Enhancing influenza vaccination in older people

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Seasonal influenza disease can be particularly severe in older people, but conventional trivalent and quadrivalent inactivated influenza vaccines can be ineffective in this age group when influenza A(H3N2) strains predominate. New enhanced trivalent vaccines are available and should be used in people aged 65 years and over.

Illness due to influenza virus infection poses a severe burden on Australian healthcare systems. Globally, the WHO estimates that seasonal influenza causes three to five million cases of severe illness and 290,000 to 650,000 deaths annually.[1] Influenza is a disease that affects both industrialised and developing countries. Although data from the developing world are limited, it is estimated that each year 99% of deaths in children under 5 years of age with influenza-related lower respiratory tract infections occur in developing countries.[2] However, influenza more often results in severe disease in people with chronic underlying conditions and in older people and most influenza-associated mortality occurs in older adults.[3]

KEY POINTS

- In Australia, the vast majority of cases of serious influenza disease and influenza-related deaths occur in adults aged 65 years and over; long-term sequelae that impact on activities of daily living are also common in this group.
- Standard influenza vaccines induce suboptimal antibody titres and show suboptimal levels of effectiveness in older adults. Two enhanced influenza vaccines are now available in Australia and should be used in older people; both have a good safety profile.
- During the 2019 influenza season in Australia, an adjuvanted trivalent vaccine that has been shown to provide enhanced protection in older adults is recommended and funded under the National Immunisation Program (NIP) for people aged 65 years and over.
- A high-dose version of the standard trivalent vaccine also provides enhanced protection in older people and is recommended for use in this group but is not funded under the NIP this year.
- The additional benefit of extra influenza B coverage and hence the need for a quadrivalent vaccine in older people has not been established. However, the benefit would be substantially less than the additional protection provided by enhanced vaccines.
- Influenza vaccine coverage in older people is about 75% each year; general practice staff are key partners in increasing this level of vaccination.

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In 2017, the largest nonpandemic influenza season on record in Australia, more than 90% of the reported 1100 influenza-related deaths were in adults aged over 65 years.[4] Much of the impact of influenza in older people is hidden and manifests as previously undetected underlying medical conditions or as a worsening of existing conditions, especially cardiovascular disease.[5] 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.[6]

Influenza can present differently in older adults, who often have a lower incidence of fever, more frequent lower 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.[7,8] Patients with underlying chronic obstructive pulmonary disease (COPD) may experience worsening respiratory status. Heart failure may be an unrecognised complication. Pneumonia is a relatively common complication, especially in people with chronic cardiopulmonary disease.

Of great importance are recent data that show influenza causing hospitalisation negatively affects functional status in older people and leads to a decline in capacity for activities of daily living after the infection.[9] As populations age, the occurrence of permanent disabilities due to influenza-related illness is increasing, causing major suffering and mandating the search for effective prevention programs.

Influenza viruses

There are two major influenza virus types that cause human illness, influenza A and B viruses, each with their own characteristics and effect on different community groups. Most severe human illness is due to influenza A viruses, further subdivided into A(H1N1) and A(H3N2) subtypes according to the two surface proteins haemagglutinin (H) and neuraminidase (N). Influenza A has its greatest impact on older adults and young infants, whereas influenza B is more likely to occur in the under 20 years age group.[10]

The highest rates of influenza-related morbidity and mortality occur in people aged over 65 years infected with A(H3N2) strains. 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.[11]

No link has been shown between levels of circulation of influenza B viruses and excess mortality or seasonal surges in hospitalisations.[12]

When I first diagnose a patient with diabetes, I don't ask them if they feel like taking insulin. Similarly, in winter when flu vaccine becomes available, I tell patients it has arrived and that I will give it to them while they are there. I get very few discussions or refusals. This is best practice.

US geriatrician

Influenza vaccine responses in older people

Immunosenescence, an age-related decline in immune function, impairs the ability of older adults to fight natural infections and also results in suboptimal immune responses to influenza vaccines.[13] Both adaptive and innate immunity decline with increasing age in the population aged over 65 years.

Although some studies have found little protection from the use of standard influenza vaccine in this older age group, conclusions are clouded by the 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 inactivated influenza vaccine may halve the incidence of laboratory-proven and clinical influenza.[14] Even when vaccination failed to stop infection, it did decrease the severity of disease, as evidenced by lower hospitalisation rates and fewer admissions to intensive care units.[15]

Influenza vaccine effectiveness in older people varies with the circulating strain, being 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).

Influenza vaccines

Influenza vaccination is recommended and funded in Australia for all people aged 65 years and over. Previously, the most widely used influenza vaccines were trivalent formulations of inactivated haemagglutinin and neuraminidase antigens representative of the predominant A(H1N1), A(H3N2) and B strains, using the selected strains recommended by WHO for each season. More recently, both influenza B strain lineages (B/Yamagata and B/Victoria) have been included in new quadrivalent influenza vaccines. The WHO recommended strains for the trivalent and quadrivalent influenza vaccines for the 2019 southern hemisphere influenza season are listed in Box 1.

Quadrivalent influenza vaccines may have benefit in children, who experience the highest burden of influenza B. However, they are relatively less advantageous for older people, in whom most serious disease is attributable to influenza A(H3N2), with little disease or serious disease being due to influenza B. Adding additional lineage coverage for influenza B to vaccines for older people would be of little benefit, as it has no impact on overcoming immunosenescence and improving effectiveness against influenza A disease.

Enhanced vaccines are required to provide adequate protection in older people.[16,17] The Australian Government funded two new enhanced vaccines for people aged 65 years and over for the first time in 2018: an adjuvanted trivalent vaccine and a

1. WHO RECOMMENDED COMPOSITION OF INFLUENZA VIRUS VACCINES FOR USE IN THE 2019 SOUTHERN HEMISPHERE INFLUENZA SEASON[1]

Quadrivalent egg-based vaccine viruses	Trivalent egg-based vaccine viruses
• A/Michigan/45/2015 (H1N1) pdm09-like virus • A/Switzerland/8060/2017 (H3N2)-like virus • B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage) • B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage)	• A/Michigan/45/2015 (H1N1) pdm09-like virus • A/Switzerland/8060/2017 (H3N2)-like virus • B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage)

TABLE. INFLUENZA VACCINES AVAILABLE FOR USE IN DIFFERENT AGE GROUPS IN AUSTRALIA FOR THE 2019 INFLUENZA SEASON

Brand name (manufacturer)	Type of vaccine	Age group
Trivalent vaccines		
Fluzone High-Dose (Sanofi-Aventis)	High-dose TIV	65 years and over
Fluad (Seqirus)	Adjuvanted TIV	65 years and over
Quadrivalent vaccines		
FluQuadri Junior (Sanofi-Aventis)	QIV	6 to 35 months
FluQuadri (Sanofi-Aventis)	QIV	3 years and over
Fluarix Tetra (GlaxoSmithKline)	QIV	6 months and over
Influvac Tetra (Mylan Health)	QIV	18 years and over
Afluria Quad (Seqirus)	QIV	5 years and over

Abbreviations: TIV = trivalent influenza vaccine; QIV = quadrivalent influenza vaccine.

high-dose trivalent vaccine. Both vaccines showed improved effectiveness in real-world studies and elicited greater antibody responses in clinical trials. In September 2017, the Chief Medical Officer of Australia issued guidance on the importance of vaccinating older patients and also of using the new enhanced vaccines in this specific age group.[18] Vaccines available in Australia in 2019 are shown in the Table.

Enhanced influenza vaccines

Adjuvanted influenza vaccine

The adjuvanted trivalent influenza vaccine not only enhances the magnitude of the immune response but also broadens the response to improve protection during years when vaccine strains do not match circulating viruses. 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.[19,20] In 2019, the adjuvanted trivalent influenza vaccine is recommended as one of the two preferred vaccines for use in older people and is funded under the National Immunisation Program (NIP).

High-dose influenza vaccine

The high-dose trivalent influenza vaccine contains 60 mcg haemagglutinin per strain, instead of 15 mcg, and produces a dose-dependent increase in antibody response. Several studies have shown that it induces higher immune responses in older adults, with improved efficacy in clinical trials against influenza infection compared with the standard trivalent influenza vaccine. The high-dose vaccine also shows improved efficacy in clinical trials.[21,22] Although high-dose influenza vaccine is recommended as a preferred vaccine for use in older people, it is not funded under the NIP in 2019.

Benefit of enhanced vaccines.

The attributable additional benefit of using an enhanced vaccine will vary from year to year depending on the predominant circulating strain (H3N2 or not) and the degree of match with the vaccine strains. However, in several real-life effectiveness studies in older people, enhanced vaccines have shown on average about 25% extra protection against disease and even higher additional protection against severe disease.[20] Given the burden of disease associated with influenza in older people, this additional protection has enormous implications. During the severe 2013-14 influenza season in the US, the Centers for Disease Control and Prevention estimated that each 5% increase in vaccine effectiveness saved 86,000 hospitalisations in that year.

Safety of enhanced vaccines

In the two decades since the adjuvanted trivalent influenza vaccine was licensed, it has established a good safety record. An integrated analysis by the manufacturer of data from 20,000 vaccinees in the safety database obtained in the strict monitoring conditions of clinical trials of the vaccine revealed a higher risk of solicited local or systemic reactions, but no increase in severe adverse effects or longer-term consequences.[23]

Similarly, safety studies with high-dose trivalent influenza vaccine showed a small increase in local injection site reactions, most commonly pain at the site, and some increase in systemic adverse event rates. These reactions were largely mild and

2. CASE STUDIES ON INFLUENZA VACCINATION

A high-risk patient reluctant to receive influenza vaccine

Jennifer, aged 68 years, attends your surgery for a repeat prescription of angina medication. She has been relatively well but occasionally experiences pain on exertion that requires treatment with sublingual nitrates. You note that she has not received influenza vaccine this year or previously.

Is Jennifer in a high-risk group?

Jennifer is in a high-risk group because of both her age and heart disease. 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.

Jennifer says she is concerned about being vaccinated. The last time she had a flu vaccine 20 years ago, she got the flu badly. She has not had a vaccine since.

What does Jennifer need to know?

There are many possible reasons that Jennifer may have had the 'flu' after vaccination in the past. These include:

- 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 Jennifer may have been infected by one of them.
- Influenza vaccine is not perfect; its 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.

Because of Jennifer's medical conditions and age, it is imperative that she is vaccinated against influenza. Australia now imports enhanced vaccines that work better in older people, and she can receive one of these free today.

The new stronger vaccines 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 Jennifer is there you should also check her pneumococcal vaccination status.

As vaccine effectiveness wanes over time should Jennifer have a booster dose later in the season?

There are few data about 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. When two doses of influenza vaccine were given in Hong Kong (a northern hemisphere and a southern hemisphere version), the increase in patient levels of immune markers was small. 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 pay personally 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.

A man worried about influenza B

Peter, aged 72 years, presents at your surgery in March to discuss influenza vaccines. He is ambivalent about receiving the vaccine because after he was vaccinated two years ago, he still got the flu. However, he is worried about media reports of the influenza B Brisbane strain and wants to protect himself against it.

What would you advise Peter?

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

Although there has been much talk in the media about strains of influenza B virus, the greatest concern for older people is influenza A(H3N2) virus, which causes most hospitalisations and deaths. The enhanced vaccines provide better protection against this subtype. There are no enhanced quadrivalent vaccines available, and adding extra limited protection against influenza B virus will not help in older people. They should receive an enhanced trivalent influenza vaccine.

While Peter is there, you should also check his pneumococcal vaccine status.

Will you give Peter influenza vaccine now?

It is not recommended that you give Peter influenza vaccine now. We know that the effectiveness of standard inactivated influenza vaccines wanes with time after administration. In older people, this applies particularly to vaccine against A(H3N2) strains, which may show no effectiveness by four to six months after administration. Some immunological data suggest that the adjuvanted vaccine available on the National Immunisation Program in 2019 provides longer protection, but the clinical relevance is not known. There is little circulation of influenza virus before June in Australia, and delaying vaccine administration in older people until early May is appropriate.

self-limiting. Again, no increase in the rate of serious adverse events was seen.[24]

Timing of influenza vaccination in older people

Recent data on influenza vaccine effectiveness over the course of the influenza season suggest that in a predominant H3N2 season, vaccine effectiveness falls about 8% per month; vaccine may no longer be effective four months after administration. This has led to debate about delaying vaccination until around May in older people in Australia to ensure they remain protected later in the influenza season.

Data show continued immunological markers for more than six months after administration of adjuvanted trivalent influenza vaccine, so timing may be less crucial with this vaccine. Nevertheless, substantial influenza activity before June is uncommon, and delaying vaccine until May appears reasonable.

Role of general practice

Vaccination is an important component of promoting healthy ageing. Current coverage rates with influenza vaccine in older people are too low, at about 75%.[25] This coverage level would not be accepted in

children, and in view of the clear benefit of vaccination and the amount of influenza-associated disease in older people, 75% coverage should not be accepted in this age group either. GPs are key to improving vaccination rates.[26] Having a clear rationale about the high risk of influenza in older people and the benefit of vaccination with a new safe enhanced vaccine, and sharing this with all patients in target groups is important. This is particularly the case for those with chronic disease. Two case studies on influenza vaccination that illustrate this approach are shown in Box 2.

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 increasing the antigen content (high-dose trivalent influenza vaccine) or adding an adjuvant (adjuvanted trivalent influenza vaccine) has translated in real-world studies to improved protection for older people.

For this reason, the Australian Government Department of Health has made available and recommended the use of high-dose trivalent influenza vaccine or adjuvanted trivalent influenza vaccine in people aged 65 years and over. Adjuvanted trivalent influenza vaccine is also currently funded under the NIP for this age group. Healthcare practitioners should note recent recommendations and ensure that their older patients are offered seasonal vaccine designed specifically to protect older people. MT

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