

# Seasonal Influenza Vaccination

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## Introduction

Influenza is an acute viral infection caused by an influenza virus typically occurring during colder winter months. Influenza viruses circulate worldwide and are classified into three seasonal types—A, B, and C. Influenza A and B viruses are further separated into subtypes (for A viruses) and lineages (for B viruses) on the basis of antigenic differences. Influenza A(H1N1) viruses, influenza A(H3N2) viruses, and influenza B viruses currently co-circulate globally. Only influenza A and B viruses are included in the annual “seasonal” influenza vaccines, because type C virus infections are much less common and only result in mild illness. Influenza viruses are transmitted primarily by droplets or respiratory secretions of infected persons.<sup>1</sup>

Influenza A and B viruses cause yearly seasonal influenza outbreaks and epidemics worldwide, with an annual global attack rate estimated at 5 – 10% in adults and 20 – 30% in children. Illnesses range from mild to severe and even death. Worldwide, these annual epidemics are estimated to result in about three to five million cases of severe illness, and about 250,000 to 500,000 deaths.<sup>1</sup> Children are efficient transmitters of influenza viruses, those younger than five years of age and particularly younger than two years have a high burden of respiratory illnesses associated with influenza. However, severe morbidity and mortality are more common among elderly people and in individuals with specific chronic medical conditions such as HIV/AIDS, asthma, and chronic heart or lung diseases. Secondary bacterial pneumonia is a frequent complication of influenza infection among these subpopulations. Influenza is associated with considerable economic burden arising from health-care costs, lost days of work or education, and general social disruption across all age groups.

Influenza A viruses may also cause worldwide pandemics characterized by rapid dissemination of new influenza A subtypes (or strains of subtypes) that have the capacity for human-to-human transmission and are sufficiently different antigenically from recently circulating influenza viruses to evade immunity in the population. Historically, major pandemics have occurred every 10 to 40 years. The most severe was the 1918 pandemic of the “Spanish flu”, which caused an estimated 20–40 million or more deaths globally. Later, less severe pandemics occurred in 1957 (“Asian flu”) and 1968 (“Hong Kong flu”). In 2009, the A(H1N1) pandemic later evolved into a seasonal pattern in 2010.<sup>1, 2</sup>

Vaccination is the primary means of preventing and reducing the burden of influenza illness. In 2003, the World Health Assembly resolved to increase the use of seasonal influenza vaccines to protect individuals at high risk for influenza and related complications.<sup>3</sup> In 2012, the World Health Organization (WHO) and its Strategic Advisory Group of Experts (SAGE) on immunization recommended that countries considering the initiation or expansion of programs for seasonal influenza vaccination should include pregnant women as the highest priority group.

The following high risk groups, in no particular order of priority, were also recommended for vaccination: children aged 6–59 months (especially 6–23-month-olds), the elderly, individuals with underlying health conditions such as HIV/AIDS, asthma, and chronic heart or lung diseases, and health care workers.<sup>4</sup> Vaccination is recommended for healthcare workers because they are at increased risk of exposure to influenza virus while the remaining groups are at particular risk of developing severe disease, i.e., disease resulting in hospitalization or death. Prevention of influenza among health workers is important because infected health workers tend to amplify transmission of influenza among care-seeking patients. Pregnant women are particularly vulnerable to respiratory illnesses compared to their non-pregnant counterparts, because pregnancy involves physiological changes in the cardiopulmonary and immunological systems. Influenza illness in pregnant women can result in fetal death, premature onset of labor, decreased birth weight, and intrauterine growth restriction (infants born small for gestational age).<sup>4,5</sup>

Influenza activity is seasonal, peaking during periods that often coincide with the colder months (November–February and May–October) in the temperate regions of the northern and southern hemisphere respectively.<sup>6,7</sup> Unlike in the temperate regions, influenza seasonality in the tropics is less distinct, with multiple, less pronounced peaks that frequently coincide with the rainy season. Some tropical countries even have year-round transmission. Influenza surveillance and pandemic preparedness has improved in many countries in the tropics and subtropics in recent years, which have allowed ascertaining transmission patterns in countries with less distinct seasonality.<sup>6,7</sup>

## Available Influenza Vaccines

The constantly evolving nature of influenza viruses requires continuous global monitoring and frequent reformulation of influenza vaccines. The WHO convenes technical consultations in February and September of each year to recommend viruses' strains for inclusion in seasonal influenza vaccines for the northern and southern hemispheres, respectively. These recommendations are based on information provided by the WHO Global Influenza Surveillance Network (GISN), now the WHO Global Influenza Surveillance and Response System (GISRS). Vaccine production takes about 6–7 months. The Northern hemisphere formulation is available by October whereas the Southern hemisphere formulation is available by April of the following year.<sup>1,8</sup> The currently available vaccines are mostly trivalent, i.e. containing three influenza virus strains: an influenza A(H1N1) strain, an influenza A(H3N2) strain, and an influenza B strain. Nevertheless, quadrivalent vaccines including an additional strain of influenza B virus thus covering the two currently circulating lineages (Yamagata and Victoria lineages) are also available.<sup>8</sup>

Two types of influenza vaccine are available: an inactivated (killed) preparation administered as an injection (IIV) and an attenuated influenza virus vaccine normally delivered intranasally. There are three types of inactivated vaccines: split virus vaccines, subunit vaccines, and whole virus vaccines. In split virus vaccines, the virus has been disrupted by a detergent in order to reduce vaccine reactogenicity. In subunit vaccines, hemagglutinin and neuraminidase, the two glycoproteins of the influenza virus membrane have been further purified by removal of other viral components. Some formulations include adjuvants and most multidose vials contain the preservative thiomersal. Live, attenuated influenza vaccines have been based on a temperature-sensitive variant vaccine virus strains that replicate well in the nasopharynx but poorly in the lower respiratory tract.<sup>8</sup> Trivalent inactivated influenza virus vaccines (TIV) are available as standard or high dose vaccines for the elderly. Live attenuated virus vaccines (LAIV) are available for use in healthy individuals only.<sup>1,8,9</sup> Quadrivalent vaccines (QIV) became available in 2012 (as either IIV or LAIV vaccines).<sup>1,9</sup> Table 1 summarizes the types of influenza vaccines that are available for use globally.

**Table 1.** Types of seasonal influenza vaccines available for use globally as of 2016

Vaccine Type	Dose	Route	Age Indications
<b>INACTIVATED INFLUENZA VIRUS (IIV) VACCINES</b>			
Trivalent, egg-based (adjuvanted or unadjuvanted)	Standard	Intramuscular	≥6 months
Trivalent, egg-based	High	Intramuscular	≥65 years
Trivalent, cell culture-based	Standard	Intramuscular	≥18 years
Trivalent, recombinant hemagglutinin influenza vaccine	Standard	Intramuscular	≥18 years
Quadrivalent, egg-based (unadjuvanted)	Standard	Intramuscular	≥6 months
Quadrivalent, cell culture-based (unadjuvanted)	Standard	Intramuscular	≥4 years
Quadrivalent, egg-based	Standard	Intradermal	18–64 years
<b>LIVE-ATTENUATED INFLUENZA VIRUS (LAIV) VACCINES</b>			
Quadrivalent since 2013-14 (previously trivalent)	Standard	Intranasal	2–49 years

## Vaccine Contraindications

**Inactivated influenza vaccines** (IIV) should not be administered to the following individuals:

- Infants <6 months of age.
- People who have experienced a severe (life threatening) allergy to a prior dose of a seasonal influenza vaccine (IIV or LAIV).
- People who have a severe allergy to a component of the IIV vaccine. Health care providers should always consult the package inserts for vaccine components.

Recommendations for vaccinating patients who are allergic to eggs are available. A recombinant hemagglutinin influenza vaccine (RIV) is approved in individuals aged 18 years and older, and people in this age group who are allergic to eggs may receive RIV.

If RIV is not available or the recipient is not 18 years or older, most egg-allergic patients can safely receive IIV. Those who have only experienced hives as a reaction to egg may receive IIV, with some additional safety precautions. Individuals with a history of severe (life threatening) allergy to eating eggs may receive IIV if it is administered by a physician experienced in the recognition and management of severe allergic conditions.

**Live-attenuated influenza virus vaccines** (LAIV) should not be administered to the following individuals:

- Children <2 years of age.
- Adults ≥50 years of age.
- Pregnant women.
- Individuals with a history of severe allergic reaction to any component of the vaccine or to a previous dose of any influenza vaccine.
- Individuals with known or suspected immunodeficiency diseases or immunosuppressed states (including those caused by HIV) or asthma or certain chronic treatments such as long term aspirin therapy.

**Cell Culture-based Inactivated Influenza Vaccine** (ccIIV3) should not be administered to the following:

- Individuals who have had a severe allergic reaction to any component of the vaccine or after previous dose of any influenza vaccine.

## Concurrent Administration of Influenza Vaccine with Other Vaccines

Inactivated vaccines do not interfere with the immune response to other inactivated vaccines or to live vaccines. Although inactivated or live vaccines can be administered simultaneously with LAIV, after administration of a live vaccine (such as LAIV), at least 4 weeks should pass before another live vaccine is administered.<sup>9</sup>

## Vaccine Safety and Adverse Events Following Immunization

Influenza vaccines are among the safest vaccines available as demonstrated by the evidence accumulated over decades of administration of hundred millions of doses among people of all ages. Influenza vaccines are generally well tolerated.<sup>2, 5, 9</sup>

### Inactivated Influenza Virus Vaccines

Studies support the safety of annual inactivated influenza virus vaccines (IIV) vaccination in children and adults.<sup>10</sup> IIV is administered as an injection and may cause pain, redness, and swelling at the injection site, and may also cause fever, malaise and myalgias, which are usually mild and go away on their own. IIV contains inactivated virus and cannot cause influenza. In one of the largest safety studies published to date, 251,600 children aged less than 18 years were screened at five managed care organizations during 1993-99 in the United States and results did not show evidence of important medically attended events associated with pediatric influenza vaccination.<sup>11, 12</sup> A recent study carried out among healthy adults  $\geq 18$  years of age showed that QIV, containing two B strains (one of each B lineage), was as safe and immunogenic as licensed TIV.<sup>13</sup> With regards to pregnant women, the WHO Global Advisory Committee on Vaccine Safety (GACVS) concluded in 2014, upon review of all safety data available globally that inactivated influenza vaccines were safe for use at any stage of pregnancy.<sup>14</sup> In the United States during 1990-2009, an estimated 11.8 million pregnant women received non-adjuvanted inactivated influenza vaccine and the national Vaccine Adverse Event Reporting System (VAERS) database received only 20 notifications of serious adverse events and 128 reports of non-serious adverse events following administration of trivalent IIV during that period. Multiple studies have not found new, unusual, or unexpected patterns of serious acute events, adverse pregnancy outcomes, or congenital anomalies confirming that IIV do not cause fetal harm when administered to pregnant women. Nevertheless, further active surveillance is warranted to continue expanding and solidifying the evidence base on the safety of vaccinating pregnant women.<sup>13</sup>

Pain and other injection site reactions are frequently reported after IIV vaccination in both children and adults. In IIV clinical trials, up to 65% of people vaccinated with IIV experienced pain at the injection site during the first week after vaccination which usually did not interfere with activity. Fever, malaise, myalgia, and other systemic symptoms can occur after vaccination with IIV, most often affecting individuals who have had no previous exposure to the influenza virus antigens in the vaccine (e.g., young children). In adults, the rate of these symptoms is similar after IIV and after a placebo injection. Vaccine components can on rare occasions cause allergic reactions (immediate hypersensitivity). Manifestations of immediate hypersensitivity range from mild urticaria (hives) and angioedema (swelling beneath the skin) to anaphylaxis. In some seasons, IIV has been associated with febrile seizures in young children, particularly when given together with 13-valent pneumococcal conjugate vaccine (PCV13) and diphtheria, tetanus and pertussis (DTaP) vaccines. Guillain–Barré Syndrome (GBS) following IIV occurs rarely. The cause of GBS, a serious neurological condition that can cause paralysis, is unknown, however, gastrointestinal and upper respiratory infections are known risk factors. Safety monitoring of seasonal IIV over the course of many years has not detected a clear link to GBS. However, if there is a risk of GBS from IIV, it would be no more than 1 or 2 cases per million people vaccinated. Each year, about 3,000 to 6,000 people in the United States develop GBS whether or not they received a vaccination –1 to 2 people per 100,000. Like other injections, IIV can also cause syncope (fainting).<sup>2, 10, 14</sup>

Trivalent IIV manufactured using cell culture technology, which are indicated for use in individuals 18 years of age and older, are administered as an injection and the most common ( $\geq 10\%$ ) local and systemic reactions in adults 18-64 years of age have been injection site pain, injection site erythema, headache, fatigue, muscle pain and malaise.<sup>14</sup>

RIV does not contain any egg protein and is approved for use in individuals 18 years of age and older. RIV is administered as an injection and similarly to the remaining IIV, may cause pain, redness, and swelling at the injection site, and may also cause fever, malaise and myalgia which are usually mild and self-limited.

**Table 2.** Summary of Mild and Severe Adverse Events After Administration of Inactivated Influenza Vaccine, WHO 2012

Nature of Adverse Event	Description	Rate/Doses
Mild	Local reactions: Injection site reactions	10-64 per 100
	Generalized reactions: Fever in children 1-5 years old	12 per 100
	Fever in children 6-15 years old	5 per 100
Severe	Anaphylaxis	0.7 per 10 <sup>6</sup>
	Guillain-Barré	1-2 per 10 <sup>6</sup>
	Oculo-respiratory syndrome (events of moderate severity)	76 per 10 <sup>6</sup>

Source: [http://www.who.int/vaccine\\_safety/initiative/tools/vaccinfosheets/en/](http://www.who.int/vaccine_safety/initiative/tools/vaccinfosheets/en/)

## Live-Attenuated Influenza Virus Vaccines

Trivalent live-attenuated influenza virus vaccines (LAIV) and closely related formulations have been well tolerated in adults, even among those with low levels of pre-vaccination antibodies. Nasal symptoms (runny nose, nasal congestion, or coryza) and sore throat were the most frequently identified adverse symptoms attributable to vaccination in conducted studies. LAIV contains attenuated viruses and cannot cause influenza. Trivalent LAIV have also been shown to be safe and well tolerated in children.<sup>10, 14</sup> For further information on safety and adverse events following immunization with LAIV, please visit: [http://www.who.int/vaccine\\_safety/initiative/tools/vaccinfosheets/en/](http://www.who.int/vaccine_safety/initiative/tools/vaccinfosheets/en/).

## Vaccine Effectiveness and Impact

Seasonal influenza epidemics can be very heterogeneous due to a population's level of immunity and antigenic changes of influenza viruses. Epidemics may differ in their timing, incidence, and severity, as well as in the match between circulating influenza virus strains and the strains included in the vaccine. In addition to age, health status, and prior immunity to influenza viruses among other factors, this match between influenza vaccine strains and circulating strains will partly dictate how well a vaccine will work, i.e. what the vaccine effectiveness will be for that particular influenza season. Countries that use influenza vaccines annually have developed efficient and practical methods to gain insight into a season's vaccine performance. Such annual evaluations of influenza vaccine effectiveness aim to guide risk communication messages to the public and health professionals, reinforce the use of complementary public health measures, such as the administration of antivirals among high risk groups, and implement measures of social distancing in seasons of poor match between circulating viruses and vaccine strains. Such information is also crucial to maintain the investments in vaccination programs, and to orient public health policies. The most popular design used to systematically measure vaccine effectiveness is the test-negative design, which compares the rates of vaccination in a group of patients that seek medical care for acute respiratory illness and that are tested for influenza virus infection. Data are collected from a network of outpatient clinics or sentinel hospitals on patients that have sought medical care for acute respiratory illness. Data on vaccination status and the laboratory findings are used to calculate an estimate of how well the seasonal vaccine prevented patients from suffering from influenza illness or its complications.<sup>15-21</sup> Since 2004, such studies have shown that during seasons when most circulating influenza viruses are similar to the viruses in the influenza vaccine, the vaccine can reduce the risk of illness caused by influenza virus infection by about 50-60% among the overall population.<sup>2, 9, 22</sup> A recent meta-analysis of 56 published test-negative design studies showed that influenza vaccines provided substantial protection against H1N1pdm09 (61%), H1N1 (pre-2009) (67%), and type B (54%), and reduced protection against H3N2 (33%).<sup>23</sup>

This monitoring of influenza vaccine effectiveness has evolved to provide timely interim effectiveness estimates that are reviewed at the bi-annual WHO vaccine strains selection consultations.<sup>24</sup> A recent systematic review has shown the concordance of interim and final estimates of influenza vaccine effectiveness.<sup>25</sup>

Monitoring influenza vaccine effectiveness over the years can also provide valuable data to revise vaccination policies in place if necessary. For example in June 2016, the U.S. Centers for Disease Control and Prevention (CDC)'s Advisory Committee on Immunization Practices (ACIP), a panel of immunization experts that advises the CDC, recommended against the use of LAIV for the 2016-2017 influenza season. This decision was based on a thorough review of vaccine effectiveness data generated by the U.S. Influenza Vaccine Effectiveness Network. The data showed poor or relatively lower effectiveness of LAIV from 2013 through 2016. Other (non-CDC)

studies supported the conclusion that LAIV worked less well than IIV during the 2015-2016 season. Therefore, the LAIV vaccine is currently not recommended in the U.S.<sup>9</sup>

Among pregnant women, studies to date have shown that the effectiveness of seasonal inactivated influenza vaccination in preventing influenza infection in the vaccinated mother was moderate while the potential for maternal vaccination to protect infants through transplacental transfer of antibodies ranged from 41% to 91%.<sup>26-29</sup> In a randomized controlled trial conducted in Bangladesh, IIV reduced proven influenza illness by 63% in infants up to 6 months of age and averted approximately a third of all febrile respiratory illnesses in mothers and young infants.<sup>26</sup> A study in the United States conducted during 2000–2009 estimated the effectiveness of influenza vaccine given to mothers during pregnancy in preventing hospitalization among their infants at 91.5% (for infants aged less than six months).<sup>30</sup> This is particularly important for infants younger than 6 months old for whom seasonal influenza vaccines are not recommended.

Evaluating the overall impact of influenza vaccination is complicated due to the heterogeneity between seasons, the varying effectiveness of influenza vaccines, and the frequent lack of influenza surveillance data pre-vaccine introduction. Instead, health authorities typically need to combine data from multiple sources to estimate vaccine impact. Thus, influenza disease burden data are combined with recurrent influenza vaccine effectiveness estimates and vaccination coverage data to provide estimates of cases, hospitalizations, and deaths averted by vaccination.<sup>21</sup> For example, for the 2013–14 influenza season, using updated estimates of vaccination coverage, vaccine effectiveness, and influenza hospitalizations, the US CDC estimated that influenza vaccination prevented approximately 7.2 million illnesses, 3.1 million medically attended illnesses, and 90,000 hospitalizations associated with influenza.<sup>30</sup> Similar to prior seasons, fewer than half of persons aged  $\geq 6$  months were estimated to have been vaccinated. If influenza vaccination levels had reached 70%, an estimated additional 5.9 million illnesses, 2.3 million medically attended illnesses, and 42,000 hospitalizations associated with influenza might have been averted.<sup>31</sup>

## Vaccination Timing and Strategies

The influenza vaccines currently in use globally need to be administered every year due to the frequent updates in the vaccine strains, but also due to their short duration of protection.<sup>2</sup> Thus, every year, influenza vaccination activities are organized shortly before the influenza season and typically start with an intensive vaccination campaign. Optimally, vaccination should occur before the onset of influenza activity in the community taking into account the average two weeks that are necessary to mount an adequate immunological response.<sup>32</sup> Therefore, it is recommended that campaigns reach the highest possible coverage of the targeted populations prior to the peak influenza activity in a country.<sup>6, 33</sup> Sometimes vaccination campaigns may benefit from piggy-backing on broader vaccination campaigns. Such is the case of the vaccination week of the Americas for countries that vaccinate against influenza in April using the Southern hemisphere vaccine.<sup>33</sup> Vaccination should continue to be offered through the routine health services as long as influenza viruses are circulating and unexpired vaccine is available.

All individuals targeted for vaccination should receive one dose of vaccine except children aged six months through 8 years who have never received influenza vaccine before, they should receive two doses of vaccine at least 4 weeks apart to ensure their optimal protection.<sup>4</sup>

Determining the best timing of vaccination is easy in temperate regions where the period of the seasonal outbreaks is well defined. It is more difficult in tropical and subtropical regions, where peaks of influenza activity are less marked. In an attempt to simplify operational guidance to countries regarding when to vaccinate and which formulation to use, a recent global review of the available evidence proposed geographical groupings of countries into vaccination zones with similar recommendations for vaccine timing and formulation.<sup>7,34</sup> The optimal timing for the annual seasonal influenza vaccination campaign based on the start of the main influenza activity period could be identified for most countries in the tropics and subtropics. Once the local seasonality is defined, countries should always use the formulation that corresponds to the most recent WHO influenza virus vaccine recommendation in order to maximize its efficacy, independent of the geographic location of the country. Countries where influenza virus circulate year-round should consider strategies to increase vaccination coverage using the most appropriate formulation instead of conducting several interventions per year.<sup>33</sup>

Influenza vaccination is recommended at any stage of pregnancy to protect both the mother and infant. During the prenatal care period, every opportunity should be used to ensure the pregnant mother has been vaccinated.

## Influenza Vaccination Promotion and Communication

Communication is critical to increase the acceptability and uptake of influenza vaccines. Messages should be adapted and tailored-made for the different audiences and local cultures. Among countries that focus on targeting high risk groups, boosting vaccination coverage will depend largely on effective communication strategies, the engagement of the scientific community and the proactive role of the healthcare personnel. Obtaining endorsements from professional societies, such as associations of obstetricians/gynecologists, infectious disease specialists, midwives, and national immunization technical advisory groups have proven to increase adherence to influenza vaccination.<sup>35</sup>

## Conclusion

In conclusion, influenza vaccines are safe and effective in preventing disease and reducing economic burden. Current efforts to measure vaccine performance and impact, complemented by disease burden and economic studies may help health authorities sustain investments in influenza vaccines. In addition to preventing disease burden, comprehensive seasonal influenza vaccination activities (including anticipating vaccine procurement needs, targeting the array of high-risk groups, effective communication, and planning the technical and operational aspects in advance) constitute the best way to prepare for a future influenza pandemic.

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