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Proportion of adult community-acquired pneumonia cases attributable to *Streptococcus pneumoniae* among Hajj pilgrims in 2016



Ali AlBarrak^a, Badriah Alotaibi^b, Yara Yassin^b, Abdulaziz Mushi^b, Fuad Maashi^b, Yassein Seedahmed^c, Mohamed Alshaer^c, Abdulaziz Altaweel^d, Husameddin Elshiekh^e, Abdulhafiz Turkistani^f, Tanaz Petigara^g, John Grabenstein^g, Saber Yezli^{b,*}

^a Prince Sultan Military Medical City, Riyadh, Saudi Arabia

^b Global Centre for Mass Gatherings Medicine, Ministry of Health, Riyadh, Saudi Arabia

^c General Directorate of Health Affairs in Makkah Region, Makkah, Saudi Arabia

^d King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia

^e General Directorate of Health Affairs in Medina Region, Medina, Saudi Arabia

^f Holy Makkah Municipality, Makkah, Saudi Arabia

^g Merck & Co., Inc., Kenilworth, NJ, USA

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ABSTRACT

Background: The Hajj mass gathering is a risk for pneumococcal disease. This study was performed to evaluate the proportion of adult community-acquired pneumonia (CAP) cases attributable to *Streptococcus pneumoniae* among Hajj pilgrims in 2016. To add sensitivity to etiological attribution, a urine antigen test was used in addition to culture-based methods.

Methods: Adult subjects hospitalized with X-ray-confirmed CAP were enrolled prospectively from all general hospitals designated to treat Hajj pilgrims in the holy cities of Mecca and Medina. Patients were treated according to local standard of care and administered the BinaxNow *S. pneumoniae* urine antigen test.

Results: From August 23 to September 23, 2016, a total of 266 patients with CAP were enrolled in the study, 70.6% of whom were admitted to hospitals in Mecca; 53% of the cases were admitted after the peak of Hajj. Patients originated from 43 countries. Their mean age was 65.3 years and the male to female ratio was 2:1. Just over 36% of the cases had diabetes, 10% declared that they were smokers, and 45.4% of cases were treated in the intensive care unit (ICU). The overall case-fatality rate was 10.1%, but was higher among those treated in the ICU and in those with invasive disease. The proportion of CAP cases positive for *S. pneumoniae*, based on culture or urine antigen test, was 18.0% (95% confidence interval 13.9–23.1%). **Conclusions:** CAP during Hajj has an important clinical impact. A proportion of CAP cases among Hajj pilgrims were attributable to *S. pneumoniae*, a pathogen for which vaccines are available. Additional studies to determine the serotypes causing pneumococcal disease could further inform vaccine policy for Hajj pilgrims.

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Introduction

The Hajj religious mass gathering hosted by the Kingdom of Saudi Arabia (KSA) is attended by millions of Muslims annually from all over the globe (Yezli et al., 2017). The event can facilitate the acquisition and transmission of infectious agents, including those responsible for respiratory tract infection, and has been

linked to both local and international outbreaks of diseases (Ahmed et al., 2006; Memish et al., 2015a,b; Yezli et al., 2016a). Examples include meningococcal disease and influenza (Salmon-Rousseau et al., 2016; Yezli et al., 2016a). Experience from Hajj shows that the implementation of appropriate prevention measures such as vaccination can significantly reduce the incidence of disease and outbreaks associated with this mass gathering. Of note is the prevention of meningococcal disease outbreaks since 2001, after the introduction of compulsory vaccination with the quadrivalent meningococcal vaccine and targeted chemoprophylaxis (Yezli et al., 2016b).

* Corresponding author.

E-mail address: SYezli@moh.gov.sa (S. Yezli).

Streptococcus pneumoniae is a common cause of pneumonia and an important cause of morbidity and mortality worldwide (Feldman and Anderson, 2016; Varon et al., 2010). Hajj presents many risk factors for pneumococcal disease acquisition and transmission. Many pilgrims are elderly with pre-existing underlying health conditions and worship under crowded conditions that promote respiratory disease transmission and infection (Al-Tawfiq and Memish, 2016). Crowding in particular has been associated with pneumococcal disease outbreaks (Banerjee et al., 2005; Mercat et al., 1991). The acquisition and transmission of *S. pneumoniae* is well documented during Hajj, independent of clinical status (Memish et al., 2016, 2015a), and the organism is a leading cause of pneumonia-related hospitalizations and intensive care unit (ICU) admissions during the event (Al-Tawfiq and Memish, 2016; Memish et al., 2014).

Vaccines against pneumococcal disease are available and are recommended for those at risk (such as the elderly and those with underlying health conditions) in many countries, including countries in the Gulf states such as Bahrain, Kuwait, Oman, Qatar, and the United Arab Emirates (Feldman et al., 2013; Tomczyk et al., 2014). The Saudi Thoracic Society has also recently published guidelines on pneumococcal vaccination for Hajj pilgrims (Alharbi et al., 2016). However, there is no official KSA recommendation for vaccination for Hajj pilgrims (Saudi Ministry of Health, 2017).

Appropriate evidence-based policies regarding vaccination for pilgrims require a better understanding of the clinical burden of the disease associated with the event (Al-Tawfiq and Memish, 2016). The evidence currently available for the burden of Hajj-associated pneumococcal disease is suggestive, but limited by the insensitivity of bacterial cultures as a means of diagnosing the full burden of invasive or non-invasive pneumococcal pneumonia (Bartlett, 2011). The addition of urine antigen testing for adult pneumonia patients is expected to add sensitivity to the etiological attribution, without inappropriately minimizing specificity (Mandell et al., 2003). The sensitivity and specificity of this test in the diagnosis of community-acquired pneumonia (CAP) due to *S. pneumoniae* have been reported to be in the range of 77%–97% and

67%–100%, respectively (Gutierrez et al., 2003; Klugman et al., 2008; Molinos et al., 2015; Song et al., 2013).

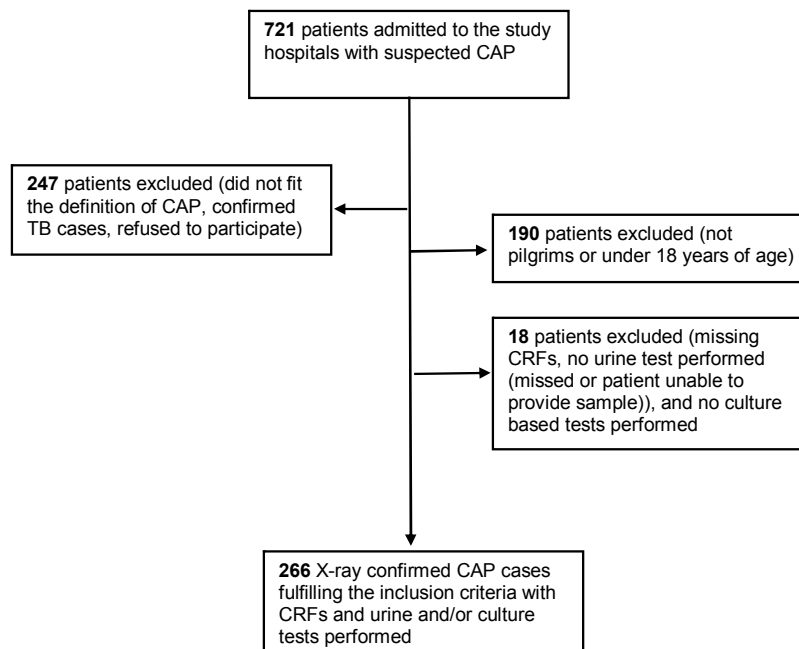
The aim of this study was to evaluate the proportion of hospitalized, X-ray-confirmed CAP attributable to *S. pneumoniae* among adult Hajj pilgrims in 2016, using the urine antigen test as well as standard culture-based tests, in order to determine the clinical burden of disease associated with Hajj and inform vaccination policy-making.

Materials and methods

Setting and study population

This was a prospective case-series study conducted in hospitals in the holy cities of Mecca and Medina, KSA. The study was conducted over a 1-month period from August 23 to September 23, 2016 (20 Dull Qida to 20 Dull Hija 1437H in the Islamic calendar) around the date of the Hajj peak of September 9. The study was therefore able to capture three time periods: pre-Hajj (August 23 to September 8), Hajj (September 9 to September 14), and post-Hajj (September 15 to September 23). Patients were enrolled from all general hospitals (excluding specialty hospitals such as obstetrics and gynecology hospitals and pediatric hospitals) designated to treat Hajj pilgrims. These included four general hospitals and seven temporary (holy sites) hospitals in Mecca and four general hospitals in Medina.

The study population comprised adult pilgrim patients aged ≥ 18 years old diagnosed with X-ray-confirmed CAP. For this protocol, CAP was defined in accordance with the US Food and Drug Administration (FDA) (US Food and Drug Administration, 2014) as an acute infection of the pulmonary parenchyma associated with symptoms such as fever or hypothermia, chills, rigors, cough, chest pain, or dyspnea, accompanied by the presence of a new lobar or multilobar infiltrate on a chest radiograph within 72 h of hospital admission. Patients with known or suspected active tuberculosis (TB; defined as smear-positive after three acid-fast bacilli tests), those < 18 years old, non-Hajj pilgrims, and



CAP, community-acquired pneumonia; TB, tuberculosis; CRF, case report form

Figure 1. Patient enrollment flowchart.

patients who did not consent to participate were excluded from the study. Based on the above criteria, 266 patients were enrolled in the study.

Data and sample collection

Following informed consent, X-ray-confirmed CAP patients were treated according to local standard of care and administered a urine antigen test for *S. pneumoniae* (Alere BinaxNow *S. pneumoniae* urine antigen test; Alere, Waltham, MA, USA). A case report form (CRF) containing patient demographic and clinical characteristics was filled out by trained investigators (to ensure consistency

across sites) for each patient using the patient's medical chart and information from the patient or a family member.

A case of X-ray-confirmed CAP was recorded as positive or negative for *S. pneumoniae* on the CRF based on findings from any one of the following microbiological tests: Alere BinaxNow *S. pneumoniae* urine antigen test, culture from a normally sterile site if conducted during routine investigation (i.e., blood, bone, cerebrospinal fluid, joint fluid, pericardial fluid), culture from a respiratory specimen if conducted during routine investigation and obtained by any of the following means ([US Food and Drug Administration, 2014](#)): (1) endotracheal aspiration in intubated patients; (2) bronchoscopy with bronchoalveolar lavage or

Table 1
Demographic and other characteristics of the pilgrim population enrolled.

Variable	Number (n)	Percentage (%)
Pilgrims enrolled	266	
Gender	265	
Male	177	66.8
Female	88	33.2
Age, years	237	
Mean (range)	65.3 (30–90)	
≤49	17	7.2
50–64	85	35.9
≥65	135	57.0
Region of residence	265	
Africa	24	9.1
MENA (excluding Turkey)	84	31.7
Asia (excluding Russia)	133	50.2
Europe and USA (including Turkey and Russia)	24	9.1
Admitted hospital location	266	
Mecca	148	55.6
Mecca holy sites	40	15.0
Medina	78	29.3
Patient had ≥2 of these symptoms	266	
Difficulty breathing	232	87.2
Chest pain	86	32.3
Purulent sputum	131	49.2
Cough	242	91.0
Patient had ≥2 vital sign abnormalities	266	
Fever	221	83.1
Hypotension	78	29.4
Tachycardia	141	53.0
Tachypnea	211	79.4
Patient had ≥1 clinical or laboratory abnormality finding	266	
Hypoxemia	165	62.0
Pulmonary consolidation	169	63.5
Elevated total WBC count or leukopenia	171	64.3
Patient is a cigarette smoker	261	
No	157	60.2
Yes	26	10.0
Unknown	78	29.9
Patient has diabetes mellitus	264	
No	149	56.4
Yes	96	36.4
Unknown	19	7.2
Admitting department	260	
Emergency room	98	37.7
Ward	95	36.5
ICU	59	22.7
Other	8	3.1
Patient treated in ICU	238	
No	127	53.4
Yes	108	45.4
Unknown	3	1.3
Antibiotic used in the 5 days prior to admission	258	
No	126	48.8
Yes	17	6.6
Unknown	115	44.6
Case outcome	238	
Died	24	10.1
Alive	214	89.9

MENA, Middle East and North Africa; WBC white blood cell; ICU, intensive care unit.

protected-brush sampling; (3) sputum obtained by deep expectoration.

Sample processing

The urine antigen test was performed at the patient's bedside as soon as possible after enrolment using the Alere BinaxNow *S. pneumoniae* test as per the manufacturer's recommendation. Other samples were handled and processed in the same hospital as per the hospital's standard procedures. The results of microbiological investigations were collected and recorded on the CRFs once available.

Data analysis

Characteristics of the study population were summarized as frequencies and percentages for categorical variables and as means with the range for quantitative variables. The association between explanatory variables and outcomes was evaluated by Chi-square test or Fisher's exact test, as appropriate. In addition, odds ratios (OR) and their 95% confidence intervals (CI) were calculated in multivariate analyses. All tests for significance were two-sided, and a *p*-value of <0.05 was considered statistically significant. All analyses were performed using IBM SPSS Statistics version 22.0 (IBM Corp., Armonk, NY, USA).

Results

Over the study period, 721 patients with suspected CAP were admitted to the 13 hospitals included in this study. Of these patients, 266 had X-ray-confirmed CAP and were enrolled in the study (Figure 1). Demographic and other characteristics of the enrolled study population are shown in Table 1. Patients originated from 43 countries, with the most represented being Indonesia (*n* = 59, 22.3%), Egypt (*n* = 27, 10.2%), and India (*n* = 26, 9.8%). All but one case entered KSA between August 1 and September 10, 2016. Most patients were elderly males (mean age 65.3 years, range 30–90 years; male to female ratio 2:1). The majority of cases (*n* = 188, 70.6%) were admitted to hospitals in the city of Mecca, the main

site of the Hajj pilgrimage, including 40 cases admitted to the four temporary hospitals at the Mecca holy sites.

The pattern of admission shows that the number of cases admitted to hospitals increased over the study period and that most cases of CAP occurred post Hajj (Figure 2, Table 2).

Cough and difficulty breathing were the most common symptoms and were present in 91% (*n* = 242) and 87.2% (*n* = 232) of the cases, respectively. Similarly, fever and tachypnea were the most common vital sign abnormalities, recorded in 83.1% (*n* = 221) and 79.4% (*n* = 211) of the cases, respectively. At least one clinical or laboratory abnormality was recorded for 63% of cases. Only 22.7% (*n* = 59) of cases were initially admitted to the ICU upon arrival at the hospital, but 45.4% (*n* = 108) of cases were treated in the ICU during their hospital stay.

Diabetes mellitus was reported by 36.4% (*n* = 96) of the study population, and 10% (*n* = 26) declared that they were cigarette smokers. Only 6.6% (*n* = 17) of the cases acknowledged having used antibiotics in the 5 days prior to their admission, although antibiotic use was unknown in a further 44.6% (*n* = 115) of the cases. All but one of the 17 cases who had used antibiotics prior to hospital admission had been on a single antibiotic. One person had taken both ceftriaxone and clarithromycin prior to hospital admission. The most common antibiotics used prior to hospital admission were cephalosporins (mainly third-generation) and penicillins.

Culture-based methods (sterile sites or respiratory specimens) were performed in 37.6% (*n* = 100) of the cases, with the etiology determined in 19.0% (19/100) of these cases. *S. pneumoniae* was identified in 13% (*n* = 13) of the samples and in 6% (*n* = 6) of samples from normally sterile sites. Other pathogens were identified in six samples, including staphylococci (*n* = 5) and *Klebsiella pneumoniae* (*n* = 1). Urine antigen tests to detect *S. pneumoniae* infection were performed in 93.6% (*n* = 249) of CAP cases; 14.5% (*n* = 36) were positive. The overall proportion of CAP cases with a positive result for *S. pneumoniae* (based on either culture-based tests or the urine antigen test) was 18% (*n* = 48).

Valid test results for both culture-based methods and the urine antigen test were available for 83 cases. Overall, agreement in results (both negative and positive) between the two methods was

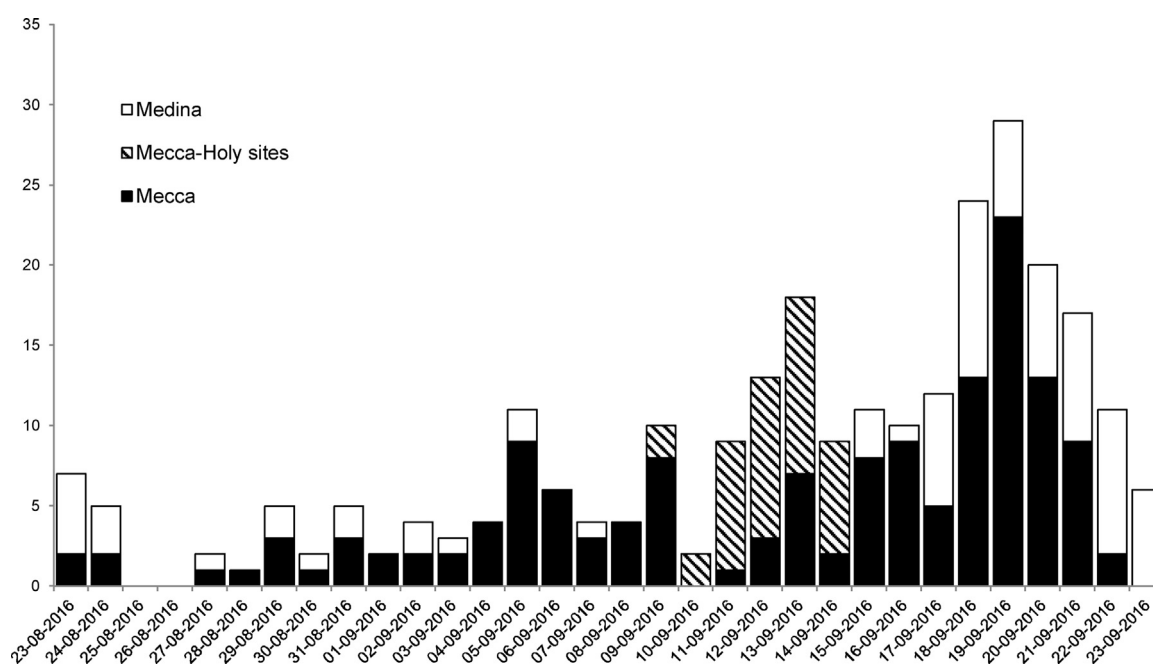


Figure 2. General pattern of community-acquired pneumonia (CAP) case admissions to hospitals during the study period.

Table 2
Community-acquired pneumonia admissions during the study period.

Period	Dates	Number of days	Number of admissions	% admissions	Average admissions/day
Pre-Hajj	Aug 23 to Sep 8	17	65	24.4	3.8
Hajj	Sep 9 to Sep 14	5	61	23.0	12.2
Post-Hajj	Sep 15 to Sep 23	9	140	52.6	15.5
Total study period	Aug 23 to Sep 23	31	266	100	8.6

found in 65 cases (78.3%). Based on these results, the sensitivity and specificity of the urine antigen test compared to the culture-based methods were calculated to be 8.33% and 90.1%, respectively.

Hospital location and treatment in the ICU were significantly associated with *S. pneumoniae* CAP cases ($p=0.01$). CAP patients admitted to Medina hospitals were less likely to have *S. pneumoniae*-attributable CAP than those admitted to Mecca hospitals (OR 0.33, 95% CI 0.14–0.80). CAP patients treated in the ICU were 2.88 times more likely to be *S. pneumoniae* CAP cases than those not treated in the ICU (OR 2.88, 95% CI 1.37–6.08). No significant association was observed between *S. pneumoniae*-attributable CAP and age, gender, pilgrim's country of origin, antibiotic use in the 5 days prior to hospital admission, smoking, or diabetes status (Table 3).

Disposition at discharge was recorded for 238 CAP cases. Twenty-four patients died, resulting in an overall case-fatality rate of 10.1%. The case-fatality rate among CAP patients treated in the ICU was nearly nine times that of non-ICU patients (22.2% vs. 2.48%). The case-fatality rate among all *S. pneumoniae*-positive cases was 16.7%, among *S. pneumoniae*-positive urine antigen test cases was 10.1%, and among blood culture-positive *S. pneumoniae*

cases was 50%. Only admission to the ICU on arrival and treatment in the ICU were significantly associated with mortality in CAP cases. Patients with CAP treated in the ICU were over 11 times more likely to die than those not treated in the ICU (OR 11.23, 95% CI 3.22–39.1).

Discussion

This study is the first to systematically enroll cases of X-ray-confirmed CAP among pilgrims during the whole Hajj season and from hospitals in the two holy cities of Mecca and Medina, giving the best estimate of the burden of CAP associated with Hajj. As there was active triaging of all cases of suspected CAP admitted to hospitals during Hajj (due to Middle East respiratory syndrome coronavirus (MERS-CoV) screening), the study is likely to have captured almost all CAP cases admitted to hospitals. CAP patients originated from a wide variety of countries with a sizable proportion being older males, which is reflective of the general population of Hajj. A number of other studies have reported that pneumonia is a leading cause of hospital admission (accounting for 15–40% of hospital admissions) during the pilgrimage (Al-Ghamdi et al., 2003; Khan et al., 2006; Madani et al., 2006; Shirah et al., 2017). However, most of these studies were limited to Mecca city alone, specific hospital(s), or to the Hajj rituals days only or a few days around that period. Hence, previous studies have likely underestimated the true burden of Hajj-associated pneumonia.

It was found that 18% of hospitalized X-ray-confirmed CAP cases among adult Hajj pilgrims in 2016 were attributable to *S. pneumoniae*. The organism is commonly isolated from Hajj pilgrims treated in clinics or hospitals during their pilgrimage. Several studies have found *S. pneumoniae* to be the cause of pneumonia in up to 10% of cases during Hajj (Alzeer et al., 1998; Asghar et al., 2011; Mandourah et al., 2012; Shirah et al., 2017), while one study found that among 38 patients treated for severe CAP at 15 facilities during the 2013 Hajj, *S. pneumoniae* was found in 56%, using the Randox respiratory multiplex array (Memish et al., 2014). Other important causative pathogens reported in these studies have included other bacteria such as *Staphylococcus aureus*, *K. pneumoniae*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa* and viruses including human rhinovirus, influenza A virus, and human coronaviruses, as well as the fungus *Candida albicans*. The results of this study are likely to be a more accurate reflection of the actual proportion of CAP caused by *S. pneumoniae* during Hajj, as the urine antigen test was used in addition to the standard culture-based methods. The test adds sensitivity to the etiological attribution without minimizing specificity (Mandell et al., 2003) and overcomes many of the limitations and difficulties in culturing *S. pneumoniae* from clinical samples (Bartlett, 2011). Although the test was highly specific in this study, it had lower sensitivity than that reported in other studies (Mandell et al., 2003).

Nearly half of the CAP cases seen in this study were treated in the ICU, reflecting the severity of the disease during Hajj. Admission to an ICU was based on patient clinical assessment and the need for respiratory or hemodynamic support (Arabi and Alhamid, 2006). Pneumonia is a leading cause of ICU admission during Hajj, accounting for 22–31% of ICU admissions, and is a

Table 3
Factors associated with *Streptococcus pneumoniae* community-acquired pneumonia cases.

Variable	OR	95% CI	<i>p</i> -Value
Gender			0.15
Female			
Male	1.67	0.82–3.40	
Age group, years			0.69
≤49			
50–64	1.46	0.29–7.17	
≥65	1.78	0.38–8.34	
Region of residence			0.32
Africa			
MENA (excluding Turkey)	0.48	0.15–1.49	
Asia (excluding Russia)	0.88	0.32–2.44	
Europe and USA (including Turkey and Russia)	0.45	0.09–2.06	
Hospital location			0.01 ^a
Mecca			
Mecca Holy sites	1.29	0.57–2.88	
Medina	0.33	0.14–0.80	
Cigarette smoker			0.06
No			
Yes	0.17	0.22–1.31	
Patient has diabetes mellitus			0.58
No			
Yes	0.81	0.40–1.62	
Admitting department			0.30
Emergency room			
Ward+ other	0.63	0.29–1.36	
ICU	1.19	0.53–2.63	
Patient treated in ICU			0.01 ^a
No			
Yes	2.88	1.37–6.08	
Antibiotic used in 5 days before admission			0.38
No			
Yes	0.65	0.13–3.09	

OR, odds ratio; CI, confidence interval; MENA, Middle East and North Africa; ICU, intensive care unit.

^a Variable (hospital location and patient treated in ICU) significantly associated with *S. pneumoniae* community-acquired pneumonia.

major cause of severe sepsis and septic shock in ICUs during the event (Madani et al., 2007; Mandourah et al., 2012; Shirah et al., 2017). The case-fatality rate for CAP patients in this study was 10.1%, which is within the range of rates reported for CAP internationally (Drijkoningen and Rohde, 2014; Vila-Corcoles et al., 2016). Also, case fatality was higher among those admitted/treated in an ICU and among those with invasive disease. This is also in accordance with other reports, including those among Hajj pilgrims (Drijkoningen and Rohde, 2014; Mandourah et al., 2012; Shirah et al., 2017), and is likely because patients treated in the ICU or those with invasive disease have a more severe illness and are at a higher risk of death.

Most CAP cases in this study were admitted to Mecca hospitals, and the number of cases increased over the study period, with the highest admission rate being after the Hajj rituals days. This pattern is in accordance with the Hajj journey and its characteristics. Most pilgrims arrive in KSA a few days (or weeks) before the Hajj ritual dates and spend time in the holy cities of Mecca and/or Medina. During the Hajj dates, all pilgrims return to Mecca to perform the Hajj rituals, most of which take place at the Mecca holy sites. Hence, the pre-Hajj period is characterized by a smaller number of pilgrims, living in less crowded environments, spread across both Mecca and Medina, and relatively free of stressors associated with performing the Hajj rituals. During the Hajj dates, the maximum numbers of pilgrims are located in a small area of Mecca performing physically challenging Hajj rituals in crowded conditions, under both physical and environmental stressors. These conditions facilitate disease transmission and render pilgrims more prone to infection. It is likely that many CAP cases admitted after Hajj were infected during the Hajj dates. This may explain the increase in the number of CAP cases post-Hajj, while the number of pilgrims in Mecca and Medina was decreasing.

Most CAP cases were elderly males and many had diabetes or were smokers. Although no significant association was found between these factors and pneumococcal pneumonia in this study, age, co-morbidities, and smoking are established risk factors for CAP, including pneumococcal pneumonia (Almirall et al., 2017; Lynch and Zhanel, 2009). The latter is a vaccine-preventable disease and the above risk factors are indications for pneumococcal vaccination in adults (Tomczyk et al., 2014). The finding that a proportion of CAP during Hajj was caused by *S. pneumoniae*, and that most of it was among individuals at risk of the disease, is significant. Currently, pneumococcal vaccination is not one of the officially recommended/compulsory vaccinations in the Hajj health requirements set by the Saudi authorities (Saudi Ministry of Health, 2017). Although some countries have recommended pneumococcal vaccination for their Hajj pilgrims (Feldman et al., 2013; Mathai et al., 2016; Rashid et al., 2013), an evidence-based policy requires a better understanding of the clinical and economic burden of the disease associated with Hajj. This study is a first step in providing such data, by defining the burden of the disease in the Hajj season using a more reliable diagnostic test for pneumococcal pneumonia. However, further studies are warranted, including accurate estimations of the incidence of the disease during the mass gathering and determining the serotypes causing the illness.

This study has some limitations. It was aimed to systematically enroll all hospitalized X-ray-confirmed CAP cases among Hajj pilgrims during the study period. However, very early pneumonia may not be apparent on chest radiographs and may have led to the exclusion of some cases from the study. Not all CAP cases were investigated using culture-based methods, which are not routinely conducted by hospitals during Hajj due to feasibility. Some of the information collected from pilgrims was self-reported (e.g., smoking status) and hence may be subject to underreporting. Also, information on the pneumococcal disease vaccination status of the cases was not collected, so it was not possible to investigate

the effect of vaccination. In addition, as no accurate data on the adult population at risk during the study period were available, it was not possible to accurately estimate the incidence of CAP during Hajj.

In conclusion, *S. pneumoniae*-attributable CAP during Hajj has an important clinical burden. Further studies, including investigations of the incidence of the disease and *S. pneumoniae* serotypes involved in the disease, as well as the identification of the population at risk, are warranted to provide a comprehensive evidence base for appropriate policy-making regarding vaccination of Hajj pilgrims.

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Ethical approval and consent to participate

The study was approved by the King Fahad Medical City Ethics Committee and the Institutional Review Board. All participants gave verbal consent before enrolment and the study was conducted in accordance with the guidelines of the Ethics Committee.

Conflict of interest

Tanaz Petigara and John Grabenstein are full-time employees of Merck & Co., Inc. The other authors have no conflicts of interest to declare.

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