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ORIGINAL ARTICLE

Synopsis of New Zealand's inaugural Influenza Symposium—influenza is a severe vaccine-preventable disease

Mary Nowlan, Nikki Turner, Tomasz Kiedrzyński, Lance Jennings

Abstract

Influenza is a vaccine-preventable disease that can lead to serious acute respiratory illnesses and other complications. Influenza viruses are widespread in wild avian species and infect several animal species in addition to humans. Constant evolutionary changes to the influenza virus make the disease challenging to control. In November 2014, the Immunisation Advisory Centre held New Zealand's inaugural Influenza Symposium (NZIS) to focus upon influenza and vaccine strategies in New Zealand.

International and local experts discussed advances in vaccine effectiveness, safety and disease prevalence and impact. Disease surveillance and vaccine effectiveness studies are identifying those at greatest risk from influenza to target vaccination campaigns. Influenza vaccine safety is closely monitored in order to improve public confidence. In New Zealand, around 27% of the total population are vaccinated against influenza annually, with 67% coverage for those aged 65 years and over who are eligible to funded vaccine.

Seasonal influenza vaccination is vigorously promoted each year to help to improve vaccine uptake. However, there are inequalities in disease impact, with the elderly and very young, socioeconomically deprived and those with Māori and Pacific Island ethnicity remaining at-risk of serious disease and hospitalisation, which may be addressed by further improving access to influenza vaccine.

This is a synopsis of the New Zealand's inaugural Influenza Symposium (NZiS) held in November 2014 by the Immunisation Advisory Centre (IMAC) to focus on influenza and vaccine strategies for New Zealand (NZ). The symposium welcomed international speakers from the Centers for Disease Control and Protection (CDC) and St. Jude's Children's Research Hospital in the United States (US), and representatives from the Ministry of Health, the Institute of Environment and Scientific Research (ESR), the University of Auckland, the University of Otago, and stakeholders and service providers throughout NZ.

In the 21st Century, influenza remains a global threat. New influenza virus strains with pandemic potential continue to emerge, while seasonal influenza results in significant morbidity and mortality, particularly, in the youngest, oldest and those with underlying medical conditions worldwide. To reduce the burden of disease, better access to effective vaccines is needed.

Influenza surveillance and epidemiology in New Zealand

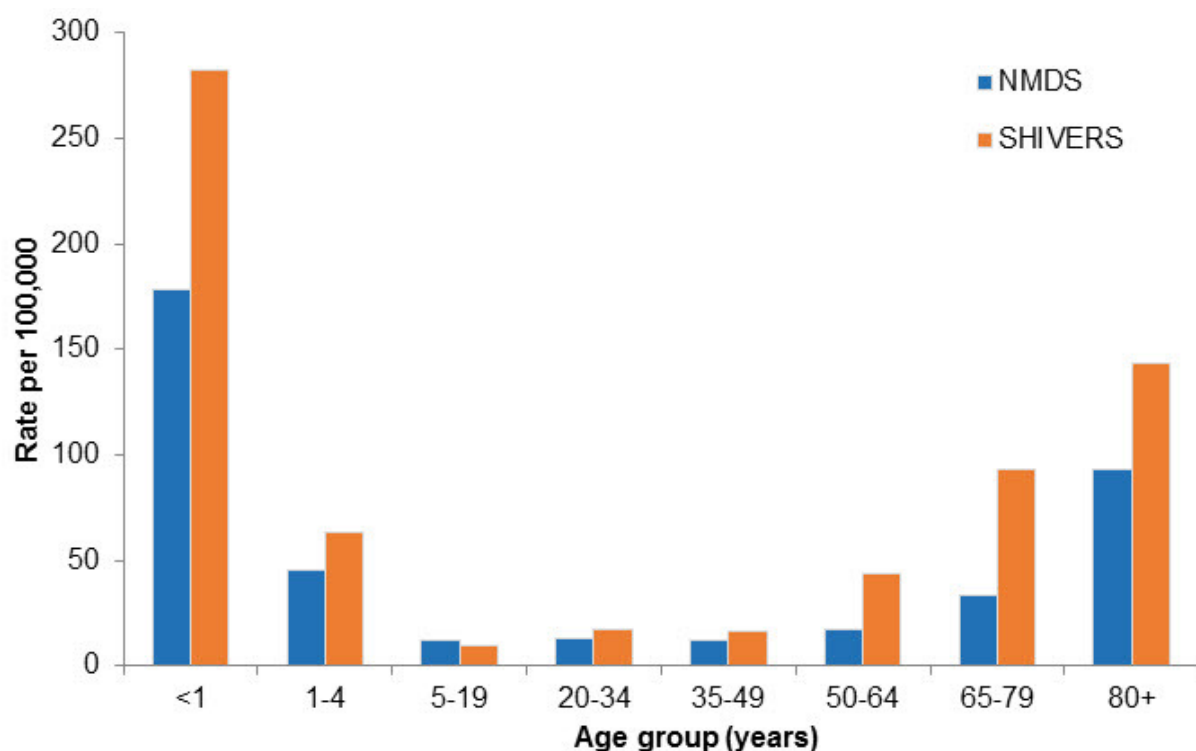
During the 1918 influenza pandemic, 8600 people died in NZ in just two months, with the greatest burden seen in Māori. Following the pandemic, the Health Act 1920 was passed providing New Zealand with an effective public health system and notifiable disease reporting.

The National Influenza Centre at the ESR has coordinated the influenza surveillance network since 1991. This network monitors the incidence of influenza-like illness (ILI) and identifies circulating influenza virus strains. Data is obtained weekly from sentinel general practices during the influenza season and virology information is collected year-round from outpatient clinics and hospital inpatients. This data is used to inform the NZ influenza prevention strategy and assist the World Health Organization (WHO) with the seasonal influenza vaccine strain selection.

The Southern Hemisphere Influenza Vaccine Effectiveness Research and Surveillance (SHIVERS) project has been conducted in Auckland since 2012, funded by the Centers for Disease Control and Prevention (CDC).¹ NZ is an ideal location for such a study on seasonal influenza as it has a winter predominance of influenza, a well characterised diverse population with almost complete (98%) registration with general practices and unique health identifiers, and the laboratory detection of influenza virus strains and other respiratory viruses by RT-PCR. Two sentinel surveillance systems are used by this study: general practice ILI surveillance and hospital severe acute respiratory illness (SARI) surveillance.

The overall study aims are to better understand the diagnosis and severity of influenza, to evaluate vaccine effectiveness, respiratory outcomes and risk factors for SARI, and to improve strain prediction for vaccines.

Figure 1. Age-specific influenza hospitalisation rates, May–September 2012, SHIVERS and NMDS data²



To date, the SHIVERS project has confirmed data from the national minimum data set (NMDS), for the age groups at highest risk for severe influenza and hospitalisation in New Zealand (Figure 1).² Further, the significance of influenza in SARI hospitalisations, particularly, of the very young, the elderly, the most socially deprived and those with Māori and Pacific ethnicities has been highlighted.³ The study is also investigating the risks associated with non-influenza causes of SARI hospitalisations.

Modelling burden of disease—the burden of disease associated with influenza is difficult to quantify, largely because influenza mortality is not always recorded or determined post-mortem. Poisson regression modelling, linking recorded respiratory disease deaths to influenza virus isolates over the 1990–2008 period, has estimated that an average of 400–500 deaths are associated with influenza

each year in NZ. This estimate was 17 times higher than the reported influenza-coded deaths; and around 86% of deaths were in the 65+ year old age group.^{3,4}

Progression of influenza to severe disease (SARI) is dependent on exposure and susceptibility. Prolonged exposure to individuals coughing and sneezing due to domestic overcrowding is associated with an increased risk of SARI. Māori and Pacific Islanders are among the most socioeconomically deprived populations in NZ, and are more susceptible to ILI developing into severe disease than other ethnicities. NZ modelling indicates that a 20–25% decrease in hospitalisation of these high-risk populations could be achieved if domestic overcrowding is removed⁵.

Influenza vaccines

Influenza vaccines have an excellent safety record, including when given during pregnancy, and provide a moderate level of protection to most people. The influenza vaccines available globally include inactivated trivalent (TIV), quadrivalent (QIV), and live-attenuated influenza vaccine (LAIV). Over 150 new influenza vaccines are also in development aimed at improving vaccine effectiveness and strain coverage.

Vaccine effectiveness—Vaccine effectiveness (VE) is a measure of how a vaccine performs in ‘real life’ at preventing disease when administered to a diverse population. SHIVERS uses a “test-negative design” to measure VE on all individuals who present to their general practice or to hospital with an acute respiratory illness (ILI and SARI) and are laboratory tested for influenza.⁶ VE is calculated as $1 - \text{OR}$ (odds of vaccination among influenza positives to the odds of vaccination among influenza negatives). Interim data for 2014 has shown that the vaccine effectiveness (VE) was 67% (95% CI 48–79%) for preventing general practice visits with influenza and 54% (95% CI 19–74%) against hospitalisations with influenza.⁷

Recent meta-analyses of data from international VE studies of ambulatory and hospitalised patients indicate that, when all variability due to age, season and year are considered, influenza vaccine has the potential to prevent over half the of all medically-attended influenza illnesses;^{8,9} this has also been demonstrated in studies of vulnerable populations, including pregnant women and severely ill children.^{10,11} VE is relative to attack rate and burden of disease. Since influenza vaccines are imperfect, many patients who contract influenza will also have been vaccinated. Research is needed to explore further whether or not disease severity is reduced by vaccination.

Options to improve VE are being investigated, particularly as the individuals at highest risk of severe influenza are likely to be poorest responders to vaccine. In the US, the Advisory Committee on Immunisation Practices (ACIP) is considering a number of ‘vaccine strategies,’ including offering a high-dose inactivated influenza vaccine for the elderly, a second dose of vaccine in the same season for the immunocompromised and alternating between live-attenuated and inactivated influenza vaccines for children to broaden the spectrum of protection year on year.¹²

Vaccine safety—Influenza vaccines have an excellent safety record. A recent Cochrane systematic review of clinical trial literature found no evidence of serious adverse events, including multiple sclerosis, optic neuritis, immune thrombocytopenic purpura, or evidence of abortion or neonatal death during pregnancy associated with seasonal or H1N1-pandemic influenza vaccines.¹³ Despite this, concerns around vaccine safety are a frequently cited reason for not receiving influenza vaccine.

Passive safety surveillance methods have occasionally highlighted adverse reactions to certain influenza vaccines, such as febrile convulsions in children under 9 years of age linked to the TIV vaccine, Fluvax®, in 2010, and more recently, the adjuvanted pandemic vaccine, Pandemrix®, has been confirmed as a trigger for narcolepsy in possibly susceptible children and adolescents. Safety signals, particularly for rarer conditions, are not likely to be detected by passive surveillance in NZ due to the small population size.

Recognising the need for better and timely safety data, innovative approaches are being employed for active surveillance of influenza vaccine safety in Australia. The SmartVax is a mobile app for vaccine recipients directly linked to the practice management system that allows the reporting of reactions by text for 3 days post vaccination; 72% of recipients responded in a 2014 study. Other examples are Vaxtracker and Ausvax.

Global influenza—the international context and ecology

Globally, short-term predictions can be made regarding future influenza strain circulation in temperate countries, while in tropical climates influenza is unpredictable. Individual influenza subtypes may show seasonal peaks of activity in tropical countries, however the contribution of each influenza-A subtype varies by time and place, making influenza circulation impossible to model and vaccine strain selection and timing decisions difficult.

One obstacle to most global immunisation programmes is the common misperception that influenza is a mild disease and of low healthcare priority. In actuality, influenza results in a substantial burden of severe disease and death in lower income countries, especially of children. Poverty is a significant risk factor for severe influenza. Limited access to immunisation increases the risk from secondary infections like bacterial pneumonia due to *Streptococcus pneumoniae*, and limited access to healthcare results in untreated chronic conditions, such as sickle cell disease, TB and HIV, which may increase influenza disease severity.^{14,15}

Pandemic influenza—From time to time novel influenza viruses emerge with pandemic potential for humans. When little or no pre-existing immunity exists, these viruses are able to spread rapidly, often with increased disease severity and mortality. Influenza viruses are usually non-pathogenic and abundant in wild aquatic birds and their environment. The transmission of influenza viruses out of their natural environment to humans is extremely infrequent and requires very close contact. Changes in viral proteins are necessary for interspecies transmission since mammals and birds have different attachment receptors.^{16,17} Table 1 describes animal hosts for influenza from whom pandemic strains could evolve. An influenza risk assessment tool (IRAT) is used by the CDC to determine the potential risks to humans from a novel viral strain.¹⁸

Table 1. Influenza ecology (adapted from presentation by R. Webby)

Animals	Viral strains	Receptor Location	Viral spread	Pathogenicity
Aquatic ducks and shorebirds	Natural reservoir, all influenza strains	Avian α 2-3 Intestinal	Faecal-oral, migratory birds in large populations; actively shedding	No disease
Domestic poultry	Certain avian strains	Avian α 2-3 Respiratory	Rapidly evolving interspecies transmission	Low or high. Includes H5, H7, H9, H10
Swine	Certain avian and mammalian	Mammalian α 2-6 Respiratory	Active influenza in pig farms, some pig to human spread.	Seasonal symptomology, H1 H3

The current seasonal influenza vaccines offer limited cross-protection and are poorly immunogenic against newly emerged drifted strains. Strain-specific pandemic vaccines are unlikely to be available to prevent influenza spread or limit disease severity in the early waves of a pandemic. However, as the number of vaccine manufacturers increases along with planned decentralisation, the capacity for vaccine production may be increased worldwide. Examples of potential pandemic avian and swine influenza strains are shown in Table 2.

Table 2. Potential pandemic influenza strains

Strain	Zoonotic species	Receptors location	Known locations	Characteristics of human disease
H7N9	Poultry	URT / LRT ^{19, 20}	China	Hu:hu – limited Severe disease in adults with comorbidities and elderly, not children High number of cases
H5N1	Poultry	LRT ²¹	S. E Asia Egypt Isolated cases reported outside of Asia	SARI, highly pathogenic Hu:hu - limited
H9N2	Poultry	URT	China, Romania, India, Vietnam, and Cambodia Egypt ²²	Seropositivity following exposure to poultry COPD risk factor for SARI
H3N2v	Swine	URT	US	Acquired at swine fairs & county shows ¹⁶ Hu:hu - limited
URT – upper respiratory tract; LRT – lower respiratory tract; Hu:hu – human to human transmission COPD – chronic obstructive pulmonary disease				

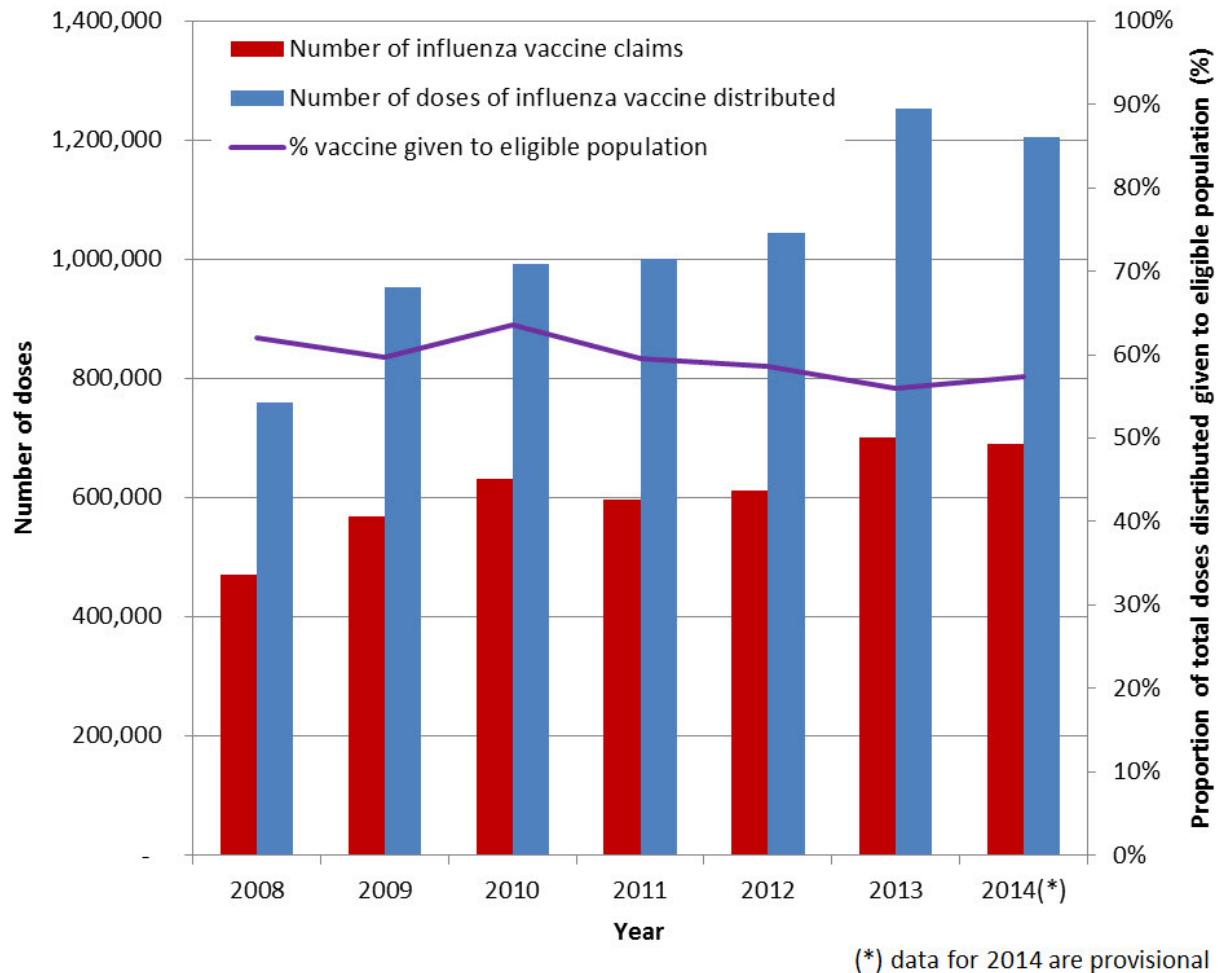
Influenza immunisation programme in NZ

To inform policies aimed at reducing the burden of disease, the Ministry of Health uses tools such as the National Immunisation Register (NIR), monitoring of vaccination claims from vaccine-eligible populations and VPD surveillance. However, the current data for monitoring influenza vaccine uptake and the determination of denominators to calculate coverage have limitations. For example, information on unfunded vaccine recipients is not recorded and the size of the population eligible for funded vaccine is only available for those aged 65 years or older.³ Nevertheless, as of September 2014, provisional data showed that the 2014 target of 1.2 million doses was achieved.

More than 60% of the 691,245 claimed doses were administered to the 65 year and over age group, with a 67% coverage, and 513,478 doses were privately purchased. Overall, the number of influenza

vaccine doses distributed and claims for funded vaccine have both increased since 2008, as shown in figure 2. Vaccination is predominantly delivered by general practices (funded and unfunded influenza vaccine), occupational health providers and vaccinating pharmacies (unfunded vaccine only).

Figure 2. Distribution and claims for influenza vaccine 2008 - 2014 (source: Ministry of Health, NZ)



Influenza vaccine promotion and service delivery in NZ—Since 2000, IMAC has coordinated the National Influenza Specialist Group (NISG) to promote influenza vaccine delivery through a coordinated national campaign. Annually, targeted “flu kits” are distributed to ensure healthcare providers are adequately equipped to promote and provide the season’s influenza vaccine. Influenza vaccination is also publicised through multimedia, and district health boards (DHBs) fund vaccination promotion locally.

Programme evaluation shows that receipt of annual influenza vaccination is becoming habitual for many of those eligible for funded vaccine. It is currently unknown how many eligible adults are receiving vaccine through workplace immunisation. Diabetes NZ reported that diabetic patients, especially with Māori or Pacific ethnicity and younger patients with type-1 diabetes, often do not consider influenza vaccination despite the high risk of severe disease and being eligible for funded vaccine. NISG announced that the 2015 campaign aims to focus more on this younger age group.

Pregnant women will also be a focus for the 2015 campaign as currently less than one third are being immunised.

General practices put considerable resources into the annual influenza campaign to raise awareness of influenza vaccination and to encourage uptake by both eligible and ineligible patients and their families. Preplanning, recall systems and dedicating resources are necessary prior to and during the influenza season.

DrInfo is an audit tool, used by about 550 practices across NZ, which identifies patients eligible for funded influenza vaccine and also offers a fully automated patient contact service. DrInfo was presented as an example of tools available to support systematic approaches to delivery in general practice. DrInfo data estimates from practice lists that 62% of elderly patients had received funded vaccine through their general practice for the 2014 season.

Vaccination in pharmacies is becoming more widely available. Of the people who purchased influenza in pharmacies in 2014, 42% had never received influenza vaccine previously, and included some eligible for funded vaccine.

Immunisation of healthcare workers—Outbreaks of influenza are common in healthcare settings worldwide, and are often under diagnosed. Nosocomial influenza infections can lead to death in the most vulnerable or prolong hospital stays leading to greater costs. In addition, the absenteeism of healthcare workers (HCWs) due to illness may result in poorer service delivery within the healthcare system.

Unvaccinated HCWs are at more than three times greater risk of having influenza than other unvaccinated adults. They are likely to be exposed to influenza aerosols if they are within two metres of infected patients^{23, 24}. A randomised clinical trial in two teaching hospitals in the US showed that vaccination was 88% effective in preventing influenza and reducing sick leave of HCWs²⁵. When HCWs in geriatric long-term care facilities in Glasgow, UK were vaccinated in a randomised study, patient mortality decreased from 17% to 10%²⁶.

Since 2010, DHBs have funded voluntary vaccination of their staff and, in 2014, in 75% of the DHBs coverage was over 50%. As HCWs have been shown to play a significant role in transmitting influenza to patients, there appears to be a role for mandatory influenza vaccination of HCWs in NZ, to benefit both patients and staff.

Conclusions and recommendations

Overall, the NZiS 2014 concluded that the healthcare community in NZ is being proactive to implement vaccination, and is collecting effective surveillance data and reporting on vaccine safety. In 2014, an estimated 27% of the population were vaccinated against influenza – which is considered a good achievement. Table 3 summarises the key issues affecting influenza immunisation programmes in NZ and areas of improvement identified by the symposium.

Through influenza surveillance and burden of disease modelling, those most at risk of hospitalisation due to SARI have been more clearly defined. The SHIVERS project has identified that there are pronounced inequalities in NZ particularly by age, ethnicity and socioeconomic deprivation levels in association with influenza hospitalisations.

A greater awareness of the severity of influenza will be necessary to improve uptake by high risk people eligible for funded vaccine. Further surveillance around the burden of disease and vaccine effectiveness and safety will be necessary to achieve this. Also improvements in the presentation of the scientific evidence are required to maintain and improve confidence both for healthcare professionals and the public.

Influenza vaccine effectiveness is moderate and the vaccine is likely to be less effective in more vulnerable groups. Alternative vaccine strategies could improve effectiveness in these higher risk groups. Much work remains to improve immunisation coverage overall and to protect individuals at greatest risk from influenza and their close contacts. Vaccination should be discussed at every opportunity by primary and secondary healthcare providers particularly for those at higher risk, including in general practices, pharmacies, outpatient clinics and with maternity providers. Globally, improvements in vaccine coverage are necessary, especially for children and pregnant women.

A possible role of universal influenza vaccination for young children in NZ was discussed. This strategy would encompass all children and eliminate the need for extra steps to identify at-risk children. Vaccination of all young children may also protect other at-risk age groups via herd immunity, since young children are the most likely to transmit influenza²⁷. However, the challenge in making such a decision is to collate sufficient evidence to quantify the risk and justify the expense. Investigations into the vaccine effectiveness and safety of inactivated versus live-attenuated influenza vaccines, as used in the UK and the US, for children are also necessary.

Table 3. Summary of the key issues and areas of improvement associated with influenza immunisation in New Zealand as highlighted by the NZiS

Inequality issues	<ul style="list-style-type: none"> • Increased risk of hospitalisation in very young, elderly and Māori/Pacific ethnicities • Poor uptake of vaccine by eligible younger age groups • Increased disease burden due to poverty related issues, particularly overcrowded and inadequate housing conditions • Improvements needed in accessibility of funded vaccine
Areas affecting vaccine uptake	<ul style="list-style-type: none"> • Only moderate vaccine effectiveness • Unfounded concerns around vaccine safety – especially in pregnancy • Public misperception that influenza is not a severe disease • Route of administration of vaccine – fear of needles
Factors affecting vaccine effectiveness	<ul style="list-style-type: none"> • Poorer immunogenicity in those most at risk • Improvements in ring protection of vulnerable needed • Limited cross-protection – requiring annual immunisation • Predictions around vaccine strains and timing are difficult, especially for influenza in tropical regions and for pandemic influenza. • Unknown effectiveness of herd immunity
Target groups for whom an increase in vaccine uptake is a priority	<ul style="list-style-type: none"> • Pregnant women • Young adults with chronic conditions • Children – under 5 years • Māori/Pacific • Healthcare workers
Further data and surveillance required	<ul style="list-style-type: none"> • Vaccine coverage – including private purchase vaccine and denominators (such as adults with chronic conditions) • Timely mortality information • Burden of disease – moderate and severe • Active safety monitoring

Competing interests: Nil.

Author information: Mary Nowlan, Medical Writer, Immunisation Advisory Centre, The University of Auckland; Nikki Turner, Director, Immunisation Advisory Centre, The University of Auckland; Tomasz Kiedrzyński, Principal Advisor, Communicable Disease Team, Public Health, Clinical Leadership, Protection & Regulation, Ministry of Health, Wellington; Lance Jennings, Clinical Virologist, Canterbury Health Laboratories and Pathology Department, University of Otago, Christchurch.

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Correspondence: Dr M Nowlan, Immunisation Advisory Centre, General Practice and Primary Health Care, The University of Auckland, Private Bag 92019, Auckland 1142, New Zealand. m.nowlan@auckland.ac.nz

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