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Hospital-based Influenza Morbidity and Mortality (HIMM) Surveillance for A/H7N9 Influenza Virus Infection in Returning Travelers

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ABSTRACT

Since 2013, the Hospital-based Influenza Morbidity and Mortality (HIMM) surveillance system began a H7N9 influenza surveillance scheme for returning travelers in addition to pre-existing emergency room (ER)-based influenza-like illness (ILI) surveillance and severe acute respiratory infection (SARI) surveillance. Although limited to eastern China, avian A/H7N9 influenza virus is considered to have the highest pandemic potential among currently circulating influenza viruses. During the study period between October 1st, 2013 and April 30th, 2016, 11 cases presented with ILI within seven days of travel return. These patients visited China, Hong Kong, or neighboring Southeast Asian countries, but none of them visited a livestock market. Seasonal influenza virus (54.5%, 6 among 11) was the most

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Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

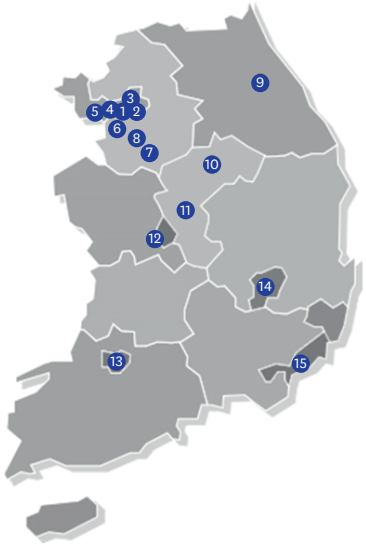
Conceptualization: Song JY, Noh JY, Cheong HJ, Kim WJ. Data curation: Noh JY, Lee HS. Investigation: Song JY, Noh JY, Lee J, Woo HJ, Lee JS, Wie SH, Kim YK, Jeong HW, Kim SW, Lee SH, Park KH, Kang SH, Kee SY, Kim TH, Choo EJ, Choi WS, Cheong HJ, Kim WJ. Writing - original draft: Song JY, Kim WJ. Writing - review & editing: Song JY, Noh JY, Cheong HJ, Kim WJ.

common cause of ILI among returning travelers, and avian A/H7N9 influenza virus was not detected during the study period.

Keywords: Influenza; H7N9 Virus; Influenza-like Illness; Surveillance

In 2011, the Hospital-based Influenza Morbidity and Mortality (HIMM) surveillance system was established in Korea.[1] Initially, the HIMM surveillance system was composed of two kinds of surveillance schemes: emergency room (ER)-based influenza-like illness (ILI) surveillance and severe acute respiratory infection (SARI) surveillance.[1,2] In early 2013, the novel avian influenza A/H7N9 virus emerged and persistently circulated in China. Given its geographically close location and frequent travel to China, experts have expressed concern about domestic inflow of avian A/H7N9 influenza virus to Korea. Thus, an additional surveillance scheme was added to the HIMM surveillance system for the early detection of novel avian A/H7N9 influenza virus from travel returners. In addition to 10 hospitals (Korea University Guro Hospital, Korea University Ansan Hospital, St. Vincent's Hospital of The Catholic University of Korea College of Medicine, Kyungpook National University Hospital, Pusan National University Hospital, Chonnam National University Hospital, Chungbuk National University Hospital, Yonsei University Wonju Hospital, Inha University Hospital, and Hallym University Kangnam Sacred Heart Hospital) participating in ER-ILI and SARI surveillance, five 500–1,000 bed hospitals (Konyang University Hospital, Konkuk University Chungju Hospital, Soonchunhyang University Seoul Hospital, Soonchunhyang University Bucheon Hospital, and Hallym University Dongtan Sacred Heart Hospital) were further included in the A/H7N9 influenza surveillance scheme (**Fig. 1**). This study was approved by the ethics committee of each institution and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practices.

Foreign travel information was collected from the patients with ILI. If the patient visited China, Hong Kong, or neighboring Southeast Asian countries within seven days before ILI development, respiratory specimens were collected using virus transport medium after



HIMM surveillance network for avian influenza A/H7N9

1. Korea University Guro Hospital
2. Hallym University Kangnam Sacred Heart Hospital
3. Soonchunhyang University Seoul Hospital
4. Soonchunhyang University Bucheon Hospital
5. Inha University Hospital
6. Korea University Ansan Hospital
7. Hallym University Dongtan Sacred Heart Hospital
8. St. Vincent's Hospital of Catholic University
9. Yonsei University Wonju Hospital
10. Konkuk University Chungju Hospital
11. Chungbuk National University Hospital
12. Konyang University Hospital
13. Chonnam National University Hospital
14. Kyungpook National University Hospital
15. Pusan National University Hospital

Fig. 1. Geographical distribution of hospitals participating in A/H7N9 HIMM surveillance.
HIMM = Hospital-based Influenza Morbidity and Mortality.

Table 1. Primer sequences for real-time polymerase chain reaction of respiratory viruses

Respiratory viruses	Target		Primer sequences
Enterovirus D68	VP1	Forward	TGT TCC CAC GGT TGA AAA CAA
		Reverse	TGT CTA GCG TCT CAT GGT TTT CAC
Wu polyomavirus	VP1	Forward	AAC CAG GAA GGT CAC CAA GAA G
		Reverse	TCT ACC CCT CCT TTT CTG ACT TGT
KI polyomavirus	VP2–3	Forward	CTA TCC CTG AAT ACC AGT TGG AAA C
		Reverse	GTA TGA CGC GAC AAG GTT GAA G
Parechovirus type 1	VP1	Forward	TCG TGG GGT TCA CAA ATG GA
		Reverse	TCC TGA GCC GAT GTT AAG CC
Parechovirus type 3	VP1	Forward	GAC AAC ATC TTT GGT AGA GCT TGG T
		Reverse	TTT TGC CTC CAG GTA TCT CCA T
Parechovirus type 6	VP1	Forward	CTG AGG ACG GTT AGG GAC AC
		Reverse	ACG ATT TTG CGA ACG TGG TG
Pteropine orthoreovirus	S2	Forward	CCA CGA TGG CGC GTG CCG TGT TCG A
		Reverse	ACG TAG GGA GGC GCA CGA GGT GGA

informed consent. ILI was defined as sudden onset of fever (> 37.8°C) accompanied by at least one respiratory symptom (cough and/or sore throat).[1] After enrollment, a rapid influenza antigen test was administered for seasonal influenza viruses, and respiratory specimens were transported to the central laboratory (Korea University Guro Hospital). All cases were tested for A/H7N9 influenza virus using the World Health Organization (WHO) real-time polymerase chain reaction (PCR) protocol.[3] At the same time, the presence of seasonal influenza virus (A/B), respiratory syncytial virus (A/B), parainfluenza virus (type 1–4), adenovirus, human rhinovirus, human metapneumovirus, human coronavirus (hCoV-229E, hCoV-OC43), human bocavirus, and enterovirus was determined using the Seeplex® RV15 PCR assay (Seegene Inc., Seoul, Korea) as described previously.[4] For test-negative cases, real-time PCR assays were conducted to detect enterovirus D68, WU polyomavirus, KI polyomavirus, parechovirus (type 1, 3, and 6), and pteropine orthoreovirus using primers presented in **Table 1**.[5-8]

During the study period between October 1st, 2013 and April 30th, 2016, 11 patients presented with ILI within seven days from travel return (**Table 2**). Seven (63.6%) of the 11 patients visited eastern China where avian A/H7N9 influenza virus was prevalent (**Table 2**). The other four patients visited Hong Kong (n = 2), Malaysia (n = 1), Cambodia (n = 1), and Vietnam (n = 1). Seasonal influenza virus was the most common cause of ILI among returning travelers. Seasonal influenza viruses were isolated from six patients (54.5%): four with A/H1N1 and two with A/H3N2 influenza viruses (**Table 2**). No other respiratory viruses, including avian A/H7N9 influenza virus, were detected. As previously reported,[9] the majority of H7N9 human cases developed after visiting live poultry markets in China; in this study, none of the eleven patients visited a livestock market while they travelled abroad (**Table 2**). Since the first report of human A/H7N9 cases in China in February 2013, the virus has been detected in domestic poultry exclusively in eastern China with limited detection in migratory wild birds according to surveillance studies.[9,10] Thus, contrary to avian A/H5N1 influenza viruses that have spread worldwide, avian H7N9 influenza viruses are, at least currently, confined within China. Actually, less than 5% of human A/H7N9 cases have been reported in countries other than China, including Hong Kong, Taiwan, Malaysia, and Canada, and all of these patients travelled to China prior to illness onset.[9,11] However, H7N9 influenza viruses are genetically more human-adapted compared to H5N1 influenza viruses, and H7N9 influenza viruses are reported to cause human infection even after casual contact such as walking through a livestock market without direct close contact.[9,10] In a similar time frame, the incidence of H7N9 human infection was 10 times higher than that of H5N1 infection.[9] Although limited to eastern China as of yet, avian H7N9 influenza virus is considered to have the highest pandemic potential among currently

Table 2. List of returning travelers who presented with influenza-like illness

No.	Age	Sex	Year	Month	Travel areas	Livestock market visit	Isolated virus
1	57	Female	2013	October	Hunan Sheng, China	No	Influenza A/H1N1
2	22	Female	2013	November	Hong Kong	No	Influenza A/H3N2
3	34	Male	2014	January	Guangzhou and Shanghai, China	No	-
4	25	Male	2014	January	Siem Reap, Cambodia	No	Influenza A/H1N1
5	38	Male	2014	January	Kota Kinabalu, Malaysia and Hong Kong	No	-
6	50	Male	2014	February	Jilin Sheng, China	No	-
7	62	Male	2014	June	Hunan Sheng, China	No	-
8	44	Female	2015	March	Beijing, China	No	-
9	62	Female	2015	October	Henan Sheng, China	No	Influenza A/H3N2
10	40	Male	2016	February	Shanghai, China	No	Influenza A/H1N1
11	68	Male	2016	March	Hanoi, Vietnam	No	Influenza A/H1N1

circulating influenza viruses.[12] Based on assessment using the influenza risk assessment tool (IRAT), the risk for H7N9 influenza virus to achieve sustained human-to-human transmission was in the moderate risk category, while the risk of public health impact was in the high-moderate risk range.[12] The geographic spread and pandemic risk might change over time with viral evolution and host adaptation. Thus, the H7N9 influenza surveillance system should be maintained on an ongoing basis and strengthened based on repetitive risk assessment. Rapid and timely reporting is the key element of the HIMM surveillance system, thereby enabling prompt response to public health threats from novel respiratory pathogens. Rapid detection should lead to the identification and characterization of pathogens with respect to transmissibility, virulence, and host susceptibility in the general population.

In this study, no human case of A/H7N9 influenza infection was found in Korea among travelers. However, Korea is geographically close to China, and travels to China are common. In addition, there is a possibility of A/H7N9 influenza influx due to increasing trade between Korea and China. Of note, human A/H7N9 influenza infection cases increased in number and the epidemic areas were extended to the northern and western regions (Beijing, Jilin, Liaoning, Gansu, Chongqing, Guizhou, and Sichuan) of China during the 2016–2017 influenza season. During the fifth epidemic wave since October 2016, the number of human cases with avian influenza A/H7N9 infection was greater than the numbers of those reported in earlier waves.[13] Accordingly, the risk of human A/H7N9 influenza infection influx has substantially increased in Korea. Therefore, the Korean A/H7N9 influenza surveillance system should be strengthened and maintained. Since the A/H7N9 influenza infection is accompanied by pneumonia in most cases, it is necessary to expand the surveillance system by including larger number of university hospitals.

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