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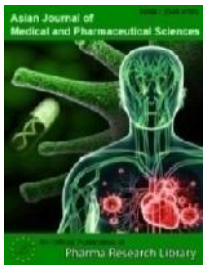

R E V I E W A R T I C L E

A Scientific Report on Influenza Virus

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A B S T R A C T

Influenza is an acute respiratory disease caused by the influenza A or B virus. 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. Children have the highest rates of seasonal influenza infection and illness in this group can amplify viral transmission in the community. Current circulating influenza strain sin humans include influenza A (H1N1), influenza A(H3N2), and both influenza B viruses (B/Victoria and B/Yamagata).The best way to prevent influenza is to administer annual vaccinations. Among severely ill patients, an early commencement of antiviral treatment (<2 d from illness onset) is associated with reduced morbidity and mortality, with greater benefits allied to an earlier initiation of treatment. Given the significance of the disease burden, we reviewed the latest findings in the diagnosis and management of influenza.

Keywords: Influenza, Virus particles, Infection, Respiratory disease, Patients, Disease

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C O N T E N T S

1. Introduction

Influenza, commonly known as the “flu”, is an acute infection of the respiratory tract caused by influenza viruses. There are three types of seasonal influenza viruses – A, B and C. Influenza A viruses are further categorized into subtypes. The 2009 pandemic influenza A(H1N1) virus (hereafter referred to as influenza A(H1N1) pdm 09) which appeared for the first time in 2009 causing a global influenza pandemic, is now a seasonal influenza virus that co-circulates with other seasonal viruses (namely influenza

A(H3N2) and influenza B viruses). Influenza viruses are genetically dynamic and evolve in unpredictable ways[1]. Influenza viruses are further classified into strains based upon antigenic properties. Humoral immunity to influenza viruses is generally thought to be strain-specific and acquired through infection or vaccination. Seasonal influenza epidemics can be caused by new virus strains that are antigenically distinct from previously circulating virus strains to which a population has immunity; this is known as antigenic drift. Uncommonly, a completely new strain of influenza will emerge to which there is little or no existing immunity, this is known as antigenic shift and such novel strains can give rise to influenza pandemics[2]. The 2009 pandemic influenza A(H1N1) virus (hereafter referred to as influenza A(H1N1)pdm09) which appeared for the first time in 2009 causing a global influenza pandemic, is now a seasonal influenza virus that co-circulates with other seasonal viruses (namely influenza A(H3N2) and influenza B viruses)[3].

History

The influenza virus has caused recurrent epidemics of acute febrile syndrome every 1 to 4 years for at least the recent centuries. The first epidemic report of an influenza-like illness was noted in 1173–74,[3] but the first definitive epidemic was reported in 1694.4 The greatest pandemic in recorded history occurred between 1918 and 1919, when approximately 21 million deaths were recorded worldwide.[5] It was among the deadliest events in reported human history. Afterward, 3 other pandemics occurred in the 20th century: the 1957 H2N2 pandemic, the 1968 H3N2 pandemic, and the 2009 influenza A (H1N1) virus (pH1N1) pandemic. In the most recent event, an influenza strain with a combination of gene segments not previously reported in the swine or human influenza virus strains was identified firstly in Mexico and then in the United States of America.[6] After the involvement of many countries, the pandemic was declared to be over in August 2010.7

2. Epidemiology

Influenza virus infections cause substantial annual morbidity and mortality worldwide including South Africa. Annual influenza epidemics result in an estimated three to five million cases of severe illness, and about 290 000-650 000 deaths globally. Influenza is an important cause of pneumonia or lower respiratory tract infection (LRTI) and approximately 8-10% of all patients with pneumonia test positive for influenza[6]. The burden of influenza in sub-Saharan Africa (and specifically in South Africa) is substantial, with some studies suggesting elevated influenza-associated mortality rates compared to other regions. During the influenza season (usually between May and September) in South African hospitals, approximately 14% of inpatients with lower respiratory tract infection and 25% of patients with influenza-like illness will test polymerase chain reaction (PCR) positive for influenza. In South Africa, it is estimated that approximately 11 800 seasonal influenza-associated deaths occur annually. In addition an estimated 47 000 episodes of influenza-associated severe acute respiratory illness occur annually of which 22 481 result in hospitalization. Approximately 5% of these deaths are in children aged <5 years. Among individuals aged ≥5 years, an estimated 50% of influenza-associated deaths are in the elderly and approximately 30% are in HIV-infected individuals. Pregnant women also constitute an important risk group for influenza-associated mortality[7]. Among an estimated 646 - 1 428 seasonal influenza-associated deaths in women of childbearing age in South Africa in recent years, the majority (~90%) occurred in HIV-infected individuals and the influenza-associated mortality was three-fold higher (Relative risk(RR) 2.8, 95% confidence interval (CI) 1 .7 – 3.9) in pregnant compared with non-pregnant women.

The highest rates of influenza-associated hospitalization are in those aged ≥65 years, HIV-infected individuals and children <5 years (in particular children < 1 year). Recent data from South Africa showed that extremes of age (<6 months [adjusted odds ratio (aOR), 37.6], 6–11 months [aOR, 31.9], 12-23 months [aOR, 22.1], 24–59 months [aOR, 7.1], and ≥65 years [aOR, 40.7] compared to those aged 5-24 years), underlying medical conditions (aOR, 4.5), HIV infection (aOR,4.3) and history of working in mine (aOR, 13.8) were significantly associated with increased risk of influenza associated hospitalization[8].

Influenza infection may trigger exacerbations of diabetes, pulmonary (e.g. asthma) or cardiovascular disease. For this reason, people with underlying chronic medical conditions are at high risk of influenza complications, often resulting in hospitalization and even death. Surveillance data from South Africa showed that having underlying illnesses (other than HIV) was a risk for influenza-associated mortality (odds ratio (OR) 2.9, 95% CI 1.2 - 7.3) [1]. Individuals with tuberculosis may also be at increased risk of influenza-associated death [15, 16]. The burden of hospitalizations and deaths due to influenza can vary substantially from year to year depending on the transmission and virulence characteristics of the circulating strain(s). In tropical areas, influenza occurs throughout the year. In temperate areas, influenza is highly seasonal and typically occurs during winter months like in South Africa[8,9].

3. Pathogenesis

Human influenza viruses are single-strand RNA viruses that belong to the Orthomyxoviridae family, consisting of the genera influenza A, B, and C viruses. Only influenza A and B viruses cause epidemics in humans[10]. Based on their main antigenic determinants, the haemagglutinin (H or HA) and neuraminidase (N or NA) transmembrane glycoproteins, influenza A viruses are further subdivided into 18 H (H1–H18),11N (N1–N11) subtypes, but only 3 hemagglutinin subtypes (H1, H2 and H3) and two neuraminidase subtypes (N1 and N2) have circulated stably in the human population and are responsible for annual epidemics. HA and NA are critical for virulence, and are major targets for the neutralizing antibodies of acquired immunity to influenza. The 2009 pandemic influenza A(H1N1) virus (hereafter referred to as influenza A(H1N1)pdm09) which appeared for the first time in 2009 causing a global influenza pandemic, is now a seasonal influenza virus that co-

circulates with other seasonal viruses (namely influenza A(H3N2) and influenza B viruses)[11].

Transmission

Influenza viruses are spread from person-to-person. They can be transmitted by exposure to infectious droplets expelled by coughing or sneezing that are then inhaled, or can contaminate hands or other surfaces. The typical incubation period for influenza is 1-4 days (average 2 days). Most persons ill with influenza shed virus (i.e. may be infectious) from a few days before symptoms begin through 5-7 days after illness onset. However, very young children can be infectious for >10 days after illness onset; adults with severe disease (e.g. viral pneumonia) may also shed virus for >10 days, and severely immune compromised persons can shed virus for even longer. Children have the highest rates of seasonal influenza infection and illness in this group can amplify viral transmission in the community[12].

4. Clinical Features of Influenza

Infection with influenza viruses can give rise to a wide range of clinical presentations, ranging from asymptomatic infection to severe illness and death depending on the characteristics of both the virus and the infected person[13]. In the majority of people, influenza is an uncomplicated illness that is characterised by sudden onset of constitutional and respiratory symptoms such as fever, myalgia, cough, sore throat, rhinitis and headache. Uncomplicated influenza illness resolves after 3-7 days although cough and malaise can persist for >2 weeks. Influenza may be associated with more severe complications including: influenza-associated pneumonia/ LRTI, secondary bacterial or viral infection (including pneumonia, sinusitis and otitis media), multi-organ failure, and exacerbations of underlying illnesses (e.g. pulmonary and cardiac illness). Rare complications include encephalopathy, myocarditis, transverse myelitis, pericarditis and Reye syndrome[14,15]. For purposes of clinical management, influenza disease can be categorized as follows:

- **Uncomplicated influenza:** ILI (Influenza-like illness) may present with fever, cough, sore throat, coryza, headache, malaise, myalgia, arthralgia and sometimes gastrointestinal symptoms, but without any features of complicated influenza.
- **Complicated/severe influenza:** Influenza requiring hospital admission and/or with symptoms and signs of lower respiratory tract infection (hypoxaemia, dyspnoea, taccypnoea, lower chest wall indrawing and inability to feed), central nervous system involvement and/or a significant exacerbation of an underlying medical condition.

Pneumonia

The most important and common complication of influenza is pneumonia, not least in high-risk individuals. Pneumonia may happen as a continuum of the acute influenza syndrome when caused by the influenza virus (primary pneumonia) or as a mixed viral and bacterial infection after a gap of a few days (secondary pneumonia)[16].

Primary Influenza Viral Pneumonia:

The illness occurs after the typical course of flu with a rapid progression of fever, dyspnea, cough, cyanosis, and difficult breathing. It happens predominantly among individuals with cardiovascular or underlying pulmonary diseases such as asthma. Physical examination is in favor of bilateral lung involvement, and imaging findings in the lungs constitute reticular or reticulonodular opacities with or without superimposed consolidation[17]. Sometimes the radiological appearance of primary influenza pneumonia can be difficult to distinguish from pulmonary edema because of the presence of perihilar congestion and hazy opacification, at least in the lower lobes. Less frequently, radiographs show focal areas of infiltration. Commonly used pneumonia severity assessment tools such as the CURB65 or the Pneumonia Severity Index are not useful in determining which patients to hospitalize due to primary influenza pneumonia since these tools have not been developed and validated during an influenza pandemic. Thus, careful history taking and examination, determination of pregnancy or hypotension, and early identification of young patients with decreased oxygen saturation, respiratory rate >25 per minute, and concomitant diarrhea are crucial for admission decision-making. The typical radiographic findings of primary influenza pneumonia are bilateral reticular or reticulonodular opacities, sometimes accompanied by superimposed consolidation. Less frequently, radiographs show focal areas of consolidation without reticular opacities. High-resolution computed tomography often shows multifocal peribronchovascular or subpleural consolidation with or without ground glass opacities. The most severe cases progress rapidly to acute respiratory distress syndrome and multipolar alveolar infiltrations[18,19]. These patients usually present with progressive dyspnea and severe hypoxemia 2 to 5 days after the onset of typical influenza symptoms. Hypoxemia increases rapidly and causes respiratory failure, requiring intubation and mechanical ventilation, maybe after only 1 day of hospitalization.

Secondary Bacterial Pneumonia:

The incidence of secondary bacterial pneumonia ranged from 2% to 18% during the influenza pandemic in 1957–58. A threefold increase in the incidence of secondary Staphylococcus aureus pneumonia during the influenza pandemic of 1968–9 compared to a non-epidemic period of pneumonia etiologies was observed. Recently, community–acquired methicillin-resistant Staphylococcus aureus was determined after seasonal influenza,but another very common etiologic bacterium is Streptococcus pneumonia. The patient has a classic influenza disease, followed by an improvement period lasting maximally 2 weeks. The recurrence of the symptoms such as fever, productive cough, and dyspnea and findings of new consolidations in chest imaging can be found in involved patients. Accordingly, a biphasic pattern of signs and symptoms in influenza labeled patients should be considered as secondary superimposed bacterial pneumonia.

Non-Pulmonary Complications:

In addition to its respiratory effects, the virus can exert effects on other body systems such as the musculoskeletal, cardiac, and neurologic systems. Myocarditis and

pericarditis constitute unusual but significant complications of seasonal or pandemic flu. In a prospective study, half of adult flu patients without cardiac complaints had abnormal ECG findings at presentation. Myocarditis mostly resolves by 28 days, and the patients have a good heart-muscle function without a reduced ejection fraction. Significant myositis and rhabdomyolysis have rarely been reported with seasonal influenza, but different amounts of creatine phosphokinase elevation have been reported in many studies after seasonal or pandemic flues. Mild myositis and myoglobinuria with tender leg or back muscles can mainly be seen in children, although they can occur in adults and be accompanied by symptoms of painful walking or standing. Other rare complications such as the Guillain–Barré syndrome, encephalitis, acute liver failure, and the Reye syndrome may happen after influenza A infection.

Risk factors for Severe Influenza

Certain groups of patients are at higher risk of developing severe or complicated disease following influenza virus infection. However, influenza virus infection can result in severe/complicated illness in previously healthy individuals. Similar to other studies showing increased risk of severe influenza associated illness in certain individuals, a recent study from South Africa has found that younger and older age (< 5 years, in particular children < 1 year, and ≥65 years) and the presence of chronic underlying medical conditions, HIV infection and pregnancy were associated with increased risk of influenza associated-hospitalization. In addition HIV-infected individuals with severe immunosuppression compared to those with mild immunosuppression had three times increased odds of influenza associated hospitalization.

Risk groups for severe/complicated influenza disease include:

- Pregnant women (including the post-partum period)
- HIV–infected individuals
- Individuals with tuberculosis
- Persons of any age with chronic disease, including: Pulmonary diseases (e.g. asthma, COPD) Immuno suppression (e.g. persons on immunosuppressive medication, malignancy) Cardiac diseases (e.g. congestive cardiac failure), except for hypertension,
- Metabolic disorders (e.g. diabetes mellitus),
- Renal disease o Hepatic disease
- Certain neurologic and neuro developmental conditions, including: disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy (seizure disorders), stroke, mental retardation, moderate to severe developmental delay, muscular dystrophy, or spinal cord injury.
- Haemoglobinopathies (e.g. sickle cell disease)
- Persons aged ≥65 years
- Persons ≤18 years receiving chronic aspirin therapy
- Persons who are morbidly obese (i.e. BMI ≥40)
- Young children (particularly <2 years of age)

Laboratory Diagnosis

The majority of influenza cases are diagnosed by their clinical manifestations and there is no need for laboratory tests. Be that as it may, in special circumstances, the diagnosis of flu necessitates laboratory confirmation using available tests such as nucleic acid tests (e.g., polymerase chain reaction [PCR]) or rapid diagnosis kits or rarely virus isolation by culture methods[20].

Rapid Diagnosis Influenza Tests:

Rapid influenza diagnostic tests detect influenza viral antigens and screen patients with suspected influenza in a timely manner in comparison to other diagnostic modalities. The most widely used technique is based on the detection of viral antigens in the respiratory secretions of patients by immunologic methods. All rapid tests are performed with ease and can provide results within 30 minutes. Each test varies with regard to whether it can distinguish between influenza A and B. Nevertheless, these tests have thus far been unable to specify types of influenza A such as H1N1 and H3N2[21]. The overall specificities achieved by these tests are high and comparable between the manufacturers.

Molecular Tests:

Due to the limitation in other diagnostic modalities in influenza detection, molecular assays have increasingly been considered the gold standard diagnostic method for the detection of the influenza virus in hospitalbased diagnostic laboratories. Although several amplification methods have been developed, the majority of the current assays—particularly those used in clinical laboratories—are based on the PCR amplification method. These tests have the ability to check several targets concurrently and thereby provide type and subtype information for each virus. Additionally, they have the ability to be adapted rapidly for the detection of novel targets; these features played a critical role during the influenza pandemic of 2009. PCR is potentially more sensitive than cell culture, and it can detect the nonviable virus in samples. The sensitivity of these tests is dependent on the sample site of the patient and is similar to that of the rapid tests. Higher sensitivity can be obtained by swab samples of a nasopharyngeal origin. PCR-based molecular assays have yielded excellent clinical utility for the detection and identification of influenza viruses at bedside as POC, and numerous Food and Drug Administration (FDA)-cleared commercial devices are now available.

Treatment

Oral oseltamivir (Tamiflu®) and inhaled zanamivir (Relenza®) (limited availability in South Africa) are chemically related antiviral medications that act as neuraminidase inhibitors and have activity against both influenza A and B. These two medications are recommended for use during the 2018 influenza season. Adamantanes (amantadine and rimantadine) are not recommended for use due to high levels of resistance. The standard adult dose and duration of oseltamivir treatment is 75mg twice daily orally for 5 days[23].

Antibiotic treatment: Antibiotics do not have a specific effect against the influenza virus but in cases of pneumonia, early empiric treatment for community acquired pneumonia is advised because of the high risk of secondary bacterial infection. Since there is increased risk of secondary

infection with S. pneumoniae, Staphylococcus aureus and Streptococcus pyogenes co-amoxiclav is a suitable empiric antibiotic.

Oxygen therapy: Monitor oxygen saturation and maintain SaO2 >90% (92-95% for pregnant women) with nasal cannulae or face mask. High flow oxygen may be required in severe cases.

Prevention of Influenza

Influenza vaccination is the most effective method for prevention and control of influenza infection available currently. In general, influenza vaccines are most effective among children ≥ 2 years and healthy adults. A meta-analysis including data from years when there was a mismatch between vaccine and circulating strains estimated a pooled vaccine efficacy (VE) of 59% (95% CI: 51-67) in healthy adults. Previous studies from South Africa have reported influenza VE estimates from2005 to 2015 which ranged between 46% and 87% when there was a good match and ranged between 14% and 38% when the circulating A(H3N2) strain showed marked genetic drift. A randomised controlled trial conducted in South Africa has shown that when pregnant women received the influenza vaccine, their risk of developing influenza was halved, as was the risk to their infants in the first 24 weeks of life. The vaccine has been shown not only to be efficacious for prevention of influenza in both mothers and their infants but also safe. Trivalent influenza vaccine has been shown to provide protection in HIV-infected adults without severe immunosuppression. Data are unclear as to the effectiveness in HIV-infected children aged <5 years. In certain groups, including the elderly, immune compromised individuals and infants, influenza vaccine is less effective; however, it may reduce the incidence of severe disease, e.g. bronchopneumonia, hospital admission and mortality.

5. Conclusion

The present review concluded that explain the patho physiology of influenza virus. Influenza epidemics and pandemics impose a heavy socioeconomic burden on all societies. Hospital admission and treatment and ICU care are more often necessary in high-risk individuals such as the elderly and pregnant ladies. However, the impact of influenza cannot be neglected even in young adults, mainly because of the loss of productivity. With concerns over increasing resistance against both adamantanes and NAIs, the risk of the development of antiviral drug resistance should be considered if we opt to treat all patients who are labeled as suffering from flu. Individuals with suspected flue with severe disease such as those with signs and symptoms of lower respiratory tract infections (e.g., dyspnea, tachypnea, and low oxygen saturation) and those who have signs of rapid clinical deterioration or those at high risk of complications should receive antiviral therapy.

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