Seroprevalence of antibody to pandemic (H1N1) 2009 among health care workers after the first wave in Hong Kong

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SUMMARY

During the first wave of an influenza pandemic prior to the availability of an effective vaccine, healthcare workers (HCWs) may be at particular risk of infection with the novel influenza strain. We conducted a cross-sectional study of the prevalence of antibody to pandemic (H1N1) 2009 among HCWs in Hong Kong in February-March 2010 following the first pandemic wave. Sera collected from HCWs were tested for antibody to H1N1 influenza virus by viral neutralization (VN). We assessed factors associated with higher antibody titers, and we compared antibody titers in HCWs with those in a separate community study. In total we enrolled 703 HCWs. Among 599 HCWs who did not report receipt of pH1N1 vaccine, 12% had antibody titer ≥1:40 by VN. There were no significant differences in the age-specific proportions of unvaccinated HCWs with antibody titer ≥1:40 compared to the general community following the first wave of pH1N1. Under good adherence to infection control guidelines, potential occupational exposures in the hospital setting did not appear to be associated with any substantial excess risk of pH1N1 in HCWs. Most HCWs had low antibody titers following the first pandemic wave.

Key words: influenza; seroprevalence; pandemic; H1N1; healthcare workers

INTRODUCTION

Prior to the availability of an effective vaccine, health care workers (HCWs) may have faced particular risk of pandemic (H1N1) 2009 infection. Infection of HCWs during a pandemic is of public health concern not only because of the impact of infection and illness on the HCWs themselves but also because HCWs have frequent contact with patients who could be predisposed to serious illness if infected with influenza, and substantial rates of absenteeism among HCWs could have adverse effects on the healthcare system.[1] In 2009 the Institute of Medicine and the Centers for Disease Control and Prevention recommended that all healthcare workers who would have contact with suspected or confirmed pH1N1 patients should don N95 respirators. Recommended practice in Hong Kong followed World Health Organization guidelines under which surgical masks should be routinely worn by all healthcare workers, standard droplet precautions should be implemented during contact with influenza patients, and greater precautions including face shields and N95 respirators used when performing aerosol-generating procedures.[2]

The first imported pH1N1 case arrived in Hong Kong on April 30 and, after sporadic imported cases through May, local transmission was identified in mid-June[3] The first wave peaked in September and had subsided by November.[3, 4] pH1N1 was a notifiable condition throughout the first wave, and 36,000 laboratory-confirmed cases were notified including 1,400 HCWs, from a local population of 7 million including 150,000 HCWs. The Hong Kong government provided pH1N1 vaccine (Sanofi Pasteur) for five target groups including HCWs starting December 21, 2009, and approximately 10% of local HCWs had received influenza vaccine by March 2010.

The infection attack rate among HCWs is likely to be greater than suggested by the notification rate (1400/150000=0.9%) because many symptomatic cases did not receive laboratory testing, while a fraction of pH1N1 infections are subclinical. Since few individuals below the age of 60 had detectable antibody to pH1N1 prior to the pandemic,[4-6] serologic studies provide a straightforward way to infer infection attack rates.[4, 5] We conducted a cross-sectional study of pH1N1 antibody among HCWs in Hong Kong following the first epidemic wave.

METHODS

Study design

We recruited HCWs between February 11 and March 31, 2010 in 6 public hospitals comprising the Hong Kong West cluster of the local Hospital Authority, with a total workforce of around 7,000 HCWs in one acute care teaching hospital and five non-acute hospitals. We established fixed study locations in each hospital, and participants were invited to attend our study site and participate in our study by open advertisement to all cluster employees. HCWs were eligible to participate if they were Hong Kong residents and had worked in the cluster for at least one month.

We aimed to recruit at least 500 HCWs who had not received pH1N1 vaccine so that we could estimate the prevalence of antibody titer ≥1:40 to within ±3.5% overall and to within ±8% within 10-year age groups. The study protocol was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster.

Laboratory methods

Serum specimens collected from participants were kept in a refrigerated container at 2-8ºC immediately after collection and delivered to the laboratory at the end of each working day for storage at -70ºC prior to testing. Sera were tested for antibody responses to A/California/04/2009 (H1N1) by a viral microneutralization (VN) assay using standard methods.[4, 7] Because the VN assay was found to have greater sensitivity for pH1N1 infection than haemagglutination inhibition (HAI) in our previous study[7] we used the VN assay as the primary serologic test in our study. We used a titer of 1:40 or greater as the threshold for seropositivity because in a previous study conducted in the same laboratory around 90% of patients with confirmed infection reached a titer of 1:40 or higher by VN at convalescence[8] whereas few individuals had titer at or above 1:40 by VN before the first pandemic wave. A randomly selected subsets of specimens plus all specimens from participants who reported laboratory-confirmed pH1N1 infection were also tested by HAI using standard methods.[7]

Statistical analysis

We compared the differences in the proportion of HCWs with pH1N1 antibody titer ≥1:40 between groups with chi-squared tests or Fisher's exact test. We compared age-specific proportions of HCWs with pH1N1 antibody titer ≥1:40 with antibody seroprevalence among blood donors determined from a separate community study also conducted after the first wave.[4] We used logistic regression to explore factors associated with antibody titer ≥1:40. Factors that were statistically significant in univariable analyses were included in multivariable models. Multiple imputation was used to allow for a small amount of missing data on some characteristics.[9]

RESULTS

A total of 703 HCWs were recruited; 104 HCWs who reported receipt of pH1N1 vaccine were excluded from the following analyses. Among the 599 HCWs who reported that they had not received pH1N1 vaccine, 74 (12%) had pH1N1 antibody titer ≥1:40 by VN. In a random sample of 59/599 tested by HAI, 9 (15%) had antibody titer ≥1:40. There was a significant difference in the proportion of HCWs with antibody titer ≥1:40 by age, with greater proportion among younger HCWs, and by occupation, with greater proportion in doctors compared to nurses (Table I). In a multivariable analysis, age remained significantly associated with an antibody titer ≥1:40 and HCWs working in the emergency room had a marginally significant higher probability of antibody titer ≥1:40 (p=0.06) (Table II).

Among the 599 HCWs, 19 (3.2%) reported laboratory-confirmed pH1N1 infection during the first wave, and 58% (95% CI: 34%-80%) of those 19 had antibody titer ≥1:40 by VN while 74% (95% CI: 49%-91%) had antibody titer≥1:40 by HAI. Among the 574 HCWs who did not report laboratory-confirmed pH1N1 infection, 11% (95% CI: 8.5%-14%) had antibody titer ≥1:40 by VN. 338/599 (57%) HCWs reported experiencing a febrile influenza-like illness since July 2009 and 19% (95% CI: 15%-23%) of those HCWs had antibody titer ≥1:40 by VN versus 4.3% (95% CI: 2.2%-7.6%) of the 255 HCWs who did not report influenza-like illness during the pandemic.

Table III shows the comparison of pH1N1 antibody seroprevalence in HCWs versus blood donors at the Hong Kong Red Cross involved in a separate community study.[4]

There was no statistically significant difference in seroprevalence by age between HCWs and the community population in March 2010 apart from a marginally significant difference in HCWs aged 25-34y (p=0.09). In a multivariable logistic regression model for the HCW and community data combined (assuming none of the community blood donors were HCWs), the probability of antibody titer ≥1:40 varied significantly by age, but not by HCW status (OR=1.40, 95% CI: 0.94-2.08, p=0.09).

DISCUSSION

The first wave of 2009 pandemic H1N1 occurred between July and November 2009 in Hong Kong.[3, 4] The community infection attack rate in the first wave was estimated at around 11%, with much higher attack rates among children.[4] In our study 19/599 (3.2%) unvaccinated HCWs reported laboratory-confirmed pandemic H1N1 infection compared to an overall rate of 1% in HCWs in Hong Kong, while 12.4% of unvaccinated HCWs had antibody titre ≥1:40. Assuming the baseline seroprevalence in HCWs was similar to the community, the estimated infection attack rate in HCWs would have been around 4-15% in different age groups (Table III), suggesting that the majority of pH1N1 infections in HCWs were not laboratory-confirmed.

Among unvaccined HCWs, 85% of HCWs who had pandemic influenza antibody titre ≥1:40 reported febrile influenza-like illness during the pandemic. While some HCWs may have had antibody titer ≥1:40 prior to the pandemic, and others may have had a febrile illness not associated with influenza infection, these data are consistent with most pH1N1 infections being symptomatic. Therefore the World Health Organization recommendation that HCWs should withdraw from work while suffering acute

respiratory illness appears to be a very reasonable precaution to reduce the risk of nosocomial transmission.

We did not identify statistically significant age-specific differences in seroprevalence in March 2010 between unvaccinated HCWs and blood donors from the general community (Table III), noting that vaccine coverage in the latter population was very low in March 2010 in Hong Kong. Thus our data are not consistent with an increased risk of pH1N1 infection in HCWs, which is in agreement with previous data indicating no excess risk of pandemic influenza in HCWs in Singapore[10] or seasonal influenza infection in HCWs in Germany.[11] We also found that there was no significant difference in seroprevalence between HCWs in an acute care hospital versus non-acute hospitals, between HCWs who did or did not have contact with suspected or confirmed pH1N1 patients, or by presence of school-age children at home (Table I). One study reported higher prevalence of pH1N1 antibody in HCWs in Taiwan compared to the general community, although age was strongly associated with seroprevalence, and age distributions differed between the HCW and community samples, possibly explaining the differences in seroprevalence.[12] Infection control procedures in Hong Kong followed the World Health Organization guidelines. It is likely that the guidelines for the appropriate use of personal protective equipment were stringently adhered to following previous experiences with Severe Acute Respiratory Syndrome in 2003 as well as intensive control efforts from dedicated infection control teams.[2]Although we did not collect detailed data on adherence to infection control measures, another study reported that failure to adhere with standard precautions such as wearing a surgical mask during contact with suspected influenza patients was associated with an increased risk of pH1N1 infection.[2]

Factors associated with a higher risk of antibody titer ≥1:40 among unvaccined HCWs included younger age and working in the emergency room, whereas other factors such as occupation, number of occupational contact with influenza patients, and seasonal influenza vaccination history were not significantly associated with risk of antibody titer ≥1:40 (Tables I and II). Younger HCWs were more likely to have antibody titer ≥1:40, consistent with higher population attack rates in younger age groups,[4] although potentially confounded by differences in age-specific ability to mount antibody response to infection. As the first point of contact with most influenza patients in a hospital setting is the emergency room, while many patients with influenza-like illness are not admitted, it is plausible that HCWs in the emergency room could face the highest and most frequent risk of infection. In addition, HCWs in the emergency room would tend to see patients earliest in their course of disease, when they might be most infectious.[13]

Influenza vaccination is the best primary prevention measure against infection, and HCWs are often one of the target groups to receive vaccine not only for their direct protection both in the healthcare setting as well as in the community, but also to indirectly protect patients against nosocomial transmission.[1, 11] In Hong Kong, HCWs were one of the target groups for pH1N1 vaccine, but coverage was low following intense media coverage of a series of adverse events potentially associated with pH1N1 vaccine. Around 15% of HCWs in our study reported receipt of one dose of pH1N1 vaccine, compared to overall vaccine coverage of around 10% of HCWs in Hong Kong. While our results suggest that following World Health Organization guidelines for infection control were sufficient to prevent substantial excess risk of

pH1N1 associated with occupational exposures in a hospital setting, vaccination is still important for protection of HCWs against infection in other settings.

It is important to note several limitations of our study. Firstly, we conducted a cross-sectional seroprevalence study following the first pH1N1 wave, and we did not have baseline (pre-pandemic) data to enable us to infer accurately attack rates among HCWs. Analysis of serological data may misclassify the infection status of some individuals. However, few adults in Hong Kong had antibody to pH1N1 at titer of 1:40 or greater prior to the first wave (Table III),[4] while most individuals infected with pH1N1 did go on to develop antibody titers ≥1:40.[5] Secondly, while we did not observe any substantial excess risk of pH1N1 infection in HCWs compared to the general community, it is possible that a smaller excess risk could exist but have been masked by community exposures in our study. Larger and more detailed studies of HCWs are certainly warranted to help understand the risk of nosocomial infection and the effectiveness of preventive measures. Thirdly, participants in our study were a convenience sample covering HCWs in both acute and non-acute hospitals, while a random sample would have been ideal albeit more difficult to implement with a high response rate. Finally, we recruited HCWs who were working in 6 public hospitals on Hong Kong island and our results may not generalize to HCWs working in other regions of Hong Kong or local private hospitals and outpatient clinics.

Our data suggest that in general HCWs in hospitals in Hong Kong, operating under the WHO infection control guidelines, did not have a higher risk of infection associated with their occupation compared to the general community. Furthermore, following the first pandemic wave, most HCWs did not have antibody titers at levels

that would typically be considered protective against infection, since vaccine uptake was very low.

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POTENTIAL CONFLICTS OF INTERESTS

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REFERENCES

1. Poland GA, Tosh P, Jacobson RM. Requiring influenza vaccination for health care workers: seven truths we must accept. *Vaccine* 2005;**23**(17-18):2251-5.

2. Cheng VC, Tai JW, Wong LM, et al. Prevention of nosocomial transmission of swine-origin pandemic influenza virus A/H1N1 by infection control bundle. *Journal of Hospital Infection* 2010;**74**(3):271-7.

3. Cowling BJ, Lau MSY, Ho LM, et al. The Effective Reproduction Number of Pandemic Influenza: Prospective Estimation. *Epidemiology* 2010;**21**(6):842-6.

4. Wu JT, Ma ESK, Lee CK, et al. The infection attack rate and severity of 2009 pandemic influenza (H1N1) in Hong Kong. . *Clin. Infect. Dis.* 2010 (in press).

5. Miller E, Hoschler K, Hardelid P, Stanford E, Andrews N, Zambon M. Incidence of 2009 pandemic influenza A H1N1 infection in England: a cross-sectional serological study. *Lancet* 2010;**375**(9720):1100-8.

6. Hancock K, Veguilla V, Lu X, et al. Cross-Reactive Antibody Responses to the 2009 Pandemic H1N1 Influenza Virus. *New England Journal of Medicine* 2009;**361**(20):1945-52.

7. Cowling BJ, Chan KH, Fang VJ, et al. Comparative epidemiology of pandemic and seasonal influenza A in households. *New England Journal of Medicine* 2010;**362**(23):2175-84.

8. Hung IFN, To KKW, Lee CK, et al. Effect of Clinical and Virological Parameters on the Level of Neutralizing Antibody against Pandemic Influenza A Virus H1N1 2009. *Clinical Infectious Diseases* 2010;**51**(3):274-9.

9. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009;**338**:b2393.

10. Chen MI, Lee VJ, Lim WY, et al. 2009 influenza A(H1N1) seroconversion rates and risk factors among distinct adult cohorts in Singapore. *JAMA* 2010;**303**(14):1383-91.

11. Williams CJ, Schweiger B, Diner G, et al. Seasonal influenza risk in hospital healthcare workers is more strongly associated with household than occupational exposures: results from a prospective cohort study in Berlin, Germany, 2006/07. *BMC Infectious Diseases* 2010;**10**:8.

12. Chan YJ, Lee CL, Hwang SJ, et al. Seroprevalence of antibodies to pandemic (H1N1) 2009 influenza virus among hospital staff in a medical center in Taiwan. *Journal of the Chinese Medical Association* 2010;**73**(2):62-6.

13. Lau LL, Cowling BJ, Fang VJ, et al. Viral shedding and clinical illness in naturally acquired influenza virus infections. *Journal of Infectious Diseases* 2010;**201**(10):1509-16.

Table I. Characteristics of 599 healthcare workers who had not received pandemic (H1N1) 2009 vaccine.

Characteristic	**No.**	**Proportion with antibody titer ≥1:40 by VN (95% CI)[a]**		**p-value[b]**
Age				
19-24 years	49	16%	(7.3%-30%)	
25-34 years	125	20%	(13%- 28%)	
35-44 years	162	13%	(8.2%-19%)	
45-54 years	190	7.4%	(4.1%-12%)	
55-64 years	72	8.3%	(3.1%-17%)	0.01
Unknown	1			
Male	106	15%	(8.9%-23%)	
Female	493	12%	(9.1%-15%)	0.43
Occupation				
Doctor	30	20%	(7.7%-39%)	
Nurse	146	8.2%	(4.3%-14%)	
Clinical supporting	235	9.4%	(6.0%-14%)	
Non-clinical supporting	144	17%	(12%-25%)	
Other	44	21%	(9.8%-35%)	0.02
Department				
Medicine	83	9.6%	(4.3%-18%)	
Surgery	54	14.8%	(6.6%-27%)	

Emergency room	9	33.3%	(7.5%-70%)	
Pediatrics	38	10.5%	(2.9%-25%)	
Other clinical departments	255	11.8%	(8.1%-16%)	
Non-clinical	147	13.6%	(8.5%-20%)	0.44
Unknown	13			
Contact with influenza patients Aug-Oct 2009				
0 per day	171	13%	(8.2%-19%)	
1-5 per day	230	11%	(7.5%-16%)	
≥ 6 per day	75	12%	(5.6%-22%)	0.89
Unknown	123			
Acute care hospital	458	13%	(10%-16%)	
Non-acute care hospital	141	11%	(6.1%-17%)	0.57
Number of school-age children at home				
0	381	12%	(9.2%-16%)	
1	116	10%	(5.5%-17%)	
≥2	94	14%	(7.6%-23%)	0.74
Unknown	8			
Received 2009-10 seasonal influenza vaccine				

No	402	13%	(9.6%-16%)	
Yes	196	12%	(7.6%-17%)	0.84
Unknown	1			
Received 2008-09 seasonal influenza vaccine				
No	368	13%	(9.3%-16%)	
Yes	227	12%	(8.4%-17%)	0.95
Unknown	4			
Received 2007-08 seasonal influenza vaccine				
No	357	12%	(9.1%-16%)	
Yes	236	12%	(8.4%-17%)	0.91
Unknown	6			

[a] Proportion of individuals with antibody titer ≥1:40 to A/CA/04/2009 by viral neutralization.

[b] p-values for association calculated by chi-squared tests or fisher's exact tests.

CI: confidence interval; VN: viral neutralization

Table II. Univariable and multivariable analysis of factors associated with antibody titer ≥1:40 to pandemic (H1N1) 2009 among 599 healthcare workers who had not received pandemic (H1N1) 2009 vaccine.

Characteristic[a]	Crude odds ratio of titer ≥1:40 (95% CI)		Adjusted odds ratio[b] of titer ≥1:40 (95% CI)	
Age, years				
19-24	0.78	(0.32-1.87)	0.74	(0.31-1.80)
25-34	1.00		1.00	
35-44	0.59	(0.32-1.12)	0.55	(0.29-1.06)
45-54	0.32	(0.16-0.64)	0.28	(0.13-0.57)
55-64	0.36	(0.14-0.93)	0.32	(0.12-0.85)
Department				
Medicine	1.00		1.00	
Surgery	1.58	(0.56-4.52)	1.57	(0.54-4.57)
Emergency room	4.53	(0.94-21.89)	4.56	(0.91-22.87)
Pediatrics	1.06	(0.30-3.75)	1.07	(0.30-3.87)
Other clinical dept	1.24	(0.54-2.84)	1.33	(0.57-3.09)
Non-clinical	1.46	(0.61-3.49)	2.07	(0.84-5.12)

[a] Multiple imputation was used to adjust for a small amount of missing data on some characteristics.

[b] Adjusted for the variables that were significant in univariable analyses i.e. age and department.

[c] Contact with patients with suspected or confirmed pH1N1 between August and October 2009.

Table III. Comparison in prevalence of antibody titer ≥1:40 to pandemic (H1N1) 2009 in health care workers versus blood donors.

Age	**General community (blood donors)**						**Healthcare workers**		**p-value[b]**
	June 2009		November-December 2009		March 2010		February-March 2010		
	n/N[a]	% (95% CI)	n/N[a]	% (95% CI)	n/N[a]	% (95% CI)	n/N[a]	% (95% CI)	
18-24y	8/287	2.8% (1.2%-5.4%)	96/548	18% (14%-21%)	20/114	18% (11%-26%)	8/49	16% (7.3%-30%)	0.97
25-34y	14/292	4.8% (2.6%-7.9%)	94/763	12% (10%-15%)	15/130	12% (6.6%-18%)	25/125	20% (13%-28%)	0.09
35-44y	13/286	4.5% (2.4%-7.6%)	54/604	8.9% (6.8%-12%)	13/122	11% (5.8%-18%)	21/162	13% (8.2%-19%)	0.68
45-54y	11/332	3.3% (1.7%-5.9%)	26/367	7.1% (4.7%-10%)	4/81	4.9% (1.4%-12%)	14/190	7.4% (4.1%-12%)	0.60
55-64y	2/163	1.2% (0.1%-4.4%)	6/131	4.6% (1.7%-10%)	1/19	5.3% (0.1%-26%)	6/72	8.3% (3.1%-17%)	1.00

[a] Number with antibody titer ≥1:40 to pandemic (H1N1) 2009 by viral neutralization / total number of subjects.

[b] p-value comparing healthcare workers in March 2010 with the community sample in March 2010 by chi-squared test.