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Journal of Hospital Infection 78 (2011) 308–311

Available online at www.sciencedirect.com

Journal of Hospital Infection

journal homepage: www.elsevierhealth.com/journals/jhin

Seroprevalence of antibody to pandemic influenza A (H1N1) 2009 among healthcare workers after the first wave in Hong Kong

Y. Zhou [a], D.M.W. Ng [a], W.-H. Seto [b], D.K.M. Ip [a], H.K.H. Kwok [b], E.S.K. Ma [c], S. Ng [a], L.L.H. Lau [a], J.T. Wu [a], J.S.M. Peiris [c,d], B.J. Cowling [a,*]

[a] Infectious Disease Epidemiology Group, School of Public Health, The University of Hong Kong, Hong Kong Special Administrative Region, China
[b] Hospital Authority, Hong Kong Special Administrative Region, China
[c] Department of Microbiology, The University of Hong Kong, Hong Kong Special Administrative Region, China
[d] HKU–Pasteur Research Centre, Hong Kong Special Administrative Region, China

ARTICLE INFO

Article history:
Received 8 September 2010
Accepted 17 February 2011
by S.J. Dancer
Available online 17 April 2011

Keywords:
H1N1
Healthcare workers
Influenza
Pandemic
Seroprevalence

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 influenza A (H1N1) 2009 (pH1N1) among HCWs in Hong Kong in February–March 2010 following the first pandemic wave. Sera collected from HCWs were tested for antibody to pH1N1 influenza virus by viral neutralisation (VN). We assessed factors associated with higher antibody titres, and we compared antibody titres 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 titre ≥1:40 by VN. There were no significant differences in the age-specific proportions of unvaccinated HCWs with antibody titre ≥1:40 compared with 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 infection in HCWs. Most HCWs had low antibody titres following the first pandemic wave.

Introduction

Prior to the availability of an effective vaccine, healthcare workers (HCWs) may have faced particular risk of pandemic influenza A (H1N1) 2009 (pH1N1) 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 use N95 respirators. Recommended practice in Hong Kong followed World Health Organization (WHO) 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 1400 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 21 December 2009, and about 10% of local HCWs had received influenza vaccine by March 2010.

The infection attack rate among HCWs is likely to be greater than that suggested by the notification rate (1400/150 000, 0.9%)

* Corresponding author. Address: School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Units 624–7, Cyberport 3, Pokfulam, Hong Kong. Tel.: +852 3906 2011; fax: +852 3520 1945.
E-mail address: bcowling@hku.hk (B.J. Cowling).

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doi:10.1016/j.jhin.2011.02.017

because many symptomatic cases did not receive laboratory testing, while a fraction of pH1N1 infections are subclinical. Since few individuals aged <60 years had detectable antibody to pH1N1 prior to the pandemic,[4–6] serological 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 11 February and 31 March 2010 in six public hospitals comprising the Hong Kong West cluster of the local hospital authority, with a total workforce of around 7000 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 titre ≥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 2–8 °C immediately after collection and delivered to the laboratory at the end of each working day for storage at −70 °C prior to testing. Sera were tested for antibody responses to A/California/04/2009 (H1N1) by a viral microneutralisation (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 serological test in this study. A titre of ≥1:40 was taken as the threshold for seropositivity because in a previous study conducted in the same laboratory around 90% of patients with confirmed infection reached a titre of ≥1:40 by VN at convalescence[8] whereas few individuals had a titre ≥1:40 by VN before the first pandemic wave. A randomly selected subset 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 titre ≥1:40 between groups with χ^2-tests or Fisher's exact test. We compared age-specific proportions of HCWs with pH1N1 antibody titre ≥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 titre ≥1:40. Factors that were statistically significant in univariate analyses were included in multivariate 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 titre ≥1:40 by VN. In a random sample of 59/599 tested by HAI, 9 (15%) had antibody titre ≥1:40. There was a significant difference in the proportion of HCWs with antibody titre ≥1:40 by age, with greater proportion among younger HCWs, and by occupation, with greater proportion among doctors compared with nurses (Table I). In a multivariate analysis, age remained significantly associated with an antibody titre ≥1:40 and HCWs working in the emergency room had a marginally significant higher probability of antibody titre ≥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 titre ≥1:40 by VN, and 74% (95% CI: 49–91) had antibody titre ≥1:40 by HAI. Among the 574 HCWs who did not report laboratory-confirmed pH1N1 infection, 11% (95% CI: 8.5–14)

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

Characteristic	No.	Proportion with antibody titre ≥1:40 by VN (95% CI)[a]	*P*-value[b]
Age (years)			
19–24	49	16% (7.3–30)	
25–34	125	20% (13–28)	
35–44	162	13% (8.2–19)	
45–54	190	7.4% (4.1–12)	
55–64	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)	
Paediatrics	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
No. 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 2009–2010 seasonal influenza vaccine			
No	402	13% (9.6–16)	
Yes	196	12% (7.6–17)	0.84
Unknown	1		
Received 2008–2009 seasonal influenza vaccine			
No	368	13% (9.3–16)	
Yes	227	12% (8.4–17)	0.95
Unknown	4		
Received 2007–2008 seasonal influenza vaccine			
No	357	12% (9.1–16)	
Yes	236	12% (8.4–17)	0.91
Unknown	6		

VN, viral neutralisation; CI, confidence interval.
[a] Proportion of individuals with antibody titre ≥1:40 to A/CA/04/2009 by viral neutralisation.
[b] *P*-values for association calculated by χ^2-tests or Fisher's exact tests.

Table II
Univariate and multivariate analysis of factors associated with antibody titre ≥1:40 to pandemic influenza A (H1N1) 2009 among 599 healthcare workers who had not received pandemic influenza A (H1N1) 2009 vaccine

Characteristic[a]	Crude odds ratio of titre ≥1:40 (95% CI)	Adjusted odds ratio[b] of titre ≥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)
Paediatrics	1.06 (0.30–3.75)	1.07 (0.30–3.87)
Other clinical department	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)

CI, confidence interval.
[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.

had antibody titre ≥1:40 by VN. Of the 599 HCWs, 338 (57%) reported experiencing a febrile influenza-like illness since July 2009 and 19% (95% CI: 15–23) of those HCWs had antibody titre ≥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 25–34 years ($P = 0.09$). In a multivariate logistic regression model for the HCW and community data combined (assuming that none of the community blood donors were HCWs), the probability of antibody titre ≥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 pH1N1 infection 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 with an overall rate of 1% in HCWs in Hong Kong, while 12.4% of unvaccinated HCWs had antibody titre ≥1:40. Assuming that 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 unvaccinated HCWs, 85% of HCWs who had pandemic influenza antibody titre ≥1:40 reported febrile influenza-like illness during the pandemic. Whereas some HCWs may have had antibody titre ≥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 WHO recommendation that HCWs should withdraw from work while suffering acute respiratory illness appears to be a 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 with that 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 WHO 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 comply 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 titre ≥1:40 among unvaccinated HCWs included younger age and working in the emergency room, whereas other factors such as occupation (after adjustment for age), number of occupational contact with influenza patients, and seasonal influenza vaccination history were not significantly associated with risk of antibody titre ≥1:40 (Tables I and II). Younger HCWs were more likely to have antibody titre ≥1:40, consistent with higher population attack rates in younger age groups,[4] although potentially confounded by

Table III
Comparison of prevalence of antibody titre ≥1:40 to pandemic influenza A (H1N1) 2009 in healthcare workers versus blood donors

Age (years)	General community (blood donors)						Healthcare workers		*P*-value[b]
	June 2009		Nov–Dec 2009		March 2010		Feb–Mar 2010		
	n/*N*[a]	% (95% CI)	*n*/*N*[a]	% (95% CI)	*n*/*N*[a]	% (95% CI)	*n*/*N*[a]	% (95% CI)	
18–24	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
25–34	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
35–44	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
45–54	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
55–64	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 titre ≥1:40 to pandemic influenza A (H1N1) 2009 by viral neutralisation/total number of subjects.
[b] *P*-value comparing healthcare workers in March 2010 with the community sample in March 2010 by χ^2-test.

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, it is plausible that HCWs in the emergency room could face the highest and most frequent risk of infection – even though many patients with influenza-like illness are not admitted. 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 with overall vaccine coverage of around 10% of HCWs in Hong Kong. Although our results suggest that following WHO guidelines for infection control was 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. First, 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 titre of $\geq$1:40 prior to the first wave (Table III),[4] whereas most individuals infected with pH1N1 did go on to develop antibody titres $\geq$1:40.[5] Second, although we did not observe any substantial excess risk of pH1N1 infection in HCWs compared with the general community, it is possible that a smaller excess risk did exist but may 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. Third, participants in our study were a convenience sample covering HCWs in both acute and non-acute hospitals; 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 six public hospitals on Hong Kong island and our results may not generalise to HCWs working in other regions of Hong Kong or local private hospitals and outpatient clinics.

Our data suggest that generally 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 with the general community. Furthermore, following the first pandemic wave, most HCWs did not have antibody titres at levels that would typically be considered protective against infection, since vaccine uptake was very low.

Acknowledgements

We thank P. Ching, S.K. Pang, A. Wong and A. Yuen for facilitating our study, and L. Chan, Q. Liao, T. So and J. Wong for assistance with the fieldwork. We thank V. Fang for technical assistance.

Conflict of interest statement

B.J.C. has received research funding from MedImmune Inc., a manufacturer of influenza vaccines. D.K.M.I. has received research funding from Roche. The authors report no other potential conflicts of interest.

Funding sources

This work has received financial support from the Area of Excellence Scheme of the Hong Kong University Grants Committee (grant no. AoE/M-12/06) and the Research Fund for the Control of Infectious Disease, Food and Health Bureau, Government of the Hong Kong SAR (grant no. PHE-20). The funding bodies were not involved in the collection, analysis, and interpretation of data, the writing of the article, or the decision to submit it for publication.

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