Chapter 8

Influenza Virus: Evolution, Pandemics, and Modern Therapeutic Strategies

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Abstract

Influenza is a highly contagious viral respiratory disease caused mainly by influenza A and B viruses, which undergo frequent antigenic changes leading to seasonal epidemics and occasional pandemics. It spreads through respiratory droplets and presents with symptoms such as fever, cough, myalgia and respiratory complications, particularly in high-risk groups like children and the elderly. Vaccination remains the most effective prevention measure, while antiviral drugs such as Neuraminidase inhibitors are used for treatment and prophylaxis. However, high mutation rates and antiviral resistance continue to challenge control efforts. Recent advances in Neuraminidase-based vaccine strategies offer promising prospects for broader and longer-lasting protection against diverse influenza strains.

Keywords: Influenza, Hemagglutinin, Neuraminidase, Oseltamivir, Zanamivir.

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1. Introduction

Influenza is a communicable viral disease that affects the upper respiratory tract, including upper and lower respiratory passages. A wide spectrum of influenza viruses causes it. Some of these viruses can infect humans, and some are specific to different species [1]. It often occurs in outbreaks and epidemics worldwide, mainly during the winter season. Significant numbers of influenza virus particles are present in the respiratory secretions of infected persons, so infection can be transmitted by sneezing and coughing via large particle droplets [2]. Influenza virus infects about 10 million persons worldwide each year. Influenza virus is characterized by a great antigenic variability. Major modifications, called antigenic shifts or type changes, occur approximately three times per century and result in worldwide epidemics--pandemics. Minor modifications, called antigenic drifts or strain changes demand new vaccine compositions each year [3].

1.1 Etiology

There are four types of influenza viruses, A, B, C, and D. Influenza types A and B cause human infection annually during the epidemic season. Influenza A has several subtypes according to the combination of hemagglutinin (H) and the neuraminidase (N) proteins that are expressed on the surface of the viruses.

Digitally colorized transmission electron microscopic view of H1N1 influenza virus particles. There are 18 different hemagglutinin subtypes and 11 different neuraminidase subtypes (H1-18 and N1-11). Influenza A viruses can be characterized by the H and N types such as H1N1 and H3N2 (Figure:1. Electron Microscopic View of H1N1 Influenza Virus Particles). Influenza B viruses are classified into lineages and strains. Influenza B viruses that have circulated in recent influenza seasons belong to one of two lineages, influenza B Yamagata and influenza B Victoria. Influenza viruses have receptors responsible for making them species-specific [4]

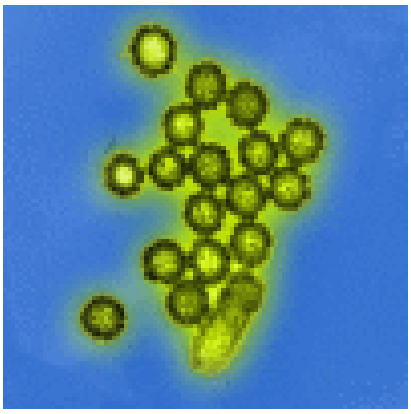

Figure 1: Electron Microscopic View of H1N1 Influenza Virus Particles

1.2 History

Influenza is a seasonal flu. It is found in the early stage of 412 BC, in the 17th Century it spread wide and got attention from both scientific and lay publications. In the 1889 Russian influenza pandemic, Haemophilus influenza was mistakenly identified as the cause of influenza. Modern science is used to study influenza. In 1933 British physiologist Walter Morley Fletcher isolated influenza as caused by flu. This virus was not identified until the 20th Century [5]. since 1997, avian influenza(H5N1) viruses have caused unprecedented widespread poultry outbreaks with high mortality in number of Asian, European, middle eastern and African countries; have infected other animals; have caused sporadic, severe and fatal human infections [6]. The most severe outbreak known, the 1918 to 1919 influenza A pandemic, was responsible for an estimated 20 million deaths globally. In the United States, the influenza pandemics of

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1957 and 1968 were associated with an attack rate of up to 50% and an estimated 100,000 deaths. Interpandemic influenza is responsible for considerable morbidity and mortality, which exceed that associated with the introduction of the pandemic strain. Influenza B infections resemble those due to influenza A, but are associated with fewer deaths [7].

2. Novel strategies for prevention and treatment of influenza

Influenza viruses continue to be a major health challenge due to antigenic variation in envelope proteins and animal reservoirs for the viruses. Vaccination is currently the most effective means of reducing morbidity and mortality during influenza epidemics. In addition, neuraminidase inhibitors have substantially improved antiviral therapy for influenza. However, influenza infection in children and the elderly remain problematic. Furthermore, major innovations in prevention and therapy will be needed to deal with an influenza pandemic. Some adverse sequelae of influenza appear to relate to impairment or pathogenic activation of immune responses. Exciting recent findings in this area, with relevance to influenza treatment, are reviewed [8].

2.1 Pandemics

Influenza A pandemics have been responsible for millions of deaths during the past several hundred years. In terms of virulence and lethality, the 1918 to 1919 influenza pandemic was the worst in history. It was unique in its predilection and lethality among young healthy adults. There has never been a satisfactory explanation for the unusual virulence of the 1918 to 1919 pandemic [9]. Influenza pandemics in this century (1946-1947, 1957 and 1968) have fascinated some people for the idea of 11-year pattern pandemic cycles. In solar physics, it is well known that sunspot cycles also have regular periods of around 11 years. This study therefore aims to investigate the association between sunspot cycles and the occurrences of pandemic influenza. The hypothesis here states that sunspot numbers can detect pandemic influenza A between 1700 and 2000 A.D[10].

2.2 Developing Treatment

Treatment of influenza by antiviral drugs can be prophylactic and therapeutic. Amantadine and rimantadine are older drugs effective in cases caused by virus type A. The newest generation of influenza antiviral agents are neuraminidase inhibitors--zanamivir and oseltamivir, effective against both virus types. The symptomatic therapy is still a basis of influenza treatment [11]. Antiviral medications can be used to treat or prevent influenza infection, especially during outbreaks in healthcare settings such as hospitals and residential institutions. Oseltamivir, zanamivir, and peramivir belong to the neuraminidase inhibitors family and can be used for the treatment of influenza A and B. The adamantanes antiviral family has two medications, amantadine, and rimantadine. Amantadine and rimantadine are effective against influenza A, but not influenza B. Oseltamivir can be used for chemoprophylaxis for individuals one year and older in cases of outbreaks and exposure in high-risk groups [12].

2.3 Differential Diagnosis

- Acute Respiratory Distress Syndrome
- Adenovirus
- Arenaviruses
- Cytomegalovirus

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- Dengue
- Echovirus infection
- Hantavirus pulmonary syndrome
- Human immunodeficiency virus infections
- Legionnaire disease
- Human parainfluenza virus [13]

3. Clinical features

Clinical symptoms such as fever, cough, gastrointestinal symptoms, coma and epilepsy were higher in the severe group. Complications such as pneumorrhagia, heart failure, septic shock, acute renal failure and influenza-associated encephalitis were higher in the severe influenza group than the death group. The laboratory findings including decreased hemoglobin, high alanine aminotransferase, high urea nitrogen and high lactate levels were risk factors for death in children with influenza [14]. Features of influenza include headache, myalgia, malaise, anorexia, sore throat, nonproductive cough, sneezing, and nasal discharge; these symptoms are not pathognomic for influenza, and asymptomatic infection can occur. The pulmonary complications of influenza include pneumonia (viral and bacterial), croup, asthma, and bronchitis. Myocarditis and pericarditis are occasional cardiac complications. Influenza has also been associated with the toxic shock syndrome, myositis, myoglobinuria, and renal failure. In view of its enormous human and economic toll, influenza remains a major target for improved vaccines and vaccine delivery, and antiviral treatment and prophylaxis [15].

3.1 Influenza vaccine

The Influenza virus A, B and C causes disease in humans, birds and animals. The Influenza type A causes moderate to severe illness in all age groups in humans while the illness caused by type B is of milder and it is primarily affecting children. Among many subtypes of influenza A viruses, currently influenza A(H1N1) and A(H3N2) subtypes are circulating among humans. Influenza is a serious public health problem that causes severe illnesses and deaths for higher risk populations. The current human pandemic A/H1N1 is an example of antigenic shift. It slowly established circulation globally; subsequently endemic/seasonal viruses in both hemi-spheres are H3N2 and H1N1. The most effective way to prevent the disease or severe outcomes from the illness is vaccination. The Trivalent Inactivated vaccines (TIV) are of three types: whole virus, split-product, subunit surface-antigen formulations and they are grown in embryonated hen's eggs. Whole-virus vaccines, because of adverse reactions, especially in children, are not currently used. Most influenza vaccines are split-product vaccines, produced from detergent treated, highly purified influenza virus, or surface-antigen vaccines containing purified hemagglutinin and neuraminidase [16].

4. Antiviral resistance in influenza viruses

Achieving adequate vaccination rates is challenging and vaccination does not always guarantee complete protection. antiviral drugs represent an important measure to reduce the risk of complications in high-risk patients. influenza viruses have a high mutation rate which causes genetic, biochemical, and pathogenic changes that represent a challenge both for the constant replacement of vaccines and reduce their susceptibility to antiviral action. This makes it necessary to determine the mechanisms of these processes, as well as their epidemiological surveillance and, of course, the development

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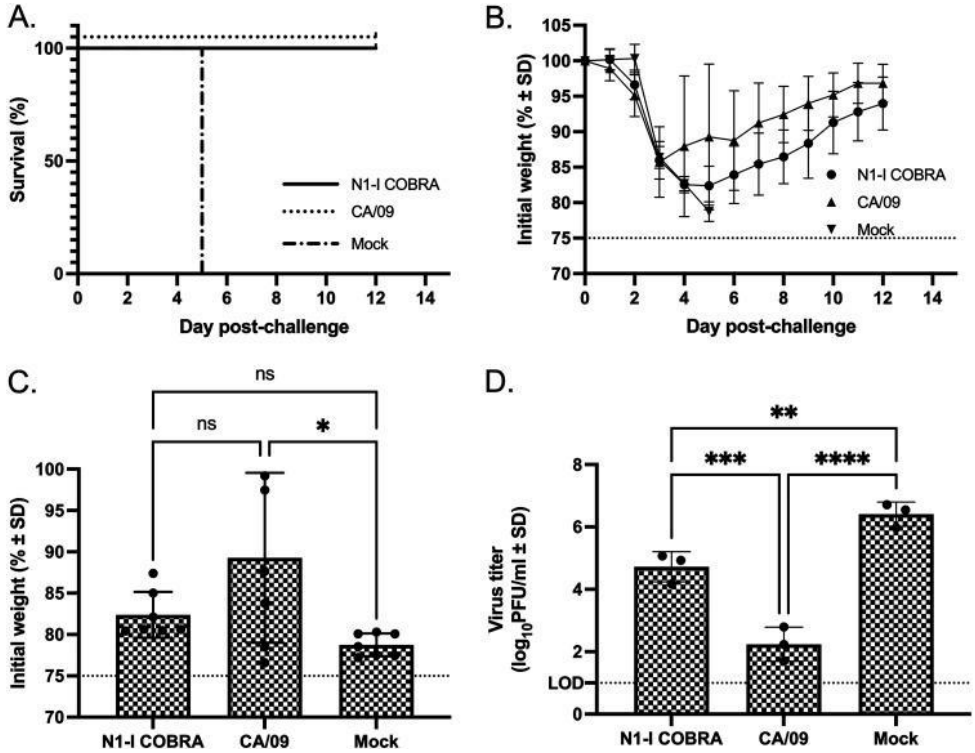
of new therapeutic options that may be available in the event of a widespread resistance phenomenon [17].

4.1 Universal Influenza Virus Neuraminidase Vaccine Elicits Protective Immune Responses against Human Seasonal and Pre-pandemic Strains



The hemagglutinin (HA) surface protein is the primary immune target for most influenza vaccines. The neuraminidase (NA) surface protein is often a secondary target for vaccine designs. computationally optimized broadly reactive antigen (COBRA) methodology was used to generate the N1-I NA vaccine antigen that was designed to cross-react with avian, swine, and human influenza viruses of the N1 NA subtype. The elicited antibodies bound to NA proteins derived from A/California/07/2009 (H1N1) pdm09, A/Brisbane/59/2007 (H1N1), A/Swine/North Carolina/154074/2015 (H1N1), and A/Viet Nam/1203/2004 (H5N1) influenza viruses, with NA-neutralizing activity against a broad panel of HXN1 influenza strains. The influenza virus NA vaccine antigen allows for protection from multiple HA subtypes and virus host origins, but it has not been the focus of vaccine development. The use of the NA antigen in combination with the HA antigen widens the breadth of protection against various virus strains. Therefore, this research opens the door to the development of a longer-lasting vaccine with increased protective breadth [18].

Figure 2: A/California/07/2009 (H1N1) pdm09 challenge results after vaccination with NA antigens. (A and B) Survival (A) and weight loss (B) curves of mice postinfection are shown. (C) The day 5 peak weight loss of the CA/09-vaccinated mice was significantly different than the mock vaccinated. The variation of the CA/09 NA-vaccinated group was greater than the N1-I-vaccinated group. (D) The viral lung titers determined through plaque assay from lung tissue on day 3 postinfection. All error bars depict standard deviations, and the statistical analysis was conducted using a one-way ANOVA with Tukey's multiple comparison. Not significant (ns); P value < 0.05 (*); P value < 0.01 (**); P value < 0.001 (***); P value < 0.0001 (****) [19].

5. Influenza surveillance

Influenza surveillance was established in 1947. From this moment WHO (World Health Organization) has been coordinating international cooperation, with a goal of monitoring influenza virus activity, effective diagnostic of the circulating viruses and informing society about epidemics or pandemics, as well as about emergence of new subtypes of influenza virus type A. As vaccination is the most effective method of fighting the virus, one of the major tasks of GISRS is developing an optimal antigenic composition of the vaccine for the current epidemic season. European Influenza Surveillance Network (EISN) has also developed over the years. EISN is running integrated

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epidemiological and virological influenza surveillance, to provide appropriate data to public health experts in member countries, to enable them undertaking relevant activities based on the current information about influenza activity. In close cooperation with GISRS and EISN are National Influenza Centers--national institutions designated by the Ministry of Health in each Country [19].

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