10 Influenza

Key information

Mode of transmission	Spread by droplets generated by sneezing and coughing, by direct or indirect contact, or by the aerosol route.
Incubation period	Usually 1–3 days (range 1–7 days).
Period of communicability	From 1–2 days before symptoms start until about day 5 of illness; may be longer in young children and if immunocompromised. Asymptomatic spread is common.
Incidence and burden of disease	Influenza epidemics occur each year. The highest burden of disease is in the very young, the elderly, pregnant women, those with co-morbid conditions, people from low income groups and Māori and Pacific ethnic groups.
Funded vaccines	• Quadrivalent inactivated split virion influenza vaccine: children aged 6 months to under 3 years (ie, aged 6–35 months): Afluria Quad Junior • adults and children aged 3 years and older: Afluria Quad.
Dose, presentation, route	0.25 mL for young children (age from 6–35 months) and 0.5 mL for older children and adults per dose Pre-filled syringe Intramuscular injection, or subcutaneous injection (if indicated)
Funded vaccine indications and recommended schedule	1 dose is recommended and funded annually from 1 April for: • pregnant women • individuals aged 65 years and older • individuals aged 6 months to under 65 years with eligible conditions (Table 10.3) • children aged 4 years or under who have been hospitalised for respiratory illness (including measles) or have a history of significant respiratory illness. Children aged under 9 years who have not previously received influenza vaccine require 2 doses 4 weeks apart (funded for children with eligible conditions).
Recommended, unfunded	Occupational: recommended for health care workers, teachers and support staff in schools and early childhood education and staff in long-term care and aged-care facilities. Recommended particularly for all close contacts (eg, caregivers, family members) of those at high risk from influenza. Universally recommended for anyone age from 6 months, annually.
Vaccine effectiveness	Depends on the match of the strains in the vaccine with circulating strains, the age of the individual and whether they have any underlying medical conditions. Vaccination can prevent disease or reduce severity.

Precautions and special considerations	Seek specialist advice for individuals who are currently being treated with immune checkpoint inhibitors, as well as those who have discontinued treatment within the past 6 months. There may be a small increased risk of fever and febrile convulsions with concomitant delivery of PCV13 and influenza vaccine in children aged 6 months to under 5 years.
Potential response to vaccine	Mild fever, headache, muscle aches, local swelling and mild pain at injection site. Children aged under 5 years are more likely than older children or adults to have a febrile reaction to influenza vaccine.

10.1 Virology

Influenza viruses belong to the Orthomyxoviridiae family, and are classified into influenza virus types A, B and C. Influenza A virus subtypes are classified based on two surface antigens:

- haemagglutinin (H), responsible for cell surface attachment during infection
- neuraminidase (N), which potentiates the release of new virions from the cell.

Subtypes which have in the past caused pandemics include the influenza A H1N1, H2N2, H3N2 and H1N1pdm09 viruses, while the H3N2 and H1N1pdm09 viruses continue to cause epidemics as seasonal influenza viruses. Influenza B has two lineages of viruses: B/Victoria and B/Yamagata, which are also associated with outbreaks and epidemics, and account for a significant proportion of the overall burden of influenza.[1] Influenza C is associated with mild cases of upper respiratory infection.

10.1.1 Antigenic drift

Influenza A and B viruses undergo frequent small changes (mutations) in their segmented RNA genome over time. The mutations can occur in the coding regions responsible for H and N surface antigens. This 'antigenic drift' leads to the emergence of new antigenic variants or virus strains.

These new strains are described by the geographic site of isolation, laboratory number and year of isolation; for example, A/Hong Kong/4801/2014 (H3N2). Because of this ongoing antigenic drift, seasonal influenza virus vaccine formulations are reviewed by the WHO bi-annually.

10.1.2 Antigenic shift

New influenza A virus subtypes emerge periodically that have caused pandemics in humans. The new virus subtype has novel H and N surface antigens result from the mixing of genomic segments of two or more influenza A viruses. This is known as 'antigenic shift'. Other possible mechanisms for the emergence of new influenza viruses are through the adaptation of avian influenza viruses to infect humans and the re-assortment of the genomic segments of multiple viruses (ie, human, avian and pig influenza viruses).

10.2 Clinical features

Influenza is contagious, with a reproductive number (R0) estimated at 1.4–4 (see section 1.2.1).[2] The virus is transmitted by respiratory droplets generated by sneezing and coughing that land directly on respiratory mucous membranes by aerosolised droplets or by direct or indirect contact (via contaminated hands or fomites).[2, 3, 4] The incubation period can range from one to seven days (average one to three days), during which time the virus replicates in the ciliated columnar epithelial cells of the upper and lower respiratory tract. An infected person is contagious from one to two days before symptoms start until about day five of the illness. Peak viral shedding occurs one to three days after the development of symptoms, diminishing to low levels by five days. Children shed more virus and remain infectious for longer than adults.

There is a wide range of symptoms, from asymptomatic to severe disease. Mild influenza with non-specific symptoms is common, resulting in a large proportion of viral transmission and undetected infections.[5] In older children and adults, the illness characteristically begins abruptly with fever and a variety of clinical symptoms, including chills, malaise, headache, myalgia, non-productive cough, rhinitis, sore throat and mild conjunctivitis. Vomiting and diarrhoea may be present. While children aged under 5 years have fever, cough and rhinitis, infants may present with unexplained fever or sepsis-like syndrome only.[3] In the young, influenza virus may cause croup, bronchiolitis and pneumonia. Fever is often less evident in the elderly, who may present with other symptoms, such as anorexia, fatigue or confusion. Influenza typically resolves after several days in most people, although cough and malaise may persist for two or more weeks.

Infections due to pandemic influenza A strains are more likely to lead to severe morbidity and increased mortality than influenza B or seasonal influenza A strains.

Influenza B infections were previously thought to generally cause more mild illness, but numerous studies indicate that there is little difference between clinical symptoms and outcomes of influenza B compared to influenza A.[1] Influenza B-associated hospitalisations and mortality may have previously been underestimated; studies have reported higher mortality following influenza B infection than A in some years.[1] Influenza B infection is more common in children aged 5–17 years than in other age groups, and disease is likely to be more severe in children than in adults.[6]

Influenza can exacerbate underlying medical conditions, such as pulmonary, cardiac or metabolic disease. Some of the many reported complications associated with influenza include pneumonia, respiratory failure, myositis, encephalopathy, myocardial infarction, myocarditis and pericarditis, Reye syndrome (associated with aspirin use in children), bronchitis, otitis media and death. The risk of complications is increased in pregnancy.[7] Also associated with influenza infection is increased frailty and cognitive decline in older people and incidence of cardiovascular disease are also associated with influenza infection.[8, 9] Influenza during pregnancy can result in poorer outcomes for the mother and her fetus, including preterm birth and fetal loss.[10, 11]

Asymptomatic influenza

The majority of influenza infections are asymptomatic, and most symptomatic cases self-manage without seeking medical help.[12, 13] Results from the 2015 New Zealand Southern Hemisphere Influenza and Vaccine Effectiveness, Research and Surveillance (SHIVERS) serosurvey showed that around 32 percent of people surveyed had serologically confirmed influenza over the 2015 season (adjusted for age and ethnicity).[5, 14] Overall only one-quarter of those reported influenza-like illness; three out of four people were asymptomatic; only 1 out of 47 visited their GP and 1 in 680 were hospitalised. Young children and Pacific people experienced the highest influenza infection attack rates.[15]

10.3 Epidemiology

10.3.1 Global epidemiology

Influenza is an important cause of disease worldwide. Annual epidemics are estimated to result in about 3 to 5 million cases of severe illness, and about 290,000 to 650,000 respiratory deaths globally.[16, 17] For example, it was estimated globally that 11.5 percent of lower respiratory tract infections (LRTI), 5.6 percent of LRTI deaths and 9.5 million LRTI hospitalisations were attributable to influenza in 2017.[18]

In temperate climates, seasonal epidemics occur mainly during winter, while in tropical regions, influenza occurs throughout the year causing outbreaks more irregularly.[16]

From time to time, pandemics occur when a new virus arises and spreads globally (see section 10.3.3). The last influenza pandemic was caused by the A(H1N1)pdm09 virus. More than 214 countries and overseas territories reported laboratory-confirmed influenza, including over 18,449 deaths.[19] Many more deaths were found to associated with the pandemic due to respiratory and cardiovascular complications.[20]

10.3.2 New Zealand epidemiology

New Zealand experiences the typical temperate climate epidemiology of influenza, with the peak incidence occurring during the winter months, however, influenza activity occurs throughout the year.

The impact of influenza in New Zealand is substantial in terms of general practice consultations, hospitalisations and deaths. The highest burden of disease is in the very young, the elderly, pregnant women, those with co-morbid conditions, people from low-income groups, and Pacific and Māori ethnic groups.

Influenza surveillance

The New Zealand influenza surveillance system compiles information from a variety of sources, including:

- national sentinel general practice-based influenza-like illness surveillance (part of the WHO's Global Influenza Programme)
- year-round laboratory-based surveillance by the regional virus diagnostic laboratories
- hospital-based severe acute respiratory infection surveillance in Auckland and Counties Manukau DHBs
- data from Healthline, HealthStat, publicly funded hospital discharges and the NIR.

Influenza prevalence and circulating strains are monitored through general practice surveillance for influenza-like illness (ILI); hospitalisations are monitored for severe acute respiratory infection (SARI) admissions; and severity is determined by the proportion of hospitalisations requiring intensive care unit (ICU) admission.[21]

For example, during the 2019 season the levels of influenza-like illness and the overall impact were low and generally just above seasonal baseline.[22] However, SARI hospitalisation rates increased earlier than in previous years and, during the winter, a higher than usual proportion of viral respiratory illnesses were due to influenza. A(H3N2) and B/Victoria strains were co-circulating. Seriousness was similar to other A(H3N2) predominant years. Influenza A viruses were detected most frequently in hospitalised patients whereas influenza B was detected more in the community. In contrast, in 2018 the predominant strain was A(H1N1)pdm09 strain which is associated with high severity in those aged younger than 65 years.[23] Over one-half of those admitted to ICUs with influenza-associated SARI in 2018 did not report any pre-existing medical risk factors, consistent with being younger.[23]

For detailed information, including influenza surveillance and influenza reports, see the ESR website (**www.surv.esr.cri.nz/virology/virology.php**).

Influenza immunisation uptake

In 2019, more than 1.35 million doses of influenza vaccine were distributed. This equated to just over one quarter of the whole population (270 doses per 1,000 population).[22] According to Ministry of Health data, publicly funded influenza vaccine uptake for individuals aged 65 years and older was around 63 percent in 2019 based on reporting from funding claims; this is likely to be an underestimate of the coverage. National influenza immunisation coverage for DHB staff increased from 45 percent in 2010 to 73 percent (ranging from 54 to 87 percent) in 2019, but remained below the goal of 80 percent coverage across all DHB staff.[24]

10.3.3 Pandemic influenza

The natural ecology of influenza type A viruses is among wild aquatic avian species, and from time to time, these viruses spill over into other species, including humans. These avian influenza virus infections are usually severe and associated with a high mortality; however, they are rarely transmitted from human to human. In the past, avian viruses have become transmissible either through adaptation or the acquisition of swine or human genomic material, and when natural immunity has been lacking in the population, have resulted in a pandemic with global spread. There have been four influenza pandemics recorded since 1918.

Pandemics have the potential to result in large numbers of severe infections, but the degree of severity is hard to predict and will depend upon many factors, including whether there is any previous community immunity. The most severe recorded influenza pandemic was the 'Spanish flu' A(H1N1) pandemic of 1918–1920, which caused an estimated 20–50 million deaths worldwide. The most recent pandemic was the 2009 A(H1N1)pdm09 strain. It was estimated that 18 percent (800,000) of the New Zealand population were infected with the virus during the first wave, including one in every three children.[25] Risk factors for severe outcomes included obesity, pregnancy,[26] diabetes mellitus and Pacific or Māori ethnicity.[25] This strain is now established as a circulating seasonal influenza strain.

Globally, in the first 16 months of the 2009 H1N1 influenza pandemic, 18,500 deaths were attributed to laboratory-confirmed influenza. When investigated further, it was estimated that over 201,000 respiratory deaths and an additional 83,300 cardiovascular deaths were associated with the pandemic – producing a rate 15 times higher than the laboratory-confirmed deaths. Of these deaths, 80 percent were younger than 65 years of age.[20]

Monitoring, surveillance and response for new pandemic strains are in place. See section 10.8.3.

10.4 Vaccines

Annual influenza vaccination is a most important measure for preventing influenza infection and mortality. The National Influenza Strategy Group, coordinated by IMAC, is responsible for New Zealand's annual National Influenza Promotional Campaign (**www.influenza.org.nz**). This campaign includes an annual influenza kit for health care professionals and a national education and communication programme.

10.4.1 Available vaccines

Funded vaccines

Two quadrivalent split virion influenza vaccines are funded.

- **Afluria Quad (Seqirus) for adults and children from 3 years of age**[27]

Each 0.5 mL dose contains 15 µg of each of the four recommended influenza strains; other components and excipients include sodium chloride, dibasic sodium phosphate, monobasic sodium phosphate, potassium chloride, monobasic potassium phosphate, calcium chloride dihydrate and water for injections to 0.5 mL. Trace amounts of the following may also be present in each 0.5 mL dose: sodium taurodeoxycholate, ovalbumin (<0.1 µg), sucrose, neomycin sulfate, polymyxin B sulfate and propiolactone

- **Afluria Quad Junior (Seqirus) for infants and children aged 6 months to under 3 years (ie, aged 6–35 months)**

Each 0.25 ml dose of Alfuria Quad Junior (Seqirus) contains 7.5 µg of haemagglutinin of each of the same four influenza strains that are in Alfuria Quad.

Availability of influenza vaccines, particularly the unfunded vaccines, can vary during the season depending on demand and supply (see **www.influenza.org.nz**).

Vaccine preparations and potential future options

Influenza vaccine preparations vary by their type, the number of influenza strains contained in the vaccine and their delivery systems. There are a range of delivery mechanisms available internationally, including intradermal injection and intranasal mists. Live attenuated influenza vaccines are delivered by intranasal spray. Some data suggest that intradermal vaccines may induce improved immune responses, particularly in older adults.[28, 29]

The seasonal influenza vaccine strains vary each year depending on the prevailing viruses. WHO conducts technical consultations in February/March and September each year to recommend viruses for inclusion in both trivalent and quadrivalent vaccines for the northern and southern hemisphere influenza seasons, respectively. In recent years, the southern hemisphere recommendations include the two influenza type A (H1N1pdm09 and H3N2) and two B (Victoria and Yamagata) strains likely to circulate in New Zealand over the coming influenza seasons.[30]

Split virion influenza vaccines

Only quadrivalent split virion influenza vaccines were available in New Zealand for the 2020 influenza season.

Quadrivalent influenza vaccines (QIVs) contain two type A and two type B influenza strains. They are split virion vaccines prepared from virus grown in embryonated hens' eggs. The virus is purified, disrupted and inactivated by splitting with beta-propiolactone or formaldehyde. QIVs offer broader protection against co-circulating B-strains and better effectiveness in seasons of B-strain mismatch than trivalent influenza vaccines (TIVs), which contain two influenza type A strains and one type B strain.[1]

Live attenuated influenza vaccines

At the time of writing, live attenuated influenza vaccines (LAIVs) were not registered in New Zealand.

LAIVs may induce stronger immune responses than TIV or QIVs, particularly in children, by mimicking natural influenza infection and evoking both mucosal and systemic immunity, including broader cellular immune responses.[31] Trivalent and quadrivalent LAIVs are licensed for use in North America for healthy non-pregnant individuals aged 2–49 years and in Europe for children aged 2–18 years.[32] LAIVs have been shown to be effective in children aged 6 months to 7 years.[33]

During the 2013/14 and 2015/16 influenza seasons, effectiveness of LAIV against the predominant A(H1N1) strain was lower in the US in children age 2–17 years than that observed in the UK during the same seasons, such that the US Advisory Committee on Immunization Practices (ACIP) temporarily withdrew its recommendations for LAIVs use during 2016/17 influenza season.[32, 34] LAIVs were reinstated during the 2019/2020 season.

UK data from the 2018/19 season showed that LAIV effectiveness in children aged 2–17 years was at least as good as QIV in children for whom LAIV is contraindicated, particularly against A(H1N1)pdm09.[34, 35, 36] It is remains unclear why there were such significant differences in effectiveness for different regions, although variations in circulating strain matches, the make-up of the LAIV itself and previous vaccination history may all have some effect.[34]

Adjuvanted and high-dose vaccines

For the 2020 season, influenza vaccines containing adjuvants or high-dose formulations were not available in New Zealand. Evidence to compare adjuvanted, high-dose and quadrivalent vaccines is currently limited and research is ongoing to evaluate their application.

Adjuvants enhance the immune response to an antigen and require less antigen (antigen sparing). Internationally, there are three adjuvants licensed for use in influenza vaccines: two oil-in-water emulsions and a third that uses immunopotentiating reconstituted influenza virosomes.[3] Vaccines with these adjuvants show modestly improved immune responses, which may be particularly useful for the elderly and young children, but may also cause more local and systemic reactions than unadjuvanted vaccines.[3, 37]

High-dose influenza vaccines containing four times more haemagglutinin antigen than standard vaccines have been shown to be more effective against influenza-related death and all-cause hospitalisation in the elderly than standard-dose trivalent vaccines.[38]

10.4.2 Efficacy and effectiveness

International data

The efficacy (prevention of illness among vaccinated individuals in controlled trials) and effectiveness (prevention of illness in vaccinated populations) of influenza vaccine depends on several factors. The age and immune competence of the vaccine recipient are important factors, as well as the match between the virus strains in the vaccine and those in circulation each year. Mismatches can evolve during a season or due to mutations occurring during vaccine manufacture (egg adaptation).[35] Previous vaccination history has been suggested to reduce the vaccine effectiveness in some cases; possibly more so when the previous vaccination was mismatched with the circulating strains at the time.[39] More recently, prior-season vaccination history has not been associated with reduced vaccine effectiveness in children or adults, and findings support annual revaccination.[35, 40, 41, 42, 43] With increasing complexity, this continues to be researched.

Two influenza B strains can frequently co-circulate, and due to the challenges involved in predicting which B strains will circulate in the upcoming season, mismatches between the B strain selected for TIVs and the circulating B strains have occurred in up to one-half of influenza seasons. The capacity of QIVs (containing two B influenza strains) to provide broader immune responses against B strains and cross-protection during B-mismatched seasons is expected to prevent more influenza cases, hospitalisations and deaths than TIVs.[1]

Data for vaccine efficacy and effectiveness of TIVs is summarised in Table 10.1.

Table 10.1: Current estimates of TIV influenza vaccine efficacy and effectiveness

Population	Type of outcome	Level of protection (95% confidence intervals)	Ref
Pregnant women	Effectiveness		
	• against confirmed influenza	50% (15–71%)	44
	• against acute respiratory illness		45
	– requiring an ED visit	81% (31–95%)	
	– or hospitalisation	65% (3–87%)	
Infants aged under 6 months whose mothers received an influenza vaccination during pregnancy	Effectiveness		
	• against confirmed influenza	41% (7–63%) to 49% (12–70%)	46 44
	• against influenza-related hospitalisation	47% (12–68%)	47
Healthy children	Effectiveness		
• aged under 2 years	• against confirmed influenza	Insufficient data under 2 years 66% (9–88%)	33, 48 49
• aged 6–35 months		66% (29–84%)	49
• aged 6 months to 17 years	• against influenza-related death	65% (47–78%)	50
• aged 2–15 years	Efficacy against confirmed influenza	64% (52–72%)	48
	Effectiveness		
	• against influenza-like illness	28% (21–35%) to 47% (33–58%)	48
	• against influenza-related hospitalisation	56% (12–78%)	51
Children with high-risk conditions aged 6 months to 17 years	Effectiveness against influenza-related death	51% (31–67%)	50
Healthy adults (aged 18–64 years)	Effectiveness		
	• against confirmed influenza	59% (53–64%) to 66% (55–75%)	52
	• and influenza-like illness	16% (5–25%) to 18% (2–31%)	
	• against influenza-related hospitalisation in New Zealand	61% (34–77%)	53
	• against influenza-like illness general practice visit in New Zealand	55% (24–73%)	

Continued overleaf

Population	Type of outcome	Level of protection (95% confidence intervals)	Ref
Adults with high-risk conditions: • heart failure • diabetes (newly diagnosed, aged 65 years or older) • chronic obstructive pulmonary disease	Risk of: • all-cause mortality • all-cause mortality • influenza-related hospitalisation Effectiveness against influenza-related hospitalisation	17% reduced risk 56% reduced risk 11% reduced risk 22% (15–27%) to 43% (34–52%)	54 55 56
Adults aged 40 years or older	Effectiveness against acute myocardial infarction	29% (9%–44%)	57
Adults aged 65 years or older	Effectiveness • against confirmed influenza • against influenza-like illness • against non-fatal and fatal complications	49% (33–62%) 58% (34–73%) 39% (35–43%) 41% (27–53%) 28% (26–30%)	58 59 58 59 59

Vaccine effectiveness in New Zealand

New Zealand data is consistent with international data. While there is some variability from year to year and with different strains, the data overall show that the point estimate for influenza vaccine effectiveness is approximately 50 percent for preventing general practice visits, hospitalisations and for both influenza type A and B strains.[53, 60, 61, 62] Estimates for vaccine effectiveness tend to be higher in children and healthy midlife adults, and lower in the elderly. Influenza vaccination significantly reduces influenza-associated ICU admissions and attenuates disease severity in adults who were infected despite vaccination.[63]

Low influenza activity over recent years in New Zealand can cause imprecision in estimating annual vaccine effectiveness.[23, 64]

Pregnant women, the fetus and neonates

A pregnant woman and her fetus are at increased risk of influenza complications.[7] Physiological and immunological changes in pregnant women increase susceptibility to influenza.[65] Hospitalisation from influenza-related cardiorespiratory disorders during the second and third trimesters was especially apparent in the 2009 pandemic.[66] Influenza immunisation is therefore recommended during every pregnancy to reduce this risk, with similar effectiveness in healthy pregnant women as in other healthy adults against laboratory-confirmed influenza.[67] During the 2012–2013 seasons in Australia, women vaccinated in pregnancy were 81 percent less likely to attend emergency departments and 65 percent less likely to be hospitalised with acute respiratory illness than those unvaccinated.[45]

Influenza immunisation during pregnancy may reduce the incidence of stillbirth. Stillbirth was half as likely among vaccinated mothers compared to unvaccinated mothers in an Australian study.[11]

Maternal influenza immunisation offers protection to the newborn through maternal antibody transfer.[31, 47, 66, 68] Influenza vaccines are not registered and have not been shown to be effective in infants aged under 6 months: therefore, immunisation during pregnancy confers protection to newborns and infants who are too young to be vaccinated.[10, 46] Maternal influenza immunisation is significantly associated with reduced risk of influenza virus infection and influenza-related hospitalisation in infants up to 6 months of age and increased influenza antibody titres are maintained in infants through to age 2–3 months.[46, 69]

Children

Influenza vaccination in children provides similar protection to that seen in healthy adults. Effectiveness against laboratory-confirmed influenza is around 65 percent in young children aged 6 months to 5 years when vaccine and circulating strains are well-matched.[48, 49, 50] Influenza vaccination offers the greatest protection against influenza-related hospitalisation to children who are fully immunised with routine vaccines.[70] QIV vaccine effectiveness against influenza hospitalisation of children in the 2018 season in Australia was estimated to be 78.8 percent (95% CI 66.9–86.4); this was when Australia expanded the funded influenza vaccination programme to preschool children, those with comorbid medical conditions and all indigenous children.[71]

The additional benefit of vaccinating children is protection of those around them, including grandparents and infants.

Healthy adults

Generally, randomised placebo-controlled trials of TIV in healthy adults support good protection against laboratory-confirmed influenza.[52] Effectiveness against laboratory-confirmed influenza is around 60 percent in adults, but varies with the match of vaccine with circulating strains (see Table 10.1).

Adults aged over 65 years

Although currently available influenza vaccines are less effective at preventing clinical illness in older people,[72] influenza vaccination does reduce hospitalisation and deaths.

Effectiveness in community-dwelling adults aged over 60 years depends on how well the vaccine matches the circulating strains.[3] Influenza vaccine was moderately effective against laboratory-confirmed influenza during an epidemic season in community-dwelling adults age 65 year or older, irrespective of vaccine strain match. Significance was less during non-epidemic seasons and varied with virus type (the highest effectiveness was against A[H1N1] and the lowest against B).[73]

Vaccination has been demonstrated to prevent hospitalisation and death in older nursing home residents.[74, 75, 76, 77] A meta-analysis across 11 studies estimated influenza vaccination effectiveness to 37 percent (95% CI: 18–53; p=0.001) against pneumonia and 34 percent (95% CI: 10–53; p=0.01) against death due to pneumonia or influenza in institutionalised older adults.[78] A 2010 Cochrane review concluded that there was insufficient evidence to support influenza vaccine effectiveness in the elderly;[79] however, reanalysis of that review and its methodology argued that there is substantial evidence for the ability of influenza vaccine to reduce the risk of influenza infection and influenza-related disease and death in the elderly.[48, 58]

Severity of influenza symptoms are modestly attenuated by influenza vaccination in the elderly.[80] Therefore, by reducing severity of disease, vaccination can reduce the risk or duration of hospitalisation. Hospitalisation and immobility in the elderly leads to physical and mental decline, increased frailty and loss of independence.[8, 80, 81, 82]

Co-morbid conditions in adults and children

Influenza vaccination has been associated with reductions in hospitalisations and deaths among adults with risk factors for influenza complications, including diabetes,[83, 84] chronic obstructive pulmonary disease[85, 86] and heart failure.[54] Obese adults have a similar risk of influenza-associated hospitalisations as those with cardiovascular disease and diabetes.[87] Among Danish adults aged under 65 years with underlying medical conditions, vaccination reduced all-cause deaths by 78 percent and hospitalisations attributable to respiratory infections or cardiopulmonary diseases by 87 percent.[88] An Australian study of adults aged 40 years and older showed that unvaccinated adults are almost twice as likely as vaccinated adults to have an acute myocardial infarct.[89, 90]

Influenza vaccination is as effective as other preventative coronary care therapies (eg, smoking cessation, statins and antihypertensives) in protection against cardiovascular events.[90]

During the 2018 season in Australia, QIV vaccine effectiveness against influenza-related hospitalisation for children with comorbidities was estimated to be 77.3 percent (95% CI 59.8–87.2%).[71]

This highlights the importance of vaccinating children, as well as adults, with comorbidities against influenza.

Herd immunity

Influenza vaccination can provide indirect protection to those who are unimmunised or respond less well to the vaccine. This has been shown in certain settings, such as within schools and nursing homes.[3] There is evidence to suggest that herd immunity can be achieved, particularly by vaccinating children.[91]

The UK has progressively rolled-out a vaccination programme using LAIV and QIV, starting with children aged 2–3 years in 2013/14 and extended to children aged 4–7 years in 2015/16. As of the 2019/2020 season, influenza vaccine is offered in the UK to all children aged 2–10 years and up to 18 years for high risk groups. Early results from school-based pilot studies provided evidence of direct effect, indirect effects and overall impact, with decreases in disease incidence and influenza positivity in vaccinated and non-vaccinated groups.[92] A systematic review found that vaccination of children conferred indirect protection in some but not all settings.[93]

Some studies suggest that herd immunity may also be achieved in nursing homes if immunisation coverage of residents is greater than 80 percent.[94] Vaccinating health care workers is likely to be an effective strategy, particularly when in contact with high-risk patients.[13]

As shown by New Zealand SHIVERS data,[5] most people who catch the virus are asymptomatic or have very mild symptoms but are at risk of spreading it, such that increased vaccine uptake (funded and unfunded) across the whole population, from 6 months of age, is likely to achieve the greatest protection.

Duration of immunity

Due to the continual drift of influenza viruses, duration of immunity provided by influenza vaccines is difficult to study. However, when the strains stay the same for consecutive years, vaccination in a previous year appears to confer immunity into the next year for healthy adults and children.[3, 32] However, shorter duration of immunity is likely in other groups, particularly the elderly.[32]

Protection due to LAIVs has been demonstrated to persist beyond a year.[95, 96]

10.4.3 Transport, storage and handling

Transport according to the *National Standards for Vaccine Storage and Transportation for Immunisation Providers 2017 (2nd edition)* (available at **www.health.govt.nz/publication/national-standards-vaccine-storage-and-transportation-immunisation-providers-2017**).

Store in the dark at +2°C to +8°C. Do not freeze.

10.4.4 Dosage and administration

The funded quadrivalent influenza vaccine should be administered by intramuscular, or subcutaneous injection, if indicated (see section 2.2.3). The contents of the syringe must be shaken thoroughly before use.

Individuals aged 9 years and older

Individuals aged 9 years and older receive a single 0.5 mL intramuscular dose of a QIV vaccine.

Children aged under 9 years

Children aged under 9 years who have not previously received influenza vaccine require two doses of vaccine four weeks apart to produce a satisfactory immune response. Children aged 6 months to under 3 years (ie, aged 6–35 months) receive a 0.25 mL dose of Afluria Quad junior; children aged 3 years and older receive a 0.5 mL dose of Afluria Quad (see Table 10.2).

Table 10.2: Recommended influenza vaccine doses in children

Age	Vaccine	Dose	Number of doses
6–35 months	Afluria Quad Junior	0.25 mL	1 or 2*
3–8 years	Afluria Quad	0.5 mL	1 or 2*

* Two doses separated by at least four weeks if the vaccine is being used for the first time. The recommended dosages for young children at different ages may vary between vaccine manufacturers, so check the manufacturer's data sheet before administering.

Immunocompromised individuals

Regardless of their age, previously unvaccinated immunocompromised individuals or those who have received a solid organ or haematopoietic stem cell transplant are recommended to receive two doses of influenza vaccine, four weeks apart (the second dose is unfunded).[97] One dose is then given in each subsequent year. (See section 4.3.)

Note: Seek specialist advice for individuals who are currently being treated with immune checkpoint inhibitors, as well as those who have discontinued treatment within the past six months. See 'Immune checkpoint inhibitor (immunostimulant) therapy' in section 4.3.2.

Co-administration with other vaccines

Influenza vaccine can be administered with other vaccines, such as pneumococcal polysaccharide vaccine, tetanus diphtheria acellular pertussis (Tdap) vaccine, the live attenuated herpes zoster vaccine[98] and the scheduled childhood vaccines. Concurrent administration of influenza vaccine and 13-valent pneumococcal conjugate vaccine (PCV13) carries an increased risk of fever.[99, 100] Separation of the vaccines by two days can be offered, but is not essential. (See also section 15.6.2.)

10.5 Recommended immunisation schedule

The optimal time to vaccinate people against influenza, particularly those in high-risk groups, is generally recommended from 1 April, annually, in advance of the usual May to September period of influenza virus activity. The vaccine can be given even when influenza virus activity has been identified, because protective antibody levels develop from four days after immunisation, with full protection after two weeks.[101] The vaccine should be administered annually to maintain immunity and to provide protection against new strains.

Vaccine effectiveness may be reduced in those at highest risk from influenza. Influenza vaccine is therefore recommended annually for everyone from the age of 6 months to reduce the spread of influenza virus and to protect against influenza-related complications. It is particularly important to vaccinate contacts of high-risk individuals, such as family and caregivers, and those working in certain occupations. See Table 10.3 for a summary of the funded and unfunded recommendations for influenza immunisation.

See the National Influenza Promotional Campaign website (at **www.influenza.org.nz**) for further information.

Table 10.3: Influenza vaccine recommendations

Note: **Funded individuals are in the shaded rows.**

Refer to the Pharmaceutical Schedule (**www.pharmac.govt.nz**) for any changes to the funding decisions.

Recommended and funded
All individuals aged 65 years and older.
Individuals aged 6 months to under 65 years who: • have cardiovascular disease (ischaemic heart disease, congestive heart failure, rheumatic heart disease, congenital heart disease or cerebrovascular disease) • have chronic respiratory disease (asthma if on regular preventive therapy; other chronic respiratory disease with impaired lung function) • have diabetes • have chronic renal disease • have any cancer,[a] excluding basal and squamous skin cancers if not invasive • have other conditions (autoimmune disease, immunosuppression or immune deficiency,[a] HIV infection, transplant recipients, neuromuscular and central nervous system diseases/disorders, haemoglobinopathies, children on long-term aspirin, a cochlear implant, errors of metabolism at risk of major metabolic decompensation, pre- or post-splenectomy, Down syndrome) • are pregnant • are children aged 4 years and under who have been hospitalised for respiratory illness or have a history of significant respiratory illness, including children aged 6 to 59 months (ie, under 5 years) who have been hospitalised for measles • are patients who are compulsorily detained long-term in a forensic unit within a DHB hospital.[b]
Recommended but not funded
Generally, this vaccine is recommended annually for all individuals age from 6 months; it is particularly important for: • individuals with asthma not requiring regular preventive therapy • individuals in essential positions, emergency responders and health care workers • individuals with hypertension and/or dyslipidaemia without evidence of end-organ disease. • individuals who may transmit influenza to persons at increased risk of complications from influenza infection, (eg, caregivers, family members, health care staff, child care staff and other close contacts) • travellers • children aged under 5 years • residents and staff of residential care facilities • the homeless.

a. Seek specialist advice for individuals who are currently being treated with immune checkpoint inhibitors, as well as those who have discontinued treatment within the past 6 months. See 'Immune checkpoint inhibitor (immunostimulant) therapy' in section 4.3.2.

b. This is a Pharmaceutical Schedule Section H – Hospital Medicines List funding restriction.

10.5.1 Pregnancy and breastfeeding

The influenza vaccine is strongly recommended, and funded, for women who will be pregnant while the vaccine is available. Pregnant women can receive influenza vaccination at any stage of pregnancy to protect themselves, their fetus and their newborn for each season they are pregnant. When pregnancy spans two influenza seasons, two vaccinations (one from each season) are recommended to protect against all the predicted strains.

Influenza vaccine is safe to administer during any stage of pregnancy or while a woman is breastfeeding. There is no evidence that influenza vaccine prepared from inactivated split virus or subunits causes damage to the fetus or neonate[102] and there is some evidence it may be protective against stillbirth.[11]

Pregnant women are at greater risk from complications associated with influenza illness.[7, 10] When pregnancy is superimposed on high-risk conditions such as asthma or diabetes, influenza-related morbidity is three to four times greater than in non-pregnant women with similar high-risk conditions.

Globally, about one-quarter of influenza-associated hospital admissions and over one-third of in-hospital deaths are in infants under 6 months.[103] Because there is no registered or effective vaccine for children aged under 6 months, vaccination during pregnancy is highly recommended to improve maternal-fetal passive antibody transfer.[10] Influenza vaccination of pregnant women has been shown to significantly decrease influenza in their newborn babies.[31, 47, 66, 68] Breastfeeding is also recommended, to deliver passive immunity to the infant.[31] (See also section 4.1.2.)

10.5.2 Children at increased risk

Influenza vaccine is recommended for all children aged 6 months and older, and is funded for those with chronic illnesses and a history of respiratory disease. Children with the following conditions should be prioritised to receive influenza vaccine due to their increased risk:

- all asthmatics on regular preventive therapy
- children aged under 5 years who were hospitalised with measles
- other children with chronic respiratory disorders (eg, cystic fibrosis, non-cystic fibrosis bronchiectasis and chronic lung disease of infancy).

Special considerations apply to children, as follows (see also section 4.3):

- Immunisation is occasionally associated with fever between 6 and 24 hours after administration. In children aged 6–24 months with significant chronic medical conditions fever may cause an exacerbation of the underlying condition.
- Children receiving cancer chemotherapy may have a weaker response to influenza vaccine. Vaccination is recommended three to four weeks after the preceding dose of chemotherapy, when the neutrophil and lymphocyte counts are each $\geq 1.0 \times 10^9$/L. Children who are no longer receiving chemotherapy can be expected to show seroconversion to vaccine three months after the cessation of chemotherapy.

Note: Seek specialist advice for children who are currently being treated with immune checkpoint inhibitors, as well as those who have discontinued treatment within the past six months. See 'Immune checkpoint inhibitor (immunostimulant) therapy' in section 4.3.2.

10.5.3 Adults at increased risk

Adults aged 65 years and older

In adults aged 65 years and older, influenza vaccine has been shown to be effective against non-fatal and fatal influenza complications, influenza-like illness and laboratory-confirmed influenza (see Table 10.1). Influenza vaccination protects against loss of independence due to increasing levels of frailty associated with hospitalisation.[8, 82, 104]

Adults with underlying medical conditions

Influenza has been associated with increased morbidity and mortality in adults with underlying medical conditions. Risk increases with multiple conditions.

Note: Seek specialist advice for individuals who are currently being treated with immune checkpoint inhibitors, as well as those who have discontinued treatment within the past six months. See 'Immune checkpoint inhibitor (immunostimulant) therapy' in section 4.3.2.

10.5.4 Recommended but not funded

Generally, influenza vaccination is recommended annually for all individuals aged from 6 months. It is particularly important for the groups listed in Table 10.2.

There are certain conditions that individually do not render a person eligible for funded influenza vaccine, but when combined, significantly increase the risk of influenza complications (this is described as 'risk stacking'). Such risks are further increased by smoking, alcohol dependency and obesity.

In order to optimise the protection of high-risk infants and toddlers, including those aged under 6 months (see Table 10.2), all household and close contacts should receive influenza vaccine (not funded unless eligibility criteria are met).

Healthy individuals of any age from 6 months and older

Healthy individuals are encouraged to have the vaccine, especially if they are in close contact with individuals at high risk of complications. Employers are encouraged to provide influenza vaccine to avoid illness in their employees, especially those engaged in health care and other essential community services. Immunising healthy individuals has been shown to be cost-effective.

Health care workers

The Ministry of Health strongly recommends, and expects, that all health care workers will receive annual influenza vaccination for their own protection and the protection of those in their care.

Travellers

Influenza vaccine is recommended for people travelling outside New Zealand, especially those who are in the at-risk groups who have not received vaccine during the previous autumn, depending on the season and their destination. In tropical countries, influenza activity can occur throughout the year but is more likely during the winter (wet) and summer seasons, while in the northern hemisphere activity is commonest between the months of December and March. Outbreaks of influenza among organised tourist groups (eg, on cruise ships) can occur throughout the year.

10.6 Contraindications and precautions

See also section 2.1.3 for pre-vaccination screening guidelines, section 2.1.4 for general contraindications for all vaccines and section 4.3.2 for immune checkpoint inhibitor (immunostimulant) therapy, particularly for oncology patients.

10.6.1 Contraindications

Influenza vaccine should not be administered to people with a history of an anaphylactic reaction to a prior dose of influenza vaccine or to a vaccine component. Egg allergy, including anaphylaxis, is **not** a contraindication or precaution: see section 10.6.3.

10.6.2 Precautions

Immune checkpoint inhibitors

Specialist advice must be sought before administering any vaccine to individuals who are currently being treated with immune checkpoint inhibitors, as well as those who have discontinued treatment within the past six months.

A cautious approach to vaccination is recommended when balancing an individual's risk of developing an immune-related adverse event, their potential risks of disease and the potential benefits of vaccination during, and for six months after, treatment with immune checkpoint inhibitors.

There are four immune checkpoint inhibitor medications currently available in New Zealand: nivolumab (Opdivo), pembrolizumab (Keytruda), atezolizumab (Tecentriq) and ipilimumab (Yervoy).

See 'Immune checkpoint inhibitor (immunostimulant) therapy' in section 4.3.2.

History of Guillain–Barré syndrome

Influenza vaccination has been suggested to increase the risk of GBS. However, no association was found between administering 16 million doses of influenza vaccine and GBS in adults aged from 65 years in the US.[105] Any potential risk increase would be less than one additional case per million doses administered.[3, 32, 106] The risk of developing GBS is increased following influenza infection, and the magnitude of the risk is several times greater than that possibly occurring following influenza vaccination.[3, 106, 107]

New Zealand hospitalisations for GBS showed no increase during the 1990s despite the marked increase in vaccine use during this period but apparent year-to-year variation was observed. In particular, the doubling of vaccine use (with the introduction of funded vaccine) in 1997 was not associated with any increase in GBS hospitalisations. No excess risk for GBS following influenza vaccine in children has been documented. No association between influenza vaccines and any other neurological disease has been substantiated.

The risks and benefits of withholding vaccination should be considered on an individual basis, based on the potential morbidity and mortality associated with influenza for that individual, including the potential risk of recurrent GBS following influenza infection.

Co-administration with PCV13

Individuals (or their parents/guardians) who receive both influenza vaccine and 13-valent pneumococcal conjugate vaccine (PCV13) should be advised of the increased risk of fever following concomitant administration of these vaccines.[99, 100, 108] Separation of the vaccines by two days can be offered, but is not essential (see also section 15.6.2).

10.6.3 Egg allergy

Influenza vaccine can be safely administered to people with a history of egg allergy, including anaphylaxis, at general practices, pharmacies or at the workplace.[109]

Reported cases of anaphylaxis after influenza vaccination in egg-allergic individuals all occurred over 30 years ago, at a time when vaccine egg (ovalbumin) content was much higher than it is now. Recent studies have shown that influenza vaccines containing less than 1 µg of ovalbumin do not trigger anaphylaxis in sensitive individuals.[109]

10.7 Potential responses and AEFIs

Split virion or subunit influenza vaccines are generally well tolerated. The safety profile of quadrivalent vaccines is comparable to that of trivalent vaccines.[32]

Potential responses associated with these influenza vaccines in adults and children include pain, redness and/or swelling at the site of injection (10–64 percent of recipients, lasting less than two days).[3] These local inflammatory responses are almost always mild. Systemic events such as headache, muscle aches and fatigue may occur in adults. Passive reporting of local and systemic reactions to influenza vaccines is more frequent for females (both young and older adults) than males.[110] Australian surveillance data (collected by AusVaxSafety) found that just over 6 percent of adults reported any adverse event following seasonal influenza vaccination, of which less than 1 percent were systemic responses (fever, rash and seizure).[111]

Systemic reactions are more likely in children not previously exposed to the vaccine or virus, these are generally self-limiting and resolve within one to two days.[32] A large post-licensure study in the US, which reviewed more than 250,000 children aged under 18 years given influenza vaccine, showed no increase in clinically important medically attended events for two weeks after vaccination compared to control periods.[112]

In early 2010, an increase in febrile seizures in children in both Australia and New Zealand were all linked to the Fluvax brand influenza vaccine. Active surveillance in Australia continues to monitor for potential safety signals.

Vaccinators need to emphasise to recipients that:

- the split virion vaccine contains components of the virus, not the intact virus, and cannot cause influenza
- local reaction and mild systemic symptoms may occur within a day or two of immunisation
- respiratory viral infections are common, and many individuals will develop one coincidentally following immunisation, and these should not be falsely attributed to the vaccine.

An association was found in 2010 between narcolepsy and one H1N1 pandemic vaccine (Pandemrix, an adjuvanted vaccine not licensed or used in New Zealand). Data from various European countries support a temporal link.[113, 114, 115] The onset of narcolepsy may be confounded by other factors, such as genetic predisposition, A(H1N1)pdm09 influenza and/or other environmental factors.[116, 117, 118] A 2018 systematic review found that although the risk of narcolepsy type 1 increased in association with this particular vaccine, it remains a rare disease and the benefit of the influenza vaccination outweighs the risk.[119]

10.8 Public health measures

Using influenza signs and symptoms to assess the burden of influenza is of limited value. There is also a significant amount of asymptomatic circulation of influenza in the community. The most sensitive diagnostic method is polymerase chain reaction (PCR) of respiratory nasopharyngeal swabs or aspirate samples.

The methods of controlling influenza are:

- immunisation
- hand hygiene (ie, regularly washing hands for at least 20 seconds and drying them for 20 seconds, or regularly using an alcohol-based hand rub)
- respiratory hygiene (ie, cough and sneeze etiquette, and the judicious use of viricidal tissues and wearing of face masks in some settings)
- social distancing (ie, persuading those with symptoms to avoid others in the community by staying away from school and work when sick; in particular, infected individuals should avoid contact with the elderly, the chronically ill, and infants and babies)
- regularly cleaning flat surfaces such as bathroom sinks, bedside cabinets, desks and tabletops
- antiviral therapy, but this has a limited role (see section 10.8.2).

10.8.1 Improving vaccine uptake

Studies in New Zealand and overseas have found that provider attitudes and provider recommendations are key to improving influenza vaccine uptake. Organised registers for recall and opportunistic immunisation are also likely to be important factors in achieving high uptake.

Every effort should be made during April to immunise all people at risk, particularly those aged 65 years and older, those aged under 65 years (including children) who have certain medical conditions, pregnant women and health care workers. During an influenza outbreak, recommend influenza vaccination to anyone at risk who was not immunised during the current season or to those who have not received an influenza vaccination for more than six months. Availability of an appropriate vaccine is the most pertinent of these factors.

Vaccination of all healthy adults and children from age 6 months is encouraged but not funded. Adult vaccination, especially for those in close contact with high-risk groups, may be funded by employers.

10.8.2 Antiviral drugs

Influenza antiviral drugs can be used to treat or to prevent influenza and can be adjuncts to influenza vaccination. Early use of antivirals, especially within the first 48 hours of illness, can reduce the duration of symptoms and the risk of complications from influenza. They are likely to be most effective against severe influenza and for those with high risk comorbidities.

It has been shown that when patients with influenza-like illness were treated in primary care with oseltamivir, recovery time was shortened compared with usual care. In older patients and those with comorbidities, in particular, even with longer previous symptom duration (48–72 hours), recovery was likely to be 2–3 days sooner following antiviral treatment than it would have been with than standard care alone.[120] Meta-analyses of the effectiveness of oseltamivir in treating uncomplicated influenza show shortened duration of symptoms for healthy adults and adolescents of around one day,[121] a 63 percent (95% CI: 19–83) decrease in risk of hospitalisation for any cause and a 44 percent (95% CI: 25–58) decrease in risk of antibiotic prescription use.[122]

For use with severe influenza, observational studies show early treatment can lead to a decreased risk of death.[123, 124] Early treatment upon hospital admission was significantly associated with reduced length of stay (by 19 percent), regardless of time since symptoms onset, compared with later or no treatment initiation. Greater reductions in length of stay were seen for pregnant women and obese patients (by 39 percent and 27 percent, respectively).[125]

Antivirals should be particularly considered for unimmunised or recently immunised contacts who are at high risk of severe disease. When used to limit the size of an institutional outbreak, antiviral drugs are usually given for a period of two weeks after immunisation or until one week after the end of the outbreak. Institutional outbreaks should be notified to the local medical officer of health.[126]

For further details about antiviral medication, refer to the *Influenza information for health professionals* website at **www.influenza.org.nz**.

10.8.3 Pandemics

At the time of a pandemic, recommended public health advice, priority groups and the timing of vaccination may be quite different from those during inter-pandemic periods. The *New Zealand Influenza Pandemic Plan: A framework for action* (available at **www.health.govt.nz/publication/new-zealand-influenza-pandemic-plan-framework-action**) describes the key phases of a pandemic and the actions and responsibilities within each phase.[127]

10.9 Variations from the vaccine data sheet

Vaccine data sheets state that the vaccine is contraindicated in individuals with a hypersensitivity to egg protein. However, the Ministry of Health recommends that individuals with hypersensitivity to eggs, including anaphylaxis, may receive influenza vaccination: see section 10.6.3.

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