Household Transmission of the 2009 Pandemic A/H1N1 Influenza Virus: Elevated Laboratory-Confirmed Secondary Attack Rates and Evidence of Asymptomatic Infections

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Background. Characterizing household transmission of the 2009 pandemic A/H1N1 influenza virus (pH1N1) is critical for the design of effective public health measures to mitigate spread. Our objectives were to estimate the secondary attack rates (SARs), the proportion of asymptomatic infections, and risk factors for pH1N1 transmission within households on the basis of active clinical follow-up and laboratory-confirmed outcomes.

Methods. We conducted a prospective observational study during the period May–July 2009 (ie, during the first wave of the pH1N1 pandemic) in Quebec City, Canada. We assessed pH1N1 transmission in 42 households (including 43 primary case patients and 119 contacts). Clinical data were prospectively collected during serial household visits. Secondary case patients were identified by clinical criteria and laboratory diagnostic tests, including serological and molecular methods.

Results. We identified 53 laboratory-confirmed secondary case patients with pH1N1 virus infection, for an SAR of 45% (95% confidence interval [CI], 35.6%–53.5%). Thirty-four (81%) of the households had ⩾1 confirmed secondary case patient. The mean serial interval between onset of primary and confirmed secondary cases was 3.9 days (median interval, 3 days). Influenza-like illness (fever and cough or sore throat) developed in 29% (95% CI, 20.5%–36.7%) of household contacts. Five (9.4%) of secondary case patients were asymptomatic. Young children (<7 years of age) were at highest risk of developing laboratory-confirmed influenza-like illness. Primary case patients with both diarrhea and vomiting were the most likely to transmit pH1N1.

Conclusion. Household transmission of pH1N1 may be substantially greater than previously estimated, especially in association with clinical presentations that include gastrointestinal complaints. Approximately 10% of pH1N1 infections acquired in the household may be asymptomatic.

The emergence of a novel swine-origin A/H1N1 (pH1N1) virus in April of 2009 led to the first pandemic of the 21st century [1]. Seroprevalence studies suggest that the rapid global dissemination of pH1N1 was facilitated by widespread lack of pre-existing immunity, especially among people <60 years of age [2, 3]. However, the secondary attack rates (SARs) and the epidemiologic risk factors for transmission of this virus have yet to be fully described. Such characterization will help to design effective public health control strategies for pH1N1 and other pandemic candidate viruses.

The household is thought to be a fundamental unit of influenza transmission because of the high frequency and intensity of contacts that occur between family members [4–7]. To date, a few household transmission studies of pH1N1 have been published [8–11], but none has systematically sought or confirmed secondary case

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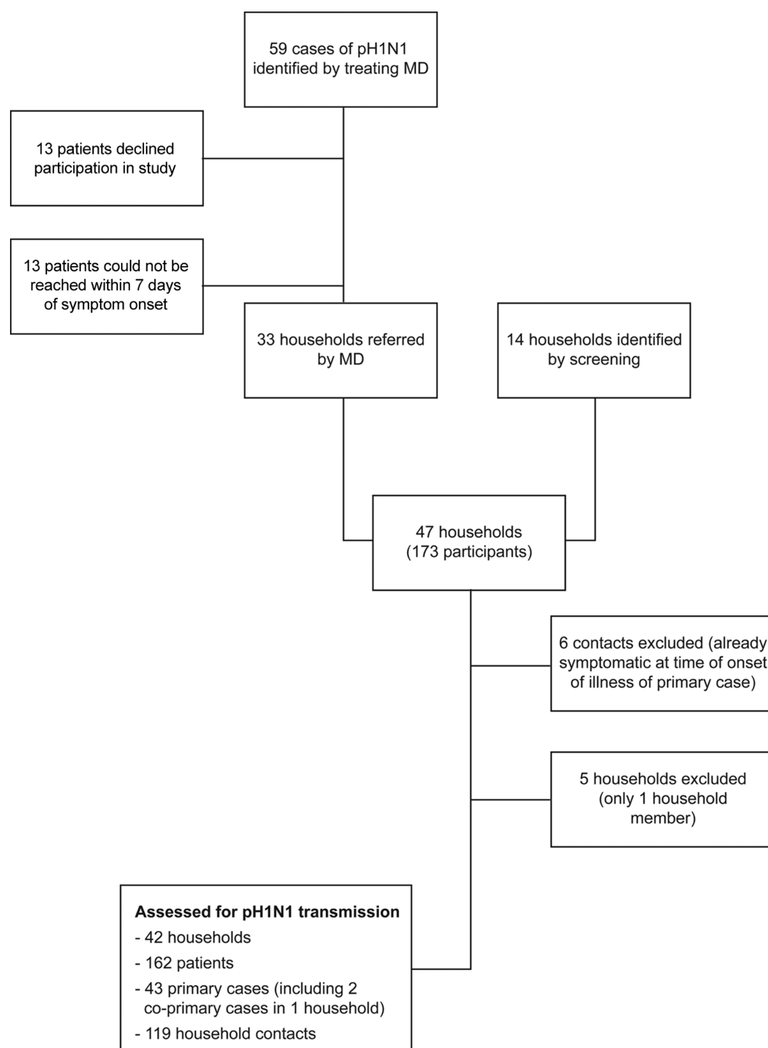

Figure 1. Flow chart of study recruitment and patient population.

patients by laboratory testing. Furthermore, the proportion of asymptomatic infections has not been specifically evaluated.

To better understand the dynamics of pH1N1 transmission within households, we conducted a prospective observational study that combined clinical data with molecular and serological diagnostic methods. Our objectives were to estimate the household SAR for pH1N1, to identify risk factors for household transmission, and to estimate the proportion of asymptomatic infections.

PATIENTS, MATERIALS, AND METHODS

Study population. This prospective observational household transmission study was performed during the first wave of the pH1N1 pandemic, from May 27 through July 10 2009, in Quebec City, Canada (population 683,000), and it was approved by the research ethics committee of the Centre Hospitalier Universitaire de Québec. Details of the research protocol have also been reported elsewhere [12].

Households consisting of ⩾2 persons were eligible for study participation when one member had pH1N1 infection confirmed by pH1N1-specific reverse-transcriptase polymerase chain reaction (RT-PCR) [13]. We identified households through pH1N1 case patients referred by their treating physician and pH1N1 case patients sought by the study team by testing symptomatic extra-familial contacts of referred case patients (Figure 1). All members of eligible households were approached for inclusion.

The primary case patient was defined as the first person in the household to develop pH1N1 illness confirmed by RT-PCR. If >1 household member developed laboratory-confirmed pH1N1 illness on the same day, both subjects were considered to be co-primary case patients.

A household contact was defined as someone living in the

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home of a primary case patient. Contacts who were already symptomatic at the time of illness onset in the primary case patient and in whom all laboratory evaluations were negative for influenza (ie, a negative RT-PCR result and no seroconversion) were excluded.

The main outcome assessed was the proportion of household contacts who became infected with pH1N1. A laboratory-confirmed secondary case patient was defined as any household contact (symptomatic or not) who developed pH1N1 infection after the primary case patient, as determined by a positive RT-PCR result or seroconversion. We also evaluated acute respiratory illness (ARI) and influenza-like illness (ILI) among household contacts. ARI was defined as the presence of ⩾2 of the following: fever (temperature ⩾37.8°C) or feverishness, cough, sore throat, or rhinorrhea. The definition of ILI was that used by the Centers for Disease Control and Prevention (CDC) [14]: fever and cough and/or sore throat without another known cause.

Clinical data. At the initial home visit, a trained research nurse obtained written informed consent from all household members and collected data for each participant with use of a standardized questionnaire. The questionnaire included information on sociodemographic characteristics, underlying medical conditions, clinical symptoms and/or signs, 2008–2009 influenza vaccination, medical management, and outcomes. Follow-up visits were performed on days 8, 11, and 3–4 weeks after disease onset, and the questionnaire was repeated each time. Study nurses gave no instructions to household members to mitigate virus spread.

Laboratory procedures. Nasopharyngeal swab samples (Copan Innovation) were collected for all household members during the first household visit. All subjects with samples with RT-PCR results positive for pH1N1 before day 8 of illness had a second nasopharyngeal swab sample obtained on day 8. Subjects who still had positive results on day 8 were retested on day 11.

Two serum samples for serological evaluation of pH1N1 infection were obtained from all subjects ⩾7 years of age, but not younger children, as per institutional review board instructions. The acute-phase serum sample was collected during the initial household visit; the convalescent-phase sample was collected 3–4 weeks later.

pH1N1 was sought in nasopharyngeal secretions by a conventional RT-PCR assay targeting the hemagglutinin (HA) gene according to a protocol developed by the National Microbiology Laboratory of Canada [13]. To optimize the sensitivity of secondary case patient detection, study specimens were retested by a conventional RT-PCR assay targeting highly conserved sequences of the matrix gene of all influenza A viruses [15]. The latter general influenza A RT-PCR has superior analytical sensitivity for pH1N1, compared with the aforementioned pH1N1 RT-PCR (2–20 copies/reaction vs 20–200 copies/reaction, respectively) [13].

All serum samples were tested by microneutralization (MN) assay and hemagglutination inhibition assay (HAI) according to World Health Organization standard protocols with modifications [16]. In-house validation of both serological assays demonstrated that the MN assay was 37% more sensitive than the HAI test at detecting pH1N1 seroconversion among RT-PCR–positive patients, and no patient demonstrating seroconversion by HAI did not seroconvert by MN (data not shown). Therefore, we used MN results as our serological standard for pH1N1 infection. Seroconversion was defined as an acute phase serum titer of <1:10 with a convalescent phase serum titer of ⩾1:40, or a significant increase (⩾4-fold) in antibody titers between the two serum samples. Samples with negative MN results were assigned a titer of 1:5 for calculating geometric mean titers (GMTs). Paired serum samples that met all of the following 3 exclusion criteria were excluded from analyses: the acute serum was drawn >7 days after the onset of the subject's illness, the acute serum titer was ⩾1:10, and there was no seroconversion. Viral culture, MN assay, pH1N1 viral load, and HA sequencing methods are detailed in the Appendix, which appears only in the online version of the journal.

Statistical analyses. Proportions and distributions were compared using the χ^2 test or Fisher's exact test. Mean values were compared using the Student's *t* test or Wilcoxon rank-sum test. Statistical significance was assessed using 2-tailed tests with an error level of .05. Univariate and multivariate log-binomial regression analyses were performed to examine the association between pH1N1 household transmission and the characteristics of the primary case patient, the household, and household contacts. Analyses were performed using SAS software, version 9.2 (SAS).

RESULTS

Households, primary case patients, and household contacts. We identified 42 eligible households with a laboratory-confirmed case of pH1N1 infection (Figure 1). These households comprised 43 primary case patients (including 1 household with 2 co-primary case patients) and 125 contacts. Six contacts were subsequently excluded because they were already symptomatic at the time of illness onset in the primary case patient and had negative results on all pH1N1 laboratory studies. Households had a mean (± standard deviation [SD]) of 2.8 ± 1.1 contacts (median no. of contacts, 3).

The baseline characteristics and clinical symptoms of the 43 primary case patients and 119 household contacts are presented in Table 1. Primary case patients were significantly younger than were household contacts, with mean ages of 13 years (range, 0.1–46 years) and 27 years (range, 0.4–62 years), respectively ($P < .001$). Ten primary case patients (23%) and 21 contacts

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Table 1. Baseline Characteristics and Clinical Symptoms of Primary Case Patients and Household Contacts

Characteristic	Primary case patients (n = 43)	Contacts (n = 119)	P
Age			
0–6 Years	12 (28)	12 (10)	
7–17 Years	25 (58)	35 (29)	<.001
≥18 Years	6 (14)	72 (61)	
Mean years ± SD	12.97 ± 9.53	26.90 ± 16.73	<.001
Median years	12	29	
Female sex	24 (56)	62 (52)	.67
Smoking history	3 (7)	20 (17)	.11
Significant comorbidity[a]			
Any	10 (23)	21 (18)	.42
Pulmonary	9 (21)	11 (9)	.05
Cardiac	1 (2)	8 (7)	.45
2008–2009 influenza immunization	8 (19)	32 (27)	.28
Symptoms[b]			
Asymptomatic	0 (0)	39 (33)	
Symptomatic	43 (100)	80 (67)	
Fever or feverishness	37 (86)	35 (44)[c]	
Cough	43 (100)	59 (74)[c]	
Rhinorrhea	36 (84)	54 (68)[c]	
Sore throat	27 (63)	53 (66)[c]	
Fatigue	38 (88)	50 (63)[c]	
Dyspnea	20 (47)	21 (26)[c]	
Chest pain	11 (26)	14 (18)[c]	
Headache	41 (95)	73 (91)[c]	
Myalgia or arthralgia	19 (44)	28 (35)[c]	
Diarrhea	14 (33)	22 (28)[c]	
Vomiting	8 (19)	8 (10)[c]	
Diarrhea or vomiting	17 (40)	26 (33)[c]	
Diarrhea and vomiting	5 (12)	4 (5)[c]	
Gastrointestinal symptoms only	0 (0)	2 (3)[c]	
Any respiratory symptom	43 (100)	73 (91)[c]	
ARI	40 (93)	61 (76)[c]	
ILI	37 (86)	34 (43)[c]	

NOTE. ARI, acute respiratory illness; ILI, influenza-like illness; SD, standard deviation.

[a] Significant comorbidity that is an indication for influenza immunization: chronic pulmonary disease, chronic cardiac disease, chronic renal disease, immunosuppressed state, or diabetes mellitus.

[b] P values were not calculated to compare the symptoms of primary case patients and symptomatic contacts, because the former group was comprised exclusively of pH1N1-affected subjects, whereas the latter group was not.

[c] Percentage represents the proportion of symptomatic contacts with that symptom.

(18%) had an underlying health condition for which influenza vaccination was recommended in 2008–2009 [17]. None were immunocompromised.

Among primary case patients, the most frequent symptoms were cough (present in 100% of patients) and headache (95%). Seventeen primary case patients (40%) reported gastrointestinal symptoms (diarrhea or vomiting). Thirty-nine contacts (33%) remained completely asymptomatic during the 3–4 week period of follow-up. Among the 80 contacts reporting ≥1 symptom, the most frequent symptoms were headache (91%) and cough (74%). No study subjects received antiviral therapy or prophylaxis or pH1N1 vaccine. Two primary case patients and 3 contacts required hospital admission for their pH1N1 illness.

Secondary case patients and SARs. Among the 119 household contacts, 53 had laboratory-confirmed pH1N1 infections, of which 31 (58%) developed ILI, 5 (9.4%) had a completely asymptomatic pH1N1 infection, and 1 (1.9%) presented with gastrointestinal symptoms only. Eight (15%) of 53 secondary

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Table 2. Secondary Attack Rates according to Characteristics of the Contact and the Household

Characteristic	No. of contacts	Laboratory-confirmed pH1N1 SAR, % (no. of cases)			ARI SAR, % (no. of cases)		ILI SAR, % (no. of cases)	
		Total pH1N1 positive	RT-PCR positive	Seroconversion[a]	Any ARI	Laboratory-confirmed pH1N1	Any ILI	Laboratory-confirmed pH1N1
Age								
0–6 Years	12	58 (7)	58 (7)	NA	67 (8)	50 (6)	58 (7)[b]	50 (6)[b]
7–17 Years	35	45 (16)	37 (13)	39 (13/33)	51 (18)	37 (13)	37 (13)	31 (11)
⩾18 Years	72	42 (30)	35 (25)	36 (23/64)	49 (35)	32 (23)	19 (14)	19 (14)
Total	119	45 (53)	38 (45)	37 (36/97)	51 (61)	35 (42)	29 (34)	26 (31)
Significant comorbidity[c]								
Any	21	52 (11)	48 (10)	44 (8/18)	62 (13)	48 (10)	29 (6)	29 (6)
Pulmonary	11	64 (7)	55 (6)	40 (4/10)	64 (7)	55 (6)	36 (4)	36 (4)
Cardiac	8	38 (3)	38 (3)	43 (3/7)	50 (4)	38 (3)	25 (2)	25 (2)
Smoking history	20	35 (7)	30 (6)	35 (6/17)	55 (11)	35 (7)	30 (6)	30 (6)
Received 2008–2009 influenza TIV								
Yes	32	56 (18)	50 (16)	44 (12/27)	53 (17)	47 (15)	34 (11)	34 (11)
No	87	40 (35)	33 (29)	34 (24/70)	51 (44)	31 (27)	26 (23)	23 (20)
Asymptomatic	39	13 (5)	8 (3)	9 (3/35)	0	0	0	0
Symptomatic	80	60 (48)	53 (42)	53 (33/62)	76 (61)	53 (42)	43 (34)	39 (31)
Fever or feverishness	35	91 (32)	86 (30)	81 (21/26)	97 (34)	89 (31)	97 (34)	89 (31)
Cough	59	71 (42)	64 (38)	63 (30/48)	98 (58)	69 (41)	54 (32)	51 (30)
Diarrhea	22	59 (13)	50 (11)	60 (9/15)	77 (17)	55 (12)	41 (9)	41 (9)
Vomiting	8	88 (7)	88 (7)	75 (3/4)	88 (7)	75 (6)	75 (6)	75 (6)
Diarrhea and vomiting	4	75 (3)	75 (3)	0 (0/1)	100 (4)	75 (3)	75 (3)	75 (3)
Household								
Presence of ⩾1 smoker	33	33 (11)	30 (10)	38 (10/26)	61 (20)	33 (11)	30 (10)	24 (8)
Size								
<5 Indviduals	65	48 (31)	43 (28)	43 (21/49)	57 (37)	42 (27)	29 (19)	28 (18)
⩾5 Individuals	54	41 (22)	31 (17)	31 (15/48)	44 (24)	28 (15)	28 (15)	24 (13)

NOTE. ARI, acute respiratory illness; ILI, influenza-like illness; RT-PCR, reverse-transcriptase polymerase chain reaction; NA, not applicable; SAR, secondary attack rate; TIV, trivalent inactivated vaccine.

[a] Among subjects with analyzable paired serum samples. Subjects <7 years of age did not have serum samples obtained.

[b] $P < .05$.

[c] Significant comorbidity that is an indication for influenza immunization included the following: chronic pulmonary disease, chronic cardiac disease, chronic renal disease, immunosuppressed state, or diabetes mellitus.

case patients were confirmed by seroconversion alone (ie, had negative PCR results). All 45 contacts with positive RT-PCR results tested positive by the general influenza A RT-PCR assay, whereas 42 (93%) of 45 tested positive by pH1N1-specific RT-PCR. Two asymptomatic infections were detected by seroconversion but not by RT-PCR, 2 were detected by RT-PCR but not seroconversion, and 1 was detected by both methods.

Thirty-four of 42 households (81%) had ⩾1 secondary case patient with pH1N1 infection as confirmed by RT-PCR and/or seroconversion, and 16 (38%) had ⩾2 laboratory-confirmed secondary case patients. In 78% and 57% of households, ⩾1 contact developed ARI and ILI, respectively. Fifty-three of 119 contacts developed laboratory-confirmed pH1N1 infection, for a SAR of 45% (95% confidence interval [CI], 35.6%–53.5%). The SARs for clinical ARI and ILI were 51% (95% CI, 42.3%–60.2%) and 29% (95% CI, 20.5%–36.7%), respectively. If laboratory confirmation was also required, the SAR was 35% for ARI and 26% for ILI.

The SARs according to the characteristics of the contacts and of the household itself are presented in Table 2. Compared with adults ⩾18 years old, young contacts (<7 years of age) experienced significantly more clinical ILI (58% vs 19%; $P < .01$) and laboratory-confirmed ILI (50% vs 19%; $P = .03$). However, young age was not associated with a significantly greater risk for acquisition of laboratory-confirmed pH1N1 infection overall (58% vs 42%; $P = .35$). Laboratory-confirmed SAR was 56% in contacts vaccinated for 2008–2009 seasonal influenza and 40% in nonvaccinated contacts ($P = .15$). No other household and contact characteristics were associated with a higher risk of pH1N1 acquisition.

The SARs according to the characteristics of the primary case patient are presented in Table 3. Among the 12 contacts exposed

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Table 3. Laboratory-Confirmed Secondary Attack Rates according to Characteristics of the Primary case patient

Characteristic of primary case patient	No. of contacts linked to primary case patient	Laboratory-confirmed SAR, % (no. of cases)		
		Total pH1N1-positive cases	pH1N1-positive cases with ARI	pH1N1-positive cases with ILI
Age				
0–6 Years	36	39 (14)	33 (12)	22 (8)
7–17 Years	69	48 (33)	35 (24)	26 (18)
⩾18 Years	14	43 (6)	43 (6)	36 (5)
All	119	45 (53)	42 (35)	26 (31)
Smoking history	6	17 (1)	17 (1)	17 (1)
Received 2008–2009 influenza TIV				
Yes	22	50 (11)	41 (9)	32 (7)
No	97	43 (42)	34 (33)	25 (24)
Symptoms				
Fever or feverishness	103	47 (48)	37 (38)	27 (28)
Cough	119	45 (53)	35 (42)	26 (31)
Diarrhea	34	53 (18)	47 (16)	38 (13)
Vomiting	19	68 (13)[a]	58 (11)[a]	47 (9)[a]
Diarrhea and vomiting	12	83 (10)[a]	75 (9)[a]	67 (8)[a]
ARI	110	45 (50)	36 (40)	26 (29)
ILI	103	47 (48)	37 (38)	27 (28)
Viral culture				
Positive at any sample time	42	55 (23)	45 (19)	26 (11)
Negative	28	43 (12)	39 (11)	39 (11)
Not done	49	37 (18)	24 (12)	18 (9)
RT-PCR on day 8 of illness				
Positive	60	47 (28)	40 (24)	28 (17)
Negative	20	40 (8)	20 (4)	15 (3)
RT-PCR viral load on day 8 of illness				
Undetectable	20	40 (8)	20 (4)	15 (3)
3–4 $\log_{10}$ copies/mL	23	52 (12)	52 (12)	35 (8)
⩾5 $\log_{10}$ copies/mL	37	43 (16)	32 (12)	24 (9)

NOTE. ARI, acute respiratory illness; ILI, influenza-like illness; RT-PCR, reverse-transcriptase polymerase chain reaction; SAR, secondary attack rate; TIV, trivalent inactivated vaccine.

[a] $P < .05$.

to primary case patients with both diarrhea and vomiting (age range of primary case patients, 7–17 years), 10 (SAR, 83%) acquired laboratory-confirmed pH1N1, with a relative risk of 2.2 (95% CI, 1.5–3.1), compared with those exposed to primary case patients who did not have both symptoms. No other characteristics of primary case patients were associated with a higher risk of pH1N1 transmission.

To further evaluate risk factors for pH1N1 transmission, variables with a significance level of <0.2 in univariate analysis (primary case patient vomiting, primary case patient vomiting and diarrhea, 2008–2009 seasonal influenza vaccination of contact, and presence of ⩾1 smoker in household) were analyzed by multivariate log-binomial regression. Because of the small sample size, we were not able to construct a multivariable model that converged. Bivariate models either did not converge or did not change the significance of associations observed in univariate analysis.

The mean ($\pm$SD) serial interval between the onset of symptoms in the primary case patient and the onset of symptoms in the 48 symptomatic laboratory-confirmed secondary case patients was 3.9 $\pm$ 3.1 days (median interval, 3 days) (Figure 2). For laboratory-confirmed ILI, the mean serial interval was 3.2 days.

HA gene sequencing. Overall, 2 different lineages of pH1N1 were identified among infected study subjects, as determined by nucleic acid sequencing of the entire HA gene (data not shown). We had HA sequence data for 24 pairs of secondary case patients and their respective primary case patient. All primary-secondary pairs were infected with the same lineage. Sequences were identical among 14 pairs (100% homology) and

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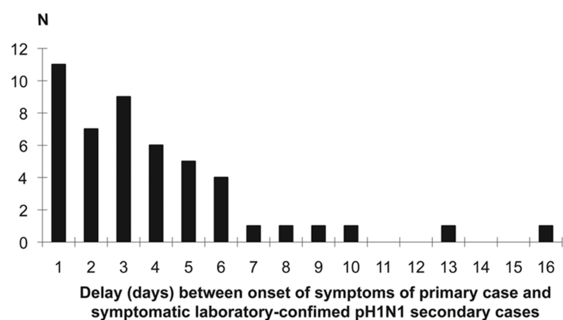

Figure 2. Serial intervals in laboratory-confirmed secondary cases of pH1N1 virus infection, showing delay between the onset of illness in primary and secondary cases. N, number of symptomatic laboratory-confirmed secondary cases of pH1N1 virus infection.

differed by only 1 nucleotide in the other 10 pairs (99.94% homology).

DISCUSSION

We report the first study, to our knowledge, to use systematic serial laboratory evaluations (including viral culture, RT-PCR, and serological testing) in combination with prospectively collected clinical data to characterize the transmission of pH1N1 within households. We observed an SAR of 45% for laboratory-confirmed pH1N1 (including 5 subjects with asymptomatic infection) with 81% of households experiencing ⩾1 laboratory-confirmed secondary case of pH1N1 infection.

During seasonal influenza A epidemics, most estimates of household SARs have ranged from 14% through 30% [4, 18–23], although SARs as high as 44%–53% have been observed [24]. However, recently published evaluations of pH1N1 household transmission reported considerably lower SARs of 4%–18% [8–11, 25]. Several differences between our study and those published to date help to explain our higher SAR. First, as previously mentioned, our households were recruited using a pH1N1-specific RT-PCR method that may not be optimally sensitive [13]. Therefore, we could not recruit primary case patients with very low viral loads (<200 copies/reaction). Second, we systematically sought secondary case patients among all household contacts (symptomatic or not) through laboratory diagnostic testing, and we performed active clinical follow-up for 3–4 weeks. All subjects were tested by RT-PCR, and those aged ⩾7 years also had a serological evaluation. In contrast, France et al [8] and Cauchemez et al [9] only used clinical syndromes, such as ILI, to identify secondary case patients, whereas Odaira et al [10] only performed RT-PCR for clinically suspected secondary cases. Influenza presents with a range of symptoms and severities, including atypical or asymptomatic infections. Clinical definitions therefore cannot fully capture incident cases and underestimate influenza infection by 25%–50%, depending on the setting [26–30]. RT-PCR is the preferred diagnostic method for influenza [29], although false-negative RT-PCR results occur [26, 29, 31, 32]. For this reason, serological evaluation used in combination with RT-PCR is useful in the research setting [32]; as demonstrated in our study, serological testing further improves case detection, although MN serologic thresholds require further evaluation for defining pH1N1 infection. In addition to poor sensitivity, as described above, clinical diagnostic criteria are not very specific and have a positive predictive value of ~77% for community-based influenza infection [32].

Nearly 10% of our laboratory-confirmed secondary case patients were completely asymptomatic, and another 2% manifested only gastrointestinal symptoms. Although asymptomatic secondary case patients contributed only marginally to our SAR, this data supports reports of subclinical pH1N1 [33, 34] and seasonal influenza infection [35]. Estimating the proportion of asymptomatic pH1N1 infections is relevant, because they may contribute to additional pH1N1 transmission [36].

Our SAR for ILI (29%) was significantly higher than that reported by Cauchemez et al [9] (10%) and France et al [8] (11.3%). The former retrospectively collected data through an internet survey, and the latter interviewed subjects once and right-censored data at 7 days after primary case patient illness onset. In contrast, our strategy of active clinical data collection through repeated home visits during 3–4 weeks allowed us to capture more symptomatic secondary cases, including 10% that occurred >1 week after disease onset in the primary case patient, although we cannot rule out the possibility of an alternate (eg, community) source for these delayed-onset cases.

Finally, antiviral use is another possible explanation for the low SARs reported by others. In the four studies reporting exposure to antivirals in their populations [8, 10, 11, 25], 26%–92% of primary case patients were treated with a neuraminidase inhibitor, and 7%–43% of contacts received antiviral prophylaxis. Neuraminidase inhibitors, to which pH1N1 is almost uniformly sensitive, reduce household transmission of seasonal influenza [18, 21] and shorten the duration of pH1N1 shedding [37]. Therefore, antiviral use likely decreases the household SAR and acts as a confounder when exploring risk factors for influenza transmission. Because none of our subjects received antivirals, we observed the natural course of pH1N1 infection and transmission within households.

In our study, the mean serial interval between the onset of illness in primary case patients and secondary case patients was 3.9 days (median interval, 3 days) for laboratory-confirmed pH1N1 infection. Only 5 of 48 symptomatic secondary case patients (10.4%) had cases that occurred later than 1 week after illness onset in their primary case patient. Although our estimate of the serial interval is slightly longer than that of Cauchemez et al [9] (mean interval, 2.6 days) , it is comparable to that of France et al [8] (median interval, 3 days) and to estimates

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for seasonal influenza [38]. These findings demonstrate that, as for seasonal influenza, measures for mitigating household spread of pH1N1 must be initiated quickly to be effective.

Household transmission studies in general cannot readily distinguish between true secondary case patients (infected by the household's primary case patient) and those who may have been infected further down a chain of household transmission (tertiary infection) or through other types of social contacts (community infections). Because we did not use mathematical modeling to adjust for these phenomena, as others have proposed [4, 5], our observed SARs and serial intervals may be overestimates. The fact that HA gene sequences obtained from our secondary case patients were identical or nearly identical to those obtained from their respective primary case patients supports transmission within the household but does not rule out the possibility of community infection or tertiary infection.

We had expected young children (<7 years of age) to transmit infection more effectively, as reported for seasonal influenza A [20] and during the 1957 and 1968 pandemics [39]. However, we saw no difference in SAR according to the age of the primary case patient. This underscores the inherent unpredictability of novel influenza virus transmission dynamics, and consequently, the potential hazards of making assumptions on the basis of knowledge from seasonal strains.

Similar to previous studies of pH1N1 virus infection [8–11] and seasonal influenza A [20], we found higher laboratory-confirmed pH1N1 SARs among children <7 years of age than among those 7–17 years of age or adults (58%, 48% and 42%, respectively), although this difference was not statistically significant. We likely underestimated the overall risk of pH1N1 acquisition in contacts <7 years of age, because we did not have serological data for this group. Nevertheless, young children did experience significantly more ILI and laboratory-confirmed ILI than did adults. However, given the sample size, our study was underpowered to detect differences in SARs between age groups.

It has recently been reported that viable pH1N1 virus and viral RNA have been recovered from stool samples obtained from infected patients [40]. We found that diarrhea (found in 33% of patients) and vomiting (19%) were not infrequent among our primary case patients, and those who experienced both symptoms were twice as likely to transmit pH1N1. To our knowledge, we are the first to report this association. It is unclear whether our observation represents increased infectivity of these patients attributable to biological factors (ie, the presence of pH1N1 in stool samples or vomitus) or behavioral factors. In addition, all of our primary case patients with vomiting and diarrhea also had fever and cough, which are factors that may also increase transmission risk.

The small sample size of this study is its principal limitation. This did not allow us to construct a multivariable model for the assessment of household transmission risk factors, precluding adjustment for potential confounders. In addition, because of ethical considerations, no serum samples were collected from children <7 years of age. Nevertheless, our findings contribute to a more accurate understanding of pH1N1 transmission and are important to inform public health interventions for mitigating virus spread.

In summary, our comprehensive household transmission study suggests that the SAR of pH1N1 may be higher than previously estimated, with 45% of household contacts developing laboratory-confirmed pH1N1. We also show that most household transmission occurs early, that asymptomatic infections are not uncommon (accounting for ~10% of cases) and that gastrointestinal symptoms are a clinical feature in approximately one-third of confirmed cases.

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