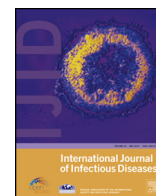




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Etiology of severe community-acquired pneumonia during the 2013 Hajj—part of the MERS-CoV surveillance program



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SUMMARY

Background: Pneumonia is the leading cause of hospital admission during the annual Islamic pilgrimage (Hajj). The etiology of severe pneumonia is complex and includes the newly emerged Middle East respiratory syndrome coronavirus (MERS-CoV). Since 2012, the Saudi Ministry of Health (MoH) has required screening for MERS-CoV for all cases of severe pneumonia requiring hospitalization. We aimed to screen Hajj pilgrims admitted to healthcare facilities in 2013 with severe community-acquired pneumonia (CAP) for MERS-CoV and to determine other etiologies.

Methods: Sputum samples were collected from all pilgrims admitted to 15 healthcare facilities in the cities of Makkah and Medina, Saudi Arabia, who were diagnosed with severe CAP on admission, presenting with bilateral pneumonia. The medical records were reviewed to collect information on age, gender, nationality, and patient outcome. Samples were screened for MERS-CoV by PCR, and a respiratory multiplex array was used to detect up to 22 other viral and bacterial respiratory pathogens. **Results:** Thirty-eight patients met the inclusion criteria; they were predominantly elderly (mean age 58.6 years, range 25–83 years) and male (68.4%), and all were from developing countries. Fourteen of the 38 patients died (36.8%). MERS-CoV was not detected in any of the samples. Other respiratory pathogens were detected in 26 (68.4%) samples. Of these, bacterial pathogens were detected in 84.6% (22/26) and viruses in 80.7% (21/26). Twenty-one (80.7%) samples were positive for more than one respiratory pathogen and 17 (65.3%) were positive for both bacteria and viruses. The most common respiratory virus was human rhinovirus, detected in 57.7% of the positive samples, followed by influenza A virus (23.1%) and human coronaviruses (19.2%). *Haemophilus influenzae* and *Streptococcus pneumoniae* were the predominant bacteria, detected in 57.7% and 53.8%, respectively, of the positive samples, followed by *Moraxella catarrhalis* (36.4%).

Conclusions: MERS-CoV was not the cause of severe CAP in any of the hospitalized pilgrims investigated. However we identified a variety of other respiratory pathogens in the sputum of this small number of patients. This indicates that the etiology of severe CAP in Hajj is complex with implications regarding its management.

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1. Introduction

Pneumonia is the leading cause of hospital admission during the annual Islamic pilgrimage (Hajj), including admission to intensive care units (ICUs), and is a major cause of severe sepsis

and septic shock in ICUs during this mass-gathering.^{1–4} Studies from seven hospitals in the Hajj premises (Mina and Arafat) reported that pneumonia accounted for 19.7% of all hospital admissions during the 2003 Hajj and 22% of ICU admissions during the 2004 season.^{1,2} The incidence of pneumonia during Hajj is also increasing. The reported incidence among Iranian pilgrims at Hajj was 24 per 10 000 in 2004 and 34 per 10 000 in 2005, which represents a greater than 50-fold increase compared with the 1986 data.^{5,6}

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Severe community-acquired pneumonia (CAP) is not uncommon during Hajj. Mandourah and colleagues investigated all critically ill patients, who were of over 40 nationalities, admitted to 15 hospitals in two cities in the 2009 and 2010 Hajj seasons.³ Pneumonia was the primary cause of critical illness in 27.2% (123 cases) of all ICU admissions and occurred most commonly in the second week of Hajj, corresponding to the period of greatest pilgrim density. Severe CAP accounted for 18.1% of all ICU admissions.

Worldwide, pneumonia is a common illness that is potentially life-threatening, especially in older adults and those with comorbid diseases.^{7,8} The etiology of pneumonia differs between and within countries depending on regional differences in prevalence and types of microorganism, and other factors such as the frequency of use of antibiotics, environmental pollution, awareness of the disease, and life-expectancy of the population.⁹ The etiology may also differ depending on whether the pneumonia is community- or hospital-acquired.^{7,8} In this context, the Hajj is a special case as it brings a large number of people, many elderly with underlying diseases, from various regions of the world, into close proximity to perform physically exhausting religious rights. These factors, combined with the common use of antibiotics among pilgrims, make the etiology of pneumonia during Hajj complex, and hence standard guidelines for the management of the disease may not always work during this mass-gathering event.

Although many pathogens have been associated with pneumonia, a small range of key pathogens are usually the cause of most cases.^{7,10} In recent years, the Middle East respiratory syndrome coronavirus (MERS-CoV) has also emerged as a cause of serious illness including severe pneumonia.¹¹ Since the first reported case of MERS in Saudi Arabia in 2012,¹² the Saudi Ministry of Health (MoH) has set up an ongoing MERS-CoV surveillance system. As part of this surveillance, it is required that all cases of severe CAP with bilateral pneumonia requiring hospitalization are investigated for MERS-CoV.

Hence, we used molecular techniques to screen the sputum of Hajj pilgrims diagnosed with severe CAP requiring hospitalization in 2013 for the presence of MERS-CoV. Other etiologies were also investigated using a respiratory multiplex array to detect bacterial and viral respiratory pathogens.

2. Methods

2.1. Patient population

All pilgrims attending the 2013 Hajj who were admitted to 15 healthcare facilities in the cities of Makkah and Medina, Saudi Arabia, and diagnosed on admission with bilateral pneumonia, were included in the study. The medical records of the patients were reviewed to collect information on age, gender, nationality, and patient outcome.

2.2. Sputum sample collection and storage

During the period 26 September to 2 November 2013, sputum samples were collected from each patient on admission, prior to any antibiotic therapy. Samples were kept refrigerated until processing.

2.3. Nucleic acid extraction and detection of MERS-CoV in sputum samples

MERS-CoV was detected in the samples using reverse transcriptase polymerase chain reactions (RT-PCR) targeting the region upstream of the E gene (*upE*) and the open reading frame (ORF) 1a (*nsp6* protein), as described previously.^{13,14} Briefly, nucleic acid was purified from a 200- μ l volume of sample using the Magna

Pure LC Nucleic Acid Extraction Kit (Roche, IN, USA). Each sample was independently tested with the two RT-PCR assays in a 25- μ l reaction containing 5 μ l of RNA, 12.5 μ l of 2X buffer (SuperScript III one-Step RT-PCR with Platinum Taq (Invitrogen, NY, USA)), 0.4 μ l of MgCl₂ (50 mM), 1 μ l of forward primer (10 μ M), 1 μ l of reverse primer (10 μ M), 1 μ l of probe (5 μ M), 3.1 μ l RNAse free H₂O₂, and 1 μ l of SSIII/Platinum Taq enzyme mix (1 U). The RT-PCR reactions were performed in a Real Time LC 480 machine (Roche, IN, USA) under the following cycling profile: one cycle of 55 °C for 20 min, followed by one cycle of 94 °C for 3 min then 45 cycles of 94 °C for 15 s, 45 cycles of 58 °C for 30 s, and a single cycle of 40 °C for 30 s. A sample was confirmed MERS-CoV-positive if both RT-PCR assays were positive, as per current recommendations.¹⁴

2.4. Nucleic acid extraction and detection of other respiratory pathogens in sputum samples

Nucleic acid was extracted from the samples using the MinElute Virus Spin Kit (Qiagen, Manchester, UK) following the manufacturer's instructions and eluted in 50 μ l nuclease-free water. A 5- μ l aliquot of each of the nucleic acid extractions was run on the respiratory multiplex array (Randox, Crumlin, UK), which is capable of detecting 22 bacterial and viral respiratory pathogens simultaneously. These are influenza virus A and B, human respiratory syncytial virus A and B, human parainfluenza virus 1, 2, 3 and 4, human coronavirus 229E/NL63 and OC43/HKU1, human rhinovirus A/B, human enterovirus A/B/C, human adenovirus A/B/C/D/E, human bocavirus 1/2/3, human metapneumovirus, *Chlamydomydia pneumoniae*, *Legionella pneumophila*, *Haemophilus influenzae*, *Bordetella pertussis*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Mycoplasma pneumoniae*.

3. Results

We collected sputum samples from all pilgrims hospitalized in 15 hospitals of two cities in Saudi Arabia who were diagnosed with severe CAP during the 2013 Hajj season. Thirty-eight patients fulfilled the inclusion criteria; they were predominantly elderly (mean age 58.6 years, range 25–83 years) and male (68.4%). All patients were from developing countries, the majority of whom (78.3%) were from Asia. The nationalities most represented were Indonesia (32.4%), Pakistan (18.9%), and India (10.8%). Of the 38 patients, 30 (78.9%) required ICU admission. Fourteen (36.8%) patients died, while the remaining patients recovered and were discharged. The mortality rate among those admitted to the ICUs was 46.6%.

MERS-CoV was not detected in any of the sputum samples. Other respiratory pathogens were detected in 26 (68.4%) of the 38 samples, while the remaining samples were negative for the 22 respiratory pathogens in the testing panel (Table 1). Of the positive samples, bacterial pathogens were detected in 84.6% (22/26) and viruses in 80.7% (21/26). Twenty-one (80.7%) samples were positive for more than one respiratory pathogen and 17 (65.3%) were positive for both bacteria and viruses.

The most common respiratory virus was human rhinovirus, which was detected in 57.7% of the positive samples, followed by influenza A virus (23.1%) and human coronaviruses (19.2%). *H. influenzae* and *S. pneumoniae* were the predominant bacteria, detected in 57.7% and 53.8%, respectively, of the positive samples, followed by *M. catarrhalis* (36.4%).

4. Discussion

Respiratory tract infections are common illnesses during the Hajj,¹⁵ and pneumonia is the leading cause of hospital admission, including admission to the ICU, during the pilgrimage.^{1–4,16} For instance, a study of hospital admissions in Makkah and Mina

Table 1
Characteristics of patients with bilateral pneumonia during the 2013 Hajj and respiratory pathogens detected in their sputum

Patient	Age, years	Gender	Patient outcome	MERS-CoV in sputum	Respiratory pathogens detected in sputum	
					Viruses	Bacteria
1	51	Male	Died	Negative	HRV	
2	67	Female	Died	Negative	HRV	SP
3	70	Male	Died	Negative	PIV3, OC43	HI, MC, SP
4	58	Male	Died	Negative	HRV	
5	75	Female	Recovered	Negative	HRV, 229E	HI, MC, SP
6	75	Male	Died	Negative	HRV, 229E, RSV-B	HI, SP, BP
7	67	Male	Died	Negative		HI, SP
8	55	Male	Recovered	Negative	HRV	HI, MC
9	66	Female	Recovered	Negative	HRV	MC
10	72	Female	Recovered	Negative	HRV	HI, MC
11	67	Male	Recovered	Negative	FLU-A	MC
12	65	Male	Recovered	Negative	HRV	HI, MC, SP
13	59	Male	Died	Negative	FLU-A, 229E	HI, SP
14	64	Male	Recovered	Negative	HRV	SP
15	59	Male	Died	Negative	FLU-A	MC, SP
16	55	Female	Died	Negative	FLU-A	HI, MC, SP
17	70	Male	Died	Negative	HRV, FLU-A	HI
18	60	Male	Died	Negative	HRV, FLU-A	HI, MC
19	57	Male	Recovered	Negative	OC43	
20	50	Male	Recovered	Negative		SP
21	55	Male	Recovered	Negative		HI, SP
22	61	Male	Recovered	Negative	HRV	HI
23	79	Male	Recovered	Negative	HRV	
24	72	Male	Recovered	Negative		HI
25	54	Male	Recovered	Negative		HI, SP
26	60	Male	Recovered	Negative	HRV	SP
27	83	Female	Died	Negative	Negative	Negative
28	50	Male	Died	Negative	Negative	Negative
29	70	Male	Died	Negative	Negative	Negative
30	42	Male	Recovered	Negative	Negative	Negative
31	-	Female	Recovered	Negative	Negative	Negative
32	25	Female	Recovered	Negative	Negative	Negative
33	26	Female	Recovered	Negative	Negative	Negative
34	27	Female	Recovered	Negative	Negative	Negative
35	58	Male	Recovered	Negative	Negative	Negative
36	25	Female	Recovered	Negative	Negative	Negative
37	72	Male	Recovered	Negative	Negative	Negative
38	50	Female	Recovered	Negative	Negative	Negative

MERS-CoV, Middle East respiratory syndrome coronavirus; HRV, human rhinovirus A/B/C; FLU-A, influenza A virus; PIV3, human parainfluenza virus 3; OC43, human coronavirus OC43/HKU1; 229E, human coronavirus 229E/NL63; RSV-B, human respiratory syncytial virus B; HI, *Haemophilus influenzae*; MC, *Moraxella catarrhalis*; SP, *Streptococcus pneumoniae*; BP, *Bordetella pertussis*.

during the 2002 Hajj reported that 39% of hospitalizations were for pneumonia.¹⁶

In the current study, as part of the Saudi MoH MERS-CoV surveillance, we investigated the etiology of severe CAP in pilgrims attending the 2013 Hajj requiring hospitalization. Most of the 38 patients were elderly, with a large proportion of males, and all were from developing countries. These observations are similar to those of previous reports investigating pneumonia during Hajj.^{17,18} For example, Alzeer and colleagues investigated 64 patients admitted with pneumonia to hospitals in the 1994 Hajj season.¹⁷ Nearly all patients were from developing countries; their mean age was 63 years (range 21–91 years) and 75% were males.

The overall mortality rate among the patients we investigated was 36.8%, and among those admitted to ICUs was 46.6%. Internationally, the reported mortality of patients with severe CAP requiring ICU admission is over 30% and the long-term mortality of CAP is between 35.8% and 39.1% at 5 years.^{8,19,20} Our results are in agreement with these figures. A few investigations have reported the mortality rates from pneumonia during Hajj. One study⁵ during the 1986 Hajj season reported a pneumonia case fatality rate of 34%, while another¹⁷ reported a mortality rate of 17% among 64 patients admitted to hospitals in the 1994 Hajj season. Mandourah and colleagues investigated severe pneumonia during the 2009 and 2010 Hajj seasons.³ Pneumonia was

community (Hajj)-acquired in 66.7% of cases and the overall short-term mortality (during the 3 weeks of Hajj) was 19.5%.

Most patients with diagnosed CAP are treated empirically and the role of microbiological testing for patients with CAP is still a matter of debate.⁷ However there is a clear rationale for establishing the causative agent to allow the optimal selection of agents against a specific pathogen and to limit the misuse of antibiotics and its consequences; it is also important to identify pathogens associated with notifiable diseases such as Legionnaires' disease and tuberculosis.²¹ The possible involvement of MERS-CoV is an additional, current, reason. Knowledge of the etiological agent of pneumonia-related illness is a challenging step in the management of pneumonia in Hajj.^{1–3,17} In general, the identification of the etiology of CAP remains difficult in any setting despite advances in microbiological and serological methods. Molecular diagnostic tests for common and atypical causative pathogens of CAP are now available and have increased the diagnostic yield and decreased the time required to render results dramatically.^{22–24}

Although many pathogens have been associated with CAP, a small range of key pathogens are the cause of most cases. Internationally, the predominant pathogen in CAP is *S. pneumoniae*.^{7,10} Other causative agents include, but are not limited to, *H. influenzae*, *M. pneumoniae*, *C. pneumoniae*, *Legionella spp*, *Chlamydia psittaci*, *Coxiella burnetii*, enteric Gram-negative bacteria

(Enterobacteriaceae), *Pseudomonas aeruginosa*, *Staphylococcus aureus*, anaerobes, and respiratory viruses (influenza virus, adenovirus, respiratory syncytial virus, parainfluenza virus, coronavirus).^{7,8} The frequencies of other causes, such as *Mycobacterium tuberculosis*, *C. psittaci*, *C. burnetii*, *Francisella tularensis*, and endemic fungi (histoplasmosis, coccidioidomycosis, blastomycosis) vary between epidemiological settings.⁷ Recently, MERS-CoV has also emerged as a cause of serious illnesses including pneumonia and is the subject of worldwide concern.¹¹

The primary objective of the study was to determine if MERS-CoV was the cause of the severe pneumonia in the hospitalized patients. Our results indicate that MERS-CoV was not the etiological agent of the illness. These results support previous reports suggesting that MERS-CoV has not so far been problematic during Hajj. A study conducted during the 2013 Hajj, the same year as our study, found no evidence of MERS-CoV nasal carriage among 5235 Hajj pilgrims screened. Two reports on French pilgrims during the 2012 and 2013 Hajj seasons also reported a lack of MERS-CoV nasal carriage among the pilgrims screened despite a high rate of respiratory symptoms.^{25,26}

We found *S. pneumoniae* to be prevalent in the sputum samples. This is in accordance with many international reports.^{7,10} Studies performed during previous Hajj seasons have reported the organism as a cause of respiratory tract infections including pneumonia.^{3,17,18} For example, among 395 sputum samples collected from Hajjis with respiratory tract infections in 1991 and 1992, *S. pneumoniae* was detected in 4.8% and 12.3%, respectively.²⁷ Among the 64 patients with pneumonia admitted to two tertiary hospitals in Makkah during the 1994 Hajj, *S. pneumoniae* was detected in 9.4% of the cases.¹⁷ A more recent study reported that 5.4% of sputum samples collected in Makkah hospitals during the 2005 Hajj contained *S. pneumoniae*,¹⁸ while 10% of sputum samples from patients with severe pneumonia during the 2009 and 2010 Hajj contained *Streptococcus sp.*³

In addition to *S. pneumoniae*, other common pathogens identified in our sputum samples were *H. influenzae*, *M. catarrhalis*, and viral agents, in particular human rhinovirus, influenza A virus, and human coronaviruses. Studies from the Gulf Corporation Council (GCC) states have found similar results. The common pathogens causing CAP in GCC states were found to be *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*.^{28,29} In addition, the importance of atypical pathogens including *M. pneumoniae*, *C. pneumoniae*, and *L. pneumophila* in the etiology of CAP in the GCC region has been documented.²⁸ Other etiologies, particularly influenza viruses, varicella zoster virus, and *M. tuberculosis*, are increasingly recognized as causative pathogens of CAP within the region.²⁸

In the context of Hajj, in addition to *S. pneumoniae*, a number of other organisms have been reported as the cause of pneumonia. These include influenza A (H1N1),³ *M. tuberculosis*,^{1,3,17,18} *S. aureus*,³ fungi such as *Candida albicans*,^{3,18} and Gram-negative organisms including *P. aeruginosa*, *L. pneumophila*, *Acinetobacter sp.*, and members of the Enterobacteriaceae family.^{3,17,18} Some, however, have dismissed many of these organisms as more likely to be respiratory tract colonizers rather than the causative agents.³⁰

In our study, respiratory pathogens were detected in 68.4% of sputum samples (26/38) and 80.7% (21/26) of these were positive for more than one pathogen. This is a higher proportion than that reported previously by Asghar et al., who isolated more than one pathogen in only 16.3% of the samples from 76 patients with confirmed CAP in the 2005 Hajj.¹⁸ In another study, a higher percentage (35%) was reported.²⁴ The differences in detection rates may reflect the differences in identification methods used in the various studies.

Our study has some limitations. In addition to MERS-CoV, our test panel detects a specific set of 22 bacterial and viral respiratory pathogens. This means that other respiratory pathogens including fungi and other viruses and bacteria not included in the panel could have been missed. This may be of importance, as organisms not included in the panel such as *M. tuberculosis*, Enterobacteriaceae, *P. aeruginosa*, and fungi, have been reported as causative agents of pneumonia during Hajj.^{3,17,18} Also, we only used sputum samples for identification, and no microbiological investigations of other samples (e.g. blood) were performed to confirm the cause of pneumonia. Finally, some of the organisms identified may have been respiratory tract colonizers and not the causative agents. In this context, a strength of our study is that the sputum samples were obtained on admission and before the start of antibiotic therapy. Collecting sputum samples after the start of antibiotic treatment would have been of little value as it would have detected mainly respiratory tract colonizers.

In conclusion, we investigated the etiology of severe CAP in 38 hospitalized Hajj pilgrims. MERS-CoV was not the cause of pneumonia in any of the patients. However, we detected a variety of pathogens in sputum samples of the patients, with most samples containing more than one agent. This observation, along with previous reports on CAP in Hajj, indicates that typical pneumonia treatment regimens may not work well during the Hajj season due to the wide variety of organisms that may be involved. This may necessitate more active investigations into the causes of pneumonia for identification and sensitivity testing in order to provide optimal treatment and a good outcome. Molecular methods can be a quick and sensitive means to determine the possible causative agents. Pneumonia is a significant illness during Hajj and interventions to reduce its burden during the pilgrimage should be adopted. Measures to reduce respiratory tract infections during Hajj are already in place.³¹ Other strategies may include improved respiratory tract infection surveillance and optimization and dissemination of recommendations for adult vaccination.^{32,33} Continuous surveillance for MERS-CoV during Hajj and outside the pilgrimage season is crucial to monitor the MERS-CoV situation in Saudi Arabia.

Conflict of interest: No conflict of interest to declare.

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