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Self-diagnosis of influenza during a pandemic: A cross sectional survey

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AMJ devised and led the study, guarantees the report and is the corresponding author. MB refined the design. JS carried out the data analysis. AMJ, JS and MB prepared the manuscript. SH and DB managed the seroprevalence study. All authors contributed to writing and revising the report.

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ABSTRACT

Background. Self-diagnosis of influenza is a mainstay of pandemic management because it may support self-management practices and reduce visits to healthcare facilities, thus helping contain viral spread. However, little is known about the efficacy of self-diagnosis of influenza, particularly during pandemics.

Methods. We used cross-sectional survey data to correlate self-diagnosis of influenza with serological evidence of 2009 pandemic influenza A(H1N1) infection (haemagglutination inhibition titres of $\geq 1:40$), and to determine what symptoms were more likely to be present in accurate self-diagnosis. The sera and risk factor data were collected for the national A(H1N1) seroprevalence survey from November-2009 to March-2010, three months after the first pandemic wave in New Zealand (NZ).

Results. The samples consisted of 318 children, 413 adults and 423 health care workers (HCW). The likelihood of being seropositive was no different in those who believed they had influenza and those who believed they did not have influenza in all groups. Among adults, 23.3% (95% CI 11.9 - 34.7) of those who reported having had influenza were seropositive for H1N1; but among those reporting no influenza, the seropositivity was 21.3% (95% CI 13 - 29.7%). Those meeting NZ surveillance or Ministry of Health influenza case definitions were more likely to believe they had the flu (for surveillance data, adult sample OR= 27.1, 95% CI 13.6 - 53.6) but these symptom profiles were not associated with a higher likelihood of H1N1 seropositivity (surveillance data adult sample OR = 0.93, 95% CI 0.5 - 1.7.)

Conclusions. Self-diagnosis does not accurately predict influenza seropositivity. The symptoms promoted by many public health campaigns are linked with self-

diagnosis of influenza, but not with seropositivity. These findings raise challenges for public health initiatives that depend on accurate self-diagnosis by members of the public and appropriate self-management action.

Key words: Influenza, Human/epidemiology/*immunology/prevention & control, diagnosis; screening; sensitivity and specificity

Article Focus

- to determine whether lay people can accurately recognise influenza infection

Key Messages

- individuals meeting influenza case definitions were more likely to believe they had influenza, however, self-diagnosis, whether by lay person or health care worker does not accurately predict influenza seropositivity

Strengths and limitations of this study

- this study provides the first published investigation of the effectiveness of self-diagnosis of influenza compared with laboratory evidence of infection in a broad population-based sample during a pandemic.
- some of the participants who believed they had the flu may have had a seasonal influenza or other respiratory pathogens (although H1N1 was the dominant influenza strain)
- this survey was based on symptom recall, rather than symptom reports. However, this may reflect the participant’s enduring perceptions of influenza, which are likely to guide their behaviour in future influenza epidemics

ORIGINAL RESEARCH

Self-diagnosis of influenza during a pandemic

Little is known about how individuals self-diagnose influenza, yet it is an important component of pandemic control and management. The use of self-diagnosis in an influenza pandemic can prevent some exposures by reducing outpatient visits to primary care clinics (1). During the 2009 pandemic, following Centers for Disease Control recommendations, patient teaching brochures advised patients to stay home and avoid contact with other people if they had influenza like illness (ILI), seeking medical assistance only in case of complications or risk factors.

The diagnosis of influenza by a lay person may be independent of medical contact, using resources such as family, friends or other non-medical sources of information such as on-line or internet resources (*independent self-diagnosis*). It may also be supported by a health professional via a helpline, without the lay person being seen for a clinical diagnosis (*assisted self-diagnosis*).

The purpose of this study was to determine whether lay people's assessment of influenza status is confirmed by serological testing, and whether the presence of particular symptoms assists individuals in the correct identification of influenza. It also aimed to measure the accuracy of self-diagnosis by health care workers (HCW). Establishing the current reliability of self-diagnosis will provide either assurances about, or identifications of shortcomings in, public health strategies to contain spread of influenza.

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2
3 **Methods and Sample**
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6 **Population sample** - This study was conducted as part of the national
7
8 Environmental Science and Research (ESR) seroprevalance study in early 2010
9
10 (2). This study used a purposive, multi-stage random cross-sectional survey of
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12 1147 subjects from selected primary care patient registers from 14 general
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14 practitioner (GP) practices. The practices were selected purposively on the basis
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16 of observed high, medium and low incidence during the pandemic and on ethnic
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18 distribution. Each practice was stratified by age and by ethnic group. Within each
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20 stratum, simple random sampling was undertaken with oversampling of Māori and
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22 Pacific respondents to improve the precision of estimates for these groups. A
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24 second sample consisted of 540 HCW (369 HCW located in Auckland and
25
26 Middlemore Hospitals, and 171 from the 14 GP practices in the community study).
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28 The HCW sample included medical, nursing, and other staff. A simple random
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30 sampling procedure was performed to select participants for this sample (2). Sera
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32 and risk factor data were collected from November-2009 to March-2010, three
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34 months after the first pandemic wave in NZ(3). Ethical approval (MEC/09/09/106)
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36 was obtained from the Multiregional Ethics Committee of the NZ Ministry of Health.
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38 Written informed consent was obtained from all participants (2).
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44 We excluded participants born before 1957, because of the higher level of
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46 pre-pandemic seropositivity in this group (2). We treated those under age 18 as a
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48 separate group, because their questionnaires were usually completed by parents
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50 (*self-diagnosis by proxy*); furthermore, their health-related behaviours were likely
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52 to be influenced or, for the very young, entirely managed by their parents.
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55 We also considered HCW separately from lay participants, however, as the
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57 sampling methods for this group were different from the main community sample
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(the geographic area was more restricted in the HCW sample), comparisons between this group and the adult community sample should be made with caution.

Laboratory testing - Blood samples were obtained by phlebotomists in the general practice clinics, and serological testing was carried out at the National Influenza Centre (NIC) at ESR using a haemagglutination inhibition assay (HI) in line with the standard protocol provided by the WHO Collaborating Centre in Melbourne. Haemagglutination inhibition (HI) titres of ≥ 40 against H1N1 were considered seroprotective as well as seropositive. Laboratory testing methods are fully described elsewhere (2).

Questionnaire - A questionnaire was administered by nurses from 14 participating general practice clinics at the time of the blood sample collection to record information about respondent demographics; whether respondents believed they had contracted influenza in 2009; and their symptoms. Questions were both multiple-choice and open-ended.

Respondents were asked "Did you have the flu or influenza over this last winter (June to August)?" with options being "yes", "possibly", "no", and "don't know". Those who believed they had suffered from influenza were asked how they knew, choosing either:

1. I could tell on my own or with the help of my family and friends;
2. I called the nurse or HealthLine and they helped me to decide; or,
3. I saw my doctor or other health professional who told me I did

Self-diagnosis was defined as including both independent and assisted forms (ie choosing 1 or 2 above) for those who responded "yes" to the question about having had influenza.

Two additional case definitions of influenza were used based on reported symptoms: influenza-like illness (ILI) defined by the NZ sentinel surveillance definition (4) of two or more symptoms from fever, muscle ache, and headache (reports of chills are included in this definition, but this information was not collected in this study) and also the NZ Ministry of Health (5) as fever, plus cough or sore throat (reports of chills or sweating are included in this definition, but this information was not collected in the study).

Demographic information included age, gender, self-identified ethnicity, and socio-economic deprivation (using NZDep, a well-validated measure of small-area socio-economic deprivation based on census-derived characteristics such as income, education and household crowding, and assigned according to domicile address (6)). Ethnicity classification used the NZ 2006 Census questions, and prioritised ethnicity coding according to Ministry of Health ethnicity data protocols (7). Participants could choose up to nine different symptoms (fever or high temperature; cough; sore throat; runny nose; red, watery or sore eye(s); headache; muscle aches and pains; weakness, tiredness or fatigue; an upset stomach, diarrhoea or vomiting to describe any illness they had during the period under study as well as the open-ended “something else (describe).”

Analysis - All statistical analyses were performed using SAS 9.2 (SAS Institute Inc, NC.) Survey analysis techniques were used to take into account differential sampling probabilities by age and ethnicity; sample weights were calculated by ESR as the inverse probability of selection of an individual within each GP practice.

Proportions (and 95% CI) were calculated using the Surveyfreq procedure, taking into account clustering by GP practice and sample weight (as described

above) for the adult/child community samples. Hypothesis tests included Rao-Scott chi-square tests (adjusted for survey design) for testing whether seropositivity rates were different between the three self-reported influenza status groups; and also for testing whether seropositivity status differed according to the decision making process by which a respondent had decided that he or she (or their child) had influenza.

Sensitivity and specificity (along with positive predictive value and negative predictive value – PPV and NPV respectively) were calculated for seropositive status as the “gold standard” measure of disease status, and three definitions of influenza “screening” tests: self-report, Ministry of Health case definition, and NZ sentinel surveillance case definition. Self-reported influenza status was reclassified as a binary variable by combining “definite” and “possibly” groups into a “positive self-report” group for the purposes of this analysis. We opted for this reconfiguration because we felt it was the most policy-relevant categorisation and would potentially translate into useful health advice (either of these groups was likely to implement influenza-related management strategies). All of these calculations and confidence intervals were performed using the Proc Surveyfreq command.

Logistic regression methods (Proc Surveylogistic) were used to investigate the relationships between case definition status (separate models for the different definitions) and (1) self-reported influenza status or (2) seropositive test results.

Results

Characteristics of the sample – For the community branch of the study, a minimum sample size of 1500 subjects were required at design prevalence of 20% and confidence level of 95% to maintain +/- 10% margin error of estimate. 1147

subjects participated fully in the study (9 did not return the questionnaire and were thus excluded from the analysis). This gave a target rate of 76%. For the healthcare worker (HCW) branch of the study, the minimum sample size was calculated using the same criteria as the community study. The number of subjects (171 primary HCWs and 369 secondary HCWs) exceeded the minimum requirement. Of the 1687 subjects with completed questionnaires and serological results across the community and HCW studies, 413 responses (unweighted frequency) were considered for the analyses of adult responses; 318 were considered as children; and 423 were HCW. This gave a final sample size of 1154 people across the three groups.

Baseline demographic characteristics of the study populations are shown in Table 1. These are unweighted frequencies and percentages: all subsequent analyses take the sampling structure into account. (2) The sample was not adequately powered to demonstrate ethnic differences in the findings reported below.

Accuracy of self-report of influenza - Seropositivity status was compared across the three self-reported influenza status groups (yes, no, or possibly had the flu in 2009). As shown in Table 2, the likelihood of being seropositive was not significantly different between the three self-reported influenza status groups in any of the three sample groups. For adults in the community sample, point estimates of seropositive status ranged from 21.3 to 25.1 across the three self-report groups; for under 18s in the same sample, seropositive rates were between 40.1 and 45.9%, which was the highest among all three groups; and for health care workers, the range was between 25.7 and 33.0% seropositive.

Table 3 shows that amongst those people who reported having had influenza, the proportion of people who were seropositive was higher amongst those who reached a decision in conjunction with a health professional than amongst those who reported reaching a diagnosis on their own (including using a telephone helpline.) While this pattern was consistent across all three sample sources, none of these differences were statistically significant (all $p > 0.3$) which is potentially reflective of the small sample sizes for this analysis.

As shown in Table 4, self-reported flu status performed poorly as a screening tool for H1N1 infection, failing to detect the majority of those who were seropositive (adult sensitivity 45.7%). Only about a quarter of those who considered themselves to have had influenza during the preceding winter showed serological evidence of this (adult PPV 24.1%). Self-reported flu status had higher sensitivity and lower specificity than the Ministry of Health and NZ sentinel surveillance case definitions. Screening performance (sensitivity, specificity, PPV, and NPV) was otherwise broadly similar across the three sets of “screening” criteria used. PPV and NPV values across all definitions followed the pattern seen for seropositive prevalence (e.g. children had the highest PPV, reflecting a higher proportion of seropositive tests.)

Seropositive status, symptom profiles and case definitions of influenza -

Using Ministry of Health and the NZ sentinel surveillance ILI case definitions, we sought to confirm whether there was an increased likelihood of seropositivity for those who met these case definitions, based on self-report of symptoms. The likelihood of being seropositive was not significantly different between these symptom profile groups for any sample group (see Table 5; 95% confidence intervals for all odds ratios included 1). People who met a case definition had a

much greater likelihood of self-reporting having had influenza (Table 5, for both definitions).

Discussion

Key findings – This study provides, to our knowledge, the first published investigation of the effectiveness of self-diagnosis of influenza compared with laboratory evidence of infection in a broad population-based sample during a pandemic. The likelihood of being seropositive was no different in those who believed they had influenza and those who believed they did not have influenza. This finding applied to HCW as well as adults and children. Our study showed that self-diagnosis in a NZ population lacks sensitivity and specificity for diagnosing influenza. The poor sensitivity may lead to people with influenza believing that they are well and therefore failing to take measures to limit their contribution to influenza spread. The lack in specificity may result in delayed medical treatment when serious treatable illness is present (8).

Strengths and weaknesses of the study: Limitations of this study include the fact that some of the participants who believed they had the flu and yet were seronegative for H1N1 may have had seasonal influenza or other respiratory pathogens. However, H1N1 was the dominant influenza strain in 2009 accounting for 77.6% of influenza viruses that were sub-typed during the year (9). Further, the fact that seasonal influenza was replaced very quickly by pandemic H1N1 palliates this limitation to some extent. A small proportion of those who were seropositive will have baseline immunity to H1N1 acquired prior to 2009, though testing of stored sera shows that the level of such infection is low, ranging from 6.5-7.5% in the 20-59 year old population (2). Further, this survey was based on symptom recall, rather than symptom reports at time of presentation. However, in

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3 this study of responses to pandemic influenza, there is some validity in focussing
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5 on recalled symptoms which may reflect the participant's enduring perceptions of
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7 influenza, which are likely to guide their behaviour in future influenza epidemics.
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9 The higher likelihood of positive serology in those adults who consulted a health
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11 professional may be related to greater severity of their disease which this study
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13 does not capture. Also, it is likely that a greater proportion of people than usual
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15 may have consulted a health care provider due to the high media attention given
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17 to 'swine-flu'. The findings of this study might not be generalizable to other
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19 influenza viruses causing seasonal and pandemic disease.
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22 **Strengths and weaknesses in relation to other studies:** Other studies have
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24 attempted to understand how lay people report ILI, but have not obtained medical
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26 or laboratory confirmation of the diagnosis as ours did (10, 11). In excess of nine
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28 H1N1 seroprevalence studies have occurred following the pandemic (12). Almost
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30 all used unlinked specimens so were not able to question participants about their
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32 symptom history (13-16). Two studies in selected military populations collected
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34 symptom data. One prospective study of Singaporean military personnel tracked
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36 symptomatic illness during the pandemic and found that less than a third of those
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38 who were seropositive reported symptoms (17). A small cross-sectional study
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40 reported seroconversion following an H1N1 outbreak in a Finnish military garrison,
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42 and found that sensitivity for seropositivity was 50% on the basis of self-reported
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44 upper respiratory tract infection (URTI) symptoms (i.e. half of those with
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46 serological evidence of infection reported a history of URTI symptoms) (18) - this
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48 compares with the sensitivities for the current dataset, which were 45.7% and
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50 48.2% for the community adults and for HCW adults, respectively. Participants in
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52 this NZ seroprevalence survey were more likely to believe they had been infected
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54 if they had symptoms commonly advertised by public health campaigns as being
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linked with the flu. However, these symptom profiles were not significantly associated with seropositivity. This finding is consistent with a recent systematic review of symptoms in volunteer challenge studies, where nearly one in three participants demonstrated no clinical symptoms of influenza, despite laboratory confirmed infection (19). The authors of that study questioned whether naturally acquired influenza might produce more marked symptoms. Our study would appear to show that this is not the case, at least for pandemic H1N1 influenza.

Implications for clinicians and policymakers: These study findings raise important questions for pandemic control policies. On the positive side, they show that the NZ public has absorbed a fairly coherent ILI case definition that includes the symptoms traditionally linked to influenza. Unfortunately, we have demonstrated that this generic picture of ILI is a poor predictor of influenza infection. The classic symptoms of influenza are nonspecific, and accompany other infections commonly seen during the influenza season. A systematic review comparing influenza symptoms to independent criterion standards for influenza highlighted that epidemiological data, for example reports of regional influenza patterns, was probably more useful than clinical indicators for predicting whether an individual had influenza (20). And daily temperature measurement plus reporting of respiratory symptoms resulted in reduced transmission of H1N1 virus (17). It is also useful to note that HCW perform no better than non-professionals; the positive predictive value of an ILI diagnosis by a HCW was 30.1%. Interestingly, this value is similar to the PPV of clinical diagnosis by a GP for patients presenting to sentinel sites over the same period in 2009 (31.3% based on 624 viruses from 1993 swabs received) (9). These findings reinforce public

health advice during the pandemic that patients should seek medical care based on disease severity, rather than for diagnostic reasons.

Further research – Given the importance of self-diagnosis to containment and mitigation measures, further investigations around the low accuracy of self-diagnosis would be useful. Prospective exploration of patient self-diagnosis at the time of respiratory infection, variations in self-diagnosis by ethnicity and SES; and self-diagnosis amongst the elderly could provide important information, particularly given the differential distribution of respiratory illness across these groups; this sample was not sufficiently powered to enable these analyses (21). Further, as the presenting symptoms of influenza may vary depending on what type of influenza is responsible—in Singapore, H1N1 and seasonal influenza had different symptom profiles, with fever and runny nose being more common among seasonal influenza cases (22) and the prevalence of specific symptoms among H1N1 cases also varied between studies (23-25)—further exploration is warranted.

Table 1. Demographic characteristics of participants (unweighted frequencies and percentages)

		Adults (18+) (n=413)		Children (<18) (n=318)		Health Care Workers (n=423)	
Factor		Frequency	Percentage*	Frequency	Percentage*	Frequency	Percentage*
Sex	Female	262	63.44	150	47.62	348	82.27
	Male	151	36.56	165	52.38	75	17.73
	Unknown	0		3		0	
Ethnicity	NZE**	160	47.76	95	42.22	289	68.97
	Māori	82	24.48	53	23.56	20	4.77
	Pacific	65	19.4	54	24	14	3.34
	Asian	22	6.57	17	7.56	92	21.96
	Other	6	1.79	6	2.67	4	0.95
	Unknown	78		93		4	
Age group	1-4			150	47.17		
	5-9			68	21.38		
	10-14			68	21.38		
	15-17			32	10.06		
	18-24	80	19.37			26	6.15
	25-34	101	24.46			137	32.39
	35-44	132	31.96			152	36.17
	45-52*	100	24.21			107	25.3

* Percentage of respondents with valid answers to question.

** New Zealand European

Table 2. Serological status according to self-reported flu status (proportions and 95%CI)

Self-reported flu status	n	% seropositive*	95% CI	p-value**
Adults (18+)[†] (n=413)				0.802
No	221	21.3	13 - 29.7	
Possibly	68	25.1	14.2 - 36	
Yes	108	23.3	11.9 - 34.7	
Children (<18)[‡] (n=318)				0.723
No	149	45.9	34.4 - 57.4	
Possibly	55	42.2	28.6 - 55.9	
Yes	86	40.1	24.7 - 55.6	
Health Care Workers^{‡‡} (n=423)				0.415
No	222	25.7	20.1 - 31.9	
Possibly	80	27.5	18.1 - 38.6	
Yes	94	33	23.6 - 43.4	

* weighted percentage

** p-values for Adults and Children in community sample from Rao-Scott chi-square test; p-value for HCW are from Pearson's chi-square test

[†] 16 Adults from community sample missing information on self-reported flu status.

[‡] 21 Children from community sample missing information on self-reported flu status.

^{‡‡} 22 HCW missing self-reported influenza status. 5 missing immunological status

Table 3. Serological status according to diagnostic approach for people self-reporting having had influenza

Method for diagnosis	n	% seropositive*	95% CI	p-value**
Adults (18+)[†] (n=108)				0.392
Health professional	37	27.1%	(7.9 - 46.3)	
Self-diagnosis	61	17.7%	(5.3 - 30.1)	
Children (<18)[‡] (n=86)				0.332
Health professional	43	39.7%	(18.4 - 61.1)	
Self-diagnosis	34	25.2%	(4.5 - 45.9)	
Health Care Workers^{‡‡} (n=94)				0.356
Health professional	25	40.0%	(21.1 - 61.3)	
Self-diagnosis	67	29.9%	(19.3 - 42.3)	

* weighted percentage

** p-value for HCW are from Pearson's chi-square test; p-values for Adults and Children are from Rao-Scott chi-square test.

[†] 10 Adults from community sample missing information on pathway of diagnosis.

[‡] 9 children missing information on pathway of diagnosis.

^{‡‡} 2 health care workers missing information on pathway of diagnosis.

Table 4. Screening performance of influenza definitions for detecting seropositive status (sensitivity, specificity, positive predictive value [PPV] and negative predictive value [NPV])

NZ sentinel surveillance ILI definition ¹			NZ Ministry of Health ILI definition ²		Self-reported flu status ³	
Measure	Point estimate	95% CI	Point estimate	95% CI	Point estimate	95% CI
Adults (18+)* (n=413)						
Sensitivity	37.7	(25.5 - 50)	38.0	(25.6 - 50.4)	45.7	(33 - 58.3)
Specificity	60.5	(53.6 - 67.4)	67.2	(60.6 - 73.8)	58.1	(51 - 65.3)
PPV	21.6	(13.6 - 29.6)	25.1	(15.8 - 34.4)	24.1	(16.2 - 31.9)
NPV	77.1	(70.6 - 83.5)	79.0	(73.1 - 84.8)	78.7	(72 - 85.3)
Children (<18)** (n=318)						
Sensitivity	32.5	(21 - 44)	36.0	(24.5 - 47.6)	42.4	(30 - 54.9)
Specificity	68.4	(58.4 - 78.4)	57.2	(47.3 - 67.1)	52.6	(42.1 - 63)
PPV	43.4	(29.1 - 57.7)	38.6	(27 - 50.1)	40.9	(29.3 - 52.6)
NPV	57.6	(48.2 - 67)	54.5	(44 - 65)	54.1	(43 - 65.3)
Health Care Workers† (n= 423)						
Sensitivity	32.5	(23.8 - 41.1)	30.7	(22.2 - 39.2)	48.2	(38.8 - 57.6)
Specificity	70.8	(65.7 - 75.9)	76.4	(71.6 - 81.2)	57.7	(51.9 - 63.4)
PPV	29.9	(21.9 - 37.9)	32.7	(23.8 - 41.6)	30.5	(23.6 - 37.3)
NPV	73.5	(68.5 - 78.6)	74.7	(69.8 - 79.5)	74.3	(68.6 - 80.1)

¹ Two or more symptoms from: fever, muscle ache, and headache

² Fever, plus cough and/or sore throat

³ Self-diagnosis, assisted-self-diagnosis, or self-diagnosis by proxy

* Adults: 16 missing self-report status.

** Children: 21 missing self-report status

† HCW: 22 missing self-report status, 5 missing immunological status.

Table 5. Association between symptom profiles and self-reported flu status (left side) and seropositive status (right side). Odds ratios and 95% CI derived from independent logistic regression models.

Self-report status		Seropositive status	
Odds Ratio	95% CI	Odds Ratio	95% CI
NZ sentinel surveillance definitions ¹			
Adults (18+)			
No or 1 symptom	Reference group	Reference group	
2 or 3 symptoms	27.1 (13.6 - 53.6)	0.93	(0.5 - 1.7)
Children (<18)			
No or 1 symptom	Reference group	Reference group	
2 or 3 symptoms	21.5 (8.98 - 51.6)	1.04	(0.52 - 1.09)
Health Care Workers			
No or 1 symptom	Reference group	Reference group	
2 or 3 symptoms	18.2 (10.3 - 32.1)	1.19	(0.75 - 1.9)
Ministry of Health (MoH) definition ²			
Adults (18+)			
Met MoH definition	11.5 (6.1 - 21.8)	1.3	(0.7 - 2.3)
Did not meet definition	Reference group	Reference group	
Children (<18)			
Met MoH definition	9.5 (4.5 - 20)	0.8	(0.4 - 1.4)
Did not meet definition	Reference group	Reference group	
Health Care Workers			
Met MoH definition	13.3 (7.4 - 23.9)	1.46	(0.9 - 2.4)
Did not meet definition	Reference group	Reference group	

¹ Two or more symptoms from: fever, muscle ache, and headache
² Fever, plus cough and/or sore throat
³ Self-diagnosis, assisted-self-diagnosis, or self-diagnosis by proxy
* Adults: 16 missing self-report status.
** Children: 21 missing self-report status
† HCW: 22 missing self-report status, 5 missing immunological status.

References

1. Centers for Disease Control and Prevention. Interim Guidance on Infection Control Measures for 2009 H1N1 Influenza in Healthcare Settings, Including Protection of Healthcare Personnel. 2009 [cited 2009 16 November]; Available from: http://www.cdc.gov/h1n1flu/guidelines_infection_control.htm.
2. Bondaranayake D, Huang QS, Bissielo A, Wood T, Mackereth G, Baker MG, et al. Risk factors and immunity in a nationally representative population following the 2009 influenza A(H1N1) pandemic. *PLoS One*. 2010;5(10):e13211.
3. Baker MG, Wilson N, Huang QS, Paine S, Lopez L, Bandaranayake D, et al. Pandemic influenza A(H1N1)v in New Zealand: the experience from April to August 2009. *Euro Surveill*. 2009;14(34):pii=19319.
4. Institute of Environmental Science and Research Ltd. Sentinel Surveillance. Wellington, NZ2010 [cited 2010 15 March]; Available from: http://www.surv.esr.cri.nz/public_health_surveillance/influenza.php#Sentinel Surveillance.
5. Ministry of Health. Guidance on the diagnosis and management of pandemic influenza H1N1. In: Population Health, editor. Wellington2010.
6. Salmond C, Crampton P, Atkinson J. NZDep2006 Index of Deprivation Wellington: Department of Public Health University of Otago2007.
7. Ministry of Health. Ethnicity Data Protocols for the Health and Disability Sector Wellington: Ministry of Health; 2004.
8. Houlihan CF, Patel S, Price DA, Valappil M, Schwab U. Life threatening infections labelled swine flu. *BMJ (Clinical research ed)*. 2010;340:c137.
9. Lopez I, Huang QS. Influenza in New Zealand in 2009. Wellington2010.
10. Friesema IHM, Koppeschaar CE, Donker GA, Dijkstra F, van Noort SP, Smallegenburg R, et al. Internet-based monitoring of influenza-like illness in the general population: Experience of five influenza seasons in the Netherlands. *Vaccine*. 2009;27(45):6353-7.
11. Tilston NL, Eames KT, Paolotti D, Ealden T, Edmunds WJ. Internet-based surveillance of Influenza-like-illness in the UK during the 2009 H1N1 influenza pandemic. *BMC Public Health*. 2010;10:650.
12. Anonymous. Seroepidemiological studies of pandemic influenza A (H1N1) 2009 virus. *Wkly Epidemiol Rec*. 2010 Jun 11;85(24):229-35.
13. Hancock K, Veguilla V, Lu X, Zhong W, Butler EN, Sun H, et al. Cross-reactive antibody responses to the 2009 pandemic H1N1 influenza virus. *N Engl J Med*. 2009 Nov 12;361(20):1945-52.
14. Miller E, Hoschler K, Hardelid P, Stanford E, Andrews N, Zambon M, et al. Incidence of 2009 pandemic influenza A H1N1 infection in England: a cross-sectional serological study. *Lancet*. [Research Support, Non-U.S. Gov't]. 2010 Mar 27;375(9720):1100-8.
15. Gilbert GL, Cretikos MA, Hueston L, Doukas G, O'Toole B, Dwyer DE, et al. Influenza A (H1N1) 2009 antibodies in residents of New South Wales, Australia, after the first pandemic wave in the 2009 southern hemisphere winter. *PLoS ONE [Electronic Resource]*. [Research Support, Non-U.S. Gov't]. 2010;5(9):e12562.
16. Wu JT, Ma ES, Lee CK, Chu DK, Ho PL, Shen AL, et al. The infection attack rate and severity of 2009 pandemic H1N1 influenza in Hong Kong. *Clin Infect Dis*. 2010 Nov 15;51(10):1184-91.
17. Lee VJ, Yap J, Cook AR, Chen MI, Tay JK, Barr I, et al. Effectiveness of public health measures in mitigating pandemic influenza spread: a prospective sero-epidemiological cohort study. *J Infect Dis*. [Research Support, Non-U.S. Gov't]. 2010 Nov 1;202(9):1319-26.

18. Aho M, Lyytikainen O, Nyholm JE, Kuitunen T, Ronkko E, Santanen R, et al. Outbreak of 2009 pandemic influenza A(H1N1) in a Finnish garrison--a serological survey. *Euro Surveill.* 2010;15(45).

19. Carrat F, Vergu E, Ferguson NM, Lemaître M, Cauchemez S, Leach S, et al. Time lines of infection and disease in human influenza: a review of volunteer challenge studies. *Am J Epidemiol.* 2008 Apr 1;167(7):775-85.

20. Call SA, Vollenweider MA, Hornung CA, Simel DL, McKinney WP. Does This Patient Have Influenza? *JAMA: The Journal of the American Medical Association.* 2005 February 23, 2005;293(8):987-97.

21. Bandaranayake D, Huang QS, Bissielo A, Wood T, Mackereth G, Baker MG, et al. Risk factors and immunity in a nationally representative population following the 2009 influenza A(H1N1) pandemic. *PLoS One.* 2010;5(10):e13211.

22. Tang JW, Tambyah PA, Lai FY, Lee HK, Lee CK, Loh TP, et al. Differing symptom patterns in early pandemic vs seasonal influenza infections. *Archives of internal medicine.* May 24;170(10):861-7.

23. Cao B, Li XW, Mao Y, Wang J, Lu HZ, Chen YS, et al. Clinical features of the initial cases of 2009 pandemic influenza A (H1N1) virus infection in China. *The New England journal of medicine.* 2009 Dec 24;361(26):2507-17.

24. World Health Organisation. Human infection with new influenza A (H1N1) virus: clinical observations from a school-associated outbreak in Kobe, Japan, May 2009. *Wkly Epidemiol Rec.* 2009;84(24):237-48.

25. Perez-Padilla R, de la Rosa-Zamboni D, Ponce de Leon S, Hernandez M, Quiñones-Falconi F, Bautista E, et al. Pneumonia and Respiratory Failure from Swine-Origin Influenza A (H1N1) in Mexico. *N Engl J Med.* 2009;361(7):680-9.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	See manuscript management system generated abstract
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	1
Objectives	3	State specific objectives, including any prespecified hypotheses	1
Methods			2
Study design	4	Present key elements of study design early in the paper	2
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	2
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	2
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	3-4
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	3
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4-5
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	4-5
		(b) Describe any methods used to examine subgroups and interactions	4-5
		(c) Explain how missing data were addressed	tables
		(d) If applicable, describe analytical methods taking account of sampling strategy	

		(e) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	No
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6 and table 1
		(b) Indicate number of participants with missing data for each variable of interest	See tables
Outcome data	15*	Report numbers of outcome events or summary measures	6-8
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	yes
		(b) Report category boundaries when continuous variables were categorized	5
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6-8
Discussion			
Key results	18	Summarise key results with reference to study objectives	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	8,9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8
Generalisability	21	Discuss the generalisability (external validity) of the study results	8,9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	See Scholar One

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Self-diagnosis of influenza during a pandemic: A cross sectional survey

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Manuscripts

Self-diagnosis of influenza during a pandemic: A cross sectional survey

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Contributors:

AMJ devised and led the study, guarantees the report and is the corresponding author. MB refined the design. JS carried out the data analysis. AMJ, JS and MB prepared the manuscript. SH and DB managed the seroprevalence study. All authors contributed to writing and revising the report.

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf and declare that (1) AJ, MB, and JS received a grant from the Health Research Council (NZ) for the submitted work; (2) None of the authors have any relationships with companies that might have an interest in the submitted work in the previous 3 years; (3) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (4) none of the authors have any non-financial interests that may be relevant to the submitted work.

ARTICLE SUMMARY

Article Focus

- to determine whether lay people can accurately recognise influenza infection

Key Messages

- individuals meeting influenza case definitions were more likely to believe they had influenza, however,
- self-diagnosis, whether by lay person or health care worker did not accurately predict influenza seropositivity

Strengths and limitations of this study

- this study provides the first published investigation of the effectiveness of self-diagnosis of influenza compared with laboratory evidence of infection in a broad population-based sample during a pandemic.
- some of the participants who believed they had the flu may have had a seasonal influenza or other respiratory pathogens (although H1N1 was the dominant influenza strain)
- this survey was based on symptom recall, rather than symptom reports. However, this may reflect the participant's enduring perceptions of influenza, which are likely to guide their behaviour in future influenza epidemics

ABSTRACT

Background. Self-diagnosis of influenza is a mainstay of pandemic management because it may support self-management practices and reduce visits to healthcare facilities, thus helping contain viral spread. However, little is known about the accuracy of self-diagnosis of influenza, particularly during pandemics.

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Methods. We used cross-sectional survey data to correlate self-diagnosis of influenza with serological evidence of 2009 pandemic influenza A(H1N1) infection (haemagglutination inhibition titres of $\geq 1:40$), and to determine what symptoms were more likely to be present in accurate self-diagnosis. The sera and risk factor data were collected for the national A(H1N1) seroprevalence survey from November-2009 to March-2010, three months after the first pandemic wave in New Zealand (NZ).

Results. The samples consisted of 318 children, 413 adults and 423 health care workers (HCW). The likelihood of being seropositive was no different in those who believed they had influenza and those who believed they did not have influenza in all groups. Among adults, 23.3% (95% CI 11.9 - 34.7) of those who reported having had influenza were seropositive for H1N1; but among those reporting no influenza, the seropositivity was 21.3% (95% CI 13 - 29.7%). Those meeting NZ surveillance or Ministry of Health influenza case definitions were more likely to believe they had the flu (for surveillance data, adult sample OR= 27.1, 95% CI 13.6 - 53.6) but these symptom profiles were not associated with a higher likelihood of H1N1 seropositivity (surveillance data adult sample OR = 0.93, 95% CI 0.5 - 1.7.)

Conclusions. Self-diagnosis does not accurately predict influenza seropositivity. The symptoms promoted by many public health campaigns are linked with self-diagnosis of influenza, but not with seropositivity. These findings raise challenges for public health initiatives that depend on accurate self-diagnosis by members of the public and appropriate self-management action.

Key words:Influenza, Human/epidemiology/*immunology/prevention & control, diagnosis; screening; sensitivity and specificity

ORIGINAL RESEARCH

Self-diagnosis of influenza during a pandemic

Self-diagnosis is an important component of pandemic control and management. The use of self-diagnosis in an influenza pandemic can prevent some exposures by reducing outpatient visits to primary care clinics ⁽¹⁾. During the 2009 pandemic, following Centers for Disease Control recommendations, patient teaching brochures advised patients to stay home and avoid contact with other people if they had influenza like illness (ILI), seeking medical assistance only in case of complications or risk factors. Whilst the accuracy of self-diagnosis has been studied for a range of common diseases (for example, uncomplicated urinary tract infections (2, 3), vaginal yeast infections (4) and malaria (5, 6)), it has not been established for influenza.

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Although self-diagnosis of influenza is clearly desirable for the purposes of infection containment, it also presents challenges to patients and doctors alike. As the social science literature clearly articulates, diagnosis is central to the practice of medicine and to defining the roles of, and boundaries between, the patient and the professional; self-diagnosis blurs these (7-10).

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The diagnosis of influenza by a lay person may be independent of medical contact, using resources such as family, friends or other non-medical sources of information such as on-line or internet resources (*independent self-diagnosis*). It may also be supported by a health professional via a helpline, without the lay person being seen for a clinical diagnosis (*assisted self-diagnosis*).

The purpose of this study was to determine whether lay people's assessment of influenza status is confirmed by serological testing, and whether

the presence of particular symptoms assists individuals in the correct identification of influenza. It also aimed to measure the accuracy of self-diagnosis by health care workers (HCW). Establishing the current reliability of self-diagnosis will provide either assurances about, or identifications of shortcomings in, public health strategies to contain spread of influenza.

Methods and Sample

Population sample - This study was conducted as part of the national Environmental Science and Research (ESR) seroprevalance study in early 2010

(11). This study used a purposive, multi-stage random cross-sectional survey of 1147 subjects from selected primary care patient registers from 14 general practitioner (GP) practices. The practices were selected purposively on the basis of observed high, medium and low incidence during the pandemic and on ethnic distribution. Each practice was stratified by age and by ethnic group. Within each stratum, simple random sampling was undertaken, with oversampling in strata for Māori and Pacific respondents to improve the precision of estimates for these groups. A second sample consisted of 540 HCW (369 HCW located in Auckland and Middlemore Hospitals, and 171 from the 14 GP practices in the community study). The HCW sample included medical, nursing, and other staff. A simple random sampling procedure was performed to select participants for this sample

(11). Sera and risk factor data were collected from November-2009 to March-2010, three months after the first pandemic wave in NZ (12). Ethical approval (MEC/09/09/106) was obtained from the Multiregional Ethics Committee of the NZ Ministry of Health. Written informed consent was obtained from all participants

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We excluded participants born before 1957, because of the higher level of pre-pandemic seropositivity in this group (11). We treated those under age 18 as a separate group, because their questionnaires were usually completed by parents (*self-diagnosis by proxy*); furthermore, their health-related behaviours were likely to be influenced or, for the very young, entirely managed by their parents.

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We also considered HCW separately from lay participants, however, as the sampling methods for this group were different from the main community sample (the geographic area was more restricted in the HCW sample), comparisons between this group and the adult community sample should be made with caution.

Laboratory testing - Blood samples were obtained by phlebotomists in the general practice clinics, and serological testing was carried out at the National Influenza Centre (NIC) at ESR using a haemagglutination inhibition assay (HI) in line with the standard protocol provided by the WHO Collaborating Centre in Melbourne. Haemagglutination inhibition (HI) titres of ≥ 40 against H1N1 were considered seroprotective as well as seropositive. Laboratory testing methods are fully described elsewhere (11).

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Questionnaire - A questionnaire was administered by nurses from 14 participating general practice clinics at the time of the blood sample collection to record information about respondent demographics; whether respondents believed they had contracted influenza in 2009; and their symptoms. Questions were both multiple-choice and open-ended.

Respondents were asked "Did you have the flu or influenza over this last winter (June to August)?" with options being "yes", "possibly", "no", and "don't know". Those who believed they had suffered from influenza were asked how they knew, choosing either:

1. I could tell on my own or with the help of my family and friends;
2. I called the nurse or HealthLine and they helped me to decide; or,
3. I saw my doctor or other health professional who told me I did

Self-diagnosis was defined as including both independent and assisted forms (ie choosing 1 or 2 above) for those who responded “yes” to the question about having had influenza.

Two additional case definitions of influenza were used based on reported symptoms: influenza-like illness (ILI) defined by the NZ sentinel surveillance definition⁽¹³⁾ of two or more symptoms from fever, muscle ache, and headache (reports of chills are included in this definition, but this information was not collected in this study) and also the NZ Ministry of Health⁽¹⁴⁾ as fever, plus cough or sore throat (reports of chills or sweating are included in this definition, but this information was not collected in the study).

Demographic information included age, gender, self-identified ethnicity, and socio-economic deprivation (using NZDep, a well-validated measure of small-area socio-economic deprivation based on census-derived characteristics such as income, education and household crowding, and assigned according to domicile address⁽¹⁵⁾). Ethnicity classification used the NZ 2006 Census questions, and prioritised ethnicity coding according to Ministry of Health ethnicity data protocols⁽¹⁶⁾. Participants could choose up to nine different symptoms (fever or high temperature; cough; sore throat; runny nose; red, watery or sore eye(s); headache; muscle aches and pains; weakness, tiredness or fatigue; an upset stomach, diarrhoea or vomiting to describe any illness they had during the period under study as well as the open-ended “something else (describe).”

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Analysis - All statistical analyses were performed using SAS 9.2 (SAS Institute Inc, NC.) Survey analysis techniques were used to take into account differential sampling probabilities by age and ethnicity; sample weights were calculated by ESR as the inverse probability of selection of an individual within each GP practice.

Proportions (and 95% CI) were calculated using the Surveyfreq procedure, taking into account clustering by GP practice and sample weight (as described above) for the adult/child community samples. Chi-squared comparisons for the complex survey data (seroprevalence community survey) were adjusted using the Rao-Scott correction(17) to allow for the impact of the complex survey structure and to test whether seropositivity rates were different between the three self-reported influenza status groups; and also to test whether seropositivity status differed according to the decision making process by which a respondent had decided that he or she (or their child) had influenza. As the HCW dataset did not derive from a complex sampling method, Pearson's chi-squared tests were used for the equivalent hypothesis tests for that group.

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Sensitivity and specificity (along with positive predictive value and negative predictive value – PPV and NPV respectively) were calculated for seropositive status as the “gold standard” measure of disease status, and three definitions of influenza “screening” tests: self-report, Ministry of Health case definition, and NZ sentinel surveillance case definition. Self-reported influenza status was reclassified as a binary variable by combining “definite” and “possibly” groups into a “positive self-report” group for the purposes of this analysis. We opted for this reconfiguration because we felt it was the most policy-relevant categorisation and would potentially translate into useful health advice (either of these groups was

likely to implement influenza-related management strategies). All of these calculations and confidence intervals were performed using the Proc Surveyfreq command.

Logistic regression methods (Proc Surveylogistic) were used to investigate the relationships between case definition status (separate models for the different definitions) and (1) self-reported influenza status or (2) seropositive test results.

Results

Characteristics of the sample –For the community branch of the study, a minimum sample size of 1500 subjects were required at design prevalence of 20% and confidence level of 95% to maintain +/- 10% margin error of estimate. 1147 subjects participated fully in the study (9 did not return the questionnaire and were thus excluded from the analysis). This gave a target rate of 76%.For the healthcare worker (HCW) branch of the study, the minimum sample size was calculated using the same criteria as the community study. The number of subjects (171 primary HCWs and 369 secondary HCWs) exceeded the minimum requirement. Of the 1687 subjects with completed questionnaires and serological results across the community and HCW studies, after excluding those respondents born before 1957, 413 responses (unweighted frequency) were considered for the analyses of adult responses; 318 were considered as children; and 423 were HCW. This gave a final sample size of 1154 people across the three groups.

Baseline demographic characteristics of the study populations are shown in Table 1. These are unweighted frequencies and percentages: all subsequent analyses take the sampling structure into account. (11)The sample was not adequately powered to demonstrate ethnic differences in the findings reported below.

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Accuracy of self-report of influenza - Seropositivity status was compared across the three self-reported influenza status groups (yes, no, or possibly had the flu in 2009). Respondents who answered “don’t know” to this question (n = 16, 21, & 22 for adult, child, and HCW samples respectively) were excluded from this analysis.

As shown in Table 2, the likelihood of being seropositive was not significantly different between the three self-reported influenza status groups in any of the three sample groups. For adults in the community sample, point estimates of seropositive status ranged from 21.3 to 25.1 across the three self-report groups; for under 18s in the same sample, seropositive rates were between 40.1 and 45.9%, which was the highest among all three sample groups; and for health care workers, the range was between 25.7 and 33.0% seropositive.

Table 3 shows that amongst those people who reported having had influenza, the proportion of people who were seropositive was higher amongst those who reached a decision in conjunction with a health professional than amongst those who reported reaching a diagnosis on their own (including using a telephone helpline.) While this pattern was consistent across all three sample sources, none of these differences were statistically significant (all $p > 0.3$) which is potentially reflective of the smaller er sample sizes for this analysis.

As shown in Table 4, self-reported flu status performed poorly as a screening tool for H1N1 infection, failing to detect the majority of those who were seropositive (adult sensitivity 45.7%). Only about a quarter of those who considered themselves to have had influenza during the preceding winter showed serological evidence of this (adult PPV 24.1%). Self-reported flu status had higher sensitivity and lower specificity than the Ministry of Health and NZ sentinel surveillance case definitions. Screening performance (sensitivity, specificity, PPV,

and NPV) was otherwise broadly similar across the three sets of “screening” criteria used. PPV and NPV values across all definitions followed the pattern seen for seropositive prevalence (e.g. children had the highest PPV, reflecting a higher proportion of seropositive tests.)

Seropositive status, symptom profiles and case definitions of influenza -

Using Ministry of Health and the NZ sentinel surveillance ILI case definitions, we sought to confirm whether there was an increased likelihood of seropositivity for those who met these case definitions, based on self-report of symptoms. The likelihood of being seropositive was not significantly different between these symptom profile groups for any sample group (see Table 5; 95% confidence intervals for all odds ratios included 1). People who met a case definition had a much greater likelihood of self-reporting having had influenza (Table 5, for both definitions).

Discussion

Key findings – This study provides, to our knowledge, the first published investigation of the effectiveness of self-diagnosis of influenza compared with laboratory evidence of infection in a broad population-based sample during a pandemic. The likelihood of being seropositive was no different in those who believed they had influenza and those who believed they did not have influenza. This finding applied to HCW as well as adults and children. Our study showed that self-diagnosis in a NZ population lacks sensitivity and specificity for diagnosing influenza. The poor sensitivity may lead to people with influenza believing that they are well and therefore failing to take measures to limit their contribution to influenza spread. The lack in specificity may result in delayed medical treatment when serious treatable illness is present (18).

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Strengths and weaknesses of the study: Limitations of this study include the fact that some of the participants who believed they had the flu and yet were seronegative for H1N1 may have had seasonal influenza or other respiratory pathogens. However, H1N1 was the dominant influenza strain in 2009 accounting for 77.6% of influenza viruses that were sub-typed during the year (19). Further, the fact that seasonal influenza was replaced very quickly by pandemic H1N1 palliates this limitation to some extent. A small proportion of those who were seropositive will have baseline immunity to H1N1 acquired prior to 2009, though testing of stored sera shows that the level of such infection is low, ranging from 6.5-7.5% in the 20-59 year old population (11). Further, this survey was based on symptom recall, rather than symptom reports at time of presentation. Symptoms reported retrospectively may well not match the actual symptoms experienced during the illness. However, the pandemic was an unusual event of some concern to the individual and recall bias tends to be minimal in such situations. Furthermore, there is some validity in focussing on recalled symptoms, because these may reflect the participant's enduring perceptions of influenza, which guide their behaviour in relation to future episodes of influenza like illness. The higher likelihood of positive serology in those adults who consulted a health professional may be related to greater severity of their disease which this study does not capture. Also, it is likely that a greater proportion of people than usual may have consulted a health care provider due to the high media attention given to 'swine-flu'. The findings of this study might not be generalizable to other influenza viruses causing seasonal and pandemic disease.

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Strengths and weaknesses in relation to other studies: Other studies have attempted to understand how lay people report ILI, but have not obtained medical or laboratory confirmation of the diagnosis as ours did (20, 21). In excess of nine

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H1N1 seroprevalence studies have occurred following the pandemic (22). Almost all used unlinked specimens so were not able to question participants about their symptom history (23-26). Two studies in selected military populations collected symptom data. One prospective study of Singaporean military personnel tracked symptomatic illness during the pandemic and found that less than a third of those who were seropositive reported symptoms (27). A small cross-sectional study reported seroconversion following an H1N1 outbreak in a Finnish military garrison, and found that sensitivity for seropositivity was 50% on the basis of self-reported upper respiratory tract infection (URTI) symptoms (i.e. half of those with serological evidence of infection reported a history of URTI symptoms) (28) - this compares with the sensitivities for the current dataset, which were 45.7% and 48.2% for the community adults and for HCW adults, respectively. Participants in this NZ seroprevalence survey were more likely to believe they had been infected if they had symptoms commonly advertised by public health campaigns as being linked with the flu. However, these symptom profiles were not significantly associated with seropositivity. This finding is consistent with a recent systematic review of symptoms in volunteer challenge studies, where nearly one in three participants demonstrated no clinical symptoms of influenza, despite laboratory confirmed infection (29). The authors of that study questioned whether naturally acquired influenza might produce more marked symptoms. Our study would appear to show that this is not the case, at least for pandemic H1N1 influenza.

Implications for clinicians and policymakers: These study findings raise important questions for pandemic control policies. On the positive side, they show that the NZ public has absorbed a fairly coherent ILI case definition that includes the symptoms traditionally linked to influenza. Unfortunately, we have

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demonstrated that this generic picture of ILI is a poor predictor of influenza infection. The classic symptoms of influenza are nonspecific, and accompany other infections commonly seen during the influenza season. A systematic review comparing influenza symptoms to independent criterion standards for influenza highlighted that epidemiological data, for example reports of regional influenza patterns, was probably more useful than clinical indicators for predicting whether an individual had influenza (30). And daily temperature measurement plus reporting of respiratory symptoms resulted in reduced transmission of H1N1 virus (27). It is also useful to note that HCW perform no better than non-professionals; the positive predictive value of an ILI diagnosis by a HCW was 30.1%. Interestingly, this value is similar to the PPV of clinical diagnosis by a GP for patients presenting to sentinel sites over the same period in 2009 (31.3% based on 624 viruses from 1993 swabs received) (19). These findings reinforce public health advice during the pandemic that patients should seek medical care based on disease severity, rather than for diagnostic reasons.

Further research – Given the importance of self-diagnosis to containment and mitigation measures, further investigations around the low accuracy of self-

diagnosis would be useful. Priorities for such research could include: more in-depth qualitative investigation of patient reports of influenza, prospective exploration of patient self-diagnosis at the time of respiratory infection, variations in self-diagnosis by ethnicity and SES and age, particularly given the differential distribution of respiratory illness across these groups (our sample was not sufficiently large to enable these analyses) (31). The presenting symptoms of influenza may vary depending on the type of influenza is responsible. In Singapore, H1N1 and seasonal influenza had different symptom profiles, with

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fever and runny nose being more common among seasonal influenza cases (32) and the prevalence of specific symptoms among H1N1 cases also varied between studies (33-35) so further exploration is warranted.

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Table 1. Demographic characteristics of participants (unweighted frequencies and percentages)

		Adults (18+) (n=413)		Children (<18) (n=318)		Health Care Workers (n=423)	
Factor		Frequency	Percentage*	Frequency	Percentage*	Frequency	Percentage*
Sex	Female	262	63.44	150	47.62	348	82.27
	Male	151	36.56	165	52.38	75	17.73
	Unknown	0		3		0	
Ethnicity	NZE**	160	47.76	95	42.22	289	68.97
	Māori	82	24.48	53	23.56	20	4.77
	Pacific	65	19.4	54	24	14	3.34
	Asian	22	6.57	17	7.56	92	21.96
	Other	6	1.79	6	2.67	4	0.95
	Unknown	78		93		4	
Age group	1-4			150	47.17		
	5-9			68	21.38		
	10-14			68	21.38		
	15-17			32	10.06		
	18-24	80	19.37			26	6.15
	25-34	101	24.46			137	32.39
	35-44	132	31.96			152	36.17
	45-52*	100	24.21			107	25.3

* Percentage of respondents with valid answers to question.

** New Zealand European

Table 2. Serological status according to self-reported flu status (proportions and 95%CI)

Self-reported flu status	n	% seropositive*	95% CI	p-value**
Adults (18+) [†] (n=413)				0.802
No	221	21.3	13 - 29.7	
Possibly	68	25.1	14.2 - 36	
Yes	108	23.3	11.9 - 34.7	
Children (<18) [‡] (n=318)				0.723
No	149	45.9	34.4 - 57.4	
Possibly	55	42.2	28.6 - 55.9	
Yes	86	40.1	24.7 - 55.6	
Health Care Workers ^{‡‡} (n=423)				0.415
No	222	25.7	20.1 - 31.9	
Possibly	80	27.5	18.1 - 38.6	
Yes	94	33	23.6 - 43.4	

* weighted percentage

** p-values for Adults and Children in community sample from Rao-Scott chi-square test;

p-value for HCW [§]from Pearson's chi-square test

[†] 16 Adults from community sample responded "don't know" on self-reported influenza status and excluded from analysis.

[‡] 21 Children from community sample responded "don't know" on self-reported influenza status and excluded from analysis

^{‡‡} 22 HCW "don't know" respondents, 5 missing immunological status, excluded from analysis.

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Table 3. Serological status according to diagnostic approach for people self-reporting having had influenza

Method for diagnosis	n	% seropositive*	95% CI	p-value**
Adults (18+)[†] (n=108)				0.392
Health professional	37	27.1%	(7.9 - 46.3)	
Self-diagnosis	61	17.7%	(5.3 - 30.1)	
Children (<18)[‡] (n=86)				0.332
Health professional	43	39.7%	(18.4 - 61.1)	
Self-diagnosis	34	25.2%	(4.5 - 45.9)	
Health Care Workers^{‡‡} (n=94)				0.356
Health professional	25	40.0%	(21.1 - 61.3)	
Self-diagnosis	67	29.9%	(19.3 - 42.3)	

* weighted percentage

** p-value for HCW are from Pearson's chi-square test; p-values for Adults and Children are from Rao-Scott chi-square test.

[†] 10 Adults from community sample were missing information on pathway of diagnosis.

[‡] 9 children were missing information on pathway of diagnosis.

^{‡‡} 2 health care workers were missing information on pathway of diagnosis.

Table 4. Screening performance of influenza definitions for detecting seropositive status (sensitivity, specificity, positive predictive value [PPV] and negative predictive value [NPV])

NZ sentinel surveillance ILI definition ¹			NZ Ministry of Health ILI definition ²		Self-reported flu status ³	
Measure	Point estimate	95% CI	Point estimate	95% CI	Point estimate	95% CI
Adults (18+) (n=413)						
Sensitivity	37.7	(25.5 - 50)	38.0	(25.6 - 50.4)	45.7	(33 - 58.3)
Specificity	60.5	(53.6 - 67.4)	67.2	(60.6 - 73.8)	58.1	(51 - 65.3)
PPV	21.6	(13.6 - 29.6)	25.1	(15.8 - 34.4)	24.1	(16.2 - 31.9)
NPV	77.1	(70.6 - 83.5)	79.0	(73.1 - 84.8)	78.7	(72 - 85.3)
Children (<18) (n=318)						
Sensitivity	32.5	(21 - 44)	36.0	(24.5 - 47.6)	42.4	(30 - 54.9)
Specificity	68.4	(58.4 - 78.4)	57.2	(47.3 - 67.1)	52.6	(42.1 - 63)
PPV	43.4	(29.1 - 57.7)	38.6	(27 - 50.1)	40.9	(29.3 - 52.6)
NPV	57.6	(48.2 - 67)	54.5	(44 - 65)	54.1	(43 - 65.3)
Health Care Workers† (n= 423)						
Sensitivity	32.5	(23.8 - 41.1)	30.7	(22.2 - 39.2)	48.2	(38.8 - 57.6)
Specificity	70.8	(65.7 - 75.9)	76.4	(71.6 - 81.2)	57.7	(51.9 - 63.4)
PPV	29.9	(21.9 - 37.9)	32.7	(23.8 - 41.6)	30.5	(23.6 - 37.3)
NPV	73.5	(68.5 - 78.6)	74.7	(69.8 - 79.5)	74.3	(68.6 - 80.1)

¹Two or more symptoms from: fever, muscle ache, and headache

²Fever, plus cough and/or sore throat

³Self-diagnosis, assisted-self-diagnosis, or self-diagnosis by proxy

* Adults: 16 “don’t know” respondents on self-reported influenza status excluded from analysis.

** Children: 21 “don’t know” respondents on self-reported influenza status excluded from analysis

† HCW: 22 “don’t know” respondents on self-reported influenza status, 5 respondents missing immunological status excluded from analysis.

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Table 5. Association between symptom profiles and self-reported flu status (left side) and seropositive status (right side). Odds ratios and 95% CI derived from independent logistic regression models.

	Self-report status		Seropositive status	
	Odds Ratio	95% CI	Odds Ratio	95% CI
NZ sentinel surveillance definitions¹				
Adults (18+)				
No or 1 symptom	Reference group		Reference group	
2 or 3 symptoms	27.1	(13.6 - 53.6)	0.93	(0.5 - 1.7)
Children (<18)				
No or 1 symptom	Reference group		Reference group	
2 or 3 symptoms	21.5	(8.98 - 51.6)	1.04	(0.52 - 1.09)
Health Care Workers				
No or 1 symptom	Reference group		Reference group	
2 or 3 symptoms	18.2	(10.3 - 32.1)	1.19	(0.75 - 1.9)
Ministry of Health (MoH) definition²				
Adults (18+)				
Met MoH definition	11.5	(6.1 - 21.8)	1.3	(0.7 - 2.3)
Did not meet definition	Reference group		Reference group	
Children (<18)				
Met MoH definition	9.5	(4.5 - 20)	0.8	(0.4 - 1.4)
Did not meet definition	Reference group		Reference group	
Health Care Workers				
Met MoH definition	13.3	(7.4 - 23.9)	1.46	(0.9 - 2.4)
Did not meet definition	Reference group		Reference group	

¹Two or more symptoms from: fever, muscle ache, and headache

²Fever, plus cough and/or sore throat

³Self-diagnosis, assisted-self-diagnosis, or self-diagnosis by proxy

* Adults: "don't know" respondents.

** Children: "don't know" respondents

† HCW: 22 "don't know" respondents, 5 missing immunological status.

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References

1. Centers for Disease Control and Prevention. Interim Guidance on Infection Control Measures for 2009 H1N1 Influenza in Healthcare Settings, Including Protection of Healthcare Personnel. 2009 [cited 2009 16 November]; Available from: http://www.cdc.gov/h1n1flu/guidelines_infection_control.htm.

2. Bent S, Nallamotheu BK, Simel DL, Fihn SD, Saint S. Does this woman have an acute uncomplicated urinary tract infection? JAMA. 2002 May 22-29;287(20):2701-10.

3. Gupta K, Hooton TM, Roberts PL, Stamm WE. Patient-initiated treatment of uncomplicated recurrent urinary tract infections in young women. Annals of internal medicine. 2001 Jul 3;135(1):9-16.

4. Roy S, Caillouette JC, Faden JS, Roy T. The role of an over-the-counter vaginal pH self-test device package insert: can subjects learn what the device is for and how to use it? Am J Obstet Gynecol. 2005 Jun;192(6):1963-7; discussion 7-9.

5. Whitty CJM, Armstrong M, Behrens RH. Self-testing for falciparum malaria with antigen-capture cards by travelers with symptoms of malaria. Am J Trop Med Hyg. 2000 Nov-Dec;63(5-6):295-7.

6. Jelinek T, Amsler L, Grobusch MP, Nothdurft HD. Self-use of rapid tests for malaria diagnosis by tourists. Lancet. 1999 Nov 6;354(9190):1609.

7. Balint M. The Doctor, his Patient and the Illness. second ed. Kent, England: Pitman Medical; 1964.

8. Blaxter M. Diagnosis as category and process: The case of alcoholism. Soc Sci Med. 1978;12:9-17.

9. Jutel A. Sociology of diagnosis: a preliminary review. Sociol Health Illn. 2009 Mar;31(2):278-99.

10. Brown P. Naming and framing: the social construction of diagnosis and illness. J Health Soc Behav. 1995;Health Module:34-52.

11. Bondaranayake D, Huang QS, Bissielo A, Wood T, Mackereth G, Baker MG, et al. Risk factors and immunity in a nationally representative population following the 2009 influenza A(H1N1) pandemic. PLoS One. 2010;5(10):e13211.

12. Baker MG, Wilson N, Huang QS, Paine S, Lopez L, Bandaranayake D, et al. Pandemic influenza A(H1N1)v in New Zealand: the experience from April to August 2009. Euro Surveill. 2009;14(34):pii=19319.

13. Institute of Environmental Science and Research Ltd. Sentinel Surveillance. Wellington, NZ2010 [cited 2010 15 March]; Available from: http://www.surv.esr.cri.nz/public_health_surveillance/influenza.php#Sentinel Surveillance.

14. Ministry of Health. Guidance on the diagnosis and management of pandemic influenza H1N1. In: Population Health, editor. Wellington2010.

15. Salmond C, Crampton P, Atkinson J. NZDep2006 Index of Deprivation Wellington: Department of Public Health University of Otago2007.

16. Ministry of Health. Ethnicity Data Protocols for the Health and Disability Sector Wellington: Ministry of Health; 2004.

17. Rao JNK, Scott AJ. On chi-squared tests for multiway contingency tables with proportions estimated from survey data. Annals of Statistics. 1984;12:46-60.

18. Houlihan CF, Patel S, Price DA, Valappil M, Schwab U. Life threatening infections labelled swine flu. BMJ (Clinical research ed. 2010;340:c137.

19. Lopez I, Huang QS. Influenza in New Zealand in 2009. Wellington2010.

20. Friesema IHM, Koppeschaar CE, Donker GA, Dijkstra F, van Noort SP, Smallegange R, et al. Internet-based monitoring of influenza-like illness in the general population: Experience of five influenza seasons in the Netherlands. *Vaccine*. 2009;27(45):6353-7.
21. Tilston NL, Eames KT, Paolotti D, Ealden T, Edmunds WJ. Internet-based surveillance of Influenza-like-illness in the UK during the 2009 H1N1 influenza pandemic. *BMC Public Health*. 2010;10:650.
22. Anonymous. Seroepidemiological studies of pandemic influenza A (H1N1) 2009 virus. *Wkly Epidemiol Rec*. 2010 Jun 11;85(24):229-35.
23. Hancock K, Veguilla V, Lu X, Zhong W, Butler EN, Sun H, et al. Cross-reactive antibody responses to the 2009 pandemic H1N1 influenza virus. *N Engl J Med*. 2009 Nov 12;361(20):1945-52.
24. Miller E, Hoschler K, Hardelid P, Stanford E, Andrews N, Zambon M, et al. Incidence of 2009 pandemic influenza A H1N1 infection in England: a cross-sectional serological study. *Lancet*. [Research Support, Non-U.S. Gov't]. 2010 Mar 27;375(9720):1100-8.
25. Gilbert GL, Cretikos MA, Hueston L, Doukas G, O'Toole B, Dwyer DE, et al. Influenza A (H1N1) 2009 antibodies in residents of New South Wales, Australia, after the first pandemic wave in the 2009 southern hemisphere winter. *PLoS ONE [Electronic Resource]*. [Research Support, Non-U.S. Gov't]. 2010;5(9):e12562.
26. Wu JT, Ma ES, Lee CK, Chu DK, Ho PL, Shen AL, et al. The infection attack rate and severity of 2009 pandemic H1N1 influenza in Hong Kong. *Clin Infect Dis*. 2010 Nov 15;51(10):1184-91.
27. Lee VJ, Yap J, Cook AR, Chen MI, Tay JK, Barr I, et al. Effectiveness of public health measures in mitigating pandemic influenza spread: a prospective sero-epidemiological cohort study. *J Infect Dis*. [Research Support, Non-U.S. Gov't]. 2010 Nov 1;202(9):1319-26.
28. Aho M, Lyytikäinen O, Nyholm JE, Kuitunen T, Ronkko E, Santanen R, et al. Outbreak of 2009 pandemic influenza A(H1N1) in a Finnish garrison--a serological survey. *Euro Surveill*. 2010;15(45).
29. Carrat F, Vergu E, Ferguson NM, Lemaître M, Cauchemez S, Leach S, et al. Time lines of infection and disease in human influenza: a review of volunteer challenge studies. *Am J Epidemiol*. 2008 Apr 1;167(7):775-85.
30. Call SA, Vollenweider MA, Hornung CA, Simel DL, McKinney WP. Does This Patient Have Influenza? *JAMA: The Journal of the American Medical Association*. 2005 February 23, 2005;293(8):987-97.
31. Bandaranayake D, Huang QS, Bissielo A, Wood T, Mackereth G, Baker MG, et al. Risk factors and immunity in a nationally representative population following the 2009 influenza A(H1N1) pandemic. *PLoS One*. 2010;5(10):e13211.
32. Tang JW, Tambyah PA, Lai FY, Lee HK, Lee CK, Loh TP, et al. Differing symptom patterns in early pandemic vs seasonal influenza infections. *Archives of internal medicine*. May 24;170(10):861-7.
33. Cao B, Li XW, Mao Y, Wang J, Lu HZ, Chen YS, et al. Clinical features of the initial cases of 2009 pandemic influenza A (H1N1) virus infection in China. *The New England journal of medicine*. 2009 Dec 24;361(26):2507-17.
34. World Health Organisation. Human infection with new influenza A (H1N1) virus: clinical observations from a school-associated outbreak in Kobe, Japan, May 2009. *Wkly Epidemiol Rec*. 2009;84(24):237-48.
35. Perez-Padilla R, de la Rosa-Zamboni D, Ponce de Leon S, Hernandez M, Quiñones-Falconi F, Bautista E, et al. Pneumonia and Respiratory Failure from Swine-Origin Influenza A (H1N1) in Mexico. *N Engl J Med*. 2009;361(7):680-9.

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	See manuscript management system generated abstract
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	1
Objectives	3	State specific objectives, including any prespecified hypotheses	1
Methods			2
Study design	4	Present key elements of study design early in the paper	2
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	2
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	2
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	3-4
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	3
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4-5
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	4-5
		(b) Describe any methods used to examine subgroups and interactions	4-5
		(c) Explain how missing data were addressed	tables
		(d) If applicable, describe analytical methods taking account of sampling strategy	

		(e) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	No
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6 and table 1
		(b) Indicate number of participants with missing data for each variable of interest	See tables
Outcome data	15*	Report numbers of outcome events or summary measures	6-8
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	yes
		(b) Report category boundaries when continuous variables were categorized	5
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6-8
Discussion			
Key results	18	Summarise key results with reference to study objectives	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	8,9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8
Generalisability	21	Discuss the generalisability (external validity) of the study results	8,9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	See Scholar One

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

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