

# Influenza vaccination in the over 65s

## Winter is coming

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Influenza infection, particularly with influenza A(H3N2) strains, can cause severe morbidity and mortality in older people. Enhanced adjuvanted and high-dose vaccines that provide superior protection than conventional quadrivalent inactivated influenza vaccines are available for people aged 65 years and older. With the possibility of an early influenza season predominated by influenza A(H3N2) in 2023, these enhanced vaccines should be offered to people in this age group. Adjuvanted vaccines are provided free for this age group under the National Immunisation Program.

Influenza virus infection can cause serious illness resulting in severe burden on the Australian healthcare system. The WHO estimates that, globally, seasonal influenza causes three to five million cases of severe illness and 290,000 to 650,000 deaths every year.<sup>1</sup> Influenza affects both industrialised and developing countries. Although data are limited, a recent meta-analysis estimated 82% of deaths in children aged under 5 years with influenza-related acute lower respiratory tract infections occurred in lower-middle income countries.<sup>2</sup> However, influenza more often results in severe disease in people with chronic underlying conditions and older people, and most influenza-associated mortality occurs in older adults.<sup>3</sup>

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### Key points

- In Australia, most cases of serious influenza disease and influenza-related deaths occur in adults aged 65 years and older; long-term sequelae that impact on activities of daily living are also common in this group.
- Standard influenza vaccines offer suboptimal levels of protection in older adults. Two enhanced influenza vaccines are available in Australia for this population; both have a good safety profile.
- The adjuvanted influenza vaccine may provide enhanced protection to older adults and is recommended and funded under the National Immunisation Program (NIP) for people aged 65 years and older in 2023.
- A high-dose version of the standard trivalent vaccine may also provide enhanced protection to older people; however, it is not funded under the NIP in 2023.
- With Omicron variants of the SARS-CoV-2 virus continuing to circulate in Australia, with significant associated mortality, the possibility of combined infections exists this coming winter.
- General practice staff are key partners in encouraging and increasing the level of vaccination coverage in older people.
- This year, the message to get older people vaccinated will require extra effort from immunisers to counter the 'post-COVID' vaccine hesitancy in this age group, reflected by poor COVID booster uptake numbers.

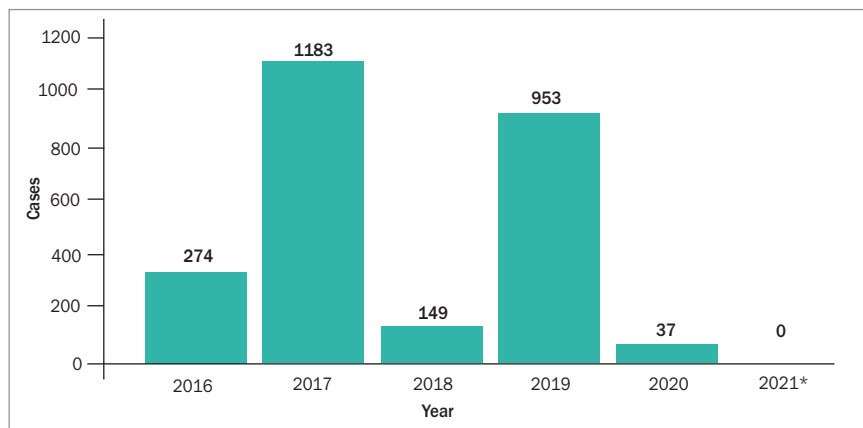


Figure. Annual laboratory-confirmed influenza-related deaths in Australia recorded by the National Notifiable Disease Surveillance System between 2016 and 2021.<sup>5,6</sup>

\* No influenza deaths were reported in 2021 due to border closures during the COVID-19 pandemic.

### Influenza in older people

The epidemiology of influenza infections has been chaotic since the arrival of the SARS-CoV-2 virus pandemic. After an intense prolonged influenza season in 2019,<sup>4</sup> the non-pharmaceutical interventions in 2020 and 2021 (i.e. lockdown and border closures) led to an absence of influenza in the winter of both those years. After international borders opened and community restrictions were eased, influenza came roaring back with an early peak in April and May of 2022 (Figure).<sup>5,6</sup>

In 2019, the largest nonpandemic influenza season on record in Australia (313,000 notifications), 86% of the reported 902 influenza-related deaths were in people over 65 years of age.<sup>4</sup> Much of the impact of influenza in older people is hidden and presents as previously undetected underlying medical conditions or as a worsening of existing conditions, especially cardiovascular disease.<sup>7</sup> For example, acute influenza can lead to decompensation in patients with congestive heart failure or diabetes mellitus and to an increased risk of myocardial infarction and stroke. As patients with these conditions are rarely tested for influenza, the burden of disease is greatly underestimated.<sup>8</sup>

Influenza can present differently in older adults, who often have a lower incidence of fever; less respiratory symptoms, such as cough, wheezing and chest pain; and atypical disease, with anorexia, mental status changes or unexplained fever as the only presenting symptoms.<sup>9,10</sup> Patients with underlying chronic obstructive pulmonary disease may experience worsening respiratory status. Acute myocardial

infarctions or heart failure may be unrecognised complications.<sup>11,12</sup> Pneumonia is a relatively common complication, especially in people with chronic cardiopulmonary disease.<sup>13</sup> Influenza may also significantly impair glucose control in patients with diabetes.<sup>14</sup>

Older people hospitalised with influenza are more likely to experience a decline in the capacity for activities of daily living after infection.<sup>15,16</sup> The occurrence of permanent disabilities from influenza-related illness is increasing as populations age, causing major suffering in older adults and mandating the search for effective prevention programs.<sup>17</sup>

### Influenza virus types

Two influenza virus types predominantly cause human illness: influenza A and influenza B, each with distinct characteristics and effects on different age groups. Influenza A viruses cause more severe illness and are further subdivided into subtypes A(H1N1) and A(H3N2), according to differences in the two surface proteins haemagglutinin (H) and neuraminidase (N). Influenza A has the greatest impact on older adults and young infants, whereas influenza B is more likely to occur in those aged under 20 years.<sup>18</sup>

The highest rates of influenza-related morbidity and mortality occur in people aged over 65 years infected with A(H3N2) strains.<sup>19</sup> There is a direct relationship between seasons when an influenza A(H3N2) strain is the predominant strain in circulation and increased hospitalisations with influenza-associated respiratory and circulatory conditions. No link

has been shown between levels of circulation of influenza B viruses and excess mortality or seasonal surges in hospitalisations.<sup>20,21</sup>

### Influenza vaccine responses in older people

An age-related decline in immune function that impairs the ability of older people to fight natural infections is known as immunosenescence and also results in suboptimal immune responses to influenza vaccines.<sup>22</sup> Both adaptive and innate immunity decline with age in those aged over 65 years. Influenza vaccine effectiveness in older people varies according to the circulating strain, and is lower in years when influenza A(H3N2) predominates. Older adults have the poorest antibody-mediated immune responses to the A(H3N2) components of vaccines and also display lower cellular immunity to influenza A(H3N2).

Results of previous studies showing that standard influenza vaccination offered little protection in this older age group may have been clouded by a mismatch in some years between viral strains in the vaccine and those circulating in the population, and the different outcomes evaluated. Indeed, studies have shown that vaccination with inactivated influenza vaccine may halve the incidence of laboratory-confirmed and clinical influenza and decrease the severity of disease, as evidenced by lower hospitalisation rates and fewer admissions to intensive care units, in those infected.<sup>23,24</sup>

The introduction of a new adjuvanted vaccine, initially trivalent but now quadrivalent, has significantly improved vaccine protection in older people. In 2019, data from Queensland showed a 60% reduction in hospitalisations in those aged over 65 years after the introduction of the quadrivalent adjuvanted vaccine, compared with a similarly intense year in 2017, when nonadjuvanted vaccine was used to vaccinate this group.<sup>25,26</sup> Vaccine effectiveness data from 2019 revealed that nonadjuvanted vaccine was more effective in older people compared with younger people using traditional quadrivalent inactivated vaccines, despite immunosenescence issues.<sup>27</sup>

### Influenza vaccines recommended for older people

Influenza vaccination is recommended and funded in Australia for all people aged 65 years

## 1. Recommended composition of quadrivalent vaccines for the 2023 southern hemisphere influenza season<sup>28</sup>

### Quadrivalent egg-based vaccine viruses

- A/Sydney/5/2021 (H1N1) pdm09-like virus
- Darwin/9/2021 (H3N2)-like virus
- Austria/1359417/2021 (B/Victoria lineage)-like virus
- B/Phuket/3073/2013 (B/Yamagata lineage)-like virus

### Quadrivalent cell or recombinant vaccine viruses

- A/Sydney/5/2021 (H1N1) pdm09-like virus
- A/Darwin/6/2021 (H3N2)-like virus
- B/Austria/1359417/2021 (B/Victoria lineage)-like virus
- B/Phuket/3073/2013 (B/Yamagata lineage)-like virus

and older. The most widely used influenza vaccines are quadrivalent formulations of inactivated haemagglutinin and neuraminidase antigens, representative of the predominant A(H1N1), A(H3N2) and both B lineages, using the selected strains for each season recommended by the Australian Influenza Vaccination Committee. The recommended strains for the influenza vaccines for the 2023 southern hemisphere influenza season are listed in Box 1.<sup>28</sup>

Enhanced vaccines are required to provide adequate protection in older people.<sup>22</sup> The Australian Government funded two new enhanced vaccines for people aged 65 years and over for the first time in 2018: an adjuvanted vaccine and a high-dose vaccine. Both vaccines showed improved effectiveness in real-world studies and elicited greater antibody responses than standard influenza vaccines in clinical trials. Vaccines available in Australia in 2023 are shown in the Table.

Since 2019, only the adjuvanted vaccine has been provided at no cost under the National Immunisation Program (NIP), although the high-dose vaccine is available on the private market and is now licensed for the 60 to 64 years age group as well as those 65 years and over.

## Enhanced influenza vaccines

### Adjuvanted influenza vaccine

The adjuvanted influenza vaccine both enhances the magnitude of and broadens the immune response to improve protection during years when vaccine strains do not match circulating viruses.<sup>29,30</sup> The adjuvant MF59 is an oil-in-water emulsion based on squalene, which enhances both antigen presentation and T-cell priming. Importantly, a number of international studies of adjuvanted influenza vaccine found a significant increase in the response to influenza A(H3N2) in people aged over 65 years.<sup>31,32</sup> In 2023, the adjuvanted influenza vaccine is recommended as one of the two

**Table. Influenza vaccines available for use in different age groups in Australia for the 2023 influenza season**

Brand name (manufacturer)	Type of vaccine	Age group
Fluzone High-Dose (Sanofi-Aventis)	High-dose quadrivalent (QIV)	60 years and over
Fluad Quad (CSL Seqirus)	Adjuvanted QIV	65 years and over
FluQuadri (Sanofi-Aventis)	QIV	6 months and over
Flucelvax Quad (CSL Seqirus)	QIV	2 years and over
Fluarix Tetra (GlaxoSmithKline)	QIV	6 months and over
Influvac Tetra (Mylan Health)	QIV	18 years and over
Afluria Quad (CSL Seqirus)	QIV	5 years and over
Vaxigrip Tetra (Sanofi-Aventis)	QIV	6 months and over

## 2. Case study: a high-risk patient reluctant to receive influenza vaccine

Lachlan, aged 68 years, attends your surgery for a repeat prescription of angina medication. He has been relatively well but requires treatment with sublingual nitrates for occasional pain on exertion. You note that he has not received an influenza vaccine this year.

### Is Lachlan at a higher risk of adverse events from influenza infection?

Lachlan is in a high-risk group for adverse events from influenza because of his heart disease and older age. People vaccinated against influenza are much less likely to have a cardiac incident than those who are not vaccinated. Many influenza cases in older people present as worsening of a chronic condition.

Lachlan is concerned about being vaccinated. The last time he had a flu vaccine 20 years ago, he says he 'got the flu badly' and has not had a vaccine since.

### What can you tell Lachlan about the safety of the current influenza vaccines?

Both enhanced influenza vaccines are inactivated and contain only protein and cannot give you influenza. There are many possible reasons why Lachlan may have had the 'flu' after vaccination in the past, including the following.

- The influenza vaccine takes about two weeks to be effective. If a person is exposed to influenza virus in this period, they can be infected.
- Many other viruses circulate in winter, and Lachlan may have been infected by one of them.
- Influenza vaccines are not perfect; their effectiveness averages about 60%, varying from year to year. People can get influenza after receiving a vaccine, but the illness is usually milder and they are less likely to be hospitalised.

It is important that Lachlan is vaccinated against influenza because of his medical condition and age. Australia now imports enhanced vaccines that work better in older people, and he can receive one of these free today. The new vaccines are stronger and may cause some local side effects at the injection site and a mild fever and aches for a day, but no increase in serious adverse effects has been seen.

While Lachlan is there, you should also check his pneumococcal vaccination status.

### As vaccine effectiveness wanes over time, should he have an influenza booster dose later in the season?

There are limited data on the benefit of repeat influenza vaccination in the same season, but recent very late influenza seasons and significant summer outbreaks raise the question about how to deal with the decline in protection over time.

Two doses of influenza vaccine have shown only small levels of increase in immune markers. No technical advisory group in any country recommends two vaccine doses in a season. Also, only one vaccine is available on the 'free list' in Australia, so patients must out of pocket for a second dose.

A number of GPs have responded to outbreaks late in the year by selecting groups of clinic patients with chronic diseases and revaccinating them. This is unlikely to cause harm, but the extent of benefit is unclear.

preferred vaccines for use in older people and is the only one funded under the NIP.

### High-dose influenza vaccine

The high-dose influenza vaccine contains 60 mcg haemagglutinin per strain, instead of 15 mcg, and produces a dose-dependent increase in antibody response. It has been shown to induce a higher immune response in older adults, with improved efficacy against influenza infection compared with the standard influenza vaccine in clinical trials.<sup>33,34</sup> Although the high-dose influenza vaccine is recommended as one of the two preferred vaccines for use in older people, it

is not funded under the NIP.

### Benefit of enhanced vaccines

The predominant circulating strain (A(H3N2) or other) and the degree of match with the vaccine strains determine the attributable additional benefit of using an enhanced vaccine (adjuvanted or high dose) in any given year. However, several real-world studies on the effectiveness of enhanced vaccines in older people have shown about 25% extra protection against disease, and even higher additional protection against severe disease.<sup>32</sup> This additional protection has enormous implications for improving the burden of

disease associated with influenza in older people and research is currently underway to quantify these benefits in Australia.

### Safety of enhanced vaccines

The adjuvanted trivalent influenza vaccine has established a good safety record since it was licensed 20 years ago, with an analysis of 20,000 vaccinations showing a higher risk of solicited local or systemic reactions, but no increase in severe adverse effects or longer-term consequences.<sup>35</sup> High-dose trivalent influenza vaccines showed a similar small increase in local injection site reactions, most commonly pain at the site, and some increase in the rate of systemic adverse events. These reactions were largely mild and self-limiting, with no increase in the rate of serious adverse events.<sup>36</sup>

### Timing of influenza vaccination in older people

Data on influenza vaccine effectiveness over the course of the influenza season suggest that in a predominant A(H3N2) season, vaccine effectiveness falls about 8% per month, and vaccines may be ineffective four months after administration. In the years before COVID-19, influenza infections predominated in June, with vaccinations administered in May. However, given the influenza season occurred earlier in 2022, mainly during April and May, and may do so again this year, delaying vaccination until May no longer appears warranted, and vaccine should be used as soon as available. Immunological markers have been shown to persist for more than six months after administration of adjuvanted influenza vaccine; therefore, timing of vaccination may be less crucial with this vaccine.

### Influenza in the era of COVID-19

Although the emphasis on SARS-CoV-2 circulation in Australia has largely disappeared from both media and political commentary, regular waves of COVID-19 Omicron variants continue. At the end of January 2023, Victoria alone saw an average of 50 deaths a day from SARS-CoV-2 infection and over 800 aged care facilities experienced COVID-19 outbreaks. In the first two months of 2023, 2409 people died from COVID-19, more than the numbers in both 2020 and 2021. The ongoing morbidity and mortality, in older people in particular, are

### 3. Case study: a woman worried about getting influenza after vaccination

Bessie, aged 72 years, presents at your surgery in March to discuss influenza vaccination. She is ambivalent about receiving the vaccine because after she was vaccinated in 2017, she still got the flu.

#### What would you advise Bessie?

In 2017, when Bessie contracted influenza after vaccination, the vaccine was poorly effective against the influenza strain circulating in the community, and Australia had a massive influenza outbreak. New enhanced vaccines are available this year that are more effective in older people, and one of them, the adjuvanted vaccine, is available free of charge to this age group.

The greatest concern for older people is the influenza A(H3N2) virus subtype, which causes most hospitalisations and deaths, and is predicted to dominate this season. The enhanced vaccines provide better protection against this subtype. Anyone aged 65 years and over should be advised to receive an enhanced influenza vaccine.

While Bessie is there, you should also check her pneumococcal vaccination status.

#### Should you offer her an influenza vaccine now?

After influenza circulated in April and May in 2022, delaying vaccine administration in older people until early May is no longer considered appropriate. Therefore, Bessie should be offered the influenza vaccine in this visit. Although the effectiveness of standard inactivated influenza vaccines wanes with time, particularly against A(H3N2) strains, some immunological data suggest that the adjuvanted vaccine available on the National Immunisation Program in 2023 provides longer protection.

associated with a decrease in the uptake of COVID-19 vaccine boosters in people of all ages.

This vaccine hesitancy may roll over to influenza vaccine uptake this year with potentially severe consequences. Outbreaks of influenza A(H3N2) already occurring in neighbouring Asian countries suggest that it will likely be the dominating subtype this winter in Australia, and have greatest impact on older people. The likelihood that both influenza and SARS-CoV-2 will circulate together this winter is high. NIP-funded influenza vaccines for those aged 65 years and older are available now and vaccination should be encouraged as soon as possible in this age group.

#### Role of GPs

Vaccination is an important component of promoting healthy ageing. The coverage rate for influenza vaccination in people aged 65 years and older was 68.9% at the end of August 2022.<sup>37</sup> Although this was the highest rate of any age group, given its clear benefits in this age group, influenza vaccination for older people should continue to be encouraged, with the aim of increasing coverage rates.

GPs are key to improving vaccination rates.<sup>38</sup> Clearly communicating the rationale for vaccination in older people, including the high risk of morbidity and mortality with influenza virus infection and the benefit of

vaccination with a new, safe enhanced vaccine, with all patients in target groups is important, particularly those with chronic disease. Two case studies illustrating this approach are shown in Boxes 2 and 3.

#### Conclusion

Influenza remains a major public health problem in Australia that causes significant severe disease, long-term disability and mortality in older people. The theoretical advantages of adding an adjuvant have translated to real-world studies to improved protection for older people. For this reason, the use of an adjuvanted influenza vaccine in people aged 65 years and older is recommended and funded under the NIP for this age group. Healthcare practitioners should note these recommendations and ensure that their older patients are offered this seasonal vaccine designed specifically to protect older people. **RMT**

#### References

A list of references is included in the online version of this article ([www.respiratorymedicinetoday.com.au](http://www.respiratorymedicinetoday.com.au)).

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