Influenza: overview on prevention and therapy

SUMMARY

Quadrivalent influenza vaccination is recommended annually for adults and children aged six months to 64 years.

High-dose or adjuvanted trivalent vaccines are recommended annually for people 65 years and over.

If started early enough, neuraminidase inhibitors reduce symptom duration by approximately one day. Treatment should be considered in patients with severe disease requiring hospitalisation or who are at risk of complications.

Chemoprophylaxis is not a substitute for vaccination but can be considered in high-risk individuals with an inadequate or ineffective vaccination status.

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Introduction

Influenza causes considerable morbidity and mortality in Australia each year. Routine vaccination is the most important intervention for preventing illness and severe complications. Hand hygiene, cough etiquette and voluntary home isolation are also important factors in reducing transmission. The mainstay of treatment is symptom control and management of secondary complications. However, a number of antiviral drugs are available to treat influenza. They also have a small role in prophylaxis.

Preventing influenza

Influenza is a viral infection, mainly of the respiratory tract. There are two influenza A subtypes circulating in humans – A/H1N1 and A/H3N2 – and two influenza B subtypes – the Yamagata and Victoria lineages.

Annual vaccination is recommended for all individuals above six months of age (with the exception of any patients who have previously experienced anaphylaxis to the influenza vaccine or one of its components). Annual influenza vaccination is funded under the National Immunisation Program for people at increased risk of influenza morbidity and mortality. This includes the following:

- those over six months of age with medical risk factors
- Aboriginal and Torres Strait Islanders aged six months and over
- all Australians aged over 65 years
- pregnant women.

Influenza in pregnancy is associated with an increased risk of maternal morbidity and mortality, along with preterm delivery. The influenza vaccine can be administered at any stage of pregnancy.

It is particularly important that healthcare providers in hospitals and general practices are vaccinated, given their likely exposure to individuals with influenza. This mitigates their potential for transmitting the virus, especially to people at risk of complications.

The antibody response to the vaccine takes approximately two weeks, with a period of optimal vaccine efficacy of around four months post vaccination. In Australia the seasonal influenza vaccine becomes available in March or April, and this is an appropriate time to vaccinate. The existence of several subtypes, along with seasonal antigenic changes, makes it difficult to predict which influenza strain will cause the most substantial burden of disease each year.

Given that the vaccine formulation is determined nine months before the influenza season, the strains included are based on the previous winter's circulating viruses, and are an informed prediction of what will be most prevalent in the coming season. Vaccine efficacy is variable from year to year and in different populations because of this.

Trivalent and quadrivalent vaccines

There is a range of different influenza vaccines available in Australia[1-7], some of which are provided through the National Immunisation Program (see Table).[8] Trivalent vaccines cover the two influenza A types and a single B lineage whereas the quadrivalent vaccines cover the additional B virus lineage. There is evidence in the transition from trivalent to quadrivalent vaccines that the

Table   **2019 Australian seasonal influenza vaccines available on the National Immunisation Program**

Type of vaccine	Age group	Brand name	Efficacy in clinical trials
Quadrivalent	6–35 months	FluQuadri Junior	The quadrivalent vaccines elicited non-inferior antibody responses to all A strains and corresponding B strains compared to a trivalent vaccine. Superior immunogenicity was shown for non-corresponding B strains in the quadrivalent vaccine.[1]
	3 years and over	FluQuadri	
	3 years and over	Fluarix Tetra	Fluarix Tetra elicited non-inferior antibody responses compared to the Fluarix trivalent vaccine and superior responses for the additional B strain not in the trivalent comparator.[2]
	5 years and over	Afluria Quad	Afluria Quad elicited non-inferior immune responses to all comparator strains when compared to two trivalent vaccines containing alternate B strains. Superior immune responses to the trivalent unmatched strains were found.[4]
Trivalent	65 years and over	Fluad (MF59-adjuvant)	Fluad (MF59-adjuvant) elicited significantly higher antibody responses compared to a non-adjuvanted trivalent vaccine in older people, including those with underlying medical conditions. Significantly higher responses were observed against heterologous A strains, and higher antibody responses were observed for H3N2 strains up to 12 months after vaccination.[6] A systematic review found that Fluad (MF59-adjuvant) was more effective than non-adjuvanted trivalent vaccine in preventing hospitalisation from pneumonia/influenza in older people (51%, 95% confidence interval 39–61%).[7]

quadrivalent vaccines confer improved protection without any obvious increase in adverse reactions.[9] The standard influenza vaccination for children and adults, including pregnant women, is now a single quadrivalent preparation. An exception to this is children aged six months to nine years who are receiving the vaccine for the first time, and those in the first year after receiving a solid organ or haematopoietic stem cell transplant. These patients should receive two doses at least four weeks apart to induce an optimal immune response.

High-dose and adjuvanted trivalent vaccines for older adults

People aged 65 and over have an increased risk of not only contracting influenza, but also of developing serious complications including heart attack, decompensated cardiac failure, pneumonia and death.[10,11]

Two new trivalent vaccines for this age group were introduced in 2018, and one (Fluad) will be funded on the National Immunisation Program in 2019.[8] They are currently not recommended for younger individuals, however recent literature suggests that recipients of solid organ transplants may also benefit from these vaccines.[12]

The high-dose preparation (Fluzone High-Dose) contains 60 microgram of the haemagglutinin antigen, which is four times more than the antigen content of other vaccine formulations for those under 65 years old. The adjuvanted vaccine (Fluad) contains MF-59, a squalene-based emulsion that can rapidly induce antigen-specific CD4 responses. This results in strong and lasting T- and B-cell memory immune responses. The advantage of adjuvanted vaccines is they induce a broad host response while at the same time being dose sparing.

Recent studies have shown that administering trivalent flu vaccines, either at higher dose or with an adjuvant to increase immunogenicity, improves vaccine efficacy in people aged 65 or more.[5,13-15] Other benefits include reduced hospitalisation for influenza and its complications, and reduced influenza-related deaths.[13,16] A significantly higher rate of injection-site reactions has been reported with these preparations compared to standard trivalent vaccines (approximately 30% vs 20% of recipients). However, there has been no observed difference in the rate of serious adverse events.[17,18]

The absence of the additional B lineage in these trivalent vaccines is not thought to be of notable detriment in older people for a number of reasons. First, the influenza A subtype A/H3N2 is likely to be responsible for the bulk of infections and serious complications in older patients. Second, a meta-analysis of several studies found that vaccination against a single influenza B strain confers up to 50% cross-protection against mismatched influenza B strains.[19]

At this stage, there have been no head-to-head trials comparing high-dose or adjuvanted trivalent vaccines with quadrivalent vaccination. New vaccine preparations (for example, using nanoparticles to carry influenza antigens) are under trial.

To date the safety and efficacy of adjuvanted or high-dose antigen influenza vaccines in pregnancy has not been established. Age-specific vaccine is recommended for pregnant women.

Antiviral drugs

There are two main classes of antiviral drugs that have been used for the treatment and prophylaxis of influenza – neuraminidase inhibitors and adamantanes. Multiple novel therapies are currently in development.

Neuraminidase inhibitors

Neuraminidase inhibitors are the mainstay of antiviral therapy against influenza. However, they need to be started within 48 hours of symptom onset and are most effective within 24 hours.

They inhibit the viral neuraminidase enzyme, preventing the virus from escaping the host cell.[20] Three neuraminidase inhibitors are currently registered in Australia – oral oseltamivir, inhaled zanamivir and intravenous peramivir.[21]

Efficacy

Oseltamivir shortens the duration of symptoms in uncomplicated influenza by approximately one day.[22,23] The majority of studies were in healthy adults, and this effect has not been shown in asthmatic children.[22,23] Inhaled zanamivir has shown a similar reduction in duration of symptoms in adults but has no significant effect in children.[22,23] Single-dose intravenous peramivir is non-inferior to oseltamivir in adults and is a potential alternative for those who cannot take oral or inhaled medicines.[24]

A newer long-acting neuraminidase inhibitor, laninamivir, achieves high concentrations in lung tissue with the potential to treat influenza following a single inhaled dose. It has comparable efficacy to oseltamivir in adults.[25,26] An intravenous form of zanamivir has been recently studied in populations with severe influenza and also shows similar outcomes to oseltamivir.[27] While these two drugs are not currently registered in Australia, intravenous zanamivir has been used through the Special Access Scheme for critically ill patients with influenza.[21]

The role of neuraminidase inhibitors in reducing influenza complications is less clear.[22,23] While oseltamivir has been shown to reduce unverified pneumonia, this has not been confirmed in trials with robust diagnostic criteria.[23] It has also not been shown to reduce the rate of hospital admissions.[22]

Zanamivir has not been found to reduce pneumonia complications and its effect on hospital admissions has not been studied.[22,23] In patients with influenza the use of neuraminidase inhibitors has been associated with a mortality benefit, with delayed treatment resulting in increased mortality.[28]

Recommendations for treatment

Prompt commencement of neuraminidase inhibitors is recommended for patients with confirmed or suspected influenza who require hospitalisation, or are at risk of complications (including children <5 years, adults ≥65 years, pregnant women, immunosuppressed patients or significant comorbidities), or have severe, complicated or progressive disease.[29-31] Therapy should begin within 48 hours of the onset of illness, but in severe disease treatment may still be beneficial if given outside this timeframe.[28,30] Treatment should also be considered in those who have household contacts who are at high risk of influenza complications.[30,31] The recommended duration of therapy (oseltamivir and zanamivir) is five days.[29] In healthy outpatients with uncomplicated influenza, treatment can be of limited benefit.[29,30] Antibiotics are only indicated when patients have bacterial complications.[29,31]

Antiviral resistance

Antiviral resistance has been well described in at-risk populations including immunocompromised hosts and young children due to a high virus burden and prolonged replication promoting resistance mutations.[32] Factors that increase the risk of resistance include suboptimal antiviral dosing and cross-transmission of resistant strains in outbreaks.[32,33] The H275Y mutation is commonly associated with oseltamivir-resistant influenza A strains, but laninamivir and zanamivir rarely show cross-resistance to strains expressing this mutation.[32]

Adamantanes

Adamantanes work by inhibiting the M2 ion channel.[20] They are not recommended due to widespread resistance in circulating influenza viruses.[20,29] Currently amantadine is the only drug to be registered in Australia for influenza. Its use is limited to prophylaxis of influenza A.[21,34] When used for treatment, amantadine shortens the duration of fever by approximately one day, but has no effect on nasal shedding or upper airways viral clearance.[34]

Antiviral prophylaxis

There is a role for neuraminidase inhibitors in prophylaxis. Oseltamivir and zanamivir are approved in Australia for this and have shown to significantly reduce the risk of symptomatic influenza.[22,23] However, chemoprophylaxis should not be considered as an alternative to vaccination.[29]

For individual benefit, post-exposure prophylaxis with neuraminidase inhibitors should be considered for contacts who are at high risk of influenza complications and cannot be (or have not been) vaccinated or are

likely to have an inadequate or ineffective vaccine response.[30] In household settings, chemoprophylaxis can be considered for remaining contacts of a suspected or confirmed influenza case, if there is another member at high risk of influenza complications.[30]

During an influenza outbreak in residential care facilities (including aged care, correctional facilities, hostels), antiviral prophylaxis should only be considered in addition to other infection control measures. The decision to administer antivirals must be made in collaboration with treating doctors, public health authorities and the local outbreak management team.[35] When used, antiviral prophylaxis should be started within 24 hours of declaring an outbreak for all asymptomatic residents (regardless of vaccination status) and all unvaccinated staff.[30,35] Chemoprophylaxis should be continued for 10 days or until the outbreak is over, whichever is longer.[35] There may be a role to extend this approach of antiviral 'ring prophylaxis' in other closed or semi-closed environments (i.e. cruise ships, military barracks, boarding schools) where antiviral prophylaxis in close contacts may truncate the spread of infection.[35,36]

Antiviral prophylaxis has also been shown to be effective in inpatient settings, particularly for immunocompromised patients.[37]

Limitations of influenza prophylaxis

Chemoprophylaxis does not completely eliminate the risk of influenza and susceptibility to infection returns once antiviral prophylaxis is stopped.[29] In an outbreak, neuraminidase inhibitors may be ineffective at preventing asymptomatic influenza (meaning transmission may still occur). In the long term, chemoprophylaxis may result in the emergence of influenza viruses with reduced susceptibility to these drugs.[22,23,32]

Novel therapies

Several novel therapies are being developed for influenza treatment. These target various stages of influenza infection including prevention of viral entry (DAS181-F03), fusion with host cells (Arbidol), viral transcription and replication (Favipiravir, Pimodovir, S 033188) and maturation of key viral proteins (nitazoxanide).[38,39] There are also several monoclonal antibodies being developed that target viral structures, primarily haemagglutinin, to neutralise the virus.[38] Combination therapy with oseltamivir, amantadine, and ribavirin has also been studied but has shown no clinical benefit over oseltamivir alone.[40]

Conclusion

Influenza infection is an important public health problem, with a substantial disease burden in Australia and worldwide. Vaccination is the most important tool in influenza prevention. Current antiviral therapies have a modest effect on symptom duration with no effect on viral shedding or disease complications. Ongoing research is required to develop more effective therapies and combat emerging antiviral resistance. ◄

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