Invited Paper

IAPSM's Position Paper on Influenza Vaccines for Adult Immunization in India

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Abstract

Influenza causes significant morbidity, hospitalizations, and mortality due to lower respiratory tract infections in India. This paper reviews the current evidence regarding influenza epidemiology, the need for vaccination, immunogenicity, and efficacy of available vaccines and provides recommendations for influenza vaccination for adults by the Indian Association of Preventive and Social Medicine (IAPSM). The risk group among adults includes people with chronic disease, the elderly, immunocompromised individuals, pregnant women, travelers, and healthcare workers. Influenza activity is affected by seasons, humidity, and latitude, leading to variability in influenza peaks in different regions of India. The most effective preventive intervention against influenza is vaccination. Current influenza vaccines have good safety profiles, vaccine efficacy, and acceptable cost-effectiveness. As the virus mutates, the vaccine composition should follow WHO recommendations for the current influenza season. Introducing readily available, conventional, and less expensive trivalent influenza vaccines under the national program can achieve maximum impact on the adult population and potentially prevent future outbreaks and pandemics. IAPSM recommends considering routine use of IIV for all individuals above 60 years, adults with comorbidities, and pregnant women in India. The program managers should consider the pattern of influenza seasonality in a particular region. Influenza surveillance conducted through a structured network of laboratories in India has the potential to provide information about circulating strains, morbidity, and mortality. IAPSM emphasizes conducting community-based studies regarding influenza's burden, vaccine efficacy, timing of vaccination, and cost-effectiveness among Indian adults to generate evidence.

Keywords: Adult immunization, IAPSM, India, influenza, influenza vaccines

Introduction

Influenza, a contagious respiratory infection caused by influenza viruses, is widespread worldwide, including in India.[1] Globally, the virus is responsible for approximately a billion cases of influenza annually, with 3–5 million people suffering from severe illness among people aged 18–64 years.[2] Global Burden of Disease data estimated that 5.6% of all deaths due to lower respiratory tract infection (LRTI) worldwide were attributable to influenza in 2017, mounting to 145,000 deaths across all age groups, and was around 0.26% of all deaths.[3] India's influenza burden was estimated to be the highest, with 26000 (95% UI 16000–37000) deaths due to influenza LRTI.[3] Influenza is the most frequently reported virus (15.4%) among viruses causing acute respiratory infections (ARI) in India, with a reported case fatality of 7.5%.[4,5] A structured network of 30 sites conducts integrated surveillance of influenza-like illness (ILI) and severe acute respiratory illness (SARI) to detect the disease burden in India. This network reported about 66,146 cases of seasonal influenza A and 2913 deaths across all age groups from 2018 to October 2023.[6] Around 10 lakh cases of ARI and ILI were reported between January and March

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2023 all over India, of which 3038 were laboratory-confirmed cases of various subtypes of influenza.[7]

Of four influenza viruses (A, B, C, and D), type A and B are of public health importance due to their potential to cause seasonal flu epidemics.[1] Type A has been classified into subtypes based on hemagglutinin (HA) and neuraminidase (NA) surface proteins. It binds to a receptor on the surface of the respiratory epithelial cell through HA glycoprotein and initiates infection. Furthermore, it damages and kills host cells by inhibiting cell protein synthesis and induces apoptotic changes in various cells. Influenza B has lineages (B/Yamagata and B/Victoria) and circulates widely only in humans. The type A and B viruses undergo antigenic "drift" and "shift," where minor and major mutations cause changes in viral protein antigenicity, leading to seasonal epidemics and pandemics. The infection is mild, and most people recover within a week without necessitating medical attention. The diagnosis of uncomplicated influenza remains clinical, and management is symptomatic. Nevertheless, influenza can potentially cause severe illness or mortality in extremes of age.

Older people have a poor ability to fight the infection due to an aged immune system. This phenomenon is known as immunosenescence, which further puts these individuals at an increased risk of infection.[8,9] People with chronic diseases, impaired immune systems, and those on immunosuppressants have an increased risk of hospital admissions.[10] Influenza virus may harm pregnant women and fetuses. Health workers are highly likely to contract the virus and may further transmit the infection, particularly to vulnerable individuals. With the high burden of the population, including the geriatric population, worsened by high population density and poor awareness about sanitation and hygiene, the increasing burden of influenza becomes even more concerning.

There is variation in the peak influenza season in different parts of India, though some activity occurs throughout the year.[11,12] In cities above 30°N latitude (e.g., Srinagar), the peak influenza season occurs during January–March in winter.[4,13] Meanwhile, the cities below 30°N latitude (e.g., Delhi, Lucknow, Pune, Allaphuza, Nagpur, Kolkata, and Dibrugarh) experience the peak during July–September. The influenza activity is affected by rain and humidity.[12,13] The recent pan-India surveillance system found peak influenza activity in North, East, Northeast, West, and Central India and some parts of South India during August–September.[14] In 2022, additional peaks were observed in South India during July–September and in Srinagar and Haldwani during May.[14] The pattern of circulating strains varied over the years.

Vaccination is the most effective preventive strategy against influenza, specifically for the elderly population and those with risk factors.[1,15] Influenza vaccination reduces the risk of pneumonia, cardiovascular events, hospitalization, and death.[16,17] Despite the evidence, India has not yet introduced the influenza vaccine in its universal immunization program. The position paper aims to review the current evidence regarding seasonal influenza vaccines and give evidence-based recommendations about their use in Indian adults.

Type of influenza vaccines available

The influenza vaccines currently available in India are listed as follows:[15,18,19]

1. Inactivated influenza vaccine (IIV)
2. Live attenuated influenza vaccine (LAIV)

Both the vaccines mentioned above are available as either a trivalent or a quadrivalent formulation. Trivalent influenza vaccine (TIV) contains two influenza type A strains (H1N1 and H3N2) and one influenza type B strain (Yamagata or Victoria lineage). The quadrivalent influenza vaccine (QIV) contains an additional influenza B strain and the same strains available in TIV.[20] The inactivated vaccines may be split virion or subunit vaccines. They are produced by propagating the virus in embryonated eggs, which are inactivated by formaldehyde and then purified. The LAIV are prepared via the reassortment of HA and NA antigens through serial egg passage or reverse genetics. This process produces a cold-adapted attenuated virus with HA and NA antigens of the target strain.[20] As the virus constantly mutates, the WHO reviews the prevalence data on the influenza virus twice a year and announces vaccine composition recommendations for the northern hemisphere (NH) and southern hemisphere (SH).[21,22] Recently, influenza H3N2 followed by influenza B Victoria and influenza A H1N1pdm09 subtypes were circulating in India.[7] These strains matched with the SH 2024 vaccine composition released by the WHO [Table 1]. It is recommended that the SH 2024 quadrivalent influenza vaccines be used in India for the current influenza season.[22]

Immunogenicity and efficacy

The efficacy of influenza vaccines varies among different age groups, populations, and seasons. A systematic review and meta-analysis showed that the pooled efficacy of TIV against clinical disease was 59% (95% CI: 51%–67%) in 18–65-year-old adults and 58% (95% CI: 34%–73%) among older adults.[23,24] The efficacy of LAIV against influenza was 53% (95% CI: 38%–65%) among healthy adults.[25] The vaccine

Table 1: Influenza vaccine composition for the northern and southern hemispheres recommended by the WHO

Formulation	Southern hemisphere (September 2023)	Northern hemisphere (February 2023)
Trivalent vaccine	-an A/Victoria/4897/2022 (H1N1) pdm 09-like virus	-an A/Victoria/4897/2022 (H1N1) pdm09-like virus
	-an A/Thailand/8/2022 (H3N2)-like virus	-an A/Darwin/9/2021 (H3N2)-like virus
	-a B/Austria/1359417/2021 (B/Victoria lineage)-like virus	-a Austria/1359417/2021 (B/Victoria lineage)-like virus
Quadrivalent Vaccine (TIV strains plus)	-a B/Phuket/3073/2013 (B/Yamagata lineage)-like virus	-a B/Phuket/3073/2013 (B/Yamagata lineage)-like virus

was protective against laboratory-confirmed influenza (relative risk: 0.5, 95% CI: 0.3–0.7) among pregnant women in low- and middle-income countries (LMIC) trials.[26] A recent trial on the efficacy of IIV conducted in rural India reported that indirect vaccine effectiveness was 47.3% (95% CI: 4.8%-70.8%) among the 18–49-year age group.[27] Menon *et al*. (2008)[28] found that the influenza vaccine was 67% effective in preventing chronic obstructive pulmonary disease (COPD) patients from ARI. A phase III trial to determine the immunogenicity and safety of subunit and split virion QIV among Indian adults found them immunogenic. Both vaccines had over 90% seroprotection rate for the type A strains and between 43% and 60% for type B strains.[29] The high-dose (HD) vaccine had a significantly higher seroconversion rate than the standard-dose (SD) vaccine.[30–32] Various studies have demonstrated that inactivated QIV is superior to TIV for the added alternate type B strains and has a non-inferior immune response for shared strains among adult subjects.[33–36]

Optimum age for vaccination

Ideally, the influenza vaccine may be administered to individuals above 6 months of age.[18,20,37,38] CDC recommends annual influenza vaccination for adults aged 19 years or older.[39] The decision to vaccinate healthy 18–49 year individuals depends on the physician's and patient's discretion. Some guidelines recommend influenza vaccination for those above 50 years of age and at a high risk of influenza,[15] while others for older individuals ≥65 years.[18,40] LAIV can be administered in the 2–49-year age group.[18] The Ministry of Health and Family Welfare (MoHFW) considers the vaccine desirable for elderly individuals (≥65 years) and for children between 6 months and 8 years.[40]

Duration of protection and repeat vaccination

The influenza vaccine takes about 2–3 weeks for the development of immunity. The viruses exhibit frequent mutations, necessitating annual vaccine updates to maintain optimal protection. The duration of protection after vaccination is variable but usually lasts for 6–12 months.[41] Immunosenescence has a role in reducing the potency of the influenza vaccines,[29] making them less effective in older people. The antibody titers decline significantly among the elderly within 6 months of receiving the IIV.[42] On repeat administration, a significant reduction in ILI and annual mortality risk by 15% was observed among older adults.[42] As vaccine-induced immunity fades with time, yearly vaccination is recommended to protect against influenza.

Administration and dosing

The IIVs are available as single-dose vials, multidose vials, and prefilled syringes. The intramuscular injection dose of IIV is 0.5 mL into the deltoid muscle. The SD trivalent and quadrivalent IIV contain 15 µg of HA subtypes per adult dose. The HD quadrivalent inactivated vaccine for older adults contains 60 µg of HA per strain. A single dose (0.5 mL) of LAIV is available as an intranasal spray and administered in each nostril (0.25 mL).[20]

A single dose of seasonal influenza vaccine is recommended annually at least 1 month prior to the beginning of the influenza season. Standard dose QIV is preferred over TIV for administration. For older people, HD inactivated QIV has been recommended since 2019.[20] The use of QIV over LAIV is recommended in the absence of solid data regarding LAIV effectiveness among various age groups.[15] Table 2 shows the vaccine recommendations for people at a high risk of influenza illness and complications.[15,18,37,40]

Storage and handling

The influenza vaccines are refrigerated at a temperature of 2°C–8°C. Domestic refrigerators should not be used for storage. Freezing and exposure to light must be avoided.[20] It is recommended to store the vaccine in its original packing to maintain the temperature and prevent administration errors. Labels may be placed on containers or shelves to avoid confusion between influenza vaccines.

Timing of vaccination

The local epidemiological data about the seasonality of influenza has a vital role in deciding the time of vaccination. The cities reporting influenza activity in the monsoon season (July–September) will require vaccination during April–June, while the cities with temperate seasonality and those in South India will gain from vaccination during September–October before the influenza activity peaks.[13,43]

Interference with concomitantly administered vaccines

The IIV can be safely administered with other inactivated or live vaccines. It may be co-administered with current COVID-19 vaccines.[44] In the case of LAIV, a gap of at least 4 weeks should be maintained when administered with another live vaccine. At the same visit, it is safe to administer measles, mumps, and rubella (MMR) or varicella vaccine with the LAIV. When administering any other injectable vaccine with

Table 2: Influenza vaccine recommendations according to disease conditions and occupation

Condition	Vaccine	Dosage
Chronic renal diseases	IIV	
Chronic liver disease, alcoholics	IIV or LAIV^	
Heart disease	IIV	
Neurological conditions	IIV	
Chronic lung disease, smokers	IIV	
Endocrinological disorders (diabetes, inherited metabolic disorders)	IIV	1 dose annually
Liver and kidney transplant recipients	IIV	
Immunosuppressed individuals*	IIV	
Malignancy	IIV	
Healthcare workers with risk of occupational exposure	IIV > LAIV$	
Residents of nursing homes or long-term care facility	IIV	
Elderly individuals ≥65 years	IIV	

Source: References 15, 18, 37, 40; *people living with HIV, people with AIDS, patient on chronic corticosteroid use; ^precaution does not apply for alcoholics; $cautiously given if caring for immunosuppressed individuals

the influenza vaccine, a separate anatomical site is preferred for both injections.[15]

Safety of vaccines

The majority of flu vaccine side effects are minor, and typical adverse reactions include local pain, redness, swelling, headache, fever, nausea, and muscle aches.[25,29,45] LAIV may cause runny nose, nasal discomfort, sneezing, and cough.[46] Studies have shown a possibility of a minimal association between the injectable flu vaccine and Guillain-Barre syndrome (GBS). However, the association was not statistically significant.[25] The GBS has not been linked to LAIV.[45] Exposure to influenza vaccine during pregnancy was not associated with abortion, neonatal deaths, congenital malformations, and prematurity. Both IIV and LAIV show good safety profiles among adults.[47]

Contraindications and precautions

Contraindications for the influenza vaccines are listed as follows:[15,48]

1. Severe allergy to any vaccine constituent (gelatin, antibiotics, and other components) in the past
2. Moderate to severe acute illness with or without fever
3. Individuals who suffered from GBS within 6 weeks of influenza vaccine administration and are currently not at a high risk of severe influenza complications
4. LAIV is contraindicated in pregnant females.

In case of acute febrile illness, the vaccination should be delayed till the person recovers. People who are allergic to eggs and those who experience reactions can receive the age-appropriate influenza vaccine. LAIV should not be given to immunosuppressed people, those with immunodeficiency syndrome or asplenia, and those on chemotherapy and corticosteroids.[49] People who care for immunosuppressed people or live in close contact may take LAIV cautiously. Corticosteroids and statins can reduce the effectiveness of the influenza vaccine. Still, those suffering from chronic pulmonary disease or on statins should receive the vaccine.[15] Antiviral medications interfere with the effectiveness of LAIV; thus, avoid using them 2 days before to 14 days after receiving the vaccine.

Influenza vaccination in special populations

1. Pregnancy: The IIV is recommended for pregnant and breastfeeding women. They may be vaccinated in any trimester.[40,50,51]
2. The LAIV should be avoided in multiple sclerosis; however, a standard dose of IIV can be given.
3. Immunocompromised individuals: IIV can be administered, but LAIV should be avoided due to the risk of activation of live virus. The healthcare workers caring for such individuals and those close to them should be vaccinated.
4. Health professionals working in the emergency department, caring for high-risk groups, laboratory staff handling the virus samples, and those involved in outbreak investigation are recommended to take a single dose of influenza vaccine.[40,52]
5. Travelers: The vaccine is recommended for people attending mass gatherings, Hajj pilgrims, and travelers.[18]

Cost-effectiveness of vaccines

A recent study provided evidence regarding influenza vaccine cost-effectiveness in upper-middle-income countries, especially for health workers and the elderly.[53,54] Another systematic review found that influenza vaccination was cost-effective for patients with COPD in LMICs.[55] Vaccination is considered cost-effective for pregnant women.[53,56] Some modeling studies have found influenza vaccines cost-effective in Asian countries with tropical and subtropical climates.[57,58] A recent cost-effectiveness analysis of universal influenza vaccination in Sri Lanka found that TIV implementation was cost-effective (incremental cost-effectiveness ratio = 3624.84 USD/DALY averted).[58] Peasah *et al*.[59] reported that hospitalization costs due to ARI are more than India's median per capita income. In the Indian context, the influenza vaccines may be considered cost-saving or cost-effective, specifically for adults >50 years.[15,59]

Implementation issues and barriers to inclusion in the national immunization program

In LMICs, adult vaccination is often relegated to a lower priority, with accessibility primarily limited to those who can afford it or individuals with specific medical conditions. Addressing these challenges becomes increasingly complex in a country as populous as India, with 1.4 billion people, especially considering the concurrent struggle against other communicable diseases.[60] The limited comprehension of influenza's prevalence, severity, and societal impact within the adult demographic complicates resource allocation and vaccine prioritization.[61] The need for yearly vaccination due to the ever-changing nature of circulating influenza viruses represents a significant barrier. A mismatch between the genetic lineage of circulating strains and vaccine strains can result in poor vaccine effectiveness, as reported in a study conducted by Mir *et al*. (2021)[62] in north India, where the vaccine effectiveness against influenza A virus was 55% but abysmal against influenza B (−12%) due to mismatch. Furthermore, the vaccine's immunity development period of 2–3 weeks necessitates administration at least a month before the onset of flu season, introducing logistical complexities.[63] The complexities regarding the determination of the optimal time of vaccination emphasize the significance of extended surveillance efforts before the decision to include the influenza vaccine in the national immunization schedule.[60]

Although adult vaccination was not part of the National Vaccine Policy developed in 2011, adult vaccines such as influenza for pregnant women and healthcare workers were being focused on by the National Technical Advisory Group on Immunization, MoHFW.[64,65] India had successfully implemented the rollout of COVID-19 vaccination among adults during the pandemic under the existing immunization program. However, limited data on the effectiveness of influenza vaccines in the Indian context, especially among

adults, and the financial burden of providing annual influenza vaccinations for the entire country may pose a substantial challenge to public finances. A web-based survey conducted among public health officials in LMICs revealed a notable lack of evidence regarding influenza burden (84%) and cost-effectiveness of vaccination programs (87%), poor perception of disease risk (79%), and a scarcity of practical public health risk communication tools (77%).[66] Concerns regarding vaccine safety and effectiveness and misperceptions about influenza vaccination among the public and healthcare providers hinder vaccine uptake.[66–68]

Future research priorities

There is an imperative need to comprehensively assess the disease burden of influenza among adults in India. This includes conducting rigorous epidemiological studies to determine the true prevalence, severity, and impact of influenza in the adult population. The inclusion of seroprevalence studies can provide valuable insights into population-level immunity against various influenza strains. Second, robust vaccine effectiveness studies are essential to ascertain the vaccine's impact on preventing influenza and associated complications in the Indian adult population. There is a need to conduct cost-effectiveness studies specific to adult influenza vaccination in India.

Strategies aimed at increasing awareness and affecting behavior change regarding adult vaccination among healthcare providers and public are essential. Research in this domain should focus on designing effective interventions tailored to the specific sociocultural contexts of the target populations. Understanding the barriers and facilitators to integrating influenza vaccination into national immunization programs is crucial. Lastly, the development of a universal influenza vaccine represents a transformative frontier in influenza research. Continued investment in this area is imperative to achieve a vaccine that provides broad, long-lasting protection against diverse influenza strains.

IAPSM's position on influenza vaccine among adults

Influenza causes substantial morbidity and mortality in India. People with comorbidities and impaired immune systems and the elderly population bear the brunt of the illness. Influenza surveillance conducted through a network of virus research and diagnostic laboratories has the potential to monitor and generate evidence regarding the same. Both IIV and LAIV have good safety profiles, vaccine efficacy, and acceptable cost-effectiveness. Based on the current evidence, IAPSM recommends considering routine use of IIV for all individuals above 60 years, adults with comorbidities, and pregnant women in India. Although QIV may be superior to TIV, maximum population impact can be achieved by introducing easily available, conventional, and less expensive vaccines under the national program. The available surveillance data on influenza activity in the country raises a crucial issue of time for administering the vaccine. The pattern of influenza seasonality in a particular area should be considered by the program managers and IAPSM members. A comprehensive understanding of the vaccine's performance in diverse Indian populations, considering factors such as strain variability and population immunity, is crucial for informed decision-making. In the end, the discovery of a universal influenza vaccine seems like a solution for all. The members of IAPSM can conduct community-based studies regarding the burden of disease, vaccine efficacy, cost-effectiveness, and timing of vaccination in their field practice areas to generate evidence.

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Conflicts of interest

There are no conflicts of interest.

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