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# 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.
Disease burden	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 in Māori and Pacific ethnic groups.
Funded vaccines	Quadrivalent inactivated split virion vaccine: <ul style="list-style-type: none"><li>• children aged 6 months to under 3 years (ie, aged 6–35 months): Fluarix Tetra.</li><li>• adults and children aged 3 years and older: Influvac Tetra.</li></ul>
Dose, presentation, route	0.5 mL per dose. Pre-filled syringe. Intramuscular injection.
Funded vaccine indications	1 dose is recommended and funded annually for: <ul style="list-style-type: none"><li>• pregnant women</li><li>• individuals aged 65 years and older</li><li>• individuals aged 6 months to under 65 years with eligible conditions.</li></ul> Children aged under 9 years who have not previously received influenza vaccine require 2 doses 4 weeks apart (funded for children with eligible conditions).
Vaccine efficacy/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.
Egg allergy	Egg allergy, including anaphylaxis, is <b>not</b> a contraindication to influenza vaccination. Influenza vaccine can be safely administered to people with a history of egg allergy, including anaphylaxis, at general practices, pharmacies or at the workplace.

*Continued overleaf*

Contraindications/ precautions	<p>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.</p> <p>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.</p>
Adverse events	<p>Children aged under 5 years are more likely than older children or adults to have a febrile reaction to influenza vaccine.</p>

## 10.1 Virology

Influenza viruses belong to the Orthomyxoviridae family, and are classified into influenza virus types A, B and C. Influenza A viruses include a number of subtypes, classified on the basis of 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 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.<sup>1</sup> 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. The mutations that occur in the coding regions responsible for H and N surface antigens lead to ‘antigenic drift’ and 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**

Novel influenza A virus subtypes have emerged periodically in the past which have caused pandemics in humans. The mixing of the genomic segments of two or more influenza A viruses leads to a new virus subtype with novel H and N surface antigens and is known as 'antigenic shift'. The emergence of novel viruses through the adaptation of avian influenza viruses to humans and the re-assortment of the genomic segments of multiple viruses, ie, human, avian and pig influenza viruses, are also recognised as possible mechanisms.

## **10.2 Clinical features**

Influenza is contagious, with a reproductive number estimated at 1.4–4<sup>2</sup> (see section 1.2.1). The virus is transmitted by respiratory droplets generated by sneezing and coughing that land directly on the respiratory mucous membranes, by direct or indirect contact (contaminated hands or fomites), or by the aerosol route.<sup>3</sup>

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.

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 rhinitis only.

There is a wide range of symptoms, from asymptomatic to severe disease. Mild influenza is common and symptoms can be non-specific, resulting in a large proportion of undetected influenza infections.

In the young, influenza virus may cause croup, bronchiolitis and pneumonia. Fever is often less evident in the elderly. Influenza typically resolves after several days in the majority of 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.<sup>1</sup> 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.<sup>1</sup>

Influenza B infection is more common in children aged 5–17 years than in other age groups, and disease is more likely to be severe in children than in adults.

In some people, 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, myocarditis, pericarditis, Reye syndrome (associated with aspirin use in children), bronchitis, otitis media and death.

## **Asymptomatic influenza**

The majority of influenza infections are asymptomatic, with most symptomatic cases self-managing without seeking medical help.<sup>4</sup> Results from the 2015 Southern Hemisphere Influenza and Vaccine Effectiveness, Research and Surveillance (SHIVERS) serosurvey showed that around 26 percent of people in New Zealand had contracted influenza over the 2015 season.<sup>5</sup> Approximately 80 percent of infected people (4 in 5 infected) were asymptomatic, with only 2.5 percent of those infected (1 in 40 infected) visiting their GP and 0.2 percent (1 in 560 infected) hospitalised.

## 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 250,000 to 500,000 deaths globally.<sup>6</sup>

In temperate climates, seasonal epidemics occur mainly during winter, while in tropical regions, influenza may occur throughout the year, causing outbreaks more irregularly.<sup>6</sup>

From time to time, pandemics occur when a new virus arises and spreads globally (see section 10.3.3). The last 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.<sup>7</sup>

### 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 may occur 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.

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

### Influenza surveillance

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

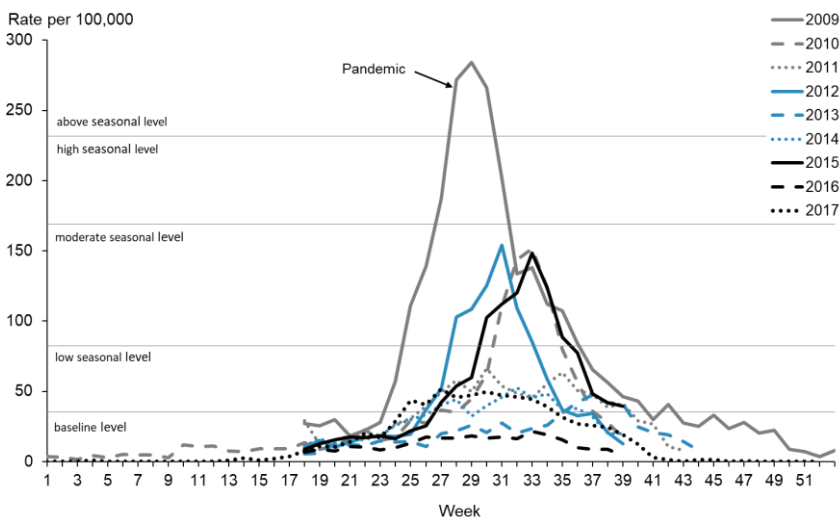
- national sentinel general practice-based influenza-like illness surveillance (part of the WHO's Global Influenza Programme)

- year-round laboratory-based surveillance by the regional virus diagnostic laboratories
- hospital-based severe acute respiratory infection surveillance in Auckland and Counties DHBs
- data from Healthline, HealthStat, publicly funded hospital discharges and the NIR.

At the time of writing, only high-level, provisional surveillance data for 2017 was available.

The national weekly consultation rate is used to describe the overall level of influenza-like illness (ILI) activity presenting to the general practice level, using the moving epidemic method to define the start of and intensity level of the influenza season.<sup>8</sup> Figure 10.1 shows the national weekly ILI consultation rates from 2009 to 2017. Although increased since 2016, the overall ILI activity remained at a low seasonal level (between 35.1 and 82.5 ILI consultations per 100,000 patient population per week).<sup>9</sup> There were 2,977 ILI cases identified in 2017, with an ILI cumulative incidence of 724.1 per 100,000 patient population.<sup>10</sup>

**Figure 10.1: Weekly consultation rates for influenza-like illness in New Zealand, 2009–2017**



Source: ESR

Influenza-associated severe acute respiratory illness (SARI) hospitalisations were high in 2017 but slightly lower than known high years (2012 and 2014).<sup>9</sup> However, intensive care unit admissions were low or comparable to these years.

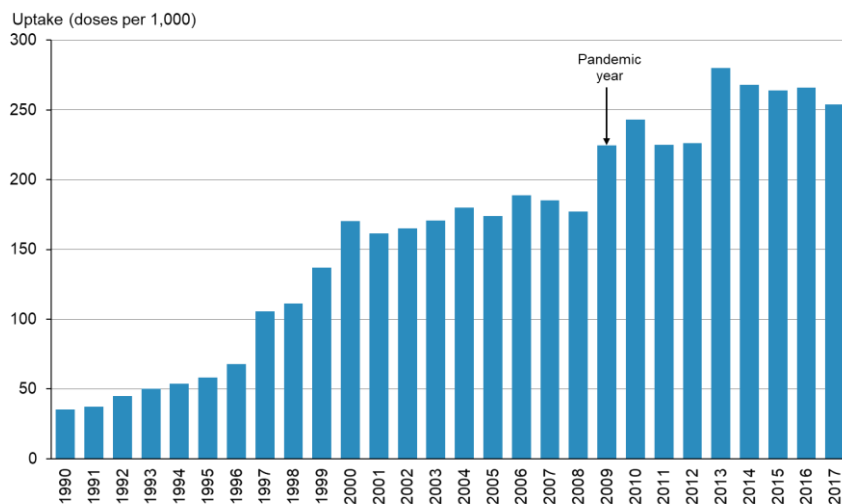
As in 2016,<sup>11</sup> influenza A(H3N2) and B(Yamagata) were the predominant influenza strains circulating in 2017, although influenza B(Victoria) co-circulated with B(Yamagata).<sup>9</sup>

## Influenza immunisation uptake

In 2017 more than 1.2 million doses of influenza vaccine were distributed.

The uptake rate of influenza vaccine (both publicly and privately funded), as estimated by vaccine distribution figures, was slightly lower in 2017 (254 doses per 1,000 population) than in the previous three years (see Figure 10.2). Publicly funded uptake for individuals aged 65 years and older was 65 percent. As this is based on immunisation claims data for publicly funded influenza vaccination, it is likely to be an underestimate.

**Figure 10.2: Influenza vaccine uptake per 1,000 population, 1990–2017**



Vaccine coverage is estimated using vaccine distribution figures.

Funded vaccine was introduced for: individuals aged 65 years and older in 1997; individuals aged under 65 years with certain medical conditions in 1999; pregnant women in 2010; children aged under 5 years with significant respiratory illness in 2013.

Source ESR and Ministry of Health

Since 2010 the Ministry of Health has requested that all DHBs provide influenza immunisation coverage data for their staff at the end of each influenza season. National influenza immunisation coverage for DHB staff is still low, but it has increased from 45 percent in 2010 to 66 percent in 2017.

### **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, 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.

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 pandemic was the ‘Spanish’ 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 10 percent (800,000) of the New Zealand population were infected with the virus during the first wave, including one in every three children.<sup>12</sup> Risk factors for severe outcomes included obesity, pregnancy,<sup>13</sup> diabetes mellitus and Pacific or Māori ethnicity.<sup>12</sup> This strain is now established as a circulating seasonal influenza strain.

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 Specialist Group coordinated by IMAC, is responsible for New Zealand's annual Influenza Communication Campaign ([www.influenza.org.nz](http://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 inactivated split virion influenza vaccines are funded.

- Fluarix Tetra (GSK) for infants and children aged 6 months to under 3 years (ie, aged 6–35 months). Each 0.5 mL dose contains 15 µg of each of the four recommended influenza strains in phosphate buffered saline; other components and excipients include hydrocortisone, gentamicin sulfate, ovalbumin ( $\leq 0.05$  µg), formaldehyde, and sodium deoxycholate.
- Influvac Tetra (Mylan New Zealand Ltd) for adults and children aged 3 years and older. Each 0.5 mL dose contains 15 µg of each of the four recommended influenza strains; other components and excipients include potassium chloride, monobasic potassium phosphate, dibasic sodium phosphate, sodium chloride, calcium chloride dihydrate, magnesium chloride hexahydrate. Each 0.5 mL dose contains residual amounts of ovalbumin ( $\leq 0.1$  µg), formaldehyde, cetrimonium bromide, sodium citrate, sucrose, gentamicin sulfate, and traces of tylosine tartrate, hydrocortisone and polysorbate 80 which are used during the manufacturing process.

#### Vaccine preparations

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 and intranasal mists. Intradermal vaccines are

generally recognised as offering similar immune responses in healthy subjects<sup>14</sup> and possibly more efficient immune responses,<sup>15</sup> particularly in the older adult population.<sup>16</sup> Live attenuated influenza vaccines are delivered by intranasal spray.

The influenza vaccine strains vary each year depending on the prevailing virus viruses. The 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. For 2018 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 season.<sup>17</sup>

#### *Inactivated influenza vaccines (split virion or subunit vaccines)*

Trivalent inactivated vaccines (TIVs) are inactivated split virion vaccines prepared from virus grown in the allantoic cavity of embryonated hens' eggs. They contain two influenza type A strains and one type B strain. The virus is purified, disrupted and inactivated with beta-propiolactone or formaldehyde.

Quadrivalent inactivated vaccines (QIVs) contain two type A and two type B influenza strains. Compared to TIVs, QIVs have the potential to offer broader protection against co-circulating B-strains and better effectiveness in seasons of B-strain mismatch.<sup>1</sup>

#### *Live attenuated influenza vaccines (LAIVs)*

LAIVs may induce stronger immune responses than TIVs, particularly in children, by mimicking natural influenza infection and evoking both mucosal and systemic immunity, and including broader cellular immune responses.<sup>18</sup> Live attenuated influenza vaccines (LAIVs; trivalent and quadrivalent) 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.<sup>19</sup> LAIVs have been shown to be effective in children aged 6 months to 7 years.<sup>20</sup>

However, based on recent observational data showing lack of effectiveness in US children aged 2–17 years for the 2013/14 and 2015/16 influenza seasons, the US Advisory Committee on

Immunization Practices (ACIP) has recommended that LAIVs not be used for the 2016/17 influenza season.<sup>19</sup>

In contrast, UK data from the 2015/2016 season has shown a LAIV effectiveness in children aged 2–17 years of 57.6 percent (95% CI: 25.1–76.0) against any influenza, with higher vaccine effectiveness (81.4 percent; 95% CI: 39.6–94.3) against the B strain.<sup>21</sup> It is not currently clear why there are such significant effectiveness differences 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.<sup>21</sup>

At the time of writing, LAIVs were not registered in New Zealand.

### *Adjuvanted vaccines*

Adjuvants enhance the immune response to an antigen. There are three adjuvants licensed (internationally) for use in influenza vaccines: two oil-in-water emulsions, and a third that uses immunopotentiating reconstituted influenza virosomes.<sup>22</sup>

Vaccines with these adjuvants show modestly improved immune responses, which may be particularly useful for the elderly, but may also cause more local and systemic reactions than unadjuvanted vaccines.<sup>22</sup> At the time of writing, influenza vaccines containing these adjuvants were not registered and/or available in New Zealand.

## **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, as well as the match between the virus strains in the vaccine and those in circulation each year. Previous vaccination history may reduce the vaccine effectiveness in some cases, possibly more so when the previous vaccination was mismatched with the circulating strains at the time.<sup>23</sup>

Two influenza B strains can frequently co-circulate, and due to the complexity 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. Because QIVs contain two influenza B strains, modelling studies suggest that QIVs are expected to prevent more influenza cases, hospitalisations and deaths than TIVs, due to their capacity to broaden the immune response against B strains and reduce the likelihood of a B-mismatched season.<sup>1</sup>

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)
Infants aged under 6 months whose mothers received influenza vaccine	Efficacy against laboratory-confirmed influenza	41–48% <sup>24, 25</sup>
Healthy children aged under 2 years	Efficacy against laboratory-confirmed influenza	Insufficient data <sup>20, 26</sup>
	Effectiveness against laboratory-confirmed influenza	66% (9–88) <sup>27</sup>
Healthy children aged 6–35 months	Effectiveness against laboratory-confirmed influenza	66% (29–84) <sup>27</sup>
Healthy children aged under 16 years	TIV vaccine efficacy in prevention of laboratory-confirmed influenza in randomised controlled trials	59% (41–71) <sup>26</sup>
Healthy adults aged 18–65 years	Effectiveness against influenza-like illness*	30% (17–41) <sup>28</sup>
	Efficacy against influenza symptoms*	73% (54–84) <sup>28</sup>
	Efficacy against laboratory-confirmed influenza	59% (51–67) <sup>20</sup>

*Continued overleaf*

Population	Type of outcome	Level of protection (95% confidence intervals)
Those aged 65 years and older	Effectiveness in preventing influenza, influenza-like-illness, hospitalisations, complications and mortality	Inconclusive due to poor quality of studies <sup>29</sup>
Those aged 65 years and older	Effectiveness against non-fatal and fatal complications	28% (26–30) <sup>30</sup>
	Effectiveness against influenza-like illness	39% (35–43) <sup>30</sup>
	Effectiveness against laboratory-confirmed influenza	49% (33–62) <sup>30</sup>

\* From age 16 years.

## 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, overall the data shows that TIV influenza vaccine effectiveness is approximately 50 percent overall for preventing both visits to the general practice and hospitalisations, for both influenza type A and B strains.<sup>31, 32, 33, 34</sup> However, estimates for vaccine effectiveness tend to be higher in children and healthy midlife adults, and lower in the elderly.

## Pregnant women and neonates

A pregnant woman and her fetus are at increased risk of influenza complications, including hospitalisation from influenza-related cardiorespiratory disorders during the second and third trimesters, and this was especially apparent in the 2009 pandemic.<sup>35</sup> Influenza immunisation is therefore recommended during pregnancy to reduce this risk. Influenza immunisation is expected to have the same efficacy in healthy pregnant women as in other healthy adults.

Maternal influenza immunisation also offers protection to the fetus through maternal antibody transfer.<sup>18, 25, 35, 36</sup> 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 have received vaccination at the time of exposure.<sup>24, 37</sup> Maternal influenza immunisation is significantly associated with reduced risk of influenza virus infection

and hospitalisation for an influenza-like illness in infants up to 6 months of age, and increased influenza antibody titres are seen in infants through to age 2–3 months.<sup>24</sup>

Influenza immunisation during pregnancy may also reduce the incidence of stillbirth. In an Australian study, stillbirth was 51 percent less likely among vaccinated mothers compared to unvaccinated mothers.<sup>38</sup>

## **Children**

The evidence for vaccine efficacy and effectiveness in very young children is varied. There is evidence to support moderate effectiveness of TIV in children aged 3 years and older.

## **Healthy adults**

Generally, randomised placebo-controlled trials of TIV in healthy adults support good protection against a variety of outcomes, particularly laboratory-confirmed influenza.

## **Adults aged over 65 years**

Although less effective at preventing clinical illness in older people,<sup>39</sup> influenza vaccination does reduce hospitalisation and deaths. A 1995 meta-analysis of 20 cohort studies in older people estimated that influenza vaccine prevented 56 percent of upper respiratory illnesses, 53 percent of pneumonias, 50 percent of all hospitalisations and 68 percent of deaths.<sup>40</sup>

There is wide variability in the estimates of effectiveness of annual influenza vaccination against influenza-like illness in nursing home residents (0–80 percent).<sup>22</sup> Vaccination has been demonstrated to prevent hospitalisation and death in these groups,<sup>40, 41, 42, 43</sup> but a 2010 Cochrane review concluded that there was insufficient evidence to support influenza vaccine effectiveness in the elderly.<sup>29</sup> However, researchers have more recently re-examined this review and its methodology and argue 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.<sup>30</sup>

## Adults with co-morbid conditions

Influenza vaccination has been associated with reductions in hospitalisations and deaths among adults with risk factors for influenza complications. 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.<sup>44</sup> Benefits from influenza vaccination have been observed for both diabetes<sup>45</sup> and chronic obstructive pulmonary disease.<sup>46</sup> 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.<sup>47</sup>

## Herd immunity

There is some evidence to suggest that herd immunity can be achieved, particularly by vaccinating children.<sup>48</sup> Some studies suggest that herd immunity may also be achieved in nursing homes if immunisation coverage of residents is greater than 80 percent.<sup>49</sup> Vaccinating health care workers is likely to be an effective strategy, particularly when in contact with high-risk patients such as in nursing homes.<sup>50</sup>

The UK has had three seasons of a progressively rolled-out vaccination programme using LAIV, starting with children aged 2–3 years in 2013/14 and then extended to children aged 4–7 years by 2015/16. There were also school-age pilot programmes in England for older children. Early results show evidence of indirect and overall impact, with decreases in disease incidence and influenza positivity in the school-age pilots versus control areas in vaccinated and non-vaccinated groups.<sup>51</sup>

## 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.<sup>19, 22</sup> However shorter duration of immunity is likely in other groups, particularly the elderly.<sup>19</sup>

Protection due to LAIVs has been demonstrated to persist beyond a year.<sup>52, 53</sup>

### 10.4.3 Transport, storage and handling

Transport according to the *National Standards for Vaccine Storage and Transportation for Immunisation Providers 2017*.<sup>54</sup> 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 (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 Influvac Tetra 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 0.5 mL dose of Fluarix Tetra; children aged 3 years and older receive a 0.5 mL dose of Influvac Tetra (see Table 10.2).

**Table 10.2: Recommended influenza vaccine doses in children**

Age	Vaccine	Dose	Number of doses
6–35 months	Fluarix Tetra	0.5 mL	1 or 2*
3–8 years	Influvac Tetra	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 are recommended to receive two doses of influenza vaccine, four weeks apart.<sup>55</sup> One dose is then given in each subsequent year. (See section 4.3.)

## **Co-administration with other vaccines**

Influenza vaccine can be administered with other vaccines, such as pneumococcal polysaccharide vaccine, tetanus diphtheria (Td) vaccine, the live attenuated herpes zoster vaccine<sup>56</sup> and the scheduled childhood vaccines. Individuals recommended to receive both influenza vaccine and 13-valent pneumococcal conjugate vaccine (PCV13) have an increased risk of fever following concurrent administration of these vaccines.<sup>57, 58</sup> 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 in high-risk groups is usually during March and April. This is 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.<sup>59</sup> 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. Therefore, it is important to consider not just individual protection but also reducing spread by vaccinating contacts of high-risk individuals, such as family and caregivers, and occupational vaccination. See Table 10.3 for a summary of the funded and unfunded recommendations for influenza immunisation.

### Table 10.3: Influenza vaccine recommendations

Note: Funded conditions are in the shaded rows. See the Pharmaceutical Schedule ([www.pharmac.govt.nz](http://www.pharmac.govt.nz)) for any changes to the funding decisions.

<b>Recommended and funded</b>
All individuals aged 65 years and older.
Individuals aged 6 months to under 65 years who: <ul style="list-style-type: none"> <li>• have cardiovascular disease (ischaemic heart disease, congestive heart failure, rheumatic heart disease, congenital heart disease or cerebrovascular disease)</li> <li>• have chronic respiratory disease (asthma if on regular preventive therapy; other chronic respiratory disease with impaired lung function)</li> <li>• have diabetes</li> <li>• have chronic renal disease</li> <li>• have any cancer,<sup>a</sup> excluding basal and squamous skin cancers if not invasive</li> <li>• have other conditions (autoimmune disease, immunosuppression or immune deficiency,<sup>a</sup> HIV infection, transplant recipients, neuromuscular and central nervous system diseases/disorders, haemoglobinopathies, children on long-term aspirin, have a cochlear implant, errors of metabolism at risk of major metabolic decompensation, pre- or post-splenectomy, Down syndrome)</li> <li>• are pregnant</li> <li>• are children aged 4 years and under who have been hospitalised for respiratory illness or have a history of significant respiratory illness</li> <li>• are children aged under 18 years living in the Seddon/Ward and rural Eastern Marlborough region (within the Nelson Marlborough District Health Board) and Kaikoura and Hurunui areas (within the Canterbury District Health Board)</li> <li>• are children aged under 18 years who have been displaced from their homes in Edgecumbe and the surrounding region</li> <li>• are patients who are compulsorily detained long-term in a forensic unit within a DHB hospital.<sup>b</sup></li> </ul>
<b>Recommended but not funded</b>
Individuals with asthma not requiring regular preventive therapy
Individuals with functional asplenia
Individuals in essential positions and health care workers
Individuals who may transmit influenza to persons at increased risk of complications from influenza infection
Travellers
Children aged under 5 years
Residents of residential care facilities
The homeless

<sup>a</sup> 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 'Oncology patients treated with immune checkpoint inhibitors' in section 4.3.3.

### **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.

Influenza vaccine is safe to administer during any stage of pregnancy or while breastfeeding. There is no evidence that influenza vaccine prepared from inactivated virus causes damage to the fetus or neonate<sup>60</sup> and some evidence it may be protective against stillbirth.<sup>38</sup>

Pregnant women are at greater risk from complications associated with influenza illness. 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.

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.<sup>37</sup> Influenza vaccination of pregnant women has been shown to significantly decrease influenza in their newborn babies.<sup>18, 25, 35, 36</sup> Breastfeeding is also recommended, to deliver passive immunity to the infant.<sup>18</sup> (See also section 4.1.2.)

### **10.5.2 At-risk children**

Influenza vaccine is funded for children aged 6 months and older 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
- 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.)

- In children aged 6–24 months with significant chronic medical conditions, influenza immunisation is occasionally associated with fever between 6 and 24 hours after administration, which 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 last dose of chemotherapy, when the neutrophil and lymphocyte counts are each  $\geq 1.0 \times 10^9/\text{L}$ . Children who are no longer receiving chemotherapy can be expected to show seroconversion 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 6 months. See ‘Oncology patients treated with immune checkpoint inhibitors’ in section 4.3.3.

### **10.5.3 At-risk adults**

#### **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).

#### **Adults with underlying medical conditions**

Influenza has been associated with increased morbidity and mortality in adults with underlying medical 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 6 months. See ‘Oncology patients treated with immune checkpoint inhibitors’ in section 4.3.3.

## 10.5.4 Recommended but not funded

Influenza vaccine is recommended, but not funded, for the groups listed in Table 10.3.

### Healthy adults

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.

In order to optimise the protection of high-risk (see Table 10.3) infants and toddlers (including those aged under 6 months) all household and close contacts should receive influenza vaccine (not funded unless eligibility criteria are met).

### 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

People travelling outside New Zealand, especially those who are in the at-risk groups who have not received vaccine during the previous autumn, are recommended to have influenza vaccination 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 and section 2.1.4 for general contraindications for all vaccines.

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 6 months. See ‘Oncology patients treated with immune checkpoint inhibitors’ in section 4.3.3.

### 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.

Fluvax is contraindicated for children aged under 5 years (see section 10.7) due to the increased risk of febrile events. The Ministry of Health recommends that Fluvax not be given to children aged under 9 years.

### 10.6.2 Precautions

#### History of Guillain–Barré syndrome

There appears to be a small increase in the risk of GBS following influenza vaccination (less than one additional case per million doses administered,<sup>19</sup> substantially less than the risk of developing severe complications from influenza infection<sup>22, 28</sup>). There is also an increased risk of developing GBS following influenza infection, and the magnitude of the risk is several times greater than that following influenza vaccination.<sup>61</sup>

New Zealand hospitalisations for GBS showed no increase during the 1990s despite the marked increase in vaccine use during this period, but did show a marked year-to-year variation. In particular, the doubling of vaccine use in 1997 (with the introduction of funded vaccine) 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 are recommended to 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.<sup>57, 58</sup> 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.<sup>62</sup>

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 one microgram (<1 µg) of ovalbumin do not trigger anaphylaxis in sensitive individuals.<sup>62</sup> The residual ovalbumin in one dose of Influvac Tetra (≤0.1 µg) or Fluarix Tetra (≤0.05 µg) is significantly below this limit.<sup>63, 64</sup>

## **10.7 Expected responses and AEFIs**

Inactivated influenza vaccines are generally well tolerated. The safety profile of quadrivalent inactivated vaccines is comparable to that of trivalent inactivated vaccines.<sup>19</sup> Placebo-controlled trials of TIVs have shown that influenza vaccine is not associated with systemic reactions (eg, fever, malaise, myalgia) in older persons and healthy young adults.<sup>19</sup> 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.<sup>19</sup> 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.<sup>65</sup>

In early 2010 there were reports of children in both Australia and New Zealand who had received the influenza vaccine and experienced febrile seizures. All of the cases were linked to the Fluvax brand of vaccine.

Vaccinators need to emphasise to recipients that:

- it is an inactivated vaccine 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.

Local reactions, including redness and induration at the injection site, may persist for one to two days in 10–64 percent of adult recipients, but these effects are usually mild.<sup>19</sup> Passive reporting of local and systemic reactions to influenza vaccines is more frequent for females (both young and older adults) than males.<sup>66</sup>

In 2010 an association was found between one H1N1 pandemic vaccine (an adjuvanted vaccine not licensed or used in New Zealand) and narcolepsy. There is now data from a number of European countries that supports a temporal link.<sup>67, 68, 69</sup> The association may have been related to the adjuvant. However, it is possible that the onset of narcolepsy may be confounded by other factors (such as genetic predisposition, (H1N1)pdm09 influenza and/or other environmental factors).<sup>68, 70, 71</sup> Further data is required to confirm the strength of this association and the size of the risk, and to identify the underlying biological mechanisms.<sup>68, 72</sup>

See section 10.6.3 for information on egg allergy.

## **Immune checkpoint inhibitors**

There have been reports of fatal myositis, myocarditis and rhabdomyolysis in patients being treated with ipilimumab with nivolumab and administered influenza vaccine.<sup>73</sup> A prospective study of



patients currently being treated with nivolumab or pembrolizumab and administered trivalent influenza vaccine found an increase in immune-related adverse events compared to unvaccinated patients being treated with these medicines.<sup>74</sup> See 'Oncology patients treated with immune checkpoint inhibitors' in section 4.3.3.

## 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 table tops
- antiviral therapy, but this has a limited role.

### 10.8.1 Improving vaccine uptake

Studies in New Zealand and overseas have found that provider attitudes and 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 March and April to immunise all people at risk, such as those aged 65 years and older, those aged under

65 years (including children) who have certain medical conditions, pregnant women and health care workers. A decision to offer immunisation in winter, during an influenza epidemic, to those who were not immunised in the autumn will depend on the circumstances of the outbreak or epidemic, among other factors. Availability of an appropriate vaccine is the most pertinent of these factors.

Vaccination of healthy adults and children is encouraged but is not funded by the Ministry of Health; adult vaccination 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. Use of antivirals very early in an illness can reduce the duration of symptoms and the risk of complications from influenza. Clinical benefit is greatest if antivirals are used as early as possible, especially within the first 48 hours of the illness.

Meta-analyses of the effectiveness of oseltamivir in treating uncomplicated influenza show a reduction in duration of symptoms for healthy adults and adolescents of around one day,<sup>75</sup> a 63 percent (95% CI: 19–83) decreased risk of hospitalisation for any cause and a 44 percent (95% CI: 25–58) decreased risk of antibiotic prescription use.<sup>76</sup> For use with severe influenza, observational studies show early treatment is critical, and can lead to a decreased risk for death.<sup>77, 78</sup>

Antivirals should be 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.<sup>79</sup>

### **10.8.3 Pandemics**

At the time of a pandemic, the 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*<sup>80</sup> describes the key phases of a pandemic and the actions and responsibilities within each phase.

## 10.9 Variations from the vaccine data sheet

The Influxac Tetra data sheet states that hypersensitivity to the residues of eggs is a contraindication to receiving influenza vaccination. The Ministry of Health recommends that individuals with hypersensitivity to eggs, including anaphylaxis, may receive influenza vaccination— see section 10.6.3.

### References

1. Ray R, Dos Santos G, Buck PO, et al. 2017. A review of the value of quadrivalent influenza vaccines and their potential contribution to influenza control. *Human Vaccines & Immunotherapeutics* 13(7): 1640–52. URL: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5512791/> (accessed 15 January 2018).
2. Fine PEM, Mulholland K. 2013. Community immunity. In: Plotkin SA, Orenstein WA, Offit PA (eds). *Vaccines* (6th edition). Philadelphia, PA: Elsevier Saunders.
3. Lowen AC, Mubareka S, Steel J, et al. 2007. Influenza virus transmission is dependent on relative humidity and temperature. *PLOS Pathogens* 3(10): e151. DOI: 10.1371/journal.ppat.0030151 (accessed 29 October 2013).
4. Hayward AC, Fragaszy EB, Bermingham A, et al. 2014. Comparative community burden and severity of seasonal and pandemic influenza: results of the Flu Watch cohort study. *The Lancet Respiratory Medicine* 2(6): 445–54. URL: <http://www.thelancet.com/journals/lanres/article/PIIS2213-2600%2814%2970034-7/fulltext> (accessed 21 November 2016).
5. Huang S (on behalf of the SHIVERS Investigation team). 2016. *Key Findings – SHIVERS*. Presented at the 2016 New Zealand Influenza Symposium (updated January 2017). URL: <http://www.immune.org.nz/sites/default/files/Conferences/2016/NZiS2016/8%201310%2020161102%20NZiS%20SHIVERSRevisedJan2017.pdf> (accessed 20 February 2017).
6. World Health Organization. 2014. *Influenza (Seasonal)*. URL: <http://www.who.int/mediacentre/factsheets/fs211/en/> (accessed 17 November 2016).

7. World Health Organization. 2010. *Pandemic (H1N1) 2009 – Update 112 (6 August 2010)*. URL: [http://www.who.int/csr/don/2010\\_08\\_06/en/](http://www.who.int/csr/don/2010_08_06/en/) (accessed 28 November 2016).
8. Institute of Environmental Science and Research Ltd. 2016. *Influenza Surveillance in New Zealand 2015*. URL: [https://surv.esr.cri.nz/PDF\\_surveillance/Virology/FluAnnRpt/InfluenzaAnn2015.pdf](https://surv.esr.cri.nz/PDF_surveillance/Virology/FluAnnRpt/InfluenzaAnn2015.pdf) (accessed 17 November 2016).
9. Institute of Environmental Science and Research Ltd. 2017. New Zealand National Influenza Centre Intelligence Report Week 39 (25 September–1 October 2017). *Influenza Weekly Update*. URL: [https://surv.esr.cri.nz/PDF\\_surveillance/Virology/FluWeekRpt/2017/MoH\\_Influenza\\_Report/MoHInfluenzaRpt201739.pdf](https://surv.esr.cri.nz/PDF_surveillance/Virology/FluWeekRpt/2017/MoH_Influenza_Report/MoHInfluenzaRpt201739.pdf)
10. Institute of Environmental Science and Research Ltd. 2018. Community and hospital surveillance – December 2017. *Influenza surveillance summary*. URL: [https://surv.esr.cri.nz/PDF\\_surveillance/Virology/FluMthRpt/2017/FluMthRpt201712.pdf](https://surv.esr.cri.nz/PDF_surveillance/Virology/FluMthRpt/2017/FluMthRpt201712.pdf)
11. Institute of Environmental Science and Research Ltd. 2017. *Influenza Surveillance in New Zealand 2016*. URL: [https://surv.esr.cri.nz/PDF\\_surveillance/Virology/FluAnnRpt/InfluenzaAnn2016.pdf](https://surv.esr.cri.nz/PDF_surveillance/Virology/FluAnnRpt/InfluenzaAnn2016.pdf) (accessed 31 January 2018).
12. Institute of Environmental Science and Research Ltd. 2009. *Seroprevalence of the 2009 Influenza A (H1N1) Pandemic in New Zealand*. URL: [www.health.govt.nz/publication/seroprevalence-2009-influenza-h1n1-pandemic-new-zealand](http://www.health.govt.nz/publication/seroprevalence-2009-influenza-h1n1-pandemic-new-zealand) (accessed 29 October 2013).
13. Siston AM, Rasmussen SA, Honein MA, et al. 2010. Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. *Journal of the American Medical Association* 303(15): 1517–25.
14. Patel SM, Atmar RL, El Sahly HM, et al. 2012. Direct comparison of an inactivated subvirion influenza A virus subtype H5N1 vaccine administered by the intradermal and intramuscular routes. *Journal of Infectious Diseases* 206(7): 1069–77.
15. Roukens AHE, Gelinck LBS, Visser LG. 2012. Intradermal vaccination to protect against yellow fever and influenza. *Current Topics in Microbiology and Immunology* 351: 159–79. DOI: 10.1007/82\_2011\_124 (accessed 12 November 2012).
16. Marra F, Young F, Richardson K, et al. 2012. A meta-analysis of intradermal versus intramuscular influenza vaccines: immunogenicity and adverse events. *Influenza and Other Respiratory Viruses* 7(4): 584–603. DOI: 10.1111/irv.12000 (accessed 15 December 2012).

17. World Health Organization. 2017. *Recommended Composition of Influenza Virus Vaccines For Use in the 2018 Southern Hemisphere Influenza Season*. URL: [http://www.who.int/influenza/vaccines/virus/recommendations/201709\\_recommendation.pdf?ua=1](http://www.who.int/influenza/vaccines/virus/recommendations/201709_recommendation.pdf?ua=1) (accessed 22 December 2017).
18. Esposito S, Tagliabue C, Tagliaferri L, et al. 2012. Preventing influenza in younger children. *Clinical Microbiology and Infection* 18(Suppl 5): 42–9.
19. Centers for Disease Control and Prevention. 2016. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices – United States, 2016–17 influenza season. *Morbidity and Mortality Weekly Report: Recommendations and Reports* 65(RR05): URL: <https://www.cdc.gov/mmwr/volumes/65/rr/rr6505a1.htm> (accessed 12 September 2016).
20. Osterholm MT, Kelley NS, Sommer A, et al. 2012. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. *The Lancet Infectious Diseases* 12(1): 36–44.
21. Pebody R, Warburton F, Ellis J, et al. 2016. Effectiveness of seasonal influenza vaccine for adults and children in preventing laboratory-confirmed influenza in primary care in the United Kingdom: 2015/16 end-of-season results. *Euro Surveillance* 31(38): pii=30348. URL: <http://www.eurosurveillance.org/images/dynamic/EE/V21N38/art22592.pdf> (accessed 7 November 2016).
22. Fiore AE, Bridges CB, Katz JM, et al. 2013. Inactivated influenza vaccines. In: Plotkin SA, Orenstein WA, Offit PA (eds). *Vaccines* (6th edition). Philadelphia, PA: Elsevier Saunders.
23. Skowronski DM, Chambers C, Sabaiduc S, et al. 2016. A perfect storm: impact of genomic variation and serial vaccination on low influenza vaccine effectiveness during the 2014–2015 season. *Clinical Infectious Diseases* 63(1): 23–32. URL: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4901864/> (accessed 7 November 2016).
24. Eick AA, Uyeki TM, Klimov A, et al. 2011. Maternal influenza vaccination and effect on influenza virus infection in young infants. *Archives of Pediatrics and Adolescent Medicine* 165(2): 104–11.
25. Poehling KA, Szilagyi PG, Staat MA, et al. 2011. Impact of maternal immunization on influenza hospitalizations in infants. *American Journal of Obstetrics and Gynecology* 204(6 Suppl 1): S141–8.

26. Jefferson T, Rivetti A, Di Pietrantonj C, et al. Vaccines for preventing influenza in healthy children. *Cochrane Database of Systematic Reviews* 2012, Issue 8, Art. No. CD004879. DOI: 10.1002/14651858.CD004879.pub4 (accessed 13 November 2012).
27. Heinonen S, Silvennoinen H, Lehtinen P, et al. 2011. Effectiveness of inactivated influenza vaccine in children aged 9 months to 3 years: An observational cohort study. *The Lancet Infectious Diseases* 11(1): 23–9.
28. Jefferson T, Di Pietrantonj C, Rivetti A, et al. Vaccines for preventing influenza in healthy adults. *Cochrane Database of Systematic Reviews* 2010, Issue 7, Art. No. CD001269. DOI: 10.1002/14651858.CD001269.pub4 (accessed 13 November 2012).
29. Jefferson T, Di Pietrantonj C, Al-Ansary LA, et al. Vaccines for preventing influenza in the elderly. *Cochrane Database of Systematic Reviews* 2010, Issue 2, Art. No. CD004876. DOI: 10.1002/14651858.CD004876.pub3 (accessed 13 November 2012).
30. Beyer WEP, McElhaney J, Smith DJ, et al. 2013. Cochrane re-arranged: support for policies to vaccinate elderly people against influenza. *Vaccine* 31(50): URL: <http://dx.doi.org/10.1016/j.vaccine.2013.09.063> (accessed 11 November 2013).
31. Turner N, Pierse N, Bissielo A, et al (on behalf of the SHIVERS Investigation team). 2014. The effectiveness of seasonal trivalent inactivated influenza vaccine in preventing laboratory confirmed influenza hospitalisations in Auckland, New Zealand in 2012. *Vaccine* 32(29): 3687–93.
32. Turner N, Pierse N, Bissielo A, et al (on behalf of the SHIVERS Investigation team). 2014. Effectiveness of seasonal trivalent inactivated influenza vaccine in preventing influenza hospitalisations and primary care visits in Auckland, New Zealand, in 2013. *Euro Surveillance* 19(34): pii=20884. URL: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20884> (accessed 3 November 2016).
33. Pierse N, Kelly H, Thompson MG, et al (on behalf of the SHIVERS Investigation team). 2016. Influenza vaccine effectiveness for hospital and community patients using control groups with and without non-influenza respiratory viruses detected, Auckland, New Zealand 2014. *Vaccine* 34(4): 503–9. URL: <http://dx.doi.org/10.1016/j.vaccine.2015.11.073> (accessed 3 November 2016).

34. Bissielo A, Pierse N, Huang S, et al (on behalf of the SHIVERS Investigation team). 2016. Effectiveness of seasonal influenza vaccine in preventing influenza primary care visits and hospitalisation in Auckland, New Zealand in 2015: interim estimates. *Euro Surveillance* 21(1): pii=30101. URL: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=21342> (accessed 3 November 2016).
35. Tamma PD, Ault KA, del Rio C, et al. 2009. Safety of influenza vaccination during pregnancy. *American Journal of Obstetrics and Gynecology* 201(6): 547–52.
36. Zaman K, Roy E, Arifeen SE, et al. 2008. Effectiveness of maternal influenza immunization in mothers and infants. *New England Journal of Medicine* 359(15): 1555–64.
37. Marshall H, McMillan M, Andrews RM et al. 2016. Vaccines in pregnancy: the dual benefit for pregnant women and infants. *Human Vaccines & Immunotherapeutics* 12(4): 848–56. DOI: 10.1080/21645515.2015.1127485 (accessed 24 September 2016).
38. Regan A, Moore HC, de Klerk N, et al. 2016. Seasonal trivalent influenza vaccination during pregnancy and the incidence of stillbirth: population-based retrospective cohort study. *Clinical Infectious Diseases* 62(10): 1221–7. DOI: 10.1093/cid/ciw082 (accessed 17 November 2016).
39. Govaert TME, Thijs C, Masurel N, et al. 1994. The efficacy of influenza vaccination in elderly individuals: a randomized double blind placebo controlled trial. *Journal of the American Medical Association* 272(21): 1661–5.
40. Gross PA, Hermogenes AW, Sacks HS, et al. 1995. The efficacy of influenza vaccine in elderly persons: A meta-analysis and review of the literature. *The Annals of Internal Medicine* 123(7): 518–27.
41. Deguchi Y, Takasugi Y, Tatara K. 2000. Efficacy of influenza vaccine in the elderly in welfare nursing homes: Reduction in risks of mortality and morbidity during an influenza A (H3N2) epidemic. *Journal of Medical Microbiology* 49(6): 553–6.
42. Gross PA, Quinnan GV, Rodstein M, et al. 1988. Association of influenza immunization with reduction in mortality in an elderly population: a prospective study. *Archives of Internal Medicine* 148(3): 562–5.
43. Saah AJ, Neufeld R, Rodstein M, et al. 1986. Influenza vaccine and pneumonia mortality in a nursing home population. *Archives of Internal Medicine* 146(1): 2353–7.

44. Hak E, Buskens E, van Essen GA, et al. 2005. Clinical effectiveness of influenza vaccination in persons younger than 65 years with high-risk medical conditions: the PRISMA study. *Archives of Internal Medicine* 165(3): 274–80.
45. Looijmans-Van den Akker I, Verheij TJ, Buskens E, et al. 2006. Clinical effectiveness of first and repeat influenza vaccination in adult and elderly diabetic patients. *Diabetes Care* 29(8): 1771–6.
46. Poole PJ, Chacko E, Wood-Baker RW, et al. Influenza vaccine for patients with chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2006, Issue 1, Art. No. CD002733. DOI: 10.1002/14651858.CD002733.pub2 (accessed 29 October 2013).
47. MacIntyre R, Heywood A, Kovoov P, et al. 2013. Ischaemic heart disease, influenza and influenza vaccination: a prospective case control study. *Heart* 99(24): 1843–8. DOI: 10.1136/heartjnl-2013-304320 (accessed 13 November 2013).
48. Mertz D, Fadel SA, Lam P, et al. 2016. Herd effect from influenza vaccination in non-healthcare settings: a systematic review of randomised controlled trials and observational studies. *Euro Surveillance* 21(42): pii=30378. URL: <http://dx.doi.org/10.2807/1560-7917.ES.2016.21.42.30378> (accessed 28 November 2016).
49. Oshitani H, Saito R, Seki N, et al. 2000. Influenza vaccination levels and influenza- like illness in long- term care facilities for elderly people in Niigata, Japan, during an influenza A (H3N2) epidemic. *Infection Control and Hospital Epidemiology* 21(11): 728–30.
50. Hayward AC, Harling R, Wetten S, et al. 2006. Effectiveness of an influenza vaccine programme for care home staff to prevent death, morbidity, and health service use among residents: cluster randomised controlled trial. *British Medical Journal* 33(7581): 1241.
51. Pebody R. 2016. *UK Paediatric Influenza Vaccine Programme*. Presented at the 2016 New Zealand Influenza Symposium. URL: [www.immune.org.nz/sites/default/files/Conferences/2016/NZiS2016/Child%20flu%20programme%20Pebody%20%20New%20Zealand.pdf](http://www.immune.org.nz/sites/default/files/Conferences/2016/NZiS2016/Child%20flu%20programme%20Pebody%20%20New%20Zealand.pdf) (accessed 28 November 2016).
52. Gaglani MJ, Piedra PA, Herschler GB, et al. 2004. Direct and total effectiveness of the intranasal, live-attenuated, trivalent cold-adapted influenza virus vaccine against the 2000–2001 influenza A(H1N1) and B epidemic in healthy children. *Archives of Pediatric and Adolescent Medicine* 158(1): 65–73.



53. Ambrose CS, Yi T, Walker RE, et al. 2008. Duration of protection provided by live attenuated influenza vaccine in children. *Pediatric Infectious Disease Journal* 27(8): 744–8. DOI: 10.1097/INF.ob013e318174e0f8 (accessed 4 November 2013).
54. Ministry of Health. 2017. *National Standards for Vaccine Storage and Transportation for Immunisation Providers 2017*. URL: [www.health.govt.nz/coldchain](http://www.health.govt.nz/coldchain) (accessed 14 February 2017).
55. Department of Health and Ageing. 2016. Vaccination for special risk groups. In: *The Australian Immunisation Handbook* (10th edition; updated August 2016). URL: <http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook10-home~handbook10part3> (accessed 1 September 2016).
56. Levin MJ, Buchwald UK, Gardner J, et al. 2018. Immunogenicity and safety of zoster vaccine live administered with quadrivalent influenza virus vaccine. *Vaccine* 36(1): 179–85. URL: <http://www.sciencedirect.com/science/article/pii/S0264410X17310964>
57. Tse A, Tseng HF, Greene SK, et al. 2012. Signal identification and evaluation for risk of febrile seizures in children following trivalent inactivated influenza vaccine in the Vaccine Safety Datalink Project, 2010–2011. *Vaccine* 30(11): 2024–31.
58. Van Buynder PG, Frosst G, Van Buynder JL, et al. 2012. Increased reactions to pediatric influenza vaccination following concomitant pneumococcal vaccination. *Influenza and Other Respiratory Viruses* 7(2): 184–90. DOI: 10.1111/j.1750-2659.2012.00364.x (accessed 15 November 2012).
59. Zuckerman M, Cox R, Taylor J, et al. 1993. Rapid immune response to influenza vaccine. *The Lancet* 342(8879): 1113.
60. Bednarczyk RA, Adjaye- Gbewonyo D, Omer SB. 2012. Safety of influenza immunization during pregnancy for the fetus and the neonate. *American Journal of Obstetrics and Gynecology* 207(3 Suppl): 38–46.
61. Vellozzi C, Iqbal S, Broder K. 2016. Guillain-Barré syndrome, influenza, and influenza vaccination: the epidemiologic evidence. *Clinical Infectious Diseases* 58(8): 1149–55. DOI: 10.1093/cid/ciu005 (accessed 14 February 2017).
62. Australasian Society of Clinical Immunology and Allergy. 2017. Vaccination of the egg-allergic individual. *ASCI Guidelines* URL: [https://www.allergy.org.au/images/stories/pospapers/ASCI\\_Guidelines\\_vaccination\\_egg\\_allergic\\_individual\\_2017.pdf](https://www.allergy.org.au/images/stories/pospapers/ASCI_Guidelines_vaccination_egg_allergic_individual_2017.pdf) (accessed 15 January 2018).

63. Mylan New Zealand Ltd. 2017. *Influvac Tetra Data Sheet*. URL: <http://www.medsafe.govt.nz/profs/Datasheet/i/InfluvacTetrainj.pdf> (accessed 20 February 2018).
64. GlaxoSmithKline Australia Pty Ltd. 2017. *Fluarix Tetra Product Information*. URL: [https://au.gsk.com/media/416636/fluairix-tetra\\_pi\\_007.pdf](https://au.gsk.com/media/416636/fluairix-tetra_pi_007.pdf) (accessed 19 January 2018).
65. France EK, Glanz JM, Xu S, et al. 2004. Safety of the trivalent inactivated influenza vaccine among children: a population-based study. *Archives of Pediatric & Adolescent Medicine* 158(11): 1031–6. DOI: 10.1001/archpedi.158.11.1031 (accessed 3 November 2016).
66. Klein SL, Marriott I, Fish EN. 2015. Sex-based differences in immune function and responses to vaccination. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 109(1): 9–15. DOI: 10.1093/trstmh/tru167 (accessed 3 November 2016).
67. National Institute for Health and Welfare (THL). 2011. *Reported incidence of narcolepsy in children and adolescents after Pandremix/Arepanrix vaccination*. URL: [https://www.thl.fi/documents/10531/104009/Narkolepsia\\_posteri.pdf](https://www.thl.fi/documents/10531/104009/Narkolepsia_posteri.pdf) (accessed 14 February 2017).
68. European Centre for Disease Prevention and Control. 2012. *Narcolepsy in association with pandemic influenza vaccination (a multi-country European epidemiological investigation)*. URL: <http://ecdc.europa.eu/en/publications/Publications/Vaesco%20report%20oFINAL%20with%20cover.pdf> (accessed 14 February 2017).
69. World Health Organization. 2011. *Statement on Narcolepsy and Vaccination*. URL: [http://www.who.int/vaccine\\_safety/committee/topics/influenza/pandemic/h1n1\\_safety\\_assessing/narcolepsy\\_statement/en/](http://www.who.int/vaccine_safety/committee/topics/influenza/pandemic/h1n1_safety_assessing/narcolepsy_statement/en/) (accessed 15 December 2012).
70. Dauvilliers Y, Montplaisir J, Cochen V, et al. 2010. Post-H1N1 narcolepsy-cataplexy. *Sleep* 33(11): 1428–30.
71. Han F, Lin L, Warby SC, et al. 2011. Narcolepsy onset is seasonal and increased following the 2009 H1N1 pandemic in China. *Annals of Neurology* 70(3): 410–7.
72. World Health Organization. 2013. Global Advisory Committee on Vaccine Safety, 12–13 June 2013. *Weekly Epidemiological Record* 88(29): 301–12. URL: [www.who.int/vaccine\\_safety/committee/reports/wer8829.pdf](http://www.who.int/vaccine_safety/committee/reports/wer8829.pdf) (accessed 4 November 2013).

73. Cancer Institute NSW. 2017. *Melanoma Metastatic Ipilimumab and Nivolumab (induction)*. eviQ Cancer Treatments Online. ID: 1694 v.2. URL: <https://www.eviq.org.au/medical-oncology/melanoma/metastatic/1694-melanoma-metastatic-ipilimumab-and-nivolumab#15627>
74. European Lung Cancer Conference (ELCC) 2017. 2017. *Press Release: Annual Flu Jab May Pose Greater Risk for Lung Cancer Patients Under Immunotherapy*. URL: <http://www.esmo.org/Conferences/Past-Conferences/ELCC-2017-Lung-Cancer/News-Press-Releases/Annual-Flu-Jab-May-Pose-Greater-Risk-for-Lung-Cancer-Patients-Under-Immunotherapy>
75. Jefferson T, Jones M, Doshi P, et al. 2014. Oseltamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments. *British Medical Journal* 348(9 April): g2545. DOI: 10.1136/bmj.g2545 (accessed 28 November 2016).
76. Dobson J, Whitley RJ, Pocock S, et al. 2015. Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials. *The Lancet* 385(9979): 1729–37. URL: [http://dx.doi.org/10.1016/S0140-6736\(14\)62449-1](http://dx.doi.org/10.1016/S0140-6736(14)62449-1) (accessed 28 November 2016).
77. Muthuri SG, Venkatesan S, Myles PR, et al. 2014. Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. *The Lancet Respiratory Medicine* 2(5): 395–404.
78. Hiba V, Chowders M, Levi-Vinograd I, et al. 2011. Benefit of early treatment with oseltamivir in hospitalized patients with documented 2009 influenza A (H1N1): retrospective cohort study. *Journal of Antimicrobial Chemotherapy* 66(5): 1150–5.
79. Ministry of Health. 2017. *Guidance on Infectious Disease Management under the Health Act 1956*. URL: <http://www.health.govt.nz/publication/guidance-infectious-disease-management-under-health-act-1956> (accessed 20 February 2017).
80. Ministry of Health. 2010. *New Zealand Influenza Pandemic Plan: A framework for action*. URL: [www.health.govt.nz/publication/new-zealand-influenza-pandemic-plan-framework-action](http://www.health.govt.nz/publication/new-zealand-influenza-pandemic-plan-framework-action) (accessed 29 August 2013).