

# Seasonal Influenza Vaccine and Increased Risk of Pandemic A/H1N1-Related Illness: First Detection of the Association in British Columbia, Canada

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(See the articles by Hung et al, on pages 1007–1016, and by Liu et al, on pages 1028–1032.)

**Background.** In April 2009, an elementary school outbreak of pandemic H1N1 (pH1N1) influenza was reported in a community in northern British Columbia, Canada—an area that includes both non-Aboriginal and Aboriginal residents living on or off a reserve. During the outbreak investigation, we explored the relationship between prior receipt of trivalent inactivated influenza vaccine (TIV) and pH1N1-related illness.

**Methods.** A telephone survey was conducted from 15 May through 5 June 2009 among households of children attending any school in the affected community. Members of participating households where influenza-like illness (ILI) was described were then invited to submit blood samples for confirmation of pH1N1 infection by hemagglutination inhibition and microneutralization assays. Circulation of pH1N1 was concentrated among households of the elementary school and elsewhere on-reserve to which analyses of TIV effect were thus restricted. Odds ratios (ORs) for the TIV effect on ILI were computed through logistic regression, with adjustment for age, comorbidity, household density, and Aboriginal status. The influence of within-household clustering was assessed through generalized-linear-mixed models.

**Results.** Of 408 participants, 92 (23%) met ILI criteria: 29 (32%) of 92 persons with ILI, compared with 61 (19%) 316 persons without ILI, had received the 2008–2009 formulation of TIV. Fully adjusted ORs for 2008–2009 TIV effect on ILI were 2.45 (95% confidence interval, 1.34–4.48) by logistic regression and 2.68 [95% confidence interval, 1.37–5.25) by generalized-linear-mixed model.

**Conclusions.** An outbreak investigation in British Columbia during the late spring of 2009 provided the first indication of an unexpected association between receipt of TIV and pH1N1 illness. This led to 5 additional studies through the summer 2009 in Canada, each of which corroborated these initial findings.

During the last week of April 2009, a laboratory-confirmed outbreak of pandemic A/H1N1(pH1N1) influenza was reported in an elementary school in a rural community of northern British Columbia, Canada [1]. This school included students of Aboriginal and non-Aboriginal background drawn from the local town (population, ~2000 persons) and surrounding 5 reserves (population, ~1000 persons) [1, 2]. Laboratory confirmation of the elementary school outbreak was

made on 3 May 2009, and the school was closed the following week. Because pH1N1 was first recognized in mid-April as a novel virus, and to learn more about its characteristics, risk factors, and impact, an outbreak investigation was undertaken by public health through a school-based telephone survey conducted between 15 May and 5 June 2009 [3]. We report findings from this investigation, which revealed a first unexpected link between prior receipt of seasonal trivalent inactivated influenza vaccine (TIV) and pH1N1-related illness in Canada.

## METHODS

### Components of the Investigation

Investigation included 3 components: a telephone survey, laboratory surveillance for respiratory viruses, and a sero-survey of affected households.

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**Telephone survey.** After identification of the elementary school outbreak, the sampling frame for investigation was broadly inclusive of all households of students enrolled in the 6 local community schools. Approximately one-half of all households in the community included at least 1 child [1].

Before initiating the telephone survey, letters were distributed via students to households to explain the purpose of the investigation. Trained interviewers then contacted households, obtained consent, and conducted telephone interviews with 1 adult per household, who provided information for all household members. The telephone survey was conducted between 15 May and 5 June 2009. Household information included the number of household members and sleeping rooms, Aboriginal versus non-Aboriginal status, and whether residency was on or off a reserve. Individual-level information included age, whether flulike symptoms were experienced and the related dates of onset, duration of time “in bed” (in days), and data on health care visits, comorbidity (corresponding to high-risk categories specified by the National Advisory Committee on Immunization [4]), and receipt of 2008–2009 and/or the 2007–2008 TIV.

**Laboratory surveillance for respiratory viruses.** All respiratory virus testing for this community was provided by the BC Centre for Disease Control (Vancouver, BC) Public Health Microbiology and Reference Laboratory (Appendix, which appears only in the electronic version of the journal). During initial outbreak investigation, nasal or nasopharyngeal specimens were collected on 29 April by public health staff from a sample of students attending the affected elementary school. Thereafter, specimens were collected during the outbreak period at the clinician’s or public health official’s discretion and were evaluated as part of routine surveillance.

**Sero-survey of affected households.** To validate the clinical case definition, community households with at least 1 member reporting ILI were subsequently invited to provide serum samples from both symptomatic and asymptomatic household members. An on-site clinic was arranged during 6–8 August 2009. Antibody response to pH1N1 was quantified using the hemagglutination inhibition (HI) and microneutralization (MN) assays (Appendix). An HI threshold of  $\geq 40$  was used to designate seropositive versus seronegative participants, and status was confirmed using the MN assay [5].

### Statistical Analysis

The primary focus of analyses presented here is estimation of the effect of receipt of the 2008–2009 TIV on risk of developing ILI during a documented pH1N1 outbreak. Symptom experience since 1 April 2009 was elicited. ILI was defined at the analysis stage as a report of fever and cough plus  $\geq 1$  of the following symptoms during that period: headache, general aches, sore throat, or prostration. Corresponding control sub-

jects were participants who had been symptomatic in the period since 1 April 2009 who did not meet the ILI case definition or who were asymptomatic. Participants aged  $\leq 6$  months as of 31 December 2008 were excluded at the analysis stage, because they would not have been eligible to receive the vaccine.

On the basis of results of serologic tests, the sensitivity, specificity, and positive and negative predictive values for the ILI case definition were explored. Odds ratios (ORs) for seasonal influenza vaccine effect (2008–2009 and 2007–2008) on ILI were computed via logistic regression analysis, with adjustment for combinations of age, chronic conditions, Aboriginal status, and household density (calculated as the number of household members/number of sleeping rooms). We also accounted for within-household clustering while assessing vaccine effect by using generalized-linear-mixed models (GLMMs) for binary outcomes, adjusting for the same covariates [6]. Because surveillance data suggested that children experienced higher pH1N1 attack rates and that older adults were at lower risk [7, 8], we explored vaccine effects stratified for participants aged  $< 20$  years and  $< 50$  years. We also explored the effect of TIV receipt on pH1N1 infection defined by HI and/or MN seropositive status.

### Human Subject Consideration

The initial telephone survey was conducted as a public health-mandated outbreak investigation, with verbal consent provided at interview. The serologic component was reviewed and approved by the Research Ethics Board of the University of British Columbia, and individual written consent was obtained for blood sample collection and analysis.

## RESULTS

### Laboratory

**Respiratory specimen surveillance.** Respiratory virus testing by the BC Centre for Disease Control for the local community included 30 specimens collected during the period 29 April through 5 June 2009. pH1N1 was confirmed in 14 of these 30 specimens by reverse-transcription polymerase chain reaction (RT-PCR). Other respiratory viruses detected in the local community during that period included coronavirus (in 2 specimens) and rhinovirus or enterovirus (in 2 specimens).

Of the 30 specimens submitted, 9 were from households of the affected elementary school that also participated in the telephone survey; pH1N1 was detected in 6 (67%) of the 9 specimens from survey participants. Five (56%) of these 9 specimens were from patients living on a reserve; pH1N1 was detected in 4 (80%) of the 5 specimens. Of note, surveillance data indicated the last detection of seasonal influenza (A/H3N2) in the local health area was in February 2009.

**Serologic test results.** In total, 135 households with at least 1 member with ILI identified during the community survey

were invited to participate in the serologic study. Ultimately, 42 households contributed serologic specimens, resulting in 106 individual serum samples available for analysis, including 58 (54%) from households associated with the affected elementary school ( $n = 45$ ) or on a reserve ( $n = 29$ ). Details of the serosurvey participants are shown in Table A1 in the Appendix.

In total, 44 (42%) of the 106 serologic survey participants reported ILI during the study period. Of the 106 serum samples, 28 (26%) had HI titers to pH1N1  $\geq 40$  (denoting seropositivity), and of these, 22 (79%) were from persons who had reported ILI. Among the 106 serologic survey participants overall, there was strong correlation between log-transformed HI and MN titers ( $\rho = 0.92$ ). Of the 28 specimens with an HI titer  $\geq 40$ , all but 3 had MN titers  $\geq 80$  and exceeding HI. Of the 3 participants whose specimens yielded MN titers less than the HI titers, none reported ILI.

Of the 45 participants from the affected elementary school households, 14 (31%) were seropositive for pH1N1 (13 of 14 persons with ILI). Of the 29 on-reserve participants, 13 (45%) were seropositive for pH1N1 (12 of 13 persons with ILI). Of the 48 serum samples from participants belonging to off-reserve households without children in the affected elementary school, 12 (25%) of 48 were seropositive for pH1N1 (8 of 12 persons with ILI).

**Clinical case definitions: characteristics in relation to serologic status.** To guide analyses, we assessed the sensitivity, specificity, and positive and negative predictive values of the ILI case definition in relation to HI or MN seropositive status (Table 1). Parameters were highest in combination among participants belonging to households associated with the initial elementary school outbreak or who lived on a reserve. The ILI case definition had less value in predicting pH1N1 seropositive status among telephone survey participants who belonged to households other than those associated with the elementary school or who lived on a reserve (positive predictive value, 38%, 68%, and 75%, respectively) (Table 1).

### Participant Characteristics

Overall, 266 households and 1154 individuals contributed to the community telephone survey. Because respiratory virus surveillance and the follow-up serologic survey both indicated greatest pH1N1 circulation among the originally affected elementary school and on-reserve households, we restricted analyses of TIV effect on ILI to those households, hereafter referred to as “elementary school” or “on-reserve” participants. The epidemic curve of ILI, by date of onset for the elementary school and/or on-reserve participants, is shown in Figure 1.

**Elementary school household participants.** There were 118 households with at least 1 child enrolled at the affected elementary school. Sixty-three of these households participated in the survey, contributing data on 271 individuals. After exclud-

ing those with unknown 2008–2009 TIV status ( $n = 17$ ) and unknown chronic conditions ( $n = 1$ ), the analysis included 253 participants associated with the elementary school. Among these participants, 36 (15%) lived on one of the local reserves. Overall, 153 (60%) of 253 persons were aged  $<20$  years. There were few older adults (11 [4%]) aged  $\geq 50$  years.

Of the 253 elementary school household participants, 66 (26%) reported ILI, with the rate highest among young children (Table 2). The secondary attack rate among elementary school households was 27% (32 of 119); after excluding on-reserve households, the rate was 20% (19 of 94). Only 1 participant reported travel to Mexico since mid-March 2009. The proportion in the fourth quartile of household density was greater among participants with ILI than among those without ILI (40% vs 20%). The proportion of participants with chronic conditions was comparable to the BC proportion overall for children and young adults ( $\sim 10\%$ ) [9]. Self-reported influenza immunization rates among non-ILI control subjects were also comparable to BC rates estimated through other surveys among children and young adults (15%–20%) in British Columbia [10].

**On-reserve household participants.** Two hundred twenty-four individuals who participated in the community survey were reported as living on a surrounding reserve. After excluding individuals with unknown 2008–2009 TIV status ( $n = 29$ ), unknown chronic condition ( $n = 1$ ), or age  $\leq 6$  months on 31 December 2008 ( $n = 4$ ), the on-reserve analysis included 191 survey participants, of whom 100 (52%) were aged  $<20$  years and 26 (14%) were aged  $\geq 50$  years.

Of the 191 on-reserve participants, 44 (23%) reported having ILI, again with the rate highest among young children (Table 2). The secondary attack rate among on-reserve households was 24% (23 of 94). None of these participants reported travel to Mexico since mid-March. The proportion of participants living in households in the fourth quartile of density was greater for on-reserve participants (39%) than for elementary school participants (25%) and among on-reserve participants with ILI (50%) than among those without ILI (35%). A higher proportion of on-reserve participants with ILI sought medical care (25 [57%] of 44), compared with elementary school participants (25 [38%] of 66). A comparable proportion for whom information was available sought care  $\leq 48$  h after onset (3 [20%] of 15 vs 3 [19%] of 16). No participant in either population was prescribed antivirals, and none were hospitalized.

A higher proportion of Aboriginals in British Columbia and Canada, compared with the general population, have at least 1 chronic condition [11, 12]. Accordingly, the proportion of young on-reserve participants in our study with at least 1 chronic condition (27 [14%] of 191) was higher than the proportion of elementary school participants and was within the

**Table 1. Characteristics of the Influenza-Like Illness (ILI) Case Definition Measured against Pandemic H1N1 (pH1N1) Serologic Status (Seropositivity vs Seronegativity) among Participants overall, Participants from Households of the pH1N1 Outbreak-Affected Elementary School, or Participants Living on a Reserve**

Characteristic	No. of participants	ILI vs no ILI <sup>a</sup>			
		Sensitivity, %	Specificity, %	PPV, %	NPV, %
Participants from elementary school outbreak-affected household					
All participants	45	93	81	68	96
Age group					
<20 years	24	92	91	92	91
<50 years	42	93	82	72	96
On-reserve participants					
All participants	29	92	75	75	92
Age group					
<20 years	13	91	NSS	83	NSS
<50 years	24	92	83	85	91
Participants from elementary school outbreak-affected households and/or on-reserve participants					
All participants	58	88	79	61	94
Age group					
<20 years	27	86	77	80	83
<50 years	52	87	81	65	94
Neither participants from elementary school outbreak-affected households nor on-reserve participants					
All subjects	48	67	64	38	85
Age group					
<20 years	19	60	56	60	56
<50 years	42	67	70	47	84

**NOTE.** Seropositivity was defined as a hemagglutination inhibition assay titer  $\geq 40$ , and seronegativity was defined as a hemagglutination inhibition titer  $< 40$ . NPV, negative predictive value; NSS, insufficient sample size owing to no on-reserve participants without ILI who were seronegative; PPV, positive predictive value.

<sup>a</sup> ILI was defined at the analysis stage as a report of fever and cough plus  $\geq 1$  of the following symptoms since 1 April 2009: headache, general aches, sore throat, or prostration.

expected range overall for young Aboriginals who lived on a reserve.

Influenza vaccination rates were higher among Aboriginals who lived on a reserve in British Columbia overall (45%) than among the general population (30%) [13]. Thus, among non-ILI control subjects in our survey, young on-reserve Aboriginals had higher influenza immunization rates (42 [29%] of 147 persons) than did elementary school household participants (26 [14%] of 187 persons) (Table 2).

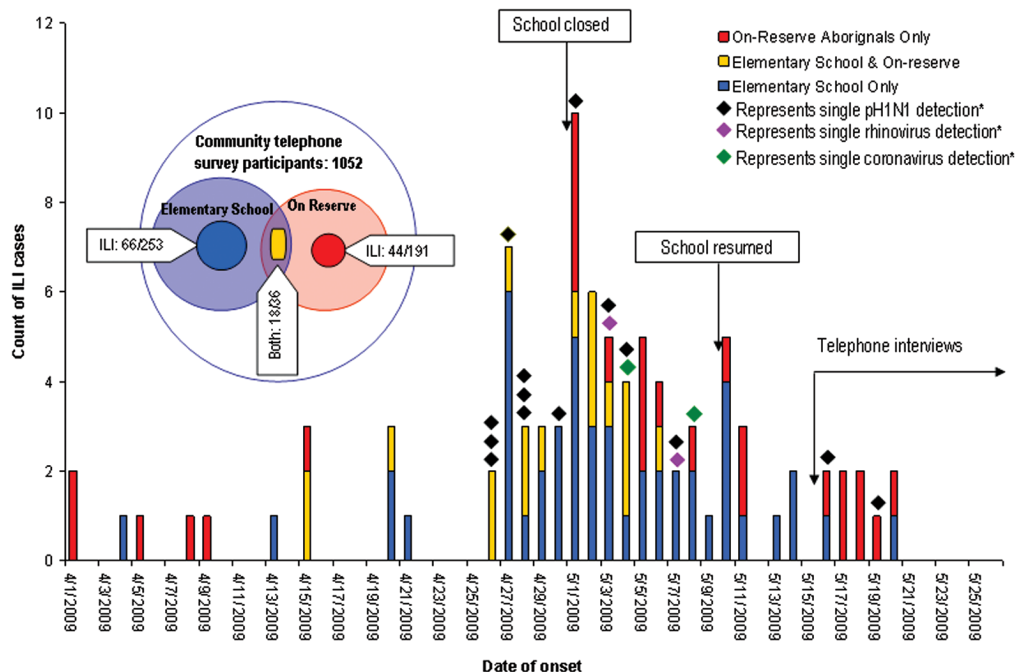
#### Effect of Seasonal Influenza Vaccine on pH1N1 Risk

Fully adjusted overall and stratified ORs for the effect of 2008–2009 TIV on ILI risk are shown in Table 3. Fully-adjusted OR overall was 2.45 (95% confidence interval [CI], 1.34–4.48) when estimated by logistic regression and 2.68 (95% CI, 1.37–5.25) by GLMM. ORs were higher with restriction to younger participants aged  $< 20$  years or  $< 50$  years and to on-reserve participants, especially with similar age restriction (Table 3). Although ORs were higher among Aboriginals who lived on a

reserve than among non-Aboriginal participants, an analysis for interaction did not reach statistical significance ( $P > .05$ ).

In additional sensitivity analyses based on logistic regression and restricted to the period of peak ILI activity (27 April–11 May 2009), the overall OR for 2008–2009 TIV effect adjusted for age, chronic conditions, Aboriginal status, and household density was higher (3.55; 95% CI, 1.70–7.34). When we used control subjects defined as fully asymptomatic persons rather than those who merely lacked ILI, the overall adjusted OR was 2.51 (95% CI, 1.3–4.82), comparable to the primary analysis.

In further sensitivity analyses based on logistic regression and restricted to participants without chronic conditions, the OR for 2008–2009 TIV effect adjusted for age, Aboriginal status, and household density was 3.44 (95% CI, 1.80–6.59). In an analysis further restricted to on-reserve participants without chronic conditions, the OR for the 2008–2009 TIV effect adjusted for age and household density was 5.38 (95% CI, 2.27–12.75). In analysis restricted to non-Aboriginal households of the elementary school population, the OR adjusted for age,



**Figure 1.** Epidemic curve of influenza-like illness (ILI), by date of onset, for participants from households of students from the pandemic H1N1 (pH1N1)-affected elementary school or on-reserve households, overlaid with respiratory virus detection through reverse-transcription polymerase chain reaction. Respiratory specimens were collected as part of passive surveillance to characterize school outbreak and virus circulation in community. No cases of seasonal influenza A/H1N1, A/H3N2, or influenza B were detected in the local health area during the displayed period. The last influenza case detected in the local health area was influenza A/H3N2 in February 2009. The serologic survey population was a subset of the telephone survey population. \*Virus detection is based on illness onset date.

chronic conditions, and household density was 1.83 (95% CI, 0.56–5.93).

ORs for 2007–2008 TIV effect were similar or slightly higher at 3.08 (95% CI, 1.71–5.58) overall. Analyses comparing the effect of having received 2007–2008 TIV only, 2008–2009 TIV only, or both the 2007–2008 and 2008–2009 vaccines versus no TIV either year yielded ORs of 2.36 (95% CI, 0.95–5.84), 1.31 (95% CI, 0.40–4.31), and 3.39 (95% CI, 1.7–6.68), respectively. However, most vaccinated participants had received vaccine in both 2007–2008 and 2008–2009, such that per-season results include small sample sizes and should be interpreted cautiously: 69 (69%) of 100 recipients of 2007–2008 TV were revaccinated in 2008–2009, and 69 (76%) of 89 recipients of 2008–2009 TV had been vaccinated in 2007–2008.

Analyses of TIV effect on serologically confirmed pH1N1 versus seronegative control subjects are shown in Table 4. Sample size was small and 95% CIs intervals were wide, but the same trend in point estimates for TIV effects was observed, with a fully adjusted OR of 2.07 (95% CI, 0.31–14.03) for 2008–2009 TIV and of 2.71 (95% CI, 0.4–18.51) for 2007–2008 TIV.

## DISCUSSION

In this article, we present the first observation of an unexpected association between prior seasonal influenza vaccination and

pH1N1 illness during the spring and summer of 2009 in Canada. Specifically, outbreak investigation conducted during the early stages of the pandemic in a northern BC community identified that participants reporting pH1N1-related ILI during the period 1 April through 5 June 2009 were more than twice as likely to report having previously received seasonal influenza vaccine.

Advantages offered by the original outbreak investigation described here include active and standardized inquiry about pH1N1-related illness, TIV receipt, and relevant covariates for all household members, obviating potential selection biases associated with differential health care access or health care-seeking behavior in other methods of participant recruitment or case detection. By restricting analysis to households with children in a single community and in groups among whom pH1N1 circulation was confirmed serologically, we ensured the population at risk was well circumscribed and that control subjects were drawn from the same source population as cases, further minimizing the risk of selection bias. To account for influential covariates, we used recognized analysis techniques of restriction as well as adjustment for age, comorbidity, household density, and Aboriginal status.

There are, however, several limitations to this study warranting cautious interpretation of the results. First, the study

**Table 2. Profile of Participants from Households Affected by the Pandemic H1N1 Outbreak: Elementary School and On-Reserve Participants, by Illness Category**

Characteristic	Elementary school participants (n = 253)		On-reserve participants (n = 191)		Elementary school and/or on-reserve participants (n = 408)	
	ILI <sup>a,b</sup> (n = 66)	No ILI <sup>a,b</sup> (n = 87)	ILI <sup>a,b</sup> (n = 44)	No ILI <sup>a,b</sup> (n = 147)	ILI <sup>a,b</sup> (n = 92)	No ILI <sup>a,b</sup> (n = 316)
	ILI <sup>a</sup> row % <sup>c</sup>	ILI <sup>a</sup> row % <sup>c</sup>	ILI <sup>a</sup> row % <sup>c</sup>	ILI <sup>a</sup> row % <sup>c</sup>	ILI <sup>a</sup> row % <sup>c</sup>	ILI <sup>a</sup> row % <sup>c</sup>
Age, years						
1–8	32 (48)	35 (19)	16 (36)	26 (18)	37 (40)	59 (19)
9–19	22 (33)	64 (34)	12 (27)	46 (31)	29 (32)	106 (34)
20–49	11 (17)	78 (42)	10 (23)	55 (37)	20 (22)	124 (39)
50–64	1 (2)	9 (5)	6 (14)	13 (9)	6 (7)	19 (6)
≥65	0 (0)	1 (1)	0 (0)	7 (5)	0 (0)	8 (3)
Total	66	187	44	147	92	316
Median age	10 (1–50)	17 (1–66)	NA	21 (1–86)	NA	17 (1–86)
Sex						
Female	33 (51)	99 (54)	28 (64)	78 (53)	50 (56)	167 (53)
Male	32 (49)	86 (46)	15 (34)	68 (46)	40 (44)	146 (47)
Chronic conditions						
Yes	4 (6)	9 (5)	10 (23)	17 (12)	14 (15)	26 (8)
No	62 (94)	178 (95)	34 (77)	130 (88)	78 (85)	290 (92)
Aboriginal status						
Off-reserve	2 (3)	16 (9)	NA	NA	2 (2)	16 (5)
On-reserve	18 (29)	18 (11)	NA	NA	44 (49)	147 (49)
Not Aboriginal	43 (68)	137 (80)	43 (24)	NA	43 (48)	137 (46)

Household density quartile <sup>d</sup>										
First to third	36 (60)	137 (80)	36 (21)	22 (50)	95 (65)	22 (19)	57 (66)	223 (74)	57 (20)	
Fourth quartile	24 (40)	34 (20)	24 (41)	22 (50)	52 (35)	22 (30)	29 (34)	77 (26)	29 (27)	
Medically attended										
Yes	25 (38)	0 (0)	NA	25 (57)	0 (0)	NA	36 (39)	0 (0)	NA	
No	41 (62)	187 (100)	NA	19 (43)	147 (100)	NA	56 (61)	316 (100)	NA	
Received 2008–2009 influenza vaccine										
Yes	19 (29)	26 (14)	19 (42)	24 (55)	42 (29)	24 (36)	29 (32)	61 (19)	29 (32)	
No	47 (71)	161 (86)	47 (23)	20 (45)	105 (71)	20 (16)	63 (68)	255 (81)	63 (20)	
Received 2007–2008 influenza vaccine										
Yes	24 (36)	29 (16)	24 (45)	26 (59)	46 (31)	26 (36)	34 (38)	66 (21)	34 (34)	
No	42 (64)	152 (84)	42 (22)	16 (36)	99 (67)	16 (14)	56 (62)	243 (79)	56 (19)	
2008–2009 influenza vaccine receipt, by category, n/N (%)										
Age, years										
1–8	9/32 (28)	5/35 (14)	NA	9/16 (56)	3/26 (12)	NA	10/37 (27)	8/59 (14)	NA	
9–19	5/22 (23)	5/64 (8)	NA	8/12 (67)	9/46 (20)	NA	9/29 (31)	13/106 (12)	NA	
20–49	4/11 (36)	13/78 (17)	NA	3/10 (30)	18/55 (33)	NA	6/20 (30)	27/124 (22)	NA	
50–64	1/1 (100)	2/9 (22)	NA	4/6 (67)	8/13 (62)	NA	4/6 (67)	8/19 (42)	NA	
≥65	0/0 (0)	1/1 (100)	NA	0 (0)	4/7 (57)	NA	0/0 (0)	5/8 (63)	NA	
Chronic conditions										
Yes	0/4 (0)	3/9 (33)	NA	4/10 (40)	12/17 (71)	NA	4/14 (29)	15/26 (58)	NA	
No	19/62 (31)	23/178 (13)	NA	20/34 (59)	30/130 (23)	NA	25/78 (32)	46/290 (16)	NA	

**NOTE.** Data are no. (%) of participants, unless otherwise indicated. ILI, influenza-like illness; NA, not available.

<sup>a</sup> ILI was defined at the analysis stage as a report of fever and cough plus ≥1 of the following symptoms since 1 April 2009: headache, general aches, sore throat, or prostration.

<sup>b</sup> Where totals do not sum, the difference is missing or unknown values.

<sup>c</sup> No. (%) of participants in the category who experienced ILI.

<sup>d</sup> Household density was calculated as the number of household members divided by number of rooms used for sleeping in the home.

**Table 3. Odds Ratios for the Effect of 2008–2009 Trivalent Inactivated Influenza Vaccine on Influenza-Like Illness Risk among Households Affected by the Pandemic H1N1 Outbreak: Elementary School and On-Reserve Participants**

Covariates	Overall	Participants aged <20 years	Participants aged <50 years
<b>Elementary school households</b>			
No. of participants	227	136	216
<b>Covariate(s)</b>			
Unadjusted	2.50 (1.28–4.92)	3.12 (1.28–7.61)	2.56 (1.28–5.15)
Age <sup>a</sup>	2.94 (1.39–6.19)	2.80 (1.12–7.01)	2.82 (1.32–6.04)
Chronic conditions <sup>b</sup>	2.50 (1.27–4.9)	3.34 (1.36–8.23)	2.57 (1.28–5.16)
Aboriginal <sup>c</sup>	1.83 (0.83–4.03)	1.79 (0.58–5.48)	1.81 (0.81–4.05)
Household density <sup>d</sup>	2.15 (1.06–4.38)	2.43 (0.94–6.28)	2.25 (1.09–4.67)
Age, <sup>a</sup> chronic conditions <sup>b</sup>	2.93 (1.39–6.18)	3.03 (1.20–7.65)	2.84 (1.33–6.08)
Age, <sup>a</sup> Aboriginal <sup>c</sup>	2.36 (0.99–5.66)	1.74 (0.56–5.46)	2.26 (0.94–5.46)
Age, <sup>a</sup> household density <sup>d</sup>	2.60 (1.19–5.66)	2.29 (0.88–5.97)	2.55 (1.16–5.62)
Age, <sup>a</sup> chronic conditions, <sup>b</sup> Aboriginal <sup>c</sup>	2.34 (0.98–5.62)	1.81 (0.57–5.72)	2.24 (0.93–5.42)
Age, <sup>a</sup> Aboriginal, <sup>c</sup> household density <sup>d</sup>	2.45 (1.00–5.98)	1.78 (0.56–5.61)	2.37 (0.96–5.81)
Age, <sup>a</sup> chronic conditions, <sup>b</sup> Aboriginal, <sup>c</sup> household density <sup>d</sup>	2.43 (1.00–5.94)	1.85 (0.58–5.91)	2.35 (0.96–5.77)
<b>On-reserve households</b>			
No. of participants	191	100	165
<b>Covariate(s)</b>			
Unadjusted	3.00 (1.50–5.99)	7.73 (2.90–20.58)	3.59 (1.68–7.66)
Age <sup>a</sup>	3.53 (1.67–7.45)	8.93 (3.15–25.28)	4.07 (1.84–9.01)
Chronic conditions <sup>b</sup>	2.76 (1.36–5.61)	8.86 (3.19–24.6)	3.34 (1.55–7.21)
Household density <sup>d</sup>	2.88 (1.43–5.79)	7.10 (2.61–19.28)	4.25 (1.84–9.84)
Age, <sup>a</sup> chronic conditions <sup>b</sup>	3.18 (1.48–6.82)	10.71 (3.55–32.28)	3.74 (1.66–8.41)
Age, <sup>a</sup> household density <sup>d</sup>	2.88 (1.43–5.79)	8.22 (2.87–23.55)	3.99 (1.79–8.91)
Age, <sup>a</sup> chronic conditions, <sup>b</sup> household density <sup>d</sup>	3.00 (1.39–6.50)	9.62 (3.13–29.52)	3.54 (1.56–8.04)
<b>Elementary school and/or on-reserve households combined</b>			
No. of participants	382	214	349
<b>Covariate(s)</b>			
Unadjusted	1.92 (1.14–3.24)	2.77 (1.37–5.6)	2.06 (1.18–3.60)
Age <sup>a</sup>	2.29 (1.32–3.98)	2.78 (1.36–5.71)	2.29 (1.28–4.11)
Chronic conditions <sup>b</sup>	1.78 (1.04–3.03)	3.00 (1.47–6.11)	1.94 (1.10–3.41)
Aboriginal <sup>c</sup>	2.12 (1.21–3.71)	3.55 (1.63–7.71)	2.25 (1.25–4.07)
Household density <sup>d</sup>	1.95 (1.15–3.31)	2.74 (1.34–5.62)	2.09 (1.19–3.69)
Age, <sup>a</sup> chronic conditions <sup>b</sup>	2.08 (1.19–3.65)	3.05 (1.47–6.35)	2.15 (1.19–3.88)
Age, <sup>a</sup> Aboriginal <sup>c</sup>	2.57 (1.43–4.65)	3.68 (1.67–8.13)	2.62 (1.41–4.89)
Age, <sup>a</sup> household density <sup>d</sup>	2.32 (1.33–4.05)	2.79 (1.35–5.78)	2.34 (1.30–4.23)
Age, <sup>a</sup> chronic conditions, <sup>b</sup> Aboriginal <sup>c</sup>	2.4 (1.32–4.37)	3.95 (1.77–8.85)	2.49 (1.33–4.67)
Age, <sup>a</sup> Aboriginal, <sup>c</sup> household density <sup>d</sup>	2.63 (1.45–4.77)	3.65 (1.65–8.07)	2.7 (1.44–5.04)
Age, <sup>a</sup> chronic conditions, <sup>b</sup> Aboriginal, <sup>c</sup> household density <sup>d</sup>	2.45 (1.34–4.48)	3.92 (1.75–8.79)	2.56 (1.36–4.81)

**NOTE.** Data are odds ratio (95% confidence interval), unless otherwise indicated. Influenza-like illness was defined at the analysis stage as a report of fever and cough plus  $\geq 1$  of the following symptoms since 1 April 2009: headache, general aches, sore throat, or prostration. Control subjects were those who had not experienced an influenza-like illness since 1 April 2009.

<sup>a</sup> Age categories were 1–8 years, 9–19 years, and >19 years (reference).

<sup>b</sup> Chronic condition categories were yes and no (reference).

<sup>c</sup> Aboriginal categories were on-reserve, off-reserve, and or Aboriginal (applied only to elementary school participants; reference).

<sup>d</sup> Household density was dichotomized as first through third quartiles (reference) versus fourth quartile.

relied upon a nonspecific clinical outcome (ILI) for defining pH1N1-related illness. There are many causes of ILI, as evidenced by other contributing viruses identified through passive surveillance during the study period. We attempted to validate the ILI case definition on the basis of pH1N1-seropositive

status, but participation in the serologic survey was self-selected, and sample size was small. Inclusion of communities where there was little or no circulation of pH1N1 would lead to outcome misclassification as evidenced by the low positive predictive value (38%) for the ILI case definition. We thus



**Table 4. Effect of 2008–2009 and 2007–2008 Trivalent Inactivated Influenza Vaccine (TIV) on Pandemic H1N1–Seropositive Status among Serologic Survey Participants Overall**

Covariate	OR (95% CI)	
	Effect of receipt of 2008–2009 TIV, with or without receipt of 2007–2008 TIV (n = 102)	Effect of receipt of 2007–2008 TIV, with or without receipt of 2008–2009 TIV (n = 101)
Unadjusted	2.07 (0.85–5.04)	1.66 (0.68–4.02)
Age <sup>a</sup>	6.01 (1.60–22.52)	7.16 (1.71–30.03)
Chronic conditions <sup>b</sup>	2.23 (0.90–5.50)	1.72 (0.70–4.19)
On-reserve status <sup>c</sup>	0.92 (0.27–3.09)	0.61 (0.17–2.13)
Household density <sup>d</sup>	1.48 (0.57–3.82)	1.19 (0.46–3.07)
Age, <sup>a</sup> chronic conditions <sup>b</sup>	6.25 (1.64–23.8)	7.42 (1.73–31.70)
Age, <sup>a</sup> household density <sup>d</sup>	2.31 (0.35–15.3)	2.94 (0.45–19.34)
Age, <sup>a</sup> on-reserve status <sup>c</sup>	4.06 (1.02–16.23)	4.91 (1.10–21.90)
Age, <sup>a</sup> chronic conditions, <sup>b</sup> on-reserve status <sup>c</sup>	2.49 (0.37–16.87)	3.11 (0.46–21.13)
Age, <sup>a</sup> on-reserve status, <sup>c</sup> household density <sup>d</sup>	1.97 (0.30–13.02)	2.57 (0.39–16.96)
Age, <sup>a</sup> chronic conditions, <sup>b</sup> household density, <sup>d</sup> on-reserve status <sup>c</sup>	2.07 (0.31–14.03)	2.71 (0.40–18.51)

**NOTE.** Most vaccinated participants had received TIV in both 2007–2008 and 2008–2009. Seropositivity was defined as a hemagglutination inhibition assay titer  $\geq 40$

<sup>a</sup> Age categories were 1–8 years, 9–19 years, and >19 years (reference).

<sup>b</sup> Chronic condition categories were yes and no (reference).

<sup>c</sup> On-reserve categories were on-reserve versus others (reference).

<sup>d</sup> Household density was dichotomized as first through third quartiles (reference) versus fourth quartile.

restricted analyses to households of the affected elementary school and on a reserve where pH1N1 circulation was more certain. This improved the positive predictive value of the ILI case definition in representing pH1N1-related illness (>60%), although some misclassification may have still occurred. The effect of any persisting misclassification due to a nonspecific outcome would be to underestimate the association between TIV and pH1N1 illness (ie, to drive the OR toward a null effect) [14].

A second limitation is that we relied on proxy report by 1 adult for all household members. Both ILI experience and TIV history may have been less well known for other household members. Third, the collection of TIV status after any ILI experience may have introduced recall bias. If recall bias related to TIV receipt were operating, it would introduce misclassification (information bias) related to exposure. Ultimately, the impact of this misclassification would depend on whether participants believed a priori that seasonal vaccine ought to have decreased or increased the risk of ILI during the study period. The lack of an immunization registry in British Columbia precluded further confirmation of immunization status.

It is noteworthy that ORs were higher among Aboriginal on-reserve participants who also had higher rates of repeat seasonal influenza immunization. Repeated vaccination has been hypothesized to block potentially cross-protective immunity otherwise afforded by heterotypic infection [15–17]. Higher ORs

among on-reserve Aboriginals could also reflect greater susceptibility to the effects of TIV on pH1N1 risk, although an analysis for interaction did not yield statistically significant results. Some studies have reported genetic polymorphisms that favor Th2 skew among Canadian Aboriginals with higher expression of interleukin-6 and lower production of tumor necrosis factor- $\alpha$ , interferon- $\gamma$ , and interleukin-10 that may be relevant to enhanced immune-mediated effects in this population [18]. Other studies have suggested that Aboriginal status is an independent risk factor for more severe pH1N1 outcomes, but we did not specifically assess that hypothesis [19]. However, higher ORs may also reflect the methodological influences of bias or confounding. Aboriginal populations are known to have higher rates of both chronic conditions and influenza vaccination [11–13]. To address this, we adjusted for comorbidity and conducted sensitivity analyses restricted to on-reserve participants without chronic conditions, resulting in similar or higher ORs. Despite these reassurances, neither residual confounding nor bias can be fully ruled out. As a final limitation, the sample sizes were small and confidence intervals were wide for stratified and serologically-confirmed analyses so that these in particular should be interpreted cautiously.

Because of limitations in study design and because they represented unexpected findings, we interpreted the results of this outbreak investigation as a paradoxical signal of possible concern—thought-provoking but inconclusive and warranting fur-

ther evaluation. Canadian investigators thus embarked on a series of confirmatory studies using more rigorous methods and laboratory-confirmed outcomes through the summer of 2009, each of which corroborated findings from this initial outbreak investigation. In combination, these showed 1.4–2.5-fold increased risk of medically attended, laboratory-confirmed pH1N1 illness among prior 2008–2009 TIV recipients [17]. An additional Canadian study using the linked Manitoba immunization registry and administrative databases has also shown similar findings of increased risk [4] (Dr Carole Beaudoin, Public Health Agency of Canada, personal communication). Thus, in Canada, 6 observational studies based on different methods and settings, including the current outbreak investigation, consistently showed increased risk of pH1N1 illness during the spring and summer of 2009 associated with prior receipt of the 2008–2009 TIV [4, 17]. Conversely, studies conducted outside of Canada have provided inconsistent results: 3 studies (from the United States and Australia) reported null effects [20–22], 4 (from the United States and Mexico) reported protective effects [23–26], and 1 other outbreak investigation (from the United States) reported increased risk [27].

Findings of pH1N1 risk associated with TIV—consistent in Canada but conflicting elsewhere—may have been due to methodological differences and/or unrecognized flaws, differences in immunization programs or population immunity, or a specific mechanistic effect of Canadian TIV. High rates of immunization and the use of a single domestic manufacturer to supply >75% of the TIV in Canada may have enhanced the power within Canada to detect a vaccine-specific effect. Given the changed immunologic landscape following the first spring-summer pandemic wave and the mass pH1N1 vaccination campaign during the fall 2009, it may not be possible to further resolve this issue epidemiologically. Studies using animal models, banked serum samples, or other *in vitro* experiments are needed to further assess this association.

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