Effectiveness of the 2009 seasonal influenza vaccine against pandemic influenza A(H1N1)2009 in healthcare workers in New Zealand, June-August 2009

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There is uncertainty whether the 2009 seasonal influenza vaccination influences the risk of infection with the 2009 pandemic influenza A(H1N1) virus. This issue was investigated in 548 healthcare workers from Capital and Coast District Health Board, Wellington, New Zealand, presenting with influenza-like illness during the influenza pandemic between June and August 2009. All workers completed an assessment sheet and had a nasopharyngeal swab tested by real-time RT-PCR. The risk of pandemic influenza A(H1N1) infection associated with the 2009 seasonal inactivated trivalent influenza vaccine was determined by logistic regression, with adjustment for potential confounding variables. In 96 workers pandemic influenza A(H1N1) RNA was detected and 452 tested negative. The multivariate analysis did not show any effect of vaccination on PCR-confirmed influenza A(H1N1)2009 infection (odds ratio 1.2, 95% confidence interval 0.7–1.9, p=0.48). We conclude that 2009 seasonal influenza vaccination had no protective effect against influenza A(H1N1)2009 infection amongst healthcare workers. To protect against further waves of the current pandemic influenza or future pandemics in which the influenza virus is antigenically distinct from contemporary seasonal influenza viruses, it would be necessary to vaccinate with a specific pandemic influenza vaccine, or a seasonal influenza vaccine that includes the pandemic influenza serotype.

Introduction

One of the important public health issues emanating from the global response to control the influenza pandemic was whether the seasonal trivalent inactivated influenza vaccination provided any protection. The novel reassortment of the influenza A(H1N1)2009 virus, combining swine, avian and human influenza genetic sequences, suggested that seasonal vaccination would confer little or no protection against this new virus [1-3]. This view was supported by a report from the United States that vaccination with seasonal influenza vaccines, regardless of whether they contained adjuvant, induced little or no cross-reactive antibody response to pandemic influenza A(H1N1) in any age group [4,5]. Consistent with these data, a case-cohort study from the United States [6], a case-control study from Australia [7], and a case series from Canada [8] have reported that the 2008/09 seasonal trivalent influenza vaccine provided no protective effect against pandemic influenza A(H1N1) infection.

In contrast, epidemiological studies from Mexico suggested that the seasonal trivalent inactivated influenza vaccine, administered as part of a national vaccination programme in 2009, provided partial protection against the 2009 pandemic influenza A(H1N1) [9,10]. In the case-control study [9], evidence was also provided that seasonal vaccination might protect against the most severe forms of the disease. It was proposed that these findings were consistent with an older report that showed that the 1967 seasonal influenza vaccine contributed towards preventing disease in the 1968/69 influenza pandemic in those who had not received the pandemic vaccine [11]. Furthermore, studies have reported variable levels of protection among infants, children and adults at times when seasonal influenza vaccine strains were not antigenically well matched to circulating endemic strains [12-17]. However, a case-control study based on Canada's sentinel vaccine effectiveness monitoring system reported that receipt of the 2008/09 seasonal influenza vaccine decreased the risk of seasonal influenza infection as expected, but was associated with an increased risk of pandemic influenza A(H1N1) infection [18]. In the same publication, two further Canadian case-control studies and one prospective cohort study were described in which seasonal influenza vaccination was associated with a 1.4 to 2.5-fold increased risk of medically attended illness due to pandemic influenza A(H1N1) [18]. Thus, epidemiological evidence exists to suggest that the 2009 seasonal influenza vaccination may increase, decrease

or have no effect on the risk of pandemic influenza A(H1N1) infection [19].

The provision of a comprehensive occupational health programme and the availability of occupational, virology and clinical databases of healthcare workers at Capital and Coast District Health Board (CCDHB) provided a unique opportunity to investigate this issue. In this prospective study, we report the potential effect of the 2009 seasonal influenza vaccine on the likelihood of acquisition of influenza A(H1N1)2009 in healthcare workers in New Zealand.

Methods

CCDHB has a comprehensive occupational health service which established an acute on-call programme for the investigation and treatment of workers who developed symptoms suggestive of influenza-like illness (ILI) during the 2009 influenza pandemic. The programme was activated in the second week of June 2009 within six weeks of the first confirmed case of pandemic influenza A(H1N1) infection in New Zealand [20]. In accordance with CCDHB policy, all staff who developed influenza-like symptoms, at work or elsewhere, were required to consult the occupational health service. The influenza-like symptoms included, but were not limited to, fever, runny nose, sore throat and cough. They completed a standardised influenza assessment sheet, provided a nasopharyngeal swab and were prescribed oseltamivir. The influenza assessment sheet collected information on variables such as age, sex, area of work, co-morbidity, pregnancy, the time between the onset of symptoms and nasopharyngeal swab, and whether the staff member self-reported having received the 2009 seasonal trivalent influenza vaccine. Travel from New Zealand in the four weeks prior to ILI was also recorded, although the virus had become largely endemic in the community by the time the data recording started.

The swabs were combined into one tube of viral and PCR transport medium and viral RNA was extracted using the High Pure Viral Nucleic Acid kit (Roche Diagnostics). Viral RNA specimens were analysed by realtime

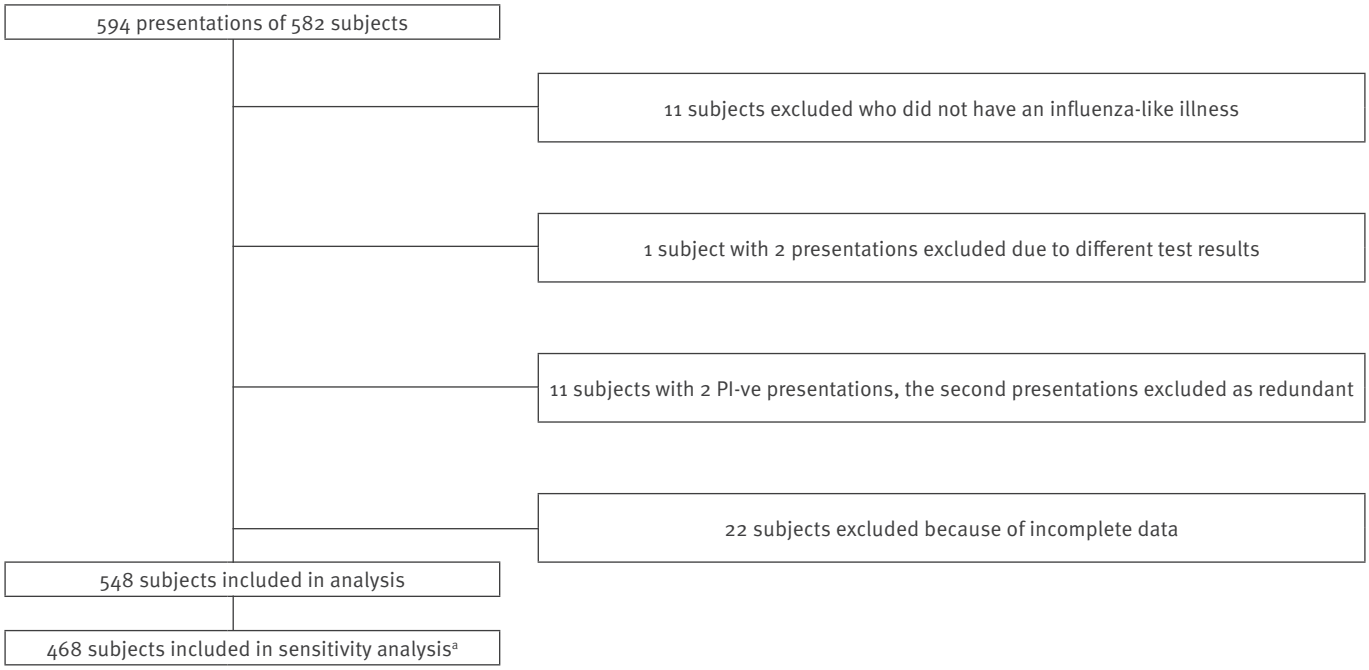
Table 1

Definition of comorbidities of study participants, New Zealand, 15 June–31 August 2009

Disorders included as comorbidity		
Respiratory	Cardiovascular	Other systemic
Asthma	Arrhythmias	Addison's disease
Bronchitis	Angina	Breast cancer on chemotherapy
Chronic obstructive pulmonary disease	Cardiomyopathy	Chronic renal failure
	Stroke	Diabetes mellitus
	Hypertension	Hepatitis B/C
	Pulmonary stenosis	Hypo/hyperthyroidism
		Inflammatory bowel disease
		Renal transplant
		Rheumatoid arthritis
		Scleroderma
		Systemic lupus erythematosus
		Thalassaemia
Disorders not included as comorbidity		
Chronic backpain/spinal fusion		
Cyclic vomiting syndrome		
Depression		
Eczema		
Epilepsy		
Fibromyalgia		
Gout		
Hypercholesterolaemia		
Irritable Bowel Syndrome		
Marfan's Syndrome		
Obstructive Sleep Apnoea		
Osteoarthritis		
Psoriasis		
Reflux gastritis		

Figure

Inclusion criteria for study participants, New Zealand, 15 June–31 August 2009 (n=582)



PI+ve: pandemic influenza A(H1N1) RNA detected by rRT-PCR; PI-ve: pandemic influenza A(H1N1) RNA not detected by rRT-PCR.

[a] 80 subjects had no documentation of OHS administered seasonal influenza vaccine

Table 2

Characteristics of healthcare workers presenting with influenza-like illness, New Zealand, 15 June–31 August 2009 (n=548)

	Mean (standard deviation)		
Variable	PI+ve N=96	PI-ve N=452	All N=548
Age (years)	37.3 (10.8)	39.5 (11.3)	39.1 (11.3)
Deprivation decile	5.4 (2.9)	5.1 (2.9)	5.1 (2.9)
Days between symptom onset and swab	1.3 (1.1) N=92	1.5 (1.6) N=418	1.5 (1.5) N=510
	n/N (%)		
	PI+ve	PI-ve	All
Male sex	30/96 (31.3)	99/452 (21.9)	129/548 (23.5)
Ethnicity			
• Not stated	8/96 (8.3)	19/452 (4.2)	27/548 (4.9)
• Māori	8/96 (8.3)	31/452 (6.9)	39/548 (7.1)
• Pacific island	9/96 (9.4)	28/452 (6.2)	37/548 (6.8)
• Other	71/96 (74.0)	374/452 (82.7)	445/548 (81.2)
Patient contact	83/96 (86.5)	353/452 (78.1)	436/548 (79.6)
Travel[a]	2/96 (2.1)	15/452 (3.3)	17/548 (3.1)
Pregnancy (women only)	1/66 (1.5)	5/353 (1.4)	6/419 (1.4)
Comorbidities	31/96 (32.3)	114/452 (25.2)	145/548 (26.5)
Hospital admission	0/96 (0)	2/452 (0.4)	2/548 (0.4)
Emergency department attendance	6/96 (6.3)	9/452 (2.0)	15/548 (2.7)
Self-reported vaccination[b]	53/96 (55.2)	233/451 (51.7)	286/547 (52.3)
OHS-documented vaccination[c]	44/83 (53.0)	186/385 (48.3)	232/468 (49.6)

OHS: occupational health service; PI+ve: pandemic influenza A(H1N1) RNA detected by rRT-PCR; PI-ve: pandemic influenza A(H1N1) RNA not detected by rRT-PCR; realtime reverse transcription PCR.

[a] International travel within four weeks before influenza-like illness symptoms.

[b] One participant missing data.

[c] Documentation of 2009 seasonal influenza vaccination in occupational health service personal files. For 80 subjects a file was not available.

reverse transcription PCR (rRT-PCR) using the Capillary Lightcycler instrument version 1.2 (Roche Diagnostics) following protocols provided by the World Health Organization Collaborating Centre for the Surveillance, Epidemiology and Control of Influenza at the United States Centers for Disease Control and Prevention [21]. Swab specimens were tested using primers targeting the influenza A matrix gene, designed for universal detection of type A influenza viruses, and the influenza A haemagglutinin (H) gene (SwH1), specifically designed to detect pandemic influenza A(H1N1)2009. A sample was defined as positive for pandemic influenza A(H1N1) when both genes were detected. Specimens testing positive for the matrix gene but with no detectable levels of SwH1 were tested for seasonal human influenza A(H1) and A(H3) virus by rRT-PCR using primers and probes from version 2007 of the CDC protocol [21]. For the purposes of the analyses in this study, participants in whom pandemic influenza A(H1N1) RNA was detected (PI+ve) were compared with participants in whom no pandemic influenza A(H1N1)2009 or seasonal strains were detected (PI-ve).

The seasonal influenza vaccine used in New Zealand in 2009 was the inactivated trivalent vaccine Fluarix (GlaxoSmithKline), containing 15µg haemagglutinin each of the three strains A/Brisbane/59/2007, IVR-148 (H1N1), A/Uruguay/716/2007, NYMCX-175C (H3N2) and B/Brisbane/60/2008.

The CCDHB and Hutt Valley District Health Board (HVDHB) patient information systems of the participants were accessed to obtain information on ethnicity and deprivation decile. In New Zealand, deprivation decile is derived from nine variables descriptive of socio-economic status relative to the location of the home, such as income, home ownership and access to transport. It ranges from 1 (least deprived) to 10 (most deprived) [22]. We also used these databases to identify whether any of the participants were admitted to or attended the emergency department of Wellington,

Table 3

Univariate associations between study participants' characteristics and confirmed pandemic influenza A(H1N1) infection, New Zealand, 15 June–31 August 2009 (n=548)

Variable	Odds ratio for association (95% confidence interval)	p value
Age (per decade older)	0.8 (0.7 to 1.0)	0.08
Deprivation decile (per level)	1.0 (0.96 to 1.1)	0.45
Male sex	1.6 (1.0 to 2.6)	0.05
Ethnicity		0.18 [a]
• Not stated	2.2 (0.9 to 5.3)	0.26 [a]
• Māori	1.4 (0.6 to 3.1)	0.76 [a]
• Pacific island	1.7 (0.8 to 3.7)	0.71 [a]
• Other	Reference level	
Patient contact	1.8 (1.0 to 3.4)	0.07
Travel[b]	0.6 (0.1 to 2.8)	0.53
Pregnancy (women only)	1.1 (0.1 to 9.3)	0.95
Comorbidities	1.4 (0.9 to 2.3)	0.15
Hospital admission	Not applicable	0.51
Emergency room attendance	3.3 (1.1 to 9.4)	0.02
Self-reported vaccination	1.2 (0.7 to 1.8)	0.53
OHS-documented vaccination[c]	1.2 (0.7 to 1.9)	0.49

OHS: occupational health service.

[a] Compared to 'Other'.

[b] International travel within four weeks before influenza-like illness symptoms.

[c] Documentation of 2009 seasonal influenza vaccination in occupational health service personal files. For 80 subjects a file was not available.

Table 4

Multivariate association between study participants' vaccination status and confirmed pandemic influenza A(H1N1) infection[a], New Zealand, 15 June–31 August 2009 (n=548)

Variable	Odds ratio for association (95% confidence interval)	p value
Self-reported vaccination	1.2 (0.7 to 1.9)	0.48
OHS-documented vaccination[b]	1.2 (0.7 to 1.9)	0.49

OHS: occupational health service.

[a] Adjusted for age, sex, ethnicity, deprivation decile, patient contact, relevant travel, pregnancy (all men coded as not-pregnant), comorbidities.

[b] Documentation of 2009 seasonal influenza vaccination in Occupational Health Service personal files. In 80 subjects no file was available.

Kenepuru and Hutt hospitals for an ILI in the two days before and the two weeks after the swab was taken. These three government-funded hospitals represent the only hospitals in the greater Wellington region which provide acute medical services. Workers admitted to hospital with an ILI were considered to have experienced a severe influenza illness.

The CCDHB occupational health service keeps the records of the assessment and treatment of healthcare workers presenting with suspected pandemic influenza A(H1N1) (including the influenza assessment sheet, PCR results and prescribed treatment). The personal files of all healthcare workers employed at CCDHB were checked for documentation of the 2009 seasonal influenza vaccination. The sensitivity analysis of the effect of the 2009 seasonal influenza vaccination was based on these records. The demographic, clinical, occupational, vaccination and virological data was entered in a database where every subject was given a unique identifier. The dataset was coded and anonymised prior to analysis.

Statistical power

With 100 cases and 450 controls and assuming a 50% immunisation rate in the controls, the study had 80% power to detect an odds ratio of 0.52.

Statistical analysis

Logistic regression was used to determine the strength of association between PCR-confirmed pandemic influenza A(H1N1) infection and self-reported seasonal influenza vaccination, unadjusted and adjusted for potential confounding variables. The variables included age, sex, ethnicity (Maori, Pacific, other, not stated), deprivation decile, relevant overseas travel, comorbidity (yes/no) (Table 1), and pregnancy (yes/no, all men coded as not pregnant). SAS version 9.1 was used for the statistical calculations.

This analysis was restricted to subjects who presented with an ILI and had documentation of the influenza assessment sheet and PCR results. Subjects who presented on more than one occasion and had different PCR results from the different presentations were excluded. In subjects who presented on more than one occasion and pandemic influenza A(H1N1) was not detected on any presentation, the data from the first presentation was included.

Results

There were 582 healthcare workers who presented on 594 occasions to the CCDHB occupational health service between 15 June and 31 August 2009 (Figure). After application of the exclusion criteria, 548 workers who had presented with an ILI were included in the analysis.

The characteristics of these participants are shown in Table 2. The mean age of the participants was 39 years (range: 20 to 69 years) and 24% were male. People of Maori and Pacific origin made up 14% of the study group. The majority of participants (80%) had clinical patient contact as part of their work. Overall, 52% of the participants self-reported having received the 2009 seasonal influenza vaccination. In 27% of participants comorbidities were reported, of which the most common were asthma and hypertension. Among the 145 healthcare workers with documented comorbidities, 82 self-reported having received the 2009 seasonal vaccine, 62 self-reported not having received it, and for one the information was missing. The mean time from the onset of symptoms to nasopharyngeal swab was 1.5 days.

Influenza A was detected by PCR in 103 of the 548 included participants. In 96 of those pandemic influenza A(H1N1) was detected, in five seasonal human influenza A(H1), in one seasonal human influenza A(H3) and in one an untypable strain of influenza A. We therefore determined 96 (17.5%) participants with confirmed pandemic influenza A(H1N1) infection (PI+ve) and 452 (82.5%) in whom pandemic influenza A(H1N1) was not detected (PI-ve).

There was no difference in the proportion of workers with and without proven pandemic influenza A(H1N1) infection who reported having received the 2009 seasonal influenza vaccination, with 53 of 96 (55.2%) infected and 233 of 451 (51.7%) not infected at an odds ratio of 1.2 (95% confidence interval (CI): 0.7–1.8, p=0.53) (Table 2 and 3). The multivariate analysis, adjusted for age, sex, ethnicity, deprivation decile, patient contact, overseas travel, comorbidity and pregnancy, did not indicate any significant risk of pandemic influenza A(H1N1) being associated with the 2009 seasonal influenza vaccine (odds ratio: 1.2, 95% CI: 0.7–1.9, p=0.48) (Table 4).

Personal files of 468 of the participants were held by the occupational health service. In a sensitivity analysis based on the documentation from these files, we saw no significant effect of 2009 seasonal influenza vaccination on the risk of pandemic influenza A(H1N1) neither in the univariate analysis (odds ratio: 1.2, 95% CI: 0.7–1.9, p=0.49) (Table 3) nor multivariate analysis (odds ratio: 1.2, 95% CI: 0.7–1.9, p=0.49) (Table 4).

PI+ve participants were similar to PI-ve participants with regard to age, deprivation decile, pregnancy, comorbidities, relevant travel, and time between symptom onset and swab (Tables 2 and 3). There was no statistically significant difference in ethnicity between the swab-negative and swab-positive group, however this analysis was limited by the small numbers of people of Maori and Pacific origin, and the point estimates were consistent with an increased risk. Likewise, the point estimate for patient contact was consistent with an increased risk, but the difference was not statistically significant (odds ratio: 1.8, 95% CI: 1.0–3.4, p=0.07).

Fifteen people with an ILI visited an emergency department in the two days before and two weeks

after presentation to the occupational health service. Participants who attended an emergency department were more likely to be PI+ve (odds ratio: 3.3, 95% CI: 1.1–9.4, p=0.02). Two people were admitted to hospital with an ILI, both of whom were PI-ve.

Discussion

In our prospective study the 2009 seasonal influenza vaccination had no protective effect against pandemic influenza A(H1N1) infection amongst healthcare workers in New Zealand. This suggests that to obtain protection against influenza A(H1N1)2009 in the current season 2010, it would be necessary to vaccinate with a specific pandemic influenza A(H1N1) vaccine, or to include the influenza A(H1N1)2009 antigenic group in the 2010 seasonal influenza vaccine.

A number of methodological issues are relevant to the interpretation of the study findings. Firstly, by recruiting healthcare workers, we were able to study a population with a high prevalence of seasonal influenza vaccination; about half of the workers included in the study had received the 2009 seasonal influenza vaccine. Secondly, by studying workers, all of whom were under 70 years-old, we were able to investigate a group that did not have prior widespread immunity to pandemic influenza, assuming that the age-specific rates of pre-existing protective antibodies in New Zealand are similar to those in the United Kingdom [23]. All subjects presenting to the occupational health service with an ILI provided nasopharyngeal swabs which were assessed by rRT-PCR. The mean time between onset of symptoms and nasopharyngeal swab was 1.5 days, with no significant difference between groups, suggesting that delay in viral sampling was unlikely to be a confounding factor [24].

Another issue is the accuracy of the seasonal vaccination records. For the primary analysis, information on vaccination status was provided by the workers when completing the influenza assessment sheet at the time of presentation to the occupational health service. As this information was provided without knowledge of the PCR results, and the seasonal influenza vaccinations had taken place in the three months before the study, we consider the findings unlikely to be influenced by recall bias. For the sensitivity analysis, seasonal influenza vaccination status was also determined from documentation in the participants' personal files held by the occupational health service. While this approach was limited by the fact that not all workers had personal files and some workers may have been vaccinated through community services, the comparable results provided internal validity to the study findings.

Pandemic influenza infection results in disease with a wide spectrum of severity, from asymptomatic to life-threatening illness [24-26]. All participants included in our analysis presented with a symptomatic ILI, which means that asymptomatic workers with influenza infection were not included in the study. Due to the low frequency of severe illness requiring hospital admission (none among the confirmed pandemic influenza A(H1N1) cases in our study) we were unable to determine whether seasonal influenza vaccination may protect against the most severe forms of the disease.

Thanks to the prospective collection of comprehensive data at the time of presentation and the availability of clinical databases, we were able to undertake multivariate analyses in which we adjusted for variables that could have influenced the association between 2009 seasonal influenza vaccination and infection with pandemic influenza A(H1N1)2009. These factors included age, sex, ethnicity, work-related patient contact, overseas travel, pregnancy and comorbidities. This approach lent strength to our statistical analysis.

Our findings add to recent data from studies that have identified no risk [6-8], a decreased risk [9,10], or an increased risk [18] of pandemic influenza A(H1N1) infection associated with seasonal influenza vaccination. An Australian study found no evidence in any age group of seasonal influenza vaccination providing significant protection against pandemic influenza A(H1N1) virus infection [7]. In that study the population had been vaccinated with an inactivated trivalent vaccine which contained the A/Brisbane/59/2007 antigenic group as the H1N1 component, the same subtype variant included in the trivalent vaccine in our study. The strength of their study was the validity of vaccination records, virological confirmation of influenza infection in subjects presenting with ILI and the age-stratified and age-adjusted analyses.

A case-control study from Mexico demonstrated that seasonal influenza vaccination had 73% effectiveness against pandemic influenza A(H1N1) [9]. This study was limited by the choice of controls, who had a higher rate of co-morbidity and for that reason may have been more likely to receive seasonal influenza vaccination, and by the fact that the vaccination status was retrospectively collected and there was no microbiological verification of the absence of influenza infection [27,28]. Similar limitations apply to a cohort study from the United States, which did not find any protective effect of seasonal influenza vaccination on pandemic influenza infection [6].

However, these potential limitations do not apply to a subsequent large surveillance study of pandemic influenza A(H1N1) virus infection in Mexico, which showed that the risk of infection was reduced by about one third in those who had been vaccinated for seasonal influenza [10]. Although it has been suggested that these study results could have been confounded by selection bias, if elderly people who are more likely to be vaccinated were less likely to be infected with pandemic influenza due to pre-existing immunity [29], this was not supported by subsequent stratified analysis [30]. Based on data from the first and second waves

of the pandemic in Mexico up to 30 November 2009, the negative association between seasonal vaccination and risk of testing positive for pandemic influenza A(H1N1) was present across all age groups, including those younger than 60 years [30].

In contrast, three case-control studies and a prospective cohort study demonstrated a statistically significant 1.4 to 2.5-fold increased risk of medically attended illness due to pandemic influenza A(H1N1) [18]. The first of these studies, based on Canada's well established sentinel vaccine effectiveness monitoring system identified that seasonal influenza vaccination increased the risk of pandemic influenza infection to a similar extent as it reduced the risk of seasonal influenza infection (+68% versus -56%) [18]. A study of an outbreak of pandemic influenza A(H1N1) infection amongst United States military personnel also identified an increased risk of infection, although this association was limited to personnel on active duty and not their family members or retired staff [33].

The reasons for these contrasting results are uncertain. It is possible that they may be due to methodological differences between the studies, or to differences in the effect of the specific vaccines, in the immunisation programmes or in population immunity [18,34]. Regardless of the underlying reasons, these epidemiological studies suggest that seasonal influenza vaccination cannot be considered or recommended as an effective strategy for the prevention of pandemic influenza infection.

In conclusion, this study has shown that the 2009 seasonal influenza vaccination provided no protection against pandemic influenza A(H1N1) infection in healthcare workers in New Zealand. To obtain protection against subsequent waves of the pandemic influenza A(H1N1)2009 by vaccination, it would therefore be necessary to either vaccinate with a specific pandemic influenza vaccine or a seasonal influenza vaccine which includes the influenza A(H1N1)2009 subtype. The findings also suggest that in future influenza pandemics in which the virus is antigenically and genetically distinct from contemporary human seasonal influenza viruses, development of a specific pandemic influenza vaccine is a high priority, as partial protection by the contemporary seasonal influenza vaccines cannot be assumed.

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