

ABSTRACT

Acute respiratory infection is a common medical problem across the world including in India. Influenza is one of the important causes of acute respiratory infection. Influenza is associated with several complications mainly secondary bacterial pneumonia. In some patients such as elderly and those with chronic medical conditions, the risk of complications is higher. Prevention of influenza plays an important role in avoiding complications. Vaccination has been proved to be an effective measure for prevention of influenza. This article discusses the basics of influenza, clinical features, and diagnosis and preventive aspects of disease focusing on vaccination.

INTRODUCTION

Acute respiratory infection (ARI) is an important health problem worldwide. Influenza is one of the most important causes of ARI. Influenza is seen across the world. The annual global attack rate of disease is estimated to be 5-10% in adults and 20-30% in children.¹ Influenza is also associated with significant economic burden because of the direct cost involved in health-care (medicines, hospital visits, hospitalization etc) as well as indirect cost in the form of loss of workday or general social disturbance among people of all age groups. Influenza can result in several complications including hospitalization and sometimes it may even lead to death.^{1,2} Because of these concerns, prevention of influenza in both healthy people as well as those at risk is of paramount importance.

INFLUENZA BASICS

Influenza is caused by viruses belonging to the family "orthomyxoviridae". Influenza virus is a single stranded RNA virus with helical shape. These are RNA viruses. Based on the presence of nuclear material i.e. core proteins, influenza viruses are divided into three different types; A, B, and C. The viruses have two types of envelope glycoproteins; haemagglutinin (HA) or neuraminidase (NA) activity. "A" type of influenza viruses are further subdivided into several types based on the type of these envelope glycoproteins (e.g. A/H1N1, A/H3N2).^{1,3} Influenza "B" and "C" viruses mainly cause disease in human being. Influenza A viruses can infect different mammalian and avian species. Type "A" virus causes moderate to severe illness. The virus can affect people of all age groups. Influenza "B" type virus generally causes milder form of illness as compared to influenza type "A" and mainly affects children.⁴ The concern of influenza in humans is mainly because of the viruses belonging to type "A" and "B" type.¹

An Indian epidemiology study, evaluating data from September 2004 to December 2008, reported that seasonal influenza A(H1N1), H3N2, and type B co-circulated in all regions without any particular pattern of movement of any subtype. Year-round limited influenza activity with peaks during rains was observed in this study.⁵

GENETIC CHANGES- A CHARACTERISTIC OF INFLUENZA VIRUSES

Influenza virus has a peculiarity of undergoing frequent mutations and genetic reassortment, resulting in generation of a new viral strain due to combination and rearrangement of genetic material. There are two processes by which the protein structure of influenza virus can change; "antigenic drift" and "antigenic shift". "Antigenic drift" i.e. minor changes in the protein structure of influenza "A" strains occurs commonly. Antigenic drift is responsible for repeated influenza outbreaks. The major changes in the influenza type A occur because of the "antigenic shift". This is the result of genetic reassortment from different influenza "A" subtypes. Antigenic shift can result in large pandemic outbreaks.¹

SPREAD OF INFLUENZA

Influenza is a contagious disease. Healthy people can also get infected with the influenza virus and transmit it to others. Transmission of infection from one person to the other occurs mainly through droplets or respiratory secretions of infected people. Transmission of influenza can also occur through direct contact with infected person or fomites.^{1,3}

PATHOGENESIS, SYMPTOMS AND COMPLICATIONS OF INFLUENZA

After the entry of influenza virus into respiratory system, the virus attaches to the respiratory epithelial cells penetrates into it. Viral replication causes destruction of the host cell, but viremia is rare. Influenza virus is shed in the respiratory secretions for about five to ten days. The incubation period of influenza is generally two days, but may range from one to four days. The presentation of infection differs from asymptomatic nature to severe illness.⁴

Influenza is different from the usual common cold. The disease illness is characterized by symptoms such as acute onset of fever, chills, rhinorrhea (running nose), cough, sore throat, headache and myalgia. In most cases, the febrile illness lasts for 3-4 days the disease resolves in 7-10 days.³

Primary influenza viral pneumonia is not a common complication, but has a high mortality rate.⁴ People can develop secondary complications because of influenza infection. Secondary bacterial pneumonia is a common complication of influenza. Bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Staphylococcus aureus* are responsible for secondary infection. Other complications associated with influenza include myocarditis or worsening of chronic bronchitis and other chronic lung diseases.⁴ The risk of complications differs among individuals. The risk is particularly higher in elderly people and those with concurrent chronic illnesses. The disease and its complications can result in significant morbidity or event mortality.¹ Mortality rate is higher in people 65 years of age and older.⁴

Diseases such as diabetes, chronic renal failure, chronic respiratory disease, heart disease and cirrhosis of liver are associated with higher risk of influenza related complications. Generally, infections in people with diabetes are more common and severe due to immunological deficiency^{6,7} and other comorbidities. Diabetics are at higher risk of developing infections and dying due to them.⁸ Given the complications related to infections in these patients, anti-pneumococcal and influenza vaccines can be useful to reduce hospitalization, morbidity and mortality.^{7,9-11} Patients with chronic kidney disease and those with end-stage renal disease are also susceptible to infection because of the immune impairment,¹² hence need special care in terms of prevention of infections.¹³ Vaccination against influenza has been shown to be associated with better survival in dialysis patients in a retrospective study.¹⁴

Influenza in patients with chronic respiratory illness is associated with adverse outcomes.¹⁵ Patients with moderate to severe chronic obstructive pulmonary disease having respiratory viral infections require more hospital visits or hospitalization^{16,17} resulting in higher utilization of health care resources.¹⁷ Mortality due to influenza in patients with acute exacerbation of COPD is more compared those who do not have influenza.¹⁵ Influenza infection in smokers can increase the risk of hospitalization.¹⁸ Influenza infection has also been linked to significant morbidity and mortality in patients with congestive heart failure.¹⁹ Influenza activity can result in higher admission rates for pneumonia, COPD, and heart failure in elderly people.²⁰ Influenza infection through activation of systemic inflammatory responses increase the risk of atrial fibrillation.²¹ Influenza increases the risk of hepatic decompensation and hospitalization in patients with cirrhosis.²² Another at risk population is pregnancy. Influenza in pregnancy is associated with adverse outcomes. Pregnant women can develop severe and sometimes even can result in mortality.²³

DIAGNOSIS

Influenza is suspected based on the clinical history and patient presentation. Confirmation of disease can be done by viral culture, reverse transcription polymerase chain reaction (RT-PCR) or demonstrating presence of specific

neutralizing antibodies in the blood.³

MANAGEMENT OF INFLUENZA

The management of influenza includes preventive aspects and the treatment component. The treatment components of influenza include timely measures for controlling the infection spread, early identification of high risk people, supportive care of patient and administration of antiviral drugs. For the prevention of disease, vaccine and chemoprophylaxis are two commonly methods. People should follow cough etiquette, use of face masks and maintain hand hygiene in order to reduce the risk of disease transmission to others.³ Antiviral agents i.e. neuraminidase inhibitors are used for the treatment of infection in affected people or prevention of influenza in high risk people. A recently published review examined the risk and benefits of these agents for influenza in people of all age and also evaluated the effect of oseltamivir on mortality in patients with 2009A/H1N1 influenza. Oseltamivir and zanamivir reduced the time to first improvement of symptoms in adults by 16.8 hours and 0.60 days respectively, demonstrating small reductions in the time to first alleviation of influenza. The review findings suggested that oseltamivir use is associated with increased risk of gastrointestinal side effects such as nausea, vomiting and psychiatric events in adults. In children, oseltamivir use was associated with increased risk of vomiting. Oseltamivir did not show protective effect on mortality among patients with 2009A/H1N1 influenza.²⁴ The findings of this recent publication suggest, that risk-benefit ratio should be considered while using neuraminidase inhibitors for the management of influenza.

PREVENTION OF INFLUENZA WITH VACCINATION

Two types of influenza vaccines are currently available; inactivated influenza vaccine and live attenuated influenza vaccine. The live attenuated vaccine is administered as nasal spray whereas inactivated influenza vaccine is administered as an injection. The trivalent vaccine provides protection against two strains of influenza "A" virus and one strain of influenza "B" strain whereas quadrivalent provides protection against one additional Influenza "B" strain. The quadrivalent vaccine is currently not available for commercial use in India.²⁵ The inactivated vaccines can be of either split virion or subunit type.²⁶ The split virus vaccines is produced by using virus which is disrupted by a detergent. In subunit vaccines, the envelop proteins are further purified by removing other viral components.¹ A study compared effectiveness of split-virion influenza vaccines versus subunit influenza vaccines in adults with >50 years who presented with acute respiratory illness during three influenza seasons. Effectiveness of split-virion vaccine in this study was 77.8% as opposed to 44.2% effectiveness with subunit vaccine.²⁶

WHO SHOULD GET VACCINATED?

Ideally every individual who is six months of age and above should get influenza vaccination every year.^{2,25}

Table 1: Recommended composition of influenza virus vaccines for use in the 2016^{28,29}

Southern hemisphere winter	Northern hemisphere winter
1. an A/California/7/2009 (H1N1)pdm09-like virus; 2. an A/Hong Kong/4801/2014 (H3N2)-like virus; 3. a B/Brisbane/60 It is recommended that quadrivalent vaccines containing two influenza B viruses contain the above three viruses and a B/Phuket/3073/2013-like virus/2008-like virus.	1. an A/California/7/2009 (H1N1)pdm09-like virus; 2. an A/Hong Kong/4801/2014 (H3N2)-like virus; 3. a B/Brisbane/60/2008-like virus. It is recommended that quadrivalent vaccines containing two influenza B viruses contain the above three viruses and a B/Phuket/3073/2013-like virus.

Vaccination is particularly important in people with higher risk for influenza-related complications. Such population include children less than five years of (especially less than two years of age), elderly people, pregnant mothers, health care workers, residents of nursing homes and other long-term care facilities, patients with certain medical conditions (e.g. asthma, chronic lung disease, cystic fibrosis, neurological and neurodevelopmental conditions, congenital heart disease, congestive heart failure sickle cell disease, diabetes mellitus, kidney disorders, liver disorders, those with weak immunity etc).

Similarly, Haj pilgrims, people attending Kumbh mela, military personnel, students living boarding schools, prisoners and students going abroad for further studies should also receive vaccination against influenza.²⁵

CHOICE OF INFLUENZA VACCINE

Both inactivated influenza vaccine and nasal spray vaccine i.e. live attenuated vaccine can be used for the prevention of influenza. Live attenuated influenza vaccine is recommended for 2-49 years of age.²⁵ Live attenuated influenza vaccine should not be used in immunocompromized patients. Similarly, in pregnancy live attenuated influenza vaccine is contraindicated.⁷ In such cases, inactivated influenza vaccine is recommended.

The Center for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) has voted against use of live attenuated influenza vaccine for use during 2016-2017 season due to its poor/relatively lower effectiveness.²⁷

NEED FOR ANNUAL VACCINATION

Serum antibodies play an important role in the protection against influenza while mucosal IgA antibodies help in providing resistance against infection. Because of the antigenic drift and antigenic shift, the protective effect of antibody induced by one strain might be decreased or lost over time. This loss of protective function

makes person susceptible for infection either because of the relative or complete unprotected against the new circulating strains.¹ Because of these characteristics of the virus, annual vaccination against influenza virus is recommended. Every adult person should be offered influenza vaccination.

WHICH STRAINS?

Continuous surveillance is very important to find out currently circulating, emerging or reemerging strains of influenza virus. The World Health Organization (WHO) through its surveillance centers across collects the data of currently circulating strains of influenza virus and predicts the likely circulating viral strains in the coming season. The WHO reviews the world epidemiological situation twice in year and if necessary recommends new vaccine strain(s) based on the available evidence. The composition of these likely viral strains is provided to the pharmaceutical companies for manufacturing vaccines. Table 1 gives WHO recommended composition of influenza virus vaccine for use in 2016.

ADVERSE EVENTS WITH INFLUENZA VACCINE

Influenza vaccine is generally very well tolerated. Even if some side effects occur, they are mostly mild and short-lasting in nature. The adverse events associated with the use of nasal vaccine include runny nose, fever, malaise, wheezing, headache, vomiting, sore throat and cough. Inactivated influenza vaccine may cause local adverse events at the site of injections such as soreness, redness and swelling.²⁵

TIMING OF VACCINATION

The peak of influenza activity differs between different countries. Saha and colleagues conducted a study to find out influenza seasonality and the best time for influenza vaccination. They examined the weekly influenza surveillance data (2006 to 2011) from different countries including India. Based on the findings, the investigators suggested that most southern and south-eastern Asian countries north of the equator should consider vaccination between April to June. Countries near the equator without a significant peak in influenza activity can base vaccination timing on local factors.³⁰ Another epidemiological study from India also suggests staged timing for vaccination against influenza.³¹ The peak season for influenza in India is typically the monsoon period. Influenza vaccine should be ideally be given before the initiation of monsoon i.e. in the months of April-May. Second peak of influenza activity is seen during winter season in northern states i.e. Jammu Kashmir, Himachal and Delhi during November-February. Tamil Nadu receives north-east monsoon, so the peak season for influenza activity for this reason is November-February. Generally, for the areas where there is peak of influenza activity in winter season, the vaccine should be administered during September-October and for remaining areas of the country where monsoon is the peak season for influenza activity, vaccine should be administered pre-monsoon i.e. during April-May.²⁵

CONTRAINDICATIONS FOR THE USE OF INFLUENZA VACCINE

Influenza vaccination should not be given to children younger than six months of age, people having known hypersensitivity to the active substance or any other ingredient in the vaccine preparation, history of chicken egg allergy or history of Guillain Barre Syndrome within six weeks of previous influenza vaccination. People with known egg allergy, need to discuss it with their physician.²⁵ Vaccination should be postponed if the person has acute febrile illness. The vaccine needs to be stored as per the recommended storage conditions.

BENEFITS OF INFLUENZA VACCINATION

Influenza vaccines are effective in reducing medical complications associated with influenza like illness. The vaccination can also mitigate economic losses by reducing work related loss or reducing absenteeism and avoid losses because of reduced productivity.³²

Influenza vaccination has shown beneficial effects in diabetic patients.^{11,33} It can reduce complications, hospitalizations and mortality among patients with diabetes.³³

Influenza vaccination is also effective in prevention of acute respiratory infections. Vaccination is associated with reduced consultations and hospitalizations in patients with chronic obstructive pulmonary disease.³⁴ In patients with chronic obstructive pulmonary disease, influenza vaccination has been shown to prevent influenza-related acute respiratory infections regardless of the severity of disease.³⁵

NEED FOR IMPROVED AWARENESS ON VACCINE

Though vaccination is an important for prevention of influenza, vaccine uptake is very poor worldwide including in India.³⁶ The rates of vaccine uptake are not only poor in community residents¹⁸ but even among the high risk population.³⁷⁻³⁹

There are several reasons for low uptake of vaccine by the community. Some of the important reasons for the less vaccination rate are low perceived risk among people, availability and access to vaccination, cost of the vaccine and insufficient information about the disease and the vaccine.³⁶ Given the risk of complications and availability of vaccine, coordinated efforts should be done to improve the uptake of vaccine in healthy people as well as those at high risk of infection.

SUMMARY

Influenza is a global health problem. The disease related concerns are more in people with other risk factors such as age or associated chronic diseases. Influenza is associated with significant economic burden, morbidity and even mortality in some cases. Prevention of influenza is important in order to avoid complications. Currently, two types of viruses are available for use; inactivated influenza vaccine and live attenuated vaccine. Spilt viron vaccine provides better effectiveness compared to subunit vaccine. The vaccines are generally very well tolerated. Live attenuated vaccine should be avoided in pregnancy

and patients with immunocompromized functions.

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