CONTROL STRATEGY FOR NOSOCOMIAL RESPIRATORY VIRUS INFECTION BASED ON COLONIZATION OF HEALTHCARE WORKERS

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Abstract. Many respiratory viruses are easily spread by human-to-human transmission, and healthcare workers (HCWs) are likely to be sources of infection. The study verified colonization rates of respiratory viruses (including H1N1) in HCWs and evaluated the necessity of nasopharyngeal swab screening in HCWs for detection of subclinical infections. First-line and non-first-line HCWs were monitored in May and August 2010 for respiratory virus colonization, obtaining 147 nasal secretion samples for RT-multiplex-PCR to identify seven respiratory viruses and RT-PCR for pandemic H1N1 2009. All participants were asked to complete questionnaire on demographics and previous clinical symptoms. Positive results for respiratory viruses were more frequent (13.3%) in first-line than in non-first-line (3.5%) HCWs in May than in August. In addition, first-line HCWs presented more frequently with respiratory virus infection-related symptoms than non-first-line HCWs. Nasopharyngeal swab screening by RT-PCR in conjunction with observations of associated symptoms in first-line HCWs could provide effective early detection and prevention of nosocomial spread of respiratory viruses.

Keywords: respiratory virus, colonization, healthcare worker, nasopharyngeal swab, South Korea

INTRODUCTION

Acute respiratory viruses are primary causes of lower respiratory tract infection in all age groups, producing significant morbidity and mortality worldwide (Lessler *et al*, 2009). Respiratory viruses can spread rapidly to patients and healthcare workers (HCWs) in hospitals after being introduced by visitors, staff or patients. Many respiratory viruses are easily transmitted by human-to-human route and thus are dispersed across the world, as has been observed with influenza pandemic (Burns, 2009; Sym *et al*, 2009).

In the first two weeks of April 2009, cases of infection from a non-typed influenza A (InfA) virus were identified in Mexico and southern California, USA, but subsequently identified as InfA virus subtype pandemic H1N1 2009 (pH1N1 2009) (Baden *et al*, 2009). After being transmitted among people in USA and Canada, the virus spread globally, and report of pH1N1 2009 infection among HCWs soon appeared (Burns, 2009). HCWs appear to

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be at high risk of contracting pH1N1 2009 infection if they do not adhere to proper infection control measures, as exemplified by an early case report from Mexico of 12% of HCWs caring for influenza cases developing respiratory symptoms (Maritz *et al*, 2010). Epidemiological reports of pH1N1 2009 estimated a case-fatality rate of 0.2-0.4%, highlighting the vulnerability of HCWs to pH1N1 2009 (Sng *et al*, 2009; Balkhy *et al*, 2010).

During the severe acute respiratory syndrome (SARS) outbreak in 2002-2003 which affected 8,422 persons, 21% of all SARS cases worldwide were among HCWs (Sng *et al*, 2009). Nosocomial virus spread in large hospitals is a major epidemic feature of early SARS outbreaks (Sng *et al*, 2009; Ho *et al*, 2006). Thus, regular nasopharyngeal swab screenings for nested RT-PCR assay in conjunction with a daily recording of body temperature of all first-line HCWs has been suggested for effective early detection of infection (Ho *et al*, 2006).

Hence, this study determined colonization rates of respiratory viruses (including pH1N1 2009) in HCWs and evaluated the necessity of nasopharyngeal swab screening for detection of subclinical infections in HCWs in Seoul, Korea.

MATERIALS AND METHODS

Subjects

One hundred and forty-seven HCWs (90 first-line and 57 non-first line HCWs) at Chung-Ang University Hospital (Seoul, Korea) were monitored in May and August 2010 for respiratory virus colonization. First-line HCWs are those individuals who have close contact with respiratory virus-infected patients, such as medical staff in emergency department, internal medicine and pediatric wards, and phlebotomists who draw venous blood specimens from respiratory virus-infected patients. All other employees who do not have close contact with respiratory virus-infected patients are classified as non-first-line HCWs. Participants were requested to complete questionnaires describing their workplace, contact history with respiratory virus-infected patients or specimens, symptoms experienced during the study period, and medical history.

The study was approved by the Institutional Review Board of Chung-Ang University Hospital (IRB No. 10-027-04-07). Prior written informed consent was obtained from all participants.

Nasopharyngeal swab collection

Nasopharyngeal swab was obtained from the right nostril at a depth of 2-3 cm using a sterile applicator previously soaked in normal saline solution. Specimens were transported at room temperature to the laboratory on the same day they were taken.

RT-PCR assay for respiratory viruses

Viral DNA/RNA was extracted from a nasal secretion sample using a Viral Gene-spin™ Kit (Intron Biotechnology, Seoul, Korea). RT-multiplex-PCR was performed using Seeplex™ RV Detection Kit (Seegene, Seoul, Korea) for identification of respiratory syncytial virus (RSV), human metapneumovirus (hMPV), adenovirus (ADV), InfA, influenza B (InfB), parainfluenza virus type 1-3 (PIV) and rhinovirus (HRV). RT-PCR for pH1N1 2009 using Seeplex FluA ACE Subtyping assay (Seegene) was conducted on samples from participants presenting with InfA.

Statistical analysis

Variables were compared among four groups from both May and August 2010, namely, first-line HCWs, non-first-line HCWs, HCWs positive for respiratory

virus, and HCWs negative for respiratory virus. Comparisons were analyzed using chi-square test for categorical independent variables. Statistical analysis was performed to examine differences among variables with regards to clinical symptoms (cough, dyspnea, fever, hoarseness, myalgia, nasal congestion, sore throat, and sputum). A p-value <0.05 is considered to be statistically significant. Data were analyzed using a Statistical Package for the Social Sciences (SPSS) version 18.0 (IBM, Armonk, NY).

RESULTS

Characteristics of participants

We enrolled 90 first-line and 57 non-first-line HCWs in the two study periods, May and August, seasons distinctive different for respiratory virus infections in South Korea, and, thus, ideal for determining colonization status of various respiratory viruses and seasonal variation. Male-to-female ratio of participants was 0.45:1, with mean ± SD age of 30 ± 5 years for first-line and 30 ± 6 years for non-first-

Table 1
Characteristics of healthcare workers at Chung-Ang University Hospital, Seoul, Korea enrolled in the study, May and August 2010.

Characteristic	First-line HCW (n=90)	Non-first-line HCW (n=57)
Age (years)		
Mean ± SD	30 ± 5	30 ± 6
Range	24 - 47	24 - 45
Male, n	31	26
Chronic condition, n (%)	17 (19)	8 (14)
DM	-	-
Asthma	1 (1)	1 (2)
COPD	-	-
Hypertension	-	2 (3)
Hyperlipidemia	1 (1)	
Anemia	3 (3)	-
Hepatitis	2 (2)	-
Allergic disease	8 (9)	3 (5)
Autoimmune disease	1 (1)	1 (2)
Thyroid dysfunction	1 (1)	1 (2)
Exposure to InfA pH1N1 2009 virus, n (%)		
May	71 (2)[a]	32 (3)
August	18 (5)[a]	4 (5)

[a]p <0.05. COPD, chronic obstructive pulmonary disorder; DM, diabetes mellitus; HCW, health care worker; InfA pH1N1 2009, Influenza A virus subtype pandemic H1N1 2009.

line HCWs (Table 1). Frequency of direct exposure to pH1N1 2009-infected patients is significantly different in May and August for both first-line (78.9% *vs* 20.0%, $p<0.0001$) and non-first-line HCWs (56.1% *vs* 7.0%, $p<0.0001$), respectively (Table 1).

Respiratory virus positivity in HCWs

In May, 12 (13%) first-line HCWs showed positive results for respiratory viruses, with HRV, InfAV, InfBV, PIV, and RSV isolated (Table 2). One of the first-line HCWs positive for InfAV was also positive for pH1N1 2009, and another positive for both InfAV and RSV. In the same month, of the non-first-line HCWs, one was positive for HRV and another for PIV. In August, only two first-line HCWs showed positive results for HRV (Table 2). Thus, in May respiratory virus infection is more frequent among first-line than non-first-line HCWs ($p = 0.048$).

Clinical symptoms of respiratory infections in HCWs

Virus-positive HCWs during both months presented with sore throat (62%), hoarseness (37%), cough (37.5%), myalgia (31%), nasal congestion (31%), fever (19%), sputum (6%), and dyspnea (6%), with significantly higher rates of sore throat, hoarseness, sputum, and myalgia than those negative for respiratory viruses ($p<0.05$) (Table 3).

DISCUSSION

In 2010, at Chung-Ang University Hospital (Seoul) there were 3,313 specimens positive for respiratory viruses using RT-multiplex PCR assay, among which 1,108 specimens were positive for InfAV pH1N1 2009 using RT-PCR assay (data not shown). Many hospital patients have serious underlying illnesses, mak-

Table 2
Respiratory virus-positive (by PCR) health care workers at Chung-Ang University Hospital, Seoul, Korea in May and August 2010.

Virus	First-line HCW Number (n = 90)		Non-first-line HCW Number (n = 57)	
	May	August	May	August
InfA (pH1N1 2009[a])	4 (1[a])	0	0	0
InfB	1	0	0	0
RSV and InfA	1[b]	0	0	0
PIV	4	0	1	0
HRV	2	2	1	0
ADV	0	0	0	0
hMPV	0	0	0	0
Total	12[c]	2	2	0

[a]With Influenza A subtype pH1N1 2009-positive (subtype confirmed). [b]With RSV and Influenza A virus. [c]With multiple respiratory virus-positive counted as one subject. ADV, Adenovirus; HCW, healthcare worker; hMPV, human Metapneumovirus; HRV, Rhinovirus; InfA, Influenza A; InfB, Influenza B; pH1N1 2009, Influenza A virus subtype pandemic H1N1 2009; PIV, Parainfluenza virus type 1-3; RSV, Respiratory syncytial virus.

Table 3
Clinical symptoms of total healthcare workers at Chung-Ang University Hospital, Seoul, Korea in May and August 2010.

Symptom[a]	Virus-positive Number (%) (*n*=16)	Virus-negative Number (%) (*n*=278)	*p*-value[b]
Nasal congestion	5 (31)	47 (17)	0.172
Sore throat	10 (62)	36 (13)	0.000
Hoarseness	6 (37)	20 (7)	0.001
Cough	6 (37)	51 (18)	0.093
Sputum	6 (37)	44 (16)	0.037
Dyspnea	1 (6)	3 (1)	0.202
Myalgia	5 (31)	23 (8)	0.011
Fever	3 (19)	16 (6)	0.075

[a]Healthcare workers may have more than a single symptom. [b]Significance at $p<0.05$.

ing nosocomial influenza infection more lethal. Chronically ill, immune-compromised, elderly, and very young patients are especially vulnerable to potentially life-threatening nosocomial infections of the lower respiratory tract (Maltezou and Drancourt, 2003; Nguyen *et al*, 2016). Pediatric patients with community-acquired influenza and HCWs constitute important reservoirs for nosocomial spread of virus infection (Maltezou and Drancourt, 2003). HCWs also play a significant role in the transmission of influenza virus in healthcare facilities, given their risk for both acquiring virus from patients and then transmitting to patients and colleagues. The appropriate use of personal protective equipment (PPE) and influenza vaccination by HCWs has been shown to reduce the transmission of influenza in healthcare settings, resulting in a decrease in influenza-related patient morbidity and mortality, as well as in HCW illness and absenteeism (Mitchell *et al*, 2012). However, reports of monitoring HCWs during acute respiratory virus infection seasons, verifying respiratory virus colonization and investigating symptoms in HCWs are rare (Ho *et al*, 2006; Sng *et al*, 2009; Balkhy *et al*, 2010).

This study reveals incidence of respiratory virus-positive cases in May were four times more frequent in first-line than non-first-line HCWs. These findings indicate that there is a significant difference in vulnerability to respiratory virus infection, including InfA pH1N1 2009 virus, between first-line and non-first-line HCWs. First-line HCWs more frequently presented with respiratory virus infection-related symptoms than did non-first-line HCWs. Sore throat (in particular), hoarseness, sputum, and myalgia are significantly more common in respiratory virus-positive than –negative HCWs. Therefore, nasopharyngeal swab screening should be performed for respiratory virus detection in first-line HCWs and in HCWs with respiratory symptoms.

Many common viral infections exhibit predictable global seasonality. For ex-

ample, influenza, hMPV and RSV predominate in winter, whereas HRV is prominent in autumn and spring (Monto, 2004; Bont, 2009; Gaunt *et al*, 2009). In Korea, the peak incidence of respiratory virus illnesses follows similar seasonal variation (Kim *et al*, 2006; Seo *et al*, 2008). In Chung-Ang University Hospital during 2010, InfAV (November-March) and RSV (December-March) were mostly detected during these winter months, while hMPV (April-June) and PIV (May-September) were most prominent in these spring and summer periods. However, HRV was diagnosed throughout the year.

This study demonstrates HCWs were positive for HRV, InfAV, InfBV, PIV, and RSV in May and only for HRV in August. These results correlate with the seasonality of respiratory viruses except hMPV and pH1N1 2009, the latter colonization being found only one HCW while the remaining InfAV-positives (possibly) being seasonal H1N1, H3N2 and H5N1 strains. The positive results for respiratory virus indicated that HCWs were vulnerable to transmission of respiratory virus infection from the patients. ADV and hMPV, on the other hand, were not detected in HCWs. It is worth noting hMPV was not identified in either May or August, its normal peak months (Kim *et al*, 2010). Previous studies have shown hMPV infection occurs early in childhood, and sero-prevalence of hMPV-specific antibodies in adults is nearly 100% (van den Hoogen *et al*, 2001; Leung *et al*, 2005). These results also reflect that colonization of respiratory viruses in HCWs provided a partial reservoir for nosocomial infection of respiratory virus according to seasonality.

The Centers for Disease Control and Prevention, Korea received 48 reports of confirmed or probable infections of InfA pH1N1 2009 virus in May 2009 (CDC, 2009). Of 26 patients with detailed case reports, 13 (50%) were HCWs who were thought to have acquired the infection in a healthcare setting, including one instance of probable HCW-to-HCW transmission and 12 instances of possible patient-to-HCW transmission. It has previously been shown nosocomial spread of respiratory viruses can cause infection among HCWs (Ho *et al*, 2006). The transmission route of respiratory viruses remains to be determined, but it is believed that nosocomial respiratory virus infections are mainly transmitted through close contact with contaminated droplets (Ho *et al*, 2006; Weber and Stilianakis, 2008). The mechanisms of person-to-person transmission of InfA pH1N1 2009 virus appear to be similar to those of respiratory viruses. Rates of secondary outbreaks of illness vary according to setting and exposed population, but estimates range from 7.6% to 33% (Maritz *et al*, 2010). In the present study, HCWs who were in close contact with respiratory virus-infected patients were also more likely to have respiratory virus infection-related symptoms and a positive test for a respiratory virus. In particular, one HCW who was infected with InfA pH1N1 2009 virus had a history of contacts with respiratory virus-infected patients and was the attending physician of a pH1N1 2009-infected pediatric patient at that time.

A number of reports have suggested protective guidelines for HCWs such as reliable access to effective PPE (gown, N95 mask, gloves, and eye protection), vaccination and antiviral drug therapy (Ho *et al*, 2006; Bont , 2009; Sng *et al*, 2009; Carlson *et al*, 2010). Taking adequate precautions against exposure and physical contact significantly reduce the risk of infection after patient interaction (Carlson *et al*, 2010; Writing Committee of the WHO Consultation on Clinical Aspects

of Pandemic (H1N1) 2009 Influenza *et al*, 2010; Fisher *et al*, 2014. Although every HCW in Chung-Ang University Hospital wore PPE (*eg*, gown, gloves and mask) and received vaccines for both pandemic and seasonal respiratory viruses, there were still several HCWs with respiratory virus colonization. Therefore, additional efficient procedures, such as RT-PCR, to screen for respiratory infection of HCWs before nosocomial spread of thee infection (as was shown in this study) are needed, especially in hospital settings.

This study has a number of limitations: (i) the study was performed during periods when the prevalence of respiratory virus, especially InfA pH1N1 2009 virus, was relatively low; and (ii) we did not perform serological assays to confirm the diagnosis of respiratory infection. However, a merit of the study is that to the best of our knowledge it is the first prospective trial study of HCWs in Korea, and it provides a significant comparison between two time periods.

In conclusion, laboratory diagnosis of respiratory viruses is a necessary first step in the preventive surveillance and treatment of respiratory illness, and nasopharyngeal swab screening provides an accurate and rapid test for early detection to prevent further spread. Nasopharyngeal swab screening by RT-PCR in conjunction with observations of associated symptoms in first-line healthcare workers offer an effective early detection and prevention of nosocomial spread of respiratory virus infections.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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