


MERS-CoV, influenza and other respiratory viruses among symptomatic pilgrims during 2014 Hajj season

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Abstract

More than two million Muslims visit Makkah, Saudi Arabia, annually to perform the religious rituals of Hajj where the risk of spreading respiratory infections is very common. The aim here was to screen symptomatic pilgrims for Middle East respiratory syndrome coronavirus (MERS-CoV) and other viral etiologies. Thus, 132 nasopharyngeal samples were collected from pilgrims presenting with acute respiratory symptoms at the healthcare facilities in the holy sites during the 5 days of the 2014 Hajj season. Samples were tested using real-time reverse transcription polymerase chain reactions and microarray. Demographic data including age, sex, and country of origin were obtained for all participants. While we did not detect MERS-CoV in any of the samples, several other viruses were detected in 50.8% of the cases. Among the detected viruses, 64.2% of the cases were due to a single-virus infection and 35.8% were due to the coinfections with up to four viruses. The most common respiratory virus was influenza A, followed by non-MERS human coronaviruses, rhinoviruses, and influenza B. Together, we found that it was not MERS-CoV but other respiratory viruses that caused acute respiratory symptoms among pilgrims. The observed high prevalence of influenza viruses underscores the need for more effective surveillance during the Hajj and adoption of stringent vaccination requirements from all pilgrims.

KEYWORDS

Hajj, influenza, Middle East respiratory syndrome-coronavirus, respiratory infections, Saudi Arabia, viruses

1 | INTRODUCTION

Hajj is a 5-day pilgrimage to the city of Makkah in Saudi Arabia performed by Muslims at least once during their lifetime. Each year, more than two million Muslims from around the world travel to Saudi Arabia to perform Hajj in the holy city of Makkah. On the first day, pilgrims start the "Tawaf" by circumambulating the "Holy Kaaba" for seven times, then the "Sa'i" by walking between the two hills of Safa and Marwah in the grand mosque, for seven times for a total of 3 km.

Eventually, the pilgrims depart to the tent city of Mina, around 5 km to the east of Makkah, where they spend the night in groups distributed in tents. Upon sunrise of the second day, pilgrims leave to Mount Arafat, where many Muslims ascend the hill of the mount of Mercy and spend the day repenting and praying. At dusk, pilgrims descend from Arafat and arrive in the valley of Muzdalifah where they spend the night in tents and collect small stones for the symbolic stoning of the devil. On the third day, Muslims move to Mina where they stay until the fifth day of Hajj performing the stoning of the devil

at the Jamarat pillars in Mina. Finally, they finish their Hajj ritual by going back to the holy mosque in Makkah to perform "Tawaf".

Overcrowding of individuals in such confined settings leads to inevitable prolonged close contact and increases the risk of spreading and acquiring respiratory pathogens among pilgrims, which raises global and public health concerns due to the high potential of international spread of such pathogens.¹⁻⁴ Another important driver of spreading and acquiring respiratory pathogens during Hajj is the great diversity of inbound viruses from around the world that can potentially spread among the immunologically naive hosts. In fact, acute respiratory infections are very common during Hajj and represent the leading cause of the most hospitalizations.³⁻⁷ It has been suggested that more than one-third of pilgrims will suffer from respiratory symptoms during Hajj mostly due to the respiratory viruses.^{2,7-12} Most commonly isolated viruses from symptomatic patients during Hajj were human rhinoviruses (hRVs), influenza virus and non-MERS human coronaviruses (hCoVs).^{2,9-20}

The emergence of the novel Middle East respiratory syndrome coronavirus (MERS-CoV) in Saudi Arabia, its endemicity, and high mortality rates (35%-40%) clearly represent another major public health concern, especially during Hajj. Since 2012, MERS-CoV caused more than 2250 confirmed cases in 27 countries in the Arabian Peninsula, Africa, Asia, Europe, and North America as of December 2018.^{21,22} Furthermore, multiple hospitals and household outbreaks have been reported mostly in the Saudi Arabia.²³⁻²⁵ More importantly, most global MERS cases were linked to travel to the Arabian peninsula. Although all surveillance studies during Hajj did not reveal any MERS-CoV infection among pilgrims,^{10,16-19,26-31} serological testing showed positivity in one Turkish pilgrim who suffered from severe pneumonia and died upon ICU admission in Turkey.⁶ Similarly, confirmed cases were reported from Dutch pilgrims returning home from the minor pilgrimage "Umrah".³² While these studies suggest that MERS-CoV might not be problematic during Hajj so far, transmission of MERS-CoV is always possible especially during these mass-gathering events which could further lead to global spread. Therefore, MERS-CoV surveillance is highly warranted among pilgrims during and after Hajj. In this study, we performed enhanced surveillance for MERS-CoV and other respiratory viruses among individuals with severe respiratory manifestation who presented to primary healthcare facilities during 2014 Hajj.

2 | MATERIALS AND METHODS

2.1 | Samples

During the 5 days of 2014 Hajj (from 3 to 7 October), a total of 132 nasopharyngeal (NP) swabs were collected from all pilgrims presenting with acute severe respiratory tract symptoms and suspected for MERS-CoV infection at seven healthcare facilities in Makkah, Mina, and Arafat. Demographic data including information on sex, age, and nationality were collected from all patients. All swabs were collected in virus transport media and were immediately used for MERS-CoV testing on site and remaining samples were stored

at -80°C until further testing for other respiratory viruses at the Special Infectious Agents Unit, King Fahd Medical Research Center, and King Abdulaziz University (Jeddah, Saudi Arabia).

2.2 | MERS-CoV detection

RNA extraction was performed using the QIAamp Viral RNA Mini Kit (Qiagen, Hilden, Germany) according to manufacturer's instructions. Extracted RNA from all samples was tested for MERS-CoV using real-time reverse transcription polymerase chain reactions targeting upstream region of the E-gene as described previously.³³ Positive and negative (no template) controls were included in all runs.

2.3 | RVP plus infinity microarray assay

Remaining NP samples were used for complementary DNA (cDNA) synthesis and microarray testing as described previously.³⁴ Nucleic acid was extracted from all samples and used to synthesize cDNA using SuperScript III First-Strand Synthesis SuperMix Kit (Life Technologies, Carlsbad, CA). All samples were then tested for hCoVs (HKU1, OC43, NL63, and 229E), influenza viruses (flu A, flu B, and flu A/H1N1), hRV (A and B), human parainfluenza viruses (hPIV) (1, 2, 3, and 4), human metapneumovirus (hMPV) (A and B), enterovirus (EV) (A, B, C, and D), human adenoviruses (hAdv) (A, B, C, and E), and human respiratory syncytial virus (hRSV) (A and B) using Infinity RVP Plus Assay on Infinity Plus Analyzer (AutoGenomics Inc., Carlsbad, CA) according to manufacturer's instructions and as previously described.³⁴ Samples were considered positive when the ratio between the virus and background signals was above the calculated threshold.

2.4 | Statistical analysis

The data were analyzed using the Statistical Package for the Social Science Software (SPSS v20.0; SPSS Inc, Chicago, IL). The χ^2 and Fisher exact tests were used to compare the proportions and a two-tailed probability value of $P < 0.05$ was considered statistically significant.

3 | RESULTS

A total of 132 pilgrims presented with severe respiratory symptoms at healthcare facilities in the holy sites during 2014 Hajj season were enrolled in this study. The mean age for all participants was 61.85 years (SD = 13.64; range, 26-95 years) with the majority being between 41 and 80 years (Table 1). The total number of males was 88 (66.7%) with the mean age of 62.73 years (SD = 13.85; range, 26-95 years), and the number of females was 44 (33.3%) with the mean age of 60.05 years (SD = 13.19; range, 30-90 years). Of the total patients, 50.8% (67 of 132) tested positive for one or more viruses with males representing 62.7% (42 of 67) of the virally infected patients compared with females who represented 37.3% (25 of 67) (Table 1). As shown in Table 1, although a majority of positive

TABLE 1 Demography of patients with acute respiratory tract infection in Hajj 2014

Variables	Infected, N (%)	Noninfected, N (%)	All subjects, N (%) ^a
Total number	67 (50.8)	65 (49.2)	132
Sex			
Male	42 (47.7)	46 (52.3)	88 (66.7)
Female	25 (56.8)	19 (43.2)	44 (33.3)
Age group, y			
21-40	7 (53.8)	6 (46.2)	13 (9.8)
41-60	19 (46.3)	22 (53.7)	41 (31.1)
61-80	32 (50.8)	31 (49.2)	63 (47.7)
>81	4 (57.1)	3 (42.9)	7 (5.3)
Unknown	5 (62.5)	3 (37.5)	8 (6.1)

^aPercent is shown out of the total subject number.

patients were older than 60 years, this difference was not significant. No statistical significance was found for comparisons of infection rates among males and females or the different age groups. One hundred and twenty-nine of the patients in this study were from 37 countries mostly from Asia and Africa followed by Europe and North America. Nationalities of three individuals were unknown. As expected, viruses were more commonly detected in patients from countries providing the largest number of pilgrims such as India and Indonesia (Figure 1), however, detected viruses were diverse and we

did not observe any specific pattern in circulating viruses in patients from India and Indonesia compared with other countries.

Among those who tested positive, 64.2% (43 of 67) had an infection due to a single respiratory virus compared with 35.8% (24 of 67) who suffered from coinfections with up to four viruses. While MERS-CoV was not detected in any of the tested samples, other viral etiologies were determined (Table 2). The most commonly detected viruses were flu A (27.8%, 27 of 97), hRV A/B (16.5%, 16 of 97), hCoV OC43 (15.5%, 15 of 97), flu B (13.4%, 13 of 97), and hCoV 229E (9.2%, 9 of 97). In single infections, flu A and B were the most frequent followed by non-MERS hCoVs and hRV (Table 2). On the other hand, the most common coinfecting virus was hCoV OC43 with the detection rate of 20.4% (11 of 54) of the coinfecting viruses in which it was detected in 11 out of the 24 coinfecting individuals. This was followed by flu A (18.5%, 10 of 54), hRV A/B (18.5%, 10 of 54), hAdv C/E (9.3%, 5 of 54), hCoV 229E (9.3%, 5 of 54), hRSV A/B (7.4%, 4 of 54), and flu B (7.4%, 4 of 54). The most common coinfections were due to the hCoV OC43 with either flu A or flu B (3 of 24 in each case) followed by flu A with either hAdv C or hRV A (2 of 24 in each case) (Table 3). Coinfections with more than two viruses were not uncommon. In fact, four patients had triple concurrent infections, and one patient had a quadruple concurrent infection (Table 3). The remaining nine coinfections were due to the unique combination of respiratory viruses (Table 3). Not surprisingly, flu A, flu B, and hCoV OC43 were the most frequently detected viruses in the most age groups (Table 3). Patterns of detected respiratory viruses suggest

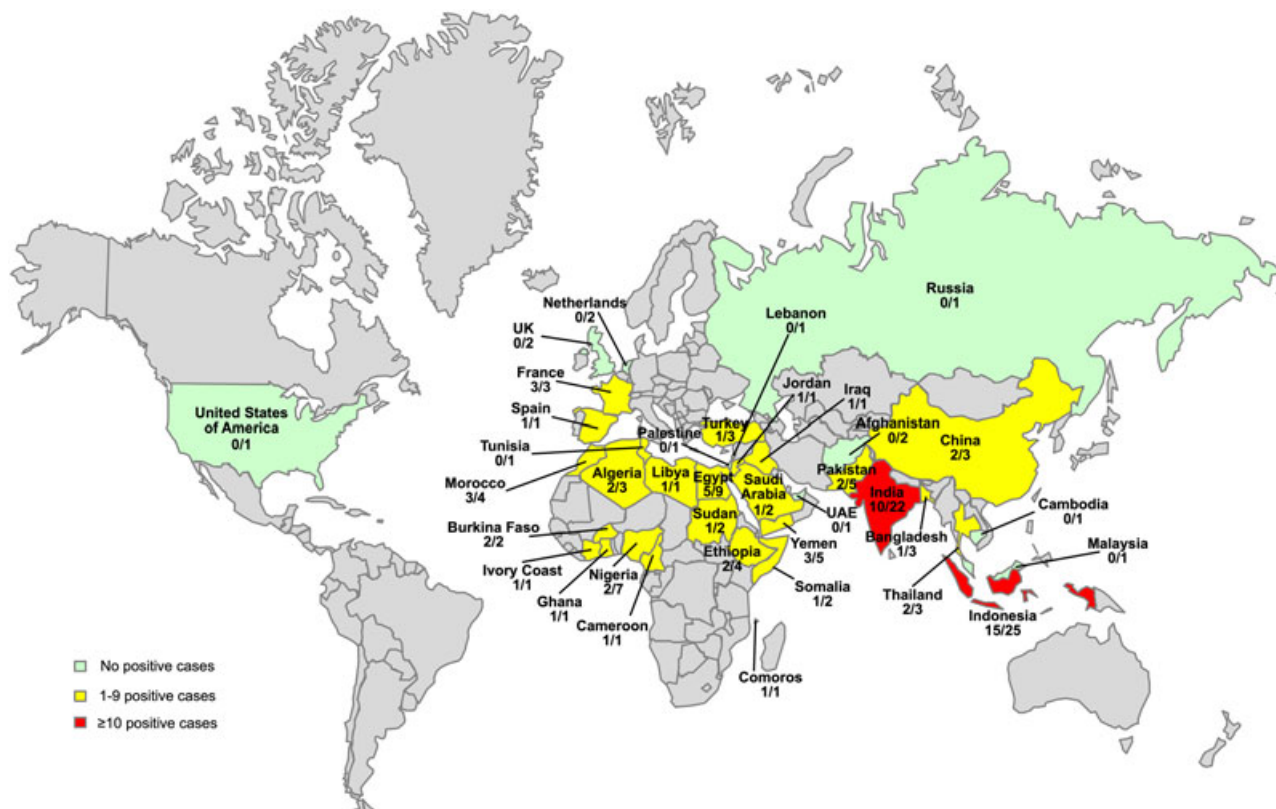
**FIGURE 1** Geographical distribution of infected and noninfected pilgrims according to their country of origin

TABLE 2 Viruses identified in patients with acute respiratory tract infection in Hajj 2014.

Viruses	Single infections, n = 43 N (%)	Coinfections, n = 54 ^a N (%)	All infections, n = 97 ^b N (%)
MERS-CoV	0	0	0
hAdv A	0	0	0
hAdv B	0	0	0
hAdv C	0	4 (7.4)	4 (4.1)
hAdv E	0	1 (1.9)	1 (1.0)
hCoV OC43	4 (9.3)	11 (20.4)	15 (15.5)
hCoV HKU1	0	0	0
hCoV 229E	4 (9.3)	5 (9.3)	9 (9.2)
hCoV NL63	0	1 (1.9)	1 (1.0)
EV A	1 (2.3)	0	1 (1.0)
EV B	0	2 (3.7)	2 (2.1)
EV C	0	0	0
EV D	1 (2.3)	1 (1.9)	2 (2.1)
hRV A	5 (11.6)	7 (13.0)	12 (12.4)
hRV B	1 (2.3)	3 (5.6)	4 (4.1)
Flu A	16 (37.2)	10 (18.5)	26 (26.8)
Flu A H1N1	0	1 (1.9)	1 (1.0)
Flu B	9 (20.9)	4 (7.4)	13 (13.4)
hMPV A	0	0	0
hMPV B	0	0	0
hRSV A	0	1 (1.9)	1 (1.0)
hRSV B	0	3 (5.6)	3 (3.1)
hPIV 1	0	0	0
hPIV 2	0	0	0
hPIV 3	2 (4.7)	0	2 (2.1)
hPIV 4	0	0	0

Abbreviations: EV, enterovirus; hAdv, human adenoviruses; hMPV, human metapneumovirus; hPIV, human parainfluenza viruses; hRSV, human respiratory syncytial virus.

^aCoinfections include all viruses detected from the 19 patients coinfecting with two viruses, four patients coinfecting with three viruses, and one patient coinfecting with four viruses.

^bIncludes all viruses detected in single infections (43) and coinfections (54).

that the most frequently detected viruses in this study such as flu A, flu B, hCoV OC43, and hRV were circulating during almost all the 5 days of Hajj compared with less common viruses such as hPIV 3, hCoV NL63, and EV (Figure 2).

4 | DISCUSSION

MERS-CoV was first recognized in 2012 and has been endemic for more than 6 years in Saudi Arabia. Transmission of MERS-CoV during mass gatherings events such as Hajj or Umrah could lead to

global spread and devastating outcomes as seen in South Korea in 2015. In addition to the current study, the several previous reports from countries such as France, India, Egypt, Saudi Arabia, Ghana, Jordan, China, Austria, the UK, and Iran have shown no record of MERS-CoV infection and/or transmission in pilgrims during Hajj suggesting that it is not MERS-CoV but other respiratory viruses that are responsible for most respiratory infections during Hajj.^{10,16-19,26-31,35} This is also in accordance with the suggestion that MERS-CoV can not be efficiently transmitted outdoors compared with indoor settings such as hospitals and homes where exposure to infectious cases is prolonged.^{7,23-25,36} Nonetheless, at least one report has provided possible serological evidence of MERS-CoV transmission during Hajj,⁶ confirming the need for continuous and effective surveillance in Saudi Arabia and in pilgrims' home countries upon return.

Accumulating evidence suggests higher prevalence and rapid acquisition of respiratory viruses among pilgrims during Hajj compared with their status before departing their home countries.^{11,12,20,37} Indeed, our report as well as others have shown a high prevalence of at least one respiratory virus in more than 50% of symptomatic pilgrims during several Hajj seasons,¹⁷⁻¹⁹ although lower rates were reported in some studies.^{9,10,17,20,29,30,35,37,38} Numerous respiratory viruses including hMPV, hAdv, hPIVs, hRSVs, and EVs are commonly isolated from symptomatic patients during Hajj with hRVs flu and non-MERS hCoVs being the most reported.^{2,9-20,38} Specifically, the several studies from Saudi Arabia, China, France, Egypt, India, Jordan, Ghana, Iran, and the UK have reported higher prevalence of flu (1.3%-20.7%) among pilgrims compared with other viruses with flu A being more common (0.6%-13.9%) than flu B (0.8%-6.8%).^{9,10,16-18,27,29,30,35,38} They also showed high rates of hAdv (0.8%-23.7%), hRVs (5.9%-16.8%), non-MERS hCoVs (0.4%-12.8%), hPIVs (0.8%-7.4%), hRSVs (0.2%-7.4%), and EVs (2.0%).^{9,10,16-18,37,38} In contrast, our current study showed flu A as the most predominant virus among symptomatic pilgrims in 2014 Hajj (27.8%) followed by non-MERS hCoVs (25.7%), hRVs (16.5%), flu B (13.4%), EVs (5.2%), hAdv (5.1%), hRSVs (4.1%), and hPIVs (2.1%). Among the non-MERS hCoVs, hCoV OC43 was detected in 15 patients compared with hCoV NL63 and hCoV 229E, which were detected once and nine times, respectively.

Coinfections with multiple viruses in symptomatic pilgrims were very common in our study and represented more than 35% of the positive cases and more than 18% of the total number of patients. This rate is markedly higher than the previously reported.^{10-13,17,18,38} Furthermore, while most of these reports have identified hRVs as the most coinfecting viruses during Hajj, our data showed hCoV OC43 as the most prevalent coinfecting virus followed by flu A and hRVs.^{10-13,17,18,38} These marked differences most probably were due to technical and methodological differences. However, it is clear that enhanced surveillance using detection assays with high sensitivity and coverage such as microarray and multiplex PCR could enhance our understanding of pathogens involved in respiratory infections during mass gatherings and ultimately lead to better infection control.

TABLE 3 Demographic data of patients with acute respiratory tract infection by pathogens identified in Hajj 2014

Infecting viruses	Number of patients (n = 67)	Age, y, N (%)					Sex N (%)	
		21-40 (n = 7)	41-60 (n = 19)	61-80 (n = 32)	>81 (n = 4)	Unknown (n = 5)	Male (n = 42)	Female (n = 25)
hCoV OC43	4 (6.0)	0	1 (25.0)	2 (50.0)	1 (25.0)	0	2 (50.0)	2 (50.0)
hCoV 229E	4 (6.0)	1 (25.0)	0	3 (75.0)	0	0	3 (75.0)	1 (25.0)
EV A	1 (1.5)	0	0	1 (100)	0	0	1 (100)	0
EV D	1 (1.5)	1 (100)	0	0	0	0	1 (100)	0
hRV A	5 (7.5)	0	2 (40.0)	2 (40.0)	0	1 (20.0)	3 (60.0)	2 (40.0)
hRV B	1 (1.5)	0	0	1 (100)	0	0	1 100	0
Flu A	16 (23.9)	3 (18.7)	7 (43.7)	4 (25.0)	1 (6.3)	1 (6.3)	10 (62.5)	6 (37.5)
Flu B	9 (13.4)	1 (11.1)	3 (33.3)	4 (44.4)	0	1 (11.1)	7 (77.8)	2 (22.2)
hPIV 3	2 (3.0)	0	0	1 (50.0)	0	1 (50.0)	1 (50.0)	1 (50.0)
Flu A + hRSV A	1 (1.5)	0	0	1 (100)	0	0	1 (100)	0
Flu A + hAdV C	2 (3.0)	0	1 (50.0)	1 (50.0)	0	0	1 (50.0)	1 (50.0)
Flu A + hRV A	2 (3.0)	0	1 (50.0)	0	1 (50.0)	0	1 (50.0)	1 (50.0)
Flu A + hCoV 229E	1 (1.5)	0	0	1 (100)	0	0	1 (100)	0
hCoV OC43 + hAdV C	1 (1.5)	0	1 (100)	0	0	0	0	1 (100)
hCoV OC43 + flu A	3 (4.5)	0	0	1 (33.3)	1 (33.3)	1 (33.3)	2 (66.7)	1 (33.3)
hCoV OC43 + flu B	3 (4.5)	0	1 (33.3)	2 (66.7)	0	0	1 (33.3)	2 (66.7)
hCoV OC43 + hRV A	1 (1.5)	0	0	1 (100)	0	0	1 (100)	0
hCoV OC43 + hRV B	1 (1.5)	0	1 (100)	0	0	0	1 (100)	0
hCoV 229E + hRV B	1 (1.5)	0	0	1 (100)	0	0	0	1 (100)
hCoV NL63 + hRV A	1 (1.5)	0	0	1 (100)	0	0	1 (100)	0
EV B + EV D	1 (1.5)	1 (100)	0	0	0	0	1 (100)	0
Flu A H1N1 + hAdV E	1 (1.5)	0	1 (100)	0	0	0	1 (100)	0
hCoV OC43 + hRV A + hRSV B	1 (1.5)	0	0	1 (100)	0	0	0	1 (100)
hCoV OC43 + hCoV 229E + flu B	1 (1.5)	0	0	1 (100)	0	0	1 (100)	0
EV B + hRV A + hRSV B	1 (1.5)	0	0	1 (100)	0	0	0	1 (100)
hCoV 229E + hRV A + hRV B	1 (1.5)	0	0	1 (100)	0	0	0	1 (100)
hCoV 229E + hRSV B + hAdV C + flu A	1 (1.5)	0	0	1 (100)	0	0	0	1 (100)

Abbreviations: EV, enterovirus; hAdv, human adenoviruses; hCoVs, human coronaviruses; hPIV, human parainfluenza viruses; hRSV, human respiratory syncytial virus.

Most Hajj pilgrims are usually old adults and elderly representing a high-risk group for influenza infection especially with the apparent high prevalence of influenza viruses during Hajj. These individuals are more susceptible to influenza viruses and prone to develop severe diseases. While seasonal influenza vaccination is recommended for all pilgrims, current Hajj regulations and guidelines for influenza vaccination require usage of seasonal trivalent vaccine formulation recommended for people younger than 65 years. These vaccines are known to be less immunogenic and less effective in the elderly compared with younger adults. In addition, the several studies have shown low vaccination coverage among pilgrims attending multiple Hajj seasons.^{9,13,20,26,29,30,39} Furthermore, detection of influenza viruses is not uncommon among vaccinated individuals during Hajj or in returning pilgrims,

mostly due to a possible mismatch between circulating and vaccine strains.^{10-16,26,29,30,38,40-42} Therefore, it is highly suggested to implement and adopt new influenza immunization guidelines for Hajj to improve vaccine coverage and to provide sufficient protection against influenza. Possible changes could include the use of quadrivalent influenza vaccines, high-dose vaccines for people older than 65 years and/or inclusion of both influenza vaccines from the northern and southern hemispheres for people younger than 65 years, especially if the two vaccines are different. Moreover, it might be beneficial to enhance human influenza surveillance during Hajj by including genetic and antigenic characterization of circulating strains to ensure strain match and to anticipate any potential early introduction of influenza viruses into Saudi Arabia. Furthermore, it is suggested that countries with

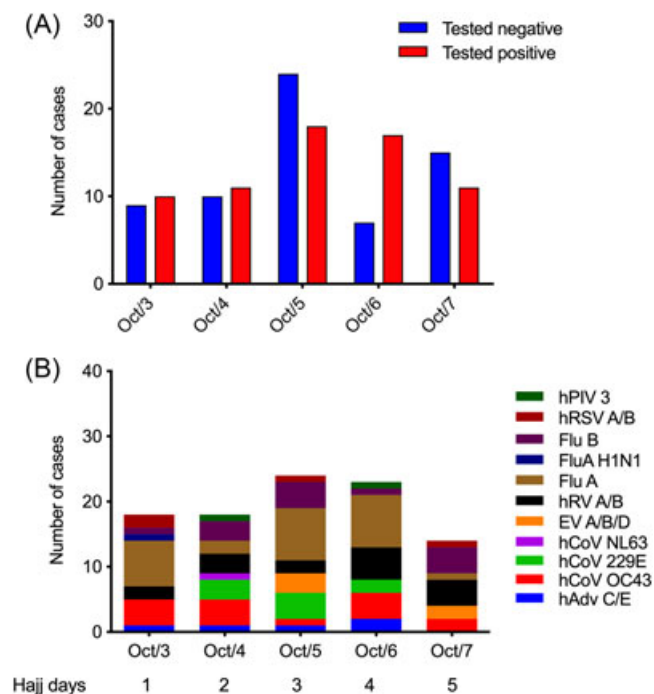


FIGURE 2 Patterns of reported respiratory symptoms and detected respiratory viruses during Hajj days. A, Bar graph showing the number of pilgrims presented with respiratory symptoms and tested for respiratory viruses with numbers of those tested positive or negative for any virus during daily. B, Bar graph showing the number of viruses detected from positive cases during the 5 days of Hajj. Day 1, Makkah then Mina in the afternoon; day 2, Arafat in the morning then Muzdalifah at night; day 3, Muzdalifah then Mina in the morning; day 4, Mina, Makkah then Mina; and day 5, Mina

pilgrims returning from Saudi Arabia enhance their surveillance for influenza viruses.

This study is presented with potential limitations. First, the use of upper respiratory samples, NP swabs, for MERS-CoV detection may have led to missed MERS cases since they have lower viral load than that in lower respiratory specimens.⁴³ However, NP swabs were used because of their easy collection and acceptance by pilgrims compared with bronchoalveolar lavages or tracheal aspirates, especially if there is no clinical indication. Second, it is possible that some MERS cases were also missed due to the asymptomatic infections or mild clinical symptoms. Therefore, larger sampling from pilgrims and their contacts as well as further testing for seroconversion might be used in future studies. Another limitation is that the microarray assay used in this study does not test for bacteria, which have been shown to represent a significant part of etiologies of respiratory illness during Hajj,^{12,19} or hRV C, which could represent a significant number of potential rhinovirus infections among symptomatic pilgrim.

5 | CONCLUSIONS

In conclusion, we investigated the etiology of acute respiratory infections in symptomatic pilgrims attending 2014 Hajj. While MERS-

CoV was not detected in any of the patients, a variety of other respiratory viruses has been found in more than half of the patients with many coinfections with multiple viruses. Our observation as well as the previous reports from Hajj indicate that enhanced and active surveillance during Hajj seasons is critical to recognize the wide variety of pathogens that might be involved in Hajj epidemics and to implement proper infection control measures. Importantly, there is an evident risk of influenza infection among pilgrims underscoring the need for targeted, active and continuous surveillance for influenza viruses not only to monitor viral circulation but also to characterize circulating viruses to better understand vaccine effectiveness and to recognize the need to improve current influenza vaccination strategies during Hajj.

CONFLICT OF INTERESTS

The authors declared that there is no conflict of interests.

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