in mitigating the impact of influenza by reducing hospitalizations and mortality rates. However, issues such as the inability to fully address viral mutations and delays in vaccine production highlight the need for improved strategies. Advances in vaccine production technologies and continued research into viral subtypes are essential for developing more effective solutions to combat influenza and its widespread impact.

Keywords: Influenza, vaccine development, viral subtypes.

1. Introduction

Influenza, or the flu, has affected humans for centuries. Reports have given evidence that Influenza pandemics has existed for at least 500 years, with inter-pandemic intervals averaging approximately 40 years. Influenza has started a long history of seasonal outbreaks and pandemics that affected public health and influences the direction of medical research. Some historians suggested that the virus has likely emerged from zoonotic transmissions, where pathogens jump from animals to humans, especially since there were increasing amount of birds and pigs during the rise of agriculture [1]. Influenza causes lung damage, which allows bacterial infections to develop. Some theories suggest that younger adults (those in their 20s and 30s) died at a higher rate because of no previous explosion. Others also suggested that their immune response overreacted to the virus (cytokine storm) damaging healthy tissues in the process. Most common symptoms and causes of the flu include sudden fever, dry cough and headaches. The most serious illness is caused by flu subtypes of A and B [2].

Influenza viruses are highly contagious and can spread through respiratory droplets when an infected person coughs, sneezes or talks. They can also survive on surfaces, leading to indirect transmission when individuals touch contaminated surfaces and then their face. The National Center for Health Statistics and the statistics have recorded a total number of 31 million cases for influenza

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in 2022-2023 flu season, and mortality rates for aged 65 years and older was around 26.6 per 100000 population [3]. This article will further analyze the current status of influenza virus research, propose the problems that may be faced in this research field, and provide feasible suggestions for future research (Table 1).

Table 1: Rate of deaths per age group.

Characteristic	Rate per 100,000 population
0-4 years	1.2
5-17 years	0.5
18-49 years	0.7
50-64 years	7.2
65+ years	26.6

2. Structure of the Influenza Virus

Influenza is part of the Orthomyxoviridae family and consists of several types, including influenza A, B and C. Influenza A viruses can infect humans and a variety of animals. It is categorized into subtypes based on two surface proteins, hemagglutinin (H) and neuraminidase (N) [4]. The most common subtypes that affects humans includes H1N1 and H3N2. These two subtypes are also included in the seasonal flu vaccine each year [5]. This type of flu is responsible for seasonal flu and causes pandemics. Influenza B primarily affects humans while also less common than type A. There are two lineages of influenza B, Victoria and Yamagata. Influenza B viruses also mutate more slowly than influenza A viruses. Compared to influenza A viruses, influenza B typically results in less severe outbreaks compared to influenza A, though it can still cause significant illness. The next type is influenza C, which apart from humans, also has been found in dogs and pigs. Type C usually causes mild respiratory illness and does not lead to epidemics, which is considered the least severe of the three types that affects humans. The last type is influenza D which primarily affects cattle and does not appear to infect humans and does not pose a risk to human health, which can be seen in table 2 [6].

Table 2: Key differences of types of Influenza

Type	Hosts	Severity of Illness	Common Symptoms	Complications
Influenza A	Humans & animals	High	Fever, cough, muscle aches	Pneumonia, respiratory failure
Influenza B	Primarily humans	Moderate	Similar to A but milder	Pneumonia, chronic condition exacerbation
Influenza C	Humans (and some animals)	Low	Mild respiratory illness	Rarely serious complications
Influenza D	Mainly cattle	None	None	None

Influenza viruses have special structures such as a vision shape, which are generally spherical or filamentous, with spherical forms measuring approximately 80-120 nanometers in diameter, while filamentous forms can exceed 300 nanometers in length [7]. This variability in shape can influence

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how the virus interacts in host cells and its overall infectivity. The virion is enveloped by a lipid membrane derived from the host cell, which contains glycoprotein spikes of hemagglutinin (HA) and neuraminidase (NA). These proteins are essential for the virus's ability to bind to and enter host cells. The HA spikes facilitate attachment to sialic acid receptors on host cells, while NA plays a critical role in the release of new virions from infected cells. Beneath the lipid envelope is the matrix protein (M1), which provides structural integrity to the virion and helps maintain its shape. Inside the virion, influenza viruses contain eight segments of negative-sense, single-stranded RNA (ssRNA). These RNA segments are associated with nucleoproteins and are crucial for encoding the viral proteins necessary for replication and infection. The viral RNA-dependent RNA polymerase complex, composed of several subunits, is also present within the virion. This is vital for transcribing the viral RNA into mRNA during the infection process (Figure 1).

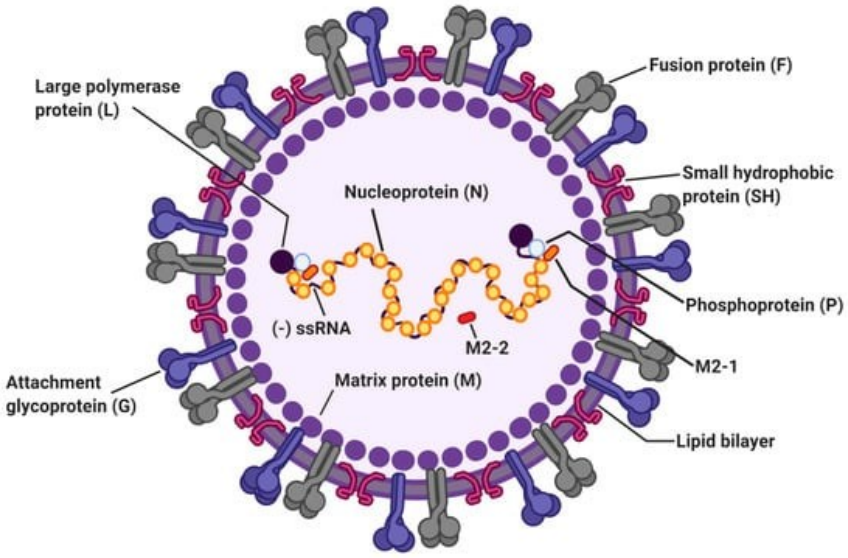


Figure 1: Respiratory Syncytial Virus (RSV) structure [8].

3. Problems with cure faced with influenza

Influenza viruses undergo continuous genetic changes through antigenic drift and antigenic shift, which significantly challenge vaccine effectiveness. Antigenic drift involves gradual genetic mutations, while antigenic shift refers to the reassortment of gene segments, often resulting in novel strains. These frequent mutations can render current vaccines less effective, as they may not provide sufficient protection against newly emerged variants. Furthermore, the reliance on embryonated chicken eggs for vaccine production introduces substantial limitations. The production process, which typically requires 6–8 months, can delay vaccine availability during outbreaks and pandemics, hindering rapid responses and global vaccine distribution.

Current influenza vaccines primarily target the HA head domain, a highly variable region susceptible to mutations. This variability underscores the need for vaccines that elicit broader immunity against multiple strains and subtypes. Research efforts are increasingly focusing on targeting conserved viral structures, such as the hemagglutinin stem, which is less prone to mutations across subtypes. By concentrating on the HA stem, new vaccine strategies aim to generate robust immune responses that remain effective despite viral mutations. This approach holds promise in addressing the primary limitation of influenza vaccines: their susceptibility to antigenic variability [9].

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In addition to vaccine challenges, treatment options for influenza are also constrained. Many human influenza A virus strains have developed resistance to M2 inhibitors like amantadine. For example, during the 2005–2006 influenza season, 193 out of 209 influenza A (H3N2) viruses demonstrated resistance to these inhibitors. As a result, current antiviral therapies are largely dependent on neuraminidase inhibitors (NAIs), which remain effective against circulating strains. However, the emergence of resistant strains poses a significant barrier to the long-term effectiveness of these antivirals, further complicating treatment efforts [10].

Another challenge in influenza vaccine development lies in the ethical and practical constraints of clinical trials. Studies often require healthy human volunteers to assess immune responses and vaccine efficacy, raising ethical concerns. Furthermore, strict inclusion criteria, such as the exclusion of individuals with significant comorbidities, can limit the generalizability of vaccine performance data, particularly in high-risk populations like the elderly or immunocompromised. Addressing these challenges is crucial for advancing influenza vaccine strategies and improving both prevention and treatment options.

4. Suggestions

To address the limitations of current influenza prevention and treatment strategies, several key improvements should be prioritized. First, there is an urgent need to develop universal influenza vaccines that target conserved viral structures, such as the hemagglutinin stem, to provide broader and more durable protection against multiple strains and subtypes. This approach can mitigate the impact of antigenic drift and shift, reducing the susceptibility of vaccines to newly emerged mutations. Second, advancements in vaccine production technologies, such as cell-based or recombinant platforms, should be pursued to overcome the time and capacity constraints associated with the reliance on embryonated chicken eggs. These modern production methods can significantly accelerate vaccine availability during outbreaks and enhance global distribution.

Additionally, efforts should focus on diversifying antiviral drug options to address the growing resistance to M2 inhibitors and the potential emergence of resistant strains to neuraminidase inhibitors. Developing novel antiviral agents with broader efficacy could enhance treatment outcomes and reduce the reliance on a single class of drugs. Moreover, ethical and practical challenges in vaccine efficacy studies must be addressed. Expanding clinical trials to include diverse populations, particularly high-risk groups such as the elderly and immunocompromised, would ensure that vaccines are effective and safe across all demographics. Finally, greater investment in global surveillance systems is essential to monitor viral evolution and resistance patterns, enabling proactive responses and informing the design of next-generation vaccines and therapeutics.

5. Conclusion

Influenza is a very serious problem every year, especially to certain age groups. It is a very special virus as it is known for its rapid growth which can infect a wide range of hosts and high variations which makes vaccines hard to target. The segmented RNA genome of the influenza A also allows for a new viral subtype to emerge and evade existing immunity from previous infections or vaccinations. The surface proteins, like HA or NA also contributes to the change in the virus and helps with the attachment and entry into host cells. Every year, millions of people are hospitalized with the influenza virus, following many deaths. These complications caused by the virus can range from mild to severe illness such as sinus inflections or pneumonia, where it targets high-risk groups more including the elderly, young children, women, and individuals with certain health conditions. Influenza is also highly contagious, as it spreads easily through saliva and can lead to outspreads. Not only does this affect individuals, it also places huge burdens on the healthcare system and the economy. During

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seasons or outbreaks, healthcare costs and strain of resources will be very high, affecting treatment for other patients, leading to a few negligence. Also, vaccines can mitigate the impact caused by any virus – in this case influenza, by reducing the chances of the virus causing actual harm to the body. It can also reduce hospitalizations as well as deaths associated with influenza. Even though that there may be several challenges hindering the optimal effectiveness of the vaccine, including inability to respond to several mutations, it can still substantially lower the risk of severe outcomes. Following these challenges, many solutions are also discussed and addressed. Such as improved strategies in the production of vaccines with better technology and researching more into the various subtypes of the virus.

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