11

Influenza

Non-live trivalent vaccine introduced in 1988
Non-live quadrivalent vaccine introduced in 2019
Live attenuated influenza vaccine introduced in 2020
Adjuvanted quadrivalent vaccine introduced in 2021

NOTIFIABLE

In some circumstances, advice in these guidelines may differ from that in the Summary of Product Characteristics (SmPC) of the vaccines. When this occurs, the recommendations in these guidelines, which are based on current expert advice from NIAC, should be followed.

Key Changes

17 December 2021

- Influenza vaccines
  - QIV cell based (not currently available)

15 October 2021

- Influenza vaccines
  - QIV high dose (not currently available)
  - QIV recombinant (not currently available)

24 September 2021

- Contraindications
  - Those with primary autoimmune neutropoenia can receive influenza vaccine unless contraindicated

3 September 2021

- Introduction
- Influenza vaccines
- Dose and route of administration
  - adjuvanted QIV
- Recommendations
  - adjuvanted QIV for those aged ≥65 years
  - definition of a carer and an at risk person
- Precautions
- Co-administration
- Adverse reactions
  - adjuvanted QIV

11.1. Introduction

Influenza is an acute illness of the respiratory tract with systemic symptoms. It affects all age groups and is characterised by the abrupt onset of fever, headache, myalgia, cough, sore throat and malaise. It is usually self-limited, with recovery in 2-7 days, but it can be severe.

Influenza is caused by a highly infectious RNA virus that spreads rapidly, especially in institutions. There are three types of influenza virus, A, B and C. Types A and B cause most influenza illness.

Influenza outbreaks occur most years (Fig 11.1), with the extent and severity varying widely. In some outbreaks, influenza A and B viruses circulate simultaneously. Pandemics provide the most dramatic evidence of the impact of influenza, although outbreaks that occur between pandemics account for greater mortality and morbidity, albeit over a longer period of time. Since 2009, influenza A (H1N1 2009), influenza A (H3N2) and influenza B have been in circulation.

Influenza A viruses infect a wide range of animal and avian species, particularly waterfowl. They have two surface antigens- haemagglutinin (H) and neuraminidase (N). The viruses are divided into subtypes, based on their H and N content. Only H1, H2, H3, N1 and N2 have been implicated in widespread human infection. Periodic mutations of the surface antigens occur. Minor changes (antigenic drift) are seen from season to season, and are the reason why the vaccine composition changes each year. Major changes (antigenic shift) occur periodically and result in an immunologically distinct virus, facilitating pandemic spread with the potential for severe morbidity and high mortality. The most recent pandemic was in 2009/2010, caused by H1N1 (2009) virus. Most seasonal influenza is caused by Type A.

Influenza B viruses only infect humans and seals. This limited host range is likely to be the reason for the lack of Influenza B virus -caused pandemics. Mutations rarely occur in influenza B. Type B causes outbreaks every few years. The illness is generally less severe than that caused by Type A.

Influenza C is a common cause of mild upper respiratory tract illness. It infects humans and pigs. Lower respiratory tract complications and systemic illness are uncommon and occur mainly in children. Most people have acquired immunity by adulthood.

Influenza epidemics begin abruptly, reach a peak over a 2-3 week period, generally last for 2-3 months and often subside as rapidly as they began. Epidemics in temperate climates begin almost exclusively during late Autumn.

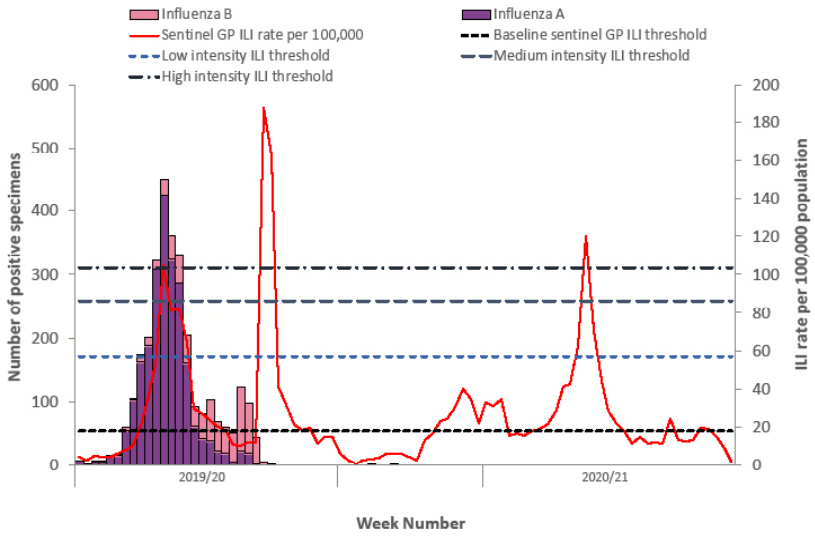
Since the start of the COVID-19 pandemic, influenza activity globally has remained at low levels. In Ireland, no confirmed influenza cases or hospitalisations were notified during the 2020/2021 season to May 2021.

The World Health Organization (WHO) has advised that current influenza surveillance data should be interpreted with caution.

The ongoing COVID-19 pandemic has influenced health seeking behaviours, surveillance and reporting in sentinel sites. Public hygiene and social measures implemented to reduce SARS-CoV-2 virus transmission have likely played a role in reducing influenza virus transmission.

Figure 11.1 Sentinel GP Influenza-like illness (ILI) consultation rates per 100,000 population, baseline ILI threshold, medium and high intensity ILI thresholds and number of positive influenza A and B specimens tested by the NVRL, by week and season (2019 - 2020).

Source: ICGP and NVRL



11.2. Transmission

Influenza is spread from person to person by aerosol, droplets or by contact with materials recently contaminated by respiratory secretions.
It is highly infectious, especially in close contact environments such as homes for the elderly. It is contagious from 1- 2 days before to 4-5 days after symptom

onset. Shedding can be more prolonged in young children and in the immunocompromised. Asymptomatic carriers may shed the virus.

11.3. Effects of influenza

Although infection may be asymptomatic in up to 75% of cases, influenza outbreaks result in significant morbidity. The incubation period is 1-4 days. Onset is sudden, with fever, rhinitis, cough, myalgia and headache. Pneumonia, either primary viral or secondary bacterial, can occur. Symptoms generally last for 3-5 days, and recovery is usually rapid.

The illness is more severe in the elderly, in those with chronic heart or lung disease, in children aged<4 years or with cerebral palsy and in pregnant women.

Eighty to 90% of reported deaths from influenza occur in the elderly, mainly from secondary bacterial pneumonia, but also from exacerbations of underlying disease e.g. chronic obstructive pulmonary disease or cardiac disease.

11.4. Influenza vaccines

Annual revaccination is recommended because immunity declines during the year after vaccination and circulating strains of influenza virus change from year to year.

Vaccines recommended by WHO are prepared each year, using virus strains similar to those considered most likely to circulate in the forthcoming season.

All licensed influenza vaccines comply with the WHO (Northern hemisphere) recommendations for the 2021/2022 season.

Two types of influenza vaccine are licensed: non-live influenza vaccines and live attenuated influenza vaccines (LAIV).

- *Non-live quadrivalent influenza vaccines (QIV)* contain antigens from two type A and two type B virus strains, cultured in fertilised hens' eggs or cell lines.

  All parenteral influenza vaccines are supplied in a prefilled syringe for IM injection.

- *Live attenuated quadrivalent influenza vaccine (LAIV)* is a reassortant influenza virus vaccine containing antigens from two type A and two type B virus strains, produced in Vero cells and cultured in hens' eggs. The

vaccine complies with WHO recommendation (Northern hemisphere) recommendation for the 2021/2022 season.

The vaccine is provided as a nasal spray suspension.

Influenza vaccines provide seasonally variable protection of 40-90% against influenza. Protective efficacy is lower in the elderly and the immunocompromised. However, influenza associated morbidity and mortality are significantly reduced in older people who have been vaccinated. Protection lasts about one year.

An up-to-date list of licensed vaccines can be accessed on the HPRA website www.hpra.ie

A list of the currently available vaccines from the National Cold Chain Service can be found at www.immunisation.ie

Influenza vaccines should be stored at +2 to +8°C.

If a vaccine has been frozen, it should not be used.

Licensed indications

Non-live quadrivalent influenza vaccine (QIV): active immunisation of adults and children for the prevention of influenza disease caused by the two influenza A virus subtypes and the two influenza B virus types contained in the vaccine.

Non-live adjuvanted quadrivalent inactivated influenza vaccine (aQIV): active immunisation against influenza in the elderly (65 years of age and over), especially those with an increased risk of associated complications.

Non-live quadrivalent influenza vaccine high dose (QIV-HD): active immunisation in adults 60 years and older for the prevention of influenza disease.

Non-live quadrivalent influenza vaccine recombinant (QIVr): active immunisation for the prevention of influenza disease in adults.

Non-live quadrivalent influenza vaccine cell based (QIVc): active immunisation for the prevention of influenza in adults and children from 2 years of age.

Live attenuated quadrivalent influenza vaccine (LAIV): prophylaxis of influenza in children and adolescents from 24 months to less than 18 years of age caused by the two influenza A virus subtypes and the two influenza B virus types contained in the vaccine.

LAIV should not be used below 24 months of age because of safety concerns regarding increased rates of hospitalisation (for any cause) and wheezing in this population.

LAIV is more effective in children than non-live influenza vaccines. In addition, LAIV may offer some protection against strains not contained in the vaccine, as well as strains that have undergone antigenic drift.

Since LAIV contains live attenuated viruses, it mimics natural infection, which induces more durable immune memory (thereby offering better long-term protection to children than non-live influenza vaccines).

As the vaccine viruses are cold adapted, they cannot replicate efficiently at body temperature. Millions of doses of LAIV have been administered in the US for over 10 years and serious illness amongst immunocompromised contacts inadvertently exposed to vaccine virus has never been observed.

Note: After LAIV administration, a positive influenza PCR result can be obtained from upper respiratory samples for up to 7 days and rarely longer.

Dose and route of administration

QIV (for those aged 6 months to 64 years)

The dose is 0.5ml given by intramuscular injection into the anterolateral thigh or deltoid.

Children under 9 years of age and those in specific at risk groups require two doses of vaccine separated by 4 weeks if receiving influenza vaccine for the first time or if their vaccination history is unknown.

All others and children aged 6 months to <9 years who have received influenza vaccine before require one dose of vaccine (Table 11.1).

Table 11.1 Schedule for QIV

Group	Number of doses
Children aged 6 months to <9 years	Two doses 4 weeks apart, if • receiving influenza vaccine for the first time or • vaccination history is unknown
Those aged 9-64 years if: • post haematopoeitic stem cell transplant • post solid organ transplant	Two doses 4 weeks apart, if receiving influenza vaccine for the first time post-transplant
Cancer patients aged 9-64 years who receive the vaccine while on chemotherapy and who complete their treatment in the same season*	Two doses Second dose at least 4 weeks after completion of chemotherapy and at least 4 weeks after 1st dose (regardless of influenza vaccination in previous seasons)
All others	One dose

* If the lymphocyte count is ≥1.0 x10^9/L

aQIV (for those aged 65 years and older)
The dose is 0.5ml given by intramuscular injection into the deltoid.

All those aged 65 and older require one dose of aQIV. A second dose is not required for those post haematopoeitic stem cell transplant, post solid organ transplant or cancer patients who receive aQIV while on chemotherapy and who complete their treatment in the same season.

LAIV (for those aged 2 to 17 years)
The dose is 0.1 ml into each nostril.

LAIV must **only** be given intranasally.

Post marketing effectiveness studies have shown that a second dose of LAIV is of little added benefit to healthy children. For this and for logistical reasons, healthy children should receive a single dose of LAIV. This recommendation is concordant with Finnish and UK recommendations.

Children aged 2 to <9 years in a clinically at risk group should receive two doses of LAIV, at least 4 weeks apart, if receiving any influenza vaccine for the first time or if their vaccination history is unknown (Table 11.2).

Table 11.2 Schedule for live attenuated influenza vaccine (LAIV)

Age Group	Dose
Children aged 2 to <18 years	One dose
Children aged 2 to < 9 years in a clinically at-risk group (section 11.5.2.iii)[1]	Two doses[2] 4 weeks apart, if: • receiving influenza vaccine for the first time or • the vaccination history is unknown

[1]LAIV is contraindicated in children
- on long-term aspirin therapy
- with severe immunocompromise due to disease or treatment (e.g. acute/chronic leukaemia, lymphoma, HIV positive not on highly active antiretroviral therapy, cellular immune deficiency, high dose steroids ≥0.5mg/kg/day in children <40kgs or other immunosuppressing drugs).
[2] QIV can be given for the second dose if LAIV is unavailable

If the child sneezes or blows their nose after LAIV administration, neither dose needs to be repeated.

Influenza antibodies take from 10-14 days to reach protective levels following vaccination.

11.5. Recommendations

The ideal time for vaccination in Ireland is before the influenza season, i.e. from September to October, but the vaccine maybe given until the end of April.

Note: if travelling to the Southern hemisphere refer to Chapter 5.

11.5.1 ***LAIV*** is recommended for all children aged 2 to 17 years.

11.5.2 ***aQIV*** is recommended for those aged ≥65 years.

11.5.3 ***QIV*** is recommended for

i. Those aged 2 to 17 years for whom LAIV is contraindicated

ii. Those aged 50 to 64 years

iii. Those aged 6 months to < 2 years and those aged 18 to 49 years at increased risk of influenza- related complications:
   - Those with chronic illness, e.g. chronic heart disease (including acute coronary syndrome), chronic liver disease, chronic neurological disease (where the neurological condition compromises clearance of respiratory secretions), chronic renal failure, chronic respiratory disease (including chronic obstructive pulmonary disease, cystic fibrosis, moderate or severe asthma, and bronchopulmonary dysplasia), diabetes mellitus, or haemoglobinopathies
   - Those with immunosuppression due to disease or treatment, including asplenia or hyposplenism, and all cancer patients
   - Those with any condition that can compromise respiratory function (e.g. spinal cord injury, seizure disorder, or other neuromuscular disorder,) especially those attending special schools/ day centres
   - Children and adults with Down syndrome
   - Children with moderate to severe neurodevelopmental disorders such as cerebral palsy and intellectual disability
   - Children on long-term aspirin therapy (because of the risk of Reye syndrome)
   - Those with morbid obesity (Body mass index >40)
   - Residents of nursing homes, old people's homes, and other long stay facilities where rapid spread is likely to follow introduction of infection

iv. Those likely to transmit influenza to a person at high risk for influenza complications (section iii)

[1] Persons with an underlying chronic health condition or Down syndrome
[2] A carer is someone who provides ongoing significant level of care to a person who is in need of care in the home due to illness or disability or frailty (HSE)

- Health Care Workers (HCWs), both for their own protection and for the protection of patients who may have a suboptimal response to influenza vaccinations (Chapters 3 and 4)
- Household contacts of at-risk persons[1]
- Out-of-home care givers[2] to at-risk persons[1].

v. Pregnant women at any stage of pregnancy

Pregnancy increases the risk of complications from influenza because of alterations in heart rate, lung capacity, and immunological function. Because non-live influenza virus vaccine is not a live vaccine it is very safe in pregnancy.

vi. People who have close, regular contact with pigs, poultry or water fowl.

Anyone who wishes to reduce their own or their child's risk of infection may choose the influenza vaccine for themselves and/or their child.

Contraindications

All influenza vaccines

- Anaphylaxis following a previous dose of influenza vaccine or any of its constituents (*other than ovalbumin – see precautions*)
- Those with severe neutropoenia (absolute neutrophil count <0.5 × 10^9/L) should not receive any vaccines, to avoid an acute vaccine related febrile episode. This does not apply to those with primary autoimmune neutropoenia who can receive influenza vaccine unless contraindicated.
- Receiving combination checkpoint inhibitors (e.g. ipilumumab plus nivolumab), because of a potential association with immune related adverse reactions.

LAIV

- Asthma
  - Those experiencing an acute exacerbation of asthma, including those who have had increased wheezing and/or needed additional bronchodilator treatment in the previous 72 hours
  - Seek specialist advice for those who require regular oral steroids or who have previously required ICU care for asthma
- Children who live with severely immunocompromised persons requiring isolation (e.g. post haematopoietic stem cell transplant)

- Concomitant use of aspirin/salicylates, because of the association of Reye syndrome with salicylates and wild-type influenza infection
- Influenza antiviral medication within the previous 48 hours
- Pregnancy
- Significant immunocompromise due to disease or treatment (see Chapter 3)
- Those post cochlear implant until the risk of a CSF leak has resolved - consult with the relevant specialist
- Those with a cranial CSF leak.

QIV is recommended if LAIV is contraindicated.

LAIV is not contraindicated for use in those with asymptomatic HIV infection, those who are receiving topical/inhaled corticosteroids or low-dose systemic corticosteroids or those receiving corticosteroids as replacement therapy, e.g. for adrenal insufficiency.

Precautions

All influenza vaccines

- Acute severe febrile illness, defer until recovery
- Egg allergy: Those with confirmed egg anaphylaxis or egg allergy can be given influenza vaccine in a primary care or school setting *with the exception of those who have required admission to ICU for a previous severe anaphylaxis to egg*.

  LAIV has an ovalbumin content of ≤0.024 micrograms per dose and egg free QIV vaccines have an ovalbumin content of ≤0.06 micrograms per dose. Adjuvanted QIV vaccine has an ovalbumin content equal to or less than 1 microgram per dose.

  LAIV is the preferred vaccine for children who have required admission to ICU for a previous severe anaphylaxis to egg as the intranasal route is less likely to cause systemic reactions; it should be given in hospital.

  Those requiring non-live influenza vaccine who have had a previous ICU admission for a severe anaphylaxis to egg should be referred for specialist assessment with regard to vaccine administration in hospital.

LAIV

Salicylates should not be used for 4 weeks after vaccination unless medically indicated, as Reye syndrome has been reported following the use of salicylates during wild-type influenza infection.

QIV

If influenza vaccine is recommended for children aged 12-23 months of age, it should be separated from PCV vaccine by at least 1 week. This is because of a slightly increased risk of febrile convulsions if the vaccines are given at the same time in this age group.

Note: There have been no reported cases of live vaccine virus transmission among health care workers. Health care workers, including those who are pregnant, should ensure they are appropriately vaccinated against influenza.

Co-administration

All influenza vaccines and other vaccines* (including COVID-19 vaccines) may be administered at the same time or at any interval.

As it is not known if COVID-19 vaccine reactogenicity is increased with co-administration, the vaccines should preferably be given in different limbs.

*except PCV for children aged 12-23 months (see Precautions above)

Adverse reactions

QIV

Local: Injection site pain and swelling are very common.

General: Fever, fatigue, myalgia, and irritability in young children are very common. Drowsiness, sweating and arthralgia are common.

Very rare: Immediate allergic reactions.

Very rare reports of Guillain-Barré syndrome (GBS) have been observed in the post-marketing setting following influenza vaccination. The incidence cannot be estimated from known data. The risk of GBS following influenza infection is several times greater than that following influenza vaccination.

aQIV

Local: Injection site pain is very common. Injection site bruising, erythema and redness are common.

General: Fatigue and headache are very common. Arthralgia, chills, diarrhoea, influenza like illness, loss of appetite, mylagia and nausea are common. Fever and vomiting are uncommon.

A higher incidence of mild post-immunisation reactions has been reported with adjuvanted compared to non-adjuvanted influenza vaccines.

Very rare: Immediate allergic reactions.

Very rare reports of Guillain-Barré syndrome (GBS) have been observed in the post-marketing setting following influenza vaccination. The incidence cannot

be estimated from known data. The risk of GBS following influenza infection is several times greater than that following influenza vaccination.

Injectable influenza vaccines are non-live and cannot cause influenza.

LAIV:

Local: Nasal congestion is very common.

General: Malaise is very common. Decreased appetite, headache, myalgia and fever are common. Fever is no more frequent than that following other recommended childhood vaccines, is generally mild and resolves in a few days.

Very rare: Immediate allergic reactions. Very rare reports of Guillain-Barré syndrome (GBS) have been observed in the post-marketing setting following influenza vaccination. The incidence cannot be estimated from known data. The risk of GBS following influenza infection is several times greater than that following influenza vaccination.

LAIV viruses cannot cause influenza as they are cold adapted and cannot replicate efficiently at body temperature.

11.6. Use of antiviral medication to prevent or treat influenza

Antivirals such as neuraminidase inhibitors can be used for treatment and prophylaxis of influenza during influenza outbreaks. If considering using antiviral medication check the HPSC website to ascertain if influenza is circulating and only use antivirals if this is confirmed.

Indications for prophylaxis include:

- Non-immunised persons in at risk groups, including health-care workers, for 2 weeks while the vaccine takes effect.
- Control of influenza outbreaks in a closed setting such as institutions with high-risk individuals.
- Protection of immunocompromised children who may not respond to vaccine.

Note: Use of antiviral medication within two weeks after LAIV administration may adversely affect the effectiveness of the vaccine.

11.7. Influenza surveillance

The Health Protection Surveillance Centre, the Irish College of General Practitioners (ICGP) and the National Virus Reference Laboratory (NVRL) have established a network of 60 sentinel practices who report on a weekly basis the number of patients seen with influenza-like illness. Virological confirmation by the NVRL is required to identify that influenza is the causative virus, with classification of type and sub-type.

Throughout the inter-season period weekly reports on clinical data, fortnightly reports on virological data and weekly or fortnightly surveillance reports are produced. Reports of worldwide influenza activity are also provided as part of the overall monitoring of influenza activity.

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