

The Saudi Thoracic Society guidelines for influenza vaccinations

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Abstract:

Influenza viruses are responsible for the influenza outbreaks that lead to significant burden and cause significant morbidity and mortality worldwide. Based on the core proteins, influenza viruses are classified into three types, A, B, and C, of which only A and B cause significant human disease and so the vaccine is directed against these two subtypes only. The effectiveness of the vaccine depends on boosting the immune system against the serotypes included within it. As influenza viruses undergo periodic changes in their antigen, the vaccine is modified annually to ensure susceptibility. In contrast to other countries, Saudi Arabia faces a unique and challenging situation due to Hajj and Umrah seasons, when millions of people gather at the holy places in Mecca and Madinah, during which influenza outbreaks are commonly found. Such challenges making the adoption of strict vaccination strategy in Saudi Arabia is of great importance. All efforts were made to develop this guideline in an easy-to-read form, making it very handy and easy to use by health care workers. The guideline was designed to provide recommendations for problems frequently encountered in real life, with special consideration for special situations such as Hajj and Umrah seasons and pregnancy.

Key words:

Influenza, vaccination, Hajj, Umrah, Saudi Arabia

Influenza virus causes significant morbidity and mortality worldwide.^[1] Persons infected by influenza virus may be asymptomatic or present with self-limited acute febrile respiratory symptoms.^[2] However, those presenting with severe illness may have significant morbidity and mortality. Such a presentation has been found to be associated with high-risk patients, e.g., elderly persons, young children, and patients of chronic medical conditions.^[3] Though prophylaxis with antiviral agents may be used to prevent influenza transmission, vaccination is considered the best method for this purpose.

As part of the commitment of the Saudi Thoracic Society (STS) toward a long-term enhancement plan for promoting best practices in the field of respiratory diseases,^[4-8] a need for development of influenza vaccination guidelines was identified. This is also justified by the fact that Saudi Arabia hosts one of the major global mass gatherings by receiving millions of pilgrims from all over the world for the purpose of the Hajj and Umrah. Therefore, the Scientific Committee for Influenza and Pneumococcal Vaccination (SCIPV) guidelines was created by STS to establish local guidelines based on international recommendations on influenza vaccination, best practices, local literature, and the current settings in Saudi Arabia. The STS guidelines for influenza vaccination aims to standardize the approach among health care professionals (HCPs) in Saudi Arabia in an attempt to support the effort

of different governmental agencies in this field, with special attention for specific situations like the Hajj and Umrah. It also aims to disseminate knowledge about vaccination against common respiratory pathogens among HCPs through up-to-date guidelines that are simple to understand and use. Of note, the recommendations related to influenza vaccination apply only to seasonal influenza and do not extend to other pandemics, like the avian flu (H5N1).

Methods

The influenza vaccination guidelines are based on international guidelines and best practices.^[2,3,9,10] International guidelines on influenza vaccination were customized based on reviewing the

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available local literature, whenever available, and the current settings in Saudi Arabia, including statements released from governmental agencies. The SCIPV is a group of Saudi experts with well-respected academic backgrounds and experience in the field of respiratory and infectious diseases. The consensus among the SCIPV was followed whenever there was a lack of appropriate evidence.^[11] The following criteria were used to grade the evidence as:

- Evidence category A: Randomized controlled trials with rich body of data.
- Evidence category B: Randomized controlled trials with limited body of data.
- Evidence category C: Nonrandomized trials and observational studies.
- Evidence category D: Consensus judgment by SCIPV members. This category is only used in cases where the provision of some guidance was deemed valuable, but the clinical literature addressing the subject was insufficient to justify placement in one of the other categories.

Each section was prepared by a member of the panel and then internally reviewed by other members. The panel conducted round-table discussions frequently and jointly. An international experts reviewed the guidelines, and his recommendations were thoughtfully considered.

Epidemiology

Influenza is a common acute respiratory illness that occurs in outbreaks and epidemics worldwide, mainly during the winter season. Attack rates of seasonal influenza in the general population typically range from 7% to 18%,^[3-5] whereas attack rates for pandemic influenza are estimated to range from 20% to 50%.^[12-16] The peak of influenza attacks occurs between October and May in the Northern Hemisphere and between April and September in the Southern Hemisphere. The World Health Organization (WHO) estimated that influenza virus causes severe illness in 3-5 million people annually.^[17] The case fatality of persons with two or more risk factors was estimated to be 377/100,000, compared with 9/100,000 for those without associated risk conditions.^[18-20]

Influenza vaccination was found to have a positive impact on health care, societal, and individual costs by reducing productivity losses and absenteeism associated with influenza-related illnesses.^[21-23] Though HCPs are among the high-risk group, there are reports showing their low compliance to annual influenza vaccination.^[24-26] Saudi Arabia is not an exception as a survey conducted in the eastern province showed lower awareness of the benefit of vaccination among HCPs.^[27] In another survey conducted in six major hospitals in Saudi Arabia, the vaccination rate among HCPs was as low as 38%. Nonavailability of vaccine was considered by 43% of HCPs to be the highest barrier for not providing vaccine for patients. Furthermore, lack of awareness of influenza vaccination was reported by almost 75%.^[28] In a campaign conducted in a tertiary care hospital in Saudi Arabia from 2003 to 2007, the coverage rate for HCPs was found to be 21-29%.^[29] However, changing the methodology by engaging the Nursing Department as a partner in a vaccination campaign increased the coverage among nurses to 80%, physicians to 74%, and paramedical personnel to 67%.

A study during the H1N1 epidemic assessed knowledge and attitudes of the Saudi public reported that 38.3% of participants were not convinced about the truth of published reports about this illness.^[30] Of those participants, 16.1% reported receiving information from health providers about influenza-related guidelines. Another study during the same epidemic confirmed the need for prevention strategies, including immunization and improved personal hygiene in the Saudi population.^[31]

Virology

Influenza viruses have a single-stranded RNA genome and belong to the family Orthomyxoviridae. Influenza virus is classified into three types based on their core proteins, type A, B, and C. Type A virus is further subdivided based on their outside envelope hemagglutinin activity or neuraminidase activity.^[32,33] Influenza B and C viruses mainly affect humans, whereas influenza A virus infects a range of mammalian and avian species and causes all influenza pandemics. While influenza C virus causes a mild form of the disease, types A and B can cause significant human disease.^[1] Influenza A virus undergoes high mutation rates. Major changes in the influenza A virus hemagglutinin and the neuraminidase are called antigenic shifts. This results in strains capable of causing epidemics or global pandemics. Minor changes so-called antigenic drifts occur almost annually and usually cause more localized outbreaks.^[34]

Clinical Manifestations

Influenza infection should be considered in immunocompetent or immunosuppressed person presents with fever and acute onset of respiratory symptoms and signs. The clinical illness of influenza can present as:

Uncomplicated influenza

In the majority of people, influenza is a self-limited infection that usually lasting 2-5 days following an incubation period of 1-4 days. However, the illness may occasionally last for 1 week or more especially in the elderly, persons with chronic illnesses, and immunocompromised persons. Influenza infection presents with abrupt onset of fever, headache, myalgia, and malaise. It is also associated with respiratory tract manifestation that includes a sore throat, nonproductive cough, and nasal discharge. Fever usually ranges from 37.8°C to 40.0°C. Influenza may also present without fever especially in the older age group. Gastrointestinal manifestations can occur in 10-20% of influenza infections, especially in children. Some patients may have persistent symptoms of weakness or easy fatigability for several weeks, which is referred to as postinfluenza asthenia.^[2]

Complicated influenza

Influenza infection can progress to more serious complications, especially in high-risk groups [Table 1], resulting in increased morbidity and mortality.^[35] Pneumonia is the most common complication of influenza, which could be attributed to primary viral pneumonia that presents with severe symptoms, high fever, and dyspnea. It could progress quickly to respiratory failure in 2-5 days.^[36,37] Secondary, bacterial pneumonia is also an important cause of morbidity and mortality, especially among older persons. Patients typically relapse with higher fevers and productive cough after initial improvement in the symptoms

Table 1: Groups at high-risk for influenza complications*

Children aged <6 years
Adults aged ≥50 years
Children and adults with chronic illness: Pulmonary (including asthma), cardiovascular (excluding isolated hypertension), renal, hepatic, hematologic, diabetes mellitus, neurologic, neuromuscular disorders, and malignancy
Immunodeficiency disease (congenital or acquired as HIV)
Immunosuppression induced by medications
Pregnancy
Children (≥6 months) and adolescents who are receiving long-term aspirin therapy
Residents of long-term care facilities
Morbid obesity (body mass index ≥40)
Residents of chronic care facilities

*Adopted from reference numbers^[9,124]

of acute influenza.^[38] The most common bacterial pathogens are *Streptococcus pneumoniae* followed by *Staphylococcus aureus*, and occasionally community-associated methicillin-resistant *S. aureus*. *Haemophilus influenzae* pneumonia may also complicate influenza.^[39,40] Mixed pneumonia can occur with features of both viral and bacterial pneumonia.

Other complications include myositis, rhabdomyolysis, myocarditis, pericarditis, and toxic shock syndrome. Central nervous system involvement includes encephalopathy, encephalitis, transverse myelitis, aseptic meningitis, and Guillain-Barre syndrome (GBS).^[41]

Transmission

Since the virus is present in the respiratory secretions of infected persons, large particle droplets (>5 μm) can easily be transmitted primarily through sneezing and coughing.^[42,43] As large particles travel for short distances of <1.5 m, transmission of infection requires close contact with an infected person.^[44] The virus can also be transmitted by contact with surfaces that have been contaminated with respiratory droplets, including shaking hands.^[45] Infectivity occurs with the shedding of the virus that starts 1-2 days prior to symptoms and until 5-7 days after the appearance of symptoms; 95% of the infectivity occurs in the first 3 days.^[46] The period of infectivity may last for 10 days or more in the elderly, persons with chronic illnesses, and immunocompromised persons.^[47]

Influenza Vaccines

Influenza vaccination is the primary tool to prevent influenza infection rather than antiviral chemoprophylaxis.^[48] The protection of influenza vaccine depends on inducing humoral immunity, namely neutralizing antibodies against viral capsular antigens, which boost the immune system against the serotypes included in the vaccine. As mentioned, influenza viruses undergo periodic changes in their antigenic envelope glycoproteins, the hemagglutinin (H) and the neuraminidase (N). This explains the spread of infection each year due to the susceptibility of the population to viruses with new antigens.^[49] Hence, vaccines are produced annually to match circulating viruses. Three major subtypes of H (H1, H2, and H3) and two subtypes of N (N1 and N2) have been described.

Influenza B viruses have less tendency for antigenic changes. Although there are many subtypes of influenza A virus, 1-2 subtypes usually circulate among the human population at any given time. Therefore, most seasonal influenza vaccines include two subtypes of influenza A virus and one subtype of influenza B; hence, it is called a trivalent influenza vaccine (TIV). Recently, quadrivalent vaccines containing two influenza A antigens and two influenza B antigens were introduced. Occasionally, the monovalent vaccine is produced against a candidate pandemic strain, such as the H1N1 vaccine during the 2009/2010 epidemic.

Vaccine production takes about 6 months from the selection of strains to final production and distribution. Two types of vaccines are produced annually; one for the Northern Hemisphere and the other for the Southern Hemisphere. This requires biannual productions of the vaccine to ensure its efficacy against related strains for both Hemispheres. Through the WHO global influenza surveillance and response system, the composition of the vaccine is adjusted based on the characteristics of circulating influenza viruses from the previous season.^[50,51] In the Northern Hemisphere, vaccine strains are selected in February and made available in August of each year; in the Southern Hemisphere, vaccine strains are selected in September and made available in April of the following year. Influenza vaccines are manufactured in two forms: Inactivated influenza vaccines (IIVs) and live-attenuated virus vaccines (LAIVs). As the LAIV is not yet available in Saudi Arabia, influenza vaccination guidelines will focus on IIV (mainly TIV).

Inactivated influenza vaccines

The influenza vaccine currently available in Saudi Arabia for persons ≥6 months of age is TIV.^[52] As the vaccine includes inactivated or killed virus, this vaccine is not considered infectious. It is administered through intramuscular injection into the deltoid muscle of the arm [Table 2]. Alternatively, it can be given subcutaneously in those persons with bleeding tendency, albeit with reduced efficacy.^[53] The protection of the vaccine depends on several factors, including the age and health status of the person being vaccinated and the match between the virus strains used in the vaccine and those circulating in the community. The overall efficacy of inactivated vaccines in preventing laboratory-confirmed influenza is >60%.^[54-57] However, despite lower efficacy in preventing influenza virus infection in elderly people,^[58,59] there is evidence that influenza vaccine lowers hospital admission rates for pneumonia and influenza, and is associated as well with reduction in mortality in elderly vaccines as compared to unvaccinated elderly persons.^[60]

Live-attenuated virus vaccine

LAIV is administered by the intra-nasal administration. Patients can shed vaccine virus strains from their upper respiratory tract for up to 7 days after receiving the LAIV and can test positive for influenza.^[61,62] Hence, the LAIV may cause a mild form of influenza illness. The LAIV is licensed for use among nonpregnant persons aged 2-49 years.^[52] LAIV is not yet available in Saudi Arabia.

Indications

The SCIPV recommends the administration of the vaccine annually due to the modification of its composition every

Table 2: Recommended doses in children and adults

Age group	Dose (ml)	Number of doses	
		First time vaccinated	Previously vaccinated
6-35 months	0.25	2 doses (4 weeks apart)	1 dose
3-8 years	0.5	2 doses (4 weeks apart)	1 dose
≥9 years and adults	0.5	1 dose	

year to match the annual circulating influenza virus strains. In Saudi Arabia, the vaccine is recommended during the influenza season that commences annually in September and ends in March of the following year.^[63] The vaccination campaign should start soon after the availability of the vaccine. The SCIPV recommends the following for influenza vaccination administration [doses are available in Table 2]:

- All persons aged ≥6 months of age, including pregnant, and breastfeeding women (evidence A).^[48,52,55,64,65]
- For children aged 6 months through 8 years, vaccination is recommended based on previous vaccination history:
 - Previously vaccinated: Administer one dose only (evidence A).^[9,55,66-68]
 - First-time vaccination: Administer two doses that are 4 weeks apart (evidence A).^[55,66,69-71]
- For children <6 months of age, vaccination is not recommended. However, it is rather recommended to ensure that people around these children are vaccinated:
- When vaccine supply is limited, vaccination efforts should be prioritized by targeting certain categories:^[72,73]
 - Persons at higher risk for influenza-related complications [Table 1] (evidence A).^[65,72,74]
 - Healthcare professionals (evidence A).^[75-78]
 - Household contacts (children and adults) and caregivers of children aged <5 years with particular emphasis on vaccinating contacts of children aged <6 months (evidence A).^[55,78-80]
 - Household contacts (children and adults) and caregivers of adults aged ≥65 years and persons with medical conditions associated with higher risk for severe complications from influenza (evidence A).^[74,81-83]

Contraindications

Influenza vaccination is recommended to be postponed if there is an acute illness, especially when associated with fever. However, whenever the acute illness is cured prior to discharge, administration of vaccination is recommended. The IIV is contraindicated in the following situations:

- Severe egg allergy. However, a person with mild allergy (e.g., hives) can receive IIV and must wait 30 min under observation in a clinical setting that can handle allergic reactions.^[9] To deal with anaphylactic or hypersensitivity reactions, immediate treatment, including epinephrine 1:1000, should be easily accessible during the administration of the vaccine.^[84] Formulations that are not produced in eggs are not yet available in Saudi Arabia. Whenever, there are significant concerns, it is recommended to consult a physician specialized in allergic diseases.
- Previous history of severe allergy to any of the components of influenza vaccine.

- History of GBS within 6 weeks from receiving influenza vaccination.^[52]
- Children <6 months of age, as no vaccine is yet approved for this category.

If there is an epidemic of influenza in the community, antiviral prophylactic therapy might be administered during the 2 weeks after receiving the vaccine to protect against the virus till the development of an adequate immune response.^[85,86] It can also be administered during the 6 weeks for children not previously vaccinated and who require two doses given at least 4 weeks apart.

Adverse Effects

The IIV is generally safe and well-tolerated in children and adults (evidence A).^[87-89] However, self-limiting minor side effects have been frequently reported, especially for those who received the influenza vaccination for the first time.^[89-92] The adverse effects include mild redness or swelling at the injection site, low-grade fever, minor body aches, and sore throat. The rate of occurrence of fever has been reported to be 12% in children aged 1-5 years, 5% in children aged 6-15 years and similar to placebo for adults.^[52,90] For those who are immunocompromised or have chronic diseases, available evidence does not show that IIV causes clinically important adverse effects.^[93,94]

Mild and self-limited oculorespiratory syndrome has been reported to occur within 24 h after receiving IIV.^[95,96] However, a Canadian study found low recurrence rates of this complication after revaccination with IIV.^[97] The presenting symptoms include red eyes, cough, wheezing, and chest tightness. However, it is still controversial whether this syndrome is a coincidental finding, or it is rather related to an immediate hypersensitivity reaction to any of the IIV components.

Serious adverse events have been rarely reported. The risk of anaphylaxis is very low (0.7 case/million doses) and considered a causal relation with influenza vaccine. Anaphylaxis is presumed to be allergic in nature and may present as hives, angioedema, wheeze and anaphylaxis.^[98,99] A slightly increased risk of GBS (1-2 cases/million) has also been reported in association with the influenza vaccine.^[41]

Influenza Vaccination for the Hajj and Umrah

The Hajj and Umrah are considered recurrent mass gatherings when millions of Muslims from all over the world come to the holy places in Mecca and Madinah in Saudi Arabia. Infections with influenza viruses are commonly found during these gatherings.^[100-103] In a study that compared the incidence of respiratory tract infections among pilgrims coming from Saudi Arabia and the United Kingdom (UK), the incidence of influenza was 10% in pilgrims from Saudi Arabia and 7% and 14% among vaccinated and nonvaccinated pilgrims from the UK, respectively.^[101]

As influenza vaccination is generally considered effective in reducing influenza-related infections, the SCIPV recommends that pilgrims get vaccinated at least 2 weeks before performing the Hajj or Umrah (evidence A).^[101,104] It is recommended to

pay special attention to those suffering from chronic diseases (cardiac diseases, renal diseases, hepatic disease, respiratory diseases, nervous system disorders, and diabetes mellitus), immune deficient patients (congenital and acquired), metabolic diseases, obese persons, pregnant women, and children aged <5 years. Similar recommendation has also been adopted by the Saudi Ministry of Health that pilgrims are to be vaccinated against seasonal influenza before their arrival into Saudi Arabia.^[105]

The Hajj seasons for the next few years will fall during the months of June to September. This raises special concern for the Hajj pilgrims arriving from tropical and subtropical areas, e.g., South and Southeastern Asia, where influenza positivity rates are higher during June to November compared with December to May.^[106,107] By collecting a weekly influenza surveillance data from 2006 to 2011 in these countries, Saha *et al.* reported the positivity rates during June to November to be 86% in Bangladesh, 80% in the Philippines, 70% in India, 43% in Indonesia, and 41% in Malaysia.^[107] Therefore, the SCIPV recommends the administration of the Southern Hemisphere influenza vaccine prior to the Hajj and Umrah for pilgrims arriving from the Southern Hemisphere (evidence C).^[106,107] Furthermore, as the Northern Hemisphere influenza vaccine is not expected to be available prior to the Hajj in the next seasons for pilgrims from the Northern Hemisphere, the SCIPV also recommends the administration of the Southern Hemisphere influenza vaccine to those pilgrims prior to the Hajj session (evidence D). This should receive special attention as the composition of the current Southern Hemisphere vaccine is based on different characteristics of circulating influenza viruses utilized for the development of the Northern Hemisphere vaccine for the previous season.^[108]

Influenza Vaccination for Pregnant and Breastfeeding Women

When compared with nonpregnant women, pregnant women infected with influenza virus are prone to severe illnesses with higher morbidity and mortality.^[109-111] They also have a greater risk for serious problems for their infants and during delivery.^[112-114] Hence, seasonal influenza vaccine is commonly used during pregnancy. To assess the safety of influenza vaccine for pregnant women, the vaccine adverse event reporting system (VAERS) project collected reported adverse events in pregnant women receiving the vaccines from 1990 to 2009.^[115] The VAERS project did not report unusual patterns of pregnancy complications or adverse fetal outcomes over these two decades. Along the same line, data from six health care organizations in the vaccine safety data link project showed no statistically significant increase in the risk of pregnancy loss 4 weeks after IIV administration.^[116] Furthermore, the passive transfer of antibodies from vaccinated women to their infants was found to reduce respiratory illness during the first 6 months of life; hence IIV is not recommended for infants during that period.^[117,118] In a randomized controlled study, pregnant women who received seasonal influenza vaccine had a reduction in febrile respiratory illnesses by 36%. The vaccine effectiveness for infants was proven by a 63% reduction of laboratory-confirmed influenza and 29% reduction in febrile respiratory illnesses.^[118] Therefore, SCIPV recommends IIV influenza vaccination for pregnant women at any stage of

pregnancy (evidence A).^[118-123] This recommendation is also extended to postpartum and breastfeeding women.

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Conflicts of interest

There are no conflicts of interest.

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