Antigen Literature Review for the New Zealand National Immunisation Schedule, 2017:
Influenza

Prepared as part of a Ministry of Health contract for services by Dr Mary Nowlan at the Immunisation Advisory Centre

This review is part of a series of antigen literature reviews commissioned by the Ministry of Health to help inform the National Immunisation Programme.

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Executive summary

Influenza is a respiratory virus that causes acute respiratory illness. Severe illness and secondary complications lead to hospitalisation and death of young children, the elderly, pregnant women and those with a range of underlying medical conditions. However, healthy children and adults can also be at risk of serious illness following influenza infection.

This is a review of the recent literature, published from January 2013 to November 2017, about seasonal influenza vaccines and vaccinations. The aim of this review is to provide insight into the most effective use of influenza vaccination for the prevention of serious disease and deaths. It has been conducted to inform decisions around the New Zealand seasonal influenza immunisation programme, to help identify target groups for seasonal influenza vaccination, provide information about which vaccines are available and most appropriate to use, and how community immunity be better achieved to protect those in whom the vaccines may be less effective or contraindicated.

As there is no universal influenza vaccine to provide effective immunity against all influenza strains, several challenges are associated with seasonal influenza vaccines. The strains of influenza virus in circulation change antigenically during the course of the season and prevalent strains differ between the Northern and Southern Hemisphere. Continual surveillance is required to predict which strains or variants are likely to be predominant each year, and vaccine composition decisions are required to be made six months prior to the season to allow time for manufacture of the vaccine. Occasionally, these predictions are inaccurate leading to poor vaccine effectiveness and apparent vaccine failure, which affects confidence in the vaccination programmes.

Influenza vaccination has the ability both to protect individuals from the infection and associated disease, and to induce herd immunity to restrict viral transmission throughout the community. With the current sub-optimal influenza vaccines, immunisation coverage in New Zealand for those at high risk of disease and for healthy adults and children is inadequate to provide individual protection, to better capture those who are at high risk from severe illness, and to generate herd protection by reducing community spread of the virus to individuals in whom the vaccines are least effective or who are unable to be vaccinated.

Inactivated influenza vaccines

The most widely used types of influenza vaccine are inactivated influenza vaccines (IIV), most of which are subunit or split virion types that contain the haemagglutinin and neuraminidase of the predicted strains. These vaccines are designed to induce neutralising antibody to prevent attachment and infection of the virus to the cells of the respiratory tract. Both trivalent and quadrivalent forms are available, containing two influenza A strains and one (TIV) or two (QIV) influenza B strains, respectively. The advantage of quadrivalent vaccines is that, since they contain both influenza B lineages, there is less potential for mismatch of B strain if the circulation lineage alters from prediction.

Safety

IIV have good safety profiles and few adverse events have been reported following vaccination. The incidence of Guillain-Barré syndrome is very rare following vaccination, at around 1 per million doses and much less than that associated with influenza disease. Although the virus used for IIV is first cultured in hens’ eggs, these vaccines are safe to give
to people with known egg allergy. However, out of caution, those who have been reported to have severe anaphylactic-type reactions to egg are recommended to be given the vaccine under specialist supervision. The rate of anaphylaxis following IIV vaccination is similar to that following other vaccines at around 1 per million doses and is as likely to be due to other vaccine components as ovalbumin (egg protein). Children may experience fever when IIV is administered concurrently with some other childhood vaccines.

There is no evidence of adverse outcomes following TIV vaccination during pregnancy, particularly when given in the second and third trimesters. Few studies have investigated outcomes following vaccination in the first trimester. One study observed an increase in rate of spontaneous abortions within 28 days of vaccination in the first trimester, only in mothers who had prior vaccination with A/H1N1pdm09-containing vaccine, although no causal link was established.

The addition of an extra influenza B strain in QIV does not alter the safety profile of IIV. There are no safety concerns identified with QIV for all age groups, during pregnancy or for those with immunosuppression.

Continued surveillance is required to ensure safety signals are detected rapidly for each season. Enhanced passive and active surveillance systems, such as text-messaging based AusVaxSafety, have previously identified any safety signals for individual vaccine brands.

**Immunogenicity**

IIV induce predominantly antibody driven immunity (humoral immunity). A role for cell-mediated responses has not been defined. No correlates of protection have been established for seasonal influenza vaccination, although in healthy adults, a haemagglutinin inhibition (HI) assay antibody titre of at least 1:40 is considered to correspond to a 50% reduction in risk of contracting influenza. However, this titre may be too low to provide seroconversion for those with poorer immune responses to the vaccine, which is particularly noted in the elderly, immunosuppressed individuals and young children. A titre of at least 1:110 was found to better predict a 50% clinical protection rate in children.

TIV have been shown to be immunogenic (based on HI titre 1:40) in children with prior immunisation experience, with cancer, and with recurrent wheeze, but not for children with HIV infections. Children aged 6-11 months have lower ability to respond to influenza vaccination than those aged 12-36 months. Children who are influenza vaccine-naïve generate a better immune response if given two separate half doses rather than one full dose.

Most studies that investigated the use of IIV in individuals with impaired antibody response (immunosuppressed, elderly, young children) concluded that more immunogenic vaccines are required to induce better immune responses in these groups. However, in the absence of improved vaccines, IIV continues to be recommended, even with sub-optimal responses, since they provide some benefit in reducing disease severity and preventing hospitalisations.

Repeat vaccination within the same season was not found to improve protection in the elderly or other high risk groups.

The effect of prior vaccination or influenza infections on seasonal influenza vaccination is complicated and influenced by multiple factors, including the genetic evolution of circulating viruses, epitope specificity, mutations induced during vaccine manufacture and life-time exposure to infection. Both boosting and inhibition of vaccination responses have been observed and appear to be influenced by influenza strains.
Co-administration with other vaccines, such as pneumococcal vaccines, does not impact on the immunogenicity of TIV or QIV in older adults.

**Effectiveness**

Vaccine effectiveness against seasonal influenza is complicated by several factors that are associated with virus-host and immuno-epidemiological interactions, including prior vaccination and exposure to different influenza strains. These influences include viral genomic variation, cross-reactivity, age-specific susceptibility as a result of birth-cohort effects, effects of repeat vaccination and potential waning of vaccine protection within seasons.

In general, IIV are around 50% effective in preventing influenza in general practice and in preventing influenza-related hospitalisations. Effectiveness varies from year to year, in different age groups, and changes to circulating strains during a season can lead to increased disease severity resulting in more hospitalisations.

Overall, no negative impact was identified on vaccine effectiveness (VE) due to any prior seasons’ vaccinations, but different studies have shown mixed results. Prior vaccination has the potential to enhance effectiveness, even when antigen matching is incomplete, and annual vaccination is recommended.

TIV uptake in children is generally low and therefore studies to estimate effectiveness in children are limited by small numbers. Overall, the adjusted VE was 55.5% (11.6-77.6%) for hospitalisations with an acute respiratory illness with fever and/or pneumonia. TIV was more protective against A/H1N1pmd09, with VE against A/H1N1pmd09 up to 91% effective for a well-matched vaccine, compared to A/H3N2 (from no effectiveness with a poor match) and B strains (from as low as 26%, due to mismatch in B lineage).

Two doses of vaccine provides improved protection against influenza compared with one dose in children aged 6 months to 8 years who have not previously been vaccinated and in immunocompromised children, regardless of prior vaccination history.

Although data is limited, IIV appears to protect pregnant women from influenza-associated hospitalisations. The risk of influenza-associated hospitalisation is up to seven times higher in pregnant women than non-pregnant women, and is highest in the later stages of pregnancy and post-partum. Vaccine effectiveness against laboratory-confirmed influenza and acute respiratory illness hospitalisations in pregnant women is similar to that seen in all adults at around 50%. There is limited data around protection of newborns. One review reported that vaccine efficacy against laboratory-confirmed influenza in infants of vaccinated mothers was shown to be 24% up to 8 weeks of age.

The effectiveness of influenza vaccines is highly dependent on vaccine uptake. When uptake is inadequate, transmission of the virus is high and those who may not have acquired sufficient antibody levels to be fully protected are at higher risk of infection, such as the elderly, young children and those with underlying medical conditions.

**Different formulations**

High-dose TIV improve immunogenicity and vaccine efficacy against influenza in older adults with comorbidities and frailty.

Intradermal IIV formulations, which contain less antigen than standard IIV, are able to induce an adequate immune response in the elderly and lower the risk of hospitalisation.
**Adjuvanted influenza vaccines**

To further improve the immunogenicity of IIV and to reduce the quantity of antigen required, adjuvants have been included in IIV formulations. Two squalene oil emulsion-based adjuvants have been included in seasonal influenza vaccines, namely, MF59® and AS03® (the latter has predominantly been used in pandemic vaccines and is not reviewed).

Few studies have been conducted in children. Safety findings show that, as would be anticipated, these vaccines are more reactogenic with increased local and systemic responses, including injection site inflammation and fever in children. These are generally mild and transient. There is no evidence of induction of autoantibodies against squalene, although insufficient data is available to report on rare adverse events.

MF59 enhances the antibody titres of TIV in adults aged 65 years and older, including against A/H3N2 strains.

The use of adjuvant in seasonal influenza vaccines improves the immunogenicity of the vaccines in the elderly and young children in whom the response to non-adjuvanted TIV is lower and short-lived, although this difference is less significant in the elderly than observed in children. Higher antibody titres are achieved in young children aged less than 3 years, with some evidence of cross-protection between vaccine and circulating influenza strains.

The addition of adjuvant is likely to reduce the quantity of antigen required in the vaccine for children, although two doses are still required for previously unvaccinated children and children aged less than 12 months.

Although limited, evidence suggests that the effectiveness of TIV can be improved in adults with the inclusion of MF59 adjuvant. No studies were identified that reported on the effectiveness of MF59-TIV in children.

**Live attenuated influenza vaccines**

Live attenuated influenza vaccines (LAIV) are administered intranasally and thereby induce different immune responses to parenterally injected vaccines. The response is predominantly mucosal and is less driven by serum antibodies targeting haemagglutinin. Therefore, it is unclear how to measure immunogenicity of this type of vaccine. Cross-protection has been suggested against conserved influenza epitopes with wider immune responses that include mucosal antibodies and CD8 T cells.

LAIV have been shown to be highly effective when given as part of a universal immunisation programme targeting preschool and school-aged children in the UK - 60-80% effective in preventing influenza-associated hospitalisation, acute respiratory illness and laboratory-confirmed influenza illness in children, and 59% effective for indirect protection against hospitalisation of adults. Younger children less than 2 years of age are also protected indirectly by vaccination of their older siblings.

Significant discrepancies in effectiveness have been observed between the UK and the US during the most recent influenza seasons, particularly in protection from A/H1N1pdm09. One explanation given for this was that the A/H1N1 strain used in the US vaccine was less thermally stable than the other strains and disruption of the cold chain potentially reduced viral potency in the US batch. Another possible explanation was that prior immunity acquired through previous vaccination or exposure to wild-type virus interfered with the ability of the A/H1N1 strain to replicate in the nasal tissue and induce immunity. However, some studies found no evidence of waning in immunity following prior exposure.

LAIV are contraindicated for children under 2 years of age and individuals with unstable asthma due to a potentially increased risk of wheeze. However, there is no evidence that
LAIV increase the incidence of wheeze or asthma symptoms in those with mild or intermittent asthma. Transient nasal congestion and rhinorrhoea have frequently been reported following LAIV administration. The risk of anaphylaxis is low, even in those with severe egg allergy.

LAIV are contraindicated for individuals with immunodeficiencies and immunosuppression. The use of low dose corticosteroids is acceptable.

Intranasal administration of LAIV is generally better accepted by parents and caregivers than injected IIV and is therefore likely to improve vaccine uptakes, provide wider protection for all children and improve the effectiveness of the influenza immunisation programme through direct and indirect protection.

**Vaccination strategies**

**Vaccination of contacts of high risk groups**

Vaccination of health care workers, social care workers and those in contact with high risk patients can help to provide protection for both the patients and the caregivers against influenza-associated illness. The evidence is consistent that influenza vaccination reduces illness in health care workers from an occupational health perspective, although the evidence for reduced absenteeism and patient safety is conflicting. Transmission of influenza is greatest when symptoms of infection are present and is longer lasting in the more severe cases, for example in those hospitalised with influenza-associated illness, therefore those caring for these patients are at risk of infection. Conversely, those with mild or no symptoms can also transmit virus, and nosocomial transmission may put vulnerable people at risk of infection. Therefore, vaccination of contacts of high-risk groups is likely to enhance both caregivers and patient safety.

Improvements in vaccine uptake in health care workers are required. There is no consensus of evidence for mandatory vaccination of health care workers, since other interventions can be employed for additional protection of staff and patients.

**Vaccination of the elderly and high risk individuals**

Improvements in vaccination coverage across all age groups is likely to improve the outcomes of influenza infection in those at increased risk from severe disease through both direct and herd immunity effects.

Broadly, the groups at highest risk from influenza include those over 65 years of age, young children, pregnant women, and children and adults with underlying medical conditions such as neurological disease, immunodeficiencies and immunosuppression, chronic liver disease, chronic renal disease, cardiovascular disease, cancer, respiratory diseases and diabetes mellitus. These risks are likely to be cumulative and individuals with multiple risk factors are likely to be at higher risk than those with one risk factor.

Poverty, overcrowded housing and obesity further increase the risk of influenza hospitalisation beyond the risks associated with age, ethnicity and comorbidities. Morbid obesity is likely to be an independent risk factor for severe influenza.

For many of these groups, the current IIV vaccines show reduced immunogenicity and effectiveness. Different formulations, including adjuvanted vaccines, high doses and intradermal administration, may improve responses in older adults and those with chronic disease. In young children, although adjuvants improve immune responses, they are likely to be more reactogenic and potentially induce higher fevers than standard IIV.
Herd immunity

Vaccination of preschool and school-age children has been demonstrated to contribute to herd immunity, thereby protecting high-risk individuals who may respond less well to the vaccines, such as the elderly.

Poor vaccine uptake is likely to limit any potential herd immunity.

International policy

In general, there is agreement between countries as to the groups that require influenza vaccination for direct protection. These include individuals aged over 65 years, pregnant women, and adults and children with chronic health conditions such as neurological conditions, heart, kidney or liver disorders, respiratory disorders, compromised immunity, diabetes, and recently included morbid obesity.

Indirect protection of those at high risk is provided by the vaccination of health care, residential care and social care workers, emergency medical responders and household contacts of those at high risk.

The UK has introduced a universal influenza immunisation programme to vaccinate preschool and school-aged children. The rationale for this is that children are the most significant transmitters of influenza virus. In this way, the vaccination of children protects younger siblings, particularly those too young to be vaccinated, and provides further protection for those in whom the vaccines provide suboptimal protection, such as pregnant mothers, grandparents and contacts with underlying diseases. The universal programme also provides vaccine to individual children at high risk of influenza, in whom vaccine uptake is otherwise low. Vaccination of children is also recommended, although not universally funded, in other countries.

Australia, Canada and the US recommended vaccination of indigenous people, who are at higher risk of influenza complications than non-indigenous populations.

Canada recommends the use of high-dose TIV in the elderly.

Vaccine options and scheduling

In general, an increase in uptake of annual influenza vaccination is required across the whole population to protect individuals and help to generate herd immunity. Vaccination of healthy children, with Q-LAIV or QIV, is likely to provide indirect protection and reduce transmission of influenza within schools, households and the wider community.

School-based programmes access a wide range of children, including those at high risk of severe disease, and do produce herd immunity. LAIV are better accepted by parents due to the intranasal administration than injected vaccines. Implementation of such programmes annually is likely to be resource intensive.

Vaccination of health care workers, childcare or residential care workers, and students in these professions, is recommended to protect both the individual and their contacts. Other occupations for whom influenza vaccination is recommended are essential emergency response staff and those working in close settings with high risk people (for example on cruise ships). There is no evidence for mandatory vaccination being a more effective strategy.

Pregnant women are at particularly high risk from the complications of influenza, particularly later in pregnancy and postpartum. Vaccine can be given at any stage in pregnancy as early as possible in the influenza season. Vaccination also provides protection for their unborn foetus and newborn infants.
The risk from influenza is highest in those with underlying comorbidities and life-style factors enhance this risk. Targeted vaccine programmes help to provide funded vaccine to those at very high risk, however, uptake is generally low in these high-risk groups. Greater gains in these groups may come via a herd immunity approach.

Quadrivalent vaccines offer broader protection against influenza B than trivalent vaccines. Although the effectiveness of influenza vaccines can wane during a season, it is not recommended to revaccinate within the same season.

Conclusions
To improve the effectiveness of seasonal influenza immunisation programmes, potential approaches identified in this review include:

1. Increase vaccination coverage and uptake to improve individual protection, across the whole population. Individuals at risk of severe disease, not currently eligible or not currently receiving vaccine, are more likely to be captured if there is a wider acceptance of the vaccines.

2. Vaccinate close contacts of high risk individuals to reduce the risk of disease transmission, as the current vaccines may not provide sufficient direct protection in these individuals.

3. Consider alternative vaccine formulations to enhance the immune response in high risk groups, particularly the elderly, such as high-dose vaccines and the use of adjuvants. The options for infants aged six months to two years are unclear.

4. Consider herd immunity strategies, for example, vaccination of all young children to help prevent viral spread, particularly to peers and family members such as grandparents and pregnant mothers. Programmatically, this would involve significant effort and realistically is only likely to be achievable with intranasal LAIV, not injectable vaccines.
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<tr>
<td>ACIP</td>
<td>Advisory Committee on Immunization Practices</td>
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<td>AE</td>
<td>Adverse events</td>
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<td>AOM</td>
<td>Acute otitis media</td>
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<td>ARI</td>
<td>Acute respiratory illness</td>
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<td>ATAGI</td>
<td>Australian Technical Advisory Group on Immunisation</td>
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<td>aTIV</td>
<td>Adjuvanted trivalent influenza vaccine</td>
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<td>BMI</td>
<td>Body mass index</td>
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<td>CDC</td>
<td>Centers for Disease Control and Prevention (United States)</td>
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<td>CI</td>
<td>Confidence interval</td>
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<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
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<td>ESR</td>
<td>Institute for Environmental and Scientific Research Ltd</td>
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<td>FluCAN</td>
<td>Influenza Complications Alert Network (Australia)</td>
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<td>GBS</td>
<td>Guillain-Barré Syndrome</td>
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<td>GISRS</td>
<td>Global Influenza Surveillance and Response System</td>
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<tr>
<td>GMT / GMTR</td>
<td>Geometric mean titre / geometric mean titre ratio</td>
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<td>General practitioner (in primary care)</td>
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<td>Human immunodeficiency virus</td>
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<td>Inflammatory bowel disease</td>
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<td>Influenza-like illness</td>
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<td>Inactivated influenza vaccine</td>
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<td>Intramuscular</td>
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<td>IPE</td>
<td>Indirect protective effectiveness</td>
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<td>LAIV</td>
<td>Live attenuated influenza vaccine</td>
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<td>LRTI</td>
<td>Lower respiratory tract infections</td>
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<td>N</td>
<td>Neuraminidase</td>
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<td>National Advisory Committee on Immunization (Canada)</td>
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<td>NNV</td>
<td>Need to vaccinate</td>
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<td>Abbreviation</td>
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<tr>
<td>NZ</td>
<td>New Zealand</td>
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<td>OR / aOR</td>
<td>Odds ratio / Adjusted odds ratio</td>
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<td>QIV</td>
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<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
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<td>SES</td>
<td>Socioeconomic status</td>
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<td>SHIVERS</td>
<td>Southern Hemisphere Influenza Vaccine Effectiveness Research Study</td>
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<td>SLE</td>
<td>Systemic lupus erythematosus</td>
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<td>Trivalent inactivated [influenza] vaccine</td>
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<td>T-LAIV</td>
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<td>TNF-α</td>
<td>Tumour necrosis factor alpha</td>
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<td>URTI</td>
<td>Upper respiratory tract infections</td>
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<td>UK</td>
<td>United Kingdom</td>
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<td>US</td>
<td>United States of America</td>
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<tr>
<td>VE</td>
<td>Vaccine effectiveness</td>
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<td>VSD</td>
<td>Vaccine Safety Datalink</td>
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1 Background

1.1 Purpose of this review

There is extensive literature around the use and design of influenza vaccines. This is a review of literature published from January 2013 to November 2017 that considers aspects of influenza vaccination related to the New Zealand National Immunisation Schedule and only vaccines that are licensed as of 2017. It was not conducted as a systematic review.

Novel technologies, pandemic vaccines or universal vaccines are not included. Focus is on safety, in terms of adverse events following immunisation (AEFI), immunogenicity and effectiveness. Identification of and options for high risk groups and community immunity are also considered.

1.2 Influenza

Influenza has the potential to be a very serious disease, with some groups at higher risk, such as the elderly, the very young and those with underlying medical conditions. Influenza viruses are rapidly changing through a process known as antigenic drift, and most years, the predominant circulating strains alter. Seasonal influenza is associated with high morbidity and mortality in the autumn and winter months (May to August in the Southern Hemisphere and October to February in the Northern Hemisphere).

There are three distinct types of influenza viruses that infect humans. Influenza A viruses have animal reservoirs, influenza B viruses have a human reservoir, and influenza C is found in children and pigs. Influenza A and B viruses are associated with annual incidence and influenza C causes sporadic upper respiratory tract illness in children.

Periodically, new influenza A virus strains emerge against which humans have little or no immunity. These are a major public health threat since they can lead to global influenza pandemics. One such pandemic, commonly known as ‘The Spanish Flu’, killed 8,600 New Zealanders within two months from October to December 1918. The rate of death in the Māori population was seven times that of the Europeans. Another, more recent, pandemic strain emerged in 2009 - the so called ‘Swine Flu’, which was caused by an influenza A H1N1 strain (A/H1N1pdm09). Global surveillance for influenza strain changes began in 1947 by the World Health Organization (WHO).

Seasonal influenza can be asymptomatic or can cause relatively mild upper respiratory tract infections (URTI) and/or lower respiratory tract infections (LRTI), such as viral bronchitis and pneumonia. These can lead to much more serious secondary bacterial infections, including invasive pneumonia and severe cardiovascular complications, which are the cause of 90% of influenza-related deaths in those aged over 65 years.

Influenza infections are responsible for up to one fifth of acute LRTI in children under 5 years of age and ageing T cell immunity impairs the ability to control infections leading to increased mortality and morbidity in the elderly. High case-fatality rates are also seen in younger people due to some strains.

Influenza viruses are further classified by antigenically distinct haemagglutinin (H) and neuraminidase (N) protein subtypes (H1-16 and N1-9). H1 (H1pdm09) and H3 are currently co-circulating in humans. There is a single influenza B type, however two lineages, namely, B/Victoria and B/Yamagata, have co-circulated since the mid-1970s. Antigenic drift occurs as the result of an accumulation of mutations in genes coding for antigenic sites that arise.
during viral replication. Variants are formed that escape existing immunity against influenza A and B viruses. This is a characteristic of the changes seen in seasonal influenza. A larger change can occur during antigenic shift in which an influenza A virus acquires an antigenically novel H through reassortment. This feature of influenza A enables the infection to cross from animals to humans and these changes are linked to the emergence of pandemic strains against which humans have no prior experience.3

1.3 World Health Organization influenza monitoring

The WHO Global Influenza Surveillance and Response System (GISRS) has conducted influenza virological surveillance since 1952. It monitors the evolution of influenza viruses and provides an alert mechanism for the emergence of influenza strains with pandemic potential. A global web-based tool collates virological data, such as the number of influenza viruses by subtype, to track global movement of influenza and to interpret epidemiology data. Data are provided by remote National Influenza Centres and other national influenza reference laboratories. The Institute of Environmental Science and Research Ltd (ESR) is the National Influenza Centre for New Zealand.4

Using the collected data, the WHO GISRS provides recommendations about laboratory diagnostics, composition of seasonal influenza vaccines for both the Northern and Southern Hemisphere seasons, antiviral susceptibility and risk assessment.

The recommendations are released around six months prior to the next influenza season in preparation for vaccine manufacture.

1.4 Influenza vaccines and challenges

Several challenges surround influenza vaccines. These include variable efficacy in different age populations, antigenic variability of circulating virus, and production limitations to ensure safe, timely and adequate supply of vaccine, including for pandemic situations.3

The roles of influenza vaccination are to:

1. Protect individual against infection and disease
2. Offer protection to high risk groups by vaccination of close contacts to reduce spread
3. Induce herd immunity to restrict viral transmission through a community

More than 150 different influenza vaccines and vaccine formulations are available or are in development. Recombinant technology has allowed safe and scalable vaccine production and different formulations and technologies, which include dose variations, alternative routes of administration and the use of adjuvants, aimed at improving immunogenicity and efficacy across different populations.3

Immunisation of individuals at high risk of influenza provides protection against infection and complications of disease. However, the current vaccines are not always effective in these groups and require annual revaccination to ensure that the protection continues for each influenza season, which is challenging for groups who are less able to generate long lasting immunity, such as infants, the elderly and the immunocompromised.

Children are the most important sources of transmission of influenza in the community, since when infected they shed virus at higher rates for longer than adults, often have poorer hygiene practices, have more frequent contact with both their peers and adults in school and day-care, and may have younger siblings or pregnant mothers and close contact with elderly grandparents. However, uptake of influenza vaccination is low in healthy children and older
children are difficult to access, unless vaccinated as part of school-based immunisation programmes.

1.4.1 Inactivated influenza vaccines

Inactivated influenza vaccines (IIV) are the most widely used influenza vaccines. Trivalent influenza vaccines (TIV) contain two types of influenza A virus (A/H1N1 and A/H3N2) and one type B; quadrivalent inactivated influenza vaccines (QIV) include both type B lineages and are becoming more prevalent in immunisation programmes. These vaccines can have different formulations, containing either whole inactivated virus, detergent-split virion or antigen subunits. Generally, subunit or split-virion vaccines have replaced whole virus vaccines because they are less reactogenic, though less immunogenic, than whole virus vaccines. Therefore, unprimed young children require two doses of split-virion or subunit vaccines.\textsuperscript{5, 6}

The production of IIV can be delayed if there are significant changes in predicted circulating strains, there is shortage of hens’ eggs (the substrate required to grow the virus), virus growth is suboptimal or they do not meet regulatory requirements. Some subunit vaccines are now being grown in mammalian cell culture rather than hens’ eggs to attempt to overcome supply issues.

IIV are designed to stimulate neutralizing antibody production to target haemagglutinin and to prevent attachment of the virus to the cells of the respiratory tract.

To improve the immunogenicity of IIV, more recent formulations that contain higher antigen doses or adjuvants are also being used. Section 4 provides further details.

1.4.2 Live attenuated influenza vaccines

Live attenuated influenza vaccines (LAIV) are designed to mimic natural infection by being administered intranasally and to induce a broader, cellular and humoral immune response. The influenza virus in these vaccines has been cold adapted to grown at 25°C in the nasal passage, not the lower respiratory tract. Master donor strains contribute conserved internal genes and the desired H and N are added by reverse genetics or reassortment. These vaccines were first developed in Russia and have been used there for over 50 years. Cold-adapted LAIV was first licensed in the United States of America (US) in 2003 using a different master donor strain.\textsuperscript{3, 6} Further detail is provided in section 5.

1.4.3 Universal influenza vaccines

The ultimate aim is to create influenza vaccines that will induce an immune response across all influenza strains, so that reformulation is not required as seasonal strain changes occur. Potential targets for a universal vaccine are conserved viral core proteins that provide cross protection through CD8+ T cells.\textsuperscript{7} Several prototype technologies and universal vaccines are undergoing clinical and preclinical development, although none are licensed.\textsuperscript{8}

Table 1 gives examples of the current influenza and vaccine technologies in clinical development adapted from a review by Krammer et al.\textsuperscript{8}
### Table 1: Overview of seasonal influenza vaccine designs and examples of technology (adapted from Krammer 2015)

<table>
<thead>
<tr>
<th>Technology</th>
<th>Type of immunity</th>
<th>Breadth of protection</th>
<th>Comments / advantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Licensed technologies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIV</td>
<td>humoral</td>
<td>strain-specific</td>
<td></td>
</tr>
<tr>
<td>LAIV</td>
<td>humoral, cellular, mucosal</td>
<td>strain specific, broader than IIV</td>
<td>mucosal administration</td>
</tr>
<tr>
<td>Quadrivalent LAIV or IIV</td>
<td>as above</td>
<td>strain-specific</td>
<td>protects against both B lineages</td>
</tr>
<tr>
<td>Recombinant (RIV)</td>
<td>humoral</td>
<td>strain-specific</td>
<td>rapid production, without infectious virus during production or antigenic changes, no eggs required</td>
</tr>
<tr>
<td>High dose IIV</td>
<td>humoral</td>
<td></td>
<td>better immune response in elderly</td>
</tr>
<tr>
<td>Adjuvanted</td>
<td>humoral</td>
<td>strain specific, broader than IIV</td>
<td>broader and stronger response, dose sparing</td>
</tr>
<tr>
<td>Cell-culture derived IIV</td>
<td>humoral</td>
<td>strain-specific</td>
<td>rapid production, no eggs required</td>
</tr>
<tr>
<td><strong>Examples of new technologies in clinical development</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterologous prime-boost regimen</td>
<td>humoral</td>
<td>broad</td>
<td>combination of LAIV or DNA primer vaccinations with IIV or recombinant booster</td>
</tr>
<tr>
<td>DNA vaccines</td>
<td>humoral</td>
<td>strain-specific</td>
<td>highly cost-effective, easy to scale up</td>
</tr>
<tr>
<td>Insect-derived or plant-derived virus-like particles</td>
<td>humoral and cellular</td>
<td></td>
<td>rapid production, without infectious virus during production or antigenic changes, no eggs required</td>
</tr>
<tr>
<td>Bacterial expressed</td>
<td>humoral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVA vectored vaccines</td>
<td>cellular</td>
<td>broad, universal</td>
<td>strong cellular response additive to seasonal IIV</td>
</tr>
<tr>
<td><strong>Other universal vaccine technologies are in clinical and preclinical development</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: IIV – inactivated influenza vaccines; LAIV – live attenuated influenza vaccine; MVA – modified vaccinia Ankara
1.5 Influenza vaccination programme in New Zealand

Influenza infection is likely to affect everyone at any stage throughout their lives. Currently in NZ, trivalent seasonal influenza inactivated vaccine (TIV) is funded for the following groups and is available in general practice and community pharmacies: 9

1. Pregnant women (any trimester)
2. Anyone aged 65 years or over
3. Anyone aged 6 months to 65 years with one or more of the following medical conditions:
   - Cardiovascular disease or cerebrovascular disease
   - Chronic respiratory disease
   - Diabetes
   - Cancer, excluding basal and squamous skin cancers if not invasive
   - Other conditions: chronic renal disease, autoimmune disease, immune suppression, human immunodeficiency virus (HIV), transplant recipients, neuromuscular and central nervous systems diseases, haemoglobinopathies, children on long term aspirin, Downs syndrome, cochlear implant, pre and post splenectomy, inborn errors of metabolism
   - Children aged 4 years and under who have been hospitalised for a respiratory illness, or have a history of significant respiratory illness.

For the 2017 season, from 1 May to 31 December 2017, influenza vaccination was funded for all children and adolescents aged 6 months to under 18 years living in earthquake impacted areas of the upper South Island. Vaccine was also provided for people under 18 years of age who were displaced from their homes by flooding in the Edgecumbe region of the Bay of Plenty.

Quadrivalent influenza vaccine (QIV) is not currently funded but is available privately, through pharmacies, occupational health providers and general practices.

1.5.1 Vaccines

The recommendations for the likely vaccine strains in the Southern Hemisphere change annually. For example, the recommended changes in the influenza vaccine composition for the 2018 influenza season in New Zealand are listed below, as of October 2017. 10

**Trivalent vaccines:**

A(H1N1): an A/Michigan/45/2015 (H1N1)pdm09-like virus

A(H3N2): A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus - replacing 2017 season

A/Hong Kong/4801/2014 (H3N2)-like virus

B: B/Phuket/3073/2013-like virus (B/Yamagata lineage) - replacing B/Brisbane/60/2008-like virus (B/Victoria lineage) used in 2017

**Quadrivalent vaccines:**

As above, with the addition of a B/Brisbane/60/2008-like virus (B/Victoria lineage)

As with the strains of influenza virus contained within the vaccines, the vaccines available in New Zealand vary each year. Table 2 lists the influenza vaccines available during the 2017 season, as of September 2017.
Table 2: Seasonal influenza vaccines available in New Zealand during the 2017 influenza season

<table>
<thead>
<tr>
<th>Vaccine type</th>
<th>Formulation</th>
<th>Brand name (manufacturer)</th>
<th>Ovalbumin</th>
<th>Funded / not funded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trivalent, inactivated</td>
<td>Surface antigen</td>
<td>Influvac (Mylan)</td>
<td>&lt;0.1μg/0.5ml dose</td>
<td>funded</td>
</tr>
<tr>
<td></td>
<td>Split virion</td>
<td>Vaxigrip (sanofi-aventis)</td>
<td>≤0.05μg per 0.5ml dose</td>
<td>unfunded</td>
</tr>
<tr>
<td></td>
<td>Split virion</td>
<td>Fluvax (Seqirus CSL)</td>
<td>≤1μg per 0.5 ml dose</td>
<td>not funded</td>
</tr>
<tr>
<td>Quadrivalent, inactivated</td>
<td>Split virion</td>
<td>FluQuadri (sanofi-aventis)</td>
<td>≤1μg per 0.5 ml dose</td>
<td>not funded</td>
</tr>
</tbody>
</table>

2 New Zealand epidemiology

The influenza season in New Zealand predominantly occurs during May to August (late autumn to early spring in the Southern Hemisphere). National hospital and general practice sentinel surveillance are maintained by the ESR. These data and year-round laboratory based surveillance data are reported to the WHO as part of global influenza virus surveillance. Strain predominance is reported and used to predict likely strains for the Northern and Southern Hemisphere seasons. Originally presenting as pandemic influenza strains, A/H3N2 and A/H1N1pdm09 viruses continue to cause epidemics as seasonal influenza viruses.

New Zealand developed the Southern Hemisphere Influenza Vaccine Effectiveness Research Study (SHIVERS), which was started in April 2012 led by the ESR and funded by the Centers for Disease Control and Prevention (CDC) in the US. This study collected data on influenza vaccination and hospitalisations associated with severe acute respiratory illness (SARI) and general practice presentations for influenza-like illness (ILI) in the Auckland and Counties Manukau District Health Boards. A serosurvey was also conducted from February to November 2015, involving around 1500 participants (children aged 0-15 years and adults) within general practices in Auckland, to provide data around the immune response to influenza exposure in a randomly selected population through the winter season.11

During the first year, the rate of SARI-associated influenza hospitalisations was shown to be 54/100,000 persons. Young children aged less than 4 years and adults aged over 65 years had the highest rate of hospitalisations. These findings led to a change in vaccination policy to include children who had a history of significant respiratory illness.12

In its second season, SHIVERS identified that the influenza-associated general practice consultation rate was around 14 times higher than SARI hospitalisation rate. Additionally, both ILI and SARI presentations demonstrated sociodemographic patterns: higher rates of ILI consultations were seen in pre-schoolers, school-age children, adults aged less than 65 years, those with Asian ethnicity and the least deprived. This was in contrast to the SARI hospitalisations, which were more frequent in children under 1 year of age, the elderly,
Māori and Pacific ethnicity and the most deprived groups. Also in 2013, the burden of non-influenza respiratory viruses, including respiratory syncytial virus and rhinovirus, in SARI and ILI cases was identified to be similar to the disease burden for the influenza.\textsuperscript{12}

In addition, the higher risk associated with influenza in pregnant women was noted: between 2012 and 2014, cumulative incidence data reveals that pregnant women were 4.88 times (95\% confidence interval [CI] 3.14–7.36) more likely to get influenza compared to non-pregnant women.\textsuperscript{13}

During the 2015 influenza season, as well as providing data around vaccine effectiveness, the SHIVERS serosurvey collected serology samples to measure the immune response to influenza infection. This serosurvey provided data on mild influenza that did not require GP consultation and information about the level of symptomatic and asymptomatic infection within the community.\textsuperscript{14}

As shown in Figure 1, preliminary SHIVERS serological data suggested around a quarter of the population would have been infected with influenza, and of these, 80\% of children and adults with influenza did not have symptoms of influenza when infected. Of those with symptomatic infections, 77\% did not seek medical attention.\textsuperscript{14} The data showed that children had the highest proportion of influenza infection: 26.1\% (95\% CI 14.5–71.7\%) of influenza infections were observed in children aged <5 years and 30.6\% (23.47–38.3\%) were in school-age children from 5–19 years; adults aged 20–64 years had 14.9\% (11.8–18.5\%) and adults over 65 years had 7.2\% (2–17.4\%) of infection in the population.\textsuperscript{14}

Further data, presented in September 2017, showed that of the 911 unvaccinated participants, 321 (35\%) were shown to seroconvert to anti-H or anti-N antibody. Of these, it was estimated that 76 (24\%, adjusted for non-reporting or non-swabbing) would have experienced influenza-confirmed ILI and only around 20\% (15/76) would have sought medical care.\textsuperscript{15}
Although the distribution of non-medically attended mild influenza and influenza cases presenting to primary care is similar across all age groups, the highest proportion of influenza infections resulting in hospitalisation (case outcome ratio 1.6% [1.3-1.9]) and death is seen in adults aged over 65 years.14

2.1 Summary

Most cases of influenza in New Zealand are mild enough not to seek medical attention and many people infected with the virus do not develop symptoms. Despite this, influenza infection represents a considerable burden on the health service, with 1 in 40 people infected presenting to general practice. Particularly for children aged less than 4 years, pregnant women, the elderly and those with underlying medical conditions, influenza can be very serious, and lead to hospitalisation (in around 1 in 560 people infected) and death (in 1 in 44,000 people infected).

3 Inactivated influenza vaccine

3.1 Background

The current use of inactivated influenza vaccines is reviewed in this section. Consideration is given to the prevention of influenza-related hospitalisations and influenza-like illnesses presenting in general practice. Literature reviewed includes the use of these vaccines in special high risk groups and during pregnancy.

The safety aspects, immunogenicity and effectiveness of inactivated influenza vaccines are considered.

Within the limitations of this review, it was not feasible to review safety, immunogenicity and efficacy of seasonal influenza vaccination following receipt of the monovalent pandemic vaccines (adjuvanted and unadjuvanted) containing A/H1N1pdm09 or vice versa, although there was a large quantity of literature published around this.

3.2 Safety of inactivated influenza vaccines

This section will consider adverse events following immunisation (AEFI) associated with vaccination with TIV and QIV. Each influenza season, the contents of the vaccines alter, and differ for the Northern and Southern Hemispheres annually, and therefore it is difficult to give details for each season’s vaccines.

3.2.1 Adults

A Cochrane Database systematic review by Demicheli et al (2014) evaluated the safety of influenza vaccines in healthy adults. It found that seasonal IIVs were not associated with severe adverse events including onset of multiple sclerosis, optic neuritis, immune thrombocytopenic purpura or Guillain-Barré Syndrome. Following vaccination, local tenderness, myalgia, systemic fever, headache and fatigue were significantly increased compared with placebo or unvaccinated controls.16

Guillain-Barré Syndrome (GBS) has been associated with some influenza vaccines in adults and the incidence increased with age. During a 1976/77 swine flu vaccination programme in the US (with monovalent vaccine not TIV), 1098 GBS cases were identified and peaked at 3.34 cases of GBS per million vaccinees by 3 weeks post vaccination in adults. Based on epidemiological data collected subsequently, the risk of GBS has been estimated to be 1-3
per million doses among adults, but these data often lack statistical power due to very low numbers of cases. The risk of GBS following IIV vaccination appears to be much less than influenza infection.\textsuperscript{17}

### 3.2.2 Children

Following a marked increase in febrile events in Australian children aged under 5 years in 2010 after receiving one brand of that season’s TIV (Fluvax and Fluvax Junior, manufactured by bioCSL), influenza vaccination was suspended briefly for that age group. Due to a decline in confidence in influenza vaccination in children, a systematic review was conducted by Li-Kim-Moy et al in 2015 to assess serious adverse events associated with contemporary TIV. A total 18 randomised controlled trials (RCT), 14 non-randomised trials, 5 cohort studies and 1 case-control study were evaluated. In non-adjuvanted vaccines, the pooled proportion estimate of fever was 6.7\% (95\% CI 3.0-11.8) after the first dose of TIV in RCTs in children aged 6-35 months and 6.9\% (5.2-8.7) in children aged 3-17 years (time after vaccination not described). For non-RCT, the pooled estimate of fever was higher because the bioCSL vaccines were included in some of these studies (for children aged 3-35 months 17.7\% [11.3-25.2] and 15.1\% [13.3-17.0] ages 3-17 years). Overall rates of fever for up to 7 days following the first dose were comparable across brands of vaccine during RCTs: Sanofi Pasteur’s Vaxigrip 5.1\% (age 3-35m) and Fluzone 4.4\% (age 3-17y); GSK’s Fluarix 4.7\% and Novartis’ Agrippal 4.0\%). The authors concluded that the low pooled rate of fever $\geq$38°C was reassuring following administration of non-adjuvanted TIV (other than the bioCSL brand vaccine). Vaccine-related severe adverse events were uncommon.\textsuperscript{18}

A paper published in 2015 by the Institute of Vaccine Safety at John Hopkins University, US, presented literature around the safety of 108 influenza vaccines (with unique names, not necessarily different vaccines) in 27 countries produced by 47 manufacturers. Most influenza vaccines were very safe and had minimal adverse events (AE). Local and mild systemic reactions were the most commonly reported AEs. Improvements in vaccine design, such as split virion vaccines, as well as the use of half doses in children age 6-35 months, have reduced the incidence of fever in children from that associated with whole-inactivated virus vaccines, from 45-69\% to 1-13\% (rates variable due to fever cut-off points used in studies). The exception was the previously mentioned high rates of febrile seizures associated with the split-virion TIV (Fluvax\textsuperscript{®} Junior) in children aged 6 months to 5 years during the 2010 season in Australia. Anaphylaxis occurs at an approximate rate of one per 1 million doses and milder hypersensitivity reactions have been reported following live and inactivated influenza vaccination.\textsuperscript{17}

Research was carried out to provide explanations for the febrile events associated with the Fluvax vaccine. Although the cause remains unknown, an association with the manufacturing process of this particular TIV has been suggested.\textsuperscript{19}

The signal for high rates of febrile seizures during the 2010 season in children was detected by an Australian active surveillance system first developed in Western Australia, known as SMARTVax. Since that time, this real-time SMS based surveillance system has grown countrywide and is known as AusVaxSafety. In 2015, weekly cumulative data on 3,340 children vaccinated with TIV showed low rates of parent-reported fever (4.4\%, n=148) and medical attendance (1.1\%, n=35) following vaccination. Fever occurred more frequently with concomitant vaccination than in those who received only influenza vaccine (60/687 [8.7\%] vs 87/2,618 [3.3\%]; p=0.000; no details of concomitant vaccines reported).\textsuperscript{20}

#### 3.2.2.1 Concomitant administration

One study that used SMS messaging conducted during the 2010/11 season in the US identified that concomitant vaccination with pneumococcal conjugate vaccine (PCV-13) was
associated with increased risk of fever. A fever of ≥38°C was reported in 37.6% children aged 6-23 months on day 0-1 as compared with 7.5% (adjusted relative risk 2.69 [1.30-5.60]) for TIV alone and 9.5% (adjusted relative risk 2.67 [1.25-5.66]) for PCV-13 alone.21

Conclusions

Few safety issues have been identified with TIV in adults and the incidence of fever in children is less than 5% overall. An increased rate of febrile seizures was observed for one brand of TIV in 2010, which has been considered unusual and likely associated with the manufacturing process at that time. Although potentially associated with influenza vaccination, the incidence of GBS in adults and anaphylaxis is very low (around 1 per million doses). Concomitant administration with other childhood vaccines may increase the risk of fever.

3.2.3 Pregnancy

Results from systematic review conducted in 2015 by McMillan et al found no evidence to indicate that maternal influenza vaccination is associated with an increased risk of fetal death, spontaneous abortion or congenital abnormalities. The review recommended that more precise estimates were required to investigate safety of giving the vaccine during the first trimester, particularly in relation to spontaneous abortion and congenital abnormalities. Many of the studies reviewed observed fetal and infant outcomes following vaccination of the mother with the monovalent A/H1N1 pandemic vaccine, with and without adjuvants, alone or in combination with seasonal TIV, but only one low quality study considered TIV alone.22

Similar findings were reported in another 2015 systematic review conducted by Fell et al, which found no strong evidence to indicate that there was an increased risk of fetal death or pre-term birth associated with the receipt of influenza vaccine during pregnancy. Studies reviewed generally reported no association or modestly decreased risks. Three studies investigating fetal death at any gestational age estimated adjusted effects in the rate of 0.56-0.79 and from four out of five studies adjusted estimates for fetal death before 20 weeks gestation were between 0.89-1.23 and 0.44-0.77 after 20 weeks. No evidence was found for increased risk of preterm birth among 19 studies following vaccination.23

A 2014 review of cohort studies, which used data from the US Vaccine Safety Datalink (VSD), was conducted to evaluate the safety of TIV vaccination during pregnancy. These studies found no association between TIV vaccination in pregnancy and hypertensive disorders, gestational hypertension, preeclampsia/eclampsia, gestational diabetes and chorioamnionitis.24

A case-control study conducted using VSD, published in 2017, evaluated the receipt of seasonal influenza vaccine containing A/H1N1pdm09 antigen within 1-28 days prior to spontaneous abortion over two influenza seasons (2010/11 and 2011/12). The overall adjusted odds ratio (aOR) was 2.0 (95% CI 1.1-3.6) for vaccine receipt in the 28-day exposure window. Primary analysis found a significant association between spontaneous abortion and IIIV, but a post hoc analysis showed that a significant association was only observed among women who had received A/H1N1 containing vaccine in the previous season (aOR 7.7 [2.2-27.3] and null for those who had not been previously vaccinated (aOR 1.3 [0.7-2.7]). It was noted however, that the study was unable to establish a causal relationship between prior vaccination and spontaneous abortion. Results from a follow-up study for subsequent seasons are anticipated in late 2018.25

As part of the FluMum study conducted in Australia, the birth outcomes for mother-infant pairs were evaluated during 2012-2014. Out of 7126 mother-infant pairs enrolled, vaccine uptake in pregnancy was 34% (51% during second trimester). Mean gestational week of
birth was 38.7 for vaccinated and 38.8 for unvaccinated group (p=0.051). Infants in the vaccinated group weighed 15g less at birth than the infants of unvaccinated mothers (-12.8-42.2, p=0.29). It was noted that 13% of mothers in the vaccinated group were more likely to have at least one comorbidity or risk-factor (p=0.007). Since there were no differences in birth weight between those vaccinated in any trimester and unvaccinated mothers, it was concluded that vaccination at any stage of pregnancy did not affect infant birthweight.

Conclusions

There is no evidence of adverse outcomes following TIV vaccination during pregnancy. Most data is available for vaccination during the second and third trimesters. However, the stage of pregnancy did not affect infant birthweight. The measurement of outcomes occurring during the first trimester, such as spontaneous abortion and congenital abnormalities, have not been fully investigated. However, an increased incidence of spontaneous abortion was detected in previous vaccinated women within 28 days of A/H1N1pmd09-containing TIV.

3.2.4 Special groups

The safety of the use of TIV in individuals with comorbidities is reviewed.

3.2.4.1 Allergy

Influenza virus used for vaccines is initially cultured in hens’ eggs and traces of ovalbumin may remain. Although modern split virion and surface antigen vaccines are further treated during the manufacturing process, there is a potential risk that ovalbumin may induce allergic reactions in individuals who are severely hypersensitive to egg proteins. Some influenza vaccines contain influenza virus that has been cultured in cell-lines and do not involve eggs at any stage of production.

Anaphylaxis reactions following influenza vaccines are rare. A VSD report on the administration of over 4.5 million doses of A/H1N1 pandemic and seasonal influenza vaccines doses during the US 2009-2010 influenza season identified four cases of anaphylaxis related to influenza vaccination (0.9 cases per million doses). No serious allergic reactions were reported in 28 studies investigating the administration of influenza vaccine to 4,315 egg-allergic recipients (including 656 with a history of anaphylaxis following egg ingestion). The rate of minor allergic reactions was the same in non-egg-allergic recipients as in egg-allergic recipients. Other components of the vaccines may induce an allergic response to susceptible individuals and caution is required for subsequent vaccinations.

3.2.4.2 Immune-mediated inflammatory diseases

The 2012 seasonal TIV was found to be safe in 67 patients with psoriatic arthritis or psoriasis. Of these patients, 55% were being treated with tumour necrosis factor (TNF)-α blockers and 31% were receiving disease-modifying anti-rheumatic drugs.

A meta-analysis found that among 1,966 patients with systemic lupus erythematosus (SLE), 32 experienced mild exacerbations of their disease following vaccination with TIV, but were not considered vaccine related. All adverse events were mild and were not significantly higher than for the general population.

No safety concerns were identified when influenza vaccine was given to children and adults with inflammatory bowel disease (IBD), including those receiving DMARD therapy.

3.2.5 Quadrivalent inactivated influenza vaccine

To provide protection against both of the circulating influenza B lineages, quadrivalent influenza vaccines have been developed that include strains of influenza B from both the Yamagata and Victoria lineages. Clinical trials have demonstrated that the additional
influenza antigen does not alter the safety profile of quadrivalent inactivated influenza vaccine (QIV) compared with TIV in adults and children aged 6 months to <9 years. A study in Western Australia found no significant difference in the reactogenicity of QIV compared with TIV when administered to 1,685 health care workers: 13.6% versus 12.8% reported any reaction 7 days post vaccination with QIV vs TIV, respectively (p=0.66). No serious adverse events were detected following vaccination with either vaccine.

As of 6 October 2017, according to the AusVaxSafety surveillance data, adverse events, including 0.9% medically attended events, were reported in 8.4% of 6,155 children aged 6 months to <5 years following the receipt of one of four QIVs as part of the Australian national immunisation programme. Of these events, 2.6% were injection site reactions, 2.3% were fever and 0.5% were rash. No seizures were detected. Adverse events were reported by 6.8% (0.4% medically attended) of children and adults aged 5 - less than 65 years (n=37,363) and by 6.0% (0.3% medically attended) of adults aged over 65 years.

3.2.6 Summary of inactivated influenza vaccine safety

In general, with the exception of the rare risk of anaphylaxis, there are no safety concerns identified for inactivated influenza vaccines administered to all age groups, including during pregnancy and to those with immunosuppression. Although prior vaccination with A/H1N1 antigen-containing vaccine was suggested to increase the risk of spontaneous abortion in pregnancy during 2010-2012 seasons, no causal associated has been established subsequently and further studies are underway. The addition of extra influenza strain in quadrivalent vaccines does not alter the safety profile of IIV. Continued and active safety surveillance is required each year, since the content of the vaccines changes annually, to enable any new safety signals to be detected rapidly.

3.3 Immunogenicity of inactivated influenza vaccines

The purpose of influenza vaccination is to protect against infection and disease, and it can also provide herd immunity by restricting virus transmission within the population. The major antigenic protein of the virus is haemagglutinin (H), which functions as a viral attachment and membrane fusion protein. Antibodies targeting haemagglutinin can neutralise the virus, and thereby prevent infection. However, due to antigenic drift, changes occur to the antigen epitope and make antibodies targeting these regions less effective. Another antigen is neuraminidase (N), which is important for the release of the replicated virus from the cell surface. Antibodies that target this protein can help to prevent influenza transmission but not infection.

CD8+ cytotoxic T cells also recognise a broad range of influenza virus antigens, including more conserved internal proteins. The ability to mount a cell-mediated response against these proteins provides cross-protection for various influenza strains. The measurement of interferon-gamma (IFN-γ) responses to vaccine antigens may also provide an additional measure of seroprotection.

Although no correlates of protection have been established against seasonal influenza, haemagglutination inhibition (HI) or neutralisation assays are used to detect haemagglutinin-specific serum antibodies and a titre of ≥1:40 is accepted as corresponding to a 50% reduction in the risk of contracting influenza in adults. However, this titre may not be appropriate for use in children. A titre of 1:110 or more was found better to predict 50% clinical protection rate in children.
3.3.1 Immunogenicity in children

A six site US-based RCT compared the immunogenicity of full versus half doses of TIV in 32 children previously primed (with two doses in prior season) and 211 vaccine-naïve children aged 6–35 months, randomised 2:1. Primed children received one dose of TIV and vaccine-naïve children received two doses. Antibody responses were not increased in the full dose versus half-dose cohort, except against A/H1N1 in primed children (geometric mean titre [GMT] difference 267.5 [95% CI 3.9-527.9]). Only the primed cohort met the WHO serological criteria for A/H3N2 (>40% seroconversion, GMT >2.5 fold and >70% with ≥1:40 HI) regardless of dose. Age differences were observed, with statistically higher titres achieved in the naïve cohort for children aged 12-35 months compared with those aged 6-11 months. The study was unable to show improved immunogenicity and protection in unprimed children following a full dose, and concluded that recommending the same dose, either half or full doses, for all children would simplify purchase, storage and administration of influenza vaccines.39

The immunogenicity of TIV was compared in overweight and obese children with normal weight children aged 3-14 years. Significantly higher or similar seroprotection rates against the vaccine strains were detected in the obese children.40

3.3.1.1 Children with cancer

Seroconversion for all three strains was significantly more likely in children with solid tumours (overall odds ratio [OR] 6.03 [95% CI 1.56-23.29], p<0.01) compared with haematological malignancies. Vaccine-naïve children under 10 years of age who received two doses of TIV vaccine (0.25 ml doses for those less than 3 years and 0.5ml doses for those older than 3 years) also were significantly more likely to respond than those who received one dose and had been vaccinated in previous seasons (OR 14.71 [1.2-170.2], p<0.03 for all three strains). Following vaccination of 100 children undergoing treatment for cancer, seroprotection rates were 55% for A/H3N2, 61% for A/H1N1 and 41% for B. Adjusted VE was estimated to be 72% (95% CI -26 to 94%).41

3.3.1.2 Children with HIV infection

The efficacy of TIV in children with HIV infection was evaluated in a double-blind placebo controlled RCT in Johannesburg, South Africa, during 2009. The median age of the 410 children was 23.8 months. The children received two doses of TIV or placebo one month apart. Seasonal influenza was confirmed in 13/205 vaccine recipients (all A/H3N2) and 17/200 placebo recipients (15 A/H3N2 and two influenza B); vaccine efficacy was 17.7% (95% CI <0 – 62.4%). There was a strain drift in wild-type A/H3N2. Seroconversion following vaccination was 47.5%, 50% and 40% for A/H1N1, A/H3N2 and B influenza, respectively. The study concluded that poor immunogenicity may explain lack of efficacy of TIV in children with HIV infection.42

3.3.1.3 Children with recurrent wheeze

An open-label multicentre phase IV RCT compared the immunogenicity of TIV in 68 healthy children aged 6 months to 3 years with 62 children with recurrent wheezing (defined as two or more reports in the first year of life). Vaccine-naïve children received two 0.25ml doses and previously vaccinated children received one 0.25ml dose of seasonal split virion TIV. Children on long-term steroid treatment were excluded; 33 children with wheeze had received low dose-steroid treatment and 29 had no steroid exposure. Both groups of children achieved immunogenicity criteria (at least 70% seroprotection; seroconversion >40%; HI ≥1:40) and immunogenicity was not statistically different between groups. Seroconversion rates against A/H1N1 were 69.1% and 66.1% for healthy and children with
wheeze respectively, and for A/H3N2 were 80.9% and 74.2% respectively. In children with wheeze, the GMT pre and post immunisation were higher than healthy children, although the GMT ratio was higher in healthy children. The study concluded that, although the numbers of participants were small, immunogenicity of TIV was demonstrated even among young children with recurrent wheeze including those who received short-term steroid treatment.43

Conclusions

Apart from children with HIV, TIV appears to be immunogenic in children with prior immunisation experience, cancer and recurrent wheeze.

Seroconversion in response to TIV was more likely in children with solid tumours than those with haematological malignancy.

However, a higher HI titre may be necessary for seroprotection in young children than for healthy adults, and therefore clinical protection rates may be lower in children, particularly in those with impaired immune responses. The youngest children (aged 6-24 months) have lower ability to generate an antibody response than older children. Two separate doses are required in unprimed children to induce the same response as in primed children after one dose.

3.3.2 Immunogenicity in special groups

3.3.2.1 Immune-mediated inflammatory diseases

A multicentre prospective study in France found that high seroprotection rates against influenza were achieved in adults with inflammatory bowel disease (IBD) who were vaccinated with TIV during 2009/10 and 2010/11 influenza seasons. Of the patients, 31 were not receiving immunosuppressive treatments, 77 were receiving immunosuppressive treatment without anti-TNF therapy and 117 received anti-TNF therapy with or without immunosuppressive treatment. Seroprotection persistence for A/H1N1 and A/H3N2 strains at 6 months and 12 months following vaccination was lower in patients receiving anti-TNF treatment, with or without immunosuppression, than those receiving immunosuppression alone: at 6 months, 30% vs 55% p=0.0015; and 17% vs 52%, p=0.0001, respectively. The study supported recommending vaccination of patients with IBD, but suggested that more immunogenic vaccines are required for patients receiving anti-TNF therapy.31

A RCT study conducted in Canada found that seroprotection to influenza vaccine was only achieved in around 45 – 80% of patients with IBD on maintenance infliximab (anti-TNF-α treatment). Timing of the vaccination relative to the infliximab infusion did not affect seroprotection.44

A meta-analysis of 18 studies found that, compared with the general population, seroprotection rates in patients with SLE were significantly lower against A/H1N1 (OR 0.36; [95% CI 0.27-0.50] and influenza B (OR 0.47 [0.29-0.76]), but not against A/H3N2 (OR 0.62 [0.21-1.79]).29 Another meta-analysis also found a significant difference in seroprotection rates between patients with SLE and healthy controls, and subgroup analyses found that patients receiving immunosuppressants (corticosteroids, azathioprine and prednisone) had significantly lower seroprotection rates.45

Patients on methotrexate treatment for rheumatoid arthritis were found to have a reduced response to influenza vaccination according to a systematic literature review (n=43; pooled OR for A/H1N1 0.44 [0.17-1.12], A/H3N2 0.33 [0.30-0.54] and B 0.29 [0.10-0.81]). For patients receiving anti-TNF therapy, the immune response was not significantly affected (n=308, pooled OR A/H1N1 0.93 [0.36-2.37], A/H3N2 0.79 [0.34-1.83] and B 0.79 [0.37-
but the confidence intervals were wide. The study concluded that vaccination still provided protection in a number of cases and was worth proposing.46

A RCT conducted in Japan found that booster doses of TIV did not improve immune responses of adults with IBD receiving immunosuppressive treatment and/or anti-TNF therapy. The study enrolled 78 patients with IBD (mean age 45.3 years [range 26-73]) and 11 healthy controls (mean 42.4 years [21 -72]) who were randomised to receive either a single dose of TIV or a second dose 3 weeks after the first. Following the first dose, seroprotection rates were high (85% for A/H1N1, 82% for A/H3N2 and 100% for B). Among the patients with IBD, there were no significant differences in GMT after single vaccination or booster vaccination (A/H1N1 p=0.09; A/H3N2 p=0.99 and B p=0.94). The study concluded that booster vaccination does not appear to be necessary in adults with IBD, although further studies are required to establish an appropriate strategy for high risk patients.47

3.3.2.2 Diabetes mellitus

The long-term immunogenicity of TIV during the 2012/13 influenza season was compared in 105 adults with type-2 diabetes mellitus and 108 controls. The immunogenicity profiles were similar between the two groups. A statistically lower long term immunogenicity (6 months post vaccination) was observed against A/H1N1 in elderly diabetic but not non-diabetic participants; a multivariate analysis concluded that this was associated with age (p<0.001) and prevaccination titre (p<0.005), not diabetes status. It was noted that during this season A/H3N2 was the dominant strain and exposure may have influenced that persistence of immunity to this strain.48

No studies were identified evaluating IIV immunogenicity in patients with type 1 diabetes mellitus.

3.3.2.3 Cancer in adults

The immunogenicity of standard dose TIV was evaluated in a pilot prospective cohort study in 38 patients with malignant tumours of the central nervous system (mean age 54 ± 13.5 years). Of these patients, 20 were taking glucocorticoids, 25 were on active chemotherapy and three were receiving radiotherapy at enrolment. Seroconversion and seroprotection rates on day 28 post vaccination were 37% and 80% for A/H1N1, 23% and 69% for A/H3N2 and 23% and 74% for B strains, respectively, all of which were significantly lower than published rates in healthy adults (p<0.001).49

3.3.2.4 Liver transplant recipients

Overall, no significant differences in antibody responses to TIV were observed in 16 adults or 15 children who had received live donor liver transplants in Japan. Seroprotection rates (HI ≥1:40) were 50-94% in adults and 27-80% in children to all three influenza antigens in two influenza seasons. Seroconversion rates (>4-fold rise in antibody) were 32-56% and 13-67% in adults and children, respectively. In both adults and children, the long term response to preceding vaccinations appeared to be insufficient.50

Conclusions

As would be anticipated, the immune response to influenza vaccine is affected by immunosuppressive therapies and immunodeficiencies. As in young children and the elderly, IIV may not induce sufficient seroprotection to prevent disease in certain groups with poorer antibody responses. More immunogenic formulations are likely to be required for immunocompromised individuals.

However, even with lower levels of protection, vaccination is likely to be beneficial in reducing disease severity and hospitalisations and is recommended. Booster vaccination
within the same season were shown not to improve seroprotection in IBD patients or healthy controls.

### 3.3.3 Previous vaccination

An antibody landscape was generated to study the immune profile of A/H3N2 evolution for 69 individuals monitored for infection over six years. Increases in antibody titres, including for previously encountered viruses, extended beyond cross-reactivity observed after primary infection. The study described a ‘back-boost’ effect, whereby a long-distance response back to previous antigenic clusters is observed, dependent on the pre-exposure antibody landscape. To investigate whether this back-boost effect could be used to improve vaccine effectiveness, sera of 225 individuals before and after vaccination were analysed to generate antibody landscapes and to identify antigenic cluster transitions. The study found that in populations with prior immunity, in the case of a mismatch in a vaccine strain due to a mistiming of pre-emptive strain update (i.e. changing the vaccine to include a predicted strain rather than keeping a previous strain), an extensive back-boost effect would be provided that could still induce equivalent antibody titres against a previous antigenic strain. In this situation, the vaccine would be effective against the antigenically novel strain to which it was targeted or be more effective against the contemporary virus if it continued to circulate. The longevity of this response was not investigated.51

Moving away from the concept of antigenic matching, a recent study conducted in Canada described the concept of immune-epidemiological factors in relation to host responses to influenza virus. Several influences affect the immune response and effectiveness of influenza vaccines. These include genetic evolution of circulating viruses, epitope specificity, egg-induced mutations in vaccine viruses and the individual ‘immune landscape’ and birth cohort effects generated by repeat vaccination and exposure to infection throughout a lifetime.52, 53 For further details see section 3.4.3.

#### 3.3.3.1 Prior vaccination of children

Although serological responses to influenza A vaccine viruses were high regardless of vaccination history, previous vaccination was associated with lower antibody titre rises in response to TIV against seasonal A/H1N1 and A/H3N2, particularly in children aged 9-17 years. However, higher antibody responses were seen among individuals primed with the same influenza B virus lineages in the preceding years, especially children aged 6-8 years, in a season in which influenza B predominated.54

A US-based study demonstrated that conserved epitopes provided immunological cross-reactivity in children either directly through vaccination with 2010/11 TIV or boosting response to the prior season’s influenza vaccine. The study collected blood samples post vaccination from 50 children aged 9-14 years (mean age 11.8 years). Of these children, 28 had received 2009/10 TIV, 10 had received 2009/10 LAIV and 32 had received the monovalent A/H1N1pdm09 pandemic vaccine in the previous season. All children showed an increase in HI titres to the three vaccine strains and 68% had a ≥4-fold rise in HI titres to the previous year’s A/H3N2 strain by day 28 post vaccination. Prior vaccine recipients did not have higher HI titres than previously unvaccinated children to the serologically distinct A/H1N1pdm09 strain, but did have higher pre-existing titres to 2010/11 A/H3N2 (p≤0.001). Although 84.2% of children who had received the 2009/10 TIV reached HI titres of ≥1:80, slightly lower HI titres against B/Bris/60 were observed when vaccinated with the same strain during the following season. The study concluded that influenza vaccination resulted in broader serological and cell-mediated immunity than to strains included in that year’s vaccine and influenced responses in the following year. Due to blood sample size limitations,
it was not determined whether priming or boosting from exposure to wild-type disease affected the immune response to subsequent vaccinations.\textsuperscript{55}

Conclusions

From these studies, it is not clear as to what effect prior vaccinations or previous influenza exposure may have on the immunogenicity, and effectiveness, of subsequent vaccinations. The influence of prior exposure appears to be strain dependent, but is also affected by variations in the virus itself and birth cohorts.

Cross-reactivity has been suggested between influenza strains to conserved epitopes between genetically related viruses. Further to this, a ‘back-boost’ effect dependent on antigenic distance to historical strains has been proposed.

Although not described in the literature, subunit vaccines that do not contain whole virus potentially lack conserved epitopes and may not induce a cross-reactive response.

3.3.4 Quadrivalent inactivated influenza vaccine

A systematic review conducted by Moa et al in 2016, based on five RCT, found QIV to be as immunogenic as TIV in adults against the influenza strains common to both vaccines. QIV induced statistically higher seroconversion rates against non-TIV B lineage, including in adults over 60 years of age.\textsuperscript{56}

3.3.5 Co-administration with other vaccines in older adults

A study conducted during the 2012/2013 influenza season in Korea randomised 220 adults aged 65 years or over to be vaccinated concurrently with TIV and 13-valent pneumococcal conjugate vaccine (PCV-13) or 23-valent polysaccharide pneumococcal vaccine (PPV-23). The participants had not previously received a pneumococcal vaccination. Comparable seroprotection rates (p=0.990), seroconversion rates (p=0.746) and GMT fold (p=0.588) were seen at one month after vaccination and immunogenicity was similar between both groups. Post vaccination GMTs of TIV+PCV-13 were significantly higher than for TIV+PPV-23 for A/H1N1, but not the other influenza strains: HI GMT 89.9 (74.5-108.4) with PCV-13 vs 66.4 (55.1-80.1) with PPV-23 (p=0.026). The authors were unable to explain this finding.\textsuperscript{57}

A phase III non-inferiority RCT conducted in France and Belgium assessed the immunogenicity of co-administration of QIV and PPV-23 in adults aged 50 years and over, as compared with separate administration. The antibody responses to the vaccine antigens were not affected by co-administration. In a cohort of adults aged 60 years and over, high risk comorbidities, including diabetes, morbid obesity, and respiratory, renal, heart, liver and neurological diseases, did not impact on QIV immunogenicity when compared with those without comorbidities.\textsuperscript{58}

The immunogenicity of co-administration of live attenuated zoster vaccine and QIV was assessed in adults aged 50 years or over during the 2015/2016 influenza season in the US. Comparable antibody responses were observed following co-administration or administration of either vaccine alone. Influenza antibody GMT ratios were 1.02 (95% CI 0.88-1.18), 1.10 (0.94-1.29) and 0.99 (0.87-1.13) for A/H1N1, A/H3N2 and B strains, respectively.\textsuperscript{59}

Conclusions

Co-administration with other vaccines does not impact on the immunogenicity of TIV or QIV vaccines in older adults.

3.3.6 Summary of IIV immunogenicity

In general, IIV are able to induce anti-H antibodies in most individuals. However, seroconversion rates are lower in children, older adults and those with immunosuppression.
Since there is no defined correlate of protection, it is unclear whether HI titres are an accurate measure of protection and higher titre thresholds may be required to achieve seroprotection in these groups.

The influence of prior vaccination and exposure to circulating virus on immunogenicity and protective immunity is also unknown. Some studies indicate a boosting of response and others a suppression, and this appears, in part, to be influenza strain dependent. Cell-mediated immune memory against conserved antigenic sites could be important in influencing the immune response to circulating strains.

### 3.4 Effectiveness of inactivated influenza vaccines

Vaccine effectiveness (VE) is a real-life measure of vaccine effect, usually obtained from test-negative designed case-control studies. Using routine surveillance systems, patients presenting with influenza-like illness (ILI) to general practice or being hospitalised with acute respiratory illness (ARI) are tested for influenza and VE is calculated from the odds of vaccination among those testing positive compared with those testing negative.

By comparison, vaccine efficacy is a measure of vaccine effect obtained under controlled clinical trial conditions - for example, comparing the efficacy in disease prevention between the test vaccine and placebo or a control vaccine. Since conventional IIV have been licensed for decades, efficacy of IIV is not considered in this review.

#### 3.4.1 Influenza presenting to general practice

As part of the SHIVERS study, the incidence of influenza-like illness (ILI) presentations was monitored in sentinel general practices in the Auckland and Counties Manukau District Health Boards. Using test-negative design, the vaccine effectiveness of each season’s influenza vaccine was estimated from 2012–2015. Interim data for 2015 estimated vaccine effectiveness against circulating laboratory-confirmed influenza to be 36% (95% CI 11-54) in general practice encounters. These findings were similar to the three previous seasons, with a point estimate VE of around 50% (37% - 50%) against general practice ILI attendance. In 2014, VE against ILI related GP visits was 67% overall and 73% against the predominant strain A/H1N1pdm09. Likewise in 2013, VE was 56% against ILI GP visits.60-63

A systematic review was conducted by Demichelli in 2014 that assessed the efficacy of influenza vaccines to prevent influenza and its complications, and the effectiveness of the vaccines to prevent ILI symptoms and associated consequences. It only considered studies of healthy individuals aged 16-65 years. The review found that the overall VE against ILI symptoms was 16% (95% CI 5-25%), which corresponded to the need-to-vaccinate (NNV) 40 individuals to prevent one case of ILI. When the vaccine strain matched the circulating strain, VE was also 16% (9-23%) and the NNV was 17 (12-29). In clinical trials, overall efficacy in preventing confirmed influenza was 60% (53-66%) with a NNV 71 (64-80), and when the vaccine strains matched VE was 62% (52-69%) with NNV 58 (52-69). Vaccination did not show an appreciable effect on working days lost or hospitalisation of healthy adults in the general population.16

**Conclusions**

Inactivated influenza vaccines have a modest effectiveness against general practice presentations for influenza, with a point estimate of around 50%.

#### 3.4.2 Influenza hospitalisation

A study in Spain considered the effectiveness of inactivated influenza vaccine on mild (outpatient) versus hospitalised (inpatient) or severe disease during 2010-2011 season.
Hospitalised patients (n=691) with laboratory-confirmed influenza were matched by age, visit date and province with an outpatient with laboratory-confirmed influenza case and an outpatient control. Severe cases were admitted to ICU or died in hospital (n=177). VE was 75% (aOR 0.25; 95% CI 0.16-0.39) in preventing influenza outpatient cases, 60% (0.4; 0.25-0.63) in preventing hospitalisation and 89% (0.11; 0.04-0.37) in preventing severe cases. Influenza vaccination was associated with a lower risk of severe influenza in inpatients (aOR 0.42; 0.22-0.80).64

Another study conducted in Spain suggested a decrease in vaccine effectiveness during the influenza season. The 2014/2015 influenza season was predominated by A/H3N2 influenza (96% of subtyped cases) with co-circulation of B influenza increasing towards the end of the season. VE decreased from 37% to -76% against A/H3N2 within 3 months since vaccination and 84% to -4% against B. During this year there was a mismatch of vaccine and circulating strain (64% discordance for A/H3N2).65

According to SHIVERS data, the protection against influenza hospitalisation is moderate.60 In 2015, VE against laboratory-confirmed influenza hospitalisations was 50% (20-68%) and for A/H3N2 was 53% (6-76%). There was a total of 754 laboratory-confirmed influenza cases. During 2014, it was identified that hospitalised patients were likely to be very young or very old, to be of Māori or Pacific Island ethnicities, have low income and to have chronic illness. VE was 42% (16-60%) and was most effective against A/H1N1pdm09 strain with an adjusted VE of 62% (38-77%).66

**Conclusions**

IIV is moderately effective in preventing influenza hospitalisations and reducing disease severity in those vaccinated, but is variable from year to year. However, changes in circulating strains during the season can result in increased disease severity.

### 3.4.3 Previous vaccination

A systematic review and meta-analysis conducted by Ramsay et al published in 2017 found no evidence overall of a negative impact on vaccine effectiveness due to receiving vaccinations in prior seasons. Compared with vaccination during the prior season only, vaccination in both seasons provided greater protection against medically attended, laboratory-confirmed influenza A/H1N1 (absolute difference in VE [ΔVE] 26%; 95% CI 15-36%) and B strain influenza (ΔVE 24%; 7-42%), but not for A/H3N2 (ΔVE 10%; -6 to 25%). Compared with no vaccination, for either season, the current season vaccine had greater protection with increased VE against influenza A/H1N1, A/H3N2 and B: ΔVE 61% (50-70%); 41% (33-48%); and 62% (54-68%), respectively. No difference in VE was observed between vaccination in both seasons and the current season only, ΔVE 4% (-7 to 15%), -12% (-27% to 4%) or -8% (-17 to 1%), respectively. The review concluded that its findings support current season vaccination regardless of prior season vaccination from a patient’s perspective, and from a policy perspective there was no overall evidence that repeated vaccination over two seasons has a negative impact on the current season vaccine effectiveness. Note that this study did not differentiate between different influenza vaccine types and was unable to adjust for match between the vaccine and circulating strains or changes in strains between seasons.67

An Australian test-negative study, using data from the Influenza Complications Alert Network (FluCAN) sentinel hospital-based surveillance programme, found that vaccination in both the current and previous seasons was associated with higher VE than vaccination in either single season against influenza hospitalisation: VE 51% vaccination in both seasons (45-57%), 33% current season only (17-47%) and 35% previous season only (21-46%). Similar results were seen for A/H1N1, A/H3N2 ad B influenza strains. The study included
6,223 influenza cases and 6,505 influenza negative controls hospitalised with ARI during 2010-2015.68

A study in Navarra, Spain, found that previous seasons’ vaccinations with split-virion influenza vaccine provided considerable residual protection against laboratory-confirmed influenza during the 2014/15 season, particularly in those vaccinated with the same vaccine composition over successive seasons. For example, adjusted VE against all influenza following two previous doses of split vaccine only was 67% (17-87) versus 42% (-31 to 74) for the current season vaccine only. However, the vaccine effectiveness of that season’s subunit vaccine was low overall and it was suggested that there was possible interference between the ‘prior-season’ split-virion vaccines (disrupted whole virus) and the ‘current season’ subunit vaccine (containing purified H and N only) – adjusted VE following one previous dose of split vaccine plus current season subunit vaccine was -16% [-106 to 35]. When the number of doses of split vaccine received in the previous two seasons was considered as a continuous variable, it was associated with increased protection against any laboratory-confirmed influenza (ρtrend = 0.016), A/H3N2 (ρtrend = 0.032) and influenza B (not statistically significant, ρtrend = 0.140). This study included 1,213 patients of whom 619 (51%) had confirmed influenza. The proportion of hospitalised cases was the same for both A/H3N2 and B cases (31% each).69

A test-negative design study examined the effectiveness of the 2015/16 seasonal TIV in Canada. During this season, A/H1N1pdm09 and B/Victoria viruses were predominant. VE was higher against the mismatched B lineage than the antigenically matched A/H1N1 strain. VE against A/H1N1 was lower among those vaccinated in both the 2015/16 and prior season than those vaccinated in 2015/16 only (41% [95% CI 18-57%] vs 75% [45-88%], respectively); however, no repeat vaccination effects were seen during the same season in the US. A decline in VE was also observed during the season, from 62% in January/February to 19% in March/April. In people born during 1957-1976, VE was only 25% (-16 to 51%). These individuals were likely to have been primed against A/H1N1 antigens earlier in life and then subsequently vaccinated with the same antigens. It was suggested that they may have suboptimal response to emergent H1N1 variations with de novo mutations (e.g. K163Q mutation). A model of 2015/16 VE by year of birth showed a U-shaped pattern with the lowest VE in people born around 1967. The authors concluded that consideration of other agent-host and immuno-epidemiological influences is required when assessing vaccine performance, beyond antigenic matching. These influences include viral genomic variation, birth/immunological cohort, repeat vaccination effects and potential waning of vaccine protection within-seasons.52, 53

3.4.3.1 Prior vaccination in children

Previous vaccination of children was considered in a study in China that compared 1,729 medically-attended laboratory-confirmed A/H1N1pdm09 influenza cases with matched healthy controls, in children aged 8 months to 6 years during the 2012/13 Northern Hemisphere season. In children aged 3-6 years with a single documented vaccination during the two prior seasons, VE was 31% (8-48%) in those who had been vaccinated two years earlier and 48% (41-80%) for those vaccinated one year earlier. VE point estimates were higher, but not statistically significant, among children with a history of previous vaccination. It was noted that this VE was against a single virus strain for which the vaccine was well matched and this study did not use a test-negative design.70

Conclusions

Vaccine effectiveness against seasonal influenza is complicated by several factors that are associated with virus-host and immuno-epidemiological interactions, including prior
vaccination and exposure to different influenza strains. These influences include viral genomic variation, cross-reactivity, age-specific susceptibility as a result of age-cohort effects, effects of repeat vaccination and potential waning of vaccine protection within-seasons.

The influence of prior vaccination in the previous season does not appear to have a significant effect on VE in general and has the potential to enhance effectiveness, even when the antigenic match is incomplete.

Further studies are required to investigate waning of VE during a vaccine season and to elucidate the effect prior season vaccination has when antigenic changes occur.

### 3.4.4 TIV effectiveness in children

The effectiveness of TIV vaccination in preventing hospitalisation of children was evaluated at the Princess Margaret paediatric hospital in Western Australia. During a 5-year period (2008, 2010-2013), 285 laboratory-confirmed influenza hospitalisations were identified, median age 3.51 years (interquartile range 1.08-7.55), most frequently presenting as ILI with at least one acute respiratory symptom and fever (74.5%) and pneumonia (23.9%). Vaccine uptake was low, 4.9% of cases and 8.5% of controls were vaccinated. VE was estimated to be 62.3% (95% CI -6.6 to 86.7%, fully vaccinated vs unvaccinated).

This hospitalisation study was conducted as an addition to the Western Australia Influenza Vaccine Effectiveness (WAIVE) study. WAIVE was an observational study in which 2,001 children, presenting at the Princess Margaret Hospital with an ILI (as defined above), were enrolled; the 2009 cohort was excluded due to the A/H1N1 pandemic. In this population, vaccine uptake was 24.0% overall, and significantly decreased between 2008/9 and 2011/12, due to febrile events in children associated with the 2010 seasonal vaccine. Influenza was detected in 289 (20.4%) of children and other respiratory viruses were detected in 1,134 (59.6%) of children. Adjusted VE was 64.7% (33.7-81.2%) against hospitalised ILI in 1,514 children using test-negative controls. In children under 2 years of age, VE was 85.8% (37.9-96.7%) using test-negative controls and 85.5% (34.7-96.8%) using other-virus-detected controls.

Using FluCAN surveillance programme data in Australia, effectiveness of TIV in children was assessed during 2014. The test-negative study compared 402 laboratory-confirmed influenza cases admitted with acute respiratory illness with non-influenza ARI cases. Adjusted VE (for age and comorbidities) was estimated to be 55.5% (11.6-77.6%) for one or more doses of TIV in preventing hospitalisation. VE against A/H1N1pdm09 was high at 91.6% (36-98.9%) and against A/H3N2 was low (adjusted VE -4.0% [-138.9-54.7%]) in fully and partially vaccinated children. The study was unable to determine VE against specific vaccine strains. Low vaccine uptake was a major limiting factor for this study. Vaccine coverage was 12.4% for full or partial vaccination of those over 6 months of age who tested negative for influenza (25/197) compared with 7.1% of those who tested positive (18/236). It concluded that TIV in 2014 was moderately effective in preventing hospitalisation of children and was most effective against A/H1N1pdm09 subtype.

A study in China compared 1,729 medically-attended laboratory-confirmed A/H1N1pdm09 influenza cases with matched healthy controls in children aged 8 months to 6 years during the 2012/13 Northern Hemisphere season. Although the rate of documented vaccination with at least one dose was low among children aged 8-35 months (14% of cases and 28% of controls) and in those aged 3-6 years (5% of cases and 12% of controls), one or more doses of TIV had a significant VE of 67% (95% CI 58-74%) among all children. VE point estimates were higher, but not statistically significant, among children with a history of
previous vaccination. It was noted that this VE was against a single virus strain for which the vaccine was well matched and this study did not use a test-negative design.\textsuperscript{70}

During November 2013 to March 2014, a total of 4,727 paediatric outpatients presenting with ILI and confirmed influenza, as assessed by an influenza rapid diagnostic test, were enrolled into a test-negative case-controlled study in Japan. Overall VE was 46\% (39-52\%) across all children aged 6 months to 15 years. Adjusted VE was 63\% (56-69), 77\% (59-87) and 26\% (14-36) against influenza A, A/H1N1pdm09 and B, respectively. The study found that TIV was more effective against influenza A than B and VE against hospitalisation due to influenza A was 76\%, particularly A/H1N1pdm09. It reported that TIV was not effective against medically attended influenza A or B in children aged 6-11 months.\textsuperscript{74}

Conclusions

Vaccine uptake among children is generally low, and therefore, estimates of vaccine effectiveness are hindered by small numbers for comparison. Vaccine effectiveness appeared to be better against A/H1N1pdm09 (up to 91\%) than A/H3N2 and B strains (as low as 26\%). This is likely to reflect A/H1N1pdm09 being the predominant strain and a mismatch to influenza B lineage in TIV during the study seasons.

3.4.4.1 Full versus partial vaccination

Some of the studies above considered full versus partial vaccination of children aged 6 months to 8 years. The Advisory Committee on Immunization Practices (ACIP) recommends children to receive two doses of vaccine if they are previously unvaccinated and one dose for subsequent seasons.

A study conducted in the US compared VE of TIV in fully and partial vaccinated children aged 6 months to 8 years across two seasons, taking into consideration prior vaccination and the number of doses. After excluding children who received LAIV, data was collected by the US FluVE network for 1,441 children with medically attended ARI. Vaccine coverage in enrolled children for one dose was 50\% and 45\% for 2011/12 and 2012/13 seasons, respectively. Significant VE was observed for both full and partial vaccination against ARI associated with all the circulating influenza viruses, and it was observed that vaccination reduced the risk of medically attended influenza ARI by around half. Previous season vaccination provided residual protection to boost the benefit of TIV. Children who received two doses of TIV in the previous season appeared to have greater protection when vaccinated in the next season (VE 58-80\% following two prior doses vs 33-42\% without prior doses), particularly against A/H3N2 for which protection was 2.4 fold higher in primed children.\textsuperscript{75}

A study in China that compared 1,729 medically attended laboratory-confirmed A/H1N1pdm09 influenza cases with matched healthy controls in children aged 8 months to 6 years during the 2012/13 season. The odds of influenza in partially vaccinated children aged 8-35 months was 1.6-fold higher (1.0-2.7) than in fully vaccinated children.\textsuperscript{70}

In the Japanese study, two doses of vaccine provided better protection against influenza illness caused by influenza A, but did not statistically add benefit compared with one dose against influenza B.\textsuperscript{74}

3.4.4.2 Immunocompromised children

Adjusted VE for influenza infection in 100 children undergoing cancer treatment was estimated to be 72\% (-26-94\%) compared with unvaccinated controls during the 2010 and 2011 seasons in Western Australia. This was comparable to geographically matched children during the same seasons. Influenza infection occurred in 2\% of the vaccinated population
compared with 6.8% of the unvaccinated controls. It was reported that all children younger than 10 years should receive two doses of TIV regardless of prior vaccination history.41

Conclusions

In some cases, one dose of vaccine is sufficient to provide protection against influenza. However, VE is improved by two doses, and by two doses given in a previous season compared with no prior vaccination. In immunocompromised children, two doses are likely to provide greater protection than just one dose, regardless of prior vaccination history.

3.4.5 Quadrivalent IIV

No literature was identified that compared the effectiveness of QIV with TIV in adults or children. The effectiveness of QIV is expected to be higher than TIV when a mismatch between the predicted B lineage in the TIV and circulating disease occurs. The available literature predominantly reported on immunogenicity and safety from QIV clinical trials.

A modelling study using individual-based simulation models was conducted to assess the effectiveness of TIV and QIV in Australia and South Africa. It predicted that, over 11 modelled years, QIV would prevent 18% more deaths and hospitalisations than TIV in South Africa, whereas, in Australia, only 2% fewer deaths and hospitalisations would result due to a good match between the TIV B lineage and circulating disease. The study showed that in Australia, vaccination coverage of 20% has reduced seasonal influenza associated hospitalisation and death by at least half. The greatest reduction in influenza burden was achieved by targeting virus transmitters first with vaccination coverage levels of over 5%. The study concluded that choosing to target those most responsible for transmission (children) with TIV, rather than vulnerable populations such as those with HIV and the elderly, was preferable to choosing between TIV or QIV. The effectiveness of QIV on reducing health burden was dependent on whether the B lineage in the TIV vaccine matches the circulating lineage.76

3.4.6 Waning of protection during a season

Some literature suggests that there is a waning of protection following sequential seasonal influenza vaccination. However, as discussed by Pebody and Mølbak, the challenge is to disentangle intra-seasonal waning of immunity from gradual antigenic changes resulting in mismatching of the circulating strains with vaccine influenza strains later in the season.77

A case-control study (I-MOVE) concluded that the time since vaccination also needs to be taken into consideration when analysing vaccine effectiveness. Data was analysed to investigate the effects of time since vaccination on influenza vaccine effectiveness (VE) against ILI presentations from 2010/11 to 2014/15 seasons in Europe. Against A/H3N2, VE reached 50.6% at 38 days after vaccination, but declined to 0% from days 111 onwards, whereas VE reached 55.3% against A/H1N1pdm09 at day 54 post vaccination and remained between 50.3% and 55.3% to the end of the season. VE against influenza B also declined from 70.7% to 21.4% from 44 days to season end, respectively. This study did not investigate the role of prior season vaccination on immunity.78

3.4.7 Summary of IIV effectiveness

The effectiveness of seasonal inactivated influenza vaccine is dependent on multiple factors, including age and immune status of the recipient, match of vaccine and circulating virus, historical exposure to influenza virus through infection and vaccination and antigenic changes in the viruses during the season.

When well matched, the ability of influenza vaccines to prevent hospitalisation is similar or possibly greater than prevention of primary care influenza presentations. The point estimate
for VE against confirmed-influenza illness is around 50% overall. However, in some years and possibly related to well matched strains, VE can increase to more than 80%.

Although data is limited, IIV are likely to protect pregnant women from influenza-associated hospitalisations. There is limited data around protection of newborns.

The effectiveness of influenza vaccines is dependent on vaccine uptake. When uptake is inadequate, transmission of the virus is high and those who may not have acquired sufficient immunity are at risk of infection, such as the elderly and those with underlying medical conditions.

4 Alternative formulations of inactivated influenza vaccine

The levels of seroprotective antibodies induced by IIV in young children, adults over 65 years and immunocompromised individuals is suboptimal to provide good protection against influenza infection and IIV are often less effective in these groups. To improve the immunogenicity of these vaccines, different options have been considered, as detailed in this section.

4.1 Route of administration

One option considered to help improve the immunogenicity, and potentially the effectiveness of inactivated influenza vaccines, is to change the route of administration from intramuscular (IM) to intradermal (ID) injection. In this way, it is aimed that more Langerhans (dendritic) cells at the site of injection are activated to induce a larger immune response and enable closer proximity to lymphatic vasculature.

Various injection systems and novel vaccine formulations have been investigated in clinical trials for the administration of TIV and QIV in the elderly and immunocompromised. Most are not licensed and therefore will not be reviewed here.\textsuperscript{79, 80}

4.1.1 Intradermal TIV in the elderly

4.1.1.1 Immunogenicity

A meta-analysis of RCTs compared the immunogenicity of an ID formulation of influenza vaccine with IM formulations in the elderly (mean study ages ranged from 69 to 82.8 years). The results showed that seroprotection and seroconversion rates were comparable for both ID group and IM group. Although local reactions were significantly more frequent in the ID recipients, systemic reactogenicity was similar. The study also found that ID formulations containing less antigen than the IM vaccines were able to induce adequate seroprotection without needing to increase antigen content. For example, in one reviewed study in a healthy population, seroprotection rates for A/H1N1 were 100% for both ID (6μg H) vs IM (15μg H) and 92.9% vs 100%, respectively, for A/H3N2.\textsuperscript{81}

An open-label RCT investigated the immunogenicity of ID and IM TIV in 100 adults living in nine nursing homes in Hong Kong (mean age 82.9 ±7.4 years) during October 2013–April 2014. Fifty participants received ID TIV (Intanza\textsuperscript{®}) and 40 received IM TIV (Vaxigrip\textsuperscript{®}). Seroconversion rates in the ID group at day 21 against A/H1N1 were significantly higher (60% vs 36%, \( p = 0.02 \)) and A/H3N2 were higher (30% vs 16%, \( p=0.09 \)) than in the IM
group. ID was shown to be non-inferior. No significant difference was seen in seroconversion rates (22% vs 20%) for influenza B, although at day 21, the GMT-fold increase was greater for ID group (4.9 [1.4-8.4] vs 2.0 [1.6-2.4], p=0.09).82, 83

4.1.1.2 Effectiveness

During the 2011/12 influenza season in Spain in community-living elderly adults vaccinated ID with a split virion TIV, the risk of hospitalisation for influenza was shown to be reduced by one-third compared with those who were vaccinated IM with a virosomal subunit TIV.84

4.1.2 Intradermal vaccination of immunocompromised adults

4.1.2.1 Immunogenicity

In a meta-analysis, Pileggi et al (2015) showed that ID influenza vaccination had comparable immunogenicity and safety to IM vaccination in immunocompromised adults (including organ transplant recipients, solid tumours, HIV-infection, and diseases causing immunosuppression; aged 18-77 years). Across six studies with a total of 673 subjects, the seroprotection overall relative risk was 1.00 for A/H1N1 and A/H3N2 and 0.99 for B influenza when comparing ID with IM administration.85

The immune response to conventional influenza vaccines has been shown to be reduced in individuals with HIV infection. An open label RCT conducted in Korea investigated IM TIV, ID TIV (9μg H) and ID TIV (15μg H) in adults aged 18-60 years with HIV-infection (majority received antiretroviral therapy, mean CD4 count was 483 and HIV RNA <50 copies/ml). It found that ID administration, even with higher antigen doses, did not induce greater immunogenicity than conventional IM TIV. Seroprotection and seroconversion rates were similar (around 80% and 50-60%, respectively).86

Conclusion

When compared with intramuscular administration, intradermal vaccination provided comparable, but not significantly improved, IIV immunogenicity in immunocompromised adults. No studies were identified that considered effectiveness in immunocompromised individuals.

ID formulations containing less antigen than the IM vaccines were able to induce adequate seroprotection in the elderly. The risk of influenza hospitalisation in elderly adults was reduced following ID rather than IM TIV vaccination.

4.2 High-dose vaccine

An alternative to altering the route of administration of IIV is to provide higher doses of antigen in the vaccine.

4.2.1 Immunogenicity

A multicentre phase II RCT compared the immunogenicity and safety of ID and high-dose TIV with standard dose TIV given IM in 1,912 adults aged over 65 years. The older participants were randomised 2:2:1:1 to receive either 15μg H per strain ID, 21μg ID, high dose (60μg) or standard dose (15μg) IM TIV vaccines, and also compared with standard IM dose given to 186 younger adults aged 18-49 years. Comparable antibody responses were induced by HD vaccine in the older adults (GMT ratio pre:post vaccination A/H1N1 11.5 [10.1-13.2]; A/H3N2 4.9 [4.3-5.6]; B 2.3 [2.1-2.5]) and the standard dose vaccine in younger adults (GMT ratio A/H1N1 7.4 [5.9-9.3]; A/H3N2 5.1 [4.1-6.4] and B 3.8 [3.2-4.5]). The study found that ID and high-dose vaccines were more immunogenic than
standard dose in older adults and that high-dose IM vaccine was more immunogenic than ID administered vaccines.\textsuperscript{87}

\subsection*{4.2.2 Effectiveness}

A high-dose TIV, which contains four-times more haemagglutinin than standard dose IIV, was developed to address the need for improved influenza protection in those aged over 65 years. In a double-blind RCT intent-to-treat analysis, the relative efficacy of high-dose vaccine compared with standard dose vaccine was 12.6\% (95\% CI -140.5 to 65.8) against laboratory-confirmed symptomatic influenza of any subtype.\textsuperscript{88}

A supplementary analysis was conducted according to vaccine recipient baseline age, high-risk comorbidity and frailty (although those with moderate or severe acute illness or who were unable to comply with study procedures were excluded from the original study). The mean age was 73.3 years in the re-enrolled cohort, and 74\% had received vaccine in the previous influenza season. High dose vaccine was significantly more effective than standard dose in both age strata against laboratory-confirmed, protocol-defined ILI: relative efficacy was 19.7\% (0.4-34.5\%) for those 65-74 years and 32.4\% (8.1-56.6\%) for participants aged over 75 years; for those with none or at least one high risk comorbidity, 22.1\% (3.9-37.0\%); and for individuals with at least one frailty-associated condition, 27.5\% (0.4-47.4).\textsuperscript{89}

A further subset of the study population was followed for two influenza seasons and analysis found that high-dose vaccine was likely to provide additional benefit and improved immunogenicity when compared with standard-dose, irrespective of the previous season’s vaccination. When compared with those who received standard-dose in both seasons, overall relative VE was 28.3\%, 25.1\% following vaccination with high-dose both years and 31.6\% for those who received standard dose then high-dose.\textsuperscript{90}

A literature review conducted by the Canadian National Advisory Committee on Immunisation (NACI) concluded there is good evidence that HD-TIV provides superior protection compared with SD-TIV in the elderly against ILI, influenza-related death and all-cause hospitalisation.\textsuperscript{91}

\subsection*{4.3 Summary}

Intradermal formulations of TIV induce as good or better immunity against influenza in older adults and those with immunocompromise as intramuscular injections. Data around vaccine effectiveness is limited, but suggests improved effectiveness in the elderly.

High dose of TIV vaccines induced a comparable antibody response in the elderly to those seen in younger adults with standard doses, and improved vaccine efficacy against influenza in older adults, including those with comorbidities and frailty, compared with standard TIV.

\subsection*{4.4 Adjuvanted seasonal influenza vaccines}

Since the effectiveness of standard doses of inactivated influenza vaccines are reduced in certain high-risk groups, e.g. elderly adults, young children and other groups with compromised immune responses to influenza, adjuvants have been used to enhance the immunogenicity of IIV vaccines.

The adjuvanted seasonal TIV, branded Flud\textsuperscript{™} (Seqirus), was first approved in Italy in 1997 and was approved for use in Europe in people aged 65 years and over. It contains an oil-in-water emulsion of squalene oil adjuvant, designated MF59\textsuperscript{®}. It was later approved in the US in November 2015.\textsuperscript{92, 93}
Another adjuvant used in influenza vaccines is AS03® (GlaxoSmithKline). It is also an oil-in-water emulsion that contains α-tocopherol (commonly known as vitamin E), squalene and polysorbate 80 (emulsifier). This formulation has predominantly been used in monovalent pandemic influenza vaccines against A/H1N1pdm09 (Pandemrix®) and the pre-pandemic A/H5N1 (‘avian flu’) vaccine for use as part of stockpile vaccines in case of public health emergencies.93, 94

Monovalent vaccines are not within the scope of this review, and literature covering the use of AS03® has not been considered unless it is directly relevant to seasonal influenza vaccine immunogenicity or effectiveness. There are various studies in the literature that consider IIV vaccination following receipt of pandemic vaccination, however, these are beyond the scope of this review.

Presented is an overview of the safety and review of literature on the immunogenicity and effectiveness of adjuvanted seasonal IIV.

### 4.4.1 Adjuvanted vaccine safety

The safety of MF59-adjuvanted influenza vaccine (MF59-TIV) was reviewed by Black et al (2015). No safety concerns were identified for its use in older adults or pregnant women.92

A theoretical concern was raised, since squalene is naturally produced in the body, that immunisation could potentially induce autoantibodies. Black reviewed a study, published in 2006, that found low levels of anti-squalene antibodies pre-vaccination and that no changes in anti-squalene IgG or IgM antibodies were observed post vaccination, when serum samples of healthy adults were compared with those from older adults who received MF59 or standard TIV.92, 95

An increased incidence of narcolepsy was observed in certain populations that received the pandemic A/H1N1 AS03 adjuvanted vaccine.96 No association with narcolepsy was identified following vaccination with MF59-TIV.97

In conclusion, data from more than 30,000 clinical trial participants and passive surveillance of more than 160 million people since 1997 have not indicated any safety concerns around the use of MF59-TIV.92

#### 4.4.1.1 Safety in children

In children aged 6-36 months, slightly increased, but small differences in local reactions and fever were reported following vaccination with MF59-TIV compared with standard TIV (for fever 15.3% MF59-TIV recipients vs 13.3% of TIV recipients).92

In a phase III observer-blind randomised study conducted in South America, Australia and South Africa from April 2011 to July 2012, the safety of MF59-TIV was compared with two non-adjuvanted TIVs (subunit and split virion) in children aged 6 to under 72 months (n=3125, 1479 and 1474, respectively). The study found that reported solicited adverse events (AE) were generally mild to moderate and transient. More of the older children in the MF59-TIV group (aged 36 - under 72 months) reported local AE, including injection site pain, than in the two non-adjuvanted TIV groups (33% vs 17% and 20%, respectively) and reported systemic AE, including fever (17% vs 6% and 5%) after the first vaccination. The incidence of fever also remained slightly higher in the adjuvanted vaccine group after the second vaccination across all age groups (14% vs 9% and 8%). The rate of severe AE was low but also higher in the MF59-TIV group than the non-adjuvanted vaccine groups (0.38% vs 0.07% and 0.14%, respectively). Fewer children experienced unsolicited AE in the MF59-TIV group than the other TIVs groups (49% vs 55% and 58%, respectively), but most frequent events were those commonly seen in a paediatric population, such as URTI,
nasopharyngitis, gastroenteritis, and no individual AE was associated with the study. Out of the 27 febrile convulsions experienced, one was possibly MF59-TIV vaccine related on day 2 and was of mild severity.\textsuperscript{98}

The safety of follow-up vaccination with MF59-TIV was compared with non-adjuvanted TIV in randomised children aged 30-36 months who had previously received two half or full doses of these vaccines or a non-influenza control vaccine, during 2010 as part of an efficacy trial. Of these children, 40 were subsequently vaccinated with MF59-TIV, 26 with TIV and 10 with MF59-TIV after control vaccine. The study found that vaccination with adjuvanted TIV produced slightly more, but acceptable, local and systematic reactogenicity compared with TIV-TIV and TIV-MF59-TIV mixed regimes. However, this study was small.\textsuperscript{99}

Conclusions

Few recent studies have been conducted evaluating the safety of MF59 in young children. Increased rates of fever (<20\%) and injection site reactions (33\% in children age 3-6 years) have been reported, that are usually mild and transient.

4.4.1.2 Safety in adults aged over 65 years

An observational, non-interventional prospective study, designated the Lombardia Influenza Vaccine Effectiveness Study, was conducted in northern Italy to evaluate the safety of MF59-TIV in comparison to non-adjuvanted TIV in adults aged ≥65 years (mean age 76.5 years in adjuvanted TIV group and 74.9 in TIV group) during three influenza seasons from 2006-2009. A total of 170,988 vaccines doses were administered (88,449 MF59-TIV and 82,539 TIV). Adverse events of special interest were rare; for most there were fewer than two cases in total for each including anaphylaxis, Bell’s palsy, encephalitis, GBS, immune thrombocytopenic purpura and vasculitis. Of the adverse events, convulsions occurred at the highest rate during 6 months following vaccination at a rate of 49.7 per 100,000 (95\% CI 35.7-67.4; 41 cases) in the standard TIV group and 44.1/100,000 (95\% CI 31.4-60.3; 39 cases) in the MF59-TIV group. The rate of convulsions was less when timing in relation to the predefined biologically plausible time window was considered, following vaccine receipt (four cases for adjuvanted TIV vs six cases for standard TIV). The study concluded that the risks of adverse events were similar for both vaccines and there was no indication that receipt of adjuvanted vaccine was associated with increased risk.\textsuperscript{100}

4.4.1.3 Safety in kidney transplant recipients

Only one study was identified that investigated adjuvanted seasonal influenza vaccines in a high risk group, other than the elderly and young children. The study compared the incidence of biopsy-proven acute graft rejection and graft rejection at 6 and 12 months in kidney transplant recipients following vaccination with either adjuvanted (n= 37) or non-adjuvanted (n=28) pandemic or seasonal influenza vaccine during the 2009/10 campaign in Spain. Four episodes of rejection occurred post-vaccination, with no differences between the groups (cumulative incidence 5.4\% vs 7.1\%, p=0.581; incidence rate 0.22 vs 0.18 per 1000 transplant days; p=0.950).\textsuperscript{101}

4.4.1.4 Summary adjuvanted vaccine safety

As would be anticipated, adjuvanted IIV are slightly more reactogenic than standard IIV, with reports of increased local reactions and fever in children. These reactions were generally mild and transient. No safety concerns were identified in adults, including those over 65 years and pregnant women, or in children from 6 months of age. Data is limited around the safety these vaccines in high risk groups with chronic disease. There is no evidence that immunisation with these adjuvants induces autoantibodies against squalene.
4.4.2 Immunogenicity of adjuvanted vaccine

4.4.2.1 Immunogenicity in adults over 65 years

The immunogenicity of MF59-TIV was reviewed by Black et al (2015). One reviewed study found that MF59-TIV induce significantly higher anti-H titres against all three vaccine strains in elderly adults; for example, 83% of MF59-TIV recipients and 62% of the TIV group had a four-fold increase in antibody response against A/H3N2 following vaccination.\textsuperscript{92}

Although superiority was not met, according to predefined criteria, MF59-TIV induced significantly higher antibody responses than TIV, particularly against A/H3N2 strains, in a RCT that included 7,082 adults aged ≥65 years.\textsuperscript{102} This may be sufficient to provide additional benefit since TIV VE was reported to be low against a predominant A/H3N2 strain during the 2016/17 season in Europe in the elderly (adjusted VE 17%).\textsuperscript{103}

A comparative RCT conducted during the 2011/12 influenza season compared the effectiveness of MF59-TIV, conventional TIV and ID TIV in 335 healthy volunteers aged at least 65 years (median age 71 years). At one month after vaccination, the GMTs for A/H3N2 in the MF59-TIV group were superior to conventional TIV, but not ID TIV (conventional vs adjuvanted p<0.001; conventional vs ID p=0.007; adjuvant vs ID p=0.052). Although GMTs for A/H3N2 remained high at 6 months post vaccination in all vaccine groups, they declined to prevaccination levels for A/H1N1 and B. A circulating A/H3N2 strain may have contributed to this finding. Non-inferiority and superiority tests found that MF59-TIV and ID TIV did not provide better immunogenicity than the conventional TIV when GMT ratios were compared at 6 months post vaccination. The study concluded that for healthy older adults all three vaccines were appropriate but MF59-adjuvanted vaccine was preferred.\textsuperscript{104}

A phase Ib proof-of-concept RCT found that both MF59-TIV and low-dose ID TIV significantly enhanced the immunogenicity of seasonal influenza vaccine compared with conventional non-adjuvanted TIV in adults aged ≥65 years.\textsuperscript{105}

Conclusion

Although not consistently superior in all studies, MF-59 adjuvanted TIV enhances the antibody response against influenza in older adults compared with conventional TIV, including against A/H3N2.

4.4.2.2 Immunogenicity in children

A phase III observer-blind randomised study was conducted in South America, Australia and South Africa from April 2011 to July 2012 to compare the immunogenicity of MF59-TIV with two non-adjuvanted TIVs (subunit and split virion) in children aged 6 to under 72 months (n=3125, 1479 and 1474, respectively). When compared with two non-adjuvanted vaccines, the study found that the adjuvanted vaccine induced a higher HI titre threshold (≥1:110) after one dose, and a faster and more persistent antibody response (from day 29 to day 209). After a second dose (day 50), significantly higher HI GMTs and seroconversion rates were seen in the MF59-TIV group than the non-adjuvanted vaccines against homologous and heterologous influenza strains.\textsuperscript{98}

A phase II RCT compared the immune responses to adjuvanted TIV and non-adjuvanted TIV in previously unvaccinated children aged less than 3 years. Both vaccines induced significant increases in vaccine strain H antibodies. More children achieved high HI antibody titres (HI ≥1:330) against the vaccine strain A/H3N2/Victoria (92% vs 23%) and B/Brisbane (40% vs 10%) induced by MF59-TIV than TIV, respectively. HI titres against A/H1N1 were higher in the adjuvant group than non-adjuvant, but were not statistically significant. MF59 induced a larger expansion of vaccine-specific CD4 T cells. Stronger antibody and T cells responses
were also observed against heterologous non-vaccine strains in the adjuvanted vaccine recipients than the non-adjuvanted TIV. The study concluded that MF59-TIV conferred a higher and broader protection than TIV in unprimed children.\textsuperscript{106}

### 4.4.2.3 Priming with monovalent adjuvanted vaccine

A single-blind RCT conducted in Europe and the Dominican Republic randomised 666 healthy children aged 6 months to 17 years to receive one of three monovalent vaccines containing A/H1N1 antigen with or without MF59 adjuvant. The study found that one dose of 3.75μg antigen with 50% of MF59 induced a HI titre $\geq 1:40$ in more than 70% of children aged 1-17 years; two doses of this formulation were required to achieve the same response in those younger than 12 months. Two doses of non-adjuvanted vaccine containing 15μg of antigen were needed to achieve an equivalent response in the 1 - <3-year and 3 - 8-year age cohorts. When a higher HI threshold ($\geq 1:330$) was considered, this titre was achieved at day 43 in 49-94% of children who received adjuvanted vaccine formulations compared with only 24% and 10% following non-adjuvanted vaccine in those aged 1-<3 years and 3-8 years, respectively. One year later, this titre was reached in more than 90% of children following a booster vaccination with seasonal TIV. There was no difference between those primed against A/H1N1 with or without adjuvant following booster vaccination with TIV one year later.\textsuperscript{107}

The immunogenicity of seasonal TIV was investigated in 274 children aged under 3 years who had previously received pandemic AS03-adjuvanted A/H1N1pdm09 vaccine or whole virus monovalent pandemic vaccine in the United Kingdom (UK). Children aged under 3 years who had previously received adjuvanted vaccine had higher HI antibody responses to A/H3N2 and B components of seasonal TIV than those who received non-adjuvanted pandemic vaccine. The study also found that priming with the adjuvanted vaccine generated cross-reactive antibody responses to A/H3N2 in children and enhanced responses to heterologous influenza subtypes in children aged younger than 3 years.\textsuperscript{108}

### 4.4.2.4 Summary of immunogenicity

Vaccination with adjuvanted TIV can enhance the immune response against influenza in young children by producing higher HI titres and prolonged antibody protection. There is also potential cross-protection between vaccine and circulating influenza strains.

The use of adjuvant can reduce the amount of antigen required in the vaccine, although two doses were required youngest recipients aged <12 months to achieve the same response as seen after one dose in older children up to 8 years of age in previously unvaccinated children.

### 4.4.3 Effectiveness of adjuvanted vaccine

#### 4.4.3.1 Effectiveness in adults over 65 years

The effectiveness of MF59-TIV in the elderly was assessed in a systematic review and meta-analysis by Dominich et al (2017). A pooled analysis of four case-control studies showed an adjusted VE of 51% (30-61%) against hospitalisation for pneumonia/influenza among community-dwelling elderly adults. Adjusted VE against laboratory-confirmed influenza was around 60% for community and mixed community/long term care facility residents. One study of MF59-TIV in residential care subjects was reviewed, which estimated the VE against influenza-like illness to be 94%. For other influenza-related outcomes, MF59-TIV was reported in one study to be effective in reducing hospitalisation for acute coronary syndrome (adjusted VE 87% [35-97%]; unadjusted VE 11% [-108 to 63%]). The adjusted VE against cerebrovascular accidents was reported as 93% (52-99%) and unadjusted VE 44% (-40-
Relative to non-adjuvanted TIV administered IM, VE for MF59-TIV tended to be higher, but a meta-analysis was not possible.\textsuperscript{109}

A literature review conducted by NACI in Canada found that there was insufficient evidence to demonstrate that MF-59-TIV was more effective than unadjuvanted-TIV in reducing the risk of influenza-related hospitalisations and complication in the elderly.\textsuperscript{91}

**Conclusion**

The effectiveness of MF59-TIV is only slightly improved compared with non-adjuvanted TIV in older adults. There is insufficient data and too much heterogeneity between study findings to show a conclusive benefit.

### 4.4.3.2 Effectiveness in children

No studies were identified that investigated the effectiveness of adjuvanted influenza vaccination in children against seasonal influenza.

### 4.4.4 Summary of adjuvanted vaccine

The use of adjuvant in seasonal influenza vaccines enhances the immunogenicity of the vaccines in the elderly and young children in whom the response to non-adjuvanted TIV is lower and shorter-lived. However, this difference is less significant in the elderly than observed in young children.

Adjuvanted vaccines are expected to improve effectiveness by enhancing the immune response against influenza antigens. Data is limited around the effectiveness of adjuvanted seasonal influenza vaccine to clearly demonstrate any potentially increased benefit, which would be of particular interest for the elderly, young children or high risk groups. However, effectiveness does not appear to be enhanced in the elderly, compared with standard TIV.

Although no safety concerns have been identified around the use of adjuvanted IIV, in some, increased reactogenicity is observed following vaccination. In young children, the likelihood of fever and localised reactions is increased.

Data around rare adverse events and theoretical potential to induce autoimmunity are limited, and where they have been investigated, such events are very rare and any potential vaccine-related causality was not able to be determined.

One study demonstrated that antigen and adjuvant sparing can be achieved with lower doses. Children under one year of age would require two doses to induce protective antibody levels.
5 Live attenuate influenza vaccine

5.1 Background

Live attenuated influenza vaccines (LAIVs) contain cold-adapted influenza virus, which are able to replicate in the cooler upper respiratory tract rather than the lungs and the lower respiratory tract.

The backbones of the licensed LAIV are cold-adapted A/Ann Arbor/6/60 and B/Ann Arbor/1/66 master donor viruses; a Russian master donor virus, A/Leningrad/134/57, has also been used in Russia and in recent clinical trials. Seasonal LAIV are created either by co-infecting cells with the vaccine master donor virus and a wild-type seasonal influenza strain or by using reverse genetics to co-transfect cells with gene segments of the donor virus in the wild-type strain. The result is an attenuated reassortant recombinant virus containing six internal genes of the master donor strains plus two antigen (haemagglutinin and neuraminidase) coding segments – these reassortant viruses are then called master virus seeds and are created for each new influenza strain to be included in the vaccine. From these master virus seeds the vaccine can be manufactured. Trivalent and quadrivalent LAIV (T-LAIV and Q-LAIV) formulations have been developed.110

LAIV are administered by intranasal spray and are indicated for children and adolescents from ages of 2 to less than 18 years. They are also approved in the European Union and North America for adults up to 49 years of age. For children who have not been previously vaccinated against influenza, two doses are given at least 4 weeks apart and are therefore recommended to receive the first dose early in the influenza season. LAIV are not currently licensed for children aged less than 2 years due to concerns around increased all-cause hospitalisation rates and wheezing in this age group, although earlier studies indicated that they were more effective in this age group than TIV. There is insufficient data around the use of LAIV in adults aged 50-64 years.110

Currently, only one brand of LAIV is licensed for seasonal influenza vaccination, and is available as T-LAIV and Q-LAIV formulations. The vaccine is marketed as FluMist® or FluMist Quadrivalent (manufactured by AstraZeneca subsidiary, MedImmune) in the US and Canada, and Fluenz® or Fluenz®-Tetra (AstraZeneca) in the European Union.

LAIV have also been used in Russia since 1987 for the prevention of influenza in children age over 3 years, adults and the elderly. The Russian vaccines are based on the A/Leningrad/134/17/57 (H2N2) and B/USSR/61/69 cold-adapted master donor viruses. This technology has been licensed to the WHO for further development of pandemic and seasonal influenza vaccines. The Russian backbone vaccine is now being manufactured in India.111

5.2 Safety of LAIV

The currently licensed LAIV is contra-indicated for children with hypersensitivity to vaccine excipients (such as gelatin or trace amounts of gentamicin) and those with anaphylaxis to eggs or ovalbumin. Since it contains live virus, the vaccine is also contraindicated for children with clinical immunodeficiency due to medical conditions or immunotherapy, but is not contraindicated for those with asymptomatic HIV, or those receiving topical, inhaled or low dose systemic corticosteroids. Due to the association of Reye’s Syndrome with wild-type influenza, it is also contraindicated for children receiving salicylate therapy.112, 113

The Institute for Vaccine Safety reviewed the safety of influenza vaccines in children. The review found that intranasally administered LAIVs, containing either Ann Arbor or Leningrad
donor viruses, produced transient rhinorrhea and nasal congestion in children. There was a small increase in risk of low-grade fever in young children and less than 1% of children experienced high fever within 24 – 72 hours following vaccination. No increase in risk of febrile seizures was reported, including following co-administration with other vaccines.17

5.2.1 Virus shedding

Since live virus is administered intranasally, there are concerns around the spread of vaccine virus through viral shedding. Shedding following LAIV vaccination was shown to be inversely correlated with age and the youngest children are most likely to shed virus over the longest time. Most young children shed virus for several days; for example, children aged 9-36 months shed virus for a mean of 7.6 days (range 1-21 days).17, 114

Q-LAIV was found to cause similar viral shedding in children and adults infected with HIV as those not HIV-infected (67% vs 50%, p=0.14, n= 46 and 56 respectively).115

5.2.2 Egg allergy

As with IIV, very low, residual traces of ovalbumin may remain in these vaccines when the virus is initially cultured in hens’ eggs. A multicentre prospective cohort study investigated the safety of Q-LAIV in children with egg allergy. The UK-based open-label phase IV study vaccinated 779 young people aged 2-18 years (median age 5.3 years), including 270 (34.7%) with previous anaphylaxis to egg and 445 (57.1%) had doctor-diagnosed asthma or recurrent wheeze. The main outcome measure was incidence of an adverse event within two hours of vaccination. For this study, vaccine was sourced with detectable ovalbumin, although the vaccine used routinely in the UK does not normally contain any detectable ovalbumin (less than 2μg/ml). No participant experienced a systemic adverse reaction attributed to LAIV. Nine participants (1.2%) experienced mild, self-limiting immediate AEFI (within 30 min) with a possible allergy cause (localised urticaria, rhinitis, oropharyngeal itch). It was concluded that risk of systemic allergic reactions associated with LAIV vaccination in children with egg allergy was low.116 In a similar study conducted by the same authors (described in section 5.2.3), it was concluded that the incidence of anaphylaxis following LAIV administration in children with egg allergy is similar to that previously reported in children without egg allergy.117

5.2.3 Recurrent wheeze

Although LAIVs are contraindicated in some countries for children with a history of wheeze, no signal for increased wheeze was found in several studies of children aged over 2 years and post licensure data have not shown an association with LAIV vaccination.17

Another UK-based study examined the safety of Q-LAIV in 282 children (median age 4.9 years, range 2-17 years) with egg allergy. Of the children, 115 (41%) had previously had anaphylaxis reactions to egg, 67% had a diagnosis of asthma/recurrent wheeze and 51% received regular preventer therapy. There were no systemic reactions in the cohort, the upper 95% CI for the incidence of systemic allergic reactions was calculated to be 1.3%. No significant increases in lower respiratory tract symptoms or worsening asthma control were observed, 26 children (9.4% [6.2-13.4%]) had lower respiratory tract symptoms within 72 hours of vaccination, including 13 with parent-reported wheeze. None required further medical intervention other than routine treatment. The study findings suggested that Q-LAIV was safe for use in children with a history of asthma or recurrent wheeze with well-controlled symptoms and no evidence of active wheezing for 72 hours prior to vaccination.117

Vaccine Safety Datalink data were analysed to assess the incidence of medically-attended respiratory events following immunisation with LAIV in people with asthma (aged 2 – 49 years) in the US. The study included 12,354 doses of LAIV, three-quarters of which were
given to children and 93% administered to individuals with intermittent or mild persistent asthma. The incidence risk ratio for hospitalised or emergency department (ED) visits for lower respiratory events (asthma exacerbation and wheeze) was 0.98 (95% CI 0.63-1.51). It was concluded that vaccination with LAIV was not associated with increased risk of medically-attended respiratory adverse events.118

A prospective observational post-marketing study in the US found that the safety of LAIV was consistent with preapproval studies and Vaccine Adverse Event Reporting System reports. No differences in the rate of medically-attended AE were found between children vaccinated with LAIV or IIV and unvaccinated controls. Asthma and wheezing AE were not statistically increased in LAIV recipients aged 24-59 months and no anaphylaxis events were reported within 3 days of vaccination.119

Conclusions
There is no evidence that LAIV vaccination is associated with medically-attended exacerbations of asthma or wheeze, particularly in children older than 2 years of age with well managed symptoms or intermittent asthma.

5.2.4 Children less than two years of age
Overall, LAIV have not been approved anywhere for children less than 2 years of age, and the data around safety is inconsistent for this age group and particularly limited for children under 2 years with a history of wheeze.17

Although the efficacy of LAIV was shown to be significantly greater than TIV (p<0.001) in the 6–59 months age group according to an RCT published in 2007, an increased risk of wheeze following LAIV administration, particularly in the 6–11 months age group, was identified following post-hoc analysis of the data (6.1% of LAIV recipients vs 2.6% of TIV recipients, p=0.002).120

Based on this single trial, LAIV was not approved by the US FDA for children less than 2 years of age due to concerns around an increased risk of wheeze. A systematic review was conducted by Prutsky et al in 2014 to further investigate the use of LAIV in young children. One observational study indicated that there is no increase in risk for hospitalisation or ED visits in children who received LAIV compared with those who received IIV, but there were limitations in the methodology. The review concluded that more evidence is needed to recommend LAIV in children less than 2 years of age with high confidence, but may provide a suitable option in special circumstances.121

5.2.5 Children with cystic fibrosis
Studies in Canada found that there was no increased risk of respiratory deterioration (incidence risk ratio 0.72; 95% CI 0.11-4.27) or all-cause hospitalisation (1.16; 0.30-4.81) for children with cystic fibrosis aged 2 to 18 years who were vaccinated with LAIV when comparing at-risk to non-at-risk periods. However, 77% of participants experienced at least one minor respiratory and/or systemic AE after LAIV vaccination during at-risk periods compared with 54% of those vaccinated during non-at-risk periods.122, 123

5.2.6 Summary of LAIV safety
LAIV appear to be generally safe and well tolerated. The most frequently observed adverse event is transient rhinorrhoea and nasal congestion, which is unpleasant but not serious, and mild fever has been reported infrequently.

LAIV vaccination was not associated with increased incidence of wheeze or exacerbations of asthma in children and adults from 2 years of age. A post-hoc analysis of a single pre-licensure study indicated increased incidence of wheeze in children aged less than 2 years.
However, since these vaccines are currently not indicated for this age group and in some countries contraindicated for older children with a history of recurrent wheeze, there is insufficient recent data to explore the potential risk further.

LAIV are safe to administer to children with a known serious egg allergy, particularly formulations with the lowest ovalbumin content. The rate of anaphylaxis is similar to that for other vaccines at around 1 per million doses.

Since LAIVs contain live virus, the incidence of viral shedding is highest and most prolonged (around 7 days) in the youngest vaccinated children. Any potential risk to immunocompromised contacts is unclear.

5.3 Immunogenicity of LAIV

LAIV can induce a variety of adaptive immune responses both in the mucosa and systemically, including serum and mucosal antibodies and cell-mediated immunity. They are suggested to be immunologically superior to parenterally administered inactivated vaccines, which predominantly induce humoral (serum antibody) immunity but not mucosal immunity. Also, LAIV potentially induce T cell immunity against conserved virus epitopes, thereby protecting against antigenic drift variants. Due to the complexity in the immune response induced by these vaccines, no correlate of protection has yet been determined.124

The multifaceted immune response to LAIV is predicted to mimic that seen following natural infection. However to induce an immune response, the virus must first infect and replicate in the upper respiratory tract, which could potentially be inhibited by the presence of pre-existing antibodies or cross-reactive T cells.125

In this section, examples of literature around LAIV immune responses are presented. The protective immune responses to these vaccines remain unclear.

5.3.1 T and B cell responses

Vaccine-induced B and T cell responses were found to persist for at least one year in the serum of children vaccinated with LAIV.126

LAIV elicited a local humoral B cell response in children aged 3-17 years vaccinated prior to scheduled tonsillectomy. Significant increases were detected in serum antibody and salivary IgA levels to A/H3N2 and B influenza strains by 14 days after vaccination in children, but not A/H1N1. The influenza virus-specific IgA levels were correlated with serum HI responses and tonsillar memory B cell responses correlated with systemic memory responses.127 Additionally, upregulation of genes indicated overall proliferation, differentiation and regulation of both B and T cells in the tonsils following LAIV vaccination of these children.128

5.3.1.1 Comparison with inactivated influenza vaccines

The mechanisms of protection provided by the two types of influenza vaccines, IIV and LAIV, are different and these vaccines induce fundamentally different immune responses. LAIV induce a broader immune response that is less antibody mediated that IIV. The differences are summarised in Table 3.125
Table 3: Comparison of immune responses to inactivated influenza and live attenuated influenza vaccine. (Adapted from Sridhar, 2015)

<table>
<thead>
<tr>
<th>Immune response</th>
<th>Inactivated influenza vaccine</th>
<th>Live attenuate influenza vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemagglutinin inhibition response</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Antibody secreting cells</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Memory B cells</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Nasal IgA</td>
<td>-/+</td>
<td>+++</td>
</tr>
<tr>
<td>Neuraminidase antibody</td>
<td>-/+</td>
<td>++</td>
</tr>
<tr>
<td>CD4 T cells</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>CD8 T cells</td>
<td>-</td>
<td>+?</td>
</tr>
<tr>
<td>Cross-protective immunity</td>
<td>-/+</td>
<td>++</td>
</tr>
</tbody>
</table>

Cao et al found that LAIV and TIV vaccines induced significantly different B cell responses in vaccinated children aged 6 months to 14 years (mean age LAIV group 9.9 ± 4.6 years and TIV group 8.5 ± 5.0 years). Distinct differences were observed at 30 days following vaccination between the B cell populations in each group: significantly more naïve, memory and transitional B cells in the LAIV group (p<0.05), but no change in plasma cells; and significantly more plasmablasts and plasma cells, but no change in naïve, memory or transitional cells in the TIV group (p<0.01). TIV induced a more robust serum antibody response, with significantly greater HI titres than LAIV for the three vaccine strains (p<0.01) and a greater rate of seroconversion: 70% for A/H1N1, 70% A/H3N2 and 30% for B strains for TIV compared with 5% A/H1N1, 2% A/H3N2 and 0% for B with LAIV. Antibody production was correlated with IFN-γ gene expression, which was induced by day 1 following TIV and day 7 following LAIV vaccination. The mechanism by which LAIV provide protection is different from TIV. It is likely to involve local immune responses in the nasal mucosa and mucosal IgA not detected in the serum and therefore not evident in assays used to measure seroconversion. Differences in IFN-γ gene expression were also noted between vaccine strains.129

5.3.1.2 Cross-protection

A proof-of-concept study found that LAIV boosted pre-existing cross-reactive T cells to genetically diverse influenza A strains in children. The youngest children showed the highest increase in T cell responses. The study found that up to 70% of children had pre-existing cross-reactive, influenza-specific T cells in the absence of pre-existing antibodies (70% to A/H1N1 and 60% to A/H3N2). It also observed that LAIV could boost CD8⁺ T cells responses to genetically diverse wild-type influenza A viruses, for at least 1 year after vaccination, to which the children could not have been previously exposed, without inducing antibody responses. CD8⁺ T cells play a role in reducing disease severity, however, only strain-specific T cells are able to neutralise the virus and prevent spread. It was concluded this study provided evidence that LAIV induces cross-reactive T cells to conserved antigens.130
5.3.2 Summary of LAIV immunogenicity

Immunity induced by LAIV differs to that seen following vaccination with IIV. Since the vaccine is administered intranasally, mucosal immunity mechanisms are activated with greater involvement of T cells and the mucosal antibody IgA.

The immunity to LAIV is multifaceted and less anti-haemagglutinin IgG antibody driven. The specific B cell immune response occurs in the tonsillar lymphoid tissue of the nasopharynx following intranasal administration.

Conventional measures of seroprotection using haemagglutinin inhibition assays to measure neutralising strain-specific IgG are not applicable for measuring responses to LAIV.

Cross-protective responses seem to be induced by activating T cells specific for conserved regions of the influenza virus.

5.4 Efficacy, effectiveness and impact of LAIV

As demonstrated for IIV, there is considerable complexity around measuring influenza vaccine effectiveness, not least due to antigenic variations and prior experience with influenza viruses.

5.4.1 Efficacy

Based on pooled data from clinical trials, LAIV have been reported to be more efficacious in children than in adults and compared with TIV. Historically, many studies did not include a placebo control, therefore a comparison of vaccinated versus unvaccinated participants has not been made. Efficacy of LAIV, as for IIV, is influenced by strain-matching and antigenic drift within a season. Post hoc analyses have found vaccine efficacy rates of between 70-94% in children against antigenically similar strains. A challenge study in adults comparing T-LAIV to placebo found vaccine efficacy to be 85% against culture-confirmed infection and respiratory illness when challenged with wild-type A/H1N1, A/H3N2 and B influenza viruses.

5.4.2 Effectiveness

During the 2015/16 influenza season, when A/H1N1pdm09 was the predominant seasonal strain, LAIV was reported to be almost completely ineffective in preventing influenza in children aged 2-17 years in the US. From CDC data, adjusted VE against all strains was 3% (95% CI -49 to 37) for LAIV vs 63% (52-72) for IIV; and -21% (-108-30) vs 65% (50-75) for A/H1N1pmd09, respectively. However, inconsistencies were seen between US-based studies: the observational case-controlled US ICICLE study (MedImmune sponsored) showed a 50% VE against A/H1N1 following LAIV vaccination across the same geographical areas and test-negative design as the CDC study.

For the 2016/17 season, in the US LAIV vaccinations were switched to IIV. Due to concerns over apparent ineffectiveness of LAIV, but not IIV, to protect against A/H1N1pdm09 influenza during the 2015/16 season, and because the same strain was to be used during the following year, ACIP made an interim recommendation not to use LAIV for the 2016/17 influenza season.

Other countries, including the UK, Canada and Finland, did not record this loss of effectiveness and continued to recommend the use of the live vaccine with around 50% VE against A/H1N1 for 2016/17 season.

A post hoc analysis of the 2013/14 test-negative case control ICICLE study compared LAIV lot effectiveness and shipping conditions. More vaccine recipients tested positive for
A/H1N1pdm09 who received LAIV lots released from 1 August to 15 September 2013 compared with later lot releases (21% vs 4%; p<0.01). The relationship between proportion of children testing positive for A/H1N1 and warmer outdoor temperatures during truck unloading was linear. It was concluded that the lack of VE observed in the US was associated with increased susceptibility of the A/California/7/2009(H1N1)pdm09 LAIV strain to thermal degradation in temperatures above recommended storage conditions.133

Differences in effectiveness were further reviewed by Pebody et al in 2017. One key difference noted between the 2015/16 LAIV and IIV formulations was that, to try to improve the thermostability of the A/H1N1 strain component, the A/California/7/2009(H1N1)pdm09-like virus was exchanged with an antigenically similar A/Bolivia/559/2013 strain in the LAIV formulation; however, in the IIV, the A/California strain was retained.134

Over three seasons of the paediatric programme in the UK, overall LAIV VE for laboratory-confirmed influenza infection in 2-17 year olds in primary care was significant at 53.1% compared with non-significant 31.5% VE of IIV. LAIV was significantly effective against A/H3N2 and B influenza, and moderately effective, though not significantly, against A/H1N1pmd09. In contrast, there was no evidence of IIV effectiveness against A/H3N2 or B, but it was 100% effective against A/H1N1pdm09 (see Figure 2). During 2016/17 season in the Northern Hemisphere, A/H3N2 replaced A/H1N1pdm09 as the dominant strain; further evaluation of H1N1 effectiveness is delayed.134

Figure 2: Summary of paediatric vaccine study sites and vaccine effectiveness findings for LAIV and IIV against A(H1N1)pdm09 for 2015/2016 in North America and Europe in children 2–17 years of age in 2015/2016 (in Finland, 2 and 3 years old only).
All studies used test negative case–control design except the Finland study (population cohort). Reproduced with permission, Pebody, 2017
A range of hypotheses have been proposed as to why A/H1N1 effectiveness is low for LAIV vaccines and further studies are required to test these.\textsuperscript{134} Possible explanations include:

1. Some vaccinees had enhanced pre-existing immunity to A/H1N1 due to increased exposure to influenza antigens through repeat vaccination or circulating disease, resulting in:
   a. Immunological interference preventing virus replication
   b. Broader, longer term immunological changes mimicking response seen in adults

2. A/H1N1pdm09 has only recently adapted to infect humans and
   a. May not be optimally adapted for replication in the human nose when administered in LAIV
   b. Unable to compete with multiple vaccine strains to stimulate immunity

3. There may be differences in programme application or study methodology to monitor vaccine effectiveness between the CDC and the UK – requiring higher powered studies with larger sample sizes and age or previous exposure stratification.

**Conclusions**

LAIV are effective in preventing laboratory-confirmed influenza in primary care in children when the predominant strains are A/H3N2 or B. However, there is less evidence to date of effectiveness against A/H1N1, particularly when it is the dominant strain.

5.4.3 **Preschool-age children**

A post-hoc meta-analysis was conducted in 2014 of two previously published RCT to evaluate the efficacy of LAIV against moderate/severe influenza (fever >39°C, acute otitis media or LRTI) in children aged 24-71 months. In study one, the LAIV efficacy versus placebo was 95.4% (88.5-98.1) in year one and 88.5% (77.4-94.9) in year two. Against milder influenza, VE was 91.4% (77.9 – 96.7) and 84.2% (56.7-94.3) year one and two, respectively. In study two, the relative efficacy of LAIV in comparison to IIV was calculated to be 52.2% (31.6-66.6) and 45.0% (28.6 – 57.5) against moderate/severe influenza and milder influenza, respectively. Although VE against influenza A strains was high during study two, VE against influenza B was only 10.3% against severe influenza and 13.6% against mild influenza.\textsuperscript{135}

5.4.4 **School-aged children**

Following pilot vaccinations in primary schools during 2014/15 influenza season, Public Health England reported a 94% reduction in GP consultations for ILI, a 74% reduction in ED attendances for respiratory illness and a 93% reduction in confirmed influenza hospitalisations of primary school-aged children. There was also a 59% reduction in adult ILI presentations in general practice.\textsuperscript{136}

As a result of these findings, the UK continued to recommend LAIV vaccination of children. The phased introduction of the universal annual influenza vaccination programme for children continued during the 2015/16 season and provided T-LAIV to all children aged 2-4 years across the UK plus Q-LAIV to school years one and two (5-6 year-olds) in England. The effectiveness of LAIV against severe influenza in children was examined using data from the UK Severe Influenza Surveillance System (USISS) that monitors laboratory-confirmed influenza hospitalisations. The study found that overall VE was 58.3% (54.5% after adjusting for geography, month and age) and when stratified against influenza strain, adjusted VE was
48.3% against A/H1N1pdm09 and 70.6% for influenza B hospitalisation. These data were in line with those seen in primary care, for which, in 2-17 year-olds adjusted VE for Q-LAIV was 57% (25.1-76.0) against any confirmed influenza, 41.5%(-8.5 to 68.5) against A/H1N1pdm09 and 81.4% (39.6-94.3) for influenza B, as shown in Table 4.137, 138

The efficacy and effectiveness of LAIV was reviewed in school-age children (aged 5 years or older) based on literature published from 1990-2014. Estimated VE against laboratory-confirmed influenza ranged from 60–82% in case controlled studies in seasons dominated by influenza A (H1N1pdm09 and H3N2) and 16-71% for IIV in the same studies in school-aged children. RCT data demonstrated that there was no decline in LAIV effectiveness with increasing age or seropositivity with age or prior vaccination, and that LAIV is as effective in school-age children as in preschool-age children. This review concluded that LAIV had substantial effectiveness in children aged 5-17 years, including direct benefits of reduced influenza illness, decreased medically-attended ARI and associated ED visits. A significant reduction in school absenteeism during the influenza season was observed in six studies of vaccinated school children.139

<table>
<thead>
<tr>
<th>Type / subtype of vaccine</th>
<th>Number of cases a (unvaccinated: vaccinated)</th>
<th>Adjusted b VE (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>Intranasal 212:26</td>
<td>57.6 (25.1 to 76)</td>
</tr>
<tr>
<td></td>
<td>Injectable 212:3</td>
<td>77.8 (7.3 to 94.7)</td>
</tr>
<tr>
<td>Influenza A/H1N1pdm09</td>
<td>Intranasal 112:22</td>
<td>41.5 (-8.5 to 68.5)</td>
</tr>
<tr>
<td></td>
<td>Injectable 112:0</td>
<td>100 (13.3 – 100)c</td>
</tr>
<tr>
<td>Influenza B</td>
<td>Intranasal 95:4</td>
<td>81.4 (39.7 to 94.3)</td>
</tr>
<tr>
<td></td>
<td>Injectable 95:3</td>
<td>56.3 (-121.6 to 91.4)</td>
</tr>
</tbody>
</table>

VE– vaccine effectiveness
a no. of controls (unvaccinated:vaccinated) intranasal 402:89; injectable 402:16
b adjusted for age, sex month, pilot area and surveillance scheme
C Cornfield’s unadjusted estimate

Table 4: Vaccine effectiveness estimates for influenza by type of vaccine in children aged 2-17 years in the UK, October 2015- May 2016 (adapted from Pebody, 2016)

5.4.5 Prior vaccination

A systematic review of four published double-blind, placebo-controlled RCTs was conducted by Caspard et al (2016) to assess the efficacy against laboratory-confirmed influenza of LAIV given over two consecutive seasons in 6,090 children (age range 18-83 months). Season two VE was 86.7% (76.8-92.4%) against influenza strains antigenically similar to the vaccine. LAIV administered over two seasons had greater efficacy than when given in season two only – relative efficacy 53.9% (17.4-74.3). Compared with placebo given in both seasons, a residual efficacy of LAIV given in only season one was 56.4% (37.0-69.8%). The review concluded that there was no evidence of decreasing efficacy when LAIV was administered during consecutive seasons.140
5.4.6 Comparison of inactivated and live influenza vaccine effectiveness in adults

LAIV and TIV showed similar effectiveness during well-matched seasons between 2006 and 2008 in preventing ILI and pneumonia among healthy adults in the US military (aged 18-49 years). Similar effectiveness was also shown in these recipients when compared in relation to health related life-style factors, such as alcohol consumption, smoking and exercise.141, 142

5.4.7 Influenza-associated acute otitis media

Pooled data from six RCT with placebo controls and two with IIV controls were analysed to compare the rates of acute otitis media (AOM) with children age 6-83 months vaccinated with LAIV. During influenza seasons, compared with placebo, LAIV efficacy against all-cause AOM was 12.4% (95% CI 2-21.6%) in year one in children aged 6-71 months and 6.2% (-12.4 to 21.7%) in year two in children aged 18-83 months (n=4,142 and 9,901, respectively). When compared with IIV, VE of LAIV was 9.7% (-2.1 to 20.1%) against febrile all-cause AOM in children aged 6-71 months (n=9,901). The estimated 12-month VE of LAIV was comparable to seven-valent pneumococcal conjugate vaccine. The study concluded that LAIV could further prevent AOM in children by reducing the risk of infection with non-pneumococcal vaccine pathogens.143

5.4.8 Summary of LAIV effectiveness

Although clinical trials have demonstrated good efficacy, particularly against influenza A strains, the data from post-licensure studies and real-world applications have mixed results, demonstrating the complexity of measuring influenza vaccine effectiveness.

The efficacy of LAIV in children was measured, and re-analysed, based on a few clinical trials. Many of the systematic reviews presented have reused the same published RCT data to draw their conclusions.

In real-life situations, there is currently conflicting evidence around the effectiveness of LAIV in preventing A/H1N1pdm09 influenza. During years when A/H3N2 and B influenza strains are predominant, LAIV have been shown to prevent influenza-related hospitalisations and laboratory-confirmed influenza illness in primary care of vaccinated children.

In the US, LAIV was not effective in preventing influenza in vaccinated children during 2015/16 season when A/H1N1pdm09 was the predominant strain.

During the same season in the UK, Canada and Finland, LAIV was at least as effective as IIV. During seasons predominated by influenza A types (H1N1 and H3N2), the estimated VE was 60-82% in vaccinated school-age children in the UK with a significant reduction in school-absenteeism and medically-attended acute respiratory illness.

Following pilot school-based vaccination programmes in the UK, a 93% reduction in confirmed influenza hospitalisations of school-age children, a 94% reduction in primary care consultations for ILI and a 74% reduction in ED visits for respiratory illness has been seen. A 59% reduction in adults presenting with ILI in general practice was also observed.

There is no evidence that revaccination over consecutive seasons reduces the effectiveness of LAIV.

Vaccination of children with LAIV can help to prevent otitis media.
5.5 Childhood immunisation programmes with live attenuated influenza vaccine

The experiences of influenza vaccination of children in England and Scotland were reviewed by Kassianos et al in 2015. In 2012, the Joint Committee on Vaccination and Immunisation in the UK recommended that healthy children and adolescents aged 2 to 17 years be included in the national immunisation programme for influenza. During 2013-14 season, LAIV was funded for children aged 2-3 years in primary care and through several pilots undertaken in primary schools across the UK with a single pilot in an English secondary school. The programme aimed to vaccinate 9 million school children during October to December. Alternative IIV were available through some pilots or general practices for children with LAIV contraindications. Early identification of high-risk children was important to ensure that they were included in the immunisation programme. Overall, vaccine uptake ranged from 39.5% in 3 year-olds in England to 67.2% in Scottish school pilots. The school-based programme was reported to be well received by parents and there was a general preference for an intranasal vaccine.\(^{144}\)

A cohort study conducted in Scotland investigated the risk factors for influenza-confirmed hospitalisation of 1,115 children aged less than 2 years during September 2009 to May 2015. The study assumed the children were not vaccinated (true for those under 6 months and uptake was estimated to be around 0.6% in those aged 6-23 months). In children aged less than 6 months, the highest risk factors for influenza hospitalisation were birth in the autumn and the presence of siblings. For children aged 6-23 months, targeted vaccination strategies towards high-risk children would have prevented only 4-6% of cases. Highest hazard ratios for those age <6 months and 6-23 months were calculated: for presence of one sibling adjusted HR = 2.02 (95% CI 1.52-2.69) and 1.18 (0.99-1.40); ≥2 siblings = 3.13 (2.32-4.22) and 1.43 (1.23-1.80), respectively; season of birth Oct-Dec = 3.56 (2.44-5.19) and 0.77 (0.63-0.95); maternal age 20-<30 years =1.47 (1.15-1.87) and 1.24 (1.05-1.46), respectively. For those with a high risk condition recorded at 6 months, HR 2.46 (1.59-3.80) and 3.04 (2.33-3.96), respectively. It was unclear what protection was provided by maternal antibody following vaccination in pregnancy. The study reported that if universal vaccination of school-age children in the UK reduces transmission as predicted, then the risk of influenza admissions by season of birth and parity may be attenuated in children age <2 years. It was strongly recommended that influenza vaccination be encouraged in older children (aged >2 years) who have younger siblings.\(^{145}\)

5.5.1 High-risk children

Chronically ill children and their household contacts in Montreal Children’s Hospital were offered influenza vaccination with either IIV or LAIV. An onsite vaccination clinic facilitated annual influenza vaccination of high-risk children at their scheduled visits. Across three influenza seasons, 2,640 high-risk children and 1,912 household members were vaccinated. LAIV was administered to 69% of high-risk children in 2012, 55% in 2013 and 47% (2014). The main reason for not receiving LAIV was contraindication. Only a small proportion of those who opted for IIV (5.9% [16/272] in 2014), who had previously received LAIV and did not present any contraindication, had previous negative experience with LAIV (11/16). When not contraindicated, LAIV was preferred by caregivers because no needle was involved (49.0%) and it was perceived as less painful (46.9%).\(^{146}\)
5.5.2 Indirect protection

Associated with LAIV vaccination of primary school-aged children, during pilot studies in the UK in 2014/15, there was a 59% reduction in adult presentations at general practice for ILI.\(^{136}\)

Indirect protection was shown in 8 out 10 school-based vaccination studies reviewed by Coelingh et al (2015) against absenteeism of older students and household members of vaccinated children during the influenza season.\(^{139}\)

A cluster RCT was conducted in 52 Hutterite colonies in Canada over three influenza seasons from 2012-2015, in which children age 3 – 15 years were vaccinated with either LAIV or TIV. The study found that vaccination of children with LAIV did not provide better community protection against laboratory-confirmed influenza than TIV (HR 1.03 [0.85-1.24]): influenza infection rate in LAIV group was 5.3% compared with 5.2% in TIV group. Vaccine uptake was similar in both groups (76.9% vs 72.3%).\(^{147}\)

5.6 Summary of LAIV

Although LAIV have demonstrated significant effectiveness against influenza-related disease, there are pronounced discrepancies in the experiences of the UK and the US during the most recent influenza seasons and in comparison to IIV containing the same virus strains. The discrepancies have been particularly observed in the level of protection when A/H1N1pdm09 strains are predominant.

The immunity induced by LAIV differs from that of IIV, resulting in activation of mucosal humoral and cellular immune response and less serum antibody. This has meant that no correlate of protection has been identified and traditional seroprotection measurements, including haemagglutinin inhibition antibody titres, are inadequate. Immunological studies have suggested that LAIV may provide cross-protection against different virus strains through conserved influenza epitopes as well as inducing a wider immune response that includes mucosal antibodies and CD8 T cells as well as serum antibody.

The UK introduced LAIV as part of a universal immunisation programme targeting preschool and school-age children as these age groups are those most likely to transmit the virus to the wider population. High levels of effectiveness have been observed in preventing influenza-related hospitalisations, acute respiratory illness and confirmed influenza illness in vaccinated children (VE around 60-80%) and unvaccinated adults (VE 59% against hospitalisation). Reducing transmission from children aged over 2 years is also likely to prevent hospitalisation of their younger siblings, particularly those less than 6 months of age who are too young to receive influenza vaccines.

It is unknown how these LAIV prevent transmission. The presence of local IgA antibodies may prevent adhesion of the virus to the upper respiratory tract, thereby inhibiting infectivity.

Prior immunity, acquired through previous vaccination or prior exposure to the virus, may interfere with the ability of the vaccine A/H1N1 strain to replicate in the nasal passage when in competition with the other vaccine strains, and to induce immunity. However, some studies have shown that there is no waning in immunity as a result of prior vaccine or wild-type virus exposure.

LAIV are contraindicated for children under 2 years of age and individuals with unstable asthma due to a potentially increased risk of wheeze. However, there is no evidence that LAIV increase the incidence of wheeze or asthma symptoms in those with mild or
intermittent asthma. Transient nasal congestion and rhinorrhoea have frequently been reported following LAIV administration. The risk of anaphylaxis is low, even in those with severe egg-allergy.

As a live vaccine, LAIV are also contraindicated for immunosuppressed individuals, although receipt of low dose corticosteroids is acceptable.

Overall, LAIV have demonstrated similar effectiveness to IIV and are found to be more acceptable to parents/caregivers, as they are administered intranasally rather than via a needle. This factor is likely to encourage better vaccine uptake, and therefore, wider protection and improved effectiveness of the influenza immunisation programme.

6 Vaccination of high risk groups

In New Zealand, the SHIVERS study demonstrated that compared with general practice patients, those hospitalised with influenza were more likely to be children aged less than 5 years (23% vs 17% of cases), adults aged 65-79 years (13% vs 3%), to be of Māori (18% vs 5%) or Pacific Island (37% vs 17%) ethnicity, to have a low income (37% vs 31%) or to have chronic disease (51% vs 25%).

In certain populations, IIV have low to moderate effectiveness. For example, pooled effectiveness data from the SHIVERS study from 2013-2015 estimated VE of 40% (14-58%) in the elderly compared with 55% (38-68%) in those aged under 17 years.

Strategies to induce more protective immune responses to the predicted influenza strains are being assessed for IIV. As presented in section 4, different IIV formulations have been used and include changing the route of administration from intramuscular (IM) to intradermal (ID), addition of adjuvant and the use of higher antigen doses.

6.1 Vaccine effectiveness in the elderly

A global individual-participant meta-analysis was conducted based on data from 4,975 community-dwelling elderly patients (1,829 influenza cases and 3,146 controls, age stratified 60-75 years and over 75 years.). It found that influenza vaccination was effective during epidemic seasons irrespective of vaccine match status (match adjusted VE 44.4% [22.6-60.0]; mismatch adjusted VE 20.0% [3.5-33.7]). Influenza vaccination was protective among elderly people with cardiovascular disease, lung disease and aged less than 75 years (adjusted VE 31.5% [6.5-49.8]; 31.2% [2.4-51.5] and 32.8% [17.1-45.5], respectively).

In an earlier systematic review of test-negative case-control studies, Darvishian et al concluded that seasonal influenza vaccination was significantly effective against laboratory-confirmed seasonal influenza in community-dwelling people aged over 60 years (during widespread outbreaks for matched strains OR 0.54 [0.46-0.62]).

A systematic review considered the VE of influenza vaccination for institutionalized older adults and found that vaccination could reduce pneumonia and death due to pneumonia or influenza. A meta-analysis across eleven studies estimated influenza vaccination VE was 37% (95% CI 18-53; p=0.001) against pneumonia and 34% (10-53; p=0.01) against death due to pneumonia or influenza.

Vaccine effectiveness is dependent on matching of vaccine and circulating influenza. During the 2014/15 Northern Hemisphere season, A/H3N2 influenza disproportionately affected
those over 65 years of age. Hence, VE was low in the elderly, primarily due to a mismatch of vaccine strain.152

A cross-sectional analysis, conducted in sentinel general practices in France during 2003-2014, evaluated whether influenza vaccination reduced the severity of influenza symptoms in the elderly. A total of 2,277 adults aged 65 years or older who consulted a general practitioner for an ARI were included, from whom nasopharyngeal swabs, demographics and disease symptom onset were recorded; 1,293 (56.8%) had been vaccinated and 675 (26.9%) had confirmed influenza, overall. Compared with non-vaccinated influenza patients, the vaccinated patients had slightly lower maximum temperature and presented less frequently with myalgia, shivering and headache. Stratified analysis found that this was limited to patients with A/H3N2 or B influenza. Following adjustment for age, virus type and season, only headache was shown to be less frequent among vaccinated individuals (OR 0.69 [0.48-0.98]. Therefore it was concluded that vaccination was modestly associated with less severe influenza among the elderly.153

The number of hospitalisations and deaths due to influenza virus are likely to be underestimated in older adults. It is difficult to provide a precise number of influenza-related deaths and hospitalisations among the elderly, unless influenza has been confirmed and recorded in the medical records, due to the high incidence of multiple underlying chronic disorders. In a literature review, Loubet et al (2016) reported that the efficacy of influenza vaccines in the elderly, overall, may have been overestimated. It was reasoned that older people with healthier lifestyles were more likely to accept influenza vaccination (described as a healthy-user effect). To control for this type of bias, a method called ‘difference in difference’ has been used that compared the association between hospitalisation and prior vaccination between periods of influenza circulation and non-circulation. This method gave a preventive efficacy of 4.6% (0.7-08.3) for all-cause mortality and 8.5% (3.3-13.5) for pneumonia hospitalisation.154

Conclusions

Effectiveness of IIV vaccination of adults aged over 65 years ranges from no effectiveness to just under 50% and is very dependent on what measures are used to assess VE. Mismatches between vaccine and circulating strain have also affected effectiveness and outcomes for the elderly.

When the severity of influenza presenting to general practice was considered, vaccination only moderately reduced symptoms of illness in the elderly, apart from headache.

6.2 Identification of high risk groups

Few studies were found in the literature that have been conducted to further identify underlying medical conditions or life-style risks that may be associated with increased severity of influenza infections. Most literature reported the incidence of influenza in already defined high risk groups.

A systematic review conducted by Mertz in 2013 found that quality of evidence to support influenza risk factors was low. The review found that the risk of death was significantly increased in the elderly [age not defined] than non-elderly people and the elderly had a higher risk of hospital admission (OR 2.95, 95% CI 1.53-5.70). The presence of ‘any risk factor’, largely based on comorbidities, was significantly associated with pneumonia, hospitalisation or death (OR 2.04, 1.74-2.39). Associated with severe outcomes were chronic lung disease, including asthma and chronic pulmonary obstructive disorder (COPD), cardiovascular disease, obesity, immunocompromise, neuromuscular disease and diabetes
mellitus, although the evidence was low or very low. The severe outcomes varied according to the risk factor; for example, asthma was associated with higher risk of pneumonia whereas COPD was associated with the likelihood of needing ventilator support. Cardiovascular disease increased the risk of death (OR 1.97, 1.06-3.67) as well as pneumonia, hospital admission and ventilator support. Immunocompromised patients and those with neuromuscular disease were at higher risk of death (OR 3.81, 1.28-11.35 and 3.21, 1.84-5.58, respectively). In contrast to pandemic influenza, pregnancy was not well studied as a risk factor for seasonal influenza. Pregnancy was a risk factor for hospitalisation and women were at higher risk of severe outcomes and mortality in the postpartum period and later in pregnancy. Data on ethnicity was also rare. In general, evidence supporting risk factors for severe outcomes was lacking, particularly for seasonal influenza rather than the 2009 pandemic influenza, due primarily to the small sample sizes.155

A greater uptake of influenza vaccination in younger at-risk adults may help to protect those at particular risk of severe influenza. A study conducted in Spain identified that in the post-pandemic years, A/H1N1pdm09 strain continued to be associated with increased risk of hospitalisation of adults aged less than 65 years compared with A/H3N2, especially in those with chronic heart disease (p=0.048), cerebrovascular disease (p=0.003) and immunosuppression (HIV, active neoplasia, active chemotherapy, transplant and chronic treatment with oral corticosteroids; p=0.005). The risk of severe outcomes was three times higher in younger adults who were not vaccinated, when adjusted for age, comorbidities, time from onset of illness and vaccination status.156

A study conducted in South Africa in low income settings identified the risk factors for hospitalised cases associated with influenza from 2009-2012. These risk factors included a previous history of smoking (case-population ratios 3.82 [95% CI 3.5-4.16]); HIV infection (3.61 [3.5-3.71]), asthma (2.45 [2.19-2.73]), prior hospital admission within 12 months (2.07 [1.92-2.23]) and tuberculosis (1.85 [1.68-2.02]). When stratified by age, the risk of hospitalisation increased in those aged <5 years and those older than 35 years. Completion of scheduled pneumococcal conjugate vaccination decreased the risk in young children (CPR 0.74; 0.71-0.77).157

6.2.1 Obesity

A study conducted in Serbia, from 2010/2011 to 2013/2014 seasons, found that 82.5% of patients hospitalised with severe influenza related disease and treated in the intensive care unit had at least one comorbidity, including chronic respiratory disease, asthma, diabetes mellitus, chronic heart disease, chronic kidney disease, chronic liver disease, chronic neurological disease, immunodeficiency condition and obesity. Obesity was found to be independently associated with severe disease and ICU admission and 11.9% of patients were excessively obese.158

A US-based study found that vaccinated obese adults had double the risk of developing influenza or ILI than vaccinated healthy-weight adults, despite robust serological immune response to the IIV (relative risk = 2.01 [1.12-3.60], p=0.02).159

Using multivariate logistic regressions models, another US study found no association between obesity and severe influenza requiring ICU admission or artificial ventilation. In comparison, underweight was associated with pneumonia (OR 1.31 [1.04-1.64]) whereas overweight or obese patients had a lower risk of pneumonia.160

A cross-sectional study using household survey data conducted in the UK found no evidence that obesity was associated with an increased risk of self-reported ILI in adults or children during the 2009 H1N1 pandemic.161
The systematic review by Mertz et al (2013) found one small seasonal influenza study that showed an increased risk of death due to influenza was associated with obesity (BMI>30; OR 30.1, 1.17-773.12). In 59 pandemic influenza studies, obesity was identified as a risk factor for death (OR 2.74 [1.56-4.80]) and also associated with hospital admission and ventilator support. Morbid obesity was identified as a potential independent risk factor after adjustment for obesity related comorbidities.155

6.2.2 High risk in children

A retrospective review of influenza hospitalisations of children under 16 years of age was conducted, from January 2011 to December 2013, in two Australian paediatric hospitals that are part of the Flu Complications Alert Network (FluCAN). During the study period, there were 740 PCR-confirmed influenza hospitalisations, of which 476 (64%) were children younger than 5 years and 99 (13.4%) were aged 0-6 months. Indigenous children represented 4.2% of all admissions in the study. Many of the children (317/740; 43%) had underlying medical conditions, most commonly immunosuppression (13.2%), neurological disease (12.7%) and chronic respiratory disease (10.4%). However, it was noted that, overall, the majority of children (57%) were previously healthy prior to admission and therefore not eligible for funded influenza vaccine. Also noted was that, since the 2009 pandemic, the use of antiviral medications in primary care was uncommon and declined over the study period (from 50% in 2009 pandemic to 15% in 2014; prescribed to 20.5% of cases upon admission in this study). There were also high rates of antibiotic use, which were prescribed to 72.3% of patients within a median of 2 days following admission. Vaccine uptake was low in all hospitalised children (5% of those with medical conditions and 0.7% without). In Western Australia, where influenza vaccine is funded for all children aged 6 months to less than 5 years, vaccine uptake in the hospitalised children was 4.3% overall compared with 1.6% in New South Wales. The review concluded that influenza has a significant impact on young children, both healthy and those with underlying medical conditions, and that improvements in vaccination coverage for all children are required for the funded immunisation programme.162

6.2.3 Socioeconomic status

As was shown in the SHIVERS study, low income is associated with an increased risk of influenza-related hospitalisation in NZ.66

A study in the US evaluated whether geocoded census-based socioeconomic determinants, such as poverty and household crowding, contributed to the risk of influenza hospitalisation further than individual level determinants, such as age and ethnicity. Using population-based surveillance, 33,515 hospitalisations associated with laboratory-confirmed influenza were analysed during 2009/10 to 2013/14 seasons. Those living in a high poverty area (with ≥20% persons living below poverty levels) had an adjusted odds ratio of 1.31 (1.16-1.47) compared with those living in areas with <5% below poverty, and those in crowded conditions (≥5% vs <5% persons in crowded conditions) had an aOR of 1.17 (1.11-1.23). For those living in areas with ≥40% female heads of households, compared with those with <5%, aOR of influenza hospitalisation was 1.32 (1.25-1.40). The study concluded that census-based determinants of socioeconomic status accounted for 11% of variability in influenza hospitalisation. When considering individual determinants, age over 65 years was the highest (aOR of 9.20 [8.72-9.70], compared with 5-17 year olds), African Americans had an aOR of (1.60-1.73) compared with Whites, and Hispanics had aOR of 1.12 (1.16-1.26) compared with non-Hispanics.163
6.2.4 Summary

The amount and quality of evidence around high risk groups for influenza is limited. Many underlying health issues potentially increase severe outcomes. Improvements in vaccination coverage across all groups is likely to improve the outcomes of influenza for those at potentially increased risk of severe disease, particularly for children.

Poverty and overcrowded housing increase the risk of influenza hospitalisation above individual determinants, such as age, ethnicity and comorbidity.

Since obesity is often associated with multiple comorbidities, its influence is likely to be additive. It is unclear whether obesity independently increases the risk from influenza, but is likely to affect severity of disease. Morbid obesity was identified as an independent risk factor for severe influenza outcomes and death during the A/H1N1 pandemic. Further investigations are required.

The quality of evidence to identify high risk groups is poor and therefore not clearly definable. Observational studies and hospitalisation records are not adequate to evaluate vaccine effectiveness and those at increased risk unless influenza has been confirmed.

6.3 Vaccine effectiveness in high risk groups

Many of the studies in the literature considered vaccine effectiveness in previously defined high-risk groups. The literature review conducted by Loubet et al investigated vaccine efficacy and coverage in adults identified as being at increased risk of influenza complications.\textsuperscript{154} Details of this review and other more recent studies is given below.

Very little of the literature considered other at-risk groups or individuals, or high-risk children.

6.3.1 Chronic obstructive pulmonary disease and chronic lung disease

An observational study, reviewed by Loubet et al, found that influenza vaccination reduced the risk of hospitalisation and death by 52% and 7%, respectively, among elderly patients with chronic lung disease. Another reviewed study suspected influenza to be the trigger in around 8% of acute exacerbations of chronic obstructive pulmonary disease (COPD).\textsuperscript{154}

Since influenza is associated with exacerbations of respiratory disorders, including asthma and COPD, the vaccination is likely to provide benefit. However, the evidence that influenza vaccination prevents influenza-related asthma complications is low.\textsuperscript{154}

A study in Taiwan of patients with COPD found that those who had received influenza vaccination had a lower rate of respiratory failure than those who had not (aOR 0.87 [95% CI 0.79-0.96]). Vaccination was not significantly associated with a reduced respiratory failure rate in those with relatively unstable disease, those under 65 years of age and those who did not receive annual vaccination. It was noted that the rate of vaccination was significantly higher in those aged ≥65 years, with more comorbidities, health care utilisation and more frequent acute exacerbations, compared with those <65 years (54.8% vs 4.0% p<0.001).\textsuperscript{164}

6.3.2 Chronic heart disease

According to the review by Loubet et al, influenza vaccination has been associated with a significant reduction in cardiovascular outcomes and mortality in patients with cardiovascular disease (relative risk of mortality 0.45 [0.25-0.76] p=0.003).\textsuperscript{154}
6.3.3 Chronic kidney disease

Although patients with end-stage renal disease have a significantly lower response rate to influenza vaccination than healthy adults, protective antibodies are induced. All-cause mortality and cardiac mortality were significantly reduced following TIV vaccination of these patients as shown by a pooled analysis of clinical trial data.\textsuperscript{154, 165}

6.3.4 Chronic liver disease

In patients with cirrhosis, seasonal influenza may result in hepatic decompensation following the production of proinflammatory cytokines due to liver tropism of the virus. One study suggested that vaccination could reduce this risk. Patients with liver disease are at increased risk of secondary infections following influenza and hence higher morbidity and mortality.\textsuperscript{154}

6.3.5 Diabetes mellitus

A study of US military personnel found that diabetes [type not defined] significantly increased the risk of death due to pneumonia and influenza in 25 to 64 year olds. This may in part be due to the increased incidence of chronic cardiovascular and kidney disease in diabetics, which were associated with severe outcomes for pneumonia and influenza.\textsuperscript{166}

A systematic review by Remschmidt et al (2015) found that the available evidence was insufficient and quality too low to determine benefit of influenza vaccination in people with diabetes for all outcomes. This was due to a lack of adequately powered RCT with laboratory-confirmed influenza outcomes and the presence of residual confounding, particularly in the elderly. In adults aged 18-64 years with diabetes, IIV was found to prevent all-cause hospitalisation and hospitalisation due to influenza or pneumonia with a pooled VE of 58\% (95\% CI 6-81\%) and 43\% (28-54\%), respectively, but no effects on all-cause mortality or ILI presentations were observed. In the majority of studies, the type of the diabetes and status of glycaemic control were not reported and no studies reported on data in children and adolescents with diabetes.\textsuperscript{167}

A retrospective cohort study examined the effectiveness of influenza vaccination in 190,492 adults aged 65 years and over with diabetes mellitus (type not defined). In this population, influenza vaccine uptake was 65.2\% at entry to the study and increased slightly with time. The VE of current influenza vaccination was 7\% in preventing community-acquired lower respiratory tract infection (95\% CI 3-12\%). When stratified according to markers of chronic kidney disease, i.e. estimated glomerular filtration rate and proteinuria status, no variation in influenza VE was detected. In comparison, VE for 23-valent pneumococcal polysaccharide vaccine (PPV-23) was 22\% (11-31\%) against community-acquired pneumonia for the first year after vaccination. The study concluded that public health benefits of influenza vaccine appears to be modest in older people with diabetes.\textsuperscript{168}

A retrospective cohort study, conducted over a 7-year period from 2003-2011 in the UK, found that influenza vaccination significantly lowered the rates of stroke (incidence rate ratio 0.7 [0.53-0.91], heart failure (0.78 [0.65-0.92], pneumonia or influenza [0.85 [0.74-0.99] and all-cause death (0.76 [0.65-0.83] during the influenza season in patients with type 2 diabetes.\textsuperscript{169}

6.3.6 Immunosuppression

6.3.6.1 HIV infection

Loubet reported that seasonal influenza is not more frequent in people infected with human immunodeficiency virus (HIV) infection, but it can increase the risk of complications and prolong the clinical manifestations. The review concluded that TIV was recommended for all HIV infected individuals, independently of their viral load and CD4 count.\textsuperscript{154}
A cohort study, reviewed by Remschmidt et al (2014), showed TIV VE against laboratory-confirmed influenza was 71% (95% CI 44-85%) in vaccinated adults with HIV. However, the efficacy of TIV in HIV-infected children aged 6-59 months was only 11% against laboratory-confirmed influenza (30 to 54%).

6.3.6.2 **Immunosuppressive therapy**

There is limited evidence evaluating the effectiveness of influenza vaccination in patients receiving immunosuppressive therapies, such as methotrexate, corticosteroids and disease-modifying antirheumatic drugs, despite the higher incidence of hospitalisation due to severe influenza in these patients. It has been reported that vaccinated patients with rheumatoid arthritis or SLE have a lower incidence of pneumonitis, acute bronchitis and viral infection than unvaccinated patients.

6.3.6.3 **Solid organ transplant**

Influenza vaccination was shown to provide protection against influenza-like illness (50-70%) and laboratory-confirmed influenza (50%) in patients awaiting and following solid organ transplantation. However, immunogenicity has been better reported than vaccine effectiveness.

6.3.7 **Summary**

The evidence around the effectiveness of influenza vaccination in certain special groups is poor, particularly in children and adolescents. Generally, it appears that IIVs are safe in all high risk groups. However, in those with lower immune responses to these vaccines, efficacy is likely to be compromised. Improvements in vaccination coverage and uptake are required to better evaluate the effectiveness of the vaccine against laboratory-confirmed influenza across all.

6.4 **Vaccine effectiveness in pregnancy**

Pregnant women experience more complications than non-pregnant women following infection with seasonal and pandemic influenza. The physiological changes that occur during pregnancy, including decreased lung capacity, increased cardiac output and altered cell-mediated immunity, increase the risk of severe influenza. Influenza infection has also been linked to premature birth, miscarriage or still birth, low birth weight and perinatal death of infants of infected mothers.

The risk of hospitalisation increases with the stage of pregnancy and in women with comorbidities. Women in the third trimester of pregnancy with at least one comorbidity have been reported 7.9 (5.0-12.5) times more likely than non-pregnant women to be hospitalised with a respiratory illness. The postpartum period is also associated with higher risk of severe outcomes and increased mortality from influenza.

Few studies were identified in the literature that considered the effectiveness of IIV in pregnancy against influenza.

A review by Marshall et al (2016) identified two RCT that assessed the efficacy of influenza vaccination in pregnancy. Both studies considered self-reported respiratory illness with fever ≥38°C. Among HIV-uninfected women, VE against influenza infection was 50.4% (14.5-71.2) in South Africa, and a study in Bangladesh suggested benefit, but was unable to demonstrate efficacy.

An observational study conducted in the US estimated adjusted VE of TIV to be 51% (8-74) against laboratory-confirmed influenza and reduced the risk of SARI associated with
influenza when administered in pregnancy. This was similar to the VE observed among all adults across the two influenza seasons.\textsuperscript{173}

The previously mentioned review by Demichelli considered IIV effectiveness in pregnancy in observational studies and, based on two studies, found that vaccination did have a modest effect against ILI presentations in pregnant women (NNV 92 [63-201]) and against laboratory-confirmed influenza in newborns of vaccinated women (NNV 27 [18-185]), although the review found that VE of vaccination during pregnancy was not statistically significant in preventing influenza symptoms in newborns. Prevention of laboratory-confirmed influenza in infants of vaccinated mothers was shown to be modest but significant (VE 24% [11-35%]) up to 8 weeks of age.\textsuperscript{16}

A retrospective cohort study in Australia found that seasonal influenza vaccination during pregnancy was associated with significantly fewer ARI hospital attendances in pregnant women. Compared with unvaccinated pregnant women, during the 2012 and 2013 influenza seasons, vaccinated women were significantly less likely to visit emergency departments with ARI (adjusted hazard ratio 0.19 [0.05-0.68]; 9.7 vs 35.5 visits per 10,000 person-days) and fewer were hospitalised with ARI (adjusted HR 0.35 [0.13-0.97]; 16.2 vs 34.0 hospitalisations per 10,000 person-days. In a cohort of 34,701 pregnant women, 3,007 (8.7%) were vaccinated.\textsuperscript{174}

A prospective cohort study (FluMum) is underway in Australia to systematically monitor influenza vaccine uptake during pregnancy and to evaluate VE of maternal vaccination in preventing laboratory-confirmed influenza of their infants up to 6 months of age.\textsuperscript{175}

Conclusions

Influenza vaccination during pregnancy provides protection to the mother against severe influenza hospitalisation in pregnancy and post-partum. The benefit of vaccinating pregnant women in preventing community influenza is less well established and is potentially similar for all adults.

Despite being recommended, there is a limited literature evaluating VE of influenza vaccination in pregnant women and their newborns. In one study, a modest VE of 24% was shown for prevention of laboratory-confirmed influenza in infants of vaccinated mothers.

6.5 Summary of vaccination of high risk groups

In general, the literature suggest that significant improvements in vaccine uptake are required across all risk groups to improve influenza vaccine effectiveness against influenza-related outcomes in individuals at high risk of complications and severe disease.

Broadly, the age groups at high risk from influenza include those over 65 years of age, young children with underlying medical conditions and pregnant women. Other groups include people with neurological disease, immunodeficiencies and immunosuppression, chronic liver disease, chronic renal disease, cardiovascular disease, cancer and respiratory disease. Also included are those with diabetes mellitus and obesity. Poverty and overcrowded housing have been shown to be additive to the risk of severe disease.

These risks are likely to be cumulative – described as ‘risk stacking’ – and individuals with multiple risk factors are likely to be at higher risk than those with one risk factor. Strategies may need to consider the effects of multiple risk factors and not just linear single factors.

To improve vaccine effectiveness in the elderly and those who are immunocompromised, improvements in immunogenicity are likely to be necessary with higher HI titres. High doses and intradermal formulations of current IIV vaccines provide improved responses.
Data around which underlying diseases are associated with an increased risk of influenza-related complications is very limited. In many cases, those at increased risk of influenza-related complications and morbidity fall into heterogeneous groups and confounding factors, such as age or other comorbidities, combined to increase vulnerability to influenza infection and secondary infections. Most studies investigated the incidence of influenza complications within the same predefined high risk groups and no important alternative groups that may also be at higher risk, such as those with mental illness, dementia or drug or alcohol abuse, have been suggested or were identified by this review.

7 Ring protection – vaccination of contacts of high-risk groups

Influenza has been shown to be prevalent in the general population, and is frequently asymptomatic (see section 2). Therefore, health care workers (HCW) and long-term care facility workers could feasibly transmit the virus to the people in their care who are often at high risk from severe influenza, such as immunocompromised patients and the elderly (for further details see section 6). They are also at risk of acquiring the infection from those in their care. Hence influenza vaccination is recommended, and in some places, mandatory for those in contact with individuals at high risk from influenza infection.

The WHO identifies risk groups as being those at increased risk of exposure to influenza virus, including HCW, as well as those at particular risk of developing severe disease. Those identified as being at higher risk of severe influenza include pregnant women, young children less than 5 years of age, the elderly and individuals with underlying health conditions, such as HIV infection and acquired immunodeficiency syndrome (AIDS) and chronic heart or lung disease.

7.1 Risks of transmission to patients

As reported by the WHO, a systematic review conducted in 2011 calculated that among unvaccinated HCW, the pooled incidence of influenza was 18.7% (95% CI 16-22%) per season; of these 7.5% were symptomatic. Therefore, these individuals posed a risk of nosocomial transmission of the influenza virus to their high-risk patients.

A subsequent systematic review was conducted by Ahmed et al in 2014 to assess the effect that influenza vaccination of HCW has on the mortality, hospitalisation and influenza cases in patients in long-term health care facilities. From four cluster randomized trials and four observational studies conducted in long-term care or hospital settings, the pooled risk for all-cause mortality was 0.71 (0.59-0.85) and for ILI presentations (as a surrogate for influenza cases) was 0.58 (0.46-0.73). Pooled estimates for all-cause hospitalisations and laboratory-confirmed influenza were not significant. Although the quality of evidence was moderate overall, moderate for mortality and low for influenza cases (ILI and laboratory-confirmed), the review found that influenza vaccination of HCW could enhance patient safety.
7.2 Risk of transmission from patients

A community-based study in Hong Kong found that those infected with influenza with few or no symptoms could potentially transmit virus to their close contacts through viral shedding. However, the mean levels of influenza viral RNA shedding in asymptomatic individuals or those with only one symptom (pauci-symptomatic) were 10-100 copies/ml less than the levels shed by symptomatic individuals, and in these individuals, that the duration of viral RNA detection was significantly shorter than for symptomatic patients with ARI.177

Fielding et al conducted a systematic review of 22 articles to assess the shedding of A/H1N1pdm09 influenza. They found, generally, that the mean duration of viral shedding was associated with the severity of clinical presentation and not age. The mean duration of viral shedding was 3-9 days for community-based studies, 7-10 for hospitalised cases and 12-18 days for cases admitted to intensive care units. In the three studies of intensive care patients, between 71-86% of patients had one or more risk factor for severe influenza (chronic renal, liver or pulmonary disease, pregnancy, diabetes mellitus, immunosuppressive therapy or obesity). In adults and children, the mean ranges for viral shedding did not differ significantly (3-8 days vs 4-8 days, respectively). One study reviewed found that A/H1N1pdm09 virus was shed the day before ARI onset in 11% (9/85) of symptomatic cases and for 3 days prior to onset in 4% of cases (3/85).178

7.3 Vaccine effectiveness

A systematic review and meta-analysis was conducted by Dini et al (2017) to assess the incidence of influenza and impact of vaccination on HCW and their patients. One meta-analysis found influenza vaccination was effective in protecting HCW from both symptomatic and asymptomatic infection. A double-blind RCT conducted over three consecutive years (1992-1995) found VE to be 88% and 89% for influenza A and B, respectively, and cumulative days of febrile respiratory illness decreased from 40.6 days /100 controls to 28.7 days per 100 in vaccinees and days of absence among vaccinated HCW decreased from 21.1 days /100 controls to 9.9 day /100 vaccinees. Other reviews found vaccine effectiveness to range from around 70–90%. There is a scarcity of data reflecting the possible benefit vaccination of HCW has on their patients.179, 180

7.4 Rationale for vaccination of health care workers

Many of the studies conducted around influenza vaccination of HCW, especially around mandatory vaccination, were conducted following the H1N1pdm9 pandemic in 2009/10, were published prior to 2013 and considered pandemic not seasonal vaccines, and are therefore outside of the scope of this literature review.

Mandatory influenza vaccination of HCW is controversial: there is no consensus as to whether there is sufficient evidence for compulsory vaccination of HCW against influenza. Other interventions, such as handwashing, wearing face masks, early laboratory detection of influenza, quarantine, avoiding admissions, antiviral drugs and asking HCW to not work with influenza symptoms, may be employed alongside vaccination to reduce the nosocomial transmission of influenza. However, Dini et al concluded that vaccination of HCW continues to be a priority and the necessary improvements in vaccine uptake can be achieved through well-designed intervention programmes and occupational health surveillance.179

A systematic review conducted in 2014 by Pitts et al found that mandatory vaccination increased vaccination rates of HCW (p<0.001 for all comparisons), but found that there was
a lack of evidence on clinical outcomes for HCW and their patients. One study reviewed, which investigated HCW sick leave pre and post mandatory vaccination, did not find a significant change in sick leave following the mandate (6.6 hours per HCW during 2006-2009 versus 7.1 hours per HCW during 2001-2005, p=0.43). At that time, no studies were found that reported on the clinical outcomes for patients within institutions with mandatory HCW vaccination. 

A systematic appraisal of systematic reviews was conducted by Kliner et al (2016) to assess the rationale for influenza vaccination of HCW in the UK, with the aim of assisting HCWs to make informed decisions since uptake of influenza vaccination is generally poor. The rationale and perspective for vaccination of HCW given as part of this review is illustrated in Figure 3. The authors found that it is difficult to interpret the evidence surrounding the use of influenza vaccination of HCWs in providing benefits for employer and patient safety, because the different systematic reviews interpreted the same studies differently. There is consistent evidence that the vaccine can prevent illness in HCW from an occupational health perspective. However, from an employer’s perspective, the evidence for a reduction in days lost due to illness and patient safety is conflicting. Most reviews conclude that further studies are required.

**Figure 3: Perspectives for benefit of influenza vaccination of health workers, evidence required and policy framing for each (reproduced from Kliner, 2016 [open access])**

7.5 **Herd immunity**

Mertz et al (2016) conducted a systematic review of literature published to March 2014 that assessed a protective effect for influenza vaccination compared with no vaccination on influenza virus infections in contacts. Nine RCT and four observational studies were included. No statistically significant herd effect was found for the occurrence of influenza in contacts across RCTs (OR 0.62 (0.34-1.12). However, one community-based RCT and the observational studies did show a significant effect (OR 0.39 [0.26-0.57] and 0.57 [0.43-0.77], respectively). Overall, the review found that the quality of evidence of an indirect or herd effect for influenza vaccination was low, and was unable to conclude in which settings a herd effect may be achieved. The authors also reported that there was little data around the indirect effects of influenza vaccination on the outcomes of influenza infections, such as hospitalisation and mortality.
A subsequent systematic review and meta-analysis was conducted by Yin et al in 2017, to assess the policy implications of indirect protection against seasonal influenza provided by the vaccination of children. The review included 30 studies and RCTs of LAIV, 11 of IIV and five compared both types of vaccine. Statistically significant indirect protection effectiveness (IPE) was reported by 20 out 30 studies, with point estimates ranging from 4% to 66%. Analysis of one cluster RCT found IPE was 60% (95% CI 41-72%) against laboratory-confirmed influenza in closely connected Hutterite colonies in rural Canada in which children aged 3-15 years were vaccinated with TIV during 2008/9. Meta-analysis of four household-based cluster RCT showed 22% (1-38%) IPE against acute respiratory infections or ILI cases in which preschool children were vaccinated with TIV.

Influenza-related mortality among the elderly was shown to be reduced by 36% following a Japanese school-based TIV programme. In other settings, the studies were heterogeneous and no conclusion could be drawn of IPE. Studies making comparison between LAIV and TIV were also too heterogeneous to make any conclusions about IPE. The review concluded that, although further large and more robust studies are needed to quantify indirect protection, the vaccination of children against influenza provided indirect protection to close community and household members, and to prevent mortality in the elderly in the wider community. However, it was noted that unvaccinated people remain susceptible to influenza and that annual vaccination is most effective at preventing influenza in individuals.

7.6 Summary

There is no conclusive evidence that vaccination of health care workers and similar occupations helps to prevent transmission of influenza to patients. However, workers with mild influenza or who are asymptomatic can transmit the virus to others, which is of particular consequence to their clients and patients with low immunity and as such at high risk of severe influenza. One systematic review concluded that vaccination of HCWs would enhance patient safety.

Conversely, the likelihood of transmission of influenza virus is greatest when symptoms are present and the more severe cases have longer periods of infectivity increasing the probability of transmission. Hence, HCW are potentially at higher risk of being infected by symptomatic patients than patients are of being infected by asymptomatic HCW. Vaccination is recommended to reduce transmission between both HCW and their patients, and to improve the safety of both.

Influenza vaccination may also help to maintain the integrity of health services by reducing absenteeism of staff during seasons of high demand, although the evidence for this is conflicting since other respiratory viral infections are likely to be in circulation at the same time as influenza.

Using systematic approaches and health promotion for improvements in vaccine uptake are generally recommended rather than mandatory vaccination of health care workers, alongside occupational health surveillance and well-designed intervention programmes.

Current evidence demonstrates that vaccination of children can contribute to herd immunity and protect high risk individuals, such as the elderly, since children are significant transmitters of influenza and most likely to be infected. However, individuals remain at risk of infection and annual vaccination is recommended where possible.
Other respiratory illness causing viruses co-circulate with influenza which reduces confidence in influenza vaccines and affect uptake. Poor vaccine coverage is likely to reduce potential herd immunity.

8 International policy and practice

8.1 Review

This section will review the international policies and practices around seasonal influenza vaccination. The content and type of influenza vaccines change with seasons and between the Northern and Southern Hemispheres. This review has been restricted to immunisation schedules and policies in Australia, Canada, UK and the US for the most recent influenza seasons (i.e. Southern Hemisphere 2017 or Northern Hemisphere 2017/18 seasons) in line with the WHO, which particularly recommends annual influenza vaccination for those at high risk of disease. Table 5 shows the recommended groups and rationale for the recommendations.

<table>
<thead>
<tr>
<th>Recommended group</th>
<th>WHO rationale for the recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnant women</td>
<td>Increased risk of serious disease in mother</td>
</tr>
<tr>
<td></td>
<td>Increased risk of death in mother and unborn child</td>
</tr>
<tr>
<td></td>
<td>Secondary effect of protection of child up to 6 months</td>
</tr>
<tr>
<td></td>
<td>Globally applicable as have contact with health services</td>
</tr>
<tr>
<td>Health care workers</td>
<td>Increased exposure to influenza</td>
</tr>
<tr>
<td></td>
<td>Reduces morbidity and mortality in patients</td>
</tr>
<tr>
<td></td>
<td>Preserves integrity of health care systems</td>
</tr>
<tr>
<td></td>
<td>Possible to implement</td>
</tr>
<tr>
<td>Children &lt; 6 months</td>
<td>No available vaccines</td>
</tr>
<tr>
<td></td>
<td>Indirect protection through vaccination of mother during pregnancy</td>
</tr>
<tr>
<td></td>
<td>Indirect protection through vaccination of close contacts</td>
</tr>
<tr>
<td>Children 6 months to &lt;2 years old</td>
<td>Experience high levels of serious illness</td>
</tr>
<tr>
<td></td>
<td>Responsible for spread in community</td>
</tr>
<tr>
<td></td>
<td>Disadvantage, costly to implement vaccination campaign, two doses of TIV required in vaccine-naive children</td>
</tr>
<tr>
<td>Children 2-5 years old</td>
<td>Large burden of morbidity</td>
</tr>
<tr>
<td></td>
<td>Respond better to vaccines than younger children</td>
</tr>
<tr>
<td></td>
<td>LAIV gives improved protection</td>
</tr>
<tr>
<td>Elderly &gt;65 years old</td>
<td>Highest risk of mortality</td>
</tr>
<tr>
<td></td>
<td>Vaccine less effective</td>
</tr>
<tr>
<td></td>
<td>Disadvantage, annual immunisation is costly to administer</td>
</tr>
<tr>
<td>Patients with chronic conditions Including those with HIV/AIDS, asthma, chronic heart or lung disease</td>
<td>Highest risk for serious disease</td>
</tr>
<tr>
<td></td>
<td>Indigenous populations may have higher rate of chronic conditions</td>
</tr>
<tr>
<td></td>
<td>Disadvantage, requires considerable resources to identify individuals</td>
</tr>
<tr>
<td>International travellers belonging to any of the above groups</td>
<td>Part of routine immunisations, particularly during influenza season</td>
</tr>
</tbody>
</table>

Table 5: WHO vaccination recommendations and rationale for groups at high risk from influenza (adapted from Sridhar, 2015 and WHO Influenza position paper, 2012)
8.1.1 United States

ACIP recommends routine vaccination of all persons from 6 months of age who do not have contraindications. Following on from the 2016/17 recommendations, LAIV are not recommended to be used during 2017/18 and ACIP will continue to review data as they become available.\textsuperscript{185}

Revaccination later in the season of persons who have already been vaccinated that season is not recommended.

Those individuals at high risk of severe medical complications due to influenza infection who are recommended to be vaccinated include:

- All children aged 6-59 months
- All adults aged 50 years or older
- Adults and children with
  - chronic pulmonary disorders (including asthma)
  - cardiovascular disorders (except isolated hypertension)
  - renal
  - hepatic
  - neurological
  - haematological
  - or metabolic disorders (including diabetes mellitus)
- Immunocompromised due to any cause (including medications or HIV infection)
- Women who are or will be pregnant during influenza season
- Children or adolescents (aged 6 months to 18 years) receiving aspirin or salicylate-containing medications at risk of Reyes syndrome
- Residents of nursing homes and long-term care facilities
- American Indians / Alaskan natives
- Extremely obese (body mass index [BMI] ≥40)

Also recommended are individuals who live with or care for any of the above, and include:

- Health care personnel, including physicians, nurses, other workers in inpatient and outpatient settings, medical emergency responders, nursing home and long-term care facility staff who have contact with residents, and students of these professions in contact with patients
- Household contacts (including children) and caregivers of children aged ≤5 years, particularly those aged <6 months, and adults aged >50 years
- Household contacts (including children) and caregivers of persons with medical conditions at high risk of severe influenza complications.

Individuals with a history of GBS within 6 weeks following previous influenza vaccination are not generally recommended to be vaccinated and may consider antiviral prophylaxis. However, in such cases with a high risk for severe influenza complications, the benefits of vaccination outweigh the theoretical risk of GBS.

For individuals with a history of egg allergy:

- Influenza vaccine is recommended if the individual only experienced urticaria after exposure to eggs
- More severe reactions to egg that required emergency medical interventions may receive vaccine in outpatients or inpatient settings under supervision
- Influenza vaccine is contraindicated for those who have experienced previous severe allergic reaction to influenza vaccine, regardless of suspect component.\textsuperscript{185}
The Infectious Diseases Society of America has published detailed guidance for timing of vaccines in individuals with specific immunocompromising conditions, as well as those with cerebral spinal fluid-oropharyngeal communication and cochlear implants. Key recommendations are summarised here.\textsuperscript{186}

- Vaccines be administered prior to planned immunosuppression: for LAIV, by at least 4 weeks prior and be avoided within 2 weeks of immunosuppression; and at least 2 weeks prior for IIV.
- Annual influenza vaccination with IIV is not recommended for those who are very unlikely to respond (but not harmed by IIV), such as those receiving intensive chemotherapy or received anti-B cell antibodies (such as rituximab or alemtuzumab) within 6 months.
- For recipients of solid organ transplants, IIV can be administered at least a month after transplant during a community influenza outbreak. Otherwise, due to the likelihood of poor response, vaccination should be withheld during intensified immunosuppression, including during the first 2 months post-transplant.
- Influenza vaccination is recommended for contacts aged ≥6 months of household contacts of immunocompromised individuals. Vaccination with LAIV should be avoided, or contact avoided for at least 7 days, for individuals living with immunocompromised haematopoietic transplant recipient within 2 months of transplant, with graft-versus-host disease or severe combined immunodeficiency.\textsuperscript{186}

\textbf{8.1.2 Canada}

The following are recommendations from the National Advisory Committee on Immunization (NACI) in Canada for influenza vaccination. Influenza vaccination is recommended for anyone aged older than 6 months without contraindications and for the following groups, in particular:\textsuperscript{187, 188}

**People at high risk of influenza-related complications or hospitalisation:**

- All pregnant women
- Adults and children with the following chronic health conditions:
  - Cardiac or pulmonary disorders (including bronchopulmonary dysplasia, cystic fibrosis and asthma)
  - Diabetes mellitus and other metabolic diseases
  - Cancer, immune compromising conditions (due to underlying disease, therapy or both)
  - Renal disease
  - Anaemia or haemoglobinopathy
  - Neurological or neurodevelopmental conditions (including neuromuscular, neurovascular, neurodegenerative and seizure disorders [including febrile seizures in children], excluding migraines and neuropsychiatric conditions.
  - Morbid obesity (BMI ≥40)
  - Children and adolescents (age 6 months to 18 years) undergoing treatment for long periods with acetylsalicylic acid, because of the potential increase of Reye's syndrome associated with influenza
- People of any age who are residents of nursing homes and other chronic care facilities
- People ≥65 years of age
- All children 6 to 59 months of age
- Indigenous peoples

People capable of transmitting influenza to those at high risk, including:
- Health care and other care providers in facilities and community settings who, through their activities, are capable of transmitting influenza to those at high risk of influenza complications
- Household contacts (adults and children) of individuals at high risk of influenza-related complications (whether or not the individual at high risk has been immunised):
  - contacts of individuals at high risk, as listed in the section above
  - contacts of infants <6 months of age as these infants are at high risk of complications from influenza but cannot receive influenza vaccine
  - members of a household expecting a newborn during the influenza season
- Those providing regular child care to children ≤59 months of age, whether in or out of the home
- Those who provide services within closed or relatively closed settings to persons at high risk (e.g., crew on a ship)

Others
- People who provide essential community services
- People in direct contact during culling operations with poultry infected with avian influenza

High-dose TIV (Fluzone® high dose) was added to the NACI recommendations for adults aged ≥65 years for the 2016/17 season. For the 2018/2109 season, NACI recommended that HD-TIV be offered over SD-TIV with the aim of providing improved individual protection against A/H3N2 in those aged ≥65 years. It reported that there was insufficient evidence to recommend MF-59-adjuvanted TIV or QIV over standard TIV.188

Children aged 2-17 years without contraindications are recommended to receive either Q-LAIV, QIV or TIV where QIV is unavailable; preferential use for LAIV in children aged 2-17 years is considered not supported by current evidence.

Children aged 6-23 months of age are recommend to be vaccinated with QIV, where available, given the burden of influenza B disease. Alternatively, either adjuvanted or standard TIV should be given, as available.

LAIV may be used in egg allergic individuals without any other contraindications.187

8.1.3 Australia

The Australian Technical Advisory Group on Immunisation recommends that everyone over 6 months of age be vaccinated against influenza. Four age-specific quadrivalent inactivated influenza vaccines are available in Australia currently. Vaccine is funded for those at high risk of influenza-associated complications, these include:189, 190

- People aged over 65 years
- Aboriginal and Torres Strait Island people aged 6 months to less than 5 years
- Aboriginal and Torres Strait Island people aged 15 years or over
- Pregnant women
- Those aged over 6 months with chronic medical conditions (further details in Table 6)
### Table 6: Medical conditions eligible for free vaccination under the Australian National Immunisation Programme (ATAGI, 2017)

<table>
<thead>
<tr>
<th>Category</th>
<th>Vaccination strongly recommended for individuals with the following conditions</th>
</tr>
</thead>
</table>
| **Cardiac disease**                                | Cyanotic congenital heart disease  
                                 | Congestive heart failure  
                                 | Coronary artery disease |
| **Chronic respiratory conditions**                 | Severe asthma  
                                 | Cystic fibrosis  
                                 | Bronchiectasis  
                                 | Suppurative lung disease  
                                 | Chronic obstructive pulmonary disease  
                                 | Chronic emphysema |
| **Chronic neurological conditions**                | Hereditary and degenerative CNS diseases  
                                 | Seizure disorders  
                                 | Spinal cord injuries  
                                 | Neuromuscular disorders |
| **Immunocompromising conditions**                  | Immunocompromised due to disease or treatment  
                                 | Asplenia or splenic dysfunction  
                                 | HIV infection |
| **Diabetes and other metabolic disorders**         | Type 1 or 2 diabetes mellitus  
                                 | Chronic metabolic disorders |
| **Renal disease**                                  | Chronic renal failure |
| **Haematological disorders**                       | Haemoglobinopathies |
| **Long-term aspirin therapy in children aged 6 months to 10 years** | These children are at increased risk of Reyes syndrome following influenza infection |

*Table 6: Medical conditions eligible for free vaccination under the Australian National Immunisation Programme (ATAGI, 2017)*

Other individuals for whom influenza vaccination is highly recommended but not funded: 189

- Aboriginal/Torres Strait Islander children aged 5-15 years
- people with Downs Syndrome
- class III obesity (BMI≥40)
- chronic liver disease
- all children aged 6 months to 5 years
- residents of aged-care and long-term residential facilities
- persons who may transmit influenza to high-risk children or adults (HCW)
- homeless people
- persons involved in the commercial poultry or pork industry
- persons providing essential services
- travellers, particularly prior to travel if it is known that influenza is circulating in destination.
8.1.4 United Kingdom

The Joint Committee on Vaccination and Immunisation in the UK recommend that all children (age 2–17 years) are offered LAIV to reduce transmission and provide protection for themselves and across all age groups.\(^{191}\)

For 2017/2018, the following groups are eligible for influenza vaccination:

- All children aged from 2 to less than 9 years as of 31\(^{st}\) August 2017 (with LAIV)
- All primary school-aged children in former pilot primary school areas (with LAIV)
- Those from aged 6 months to less than 65 years in clinical risk groups
- Pregnant women
- Those aged 65 years or older
- Those in long-stay residential care homes
- Carers.

It is also recommended that frontline health and social care workers be provided influenza vaccination by their employers, to help to protect staff and their service users.

Clinical risk groups for whom influenza vaccination is to be offered during 2017/18, include patients with:\(^{192}\)

- Chronic respiratory, heart, kidney, liver or neurological diseases
- Diabetes – type 1 or 2, requiring insulin, hypoglycaemic drugs or diet controlled
- Immunosuppression
- Asplenia or spleen dysfunction, including homozygous sickle cell disease and coeliac syndrome
- Morbidly obese (BMI≥40 – many of whom are likely to have already eligible conditions).

New additions to the 2017/18 programme were:\(^{191}\)

- Morbidly obese
- School reception aged children (ages 4-5 years will be offered LAIV at school rather than general practice)
- School year 4 (ages 8-9 years)
- Eligible adults (from 18 years of age) will be able to receive vaccine in pharmacies.

Targets for coverage have been set, with 75% uptake for adults aged ≥65 years and HCW, 55% for ‘at risk’ adults including pregnant women, and 40-65% for children aged 2-8 years.\(^{191}\)

8.2 Summary

In general, there is agreement between countries as to which groups are at higher risk of influenza and therefore require influenza vaccination for direct protection, including those aged over 65 years, pregnant women, and adults and children with chronic health conditions such as neurological conditions, heart, kidney or liver disorders, respiratory disorders, immunocompromised, diabetes, and more recently included, the morbidly obese. Direct protection for the individuals and indirect protection are provided by the vaccination of health care, residential care and social care workers, emergency medical responders and household contacts of those at high risk.

Australia, Canada and the US recommended vaccination of indigenous people, who are at higher risk of influenza complications than non-indigenous populations.
High dose QIV is recommended in Canada for the over 65 year age group rather than adjuvanted IIV vaccine. Infants (age 6-23 months) are recommended QIV, due to high influenza B burden in this age group, or adjuvanted TIV in preference to standard TIV, as available.

The UK has an extensive programme to vaccinate preschool and school-aged children to provide further direct and indirect community protection. This programme is expected to also protect younger siblings, particularly those too young to be vaccinated and further protect vaccinated pregnant mothers and grandparents.

9 Vaccines and options for scheduling

9.1 Vaccine options

The roles of influenza vaccination are to:

4. Protect individual against infection and disease
5. Offer protection of high risk groups by vaccination of close contacts to reduce spread
6. Induce herd immunity to restrict viral transmission through a community.

This section will consider how these roles can be achieved through immunisation programmes.

Key to the success of any such immunisation programme is high uptake of the vaccine. To achieve herd immunity, coverage rates as low as 30% are likely to be effective (personal communication with Prof Andrew Pollard, JCVI, November 2017). The UK has achieved good coverage in school-age children with school-based programmes and is showing herd immunity effects across other age groups. Systematic approaches, usually in primary care, are needed to obtain high uptake of high risk groups. Generally, in targeted programmes to high risk groups it is difficult to obtain high coverage. Occupational health providers can obtain good coverage, such as those who frequently conduct workplace vaccinations, and similar programmes can be made available in residential care facilities and retirement villages.

9.2 Types and formulations of vaccine

9.2.1 Inactivated influenza vaccine

The point estimate effectiveness for IIV is around 50%. One of the challenges for seasonal influenza vaccination is to achieve adequate coverage levels. Poor responses in some high risk individuals and mismatched viral strains have affected confidence in influenza vaccines and thereby prevents high coverage and annual uptake.

Quadrivalent formulations of IIV provide wider protection against influenza B, and reduce the risk of mismatch to the B lineage.

9.2.1.1 Alternative formulations

Some individuals are at high risk from severe influenza because they are unable to mount an adequate immune response against the virus. Likewise, these groups are also less able to respond to the standard IIV.

More recently licensed vaccine formulations of IIV have been developed to improve the response through the use of adjuvants (in particular, squalene-containing oil-emulsion...
adjuvants like MF-59) or intradermal administration, which is more complicated to administer for vaccinators correctly. These formulations have variably been shown to enhance the immune response to influenza vaccination in older people when compared with non-adjuvanted or intramuscular administration. High dose formulations have also been used in the elderly that have induced similar responses as seen with standard doses in younger people. Although the data is limited, effectiveness appears to be improved with high dose vaccines. The data around the effectiveness of these formulations is limited in immunocompromised individuals.

Adjuvanted vaccines, by the nature of enhancing the local immune response, are more reactogenic than standard IIV and may not be suitable for use in young children, due to an increased risk of fever.

9.2.1.2 Revaccination in the same season

Although effectiveness of IIV appears to wane during the season, this is likely due to drift in viral antigens rather than decline in antibody protection. Although the latter may be a contributing factor to lack of effectiveness in those who may have a suboptimal immune response, it is not recommended to revaccinate with the same vaccine within a single season.185

9.2.1.3 Summary

The current IIV only have modest effectiveness, particularly in people with lower immune responses who are most likely to develop severe disease, which include the elderly, infants and immunocompromised individuals. Strategies to improve responses include the inclusion of adjuvants, and intradermal and high dose formulations.

High dose and intradermal vaccine formulations can improve the immune response in the elderly. High dose vaccine significantly improved vaccine efficacy in the over 75 year olds. There is limited evidence that adjuvanted vaccines improve immunogenicity in the elderly. In children younger than 2 years of age, all demonstrate improved immunogenicity, but these vaccines are likely to increase the risk of fever.

9.2.2 Live attenuated vaccine

As discussed in section 5, there are several advantages to using LAIV in children over IIV. The intranasal administration of the vaccine is more appealing to parents, and thereby, likely to be much more effective for uptake in children. Also, there is some suggestion that LAIV provide immunity to conserved influenza epitopes and allow cross-protection, therefore broader protection. Recent experiences in the US have raised questions around the vaccine’s effectiveness against A/H1N1pdm09 influenza, in contrast to the UK experience to date. The UK has continued LAIV vaccination of children in preschool and school-based programmes for the next influenza season, and therefore its surveillance data will be reported next year (in 2018).

9.3 Routine universal vaccination of children

9.3.1 Vaccination of healthy children

It is recommended, to help prevent the transmission of influenza, that everyone over the age of 6 months is vaccinated annually.

A recent literature review by Principi and Esposito (2017) considered the debate around influenza vaccination of healthy children.193 In many countries, children are not a priority to be vaccinated against influenza unless they have underlying health issues. Epidemiological
studies have identified a potential need to vaccinate healthy children to provide direct protection. A reviewed study, published in 2000, found that in the US an estimated 6-15 outpatient visits and 3-9 courses of antibiotics per 100 children were associated with influenza and 10-39% increase in antibiotic prescriptions during influenza seasons compared with periods with low influenza circulation. The influence of influenza on morbidity and mortality of children is likely to be under-estimated since laboratory-confirmation of influenza in cases hospitalised with acute respiratory illness is uncommon or the virus is undetectable. Universal vaccination of children has the potential to reduce school absenteeism, provide community immunity and improve the uptake of influenza vaccine, particularly to capture those children at higher risk from severe disease. For example, a study published in 2012 found that for every 20% increase in vaccination rate in primary school children in the US, there was a 4% reduction in absenteeism, including in older unvaccinated children. Significant reductions in community influenza and ILI-associated emergency care visits have been observed as far back as 1969, where large school-based vaccination programmes have been implemented. The impact of school-based programmes may be greater than programmes targeting people aged ≥65 years.\(^\text{193}\)

**9.3.2 Indirect protection from vaccinated children**

Children have been identified as an important source of transmission of influenza virus to the community, particularly to their peers, family members with high risk of complication such as infant siblings, pregnant mothers, grandparents and those with chronic disease or immunosuppressive therapies.

Indirect protection against influenza of household contacts and close community members has been demonstrated following the vaccination of pre-school or school aged children with either IIV or LAIV.

A systematic review conducted by Yin et al in 2017 found that, although further large and more robust studies are needed to quantify indirect protection, the vaccination of children against influenza provided indirect protection to members of closely connected communities against laboratory-confirmed influenza, household members against acute respiratory illness or ILI, and the elderly in wider community against influenza-related mortality. However, unvaccinated people remain susceptible to influenza and annual vaccination is most effective at preventing influenza in individuals.\(^\text{184}\)

**9.4 Vaccination of special groups**

In general, the uptake of influenza vaccination is low in many high-risk groups, and therefore limiting protection for those at high risk of severe disease. There are known groups which have been identified as being at increased risk, however, few recent studies have further investigated other potential groups in which to target vaccination.

As has been described in studies of pneumococcal vaccination, potentially, the risk of influenza may increase with the number of comorbidities an individual has where each underlying disease may not in itself significantly increase risk but when all are considered results in an accumulative risk – described as risk stacking.\(^\text{194}\)

Universal uptake of influenza vaccination may be a more effective strategy via the provision of herd immunity, both to protect those in whom the vaccine response is not optimal and to potentially capture more individuals who are at known or currently unrecognised as being at increased risk from the disease.
9.4.1 Occupational vaccination

The vaccination of all front-line health care workers, particularly those working in residential care and with high risk groups, is highly recommended to protect both the employee and their patients.

9.4.2 Pregnant women and young infants

Vaccination with IIV is recommended at any stage during or immediately prior to pregnancy to help protect the woman from severe disease. No safety issues to the fetus have been demonstrated to date.

There are also advantages to infants born to vaccinated mothers, particularly those who are vaccinated later in pregnancy. It was shown that infants born early in the influenza season were at the greatest risk from influenza in their first 6 months. However, antibody protection provided to infants from their mothers is short lived (around 8 weeks) and VE declines before 6 months of age.193, 195

9.4.3 Adults aged over 65 years

Although the immunogenicity of IIV is lower in older adults than in those under 65 years, vaccination is recommended as important to help reduce the burden of influenza in older people. Consideration of more effective types of vaccine is required (see section 4).

9.5 Summary

The first step to improving protection provided by influenza vaccination is to increase the uptake of the vaccine across the population as a whole. In doing this, those at high risk from influenza are likely to be protected directly and indirectly. Some high risk groups have poor individual responses to vaccines, many do not access vaccines in targeted strategies, and targeted strategies do not cover all high risk, particularly those who may have more than one risk factor; therefore theoretically, herd immunity approaches may offer better protection than individual protection.

Children have been shown to be significant transmitters of the disease to their peers, younger siblings and household contacts, and likely to be ideal targets introducing a herd immunity strategy. The UK is currently applying a herd immunity strategy via universal vaccination of preschool and primary school aged children using a LAIV. Early data is suggesting that this strategy is likely to be effective.

10 Future vaccine development

As demonstrated in this review, the influenza vaccines currently available have limitations in terms of efficacy in certain populations and a lack of cross-reactivity. Another limitation is the time taken to manufacture each season’s vaccines, which can result in mismatch of vaccine and circulating viral strains or a drift in variants during the season.5

An Achilles heel of the current influenza vaccines is the requirement for extensive global surveillance to try to predict the next seasons’ strains and manufacturing resources required to produce new stocks biannually.1 Related to this are:

1. Variable efficacy in specific populations – poor immunogenicity and inability to induce long-lasting serum antibody. This requires strategies for new vaccines or vaccine formulations to improve responsiveness.
2. Variable virus – antigenic matching with changing circulating strain. Improvements could be achieved with vaccines that target conserved virus regions.

3. Production time frame – no flexibility for unanticipated delays. Large quantities of vaccine are required annually. Need to improve viral growth and increase immunogenicity (dose sparing).

4. Resource-poor countries have limited vaccine available – need for more scalable and cheaper platforms to induce longer lasting immunity.

The future aim of influenza vaccine design is to produce ‘universal’ influenza vaccines targeted against non-variable antigenic proteins to induce cross-reactive antibodies. Until a universal vaccine has been developed, strain-specific influenza vaccines require to be more rapidly produced, less reliant on egg supply and with a reduced risk of antigenic drift occurring during production.

10.1 Egg versus cell culture

The first stage of influenza virus production has traditionally required culture in fertilised chicken eggs. This is time intensive, relies on a continuous egg supply and the ability of the virus strain to grow well. There is a risk of contaminants and antigenic alteration with repeat passages. However, this method is well characterised and has been the industry standard for several decades. Due to the potential presence of ovalbumin, there is theoretically a slightly increased risk of egg allergy-induced anaphylaxis.

Once the master seed strains have been created in eggs, more manufacturers are using mammalian cell culture to produce influenza virus. In theory, cell cultures are more scalable and easier to manipulate than egg cultures. They induce fewer adaptive mutations resulting in less antigen alteration than is seen in eggs.

The challenge for enabling the use of cell cultures exclusively, without requiring eggs, is being able to identify antigens using plasmid systems to produce viral proteins and viral RNA simultaneously. In cell culture, the viable virus can be collected in the culture supernatant (growth medium). This enables cryopreservation of virus, to maintain a virus stock, and then allowing production to be scaled up at any time in high yield bioreactors.

One influenza vaccine manufactured solely in cell culture was approved during the 2015/16 season in the EU and the US for adults 18-50 years. Optaflu® / Flucelvax® (Seqirus) is grown in Madin-Darby canine kidney cells (MDKC).

Reverse genetics is a molecular technique use to generate a specific virus phenotype and is used to create reassortant influenza virus for LAIV. However, its use is limited for IIV.

10.2 Recombinant influenza vaccines

Recombinant influenza vaccines contain recombinant haemagglutinin antigens that are produced in insect cells. Insect cells are infected with baculovirus engineered to contain the corresponding H gene. These vaccines do not require influenza virus to produce the H antigens. The first recombinant vaccine was licensed for use in adults in the US in October 2013 (Flublok and Flublok Quadrivalent, Protein Sciences Corporation).
11 Methodology for review

11.1 Objectives

The objectives of this literature review were to summarise updates and advances to seasonal influenza vaccines as described in national and international literature. The focus of the review was on literature published between January 2013 – November 2017 and of the most relevance to the New Zealand health setting. It was not conducted as a systematic review.

Areas covered include:

1. Safety
2. Effectiveness in disease control
3. Implementation issues, including possible impact on uptake
4. Differences that need to be considered for each age group and risk groups
5. Different options for the schedule
6. Different vaccine options for the influenza
7. Current international research and evidence around the use of vaccines.

Literature around pandemic influenza vaccines and disease were not included.

11.2 Literature search strategy

Ovid Medline search terms and strategy

As of 1 September 2017

Influenza vaccines [MeSH focus] limit admin/AE/contraindications/immunology/therapeutic use = 11608

1. Limit English humans 2013-current = 2807

Safety (title) +1 = 211 removed duplicates 164
Immunogenicity (title) AND 1 = 221 removed duplicates 154 (96 same as safety)
Effectiveness AND 1 = 294 (removed duplicates) and cost = 240
Children (title) AND 1 = 272 (removed duplicates) = 230

Pubmed

Systematic review and influenza vaccine*

Limit human, English 2013-31/8/17 = 62 – 34 selected (after duplicates removed)

Occupational and “influenza vaccination” = 245
Limit 01/01/2013 – 11/09/17, English = 79; selected 48

Scopus search terms and strategy

Scopus – as of 1 September 2017

TITLE-ABS-KEY ( "influenza vaccine" ) AND DOCTYPE ( ar OR re ) AND PUBYEAR = 6,776
Limit to medicine / immunology; English, journals
TITLE-ABS-KEY ( "influenza vaccine" ) AND DOCTYPE ( ar OR re ) AND PUBYEAR > 2012 = 5369
Seasonal influenza = 3194
Safety =1610
Immunogenicity = 1323
Vaccine effectiveness = 1723

Literature specifically related to pandemic influenza, particularly the A/H1N1pdm09 were excluded, unless considered to be related to seasonal influenza vaccines and vaccination. Within the library, 61 references specified A/H1N1pdm09 in their title.

Grey literature
Conference and symposium presentations on the SHIVERS study were included.

Additional searches
Where questions arose, additional searches were undertaken to obtain further data relating to each particularly question. Where articles were missing they were accessed and added to the library. All duplicates were removed from the final library.

Final Endnote Library 772 references
Where systematic reviews and/or meta-analysis were available the preceding literature has been excluded from the review, unless further details were required.

Literature related solely to monovalent pandemic vaccines (H1N1 or H5N1) was discarded where easily identifiable.

11.3 Study designs
The studies included in this review are meta-analysis, systematic reviews, reviews, randomised controlled trials, case-control studies, case reports and observational studies using database matching. Cost-effectiveness and cost-benefit analyses were not included.
12 References


91. NACI. An Advisory Committee Review National Advisory Committee on Immunization (NACI): Literature Review Update on the Efficacy and effectiveness of High-Dose (Fluzone® High-Dose) and MF59-Adjuvanted (Fluad®) Trivalent Inactivated Influenza Vaccines in Adults 65 Years of Age and Older [Internet]. Public Health Agency of Canada; 2017.


