



Seroprevalence of the 2009 influenza A (H1N1) pandemic in New Zealand

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Summary

A national representative seroprevalence study of Pandemic Influenza A (H1N1) 09 in the general population in New Zealand was essential to evaluate immunity and incidence of infection in populations, to identify protective or risk factors and groups at higher risk, and to provide evidence for decisions on effective vaccination and other public health interventions. This study evaluated immunity in the community and among healthcare workers (HCWs).

We collected 1696 serum samples and individual risk factor data by questionnaire between November-2009 and March-2010, three months after the 2009 H1N1 pandemic. Participants aged at least one year were randomly sampled from selected general practices countrywide and hospitals in the Auckland region. In addition, 521 pre-pandemic sera collected during 2004 to April-2009, were used to establish baseline immunity. All samples were tested for haemagglutination inhibition (HI) antibody to 2009 H1N1. A titre of 40 or higher was taken as being seroprotective, and the participant was considered to have immunity to 2009 H1N1 influenza.

The overall community seroprevalence was 26.7% (CI:22.6-29.4) for the study population. The seroprevalence varied with age and ethnicity. Children aged 5-19 years had the highest seroprevalence 46.7% (CI: 38.3-55.0), a significant increase from the baseline 14.0% (CI:7.2-20.8). This is followed by pre-school children aged 1-4 years at 29.5% (CI:21.2-38.0) an increase of 23.5% from a baseline of 6.0% (CI:0.9-11.0). Age group 60+ had no significant difference in seroprevalence between the serosurvey, 24.8% (CI:18.7-30.9), and baseline, 22.6% (CI:15.3-30.0).

Pacific Peoples had the highest seroprevalence 49.5% (CI: 35.1-64.0) followed by Maori at 36.3% (CI: 28.0-44.6). Pacific and Maori peoples also had much higher hospitalisation and intensive care unit admission rates compared with European and other groups. This finding is consistent with the clinical surveillance results reported during the pandemic.

Primary (29.6%, CI: 22.4-36.3) and secondary (25.3%, CI: 20.8-29.8) healthcare workers (HCW) had no significant difference in seroprevalence compared to the community participants. The seroprevalence for doctors, 29.9% (CI:21.9-37.9), was slightly higher than that of nurses, 27.5%(CI:21.3-33.7), which is higher than the 'other' occupational category 25.0%(CI:18.7-31.3), but there is no significant difference demonstrated in this sample.

Multivariate analysis indicated age as the most important risk factor followed by ethnicity and a history of previous seasonal influenza vaccination. The likelihood of immunity to pandemic influenza among the age group 5-19 and age group 1 – 4, respectively, was 5.3 times (CI:3.2-8.7) and 3.5 times (CI:2.0-6.2) higher compared with that of age group 40-59 (the reference group). No significant regional variation was observed. The likelihood of immunity to pandemic influenza was 2.2 times (CI:1.5-3.4) higher among the Pacific People compared with that of the “Other” ethnic group (the reference group).

Our cross-sectional study showed that participants with a history of any seasonal influenza vaccination were 1.8 times ($p=0.012$) more likely to have HI titres of ≥ 40 compared with those who have never been vaccinated. This protective effect was more marked in the younger age groups, 1-4 and 5-19 years. The overall low level of cross-reactive antibodies acquired from seasonal A(H1N1) vaccination however, would not provide effective protection against 2009 H1N1 among individuals, particularly for those aged less than 60 years. Such optimal protection against 2009 H1N1 would only be achieved with strain-specific pandemic vaccine.

Based on the questionnaire survey approximately 45.2% of seropositive individuals had no symptoms giving an indication of a relatively ‘silent’ spread of the disease in a naive population. Such findings have major implications for limiting spread of the infection in a second wave of 2009 H1N1.

Severity of disease is indicated by hospitalization and mortality. Based on our findings of the total number of symptomatic cases estimated at 428,463 the case fatality rate was 8.2 per 100,000 (0.008%, 35/428,463) and the hospitalization rate was 262 per 100,000 (0.262%, 1122/428,463). Both these estimates are lower than previously estimated values.

In conclusion, the pandemic virus was highly infectious resulting in substantial proportions of both symptomatic and asymptomatic infections. Based on age and ethnicity standardisation to the national population, an estimated 29.5% of New Zealanders (1.3 million) had immunity to 2009 H1N1 at the end of the study period. An estimated 18% of the NZ population (800,000) were infected with the virus during the first wave including one child in every three. Older people had a high prevalence of pre-existing immunity which protected them against infection. Being a healthcare worker did not appear to increase the risk of infection compared to the general population. Pacific Peoples had the highest seroprevalence in comparison to other ethnic groups.

The results of this seroprevalence study would support vaccination strategies to target those at risk of adverse health outcomes and boosting immunity in specific population groups (such as children, Pacific/Maori people) to prevent further transmission.

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1 Introduction

The detection of the 2009 pandemic influenza A (H1N1) (2009 H1N1) virus in the United States and Mexico in April 2009, followed by widespread infection worldwide, prompted the World Health Organization (WHO) to declare the first pandemic in 41 years.¹⁻³ Non-seasonal influenza (capable of being transmitted between human beings) became a notifiable and quarantineable disease in New Zealand on 30 April 2009. From 1 April to 31 December 2009, a total of 3211 confirmed cases of 2009 H1N1 had been reported to the national notifiable disease database (EpiSurv), including 1122 hospitalisations and 35 deaths.⁴ Highest notification rates were seen in the less than one year age group, and high notification and hospitalisation rates were seen among Pacific Peoples and Maori.

Estimating the true number of pandemic influenza cases in New Zealand from notification figures is not possible as the vast majority of such cases were not notified after community spread was established in the country in June 2009. Sentinel systems for influenza detection while useful for early warning do not enable estimation of disease prevalence as many ill people may not seek medical care. Even those that seek care may not be investigated further to establish a diagnosis. The proportion of asymptomatic individuals in the community is unknown as is the national population immunity status. Various models have been utilised to estimate the progress of the first wave of the pandemic but these have had to depend on imprecise assumptions as many key variables are unknown.

Public health measures including vaccination are available to minimise the impact of the pandemic. A direct serological measure of the population immunity profile in a community is essential for evidence-based decisions on a targeted and cost-effective vaccination programme. A direct measure of the baseline age-specific immunity profile of the population and the changes that resulted from 2009 H1N1 during the first wave provides new insights on the incidence of clinical and subclinical infection as well as higher risk groups with related risk factors, to inform modelling initiatives for predicting future disease incidence and effective interventions.

This report describes the population immunity profile from the results of a randomized cross-sectional seroprevalence study in the community and a study of healthcare workers after the first wave of 2009 H1N1. The incidence of 2009 H1N1 was estimated by measuring neutralising antibodies to 2009 H1N1 before and after the first wave. The risk factors for 2009 H1N1 were also documented by information collected from questionnaires.

2 Methods

2.1 Study design and population

Both the community and healthcare worker studies involved a multi-stage random cross-sectional serological survey and a questionnaire evaluating demographics and potential risk factors.

2.1.1 Community study

The study population consisted of the registered patients enrolled in the selected GP practices and were individuals residing in New Zealand before, during and after the first wave of the pandemic. Random samples of patients stratified by age group and ethnicity were obtained from the study population during the period November 2009 to March 2010 when only 3 cases of 2009 H1N1 were notified in New Zealand (Figure 1). Therefore, serological results from these samples reflected immunity acquired during the first wave from April to September 2009 as well as any pre-existing immunity. The Table 1 below indicates the population specifications.

Table 1 Population specifications at national level

Population	Definition and criteria
External population	NZ population
Target Population	GP enrolled population
Study population	All individuals residing in New Zealand prior to the onset of the pandemic and during its course and preferably registered with one of the selected Sentinel GP practices across the country
Sample	Randomly selected patients from the study population stratified by age and ethnicity

This study included 14 GP practices across the country, located in Auckland, Waikato, Bay of Plenty, Mid-Central, Wellington region (Newlands, Porirua, and the Hutt Valley), Canterbury, and Otago. The study localities were selected in predetermined areas based on observed incidence rate during the pandemic as high, medium and low, as well as the ethnic distribution. Within each study area GP practices were approached (initially through the Medical Officers of Health in most cases) requesting participation. Practices already participating in the sentinel system for seasonal influenza surveillance were preferred.

Within each practice, registered and enrolled patients were stratified by age group and ethnicity. Age (in years) was categorised into five groups as 1 to 4, 5 to 19, 20 to 39, 40 to 59, and 60 or older. Ethnicity was recorded according to New Zealand census classification, but was divided into three categories as Maori, Pacific Peoples and Other (other than Maori and Pacific Peoples ethnic groups) for the analysis. The stratification by age group and ethnicity resulted in 15 strata. Within each stratum simple random sampling was performed to select sufficient numbers of participants. Taking into account stratification, a minimum sample size of 1500 participants was required, at design prevalence of 20% and confidence level (CI) of 95%, to maintain +/-10% acceptable margin error of the estimate.

Following random selection from the study population, a selected individual was contacted by telephone. A questionnaire was administered to collect exposure and risk factor information. The questionnaire included information on the participant's demographics, history of influenza-like illness (ILI) and other acute illnesses, contact with ILI patients, general health status, vaccination history, and living conditions. Information sheets, consent forms and blood sample request forms were made available to the participants. Arrangements were made to counteract the expected low response from minority ethnic groups by systematic recruitment during consultations. Three general practices in high minority group communities utilized recruitment at consultation as the preferred method. Similar expected low response for the very young was minimised by offering finger-prick sampling. A 5 ml venous or finger-prick blood sample was collected and transported to the WHO National Influenza Centre (NIC) at Institute of Environmental Science and Research (ESR) for haemagglutination inhibition testing. In total 1156 participants were enrolled in the community study. Of these, nine participants did not have sufficient blood volume for analysis.

In an effort to measure any recruitment bias we asked non-respondents to inform the person contacting them by telephone if they had had an ILI or doctor diagnosed 2009 H1N1 during the pandemic. We also obtained information on their age and ethnicity to enable comparison with the demographics of participants.

2.1.2 Healthcare worker (HCW) study

The study population included secondary HCWs located in Auckland and Middlemore hospitals and primary HCWs from the GP practices included in the community study. HCWs were divided into three categories as medical, nursing, and other staff (including allied health and support staff). A stratified random sample was obtained from the hospital HCWs. A simple random sampling procedure was performed within general practices that had more than 25 staff members to select sufficient numbers of participants. Practices with less than 25 staff were encouraged to recruit all staff members. In total 540 HCWs were enrolled in the study during the period January to March 2010. This comprised 369 secondary HCWs and 171 primary HCWs.

2.1.3 Baseline study

The baseline immunity to 2009 H1N1 was measured from 521 serum samples taken before 22-April 2009 from individuals aged 1 to 98 years. 184 serum samples collected from children aged 1-19 years during 2004-2005 were obtained from ESR's Invasive Pathogen Laboratory and 337 collected from adults aged 20+ years during 16-December 2004 to 22-April 2009 were obtained from NIC. These were residual samples from opportunistic sera submitted to the laboratories for diagnostic testing or antibody screening. Only information about age, sex, sample collection date and collecting laboratory was available for these samples.

2.2 Data collection

Figure 1 below shows the study period in relation to the epidemic curve of the first wave of pandemic influenza in New Zealand.

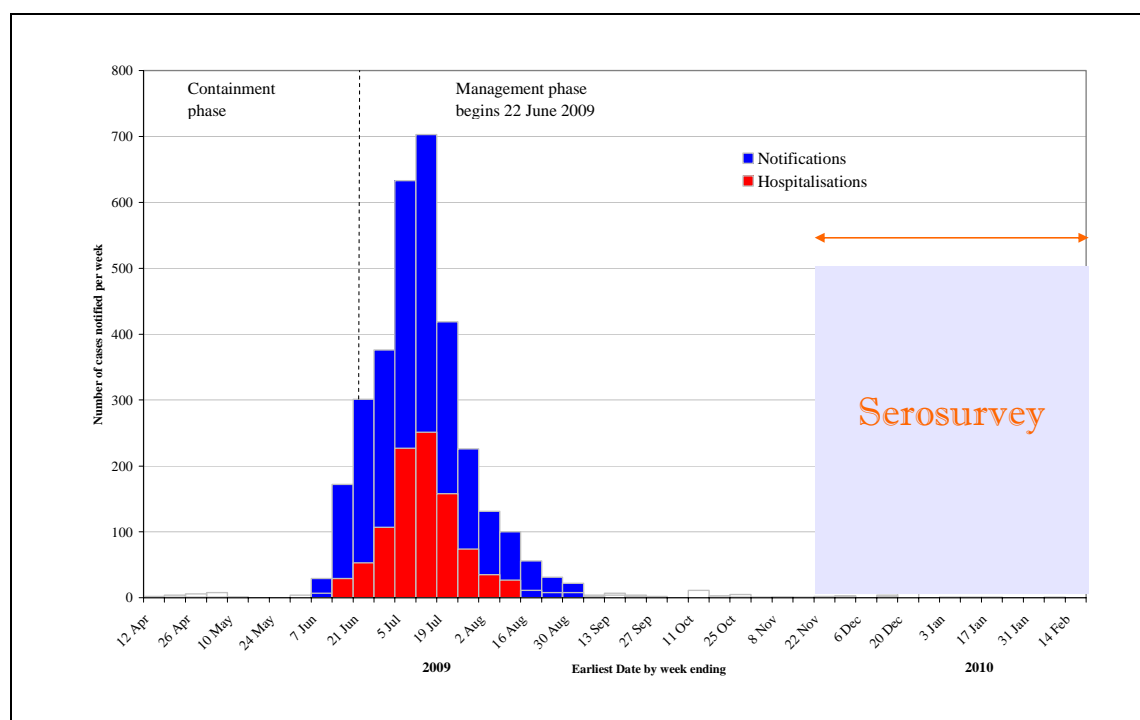


Figure 1 Epidemic curve of the first wave of pandemic influenza in New Zealand and the serosurvey period

2.2.1 Serosurvey data

We collected a total of 1156 samples for the community seroprevalence study, and 540 for the HCW study (including 171 primary HCWs, and 369 secondary HCWs), as well as individual risk factor data through a questionnaire between November-2009 and March-2010, three months after 2009 H1N1. All samples were tested for haemagglutination inhibition (HI) antibody to 2009 H1N1. A titre of 40 or higher was considered seropositive, and the participant was considered to have immunity to 2009 H1N1 pandemic.

The questionnaire was pretested at the Ropata Medical Centre, one of the participating practices. It consisted of 28 questions including information about participant's demographics, influenza-like illness (ILI) and other acute illnesses over the last winter, contact with ILI patients over the last winter, general health, vaccination, and living situation. Ropata Medical Centre was used as a proof of concept for the study to determine feasibility.

Table 2 shows demographic characteristics of the total samples collected for the community seroprevalence study, healthcare workers, and baseline data.

Table 2 Sample demographics for the community study, healthcare worker, and baseline data

Demography	Community Study		Healthcare workers		Baseline	
	Number of samples	Percent (%)	Number of samples	Percent (%)	Number of samples	Percent (%)
Age group (years)						
1 to 4	152	13.2			84	16.1
5 to 19	209	18.1			100	19.2
20 to 39	221	19.2	238	44.2	106	20.4
40 to 59	258	22.4	250	46.4	107	20.5
60 and over	314	27.2	51	9.5	124	23.8
Ethnic group						
Maori	184	15.9	24	4.6		
Pacific	171	14.8	18	3.4		Not Available
Other	801	69.3	485	92.0		
Gender						
Female	640	55.6	436	80.7	176	52.4
Male	511	44.4	104	19.3	160	47.6
Study area						
Auckland	269	23.3	423	78.3		
Waikato	107	9.3	-	-		
Bay of Plenty	122	10.6	18	3.3		
MidCentral	113	9.8	-	-		Not Available
Wellington	370	32.0	78	14.4		
Canterbury	109	9.4	-	-		
Otago	66	5.7	21	3.9		
Overall	1156		540		521	

2.3 Laboratory method

Antibodies against the pandemic A(H1N1)09 virus were detected by using haemagglutination inhibition (HI) assay, according to standard methods^{5, 6} at the WHO NIC, ESR. NIC followed the standard operating procedures provided by the WHO Collaborating Centre (WHOCC) in Melbourne, Australia. Verification procedures confirmed the specified performance characteristics of the assay as previously determined by WHOCC regarding accuracy, precision and the reportable range. A panel of positive sera (20) with known HAI titres were sourced from the WHOCC-in Melbourne. In addition, a panel of presumed negative sera (61) collected prior to May 2009 were sourced from NIC's retrospective sera collection.

The HI assay used 1.0% guinea pig erythrocytes. A reference antigen, pandemic influenza A/California/7/2009 virus propagated in embryonated chicken eggs, was provided by WHOCC-Melbourne. Serial two-fold dilutions of serum were tested beginning with a 1:10 dilution and a final dilution of 1:1280. Suitable control serum samples were included in all assays, including post-infection ferret serum samples raised against the A/Auckland/1/2009 strain and a known human sample with a known HI titre as a positive control. All human sera samples were treated with receptor destroying enzyme (RDE) (Vibrio Cholera Neuraminidase) and guinea-pig erythrocytes to inactivate non-specific inhibitors of viral haemagglutination. The antibody level was measured as the titre of haemagglutination inhibition. The reciprocal

of the highest dilution causing complete haemagglutination inhibition of erythrocytes by the 2009 H1N1 virus was used as a measure of the antibody level to the pandemic virus. It has been shown that serum HI antibody titres of 40 and more (40+) are correlated with a reduction of 50% of the risk of contracting an influenza virus infection or influenza disease.⁷⁻¹⁰ Thus, in this study, an HI titre of equal to or greater than 40 is used as the threshold of seroprotection as well as seropositivity. Geometric mean titres (GMTs) were estimated by assigning a value of 10 for titres of 10 or lower and a value of 1280 for titres of 1280 or higher.

2.4 Data analysis and statistics

For the community seroprevalence study, individuals have had different probabilities of being selected for the sample, due to stratification and unequal allocation. Therefore, stratified and weighted analysis was performed to account for the study design. Rao-Scott Chi-squares test, which is a design-adjusted version of the Pearson chi-square test was used to test the significance of the estimates at p value equal to 0.05.

Descriptive analysis

We performed descriptive analysis for the categorical and numerical data using the SURVEYFREQ and SURVEYMEANS of SAS 9.1 version (SAS Institute Inc., Box 8000, Cary, NC), respectively. These procedures allow incorporating the sample design by specifying the age-ethnicity strata and sampling weights.

Multivariable analysis

The main hypothesis being tested in this analysis was whether age group or ethnicity affected the likelihood of infection to pandemic A(H1N1) 09. Multivariable survey logistic regression was the method of choice since the outcome was binary (1 = evidence of infection to pandemic A(H1N1) 09, 0 = no evidence). From the 1122 participant, this analysis included 820 who had complete information for age, ethnicity, serology results, and for selected risk factors.

Univariable screening analysis for inclusion was done at $P < 0.2$. Variables associated with seropositive test at $P \leq 0.2$ were then included into a multivariable survey logistic regression model. Pearson correlation was performed to assess the correlation between risk factors. If factors were significantly correlated, then only one of these was selected for the model. Variables were allowed to remain in the model if statistically significant at $P < 0.05$ using stepwise selection, with seroprotective status (0/1) as the dependent variable. Potential confounders such as housing condition and seasonal vaccination history were forced into the model. Interaction terms were constructed from main effect variables and tested for significance. The final model included age group, ethnic group and sex, vaccination history, chronic illness, and reported damp housing as independent variables:

$$\text{Log}(P/1-P) = \beta_0 + \sum \beta_i X_i$$

where P is the probability of seropositive test ($P(\text{titre} \geq 40)$), given explanatory variables X_i , age group (categorized as 1-4 years, 5-19, 20-39, 40-59, and 60+), ethnic group (prioritise: Maori, Pacific, and Other), vaccination history (yes=either have had seasonal influenza vaccination in the past or in the past year, no= never been vaccinated against seasonal influenza), prior chronic illness (yes, no), reported damp housing (yes, no), and study area; β_0 , the log odds for seropositive test, provided all $X_i = 0$; β_i , change in the log odds for a unit

increase in Xi. Since damp housing correlated with those also reporting cold or musty housing conditions we used the latter in our model. Statistical analyses were performed using SAS version 9.1 (SAS Institute Inc., Box 8000, Cary, NC).

2.5 Funding source and ethics approval

The Ministry of Health provided the funding for this cross-sectional seroprevalence study. The ethics approval (MEC/09/09/106) was obtained from the Multiregional Ethics Committee.

3 Results

3.1 2009 H1N1 seroprevalence

The breakdown of samples tested and crude frequencies of seropositive participants by age group and ethnicity are shown in Table 3. The sample age ranged from one to 89 years with the median of 39 years (first Quartile=14, third Quartile=61). The household size ranged between one and 350 residents with a median of four (first Quartile =2, third Quartile=5).

Table 3 Number tested by age group and ethnicity (number of positives)

Age group (years)	Ethnic group			Total
	Maori	Pacific People	Other	
1 to 4	23 (8)	28 (14)	101 (33)	152 (55)
5 to 19	42 (22)	37 (21)	130 (59)	209 (102)
20 to 39	41 (10)	33 (18)	147 (33)	221 (61)
40 to 59	40 (13)	42 (11)	176 (32)	258 (56)
60 and over	37 (9)	31 (9)	246 (55)	314 (73)
Total	183 (62)	171 (73)	800 (212)	1154 (347)

Two samples did not have age data and were not included

3.1.1 Immunity by age group, ethnicity, gender and study area

We completed the analysis for the 1147 participants from the community who had serology results and completed questionnaires, 532 healthcare workers, and 521 baseline samples. Table 4 depicts 2009 H1N1 seroprevalence in the community, healthcare workers, and baseline samples by demographic information. The overall community seroprevalence is 26.7% (CI:23.4-29.9). Seroprevalence varied across age groups with school age children (5-19 years) having the significantly highest seroprevalence 46.7% (CI:38.3-55.0). Pacific Peoples had significantly higher seroprevalence 49.5%(CI:35.1-64.0) than Maori and Other ethnic groups. There was no statistically significant difference in seroprevalence by sex or by study area. The seroprevalence of primary HCWs 29.6% (CI:22.6-36.5) and secondary HCWs 25.3% (CI:20.8-29.8) showed no difference from the community participants. In the baseline study, the proportion of older adults aged 60+ 22.6% (CI:15.3-30.0) with cross-reactive antibodies to 2009 H1N1 was higher than that of children and adults. Taking the product of age-specific seroprevalence rates and population size, an estimate of 1.3 million of the New Zealand population are now immune to the 2009 H1N1 virus.

Table 4 2009 H1N1 seroprevalence in the community, healthcare workers, and baseline samples

Sero-survey	No. Tested	No. Sero Positive	Seroprevalence (95% CI)	P-value for group
Overall*	1147	347	26.7 (23.4-29.9)	
Age group (years)¹				<0.001
1 to 4	148	55	29.5 (21.0-38.0)	
5 to 19	206	102	46.7 (38.3-55.0)	
20 to 39	221	61	22.2 (15.6-28.9)	
40 to 59	258	56	20.2 (14.0-26.5)	
60 and over	314	73	24.8 (18.7-30.9)	
Ethnic group²				0.001
Maori	181	62	36.3 (28.0-44.6)	
Pacific	167	73	49.5 (35.1-64.0)	
Other	799	212	25.9 (22.4-29.4)	
Sex*				0.94
Female	636	194	26.5 (22.2-30.9)	
Male	506	152	26.8 (21.8-31.8)	
Study area*				0.36
Auckland	262	82	23.6 (16.3-30.8)	
Waikato	107	22	20.0 (10.2-29.7)	
Bay of Plenty	122	38	27.7 (18.5-36.9)	
MidCentral	113	36	26.4 (16.8-36.0)	
Wellington	369	117	30.2 (24.5-36.0)	
Christchurch	109	32	19.4 (11.1-27.7)	
Otago	65	20	29.4 (16.8-41.9)	
Healthcare workers				
Primary	169	50	29.6 (22.6-36.5)	
Secondary	363	92	25.3 (20.8-29.8)	
Baseline immunity				
Overall	521	62	11.9 (9.1-14.7)	
Age group (Years)				<0.001
1 to 4	84	5	6.0 (0.9-11.0)	
5 to 19	100	14	14.0 (7.2-20.8)	
20 to 39	106	8	7.5 (2.5-12.6)	
40 to 59	107	7	6.5 (2.0-11.1)	
60 and over	124	28	22.6 (15.3-30.0)	

P-value calculated using the Rao-Scott chi-square test

¹ Ethnicity-adjusted estimates for the study population

² Age-adjusted estimates for the study population

* Age- and ethnicity-adjusted overall estimate

Figure 2 and Figure 3 illustrate seroprevalence distribution by age group and ethnicity. The higher proportions in the 5 to 19 age group and Pacific Peoples can be clearly observed in the study population.

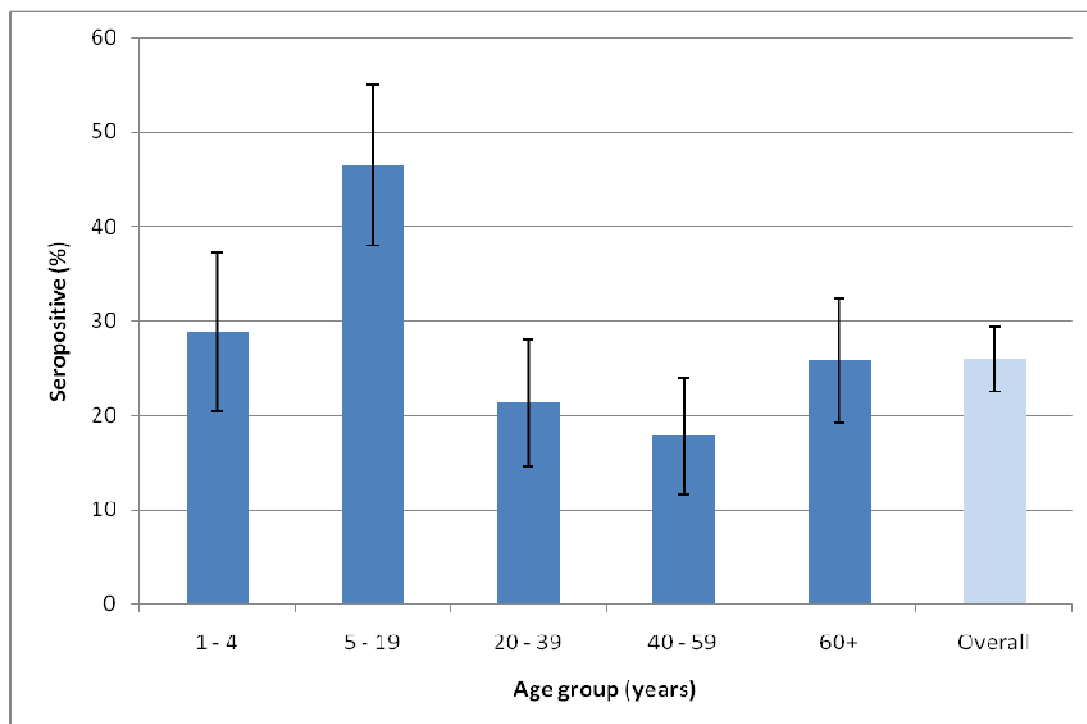


Figure 2 Distribution of ethnic-adjusted seroprevalence by age group for the study population

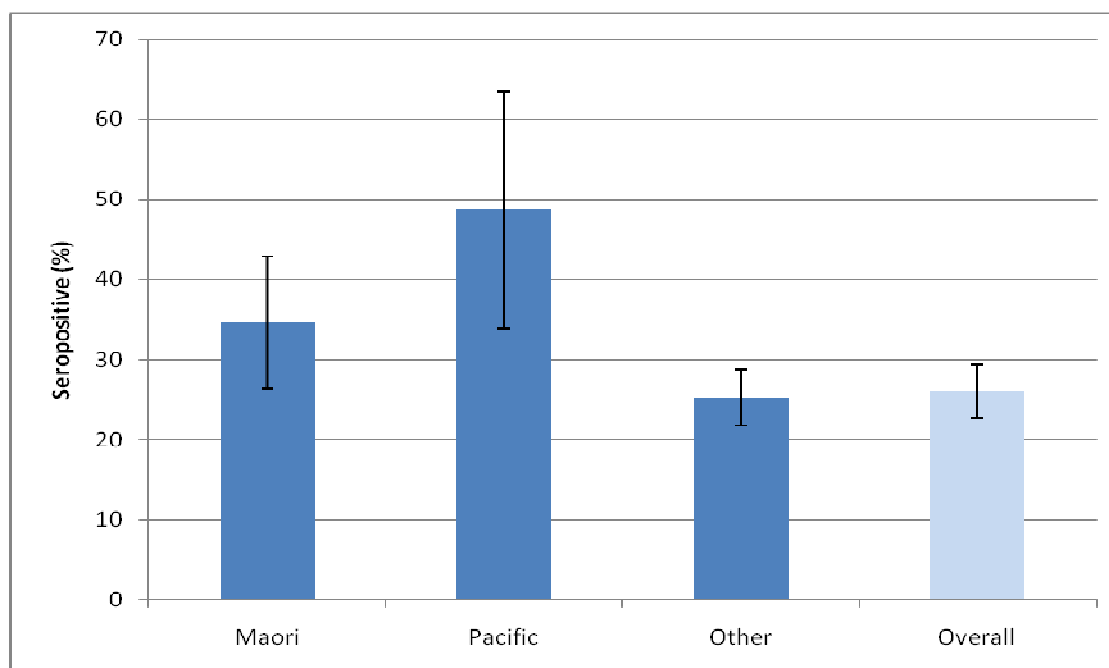


Figure 3 Distribution of age-adjusted seroprevalence by ethnic group for the study population.

3.1.2 Seroprevalence by study area

Figure 4 shows the age and ethnicity-adjusted seroprevalence by study area. Overall, geographic variation did not prove significantly different, given the sample size for the selected DHBs.

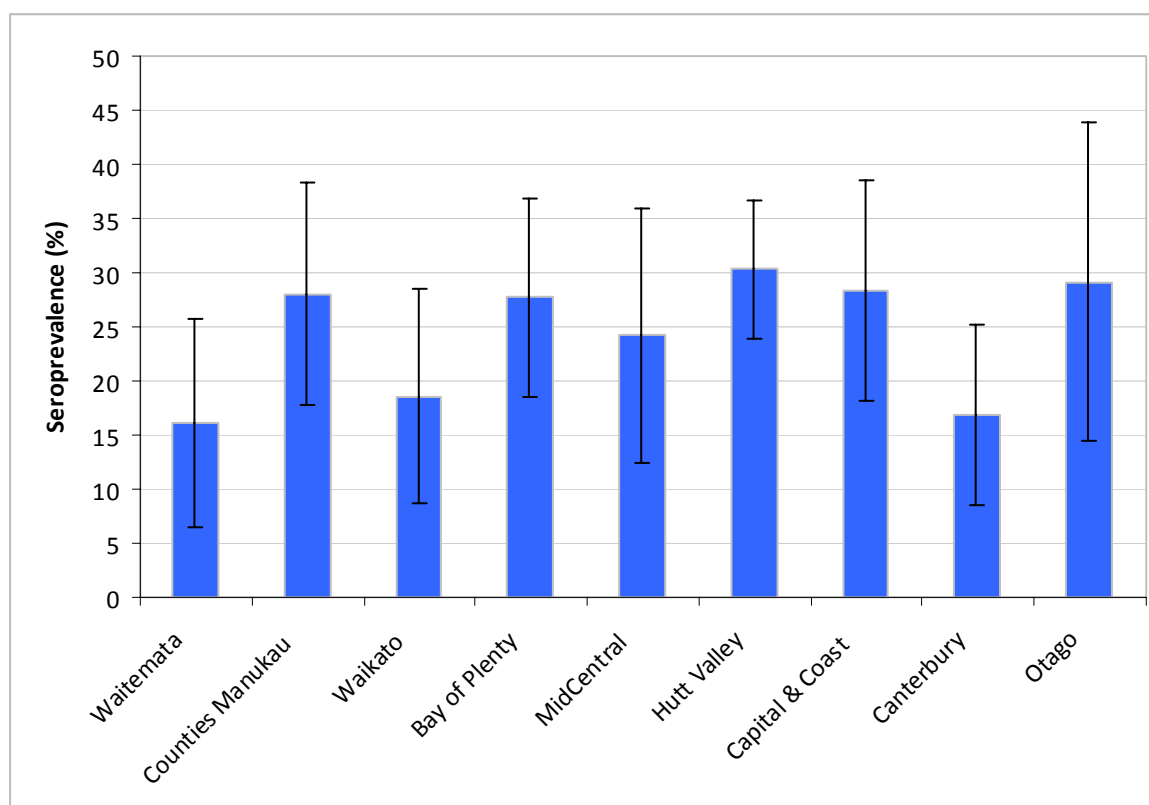


Figure 4 Seroprevalence by study area among community participants

3.1.3 Immunity by selected factors

Selected factors from the questionnaire were analysed (Table 5). Factors such as Tamiflu uptake, smoking, chronic illness and housing conditions of cold, damp and musty did not show any difference between seropositive and seronegative groups.

The number of people per household was investigated as a possible risk factor for seroprevalence, as it produces a significant association in univariate analysis. There is an apparent increase in the seroprevalence when household size is larger than the median size of four people, 30.6% (CI:23.4-37.8), compared to households up to median size, 24.0% (CI:20.3-27.6). Participants in single, and dual occupancy dwellings show similar levels of low seroprevalence (Table 5). Bedroom deficit is a measure of the insufficiency of bedrooms in relation to the total number of people occupying the dwelling. This index is amended from the New Zealand index to allow for the data collected in this survey, and is therefore not immediately comparable (see footnote under Table 5). Those with an index greater than one are slightly more at risk than those with an index up to one, but this difference is small, and statistically insignificant. Variations in seroprevalence associated with household size can be explained by the age and ethnicity profile of larger households.

Table 5 Seroprevalence by selected factors listed in questionnaire

Sero-survey	No. Tested	No. Sero-Positive (Titre \geq 40)	Seroprevalence* % (95% C.I)	P-value for group ¹
Flu last winter				0.99
Yes	420	135	26.8 (21.2-32.3)	
No	676	194	26.5 (22.3-30.8)	
Unknown	51	18	27.6 (10.3-45)	
Symptoms				0.76
Yes	670	217	27.1 (22.7-31.5)	
No	477	130	26.1 (21.1-31.1)	
ILI (2 or more symptoms)				0.61
Yes	619	206	27.5 (23-32.1)	
No	528	141	25.8 (21-30.6)	
Treating ILI				0.70
Sought medical attention				
Yes	372	121	25.6 (19.5-31.7)	
No	775	226	27.2 (23.2-31.2)	
Phone GP	74	26	27.9 (13.3-42.5)	0.86
Consult GP	260	87	27.3 (19.6-35.0)	0.86
Visit hospital ED	29	8	43.4 (9.5-77.3)	0.27
Days off due to ILI				0.86
0 days	271	86	27.3 (20.3-34.3)	
1-3 days	187	63	24.0 (16.6-31.4)	
4-7 days	115	35	29.3 (17.9-40.8)	
7 + days	47	16	29.0 (12.3-45.7)	
Days off to care for ILI				0.73
0 days	318	93	26.8 (20.8-32.8)	
1-3 days	41	12	17.8 (1.7-33.9)	
4-7 days	19	5	29.1 (0.3-58.0)	
7 + days	2	1	43.5	
History of seasonal influenza vaccination				0.67
Yes	542	160	27.0 (22.2-31.7)	
No	578	177	25.5 (21.0-30.0)	
Tamiflu uptake				0.69
Yes	19	5	32.8 (7.4-58.3)	
No	620	202	27.2 (22.7-31.8)	
Chronic illness				0.39
Yes	298	94	29.1 (22.3-36.0)	
No	849	253	25.8 (22.1-29.5)	
Smoking cigarettes				0.98
Yes	154	50	26.1 (16.9-35.2)	
No	802	218	26.2 (22.4-29.9)	
Cold House				0.98
Yes	521	167	26.2 (21.0-31.4)	
No	521	149	26.1 (21.5-30.7)	
House colder than previous year				0.77
No	521	149	26.1 (21.5-30.7)	
Sometimes	285	84	23.2 (16.5-29.9)	
Often	118	37	31.4 (20.2-42.5)	
Always	118	46	28.3 (16.1-40.6)	
Damp House				0.80
Yes	205	64	23.3 (15.2-31.3)	
No	598	176	25.7 (21.2-30.2)	
Musty House				0.90
Yes	158	56	24.9 (15.5-34.4)	
No	683	195	25.2 (21.0-29.4)	
Houshold size (persons)				NA
1	95	20	21.1 (12.7-29.4)	
2	277	60	21.7 (16.8-26.5)	
\leq median (4)	788	201	25.5 (22.5-28.6)	
$>$ median (4)	299	116	38.8 (33.2-44.4)	
Bedroom deficit ²				0.00
\leq 1	562	140	24.3 (20.0-28.6)	
$>$ 1	525	177	26.9 (21.7-32.1)	

Abbreviations CI, confidence interval,

¹P-value for the variable calculated using Rao-Scott Chi-square test

²Calculation based on an amended version of the New Zealand bedroom deficit index:

(0.5*persons under 5 + number of couples + number of children over 5 + number of adults (>=18 years))/bedrooms

*Age-ethnic adjusted seroprevalence

3.1.4 Vaccination history

Table 6 shows the proportions of the total samples in the community and HCW surveys with any or recent seasonal influenza vaccination. Overall our findings indicated a reasonable level of vaccine uptake among the older age groups in the community as well as the HCWs.

Table 6 Percentage of the samples with seasonal influenza vaccination history in the community and healthcare worker surveys

Demography	Any history of seasonal flu vaccination			Last year seasonal flu vaccination		
	Number of samples	Vaccinated	Percent (%) of total sample	Number of samples	Vaccinated	Percent (%) of total sample
Overall¹	1127	545	48.4	1106	395	35.7
Age group (years)						
1 to 4	148	17	11.5	141	11	7.8
5 to 19	200	43	21.5	194	27	13.9
20 to 39	213	106	49.8	207	51	24.6
40 to 59	252	137	54.4	251	91	36.3
60 and over	314	242	77.1	311	215	69.1
Ethnicity						
Maori	172	70	40.7	166	49	29.5
Pacific	164	81	49.4	153	52	34.0
Other	793	394	49.7	787	294	37.4
Healthcare Workers						
Overall	534	431	80.7	531	367	69.1
Sector						
Primary	171	142	83.0	170	123	72.4
Secondary	363	289	79.6	361	244	67.6
Profession						
Doctors	128	112	87.5	128	96	75.0
Nurses	200	155	77.5	198	127	64.1
Auxiliary	185	152	82.2	184	134	72.8

¹ Community based survey

Table 7 shows the descriptive analysis of age and seasonal influenza vaccination. Individuals with previous seasonal influenza vaccination showed higher geometric mean titres than those without vaccination; particularly in children aged 1-4 and 5-19 years.

Table 7 Effect of seasonal influenza vaccination on geometric mean titres by age groups

Age group (years)	Any seasonal influenza vaccination history			No seasonal influenza vaccination history		
	No. Tested	GMT	95% CI	No. Tested	GMT	95% CI
1 to 4	14	72.5	(47.0-97.9)	130	26.1	(16.8-35.4)
5 to 19	43	52.6	(39.3-65.9)	154	29.5	(20.7-38.3)
20 to 39	106	22.2	(14.5-30.0)	107	20.9	(12.9-29.0)
40 to 59	137	17.1	(12.4-21.7)	114	15.2	(11.7-18.7)
60 and over	242	20.2	(15.1-25.3)	72	14.7	(9.30-20.2)

3.1.5 Asymptomatic infections

Based on the questionnaire survey (Table 8) approximately 45.2% (CI:38.0-52.4) of seropositive individuals had no symptoms. This proportion is higher than previously estimated in New Zealand.¹¹ Asymptomatic individuals remain an important group in relation to the spread of the virus and have implications for public health interventions.

Table 8 Proportion of asymptomatic cases in seropositive community participants

	No. of immune Respondents	Adjusted proportion* (95% CI)
Symptom	347	
No	130	45.2 (38.0-52.4)
Yes	217	54.8 (47.6-62.0)

*Age and ethnicity-adjusted proportion in immune respondents by clinical status

3.1.6 Risk factor analysis

The main hypothesis being tested in this analysis was whether age group and ethnicity affected the risk of infection with 2009 H1N1. Table 9 shows the outputs from the multivariable survey logistic model. Younger age groups were associated with an increased likelihood of immunity. The likelihood of immunity to pandemic influenza among the age group 5-19 and age group 1 – 4, respectively, was 5.3 (CI:3.2-8.7 p<0.001) times and 3.5 (CI:2.0-6.2 p=0.029) times higher compared with that of age group 40-59 (the reference group).

The likelihood of immunity to pandemic influenza was 2.2 (CI:1.5-3.4 p<0.001) times higher among the Pacific People compared with that of the “Other” ethnic group (the reference group). These results have confirmed the findings in the descriptive analysis as shown by the overall ethnicity effect (p=0.03). Participants with previous seasonal influenza vaccinations were 1.8 times (p=0.002) more likely to have a seropositive test compared with those who have never been vaccinated.

Table 9 Results from the multivariate survey logistic regression model for selected factors

Risk factors	Odds Ratio for immunity	Lower CI	Higher CI	P - value
<i>Age group (years)</i>				
1 to 4	3.5	2	6.2	<0.001
5 to 19	5.3	3.2	8.7	< 0.001
20 to 39	1.4	0.85	2.3	0.18
40 to 59	Reference	-	-	-
60 and over	0.95	0.6	1.5	0.84
<i>Ethnic group</i>				
Maori	1.4	0.95	2.2	0.09
Pacific	2.2	1.5	3.4	<0.001
Other	Reference	-	-	-
Sex (male/female)	0.82	0.59	1.1	0.21
Any vaccination history (yes/no)	1.8	1.2	2.6	0.002
Prior chronic illness (yes/no)	1.2	0.81	1.7	0.41
Damp housing (yes/no)	1.1	0.83	1.4	0.62

3.1.7 Pre-existing immunity

We measured the baseline seroprevalence of antibodies to pandemic A (H1N1) 09 virus using a total of 521 pre-pandemic sera. Pre-existing immunity was highest in the older adults (60+ years) with 22.4%, followed by the 5-19 age groups with 14%, and children 1-4 years (8%), young adults 20-39 years (7.5%) and adults 40-59 years (6.5%). The results are shown below.

Figure 5 shows the proportion of seropositive by age group in the baseline sample versus the survey sample. Pre-existing immunity, by this measure, is significantly greater in the 60 + years group over all groups except the 5 – 19 years. In all age groups, except the 60+, the proportion of seropositive is significantly greater in the serosurvey. The two youngest age groups exhibit the largest increase in seropositivity, whilst the oldest group (60+) does not significantly change between the baseline and the cross-sectional serosurvey.

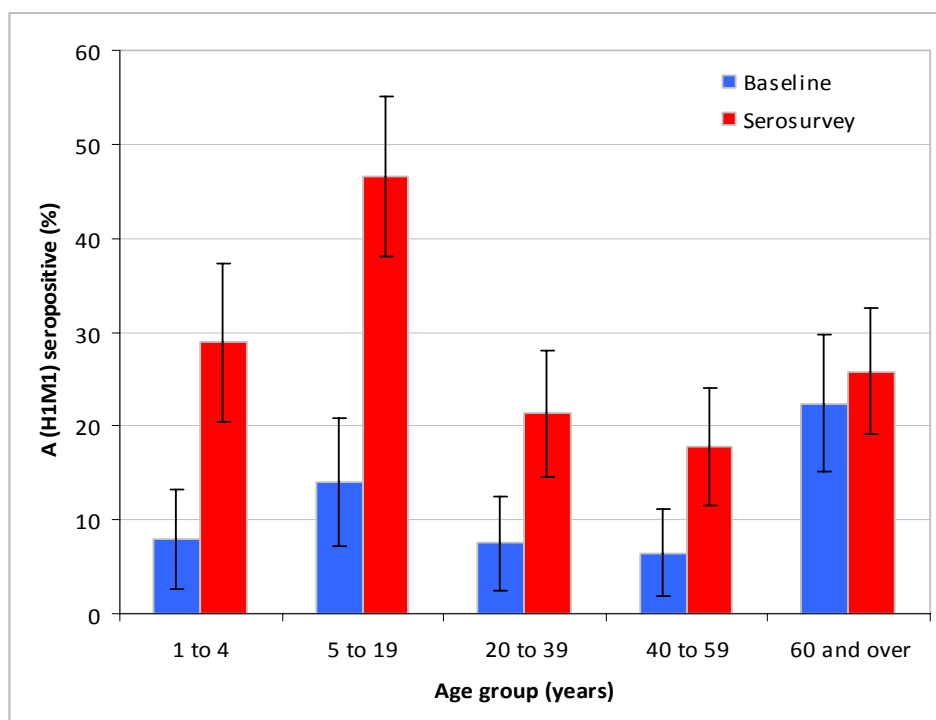


Figure 5 Age-specific seroprevalence in the baseline and the serosurvey study.

3.2 Estimated 2009 H1N1 incidence

The difference in the proportion of seroprotected individuals from the baseline and the serosurvey of 2009 H1N1 was considered as a proxy measure of the incidence of infection due to the pandemic virus¹². Figure 6 shows proportions of the baseline and serosurvey samples equal to or above each titre level for the 5-19 years and the 60+ year's age groups. School aged children showed the difference between the baseline and survey at every titre level while older adults had little difference at any titre level.

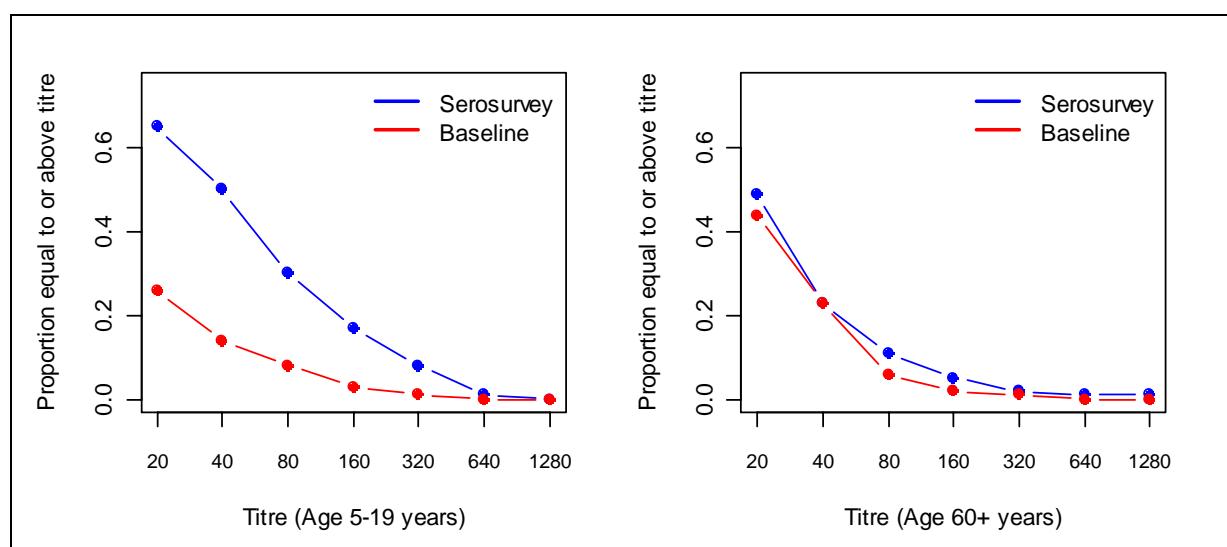


Figure 6 Proportions of samples equal to or above titre for the age groups 5 to 19 (left) and 60+ (right), baseline and serosurvey

Table 10 compares the difference in the proportion of individuals with HI titre of ≥ 40 , ≥ 20 and GMT between the baseline and serosurvey samples among different age groups. If a titre level of 40 is taken as indicative of infection, 18.3% of the total population was exposed. This increases to 26.6% if a titre level of ≥ 20 was used.

Table 10 Estimated national incidence of infection using differences of seropositives from serosurvey and baseline

Age Group (years)	National Population ¹	Proportion Sero-positive (Titre ≥ 40)			Proportion Sero-positive (Titre ≥ 20)			Geometric Mean Titre		
		Serosurvey*	Baseline	Estimated population Infected (%)	Serosurvey*	Baseline	Estimated population Infected (%)	Serosurvey	Baseline	Ratio
1 to 4	300050	34.3	6.1	84692 (28.2)	54.0	13.4	121719 (40.6)	28.8	11.8	2.44
5 to 19	911890	48.3	14.0	313072 (34.3)	63.0	26.0	336991 (37.0)	32.7	14.3	2.29
20 to 39	1153130	25.1	7.5	202954 (17.6)	48.4	12.3	416507 (36.1)	21.6	12.0	1.80
40 to 59	1154250	20.9	6.5	166625 (14.4)	41.3	20.6	239497 (20.7)	16.8	12.2	1.38
60+	749560	24.5	22.6	14524 (1.9)	47.4	44.4	22437 (3.0)	18.8	16.8	1.12
Total	4268880			781867 (18.3)			1137150 (26.6)	22.0	13.5	1.63

* Age-ethnic adjusted proportion for NZ population

Our population incidence estimates (781,867 cases) are substantially higher than the case estimates from various clinical surveillance data.¹¹ Based on the questionnaire survey approximately 45.2% of seropositive individuals had no symptoms and 54.8% had symptoms. This gives an estimated total of 428,463 symptomatic cases. Taking case estimates from the serosurvey and the known number of deaths (35) associated with symptomatic 2009 H1N1 cases, the case fatality rate could be as low as 8.2 per 100,000 (0.008%, 35/428,463). Furthermore using hospitalisations as an indicator of severity with 428,463 symptomatic cases and 1122 hospitalised cases, this gives a rate of severe hospitalised influenza as 262 per 100,000 (0.262%, 1122/428,463).

3.3 Healthcare workers study

Table 11 gives the summary distribution of primary and secondary healthcare workers tested for pandemic influenza H1N1 09. Overall, the seroprevalence is 26.7% (CI:22.9-30.5). For the sample size used in this study, no significant difference was found between the primary and secondary sectors, and that of the general population. The seroprevalence for doctors, 29.9% (CI:21.9-37.9), was slightly higher than that of nurses, 27.5% (CI:21.3-33.7), which is higher than the 'other' occupational category 25.0% (CI:18.7-31.3), but there is no significant difference demonstrated in this sample.

Days off due to, or caring for, influenza-like illness increased with seroprevalence. The numbers reporting Tamiflu uptake were low and no association between uptake and seroprevalence can be drawn. Smoking and housing condition were not associated with significant differences in risk in this sample. The proportion of seropositive respondents who self-reported any symptoms, or ILI symptoms (two or more), were broadly in line with those reported in the general population serosurvey. These findings mirror the calculation for numbers of asymptomatic infections estimated in the population based survey.

Table 11 Distribution of primary and secondary health care workers and pandemic influenza H1N1 09 seroprevalence including confidence limits

Sero-survey	No. Tested	No. Sero-Positive (Titre \geq 40)	Seroprevalence* % (95% C.I)
Overall	532	142	26.7 (22.9-30.5)
Sector			
Primary	169	50	29.6 (22.7-36.5)
Secondary	363	92	25.3 (20.9-29.8)
Occupation			
Doctor	127	38	29.9 (21.9-37.9)
Nurse	200	55	27.5 (21.3-33.7)
Other	184	46	25.0 (18.7-31.3)
Sex			
Female	429	113	26.3 (22.2-30.5)
Male	103	29	28.2 (19.4-36.9)
Treating ILI			
Sought medical attention	109	35	32.1 (23.3-40.9)
Phone GP	8	3	37.5 (1.55-73.4)
Consult GP	84	27	32.1 (22.1-42.2)
Visit hospital ED	6	2	33.3 (0.00-74.7)
Days off due to ILI			
0 days	124	28	22.6 (15.2-30.0)
1-3 days	136	33	24.3 (17.0-31.5)
4-7 days	57	19	33.3 (20.9-45.7)
7 + days	11	4	36.4 (6.43-6.63)
Days off to care for ILI			
0 days	417	110	26.4 (22.1-30.6)
1-3 days	43	12	27.9 (14.3-41.5)
4-7 days	12	4	33.3 (5.40-61.3)
7 + days	4	1	25.0 (0.00-74.1)
History of seasonal influenza vaccination			
Yes	425	115	27.1 (22.8-31.3)
No	102	26	25.5 (17.0-34.0)
Tamiflu uptake			
Yes	21	4	19.0 (1.80-36.3)
No	307	84	27.4 (22.3-32.4)
Chronic illness			
Yes	80	24	30.0 (19.9-40.1)
No	452	118	26.1 (22.0-30.2)
Smoking cigarettes			
Yes	20	5	25.0 (5.48-44.5)
No	508	136	26.8 (22.9-30.6)
Cold House			
Yes	415	109	26.3 (22.0-30.5)
No	109	30	27.5 (19.1-36.0)
House colder than previous year			
No	229	62	27.1 (21.3-32.9)
Sometimes	186	47	25.3 (19.0-31.5)
Often	69	19	27.5 (16.9-38.2)
Always	40	11	27.5 (13.5-41.5)
Damp House			
Yes	146	36	24.7 (17.6-31.7)
No	380	105	27.6 (23.1-32.1)
Musty House			
Yes	101	25	24.8 (16.3-33.2)
No	425	116	27.3 (23.0-31.5)

Abbreviations CI, confidence interval

* Age-ethnic adjusted seroprevalence

Table 12 shows a significant difference in ILI or symptom presentation among unvaccinated HCWs.

Table 12 Distribution ILI symptoms in unvaccinated HCWs

	No history of vaccination		Not vaccinated last year	
	No. of Respondents	Proportion (95% CI)	No. of Respondents	Proportion (95% CI)
Symptoms				
Yes	67	65.1 (55.7-74.4)	107	65.2 (57.9-72.6)
No	36	35.0 (25.6-44.3)	57	34.8 (27.4-42.1)
ILI (2+ symptoms)				
Yes	64	62.1 (52.6-71.7)	104	63.4 (56.0-70.9)
No	39	37.9 (28.3-47.4)	60	36.6 (29.1-44.0)

3.4 Respondent Bias

The non-respondent rate was relatively uniform across age group and ethnicity, with a slightly higher rate among children of Pacific Peoples. We also tested whether those that had self-reported ILI last winter were more likely to participate in the survey. Of those who had no ILI last year, 65% participated in the survey, whereas 82% of those who reported ILI participated. While this has the potential of introducing bias and over-estimating seroprevalence, the study has shown that there was no association between having ILI and the probability of a seropositive test.

4 Discussion

This is the first large randomised cross-sectional serological study reported from the southern hemisphere where the first wave of 2009 H1N1 coincided with seasonal influenza infections. It provides useful information on the population immunity profile in New Zealand and new insights on the epidemiology of the pandemic virus infection during the first wave. In addition, this survey, utilising a large randomly selected sample, was unique in assessing the seroprevalence of the New Zealand population to 2009 H1N1. It was a simple, replicable and extendable design which produced adequate response rates while minimising the in-built bias inherent in other seroprevalence study designs. It proves the usefulness and feasibility of this design for a serological study of disease prevalence.

The highest proportion of individuals with protective immunity levels was found in children aged 5-19 years at 46.7% with a significant increase of 32.7% from the baseline immunity of 14.0%. The effective reproduction rate is very high in the younger age groups due to high contact rates. The higher infection rate with the pandemic virus in the school age children accords with the notion that the school age children constitute the main conduit for spread of influenza, due to generally higher levels of contact in school. In this respect our results were very similar to the findings reported in the England study.^{12, 13}

A high proportion of older adults (22.6%) had cross-reactive antibodies against 2009 H1N1 before the first wave. Older adults might acquire pre-existing immunity to 2009 H1N1 virus, presumably as a result of previous exposure to a 1918-like A(H1N1) virus circulating in earlier decades during 1918-1957 or a lifetime of exposure to influenza A, which has resulted

in broad heterotypic immunity.^{10, 14-17} Pre-existing immunity in older adults may have protected them against 2009 H1N1. This is consistent with clinical surveillance reported in NZ that pandemic cases were concentrated in younger age groups.^{11, 18} In addition, older adults (24.8%) had HI titre of ≥ 40 in the serosurvey with little increase from the baseline and no increase in GMT. However, we only assessed neutralising antibody against 2009 H1N1 haemagglutinin in this study. It is possible that heterotypic immunity to influenza from antibody against the neuraminidase or cellular responses to highly conserved viral epitopes might have also contributed to the apparent protective effect in older adults.¹⁹ Further study on the effect of heterotypic immunity on age-specific populations is needed.

An overall low proportion of children and adults (1-59 years) had cross-reactive antibodies to 2009 H1N1 in the baseline. However, 6% of young children aged 0-4 years had HI titres of ≥ 40 in the baseline, higher than 1.8% reported by the England study,¹² but not significantly different. The difference may reflect the varied influenza exposure these young children experienced in two countries. Also, the relatively small number of serum samples in the baseline was opportunistic diagnostic samples without randomisation and with no information on seasonal influenza vaccinations. This is one of the limitations of this study regarding the representativeness of baseline samples across all age groups. Random sampling of the population for the baseline would be ideal.

There was a significant difference in seroprevalence between ethnic groups in the descriptive analysis, with higher seroprevalence in Pacific Peoples, followed by those of Maori origin. These results were confirmed in the multivariable analysis. Pacific and Maori peoples also had much higher hospitalisation and intensive care unit admission rates compared with European and other groups. Further study on ethnic inequalities such as health and environmental factors contributing to 2009 H1N1 infection is needed.

The high proportion of asymptomatic infections among the seropositives gives an indication of a relatively 'silent' spread of the disease in any naive population. While asymptomatic individuals are less infective, their role in the spread of 2009 H1N1 cannot be discounted. This finding has important implications for public health policy measures that were instituted at ports of entry and educational institutions during the first wave of the pandemic. It underscores the need for vigilance both at the community and individual levels to reduce the spread of disease. Basic hygiene measures such as regular hand-washing become important whether or not one has a ILI.

The seroprevalence among primary and secondary healthcare workers did not differ significantly with that of the general population. This result is in contrast to the seroprevalence study in Taiwan, where a significant difference was found between front-line hospital workers (20% of seroprevalence) and the general population (less than 3%)²⁰. In addition, there was no significant difference in seroprevalence among doctors, nurses and support staff. Further study with individualised information regarding risk exposures and personal protective measures is needed.

The difference in the proportion of individuals with HI titre of ≥ 40 between the baseline and serosurvey among different age groups, was considered an appropriate proxy measure of the incidence of infection due to 2009 H1N1¹². There are some limitations associated with this measure. Firstly, incidence estimates require comparison of the proportion of neutralizing antibodies against 2009 H1N1 before and after the pandemic, which reduces the precision of

the estimate for a given sample. Secondly, this measure may lead to an underestimate of the true exposure to 2009 H1N1 because the threshold of HI titre of 40 may underestimate the proportion of individuals who have been exposed to 2009 H1N1 yet their immune response has not reached the accepted protective level. Thirdly, this measure assumes that all age groups respond to the pandemic virus in the same way immunologically. This is a simplified assumption for a complex host immunological response among specific age groups. 2009 H1N1 triggered different response in titres of neutralizing antibodies in different age groups, doubling titres in children aged under 5 years, causing a 4-fold increase in school age children and no change in older adults. Lastly, this measure may underestimate incidence for individuals who were infected with 2009 H1N1 but never developed HI antibodies. Further studies are needed to define a serological marker of infection specific to 2009 H1N1 that does not detect cross-reactive antibodies generated by exposure to other seasonal influenza A(H1N1) viruses.

Our serosurvey showed that previous seasonal influenza vaccination was associated with higher HI titres against 2009 H1N1, similar to the findings in other reports.^{19 13} Hancock et al analyzed stored-serum samples from trials of seasonal trivalent inactivated vaccine predating the 2009 pandemic and showed the presence of cross-reactive antibodies to 2009 H1N1 in adults and very little response in children.¹⁹ The same study showed that vaccination with the seasonal vaccine resulted in a doubling in titres of these cross-reactive antibodies. Interestingly, our study also showed that participants with any previous seasonal influenza vaccination were 1.8 times ($p=0.002$) more likely to have HI titres of ≥ 40 against 2009 H1N1 compared with those who have never been vaccinated. However, the overall low level of cross-reactive antibodies acquired from seasonal A(H1N1) vaccination would not provide effective protection against 2009 H1N1 among individuals, particularly for those aged less than 60 years. The optimal protection against 2009 H1N1 in individuals of all ages would only be achieved with strain-specific pandemic vaccine.

Based on our overall results, approximately a third of the NZ population now have immunity to 2009 H1N1. At the time of writing, nearly one million New Zealanders have been vaccinated since March 2010 (personal communication, Ministry of Health, 2010). This provides a reasonable level of protection against the virus for the whole population which could mean a milder second wave in comparison to the first. However, there is marked variation in immunity levels in different age groups. Such groups also have differing contact rates and varied pertinent behaviours. High contact rates in school-aged children, remain a key factor in the transmission of infection even where there are high levels of immunity. Hence it is essential to promote basic public health measures such as personal hygiene in addition to immunisation.

Vaccination strategies include targeting people at risk of adverse health outcomes and boosting population immunity to prevent transmission. Our findings can help public health authorities to make evidence-based decisions on vaccination and priority listing. For example, children 5-19 years may have played an important role in the community transmission of infection and could be targeted for vaccination in order to attain herd immunity. All of these conclusions however assume a second wave without any major structural change in the virus.

5 Conclusions

- The A(H1N1) pandemic virus was highly infectious and it reached a large proportion of the population in a short time frame. This has resulted in higher than expected levels of immunity.
- Based on the questionnaire survey approximately 45.2% of seropositive individuals had no symptoms.
- An estimated 29.5% of the NZ population (1.3 million) now have immunity to 2009 H1N1.
- An estimated 18% of the NZ population (800,000) were infected with the virus during the first wave.
- One in every three school aged children (5-19 years) had the infection with the pandemic virus.
- One in four preschoolers (1-4 years) had also been infected with the pandemic virus.
- Older people had a high prevalence of pre-existing immunity which protected them against infection.
- Being a healthcare worker did not appear to increase the risk of infection compared to the general population.
- Pacific Peoples had the highest seroprevalence in comparison to other ethnic groups.
- The case fatality rate was 8.2 per 100,000 (0.008%, 35/428,463) based on the estimated number of symptomatic cases.
- The hospitalisation rate as an accurate indicator of severity, was 262 per 100,000 (0.26%, 1122/428,463) based on the estimated number of symptomatic cases.
- The results of this seroprevalence study would support vaccination strategies targeting those in specific population groups (such as children, Pacific/Maori people) to prevent further transmission, in addition to the known high-risk conditions such as pregnancy, chronic illness.

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