2012 Antigen Review for the New Zealand National Immunisation Schedule: Influenza

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Prepared by a scientific team incorporating the Immunisation Advisory Centre, The University of Auckland Institute of Environmental Science and Research Ltd.

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Executive summary

Epidemiology

The impact of influenza in New Zealand (NZ) over the past 20 seasons, since the sentinel surveillance systems commenced, has been substantial in terms of General Practitioner (GP) consultations, hospitalisations and deaths. The 1997 policy change offering influenza vaccination free to all ≥ 65 years was associated with a significant reduction of influenza mortality in the elderly population. High influenza-like-illness consultation rates and high hospitalisations continue to be reported, especially among young children under five years, in particular, the under one year olds. New measures to prevent influenza-related hospitalisations, particularly among young children are needed.

Since 2002, influenza virus strain surveillance in NZ has frequently recorded co-circulation of four antigenically distinct viruses: A (H1N1), A (H3N2), B/Yamagata lineage and B/Victoria lineage virus. NZ influenza virus circulation pattern supports the introduction of quadrivalent vaccines which contains these four antigenically distinct influenza viruses.

Safety

1. Overall, the traditional trivalent inactivated influenza vaccines (TIV) have an extensive and excellent safety record around their use in all populations, including pregnant women. However, several issues for safety have arisen over the past two years, largely as an indirect result of the 2009 pandemic:

2. The finding that seasonal trivalent inactivated influenza vaccines can cause significant febrile events in children. This is primarily associated with CSL’s TIV influenza vaccine that contained the pandemic H1N1 strain; however, other brands were also associated with higher rates of febrile events. There was also a slightly higher risk for febrile convulsions associated with the co-administration of TIV and pneumococcal vaccine. This has highlighted the importance of safety monitoring annual antigenic changes, and monitoring/comparing the behaviours of different brands of TIV.

3. Theoretical safety concerns around the use of repeat annual vaccination with TIVs for children.

4. There appears to be a small excess in risk for Guillain-Barré Syndrome (GBS) following TIV vaccination (less than one additional case per million persons), although, the risk from influenza infection is much greater.

5. The use of the live attenuated influenza vaccines (LAIV) increases risk for wheezing events in recipients less than two years of age. This has led to the exclusion of this age group in the recommendations for use of the vaccine. While more recent data has suggested this may be less of a problem than originally considered, further research is required to clarify the risks for this group. There are no issues identified around the use of LAIV in mild to moderately immunocompromised children despite cautions remaining for this group.

6. An association has been shown for one adjuvanted H1N1 pandemic vaccine with narcolepsy. This does not extend to non-adjuvanted vaccines. It is possible that the onset of narcolepsy may be confounded by other factors, therefore the incidence of narcolepsy with influenza is unknown currently, and further data is required to confirm a causal link.

Immunogenicity/efficacy

TIVs are generally recognised as effective for healthy adults, particularly when the vaccine and circulating virus are antigenically similar. Traditionally, the TIVs generate poor immune responses in the elderly, the very young and some high risk groups, particularly the immunocompromised. These groups tend to be those at higher risk of disease and no randomised control trials (RCT) of TIV in adults over the age of 65 years have been conducted to confirm the efficacy. There remains a need for more high quality studies in young children, older adults and those with a variety of co-morbidities.
Adjuvanted vaccines are more immunogenic than unadjuvanted vaccines. However, there is no efficacy or effectiveness data on adjuvanted vaccines.

Intradermal (ID) vaccines do not generate higher antibody titres than IM vaccines in healthy adults, although higher doses of ID vaccine can improve immunogenicity in the elderly.

LAIV vaccines generate a different immune response to TIV, therefore, immunogenicity data is not directly comparable. While LAIV vaccines appear to provide superior protection in children compared with TIV, the TIV appear better in healthy adults compared to children.

There is some evidence to suggest herd immunity, particularly via vaccinating children, can be achieved providing coverage is very high. Vaccinating healthcare workers to protect the highly vulnerable is likely to be an effective strategy, though data is limited.

The duration of immunity provided by influenza vaccines is difficult to study due to the continual strain shifts. However, in the years when strains have remained the same, vaccination in a previous year appears to confer immunity in the next year. Protection from LAIV has been demonstrated to persist beyond a year. The addition of ‘B’ strain in seasonal influenza vaccines is likely to improve effectiveness moderately.

Options for Vaccine Schedules

Current international recommendations are conflicting as to whether annual vaccination of healthy adults with TIV is cost saving.

The options to consider when improving vaccine schedules are both broad and targeted including:

1. The use of quadrivalent vaccines - a quadrivalent option for inactivated influenza vaccine is likely to modestly improve the performance of these vaccines.

2. ID vaccination for the elderly and immunosuppressed allows for antigen sparing, but there is little evidence that the immune response is superior or that better protection is afforded, except in the elderly.

3. Higher antigen dose or two dose regimes

4. Generally, in the elderly and immunosuppressed, adjuvanted vaccines provide superior responses than TIV, and formulations of adjuvanted TIV with higher antigen doses, generally, appear more immunogenic than standard TIV.

5. Vaccination of healthcare workers and other close contacts are likely to be sensible strategies, albeit based on relatively limited data.

6. For children two years up to 18 years, LAIV provide superior performance over TIV. There is increasing evidence that annual vaccination of children two years of age and older with LAIVs offer benefits, both for direct protection and indirect protection, to other members of the community.

7. There is a lack of data to support effectiveness of TIV in the very young. Strategies for this age group include consideration of lowering the age of delivery of LAIV and herd immunity strategies. For children less than two years of age, the LAIV elicit good immune responses, but currently, are not recommended due to possible increased risk of wheezing episodes. Emerging data suggests adjuvanted vaccines may work better in this group, although, there is little evidence to indicate any influenza vaccines elicit good responses in infants less than six years of age.

8. More recently, identified high risk groups for targeting influenza vaccination strategies include the morbidly obese and pregnant women. Cocoon strategies sound pragmatically sensible and are advocated in some countries, but they are difficult to implement and as yet, there is no data to support their effectiveness in reducing influenza morbidity in infants.
Implementation Issues
LAIVs are contraindicated in the immunocompromised and those receiving salicylic acid, and are not to be administered to healthcare professionals who interact with high risk patients. LAIVs are recommended not to be used in infants under 12 months, individuals with severe asthma or active wheezing and individuals who are pregnant or breast-feeding. Vaccine recipients should avoid close association with severely immunocompromised individuals for on to two weeks following immunisation.

Adjuvanted vaccines increased local reactogenicity and the potential for increased incidence of narcolepsy. ID vaccines can also have increased local reactogenicity, but despite this, are frequently more acceptable to recipients than intramuscular (IM) injections.

Improving Coverage
Recent studies on vaccination for healthy adults highlight the advantages of onsite work vaccination clinics to improve coverage. For improving national immunisation rates overall clear leadership, effective communication about performance and methods, and financial targets to incentivise practices improved vaccine coverage of the seasonal influenza targeted programme. Improving vaccination rates for healthcare workers highlight advantages with mandatory vaccination policies, such as making it a condition of employment, alongside effective senior leadership support. A key factor in improving uptake rates for elderly is the engagement of the treating physician. Use of effective integrated systems, alongside provider and public education, is needed to improve vaccination rates for pregnant women. Immunisation registers and effective surveillance systems are important elements of a successful national immunisation programme.

International Policy
Current international policies are a mixture of individual protection strategies and herd immunity. In general, the European Union (EU) countries have more conservative strategies. Different available licensed vaccines in different areas also are likely to significantly affect policy decisions.
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Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACIP</td>
<td>Advisory Committee On Immunisation Practices</td>
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<tr>
<td>AEFI</td>
<td>Adverse Event Following Immunisation</td>
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<td>AIVC</td>
<td>Australian Influenza Vaccine Committee</td>
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<td>AOM</td>
<td>Acute Otitis Media</td>
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<tr>
<td>CAP</td>
<td>Community Acquired Pneumonia</td>
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<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
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<tr>
<td>CTL</td>
<td>Cytotoxic T-cells</td>
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<tr>
<td>DMARD</td>
<td>Disease-Modifying Antirheumatic Drug</td>
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<tr>
<td>EDTA</td>
<td>Ethylenediaminetetra-acetic acid</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration (US)</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</td>
<td>Geometric mean titre</td>
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<tr>
<td>GP</td>
<td>General Practitioner</td>
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<tr>
<td>ICD</td>
<td>International Classification of Diseases</td>
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<tr>
<td>ID</td>
<td>Intradermal</td>
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<tr>
<td>IEM</td>
<td>Institute Of Experimental Medicine (Russia)</td>
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<tr>
<td>ILI</td>
<td>Influenza-Like Illness</td>
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<tr>
<td>IM</td>
<td>Intramuscular</td>
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<tr>
<td>IPD</td>
<td>Invasive Pneumococcal Disease</td>
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<tr>
<td>JCVI</td>
<td>UK Joint Committee of Vaccination and Immunisation</td>
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<tr>
<td>LAIV</td>
<td>Live Attenuated Influenza Vaccine</td>
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<tr>
<td>NIC</td>
<td>National Influenza Centre</td>
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<tr>
<td>NICU</td>
<td>Neonatal Intensive Care Unit</td>
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<tr>
<td>NMDS</td>
<td>National Minimum Dataset</td>
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<tr>
<td>NP</td>
<td>Nasopharyngeal</td>
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<tr>
<td>NZ</td>
<td>New Zealand</td>
</tr>
<tr>
<td>OM</td>
<td>Otitis Media</td>
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<tr>
<td>OPA</td>
<td>Opsonophagocytic Activity</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase Chain Reaction</td>
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<tr>
<td>PCV</td>
<td>Pneumococcal Conjugate Vaccine</td>
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<tr>
<td>PCV-10</td>
<td>10-Valent Pneumococcal Conjugate Vaccine With Serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F And 23F</td>
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<td>PCV-7</td>
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<td>PPV</td>
<td>Pneumococcal Polysaccharide Vaccine</td>
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<td>PPV-23</td>
<td>23-Valent Pneumococcal Polysaccharide Vaccine With Serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F And 33F</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>Q/LAIV</td>
<td>Quadrivalent Live Attenuated Influenza Vaccine</td>
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<tr>
<td>RCT</td>
<td>Randomised Control Trial</td>
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<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
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<tr>
<td>SIIL</td>
<td>Serum Institute of India Ltd</td>
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<tr>
<td>SpA</td>
<td>Spondyloarthropathies</td>
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<tr>
<td>T/LAIV</td>
<td>Trivalent Live Attenuated Influenza Vaccine</td>
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<tr>
<td>TIV</td>
<td>Trivalent Inactivated Influenza Vaccine</td>
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<tr>
<td>TNF</td>
<td>Tumour necrosis factor</td>
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<tr>
<td>UK</td>
<td>United Kingdom</td>
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<tr>
<td>US</td>
<td>United States</td>
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<tr>
<td>VAV</td>
<td>Virosome-adjuvanted vaccine</td>
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<td>WHO</td>
<td>World Health Organization</td>
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1. Background – Influenza vaccines

Influenza viruses can be divided into three genera – *influenzavirus A, B and C*. They are classified based on the antigenic differences of two structural proteins, the nucleoprotein and the matrix protein. Influenza A viruses are further classified based on their major membrane glycoproteins haemagglutinin (HA) and neuraminidase (NA). There have been 17 HA subtypes identified and nine NA subtypes.

There are two genetically distinct lineages of type B influenza viruses. These are B/Victoria/02/87-like and B/Yamagata/16/88-like, which have been circulating since 1985. Immunity to one of these lineages does not confer immunity to the other.

The nomenclature of the influenza viruses that infect humans is based on the type of isolate/geographical location of isolation/laboratory number/subtype of HA and NA.

The isolation of influenza A virus in 1933 led to the discovery that influenza viruses were the cause of regular epidemics and pandemics of respiratory diseases. The development and testing of the first vaccines against influenza began in the 1930s. Based on trials conducted among military recruits and college students, commercial influenza vaccines were licensed in the US in 1945. These first vaccines were inactivated whole virus vaccines. Since the 1970s most influenza vaccines have been subvirion (or split).

The process for the manufacture of inactivated influenza vaccines generally involves growing the viruses in animal derived substrates – usually the allantoic cavities of embryonated chicken eggs, although other animal cell lines are now used, such as Vero or MDCK. After harvest, inactivation is achieved by either treatment with formalin or β-propiolactone. Purification to remove non-viral proteins and manufacturing impurities is carried out with the monovalent strains, at which point, they are combined. Splitting of the whole virus into subvirions is achieved by treatment with a solvent, such as detergent or ether. The agent disrupts the viral lipid envelope. Additional purification steps may also occur.

Traditionally adjuvants have not been used with influenza vaccines, however, there are now internationally licensed influenza vaccines adjuvanted with aluminium salts and the proprietary adjuvants MF59 (Novartis) and AS03 (GSK).

Live attenuated influenza vaccines (LAIV) are able to overcome some of the limitations of the inactivated vaccines. Seasonal live influenza vaccines contain three (and recently, four) cold-adapted temperature sensitive, attenuated influenza viruses (two ‘A’ strains and one ‘B’ strain). These viruses are only able to replicate at temperatures less than 25°C. Attenuation has been achieved through recombinant technologies, such that, each vaccine virus contains six genes from a master donor viral stock and two genes that encode the haemagglutinin and neuraminidase glycoproteins of the seasonal choice of wild virus. Recently, quadrivalent live influenza vaccines which contain two ‘A’ and two ‘B’ strains have been evaluated.

The aim of this report is to summarise some of the key literature on influenza vaccines and vaccination that has been published during 2009 – 2012. The report was completed in early 2013, and subsequently reviewed prior to publication in 2014. During an edit of this review in 2014, reference updates were inserted where the data referenced had been published since 2013. A full review of data and vaccination schedules was not conducted.
2. Methodology for review

2.1 Objectives for review

The objectives for this review have been informed by the general specifications for the 2012 NZ antigen review and the specific specifications for influenza vaccines. These are listed below. The dates for publication are between 2009 and 2012 as per the brief. This is not a systematic review or a critique of the literature. The choice of articles reviewed is based on the purposeful selection of recent reviews and studies that may best inform policy discussions around influenza vaccines for NZ.

- General specifications
  - Safety
  - Effectiveness
  - Implementation issues (practicality and possible impact on uptake)
  - The differences that need to be considered for each age group such as the variable severity of diseases and issues for vaccination
  - Different options of placement on the schedule, based on international findings and best practice
  - Different vaccine options and comparisons between the options
- Specific specifications for influenza
  - Evidence for including live attenuated influenza vaccines (LAIV) for children on the Schedule.
  - Investigation of whether the vaccine should be provided to household contacts of high risk.
  - Consideration of the right set of criteria for high risk children.
  - Evidence for funding Intanza® for the elderly – for example, proof of greater effectiveness.
  - Evidence of international programmes for “at risk” groups such as smokers and mental health patients.
  - Investigation of the different forms of influenza protection, including various vaccines, nasal sprays, Intanza®.
  - Evidence for administering the vaccine to children and possibly providing a universal vaccine for children, including considerations of febrile convulsions.
  - Effectiveness and health risks for different groups, including by age group.
  - Duration of protection provided by vaccines.

2.2 New Zealand epidemiology

The New Zealand (NZ) epidemiology of influenza is provided by ESR and summarises the results from influenza surveillance in NZ. Information on influenza morbidity, sourced from the Ministry of Health’s National Minimum Dataset, and the estimates of influenza vaccine coverage are sourced from Health Benefits Ltd.

Influenza-like illness (ILI) is defined by a standardised case definition, which is, ‘acute upper respiratory tract infection characterised by abrupt onset and two of the following: fever, chills, headache and myalgia.

The national level of ILI activity is described using a set of threshold values. Based on the influenza ILI consultation rates in NZ during 1990–1999, various levels of influenza activity, such as baseline, normal seasonal influenza, higher than expected influenza activity, severe epidemic level are described by using different ILI consultation rates.
2.3 Literature search strategy

The points below have formed the focus of the literature search:

- Safety
  - Of particular interest:
    i. Safety of influenza vaccine in infants
    ii. Safety in older adults
    iii. Pyrogenicity
    iv. Immunological safety
- Effectiveness in disease control
  - Effect on ILL, laboratory confirmed influenza in the following age groups:
    i. Infants and children under two years of age
    ii. School children
    iii. Older adults
    iv. Differences between current trivalent inactivated influenza vaccines and new generation vaccines
  - Indirect effects/herd immunity
  - Duration of protection
- Immunogenicity
- Implementation issues (practicality of and possible impact on uptake).
- Differences that need to be considered for each age group, and groups with particular needs, for example, the variable severity of disease and immunisation concerns that differ with:
  - Age
  - High-risk groups – definition of which groups most likely to benefit and which vaccine/s
- Different options for placement on the schedule, based on international findings and best practice.
  - Schedules for healthy people
  - Schedules for high-risk children
  - Schedules for high-risk groups
- Different vaccine options and comparison between the options.
  - Current inactivated TIV
  - Live attenuated influenza vaccines
  - Adjuvanted influenza vaccines
  - Cell-based influenza vaccines
- Current international research and evidence around use of vaccines.

Other areas of special interest:

- Evidence for including LIAV for children on the schedule.
- Investigation of whether the vaccine should be provided to household contacts of high risk.
- Consideration of the right set of criteria for high risk children.
- Evidence for funding ID influenza vaccine (Intanza® - currently not funded) for the elderly – for example, evidence of greater effectiveness.
- Evidence of international programmes for at-risk groups such as smokers and mental health patients.
- Evidence for administering the vaccine to children and possibly providing universal vaccination for children, including considerations of febrile convulsions.
- Effectiveness and health risks for different groups, including by age group.
- Duration of protection provided by vaccines.

2.3.1 Medline search terms and strategy

MeSH term: Influenza Vaccines
11404
Limit to Humans, English, 2009 – current
3162
NOT Costs and Cost analysis
2976
NOT qualitative, interview, parent, physician, survey, attitudes
2496
MeSH term: AND Adverse Effects
1088
Match 2496 against 1088
419
Safety as keyword
175 (keep and view)
MeSH term: AND Effectiveness
190 (keep and view)

2.3.2 Cochrane Library search terms and strategy
Search term Influenza Vaccin*
Limit to Cochrane Reviews, Other Reviews, Trials 2009-present
23 results (keep and view)

2.3.3 Scopus search terms and strategy
Influenza Vaccin* Published 2011 – present
5514
Limit to: Medicine, humans, vaccination, influenza vaccine, journals
3851
Exclude Letter, Short survey, editorial and erratum
1051 (keep and view)
Reject social science articles. Delete duplicates
Final EndNote library after literature search and revisions: 683

2.3.4 Grey literature
Further information was sought from industry to provide additional information on new influenza vaccines.

2.3.5 Additional searches
Where questions arose additional searches were undertaken to ensure there was no further available data. Where articles were missing they were accessed and added to the library. A further 124 articles were accessed.

2.3.6 Final library
The final library includes 807 references. Where systematic reviews and/or meta-analysis were available the preceding literature has been excluded from the review.

Figure 1. Flow of selection of articles for review

2.4 Participants/populations
The population for a potential universal programme are infants and children under two years of age. High risk groups cover all ages, and adult populations in this context are over 18 years of age.

High risk persons identified from the literature include:
• Children aged six months to four years.
• Persons aged over 50 years.
• Children and adolescents who are receiving long-term aspirin therapy and at risk for Reye syndrome after influenza infection.
• Women who will be pregnant during the influenza season.
• Persons with chronic pulmonary (including asthma) or cardiovascular (except isolated hypertension), renal, hepatic, neurological, haematological or metabolic disorders including diabetes.
• Indigenous populations.
• Morbidly obese (BMI >40).
• Persons who have immunosuppression.
• Residents of nursing homes and other long-term care facilities.
2.5 Interventions

The interventions included are:

- Inactivated influenza vaccines
- Live Attenuated Influenza Vaccines
- Adjuvanted influenza vaccines
- ID influenza vaccine

The controls are placebo or another influenza vaccine, usually TIV. Some studies have used an unrelated vaccine such as pneumococcal vaccine.

2.5.1 Inactivated influenza vaccine

The first commercial inactivated vaccines were approved for use in the United States (US) in 1945. These were whole virus vaccines. Most of these vaccines are grown in the allantoic cavity of embryonated chicken eggs. More recently vaccines have been produced in animal cells, either the VERO cell line or the MDCK (canine kidney) cell line. The viruses are inactivated by either formalin or β-propiolactone followed by purification processes. Most inactivated vaccines are split using a detergent which disrupts the viral envelope followed by further purification. The primary immunogen in inactivated vaccines is haemagglutinin and is the formally quantified antigen. There will also be varying amounts of neuraminidase (NA), viral protein M and NP.

Preparations for monovalent, bivalent, trivalent, quadrivalent and pentavalent influenza vaccines are produced.

2.5.1.1 Intradermal vaccines

ID vaccines are likely to improve immunogenicity due to the abundance of dendritic cells present in the dermis. There is one ID influenza vaccine available, sanofi pasteur’s Intanza® which is licenced for adults over 18 years of age.

2.5.2 Live attenuated influenza vaccine

There are currently three LAIVs available on the global market. These are produced by MedImmune (US), Russian Institute of Experimental Medicine (IEM) and the Serum Institute of India Ltd (SIIL).

The Russian Institute of Experimental Medicine (IEM) has been using LAIVs in adults since 1980 and in all ages since 1987, and currently more than 100 million doses have been distributed throughout Russia and the Commonwealth of Independent States. This vaccine has been tested in over 126 clinical trials involving over 500,000 adults (1). The WHO issued sub-licenses to the Russian technology to three global manufacturers, which include the SIIL who launched a WHO pre-qualified H1N1 pandemic vaccine (Nasovac®) in 2010.

The US licensed the MedImmune FluMist® in 2003 and over 50 million doses have been distributed since. In February 2012, the US FDA reviewed a supplemental biologicals licence application to modify the formulation of their trivalent LAIV to include a second B strain. The data for this modification were obtained from two pivotal studies, one in a paediatric population and the other in an adult population. There was also a study conducted in adults using a proprietary administration device (2).

2.5.2.1 The Quadrivalent Live Attenuated Influenza Vaccine (Q-LAIV, MedImmune)

Each dose of the quadrivalent vaccine Q/LAIV contains $10^{7.0} +/- 0.5$ FFU each of four cold-adapted attenuated temperature sensitive 6:2-reassortment influenza strains of A/H1N1, A/H3N2, B/Victoria lineage, B/Yamagata lineage. Excipients are monosodium glutamate, hydrolysed porcine gelatin, arginine, sucrose, dibasic potassium phosphate, and monobasic potassium phosphate. Each dose contains residual amounts of ovalbumin and may also contain residual amounts of gentamicin sulphate and ethylenediaminetetraacetic acid (EDTA). The proposed indication is for use in children aged two years to adults up to 49 years.

2.5.3 Adjuvanted influenza vaccine

As well as aluminum salts, there are three adjuvants that have been licensed for use in influenza vaccines. MF59 from Novartis, AS03 from GSK and immunopotentiating reconstituted influenza virosomes.

2.6 Study designs

The studies included in this update are meta-analysis, systematic reviews, reviews, randomised controlled trials, and observational studies using database matching. Conference abstracts have also been added.
3. Recent New Zealand epidemiology

The national influenza surveillance system in NZ is an essential public health component for assessing and implementing strategies to control influenza because influenza can cause substantial morbidity and mortality in a short space of time. The purpose of influenza surveillance is to collect, collate, analyse and disseminate information on influenza activity that will assist in the assessment, prevention and control of the morbidity and mortality associated with the infection and its complications. The national influenza surveillance in NZ aims at monitoring incidence and distribution of influenza, early detection of influenza epidemics and identifying the predominant circulating strains. The surveillance system includes sentinel general practice (GP) surveillance, laboratory-based surveillance, hospitalisations and mortality surveillance, and immunisation coverage surveillance.

Annual influenza immunisation is the primary method for reducing the impact of influenza in NZ. In 1997, the Ministry of Health made influenza vaccination available free to persons aged 65 years and older and in 1999, this policy was extended to risk groups less than 65 years (3).

This section summarises the community disease burden of influenza, the circulating influenza virus strains, hospitalisations, mortality, and immunisation coverage in recent years.

3.1 Overview of New Zealand epidemiology

3.1.1 Sentinel general practitioner based influenza surveillance

The sentinel general practitioner (GP) surveillance system was established in 1991 as part of the World Health Organisation (WHO) global programme for influenza surveillance. It is operated nationally by the Institute of Environmental Science and Research (ESR) and locally by surveillance coordinators within the public health unit in each district health board. The system operates in the winter, usually from May to September each year. It is based on a network of volunteer sentinel GPs distributed on a population density basis of about one per 50 000, covering roughly 10% of the NZ population. Figure 2 provides an example of population coverage by sentinel GP surveillance in 2006.

Figure 2. Percentage of population covered by sentinel GPs in New Zealand in 2006
Each sentinel practice records the daily number of consultations for influenza-like illness (ILI), along with the patient’s age group, on a standardised reporting form. The case definition used for ILI is an acute respiratory tract infection characterised by an abrupt onset of at least two of the following: fever, chills, headache and myalgia. These data are collected by the local co-ordinator by email, phone or fax each Friday. The consultation rates were calculated using the sum of the patient populations, reported by the participating practices, as the denominator. The denominator for the age-specific ILI rate calculation was based on the NZ census data with the assumption that age distribution of the GP patient population was the same as the NZ population, because the age-specific patient population data were not provided by the participating practices. In addition, each sentinel practice also collects three respiratory samples, as nasopharyngeal or throat swabs, each week from the first patient seen with an ILI on Monday, Tuesday and Wednesday of the week. These samples are forwarded to the WHO National Influenza Centre at ESR or one of three hospital laboratories in Auckland, Waikato and Christchurch for virus isolation and identification.

The criteria for a laboratory identification of influenza are the isolation of the virus or the direct detection of viral antigen. Influenza isolates are typed as being types A and B, and influenza A isolates are further subtyped as being AH1 and AH3. The virus isolation data are forwarded by hospital laboratories to ESR each Monday. ESR reports the national information on epidemiological and virological surveillance of influenza weekly, monthly and annually to relevant national and international levels, including the WHO Flunet (4).

The national weekly ILI consultation rates for 1997-2012, in comparison to 1992-1996, are shown in Figure 3 (5). During 1997-2012, the average annual cumulative incidence of ILI consultation for the winter period was 1741 per 100 000, ranging from 697 – 2124/100,000. This is lower than 2931 per 100 000 during 1992-1996. The average peak rate for 1997-2012 was 180 per 100 000, which was lower than 308 per 100 000 for 1992-1996.

Figure 3.
Weekly consultation rates for influenza-like illness in New Zealand, 1992-2012
Rates of consultations for ILI from sentinel surveillance were calculated for each age group. During 1997-2006, the average weekly ILI consultation rates in children <one, one to four years, five to 19 years were 117, 122 and 69 per 100,000, respectively. This was lower than 341, 275, and 134 per 100 000, respectively, for the same age groups during 1992 to 1996. For historical reasons, the ILI consultation rates for the elderly population were not consistent. The ILI consultation rate for persons 60+ years was provided during 1992 to 1999, whereas the ILI consultation rate for persons 65+ years was provided during 2000 to 2006. The average weekly ILI consultation rates for persons in 60+ years were 87 and 47 per 100,000 during the periods of 1992-1996 and 1997-1999, respectively. During 2000 to 2006, the average weekly ILI consultation rate for persons in 65+ years was 19 per 100,000. The average weekly ILI consultation rates for persons 20 to 59 years were 127 and 91 per 100 000 during the periods of 1992 to 1996 and 1997 to 1999, respectively. The average weekly ILI consultation rate for persons 20 to 64 was 45 per 100 000 during 2000 to 2006.

3.2 Laboratory based influenza surveillance

The National Influenza Centre (NIC) at ESR (previously the National Health Institute) was designated by the NZ Ministry of Health and recognized by the WHO in 1954. Since that time, the NIC at ESR has served as a key point of contact for both the WHO and Ministry of Health regarding virological and epidemiological surveillance of influenza, as well as the provision of influenza virus isolates to the WHO Global Influenza Surveillance Network.

The NIC and three hospital laboratories at Auckland, Waikato and Christchurch form a laboratory network. The NIC collates all-year-round laboratory testing information on influenza, nationally, mainly from hospital in-patient and outpatients. This laboratory network conducts strain surveillance (initial typing and sub-typing) for influenza from the respiratory specimens collected from sentinel GPs and non-sentinel (hospital) clinicians. The majority of influenza viruses are forwarded to the WHO Collaborating Centre in Melbourne for further characterization.

Figure 4 shows the number and percentage of typed and subtyped influenza viruses (not including A not subtyped) from 1990 to 2012. These isolates include those collected mainly from hospital in-patients and outpatients and those collected through the sentinel GP system.

![Influenza viruses by type and subtypes, 1990-2012*](image)

*2009 to 2011 A(H1N1) is influenza A(H1N1)pdm09
Overall, the patterns of the predominant strains during 1990-2012 are described below:

- Influenza A (H1N1)pdm09 strain has become the predominant strain in 2010 and 2009.

Figure 5 shows the number and percentage of all antigenically typed B viruses from 1990 to 2012. Since the introduction of the B-Victoria lineage viruses into NZ in 2002, this strain predominated over the B/Yamagata lineage viruses in every three years in NZ in 2002, 2005, 2008 and 2011.

Two distinct lines of influenza B have co-circulated in many countries during recent years. This dates from the late 1980s, when the B/Panama/45/90 variant of influenza B was first observed. This strain and its further variants of the Yamagata/16/88 lineage (most recently representative strain-B/Wisconsin/1/2010) spread worldwide, whereas strains of the previous B/Victoria/2/87-like viruses continued to circulate in Asia and subsequently underwent independent evolution as an antigenically distinct lineage (most recent representative strain-B/Brisbane/60/2008). For reasons not wholly understood, the B/Victoria/2/87 lineage viruses remained geographically restricted to Asia until 2001. In 2002, the B/Victoria/2/87 lineage viruses spread and became the predominant viruses worldwide. The B-Victoria lineage viruses were introduced into NZ in 2002. Since then, like many other countries, including Australia and South Africa, NZ has frequently recorded co-circulation of four antigenically distinct viruses: A (H1N1), A (H3N2), B/Yamagata lineage virus and B/Victoria lineage virus. The NZ influenza virus circulation pattern supports introduction of quadrivalent vaccine which contains these four antigenically distinct influenza viruses.

Figure 5. Influenza B antigenic types, 1990-2012
3.3 Influenza hospitalisations

Hospital admission data for influenza form the basis of influenza hospitalisation surveillance, based on the International Classification of Diseases (ICD; ninth and tenth revisions, ICD-9CM 487 or ICD-10AM J10-J11) from the NZ Health Information Service’s National Minimum Dataset (NMDS). Influenza-related hospitalisations were conservatively taken to include only those where influenza was the principal diagnosis.

The national ICD-coded influenza hospitalisation data (ICD-10AM codes J10-J11) showed that the influenza activity in 2012 was the third highest recorded between 1990 and 2012 (Figure 6). Influenza hospitalisation surveillance recorded an increasing trend during 1990-2012. The increase of influenza hospitalisation during 2009 – 2012 was largely due to sensitive Polymerase Chain Reaction (PCR) diagnostic assay replacing other traditional assay methods (rapid antigen testing and viral culture) and high level of A(H1N1)pdm09 circulation. Further analysis is required to understand all contributing factors to the increase in hospitalisation reports during 1990-2012, such as improvements in coding, more specimens being tested due to changes in hospital diagnostic practice, possible access problems in primary care, changes in admission criteria, changing demographics, predominance of AH3N2 viruses in many recent influenza seasons, predominance of A(H1N1)pdm09 viruses, and/or a true rise in influenza-like illness (6).

![Figure 6. ICD coded influenza hospitalisations, 1990-2012](image)

*Data from 1 Jan to 23 November 2012 only

During 1990-2006, the overall influenza hospitalisations showed a statistically significant increase in the trend (Poisson regression analysis, p<0.0001) (Figure 7). A total of 4087 influenza hospitalisations were recorded during 1997-2006. The average annual hospitalisation rate for influenza was 10.4 per 100 000 during 1997 to 2006, higher than 6.5 per 100 000 during 1990 to 1996. The first and second highest hospitalisations were 580 in 2003 and 518 in 1999 – both years predominated by influenza AH3N2.

![Figure 7. ICD coded influenza hospitalisations, 1990-2006](image)
When average hospitalisation rates among different age groups were compared for the two periods (1997-2006 versus 1990-1996), it was noted that children aged under one, one-four, five-19 years had a statistically significant increase of the average hospitalisation rate for 1997-2006 compared with 1990-1996 (Chi square test, p<0.0001) (Figure 8). High rates of hospitalisations among young children have also been reported in US (7, 8). New measures to prevent influenza-related hospitalisations among young children are needed. The average hospitalisation rate among persons 65+ years did not show a statistically significant difference between the two periods.

Figure 8. Comparison of influenza hospitalisation rates by age group
3.4 Influenza mortality

Deaths from influenza (ICD-9CM 487 or ICD-10AM J10-J11) from the NMDS constitute influenza mortality surveillance. These mortality data were only available up to 2010 (Figure 9).

The influenza mortality data were compared between 1997-2003 and 1990-1996. There were 82 influenza fatalities recorded for 1997-2003 (an average annual rate of 0.3 per 100 000), lower than that of 284 for 1990-1996 (an average annual rate of 1.1 per 100 000). In other words, influenza-related mortality has been reduced by 71% (202/284) during 1997-2003 compared to 1990-1996 (Chi square test, p<0.0001).

During 1997-2006, the highest number of deaths due to influenza was 27 in 1999 when influenza A/Sydney/5/97 (H3N2)-like viruses predominated.

During 1990-2003, the average annual death rate was markedly higher in those 65+ years (5.8 per 100 000) compared to those zero-64 years, counting for the majority of deaths (94%, 343/366). When average mortality rates among different age groups were compared for two periods (1997-2003 verse 1990-1996), it was noted that elderly persons 65+ years had statistically significant decrease of the influenza mortality rate (2.27/100 000) during 1997-2003 compared to the rate (9.38/100 000) of 1990-1996 (Chi square test, p<0.0001) (Figure 10).
Influenza mortality surveillance recorded an average annual mortality rate of 0.3 per 100,000 during 1997-2003, significantly lower than 1.1 per 100,000 during 1990-1996. ICD coded influenza deaths are useful for monitoring year-to-year trends and variability in the severity of influenza. However, they often underestimate the total burden of influenza because many deaths are caused by other secondary complications of influenza (8). Mills et al. assessed the aggregate burden of infectious disease in NZ in terms of mortality during 1980-1998 (6). They found that deaths attributable to infectious disease was stable or declined slightly during 1980-1996, with a further fall from 1996, almost all of which was due to a fall in mortality from infectious respiratory diseases. This fall could be an artifact of changes in coding practice in response to the NZ Health Information Service’s “Guide to writing Death Certificates”. This might have resulted in an increase in classifying chronic diseases as the primary cause of death and a reduction in pneumonias and “ill-defined” causes. However, a true decrease of influenza mortality since 1997 cannot be excluded. Further studies, including modelling, are required to provide a more accurate estimation of the burden of influenza on mortality in NZ.

Introduction of routine influenza vaccination among the NZ elderly was associated with a significant decrease of influenza mortality. A statistical association cannot be taken as proof of cause and cannot be used make claim that the policy changes resulting in greater uptake of the influenza vaccine is directly responsible for the decrease in mortality. However, the observed inverse relationship gives some justifications to speculate that this might be so. Further studies on the vaccine effectiveness are needed to understand the extent of beneficial effect of vaccination in NZ. The effectiveness of influenza vaccination in reducing influenza related mortality in the elderly is currently under debate (7, 9). Influenza vaccination has been reported to be highly effective at reducing influenza-related mortality in elderly people (10-12), although Simonsen et al. reported no improvement in influenza-related mortality in the elderly in the US, despite increasing influenza vaccination coverage (13). Despite the current scientific debate, people aged 65 years and older should continue to receive influenza vaccination every year, since the burden of influenza in this group is high, and even modest protection for severe outcomes is certainly better than none at all.

3.5 Influenza immunisation

In 1997, influenza vaccination was made available free to those 65+ years and in 1999 free vaccination was extended to risk groups less than 65 years. The data that medical practitioners provide to Health Benefits Limited to claim reimbursement are used to estimate coverage in these two groups. The denominator for the vaccine uptake rate was based on the NZ census data for intervening years. Figure 11 shows estimated influenza vaccine uptake during 1990-2011. Since 1997, when immunisation benefit claim data became available, influenza immunization rates among those aged 65+ years were estimated to increase from 39% in 1997, 55% in 1999 and 62% in 2002 (14). The average annual vaccine uptake was 156 doses per 1000 during 1997 to 2006, three times higher than 50 doses per 1000 during 1990 to 1996 (5).
3.6 Influenza vaccine strain selection

Optimal vaccine efficacy is dependent upon achieving a close antigenic match between the vaccine and circulating strains. Achieving this close match is possible through the WHO Global Influenza Surveillance and Response System (GISRS). NZ has been an active participant of GISRS since 1954. As a result, some influenza isolates, such as A/Wellington/1/2004 have been selected as vaccine strains in the past.

A combination of antigenic and genetic analyses is used to identify emergent antigenic variants of potential future epidemic importance and for consideration of their inclusion in vaccines. Antigenic relationships among contemporary viruses and vaccine strains are of prime importance in determining vaccine composition. These relationships are evaluated mainly in haemagglutination inhibition (HI) tests using post-infection ferret sera against egg and/or cell grown reference and vaccine viruses using red blood cells principally from turkeys but also from other species, as appropriate. Virus neutralisation tests provide complementary data. Antigenic cartography is used as an additional analytical tool to visualise and integrate antigenic data. Phylogenetic analyses of HA and NA genes help to define the genetic relatedness of antigenic variants to their predecessors and to elucidate the molecular basis for antigenic drift. The spread of antigenic variants associated with influenza outbreaks in different countries is also an important criterion for selection of epidemiologically relevant vaccine candidates.

The World Health Organization (WHO) makes twice-yearly recommendations to guide national/regional authorities on the formulation of influenza vaccines. One recommendation is made in February for the northern hemisphere winter and another recommendation is made in September for the southern hemisphere winter.

It should be noted that the WHO recommendations are made with respect to reference strains which may or may not be suitable for vaccine production. Thus, even where the WHO recommendation is adopted, it is necessary for country/regional authorities to approve the specific vaccine strains to be used and this, in turn, requires the preparation of specific reagents for vaccine standardisation.

Since 1969, the Australian Influenza Vaccine Committee (AIVC), with representatives from NZ, Australia and South Africa, has met annually in October to approve or update the WHO recommended formulation for influenza vaccines intended for the following winter (March to September of the following year) for these countries. NZ uses the influenza vaccine strains recommended by AIVC in the subsequent year. Table 1 shows influenza vaccine recommendations for NZ during 1991-2013.

3.7 Summary New Zealand influenza epidemiology

In summary, this section compares the main influenza surveillance data sources in recent years. The impact of influenza in NZ over the past 20 influenza seasons has been substantial in terms of GP consultations, hospitalisations and deaths. The 1997 policy change of influenza vaccination was associated with a significant reduction of influenza mortality in elderly population. High ILI consultation rates as well as high hospitalisations among young children aged <1 year and 1-4 years were reported. New measures to prevent influenza-related hospitalisations among young children are needed. Since 2002, influenza virus strain surveillance in NZ has frequently recorded co-circulation of four antigenically distinct viruses: A(H1N1), A(H3N2), B/Yamagata lineage and B/Victoria lineage virus. The NZ influenza virus circulation pattern supports introduction of quadrivalent vaccine which contains these four antigenically distinct influenza viruses.

This report demonstrates that an integrated virological and epidemiological surveillance system for influenza is essential for monitoring the disease burden, identifying circulating strains, guiding effective vaccination and planning for a potential pandemic.
### Table 1. Influenza vaccine recommendations for New Zealand, 1991-2013

<table>
<thead>
<tr>
<th>Formulation Recommendations</th>
<th>Vaccine used</th>
<th>A H3N2</th>
<th>A H1N1</th>
<th>B</th>
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<tr>
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<td>A/New Caledonia/20/99</td>
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<td>2001</td>
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<td>A/New Caledonia/20/99</td>
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<td>A/Singapore/6/86</td>
<td>B/Yamagata/16/88</td>
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</tbody>
</table>

* WHO recommendations are for the Southern Hemisphere winter; ** WHO recommendations are for the Northern Hemisphere winter; ***USA selected the variant A/Texas/36/91
4. Safety

4.1 Objective

The objective of this section is to review the most recent safety data for currently licenced influenza vaccines excluding pandemic vaccines. The focus is on new information since the publication of the 2011 Immunisation Handbook, and on the new generation vaccines with some consideration for any recent updates to TIV. Only Adverse Events Following Immunisation (AEFI) that have been considered subsequent to the pivotal clinical efficacy trials are reviewed here and any major clinical differences between vaccine types.

4.2 Outcomes

Outcomes are vaccine safety including adverse events following immunisation (AEFI) and serious adverse events (SAE). Excluded is reactogenicity (injection site reactions and minor systemic reactions) as these are thoroughly considered in the pivotal licensure studies (15-17).

4.3 Review

4.3.1 Safety of inactivated influenza vaccines

Recent Cochrane reviews have been conducted on the safety of TIV in healthy children, healthy adults, healthcare workers who work with the elderly and the elderly (16-18).

Large post licensure studies in the US among children enrolled in health maintenance organisations strongly support the overall safety profile of TIV with few serious health events in adults and children (19-25). However, after initial licensure, there has been less focus on the reactogenicity profile with minimal attention given to the possible effects of changing antigenic composition and different immunogenicity and safety profiles across different brands (26).

The antigenic presentation of seasonal influenza vaccines changes almost every year. Extensive data from passive surveillance systems and epidemiological studies supports the overall safety profile of TIV with few serious health events in adults and children (19-25). However, after initial licensure, there has been less focus on the reactogenicity profile with minimal attention given to the possible effects of changing antigenic composition and different immunogenicity and safety profiles across different brands (26).

Furthermore large scale clinical studies evaluating influenza vaccine in children are lacking (17). Having robust data on the safety profile of vaccines and to be able to communicate this rapidly and transparently is important for making informed decisions about vaccine indications and recommendations, and the maintenance of public confidence in vaccines. A lack of paediatric clinical data and the limitations of passive post licensing safety surveillance systems can make this a difficult task (27).

4.3.1.1 Febrile events

In 2010, a single brand of trivalent seasonal influenza vaccine, Fluvax® and Fluvax Junior®, from CSL, was found to be highly pyrogenic in young children, primarily, aged five years and under, a problem that resulted in the temporary suspension of the use of all brands of influenza vaccine in Australian children (28, 29). The rate of febrile convulsion in Australian children under five years of age following this brand of TIV was estimated to be 3.3 per 1000 doses based on passive surveillance notifications, emergency department presentations and a small retrospective survey (30).

A NZ retrospective telephone survey, of parents of infants and children (4088 doses) who received at least one dose of the vaccines of interest, found a risk for febrile convulsive seizure of 35 per 10,000 doses among children aged six months to eight years within 24 hours of receiving Fluvax® vaccine. There were no cases of convulsion following 3223 doses of other vaccine brands. Febrile events within 24 hours of vaccination were significantly more common following Fluvax® and to a lesser extent Influvac®. In addition, when fevers were measured, they were more likely to be higher in the Fluvax® recipients. Febrile events within 24 hours of vaccination were significantly more common following Fluvax® and to a lesser extent Influvax®. In addition, when fevers were measured, they were more likely to be higher in the Fluvax® recipients. Recipients of Fluvax® were more likely to seek medical advice and emergency assistance. Data for older children suggested this problem extended beyond age five albeit to a lesser extent. Of 4088 doses given, 865 were Fluvax®, 2571 Vaxigrip®, 204 Influvax®, 438 Fluarix® and 10 Celvapan. Three febrile convulsions followed Fluvax®, a rate of 35 per 10,000 doses. No convulsions occurred following any dose of the other vaccines. There were nine febrile events that included rigors, all following Fluvax®. Fever occurred significantly more frequently following administration of Fluvax® compared with the other brands of vaccines (p<0.0001) and Fluvax® recipients were more likely to seek medical attention. Influvax® also had higher rates of febrile reactions (OR 0.54, 95% CI 0.36-0.81) than...
the other two brands Vaxigrip® (OR 0.21, 95% CI 0.16-0.27) and Fluarix® (OR 0.10, 95% CI 0.05-0.20). After multivariable analysis vaccine, European ethnicity and second dose of vaccine were significantly associated with reporting of fever within 24 hours of vaccination (31).

After febrile convulsions were seen to be associated with 2010 inactivated influenza vaccine administered in the Southern Hemisphere, near real time surveillance was conducted in the US using the Vaccine Safety Datalink Project. Concomitant administration of PCV-13 with inactivated influenza vaccine doubled the incidence risk ratio from 2.4 and 2.5 respectively to 5.9 when given together in this age group (32).

4.3.1.2 Guillain-Barré Syndrome

Conclusions from the most recent Cochrane review of influenza vaccines in health adults found 1.6 cases of Guillain-Barré syndrome (GBS) per million vaccinations (16). There have been a number of studies investigating the association of the recent pandemic vaccine preparations with GBS, particularly in view of the risk associated with the 1976 pandemic swine influenza. An excess risk with the 2009-2010 H1N1 was found among 45 million residents in the US of 0.74 additional cases per million doses of vaccine (95% CI 0.04-1.56) which is in line with estimates for seasonal vaccines (33). Using the same population, the US CDC estimated the attributable risk for GBS associated with 2009-2010 vaccines to be 1.5 (95% CI 0.3 – 3.4) and 2.8 (95% CI 0.6 – 7.4) depending on the analyses method – similar to seasonal influenza (34).

4.3.1.3 Infants and toddlers

4.3.1.3.1 Infants under six months of age

A double blind, randomised, placebo-controlled trial among 1375 healthy infants aged 6-12 weeks of age receiving two doses of sanofi pasteur’s Fluzone® vaccine, one month apart in combination with scheduled vaccines, found no significant differences between TIV and placebo groups for any safety outcome (35).

4.3.1.3.2 Children two to sixteen years

The 2012 Cochrane review of vaccines for preventing influenza in healthy children assessed 75 studies with 300,000 observations. Variability in study designs and presentation of data made meta-analysis of the safety data impossible (17).

4.3.1.4 Preterm infants

Infants and children born prematurely are at higher risk of influenza-related complications. TIV has been demonstrated to be well tolerated in infants and toddlers aged six months to 17 months who have been born prematurely (36).

4.3.1.5 Pregnant women and their infants

Influenza vaccines have been recommend for and used in pregnant women since the 1960s and there is considerable safety data. A review of the available data supports a good safety profile of influenza vaccines in pregnant women and no concerns with regard to fetal and neonatal outcomes have been identified (37).

4.3.2 Safety of live attenuated influenza vaccine

4.3.2.1 Safety of LAIV in adults

Since the initial clinical trials of LAIV there have been more than 50 million doses administered in the US. The most common reactions to LAIV in adults are runny nose, headache and a sore throat (38). Reactions are less likely after subsequent doses (39). A post marketing evaluation databases of the safety of the MedImmune Ann Arbor strain of LIAV in adults (18-49 years) using the Kaiser Permanente assessed medically attended events and serious adverse events in LAIV recipients with a range of control methods. The study included 21,340 LAIV vaccinees, 18,316 TIV vaccinees and 21,340 unvaccinated persons. There were no medically attended events or serious adverse events suggesting an excellent safety record associated with LIAV. There were two serious events, migraine/sinusitis and Bell’s palsy, which were considered possibly or probably related to the LIAV (40).

4.3.2.1.1 Safety of LAIV in pregnant women

In a search of the VAERS database for adverse events in pregnant women receiving influenza vaccines, 148 had received TIV and 27 had received LAIV. The most common pregnancy-specific event was spontaneous abortion. There were 17 (11.5%) after TIV and 3 (11%) after LAIV. There were no unusual patterns of pregnancy complications or fetal outcomes associated with either vaccine type (41). Data from a health insurance database of 50 million individuals found cases where women had been pregnant and received the LAIV. All outcomes were from LAIV exposure occurred at rates similar to those observed in
unvaccinated women (42). During the pivotal studies eight pregnancies were reported. Seven received the vaccine and pregnancy outcomes were known for six of these women, all delivered healthy babies (2).

4.3.2.2 Safety of LAIV in infants and children

4.3.2.2.1 Safety of LAIV in children with precautions against use

The original clinical review of FluMist® in 2003 indicated that children aged between 18 months and five years of age who received LAIV were more likely to experience asthma or reactive airway symptoms in the 42 days following vaccination in one study. This was identified as a potential safety signal and a precaution against using the vaccine on subjects with a history of asthma was issued until further evaluation occurred (2).

When the US approved LAIV for children aged 24 to 59 months, there were precautions against use in children under 24 months, children with recurrent wheezing, asthma and altered immunocompetence. A post marketing evaluation was conducted to assess the safety of LIAV in these non-recommended children. There were 675 children under two (126 under six months). There was a trend for fewer LIAV recipients among asthmatics and among children with wheezing the rates of administration were similar to children without this precaution. There were 57 immunocompromised children vaccinated with LAIV. This study found that over two seasons in this cohort of children not recommended to receive LAIV there were no safety signals identified. Rare events could not be excluded due to the relatively small numbers (43).

4.3.2.3 Safety of Q/LAIV

The safety of Q/LAIV was assessed in 1198 adults 18-49 years receiving the vaccine via the BD Accuspray™ delivery device or another proprietary device, and 1382 children, also receiving the vaccine via the BD Accuspray™. In the paediatric studies, 299 subjects received one dose and 1083 received two doses. Solicited events were monitored for 14 days and serious and non-solicited events were monitored until day 28. In addition, specific events of interest (such as serious events and new onset chronic disease) were monitored for six months. No major safety concerns were identified (2).

There have been no studies evaluating concomitant administration of other vaccines with Q/LAIV or evaluations of Q-LAIV in children younger than two years of age due to previous associations of wheezing in this age group with the trivalent LAIV (2).

4.3.2.4 Safety of LIAV in immunocompromised persons

In a small randomised placebo controlled trial of LAIV in 20 children with cancer, aged five-17 years who were mild to moderately immunocompromised, no serious adverse events were reported and prolonged viral shedding was not detected. Immunogenicity was moderate (<50%, over four-fold rise) (46).

A randomised study compared the safety of LAIV compared with TIV among 55 participants aged two-21 years with mild to moderate immunosuppression (mean age 10 years). Prolonged viral shedding was not detected and the vaccine was well tolerated (47).

4.3.3 Safety of adjuvanted influenza vaccine

4.3.3.1 Narcolepsy

In August 2010, concerns that narcolepsy could be a side effect of the monovalent pandemic H1N1 influenza vaccine, Pandemrix™ (GSK, monovalent ASO3-adjuvanted), were raised in reports from Finland and Sweden (48). The findings in Finland concluded that the risk of narcolepsy in the four to 19 age group was nine times higher than in the same age group who were unvaccinated (49, 50). Children under four years old or adults over 19 years showed no increased incidence of narcolepsy (48).

Narcolepsy has its typical onset in adolescence and young adulthood.
Narcolepsy is a condition that has a strong genetic linkage, being seen in those who have the (HLA) HLA-DRB1*1501-DQB1*0602 genotype. In Finland, all the cases of narcolepsy tested had that genotype (50).

It does not appear that reports of narcolepsy following vaccination against pandemic influenza occurred in all countries where Pandemrix™ was used, and countries who used other pandemic vaccines did not record an increase in narcolepsy cases (50). No case of narcolepsy and no evidence of an increased risk of sleep-related adverse events were found in recipients of MF59-adjuvanted A (H1N1) pandemic and other MF59-adjuvanted influenza vaccines (51).

In China, a retrospective analysis of diagnoses occurring 1998–2010, found a three times increase in narcolepsy following the 2009 H1N1 winter influenza pandemic. Only 8 of 142 (5.6%) patients recalled receiving an H1N1 vaccination, therefore this increase could not be explained by vaccination. Narcolepsy onset is highly correlated with seasonal and annual patterns of upper airway infections, including H1N1 influenza (52). Studies have found evidence that streptococcal infections are probably a significant trigger for narcolepsy (49, 52, 53). Difficulty in documenting a specific association between narcolepsy onset and H1N1 infection or vaccination occurs because many of the population were either vaccinated or had H1N1 infection (49).

A temporal link between vaccination and disease onset may be confounded by an increased awareness of narcolepsy, faster diagnosis and increased identification of cases (49). An increased risk of narcolepsy has not been observed in association with the use of any vaccines whether against influenza or other diseases in the past (50).

4.3.3.2 Egg allergy

The current US Centers for Disease Control and Prevention (CDC) advice is that, for persons with a history of egg allergy who have experienced only hives, vaccination should be with TIV rather than LAIV and observation for at least 30 minutes after vaccination (54). Those who have had reactions to egg protein that include angioedema, respiratory distress, light-headedness, recurrent vomiting or who have required emergency adrenalin intervention are more likely to have a systemic or anaphylactic reaction and should be referred. Algorithms have been developed and advise that those who can eat lightly cooked egg without reaction or with only hives can be vaccinated; those who experience other symptoms such as cardiovascular changes, respiratory distress or gastrointestinal symptoms require further evaluation (54).

4.4 Summary vaccine safety

Overall, TIV influenza vaccines have an extensive and excellent safety record when used in populations including pregnant women. Three issues for safety arose over the past two years, largely, as an indirect result of the 2009 pandemic. One was the finding that seasonal trivalent inactivated influenza vaccines can cause significant febrile events in children. This observation was associated primarily with CSL’s TIV influenza vaccine that contained the pandemic H1N1 strain; however, other brands were also associated with higher rates of febrile events. There was also a slightly higher risk for febrile convulsions associated with the co-administration of TIV and pneumococcal vaccine.

There appears to be a small excess in risk for GBS following influenza vaccination, at less than one additional case per million persons; the risk from influenza infection is much greater.

The important issue of note around the use of LAIV vaccines is the possible risk for wheezing events in recipients less than two years of age, which has led to the exclusion of this age group in the recommendations for use of the vaccine. More data is required to clarify the risks for this group. There are no issues identified when administering LAIV in mild to moderately immunocompromised children. There is limited published data on the safety of the Nasovac™ LAIV.

In 2010, an association between one adjuvanted H1N1 pandemic vaccine and narcolepsy was found. There is now data from a number of countries that together support a temporal link. However, it is possible that the onset of narcolepsy may be confounded by other factors and further data is still required to confirm a causal link.
5. Immunogenicity, efficacy, effectiveness and vaccine impact

5.1 Objective

The objective of this section is to review the most recent performance data for currently licenced influenza vaccines. The focus is on the new generation vaccines with some consideration for any recent updates to TIV. Consideration is given to relevant immunogenicity data, efficacy and effectiveness studies that contribute to the current understanding of the effectiveness of influenza vaccines and evidence of their impact in populations.

5.2 Outcomes

The outcomes considered for this review are:

- Influenza-like illness
- Laboratory confirmed influenza
- Pneumonia
- Otitis media.
- Immunogenicity
- Community immunity (herd immunity)
- Hospitalisations
- Duration of protection

5.3 Review

There are a range of factors that affect the efficacy and effectiveness of influenza vaccination as well as the measurements of these outcomes.

- Antigenic similarity between the vaccine strains and those that are circulating.
- Location of the study – variability in intensity of transmission and predominant circulating strains.
- Annual illness rates.
- Specificity of the outcome being measured in the study.
- Highly specific laboratory confirmation.
- Clinical outcomes such as ILI or influenza related visits, hospitalisations or deaths.

- Immunocompetence of the vaccine recipient.
- Study design
  - Randomised control trials (RCT) with laboratory confirmed influenza as the outcome are difficult to conduct among groups for whom the vaccine is already recommended.

The more specific outcomes tend to be associated with higher estimates of efficacy.

The 2012 Cochrane review of influenza vaccines in healthy children could find no evidence for effects in children aged two years or younger (17).

Based on observations of around 20,000 children in randomised studies, the inactivated vaccines have an overall efficacy against influenza of 59%. To prevent one case of influenza, 28 children, over the age of 6 years, need to be vaccinated for inactivated vaccines. Estimates from cohort studies have a higher estimate of up to 64% efficacy and 56% effectiveness. For other outcomes, such as school absences, outpatient attendance, AOM or socioeconomic impact there is little evidence (17).

Generally, vaccine effectiveness is in the range of 50-80% for older children and healthy adults with limited data available for other age groups.

5.3.1 Immunogenicity

There is no known immune correlate of protection for influenza vaccines. However, anti-haemagglutinin antibody titres of 1:32 to 1:40 following inactivated influenza vaccine represent a level at which around half of individuals are likely to be protected. These measures appear to underestimate the clinical efficacy and effectiveness of LAIV.

5.3.1.1 Immunogenicity of inactivated vaccines

The vigour of the serum antibody response to inactivated vaccines is dependent on age and pre-existing antibodies. In previously primed persons, the response is primarily IgG and in un-primed children IgM may dominate. The numbers of influenza-specific plasma cells in peripheral blood peak around one week after vaccination, followed by peak antibody
levels at two to four weeks in previously primed healthy vaccinees. In the elderly and un-primed persons, this peak occurs at around four weeks.

Intramuscular (IM) administration of TIV may induce local influenza virus-specific IgA of oral and respiratory secretions and this response is stronger in persons primed by natural infection (55).

It appears that increasing the amount of HA increases serum antibody in a dose dependent manner. This is also observed in the elderly (56-59). As of 2013, studies are being conducted to determine if the higher titres predict better effectiveness.

Cytotoxic T-cells (CTL) are important in the immunity to influenza. The cellular response to TIV is influenced by age, type of vaccine and pre-vaccination immune status. While whole-virion vaccines induce good responses, subunit vaccines induce relatively poor CTL responses with the duration lasting from one month to one year. CTL responses are poorer in the elderly (60-62).

5.3.1.1.1 Immunogenicity of intradermal vaccines

In a meta-analysis of intradermal (ID) influenza vaccines, comparing immunogenicity of ID and IM administration, there was no overall significant difference in geometric mean titres (GMT) between the two administration strategies. There was an association between increasing doses of ID vaccine and increasing immunogenicity (p=0.01). Higher doses of ID vaccine in older populations produced a higher response (63).

5.3.1.1.2 Immunogenicity of adjuvanted vaccines

A range of adjuvanted vaccines have been trialled, particularly in monovalent pandemic antigen preparations, for example, in a H1N1 monovalent vaccine trial, a 3.75µg MF59 adjuvanted vaccine was compared with a 15µg unadjuvanted vaccine in healthy adults. This immunogenicity study with 60 patients given unadjuvanted and 46 given adjuvanted vaccine showed no significant difference in GMT at one month post vaccination, and higher seroprotection rates at six and 10 months post vaccination for the adjuvanted vaccine. The authors concluded that low dose MF50 adjuvanted vaccine might induce excellent long-term immunity that is comparable to convention vaccines in healthy adults aged 18-64 years (64). In general, adjuvanted vaccines appear to elicit a more robust response in the elderly ≥65 years and second doses of adjuvanted vaccines boost titres effectively in adults and the elderly giving increases in the durability of immune responses at six months (65). Adjuvanted vaccines have also been trialled with H1N1 monovalent vaccines in children: a Japanese study using ASO3 adjuvanted H1N1 vaccine in children aged six months to 17 years in a two dose regime showed strong immune responses persistent up to six months (66). Data on the effectiveness of adjuvanted vaccines in children under two years of age is still limited (67).

5.3.1.2 Immunogenicity of inactivated vaccines in infants under six months

A double blind, randomised, placebo-controlled trial among 1375 healthy infants aged six-12 weeks of age, receiving two doses of sanofi pasteur’s Fluzone™ vaccine one month apart in combination with scheduled vaccines, found increased influenza-specific antibodies in TIV recipients against all three vaccine strains compared with placebo recipients (p<0.001). Over 90% of TIV recipients had antibody ≥1:40 for at least one vaccine strain and 50% for two strains compared to 16% and 1%, respectively, in the placebo groups (35).

5.3.1.3 Immunogenicity of live attenuated vaccines

LAIV do not induce the same type of immune response as TIV. TIV induce humoral responses, primarily, and associated circulating antibodies, whereas, LAIV induce both humoral and cellular immunity. The traditional measures of immune response are not as applicable to LAIV as they are to TIV, partly because of the mucosal immunity that LAIV generate. Although these vaccines have been demonstrated highly efficacious at preventing influenza infection, there are no well-established serological correlates of infection. Currently, the WHO recommends that when evaluating the immunogenicity of LAIV, it is appropriate to demonstrate serological response in most vaccinees (68). While the HAI antibody is the best measure of a correlate of protection, vaccine failures can occur in persons with high titres. These titres are not alone sufficient for determining vaccine efficacy, therefore, there is no absolute correlate of protection (69).

The current measure, a serum haemagglutinin inhibition (HAI) antibody titre of 1:40 (or 1:32), is the 50% protective titre.
5.3.1.4 Immunogenicity of Nasovac S Live attenuated monovalent nasal delivery (pandemic strain H1N1)

The immunogenicity of Nasovac S is in line with other LAIV with seroconversion rates among adults for H1N1 of 43%, N3N2 of 64% to 72% and B 64% to 72%. In children the seroconversion rates are 52% to 55% for N1N1, 61% to 75% for N3N2 and 90% for B. Similar rates were reported in subjects over 49 years (unpublished data 2012).

5.3.1.5 Immunogenicity of Quadrivalent FluMist (Q/LAIV)

5.3.1.5.1 Quadrivalent live attenuated influenza vaccine

The immunogenicity of a quadrivalent LAIV (Ann Arbor strain, MedImmune) was assessed in a randomised double blind study using two TIV vaccines with different ‘B’ lineages and an investigational quadrivalent vaccine in children aged two to 17 years of age. The immunogenicity of the Q/LAIV was non-superior to that of the T/LAIV (44).

The efficacy of Q/LAIV was inferred based on non-inferiority to HAI antibody responses to two formulations of trivalent FluMist®, each with a different B strain. The primary endpoint was an upper bound of the 95% confidence interval (CI) of the ratio of HAI Geometric Mean Titres (GMT) for trivalent FluMist® divided by Q/LAIV of < 1.5 for all 4 strains included in the Q/LAIV. The endpoints were all met (2). However, as noted above, compared with inactivated vaccines the HAI for LAIV can be relatively low despite the vaccine being relatively efficacious.

5.3.2 Protection against disease outcomes

5.3.2.1 Protection provided by inactivated trivalent influenza vaccines

5.3.2.1.1 Infants and children

There is evidence to support moderate effectiveness of TIV in children three years of age and over with a number of studies recommending two doses for younger children who are previously unvaccinated. The current data for vaccine efficacy and effectiveness in infants and children is summarised in Table 2.

Table 2. Recent TIV vaccine efficacy and effectiveness studies conducted in infants and children. Adapted from Vaccines 6th edition (70) and updated as of 2012.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population age</th>
<th>Study design</th>
<th>Study years</th>
<th>Outcomes and VE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jefferson 2012 (17)</td>
<td>Under two years</td>
<td>Systematic review</td>
<td>N/A</td>
<td>Insufficient data to support VE against LCI</td>
</tr>
<tr>
<td>Cochran 2010 (71)</td>
<td>6-23 months</td>
<td>Retrospective cohort</td>
<td>2003-2006</td>
<td>76% VE against LCI 2005-6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No effectiveness 2003-4 or 2004-5</td>
</tr>
<tr>
<td>Heinonen 2011 (72)</td>
<td>9 months to 3 years</td>
<td>Prospective cohort</td>
<td>2007-2008</td>
<td>66% VE against ILI</td>
</tr>
<tr>
<td>Kelly 2011 (73)</td>
<td>6-59 months</td>
<td>Case-control</td>
<td>2008</td>
<td>58% VE against medical visits; test negative control design</td>
</tr>
<tr>
<td>Vesikari 2011 (74)</td>
<td>6-71 months</td>
<td>RPCT</td>
<td>2007-8 and 2008-9</td>
<td>43% (CI 15-61%) VE against PCR-confirmed influenza (unadjuvanted) 86% (CI74-93%) VE (MF59-adjuvated vaccine)</td>
</tr>
<tr>
<td>Jefferson 2012 / 2008 (17, 75)</td>
<td>Under 16 years</td>
<td>Systematic review and meta-analysis</td>
<td>N/A</td>
<td>59% (41% - 71%) efficacy against LCI 36% (24% - 46%) effectiveness against ILI</td>
</tr>
</tbody>
</table>
5.3.2.1.2 Healthy adults under 65 years of age.

Generally, randomised placebo controlled trials of TIV in healthy adults support good protection against a variety of outcomes, particularly laboratory confirmed influenza. The effectiveness is predictably lower during seasons where the vaccine strains are not well matched to those that are circulating. The current data for the efficacy and effectiveness of TIV in healthy adults is summarised in Table 3.

Table 3. Recent TIV vaccine efficacy and effectiveness studies conducted in adults under 65 years of age. Adapted from Vaccines 6th edition (70) and updated as of 2012.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population age</th>
<th>Study design</th>
<th>Study years</th>
<th>Outcomes and VE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jefferson 2010 (16)</td>
<td>16-65</td>
<td>Meta-analysis</td>
<td>NA</td>
<td>30% (17%-41%) VE against ILI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>73% (CI 54%-84%) VE against influenza symptoms</td>
</tr>
<tr>
<td>Osterholm 2012 (76)</td>
<td>18-65 years</td>
<td>Systematic review and meta-analysis</td>
<td>N/A</td>
<td>59% (CI 51%-67%) Efficacy against influenza</td>
</tr>
<tr>
<td>Monto 2009 (77)</td>
<td>18-49</td>
<td>RPCT</td>
<td>2007-2008</td>
<td>68% VE against LCI</td>
</tr>
<tr>
<td>Beran 2009 (78)</td>
<td>18-64</td>
<td>RPCT</td>
<td>2006-2007</td>
<td>62% VE against LCI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>67% VE against vaccine matched strains</td>
</tr>
<tr>
<td>Jackson 2010 (79)</td>
<td>18-49</td>
<td>RPCT</td>
<td>2005-6 2006-7</td>
<td>49% VE against CCI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>63% VE against C or SCI</td>
</tr>
<tr>
<td>Barrett 2011 (80)</td>
<td>18-49</td>
<td>RPCT</td>
<td>2008-2009</td>
<td>78% VE against matched, CCI</td>
</tr>
</tbody>
</table>

ILI – influenza-like illness; CCI - culture confirmed influenza; SCI - serologically confirmed influenza; LCI – laboratory confirmed influenza; RPCT – randomised placebo controlled trial

5.3.2.1.3 Older adults over 60 years of age

Only one randomised placebo-controlled trial on the efficacy of inactivated influenza vaccine has ever been reported among elderly persons. The trial investigated a quadrivalent vaccine administered to 1838 Dutch participants aged over 60 years in 1991 to 1992. This study found a halving of the risk for serological influenza in the vaccinated group (RR 0.5; 95% CI 0.35-0.61) (81). There is an overall lack of high quality data to support the effectiveness of TIV in older adults (15).

5.3.2.2 Additional protection from quadrivalent inactivated vaccines

Due to challenges in accurately predicting which influenza B lineage will be circulating in a given season, the addition of a second B lineage is expected to improve the vaccine effectiveness. US data on the annual incidence of influenza-associated outcomes over 10 years, analysed virological circulation, vaccine coverage and vaccine effectiveness to assess the potential public health impact of including a second B-strain in the seasonal influenza vaccine. The study concluded a modest reduction in influenza-associated outcomes would result from the addition of the second influenza B lineage (82). Clinical trials to assess the efficacy and effectiveness on the quadrivalent inactivated vaccines are in progress (32).

5.3.2.3 Protection provided by live attenuated influenza vaccines

Randomised controlled trials of LAIV usually favour the vaccine when compared with placebo or no intervention (17).

5.3.2.3.1 Live attenuated vaccine in children

A 2012 meta-analysis of the efficacy and effectiveness of influenza vaccines found the pooled efficacy, from 10 RCT of LAIV in children aged six months to seven years, to be 83% (95% CI 69%-91%). There were no such trials for children aged eight to 17 years (76). Another 2012 meta-analysis of nine RCT, which included children aged 6 months to 17 years, reports an efficacy for LAIVs against placebo of 83% (95% CI 78%-87%) and efficacy against TIV of 44-48% (83).

In a RCT of 3200 children aged six months to 36 months, the efficacy of one versus two doses of LAIV against influenza was assessed. Vaccine efficacy against similar strains was 73.5% after two doses and 57.7% after one dose. In the second year, the efficacy in those who received two doses in the first year was 73.6% and 65% in those who received one dose in the first year. In participants who received two doses in year one and a placebo in year two, the year two efficacy was 57% (84).
5.3.2.3.2 Live attenuated vaccine in adults

An effectiveness study of more than one million active duty non-recruit military service members, aged 17 to 49 years who were stationed in the US for the three season study period of 2004 to 2007, were assessed for incidence of healthcare encounters that resulted in a primary diagnosis code consistent with pneumonia or influenza. In all three seasons, TIV vaccination was associated with lower incidence of pneumonia and influenza compared with no immunisation, and in the 2006 to 2007 season, LAIV was associated with lower rates than TIV. However, overall among this population LAIV was associated with less effect than TIV, primarily in persons who had been annually vaccinated with TIV (85).

LAIV elicits a more robust immune response and increased viral replication in unprimed subjects. A comparison, over the same time period of military recruits who are immunised annually against influenza and non-recruits who have a very low uptake of annual influenza vaccine, found that TIV provided better protection among non-recruits and LAIV provided better protection in recruits. The proposed reason for this is that the recruit population was more naïve to influenza than the non-recruits. The study concluded that in adult populations who are relatively naïve to influenza the LAIV should be preferentially used and in adults regularly immunised with TIV, a preference for TIV was indicated (86).

5.3.2.4 Nasovac S

There is currently little efficacy data available for Nasovac S and none has yet been published (87). The safety data are discussed in 4.3.2. Much of the data around the likely efficacy of this vaccine comes from the Russian parent vaccine for which there is 50 years’ worth of data (1). In a published placebo controlled trial that randomised schools to vaccine or placebo over two years, efficacy ranged between 24% to 52% in 1990, depending on the age group of the children, and 22% to 40% in 1991. Herd immunity was also observed (88). As of early 2013, clinical studies evaluating Nasovac® are underway (89).

5.3.3 Herd immunity

Influenza vaccination has been demonstrated to provide herd immunity. Vaccination of those most likely to acquire and transmit influenza may reduce the overall occurrence of influenza in the community. It is likely that high coverage rates (>80%) are needed in order to achieve this (90). There are a number of studies that have demonstrated the impact of vaccinating schoolchildren, in particular, on the morbidity on other community groups (91, 92).

Other recent studies evaluating the benefit of vaccinating school children indicate modest benefits to other children and adults including household contacts (93-95).

A cluster randomised trial among Hutterite communities in Canada allocated the communities to vaccination or no vaccination of school-aged children. The outcome was PCR-confirmed influenza in children and adults in the community. There was a protective effect of 61% afforded to non-vaccinees in the communities where children were vaccinated (96).

A study examining community effects in Canada found that the introduction of a universal influenza vaccination programme in Ontario resulted in decreases in influenza-related mortality, hospitalisations, emergency department use and physician office visits compared with other provinces (97).

A Japanese study, which compared years of population data from both Japan and the US, concluded that the vaccination of school children provided a reduction in influenza mortality in older people (98). However, this study has been criticised (99, 100).

The strategy of utilising ‘herd immunity’ to reduce spread of the organism in the community and to protect the more vulnerable seems attractive, when considering the current challenges of poor efficacy of TIV vaccines, particularly in the very young, the elderly and high risk groups,

Many papers have stressed the difficulties of providing a universally accepted definition of the concept of herd immunity. Valleron concludes in a commentary article that “qualitatively, one can say that herd immunity is achieved in a population that includes persons susceptible to an infectious agent if there is no outbreak when new infections are introduced” (101).

A modelling approach, used to determine what the influenza vaccination coverage would need to be to establish ‘herd immunity’ in an at-risk population,
found that 80% coverage would need to be obtained for healthy populations and 90% coverage for elderly and high risk persons (102). The authors concluded with a recommendation to vaccinate low risk persons, particularly children, for herd immunity protection reasons. However, successful herd immunity is limited by the obvious heterogeneities in contacts, risk and vaccine coverage seen across the different sectors of the population (101). Furthermore, because there are animal reservoirs, there is no hope for eradicating influenza, even if the proportion vaccinated is much higher than the threshold proportion corresponding to herd immunity.

5.3.4 Duration of protection

The duration of protection from influenza illness following vaccination with TIV vaccines has been studied. In 1968, a group of school children were vaccinated with the A/Hong Kong/68 vaccines and observed over three epidemics caused by the same strain. The vaccine was 67% effective after three years (103). Immunisation with TIV, before the 1982-83 epidemic, provided 100% efficacy against H1N1 in the first year and 68% in the second year without re-vaccination (56).

Serum antibodies reduce rapidly over the year following annual influenza vaccination. Elderly, who have received repeated influenza vaccinations, develop lower peak HI titres and these levels return to baseline more rapidly than in young healthy adults receiving influenza vaccine for the first time. In contrast, immunity to HA can persist for decades after natural infection (104-106). In contrast to the apparently limited duration of immunity induced by inactivated vaccines, there may be longer persistence of immunity from LAIV, particularly from the first exposure (107, 108). Serum antibodies in LAIV recipients have been observed to increase months after vaccination providing prolonged humoral immunity (108). Protection provided by LAIV has been demonstrated to persist beyond a year (109, 110).

5.3.5 Vaccine performance in high risk groups

High-risk groups identified as indications for influenza vaccination have been summarised by the ACIP (70, 111). These groups include:

- Children aged six months–four years (59 months).
- Persons aged ≥ 50 years.
- Children and adolescents (aged six months–18 years) who are receiving long-term aspirin therapy and who might be at risk for experiencing Reye syndrome after influenza virus infection.
- Women who are or will be pregnant during the influenza season.
- Adults and children who have chronic pulmonary (including asthma) or cardiovascular (except isolated hypertension), renal, hepatic, neurological, haematological or metabolic disorders (including diabetes mellitus).
- Persons who are morbidly obese (body mass index ≥ 40).
- Persons who have immunosuppression (including immunosuppression caused by medications or by HIV); and
- Residents of nursing homes and other long-term care facilities.

Generally, among persons with chronic medical or immunocompromising conditions, serological responses to influenza vaccination are lower.

5.3.5.1 Nursing home populations

There is wide variability in the estimates of effectiveness of annual influenza vaccination in nursing home residents (0-80%). Vaccination has been demonstrated to prevent hospitalisation and death in these groups (112-115). Some studies support rates of 80% coverage in nursing homes provides herd immunity (116). The vaccination of healthcare workers also reduces the morbidity and mortality among the residents (117-121).

5.3.5.2 Immunosuppressed

In a randomised study compared the immunogenicity of LAIV with TIV, among 55 cancer patients aged two to 21 years (mean age 10 years) with mild to moderate immunosuppression. Participants were randomised to LAIV or TIV. Prolonged viral shedding was not detected. TIV was more immunogenic in this group than LAIV (47).
5.3.5.3 Cardiac patients
A cohort study in Spain, among community-dwelling elderly people over the age of 65 years who had congestive heart failure of coronary artery disease, found a benefit from influenza vaccination with a 37% reduction in winter mortality in vaccinated persons during the study period 2002-2005. This study is subject to the inherent problems of non-randomisation (122). Another study in Taiwan, using a National Insurance database, also found a reduction in all-cause mortality in elderly patients with ischemic heart failure as well as a reduction in hospitalisations (123).

5.3.5.4 Cystic fibrosis
A Cochrane review (updated 2011) of vaccines for preventing influenza in people with cystic fibrosis concluded that there is currently no evidence that influenza vaccine given to people with cystic fibrosis is of benefit. There is a lack of good quality clinical studies for this group (124).

5.3.5.5 Chronic suppurative lung disease/bronchiectasis
A Cochrane review in 2010 could find no eligible trials of the effectiveness of influenza vaccine in children and adults with bronchiectasis in reducing the severity and frequency of respiratory exacerbations or pulmonary decline (125).

5.3.5.6 HIV/AIDS
A current Cochrane protocol is evaluating the effectiveness of influenza vaccine in people with HIV and people with AIDS (126).

5.3.5.7 Children being treated for cancer
There are no studies in this group that report on clinical outcomes. A Cochrane review assessing influenza vaccine in children being treated with chemotherapy concluded that paediatric oncology patients receiving chemotherapy are able to mount an immune response to influenza vaccination. However, the clinical relevance of this immunity is unknown (127).

5.3.5.8 Immunosuppressed cancer patients
There is currently a Cochrane protocol to evaluate the efficacy and effectiveness of influenza vaccine in people who are immunosuppressed due to malignancies (128).

5.3.5.9 Pregnancy and infant outcomes
There is currently a Cochrane protocol to evaluate the efficacy and effectiveness of influenza vaccine on maternal, neonatal and infant health outcomes (129).

5.3.5.10 Obesity
Obesity has been found to be associated with an impaired immune response to influenza vaccination. BMI was correlated a greater decline in influenza antibody titres post vaccination. Obese individuals demonstrate a decreased CD8+ T-cell activation and decreased expression of functional proteins when compared with healthy weight individuals (130).

5.3.5.11 Preterm infants
Infants and children born prematurely are at higher risk of influenza-related complications. TIV has been demonstrated to be well tolerated in infants and toddlers aged six months to 17 months who were born premature. Premature infants have been demonstrated to produce higher antibody titres than term infants (36).

5.3.5.12 Healthcare workers who work with the elderly
A Cochrane review assessed studies vaccinating healthcare workers and the incidence of influenza, complications and ILI in the residents over 60 years of age in long-term care facilities. The authors found no effect for the specific outcomes. There was an effect of influenza vaccination against ILI, GP consultations for ILI and all-cause mortality in the over 65s. There was no evidence that only vaccinating healthcare workers prevents laboratory confirmed influenza, pneumonia or death from pneumonia in elderly residents on long-term care facilities (18).
5.4 Summary of effectiveness

ID vaccines do not generate higher antibody titres than IM vaccines in healthy adults. Higher doses of ID vaccines can improve immunogenicity in the elderly. There are no RCT of TIV in adults over the age of 65 years; hence, efficacy is difficult to measure. Adjuvanted vaccines are more immunogenic than unadjuvanted vaccines. However, there is no efficacy or effectiveness data on adjuvanted vaccines.

LAIV vaccines generate a different immune response to TIV therefore immunogenicity data is not directly comparable. LAIV vaccines appear to provide superior protection in children when compared with TIV, which is moderately effective in children three years of age and over, however, TIV appears better in healthy adults.

The addition of an extra influenza ‘B’ strain in seasonal influenza vaccines is likely to moderately improve effectiveness. The quadrivalent inactivated influenza vaccine demonstrated efficacy against symptomatic influenza by 58% in a season with a good match.

There is some evidence to suggest herd immunity, particularly via vaccinating children, can be achieved providing coverage is very high. Vaccinating healthcare workers is likely to be an effective strategy, particularly for nursing homes.

While duration of immunity provided by influenza vaccines is difficult to study due to the continual strain shifts, the years when strains have remained the same vaccination in a previous year appears to confer immunity in the next year. Protection from LAIV has been demonstrated to persist beyond a year.

There remains a need for more high quality studies in young children, older adults and those with a variety of co-morbidities.
6. Age-specific issues

6.1 Objective
This section considers the differences that need to be considered for various age groups. Literature for age-related morbidity and mortality is included. Issues around the use of available vaccines, in age groups other than infants and young children, is also considered.

6.2 Review

6.2.1 Vaccine issues for different age groups

6.2.1.1 Vaccine safety
There are two influenza vaccine safety issues that have emerged during the last four years.

The increased risk for febrile events associated with CSL’s Fluvax® vaccine in infants and children under the age of nine years of age.

The association of adjuvanted vaccines and narcolepsy in children aged four to 19 years observed in some countries.

The issue around febrile events is easily mitigated through monitoring the different behaviours of TIV and appropriately using different brands of TIV in the younger age groups.

Until resolved, the issue of narcolepsy can likely be mitigated by restricting the use of adjuvanted vaccines to older age groups.

LAIV are not currently recommended for use in children under two years of age due to possible increased risk of wheezing episodes associated with the vaccine. Recent data suggests that this may not be a significant problem and less restricted use may be warranted.

6.2.1.2 Vaccine effectiveness
Influenza vaccine effectiveness varies by age and vaccine given. The lack of data on efficacy and effectiveness for infants and children and older adults remains a challenge, particularly for inactivated vaccines.

6.2.1.2.1 Infants and children
LAIV have been demonstrated to be more efficacious and effective in children than TIV.

6.2.1.2.2 Young adults
Inactivated vaccines may be more effective in younger adults than LAIV.

6.2.1.3 Elderly
ID delivery, higher dose antigen and adjuvanted vaccines are likely to be more effective in the elderly. There are two mechanisms to better protect this age group, particularly, those who as individuals have poor immune responses to current vaccines:

1. Herd immunity through high vaccine uptake and
2. Cocoon protection via vaccinating those in close contact, such as healthcare workers and close family contacts.

6.2.1.3 Vaccine dosing
For inactivated vaccines that are un-adjuvanted, children under three years of age are recommended to have half the 15µg of HA component (7.5µg) based on both reactogenicity and immunogenicity data.

People who have been unexposed to influenza through natural infection of vaccination require two doses to achieve high antibody titres. Recent studies confirm the need for two doses in children less than nine years.

Dosage responses in the elderly suggest that increased doses can increase antibody levels without increasing reactogenicity. The ID route requires less antigen to produce a comparable response but is more reactogenic.
6.3 Summary of age-specific issues

Recent arising safety issues have included increased febrile reactions and febrile convulsions with one brand of TIV (Fluvax®) in children under 9 years of age. This has highlighted the importance of safety monitoring annual antigenic changes, and monitoring/comparing the behaviours of different brands of TIV. There is an association with narcolepsy and one brand of adjuvanted influenza monovalent pandemic vaccine, which does not appear to extend to non-adjuvanted or seasonal vaccines. LAIV vaccines have safety concerns in children under two years of age with wheezing, although, recent data have suggested that this may be less of a problem that originally considered.

Certain age groups, particularly the elderly and very young, respond poorly to currently available influenza vaccines, yet often carry the highest burden of disease. Strategies for the elderly include adjuvanted vaccines, two dose strategies, increasing antibody levels, ID delivery, herd immunity and cocoon protection strategies. Strategies for the very young include consideration of lowering the age of delivery of LAIV and herd immunity strategies.
7. Vaccine options

7.1 Objective

The objective for this section is to consider the different vaccine options available internationally that are currently or potentially available to NZ for consideration on the national schedule. The focus is on the generic type of vaccine, not the specific trade name. Availability of vaccines to NZ is dependent on receiving licensure through Medsafe.

7.2 Review

An increasing array of influenza vaccines are, or are expected to be, available. The current TIV vaccines are of three types: whole virus, split-product and subunit surface-antigen formulations. Whole-virus vaccines are not currently used, especially in children, due to reactogenicity (140).

ID TIV formulations are available using a smaller needle and less viral antigen than the standard IM delivery. Intranasal delivery is now well established with the LAIV vaccines. Sublingual has been proposed as a possibly safer alternative route than intranasal, but immune responses are not as high as intranasal (141).

7.2.1 Implications for vaccines and vaccination

The challenge for influenza control via immunisation is that effectiveness of the current influenza vaccines tends to be lower in groups who are at higher risk from influenza morbidity and mortality i.e. the elderly, very young and the immunocompromised. Efforts to identify formulations with improved immunogenicity and clinical protection continue to be a focus of researchers, manufacturers and governments. The potential of high-dose antigen formulations and adjuvants in improving immune response are major current targets (65). Adjuvants can also potentially lead to broader immune responses, which can confer protection against heterologous strains (65). The potential for improved immune response via different mechanisms of delivery, in particular, the use of ID routes is also a focus (67).

The development pipeline is being driven by several factors, including the international demand for more seasonal influenza vaccine, the desire for faster production and less-expensive alternatives, better performance in high-risk populations, particularly the elderly, young children and the immunocompromised, and the desire to elicit more broadly cross-protective antibodies to reduce the requirement for annual vaccinations (142).

While it is often hard to compare across different vaccines, current summary data would suggest that inactivated vaccines are more immunogenic in younger adults than in older, in individuals previously seropositive to the vaccine antigen at baseline and in recipients of the adjuvanted vaccines. Adjuvanted vaccines can be delivered using lower antigen doses in all ages, showing the dose-sparing advantages of adjuvants. This is likely to be more important during pandemics when supplies are limited and demand is high. Adjuvanted vaccines do elicit significantly more injection-site reactions than adjuvanted, although to date, systemic reactions are comparable (142). Nasally administered live attenuated influenza vaccines (LAIV) induce stronger responses than TIV, evoking both mucosal and systemic immunity, and including broader cellular immune responses (67).

7.2.2 Internationally licensed but not currently in NZ

The standard seasonal trivalent inactivated vaccine (TIV) is now being produced with a higher-antigen dose for an improved immune response in older adults. Quadrivalent vaccines, which add a second strain of B subtype in order to reduce the potential for vaccine mismatch, are now licensed internationally, and are expected to become available in NZ soon. The potential impact of these over the TIV vaccines is expected to vary between seasons, but is expected to give further modest reductions in influenza-associated outcomes (82). For example, modelling suggests a reduction of 2200-970,000 influenza illnesses, 14-8200 fewer influenza-associated respiratory hospitalisation and 1-485 fewer influenza-related deaths in the US
population (82). The ability of a quadrivalent vaccine to perform better than a trivalent vaccine will depend on the vaccine match, including the amount of influenza B in circulation that is different from that in the trivalent preparation.

Live attenuated vaccines (LAIV) are currently licensed in the US and Europe. The LAIV are now also being produced in quadrivalent formulations (143).

Internationally licensed inactivated seasonal vaccines include those manufactured in cell culture, subvirion vaccines combined with the oil-in-water adjuvant MF59 for elderly ≥ 65 years, and whole virus and virosomal vaccines (142).

Non-egg-based vaccines, grown in cell lines, are expected to be available internationally in the next few years (144). Studies to evaluate safety and immunogenicity of cell culture-derived vaccines have shown that safety and immunogenicity has been demonstrated to be comparable with cell culture derived versus egg-derived vaccines in adults and in the elderly (145).

### 7.2.3 Options for the elderly

Current licensed TIV vaccines are poorly immunogenic and less effective in the elderly (146). Alternative vaccine options include adding adjuvant, increasing the antigen dosage and offering two-dose schedules. However to date, studies on the latter two options have given conflicting results with regard to antibody titres (58, 147, 148). The benefits seem to depend on the specific vaccine cohort and on the timing of booster intervals.

A high dose TIV has been licensed in the US for use in the elderly (58). Two adjuvanted vaccines, one subunit adjuvanted with MF59 and a virosomal vaccine have recently been registered in several countries, and shown to include higher anti-haemagglutinin antibody titres compared with non-adjuvanted vaccines in the elderly, in several studies (149-153). Other studies have not confirmed the increased immunogenicity (154, 155). A reduced-dose, inactivated, whole virion trivalent influenza vaccine, which used a 6µg dose adjuvanted to aluminium phosphate gel, gave equivalent, but not improved, antibody responses in 120 adults and 114 elderly (>60 years) compared with the conventional trivalent vaccines (156).

Summary reports recommend that further investigations are required to clarify these issues and to confirm the clinical benefits of adjuvanted vaccines, two-dose schedules and increasing antigen dose in the elderly (146).

### 7.2.4 Options for children

As the traditional TIV vaccines have not been highly effective in children, many countries are moving to using the LAIV vaccines (67). However, LAIV are not currently recommended for use in children under two years or in immunocompromised children (see 4.3.2.2). Good immunogenicity results are seen in children less than two years of age, but the risk of bronchospasm is the main reason why the USA and European health authorities have not licensed LAIV for use in children younger than two years or age, or in those who have previously experienced severe obstructive respiratory problems.

Alternatives include adjuvanted vaccines. The adjuvanted vaccine with MF59 has been used in the elderly since the 1990s. A range of published data shows this vaccine, used in a two-dose regime in healthy children six months to three years of age, can produce good immunogenicity outcomes and was well tolerated in young children, although as with other age groups, more injection site reactions were seen (157). Virosome-adjuvanted vaccine (VAV) is the only adjuvanted influenza vaccine licensed for use in children in some of the European countries, but not in the USA (67). VAV have stronger T cell responses and greater immune stimulation, and good results have been seen in adults and healthy children. Immunogenicity data to date suggests VAV are around 84% effective in preventing laboratory confirmed influenza-A in children three to 14 years (158). However, there is currently very limited, albeit promising, data available for younger children, six months to three years and no efficacy studies on children under two years of age (67).

ID administration has been shown to be effective in the elderly, but paediatric data is limited currently, and further research is needed to answer whether ID is a possible option for young children (67).

Children under six months of age do not produce strong immune responses to any of the available influenza vaccines (67). The young infant’s post vaccination immune response may be hampered by maternally transferred antibodies. Circulating antibodies from breast feeding may also protect infants. Several studies have supported the finding that mothers vaccinated during pregnancy have significantly higher antibody levels than those of unvaccinated mothers, and the infants have reductions in the incidence of influenza disease in the first six months ranging from 41% to 90% (67).
7.2.5 Options for immunosuppressed patients

A prospective controlled trial investigated whether improved responses were seen in immunocompromised patients vaccinated with an AS03 adjuvanted A/H1N1. A total of 149 patients with rheumatoid arthritis, spondyloarthropathies (SpA), vasculitis or connective tissue disease and 40 healthy individuals received a single dose of vaccine. All patients showed significant antibody rises, reaching a maximum three weeks post vaccination, but declining to levels below protection at six months post vaccination (p= 0.001). Seroprotection was more frequently reached in SpA and connective tissue disease than in rheumatoid arthritis and vasculitis patients (80% and 82% and 57% and 47%, respectively). There was a significant negative impact associated with the drugs methotrexate (p < 0.001), rituximab (p = 0.0031) and abatacept, a disease-modifying anti-rheumatic drug (DMARD) (p = 0.045). Other DMARDs, glucocorticoids and TNF blockers did not significantly suppress the response (p = 0.06, 0.11 and 0.81, respectively). Disease reactivation that was possibly related to vaccination was suspected in 8 of the 140 patients. A linear decline in response was noted in patients with increasing age (p < 0.001). The authors concluded that “vaccination response is a function of disease type, intensity and character of medication and age”. A single injection of adjuvanted influenza vaccination appears sufficient to protect many patients, but note the waning immunity at six months, and the reduced effects with increasing age (159).

Using booster doses of standard TIV vaccines has not been shown to have effect in haemodialysis patients (160).

A two-dose adjuvanted pandemic H1N1 vaccine using the squalene-based adjuvant AS03 was trialled in 206 solid organ transplant recipients and 138 healthy adult controls. Seroprotection was achieved by only 70% of transplant recipients compared to 87% of controls, with significant differences between different groups (lung 44%, heart 72%, kidney 83%, liver 83%, and pancreas 85%). Overall, GMT were threefold lower in transplant recipients than controls. While the vaccine was safe in transplant recipients, it did not provide adequate protection in many cases, particularly for lung transplant recipients (161).

7.2.6 Vaccine technology on the horizon

A range of future vaccine options are feasible, with some interesting examples, as below:

1. A range of adjuvanted vaccines continue to be reported in animal studies and early phase trial data (162). Vaxjo, a web-based central database and analysis system, stores and analyses vaccines adjuvants and their usages in vaccine development, and as of early 2013, it lists 103 vaccine adjuvants on the database (163).

2. Animal data is available on the immunogenicity response of an oral mucosal vaccine candidate that is using a replicating vector pMG36# to expresses the haemagglutinin protein in a live carrier, Lactococcus lactis (164).

3. An influenza iscomatrix adjuvanted vaccine, delivered intranasally to sheep using a gel, showed broad immune response and memory at 12 months post-delivery (165). A nanoemulsion mucosal adjuvant W(80)5EC vaccine containing the seasonal influenza antigens, administered intranasally, has been trialled safely in a phase I trial in 199 adults; it was well tolerated and elicited both systemic and mucosal immunity following a single dose (166).

4. Using synthetic DNA approaches, particularly for pandemic vaccines, has the advantage of not needing to handle wild-type viruses, and significantly reduces the time required to generate and distribute the vaccine seed virus and vaccine manufacture (167).

5. The holy grail of influenza vaccination is to achieve a vaccine that can protect against all influenza strains, and therefore, remove the need for annual vaccination. Early animal studies are focused on this challenge with some novel opportunities. A study, published by Schmitz et al., was looking at a vaccine targeting a highly conserved extracellular domain of M2 (M2e) (168).
7.3 Summary for vaccine options

There are a number of vaccine options that are likely to be more effective in a variety of population groups for whom currently used TIV is either poorly efficacious or there is a lack of data to support efficacy. A quadrivalent option for inactivated influenza vaccine is likely to improve the performance of these vaccines, although probably modestly.

For children less than two years of age, the LAIV elicit good immune responses, but are currently not recommended due to possible increased risk of wheezing episodes. There is a lack of data to support effectiveness of TIV in the age group. Emerging data suggests adjuvanted vaccines may work better in this group, although there is little evidence to indicate any influenza vaccines elicit good responses in infants less than six months of age, though preterm infants have better responses than term infants.

For children up to 18 years, LAIV vaccines provide superior performance over TIV.

Generally, in the elderly and immunosuppressed, adjuvanted vaccines provide superior responses to TIV and formulations of adjuvanted TIV with higher antigen doses also appear better than standard TIV. ID vaccination allows for antigen sparing, but there is little evidence that the immune response is superior or that better protection is afforded.
8. Options for scheduling

8.1 Objective
This section reviews the evidence for different options for placement of influenza vaccine as a universal option, consideration for the childhood immunisation schedule and for special groups.

8.2 Review
Current NZ licensed seasonal vaccines consist of only the TIV, with either IM or ID delivery.

Review articles have commented on the concerns that, overall, mediocre and plateauing population immunisation coverage in many areas and age groups, disproportionate burden of severe illness in older adults, and lower vaccine effectiveness in the groups most affected highlights the need for better formulations and strategies to improve vaccine efficacy (65).

TIV are generally recognised as effective for healthy adults, particularly when the vaccine and circulating virus are antigenically similar. US summary economic models support the economic benefits of influenza vaccination in healthy working adults as exceeding the costs of vaccination or representing good value (169). Although, other summary analyses conclude that vaccination of healthy working-age adults is generally not cost saving and requires an investment to gain general health benefits (170).

A Cochrane meta-analysis concluded that 28 children over the age of six need to be vaccinated to prevent one case of influenza (infection and symptoms) and eight need to be vaccinated to prevent one case of influenza-like-illness. To date, there is no evidence for an effect on secondary cases, lower respiratory tract disease, drug prescriptions, otitis media and its consequences and socioeconomic impact. There is weak evidence of reduction in school absenteeism by children and caring parents from work. This Cochrane review also concluded that reliable evidence on influenza vaccines is thin and expressed concerns around the overemphasis from industry-funded studies (17).

Effectiveness of TIV vaccines for the elderly, for children under three years of age and the immunocompromised is not so clear (171). TIV in children aged two years or younger have not been shown to be significantly more efficacious than placebo (17). Vaccination has shown to be safe and effective for pregnant women and for disease reduction in their infants (172, 173). Future strategies for protection of the more vulnerable are likely to be either a greater focus on herd immunity, or enhancing their immune response in order to offer more effective protection (171).

8.2.1 Targeted vaccination
If a vaccination strategy also includes some herd immunity intent then coverage targets need to reflect this. The current vaccine coverage targets in many countries of 75% or lower, such as in NZ and many parts of Europe, will not be sufficient to achieve herd immunity (102).

Vaccination of healthcare professionals is frequently advocated to protect the vulnerable, such as the elderly. Studies have shown that high vaccine coverage rates in extended care facilities may result in lower patient mortality and influenza-like illness (18, 174). However, a recent systematic review of RCT of healthcare professionals working with people over 60 concluded that there was an effect on nonspecific outcomes, such as influenza-like illness, general practitioner consultations and all-cause mortality. There was no effect shown for specific outcomes, such as laboratory-confirmed influenza, pneumonia and death from pneumonia (175).

A review of the grey literature and electronic healthcare databases was undertaken to review the effectiveness of vaccinating healthcare workers to provide indirect protection for patients at risk from severe disease. This review concluded that there was likely to be a protective effect for patients in residential care settings, but evidence was insufficient to extrapolate this to other at-risk patient groups (176).

The immunisation strategy of ‘cocooning’ is currently recommended by the ACIP in the US, to offer seasonal influenza vaccination to close contacts of newborn infants and high-risk children, such as parents, family members and caregivers. It is currently unclear whether cocooning is effective in preventing immunisation morbidity in these groups (151). Implementation of cocooning has many challenges, both at the individual-level and system-level, and further research evaluating its effectiveness is required (152).
8.2.2 Schedules for adults

The LAIV vaccine is licensed in the US for children from two years of age and healthy adults under the age of 50 years. This vaccine has the advantage of offering mucosal as well as systemic immunity and is needle free. A study of adults aged 18-49 concluded that, while the LAIV is efficacious in preventing laboratory-confirmed influenza, it was not as efficacious as the TIV in this age group. This is in contrast to the findings in children and the current opinion is that the traditional TIV is still the preferred vaccine for adults (77, 144, 177).

The UK Joint Committee of Vaccination and Immunisation (JCVI) concluded in November 2011 that extending the influenza vaccination programme to all adults aged 50 to less than 65 years is unlikely to be cost effective (178).

8.2.3 The elderly

Optimising influenza vaccination for the elderly is an important focus, and as current TIV vaccines are not ideal for the elderly, strategies that offer indirect protection by vaccination of other populations are alternative options (171). This includes vaccination of healthy children to decrease the incidence of influenza transmission, since children are very effective transmitters of influenza (153). Other strategies include vaccination of healthcare workers, although many Western countries get disappointingly low coverage.

The use of adjuvanted or higher-dose vaccines enhance vaccine immunogenicity to some degree in the elderly, however, it is not yet clear how this will translate into protection against influenza outcomes. Furthermore, there are concerns that these strategies may “overstimulate the naïve cell pool that is reduced the most during the immunosenescence process, without consideration of the pool that affects the immune response the most i.e. senescent cells” (171).

8.2.4 Immunosuppressed

Most groups of immunocompromised patients show an impaired response to influenza vaccination, in antibody response, cellular response and in clinical protection. For example, post vaccination antibody titres are lower in haematological stem cell transplantation patients and patients treated with rituximab (155).

There is potential for ID vaccination to be more effective than IM, but currently, there is still little data in this area (155).

Safety and efficacy of administering seasonal TIV to patients with systemic-onset juvenile idiopathic arthritis treated with the immunosuppressive monoclonal antibody drug tocilizumab was tested in 27 patients and 17 healthy controls (179). The authors showed efficacy did not differ significantly between the groups and concluded that it was safe and effective to use influenza vaccine in this group. As in many of these high risk group studies, there were small numbers in this study, and on a precautionary note, there is a case report published of a three year old receiving tocilizumab who experienced a relapse of systemic juvenile idiopathic arthritis after receiving TIV vaccination (180).

An adjuvanted influenza monovalent vaccine using the adjuvant ASO3 appears to be safe for use in cancer patients receiving chemotherapy, and moderately effective (48% seroconversion after one dose and 73% after two doses) (181).

Antibody responses were measured from 57 haemodialysis and 48 renal transplant recipients to TIV vaccines and adjuvanted H1N1 vaccine. For haemodialysis patients, seroprotection was achieved for 35% to pandemic H1N1 and 37% to seasonal influenza and against both in 14%. For transplant recipients, antibody titres against H1N1 were 48%, 31% against seasonal and 19% against both. Younger patients (<60 years) achieved higher seroprotection than older. Of note, low seroconversion rates may not necessarily translate into increased illness. The authors comment that new vaccines and altered vaccination regimes are likely to be necessary to achieve higher antibody levels in these patient groups. Suggestions include using ID vaccines, improved adjuvants, vaccination of healthcare worker and other contacts (182).

8.2.5 Other high risk groups

Children with sickle cell disease on chronic transfusions appear less likely to respond to monovalent pandemic H1N1 vaccine that non-transfused children (183).

8.2.6 Children

Children have the highest rates of influenza infection and they play a significant role in the transmission of influenza due to their high contact intensity in preschool, school settings and in the home. They also have higher rates of viral shedding. There is growing evidence that childhood vaccination can prevent influenza within the household and the community (refer to section 5.3.3 on herd immunity). This also has the potential to reduce the disease burden in the
elderly and other high risk groups, where influenza vaccines are not currently highly effective on an individual basis (146).

Yearly administration of seasonal influenza vaccination is widely recommended for high risk children in most countries, but the current role for its use in healthy children still continues to be debated (67). In the US, annual vaccination has been recommended for all children since 2008, and many Asian and Latin American countries recommend universal annual vaccination for younger children. In contrast, most of the EU currently continues to recommend targeted vaccination only for children. Two meta-analyses have reviewed whether the current vaccines are effective enough to support their universal use in healthy children and have reached opposite conclusions (17, 75, 184).

The UK Joint Committee on Vaccination and Immunisation (JCVI) in a statement in November 2011 concluded that extending the national immunisation programme to low risk children was likely to be cost effective, “particularly when considered over a number of years” as it could provide both direct protection and indirect protection to lower influenza transmission from children to other children, the rest of the population and particularly those in the high risk groups. Extending vaccination to all children six months to 17 years was considered the most cost effective option (178).

8.2.6.1 New-borns and infants

Infants under six months of age are at highest risk of severe influenza disease. All licensed TIV vaccines currently have poor immunogenicity in this age group, or there are concerns over severe adverse events with adjuvanted-TIV and LAIV. Maternal vaccination strategies are effective for new-born and young infants, by offering transplacental antibody protection (173). Studies, to date, have looked at the impact of maternal vaccination on respiratory illness in the infant and shown significant reduction in disease and hospitalisation rates in the infant for the first few months of their life (185, 186).

8.2.6.2 Otitis media and children

The Cochrane collaboration is currently undertaking a review of the effectiveness of influenza vaccines for preventing acute otitis media in infants and children (187). Results from this study are not yet available, as of early 2013.

8.2.7 Safety considerations for repeat annual vaccinations

There are theoretical concerns, but no clear evidence, as to the risk associated with repeated immunisation of children in particular with TIV vaccines (143). A randomised controlled trial, using TIV or placebo in 64 children aged six-15 years, showed that recipients of TIV in the first year had lower antibody titre rises in the second year to seasonal influenza strains, for which the vaccine strains remained unchanged. Antibody responses to a different influenza B strain in the second year were unaffected. Children who received TIV in both years showed higher antibody titres against pandemic H1N1 which was not included in either TIV vaccine. The authors concluded that humoral antibody responses to TIV may be lower in children receiving repeated vaccinations, but still gave seroprotection in most subjects. The study was underpowered to explore whether these differences translate to differences in vaccine efficacy (188).

One mathematical model has suggested that when competition between acquired and vaccine induced immunity is taken into account, that vaccination at a young age may increase the risk of influenza at older ages (189).

Previous influenza vaccination or previous exposure to the virus can act as an important confounding factor in vaccination outcomes (155). Some studies have shown lower post-vaccination titres in those with a history of previous vaccination. This has been described and named the ‘Hoskins paradox’ after the author of several studies in the early 1970s. Two possible processes have been proposed for this:

1. Neutralization of vaccine antigen (or the forming of immune complexes) by circulating antibodies
2. A related antigen (a drift variant) boosting the response to the original antigen, instead of to the newly administered antigen if there is enough similarity – called the ‘original antigenic sin’ (155).

Prior receipt of seasonal influenza vaccine has been independently associated with lower post vaccination serum HI antibody titres in both adjuvanted and non adjuvanted pandemic H1N1 vaccines (65). Epidemiological and immunological studies in Japan, Canada and Hong Kong have reported results showing that the delivery of the seasonal TIV vaccination prior to receiving the pandemic vaccination may increase the risk of the pandemic illness (190-192). Other epidemiological studies in Australia and Mexico have not supported these findings and showed no or partial benefit (193, 194).
These findings may be due to unidentified confounders, a proxy variable for something that increases onset, or a true association, which could be an antibody-dependent enhancement to enhance cell uptake of H1N1 virus (190). Mechanisms such as suggested above with the ‘Hoskins paradox’ are possible explanations.

8.3 Summary of schedule options

TIV are generally recognised as effective for healthy adults, particularly when the vaccine and circulating virus are antigenically similar. Current international recommendations are conflicting as to whether annual vaccination of healthy adults is cost saving.

The effectiveness of TIV vaccines for the elderly, high risk groups – in particular, the immunocompromised and for children under three years of age is not clear. ID vaccines for the elderly and immunosuppressed as well as improved adjuvants all have the potential to improve effectiveness. Vaccination of healthcare workers and other contacts are likely to be sensible strategies albeit based on relatively limited data.

There is increasing evidence that annual vaccination of children two years of age and older with LAIV offer benefits both for direct protection and indirect protection to other members of the community.

There remain theoretical safety concerns around the use of repeat annual vaccination with TIV for children.
9. Implementation issues

9.1 Objective

The objective of this section is to review the most recent data – new issues arising since the 2011 Immunisation Handbook - for currently licenced influenza vaccines with respect to potential implementation issues in the NZ context. This includes types and timing of schedules for a universal childhood schedule, co-administration, specific vulnerable population groups and adult schedules. A focus is also on use of LAIV vaccines in the universal childhood programme and for the vulnerable groups and adult populations there is consideration for any recent updates to use of attenuated vaccines. Issues for implementation in pandemic situations is not considered in this report.

9.2 Review

9.2.1 Protecting High Risk Groups

Findings from the pandemic H1N1 experience have highlighted two important groups that are at risk of severe disease: pregnant women and severely obese with a BMI ≥40 kg/m² (195).

9.2.1.1 Infants less than one year of age

With the H1N1 pandemic, there was a high incidence of infants hospitalised with H1N1 influenza. A US report of critically ill infants, under one year of age admitted to intensive care in California, showed that out of 77 infants, 46 (60%) had at least one reported chronic medical condition and 27 (35%) were preterm with a gestation of under 36 weeks (196). The authors recommend vaccination among contacts of all infants less than six months of age. An H1N1 outbreak reported in a tertiary level NICU in Greece showed a very low influenza vaccination of 15% among the nursing staff and concluded that nosocomial influenza can cause considerable morbidity, especially in high risk neonates, and is readily transmissible by unvaccinated staff members who contract influenza (197). Vaccination of healthcare workers, in contact with infants, is recommended. Maternal vaccination strategies are effective for newborn and young infants, by offering transplacental antibody protection (173). Cocoon strategies are advocated in some countries, but as of early 2013, there is no data to support their effectiveness in reducing influenza morbidity in infants (151).

9.2.2. Concomitant delivery

Concomitant delivery with polysaccharide pneumococcal vaccines for adults and elderly is safe and effective (145). The pneumococcal vaccine PCV13 can be safely and effectively delivered concomitantly with TIV vaccines in adults aged 50-59 and ≥ 65 years (198).

The meningococcal serogroups A, C, W-135, Y tetanus toxoid conjugate vaccine (ACWY-TT) and the seasonal influenza virus vaccine are immunogenic and well-tolerated when co-administered in adults (199).

LAIV can be co-administered with vaccines for measles, mumps, varicella, oral polio vaccine. Caution has been raised in relation to co-administration with the rubella vaccine, as changes to the immune response of the rubella vaccine have been noted, although this is not likely to be of clinical relevance with use of a two dose MMR regime (200).

9.2.3 Use of LAIV

There are concerns regarding infection control precautions and restrictions surrounding the use of LAIV with healthcare professionals, because it is a live viral vaccine (144). Shedding of the attenuated virus is common in the first few days following vaccination. Reversion to wild type virus has not been demonstrated despite extensive testing, and no secondary transmission has been reported. There has been one documented episode of the LAIV virus transmitted in a day-care attendee as part of an RCT. However, on the basis of this theoretical concern for transmission, the US ACIP recommend that LAIV are not to be administered to healthcare professionals who interact with high risk patients (144).

9.2.3.1 LAIV contraindications

The vaccine is contraindicated in all individuals with hypersensitivity to any of the active substances, individuals who are clinically immunodeficient and individuals receiving salicylate therapy. It is not recommended for use in infants under 12 months, individuals with severe asthma or active wheezing and individuals who are pregnant or breast-feeding (200). Vaccine recipients should avoid close association with severely immunocompromised individuals for 1-2 weeks following immunisation (200).
9.2.4 Use of adjuvanted Vaccines

Adjuvanted vaccines have the potential to be more effective in all age groups, however, also do tend to have increased local reactogenicity. Furthermore, the association of narcolepsy with a pandemic adjuvanted vaccine highlights the importance of needing strong post market surveillance to monitor the safety and effectiveness of any new vaccine introduced (142).

9.2.5 Use of intradermal (ID) delivery

ID vaccines are generally recognised as offering similar immune responses in healthy subjects, and possibly more efficient immune responses, particularly in the older adult population (63, 155, 201). They have potential benefits in terms of allowing greater vaccination coverage in times of vaccine shortage. The vaccine technique is more time consuming and technically difficult, although, this has now been overcome with better ID vaccination devices. Local side effects are more severe and frequent upon ID vaccination when compared to IM vaccination (155). The ID vaccine with the microinjection system is well received and preferred by vaccinees, based on feedback that it is considered minimally painful compared to the IM vaccine (202, 203).

9.2.6 Delivery in the workplace

A US study used a decision analytic model to compare different models of delivery for clinics for seasonal influenza vaccine in small to medium companies of 50 – 250 employees. This showed that on-site influenza vaccination clinics were generally cost-saving, based on less lost productivity, and those offering choice over incentive were slightly less costly. Incremental costs were generally lower in larger firms, where the 'flu was more contagious in the environment and the vaccine more effective (204).

9.2.7 Strategies to increase coverage

9.2.7.1 General population

A UK review using logistic regression analysis of data from a cross-sectional online questionnaire of 795 general practices across England concluded that there were seven independent factors associated with higher vaccine uptake. Having a lead staff member for planning the influenza campaign and producing a written report of practice performance predicted an 8% higher vaccination rate for patients aged ≥ 65 years. Sending a personal invitation to all eligible patients predicted a 7% higher vaccination rate. Using a lead member of staff to identify eligible patients predicted a 4% higher vaccination rate. The provision of influenza vaccine by midwives was associated with a 4% higher vaccination rate in pregnancy women. Overall, vaccine coverage of the seasonal influenza targeted programme was improved by clear leadership, effective communication about performance and methods, and financial targets to incentivise practices (205).

9.2.7.2 Healthcare workers

A meta-analysis reviewed the most important predictors for seasonal influenza vaccine acceptance among healthcare workers in hospitals and concluded that knowing the vaccine is effective, being willing to prevent influenza transmission, believing that influenza is highly contagious, believing that influenza prevention is important and having a family that is usually vaccinated were all statistically significantly associated with a twofold higher vaccine uptake (206). These predictors are recommended to be targets when developing new influenza vaccination implementation strategies for hospital-based healthcare workers.

A US study was conducted in a large integrated health service delivery system in Wisconsin/Illinois that services over 1.2 million patients annually with 30,000 employees, which adopted a policy of annual influenza vaccination as a condition of employment. This intervention increased the percentage of employees vaccinated from 71% to 97.7% within one year of implementation, and there was no service disruption. Exemptions were allowed for specific medical and religious reasons. Senior leadership support was seen as critical to the programme’s success. The study also concluded that no medical or economic reactions to the intervention were unable to be managed, and the recommended that health services that currently do not achieve high employee influenza vaccination rates adopt a similar process (207).

The strongest predictor of influenza vaccine compliance, among hospital and non-hospital healthcare workers in the US setting, was the existence of a mandatory vaccination policy (208). Review articles have supported the recommendation that mandatory immunisation is likely to be the best strategy for increasing the vaccine coverage rate in the healthcare worker population (171). In 2009, the US ACIP introduced recommendations for influenza vaccination for all children. A survey reviewed the healthcare provider adherence to the new recommendations and showed that overall in the first year, two thirds of paediatricians and one half of family medicine physicians reported adherence, although less than one quarter were actively engaging
in reminder/recall efforts. Practices that adhered to the national ACIP recommendations were more likely to put a substantial effort into promoting vaccination opportunities (209).

9.2.7.3 The elderly
A Spanish study used logistic regression to analyse factors influencing continued adherence to influenza vaccination in 64,245 elderly persons vaccinated in the preceding season. Continued adherence to annual vaccination increased with the greater number of physician visits per year, was lower in women, lower in the 65-69 year age group and in those ≥ 95, in those hospitalised or diagnosed with any major chronic condition in the previous year and in people with haematological cancer or dementia. Districts and physicians with higher coverage in the previous season continued to have higher coverage in the following seasons. The most important factor, overall, was the treating physician (210).

9.2.7.4 Pregnancy
Patient barriers to accepting influenza vaccination during pregnancy include safety concerns, lack of knowledge about influenza, fear of needles, vaccination history, general mistrust of the medical establishment, lacking an established relationship with the healthcare providers and access to care issues. Effective interventions include organizational change, provider reminders, provider education and feedback (211). A US retrospective cohort study comparing vaccination rates among pregnant women, when given no reminders versus provider-focused reminders, showed vaccination rates on 1,367 reviewed records increased from 504 to 863, an increase from 15 to 52%. The conclusions were that a low-cost provider-focused reminders improved vaccination rates. Additional measures were suggested included patient and provider education, dedicated vaccination clinics and standing orders (212).

An Australian study reviewed an education programme for maternity staff and pregnant women aimed at improving vaccine uptake in 2011. The intervention increased vaccination rates from 30% in 2010 to 40% in 2011 with fewer women citing safety concerns (213). Comments from the participants did suggest that vaccination rates could have been much higher, maybe as high as 78%, if influenza vaccination had been integrated as part of the hospital-based antenatal care. Simple provider strategies, such as ‘best practice alerts’ show significant improvements in immunisation uptake (214).

9.2.7.5 Household Contacts
A US study looked at the feasibility of offering free influenza vaccine to household contacts of all children aged <60 months who received primary care at a medical centre in Dallas. Overall, vaccine was administered to 1,042 household contacts of 611 paediatric patients, demonstrating this is feasible. This study did not have any outcome measures for reduction in disease (215).

9.2.8 Immunisation registers
A 2012 report on the Norwegian national immunisation register, which has been nationwide since 1995, concluded that national registers are rich sources for high quality surveillance of vaccination coverage, measuring effectiveness, vaccine failure, adverse event monitoring and research (216).

9.2.9 Vaccine Surveillance Systems
A pilot study of active surveillance system for monitoring influenza vaccine adverse events that can be used in mass vaccination settings was reported in the US. This study recruited 605 adult vaccinees, from a convenience sample of 12 influenza vaccine clinics, who provided daily reports on adverse reactions following immunisation using an interactive voice response system or the internet for 14 days post vaccination. Overall, 90% made at least one daily report and 49% reported daily for the full period. The authors concluded that this is a feasible system and offering multiple modes of reporting encourages high response rates (217).
9.3 Summary for implementation issues

More recently identified high risk groups for targeting influenza vaccination strategies include the morbidly obese and pregnant women. Cocoon strategies sound pragmatically sensible and are advocated in some countries, but they are difficult to implement and there is no data yet to support their effectiveness in reducing influenza morbidity in infants.

LAIV are contraindicated in the immunocompromised and those receiving salicylic acid, and are not to be administered to healthcare professionals who interact with high risk patients. LAIV are recommended not to be used in infants under 12 months, individuals with severe asthma or active wheezing and individuals who are pregnant or breast-feeding. Vaccine recipients should avoid close association with severely immunocompromised individuals for 1-2 weeks following immunisation.

Adjuvanted vaccines increased local reactogenicity and the potential for increased incidence of narcolepsy. ID vaccines can also have increased local reactogenicity but are frequently more acceptable to recipients than IM

Recent studies on vaccination for healthy adults highlight the advantages of onsite work vaccination clinics. For improving national immunisation rates:

• Overall clear leadership.

• Effective communication about performance and methods.

• Financial targets to incentivise practices improved vaccine coverage of the seasonal influenza targeted programme.

Improving vaccination rates for healthcare workers highlight advantages with mandatory vaccination policies, such as making it a condition of employment, alongside effective senior leadership support. A key factor in improving uptake rates for elderly is the engagement of the treating physician. To improve vaccination rates for pregnant women requires the use of effective integrated systems alongside provider and public education. Immunisation registers and effective surveillance systems are important elements of a successful national immunisation programme.
10. International policy and practice

10.1 Objective
To summarise some of the international experience on the use of influenza vaccines and position statements and policies from countries with comparable populations to NZ.

10.2 Review

10.2.1 Children
Universal childhood vaccination is not currently recommended in most countries, but recommendations vary.

Table 4. Review of Influenza vaccination recommendations for children (67)

<table>
<thead>
<tr>
<th>Country Type</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO/Europe</td>
<td>Recommend that member states vaccinate all individuals ≥ 6 months</td>
</tr>
<tr>
<td>European Union</td>
<td>Six member states currently recommend paediatric vaccination: recommendations vary</td>
</tr>
<tr>
<td></td>
<td>by country:</td>
</tr>
<tr>
<td></td>
<td>- 6 months to 18 years: Austria, Estonia and Slovakia</td>
</tr>
<tr>
<td></td>
<td>- 6 to 35 months: Finland</td>
</tr>
<tr>
<td></td>
<td>- 6 to 24 months: Slovenia, Latvia</td>
</tr>
<tr>
<td>USA/Canada and PAHO countries</td>
<td>USA: all individuals ≥ 6 months of age</td>
</tr>
<tr>
<td></td>
<td>Canada: children 6 to 24 months of age, and encourages all individuals ≥ 6 months</td>
</tr>
<tr>
<td></td>
<td>of age to be vaccinated</td>
</tr>
<tr>
<td></td>
<td>Currently 27 PAHO countries and territories recommend paediatric seasonal influenza vaccination</td>
</tr>
</tbody>
</table>

10.2.2 United States
The US ACIP advice for 2012-2013 season recommends annual vaccination for all persons six months and older. Children six months to eight years need two doses of vaccine at least four weeks apart during their first season for vaccination. Any child who have not previously received a vaccine containing H1N1 antigen are recommended to have two doses (54).

Adjuvanted vaccines have not yet been licensed in the USA (65).

10.2.2.1 Influenza vaccination in the Military
The US military have been increasingly using LAIV in preference to TIV since 2004, and it is now the preferred vaccine for service members with TIV being reserved for those with higher risk for respiratory diseases or contraindications to the LAIV (85, 86).

10.2.3 United Kingdom
The current UK policy is to use TIV vaccines and fully fund annual influenza vaccination for all persons aged 65 years and older, and all those six months of age and older in clinical risk groups, including pregnant women (218).

In 2012, the UK JCVI recommended the annual use of the LAIV in all children aged two to 17 years (178). This is expected to be implemented in October 2014.

10.2.4 European Union (EU)
Vaccination guidelines in Europe are in general much more conservative than in the US. All 29 European countries recommend vaccination for children at risk of influenza complications, but only six (Austria, Estonia, Finland, Latvia, Slovakia and Slovenia) recommend vaccination children with no other risk indications (153). Most European countries recommend vaccination of all ≥ 65 years, except for Austria, Germany, Hungary and Russia who recommend all ≥ 60 years of age (171).
The LAIV vaccine, Fluenz™, is recommended in the EU for the prevention of influenza in children aged two to <18 years (200).

Adjuvanted vaccines, particularly monovalent H1N1, are licensed and have been used in many parts of Europe (65).

10.2.5 Australia
Currently only TIV vaccines are used in Australia. Annual influenza vaccination is funded for the following groups: all persons aged 65 years and older, all persons aged six months and older with medical conditions, pregnant women; persons aged 15 years and older who identify as Aboriginal or Torres Strait Islander. As of 2012, annual influenza immunisation is not funded, but strongly recommended, for any adult or child and for all household contacts of children and adults with a medical condition placing them at increased risk of influenza complications. These recommendations remain in place in 2014 (219).

10.3 Summary of international policy and practice
Current international policies are a mixture of individual protection strategies and herd immunity. In general, the EU countries have more conservative strategies. The different available licensed vaccines in different areas also are likely to significantly affect policy decisions.
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