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RESEARCH ARTICLE

Respiratory pathogens among ill pilgrims and the potential benefit of using point-of-care rapid molecular diagnostic tools during the Hajj

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ABSTRACT

We investigated respiratory pathogens among ill Hajj pilgrims from Marseille. We also discuss the potential role of point-of-care (POC) rapid molecular diagnostic tools for this purpose. Clinical data were collected using a standardised questionnaire. Influenza A and B viruses, human rhinovirus and human coronaviruses, *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae* and *Klebsiella pneumoniae* were investigated using real-time PCR in respiratory samples obtained during travel, at the onset of symptoms. 207 participants were included. A cough, expectoration, rhinitis and a sore throat were the most frequent respiratory symptoms, followed by loss of voice and dyspnoea. 38.7% and 25.1% of pilgrims reported a fever and influenza-like symptoms, respectively. 59.4% pilgrims received antibiotics. Rhinovirus (40.6%) was the most frequent pathogen, followed by *S. aureus* (35.8%) and *H. influenzae* (30.4%). Virus and bacteria co-infections were identified in 28.5% of participants. 25.1% pilgrims who were positive for respiratory bacteria did not receive antibiotic treatment. In the context of the Hajj pilgrimage, it is important to detect infections that can be easily managed with appropriate treatment, and those that can affect prognosis, requiring hospitalisation. POC rapid molecular diagnostic tools could be used for patient management at small Hajj medical missions and to rationalise antibiotic consumption among Hajj pilgrims.

KEYWORDS

Hajj, pilgrims, respiratory tract infections, point-of-care laboratory

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INTRODUCTION

According to the World Health Organization "A mass gathering is a planned or spontaneous event where the number of people attending could strain the planning and response resources of the community or country hosting the event" [1]. International travellers attending mass gatherings are exposed to specific infectious risks, particularly respiratory and gastrointestinal infections [2].

The Hajj or pilgrimage to Mecca in Saudi Arabia, is one of the largest annual religious mass gatherings in the world, attended by over two million people travelling from over 184 countries [3]. Each year, about 2,000 pilgrims from the city of Marseille, France, take part

in the pilgrimage [4]. The Hajj takes place over five days during Dhul al-Hijjah – the last month of the Islamic calendar, but pilgrims generally stay in Saudi Arabia for between three to four weeks to visit the Great Mosques [3].

Infections are common among Hajj pilgrims. In one study conducted during the 2016 Hajj, infectious diseases accounted for 53% of outpatient diagnoses. Upper and lower respiratory tract infections (RTI), acute gastroenteritis and serious diabetes-related infections, cellulitis and pneumonia are the most common infections among pilgrims [5]. Most pilgrims develop respiratory symptoms during the Hajj, particularly a cough [6]. Numerous studies conducted among Hajj pilgrims have also demonstrated a high prevalence of the acquisition of respiratory pathogens, including bacteria that are multi-resistant to antibiotics [7, 8].

Although a medical prescription has been required since more than 30 years in order to be given antibiotics in Saudi Arabia [9], many pilgrims take antibiotics without a prescription [10]. It is generally recommended that a microbiological assessment be performed for appropriate antibiotic use. To date, there have been many studies identifying respiratory pathogen carriage in pilgrims. However, most of these studies focussed on the periods before and after the pilgrimage, or studied pilgrims who were hospitalised in Hajj healthcare facilities where molecular diagnostics are available [11]. Studies to detect pathogens responsible for respiratory tract infections among pilgrims suffering from mild symptoms and consulting at Hajj medical missions, or consulting accompanying doctors remain limited. It is difficult to diagnose the cause of respiratory infections in these patients because of the large number of consultations. Moreover, the results need to be available in a short time to help doctors giving appropriate treatment.

Point-of-care (POC) rapid molecular diagnostic tools consist of mobile devices with test kits which are used to detect pathogens in human specimens. Due to their simplicity, convenience, quick implementation time, and the fact that they are not labour-intensive, these tools quickly attracted the attention of clinical practitioners. Today, molecular diagnostics is shifting from centralised laboratories to molecular testing at the local point-of-care in order to ensure the fastest patient treatment. POC rapid molecular diagnostic tools make quick, easy-to-use testing available in patient situations where a rapid diagnosis is required, especially in the context of treating a multitude of patients with infections. In addition, the use of more sensitive and specific molecular tests promotes more appropriate antibiotic use and improves overall infection control [12, 13]. Getting the appropriate antibiotics quickly, in an effective time frame, and ensuring that antibiotics are not prescribed for unnecessary conditions are key issues. POC rapid molecular diagnostic tools have the potential to help prevent the spread of infectious diseases and impede antibiotic resistance [12, 13].

We conducted this study among French pilgrims presenting with the symptoms of a respiratory tract infection during Hajj pilgrimages between 2014 and 2018. Pilgrims were sampled at the onset of symptoms and were investigated using PCR for pathogens which were potentially responsible for these symptoms. In this study, we also discuss the role of POC rapid molecular diagnostic tools in the context of Hajj medical missions.

MATERIALS AND METHODS

Participants and study design

As part of a study aiming at investigating the acquisition of respiratory pathogens during the Hajj in 2014–2016 and in 2018, pilgrims travelling from Marseille in France to Mecca in Saudi Arabia were recruited through a private specialised tour agency and were included in the study on a voluntary basis [14, 15]. Pilgrims were systematically sampled before departing from France and upon their return from Saudi Arabia (these results have been previously published [14, 15]). In the present study, we focus on sampling conducted during travel at the onset of symptoms. They were accompanied by a bilingual (Arabic and French) medical doctor who travelled with the group. If they presented with respiratory symptoms during their stay in Saudi Arabia, they were invited to consult the group doctor. A standard set of questionnaires was developed to collect information on demographics (age and sex), medical history (chronic comorbidities) and immunisation status, as well as clinical symptoms and antibiotic use. In addition, information on compliance with the use of facemasks, hand washing, the use of hand gel and disposable handkerchiefs was also collected. Influenza-like illness (ILI) was defined as the presence of a cough, a sore throat and a subjective fever [16]. Pilgrims were considered to be immunised against influenza when they had been vaccinated within the past year and up to 10 days before departure. Participants were considered to be immunised against invasive pneumococcal disease when they had been vaccinated with the 13-valent pneumococcal conjugate vaccine (PCV-13) in the past five years [17–26]. In order to identify the agents associated with the reported respiratory tract infection symptoms, nasopharyngeal swabs were taken from all symptomatic pilgrims who visited the doctor.

Respiratory specimens

Samples were taken by the doctor who accompanied the group, in a standardised way, at the onset of respiratory symptoms. After being collected, nasopharyngeal swabs were transferred to Sigma-Virocult® medium and kept at room temperature until returning to France and were stored at −80 °C until processing.

Identification of respiratory pathogens

By using the EZ1 Advanced XL (Qiagen, Hilden, German) and the Virus Mini Kit v2.0 (Qiagen), DNA and RNA were extracted from the respiratory samples according to the manufacturer's recommendations.

The Multiplex RNA Virus Master Kit (Roche Diagnostics, France) was used to identify influenza A and B viruses and human rhinovirus with one-step simplex real-time quantitative RT-PCR amplification procedure. Common human coronaviruses, including types 229E, NL63, OC43, and HKU1 were tested using a one-step duplex quantitative RT-PCR amplification using the HCoV/HPIV-R Gene Kit (REF: 71-045, bioMérieux, Marcy l'Etoile, France), in accordance with the manufacturer's recommendations. In addition, all samples in this cohort were retrospectively tested for SARS-CoV-2 by real-time reverse-transcription-PCR (qPCR) as previously described [27].

To identify respiratory bacteria, real-time PCR amplifications were performed using LightCycler® 480 Probes Master kit (Roche Diagnostics, France) according to the manufacturer's recommendations. The *nucA* gene of *Staphylococcus aureus*, the *SHD* gene of *Haemophilus influenzae*, the *lytA CDC* gene of *Streptococcus pneumoniae* and the *phoE* gene of *Klebsiella pneumoniae* were amplified with the internal DNA extraction control TISS. Other respiratory pathogens such as respiratory syncytial virus, human metapneumovirus, human adenovirus, *Mycoplasma pneumoniae* and *Bordetella pertussis* were not tested, due to a low positive proportion (<2%) among French and other international pilgrims [28–31].

The internal controls MS2 phage and TISS were also tested to verify the RNA and DNA extraction, respectively, as previously described [32]. Negative controls (PCR mix only) and positive controls (RNA from viral strains or DNA from bacterial strains) were included in each run. Positive results were defined as the amplification with a cycle threshold (CT) value ≤35. A threshold value of 35 was used in each experimental run and we calculated the RFU cut-off value recommend by CFX Manager Software Version 3.1 (Bio-Rad) in order to verify the positive cases. Results were considered to be positive when the cycle threshold value of real-time PCR was greater than the cut-off value. All quantitative real-time PCR tests were performed using a C1000 Touch™ Thermal Cycle (Bio-Rad, Hercules, CA, USA).

Statistical analysis

The STATA software version 16.0 (Copyright 1985-2015 StataCorp LLC, http://www.stata.com) was used for statistical analysis.

The quantitative variables were presented as median, interquartile and range, while the qualitative variables were presented as number and percentage.

Ethics statement

The protocol was approved by the Aix-Marseille University institutional review board (23 July 2013; reference No. 2013-A00961-44).

The study was performed according to the good clinical practices recommended by the Declaration of Helsinki and its amendments. All participants provided their written informed consent.

RESULTS

Characteristics of study participants

During the 2014–2016 and 2018 Hajj seasons, 380 pilgrims reported having suffered from at least one respiratory symptom during their stay [14, 15]. The study included 207 pilgrims who consulted the accompanying doctor and provided respiratory samples obtained at the onset of symptoms (9 in 2014, 92 in 2015, 24 in 2016 and 82 in 2018). These pilgrims were not admitted to healthcare facilities in Saudi Arabia for the treatment of respiratory symptoms. Their median age was 62 years and the male to female sex ratio was 1:1.3. Diabetes mellitus was the most frequent comorbidity, followed by high blood pressure and chronic respiratory diseases (Table 1).

About one-third of pilgrims reported being vaccinated against influenza and invasive pneumococcal disease. Regarding non-pharmaceutical individual preventive measures, about two-thirds of the pilgrims reported using face masks and disposable handkerchiefs during the pilgrimage and about half of them reporting more frequent hand hygiene practices (Table 1).

Clinical symptoms

A cough, expectoration, rhinitis and a sore throat were the most frequent respiratory symptoms, followed by loss of voice and dyspnoea. A fever was reported by 38.7% of ill pilgrims and one-quarter were considered to have an ILI. Regarding treatment, 59.4% of pilgrims received antibiotics. Only one participant was hospitalised due to diabetes (Table 2).

Identification of respiratory pathogens

Figure 1 shows the prevalence of respiratory pathogens among symptomatic Hajj pilgrims. Overall, 84.1% of participants

Table 1. Comorbidities of French pilgrims and individual preventive measures used during the Hajj

Variables	*n*	%
Chronic diseases		
Diabetes mellitus	67	32.4
High blood pressure	58	28.0
Chronic respiratory diseases	31	15.0
Chronic cardiac diseases	20	9.7
Chronic kidney diseases	4	1.9
Immunodeficiency	3	1.5
Individual preventive measures		
Vaccination against influenza	61	29.5
Vaccination against invasive pneumococcal disease	64	30.9
Use of face masks	136	65.7
Use of disposable handkerchiefs	140	67.6
Washing the hands more often than usual	101	48.8
Use of hand disinfectant gel	108	52.2

Table 2. Clinical symptoms and treatment (N = 207)

Symptoms	*n*	%
Dry cough	90	43.5
Expectoration	101	48.8
Rhinitis	134	64.7
Sore throat	131	63.3
Fever	80	38.7
Loss of voice	65	31.4
Influenza-like illness	52	25.1
Dyspnoea	32	15.5
Antibiotic treatment	123	59.4
Hospitalisation	1	0.5

were positive for at least one pathogen. 48.3% and 64.3% of pilgrims tested positive for at least one respiratory virus or bacteria, respectively. Rhinovirus (40.6%) was the most frequent pathogen, followed by *S. aureus* (35.8%) and *H. influenza* (30.4%) (Fig. 1). Virus and bacteria co-infections were identified in 28.5% of participants. A total of 33.8% pilgrims tested positive for two pathogens, while 12.1% and 1.4% participants were positive for three and four pathogens, respectively (Fig. 1). Of note, no sample tested positive for SARS-CoV-2.

Identification of respiratory bacteria and antibiotic treatment among ill pilgrims

Table 3 shows the proportions of the identification of respiratory bacteria and antibiotic treatment. Of the 207 symptomatic pilgrims, 25.1% who tested positive for respiratory bacteria did not receive antibiotic treatment. In contrast, 20.3% of the pilgrims were treated with antibiotics but tested negative for the respiratory bacteria. Table 4 shows virus-bacteria co-infection among Hajj pilgrims with respiratory symptoms.

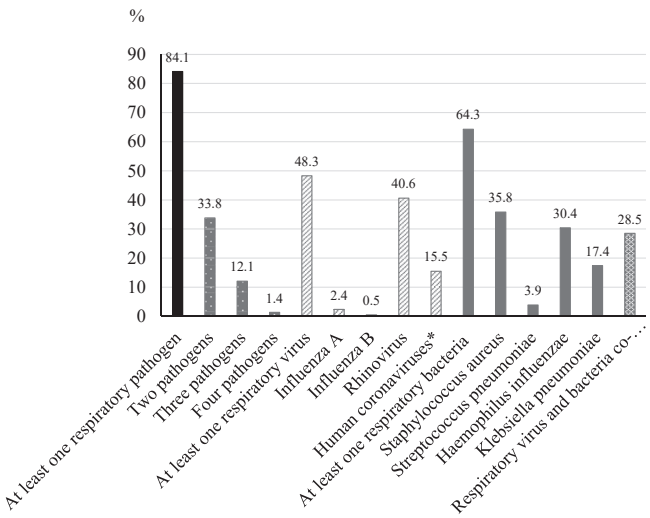

Fig. 1. Prevalence of respiratory pathogens among symptomatic Hajj pilgrims. *229E (n = 20), NL63 (n = 6), OC43 (n = 10), HKU1 (n = 1), SARS-CoV-2 (n = 0)

Table 3. Antibiotic treatment according to microbiological data

Patients positive with at least one respiratory bacteria	Antibiotic treatment	
	Yes	No
Yes*	81 (39.1)	52 (25.1)
No	42** (20.3)	32 (15.5)

*59 pilgrims were also positive for at least one virus, including 38 patients who were treated with antibiotics.
**27 pilgrims were positive for at least one virus; the 15 remaining were negative for all tested pathogens.

Table 4. Virus-bacteria co-infection among Hajj pilgrims with respiratory symptoms

Co-infection	Number of patients
Influenza B, *Haemophilus influenzae*	1
Human rhinovirus, *Staphylococcus aureus*	17
Human rhinovirus, *Haemophilus influenzae*	9
Human rhinovirus, *Streptococcus pneumoniae*	1
Human rhinovirus, *Klebsiella pneumoniae*	4
Human coronavirus, *Staphylococcus aureus*	2
Human coronavirus, *Haemophilus influenzae*	3
Human coronavirus, *Klebsiella pneumoniae*	1
Human coronavirus, *Staphylococcus aureus, Haemophilus influenzae*	1
Human rhinovirus, Human coronavirus, *Staphylococcus aureus*	4
Human rhinovirus, Human coronavirus, *Haemophilus influenzae*	1
Human rhinovirus, *Staphylococcus aureus, Haemophilus influenzae*	7
Human rhinovirus, *Staphylococcus aureus, Streptococcus pneumoniae*	1
Human rhinovirus, *Staphylococcus aureus, Klebsiella pneumoniae*	2
Human rhinovirus, *Haemophilus influenzae, Klebsiella pneumoniae*	2
Human rhinovirus, *Staphylococcus aureus, Haemophilus influenzae, Klebsiella pneumoniae*	1
Human rhinovirus, Influenza B, *Staphylococcus aureus, Klebsiella pneumoniae*	1
Human rhinovirus, Human coronavirus, *Staphylococcus aureus, Klebsiella pneumoniae*	1

DISCUSSION

RTIs are very common among Hajj pilgrims. Cohort studies showed that between 53% and 93.4% of pilgrims presented respiratory symptoms during their pilgrimage [14, 15, 28]. These are the main reason for hospitalisation in healthcare facilities in Mecca during the Hajj each year [33]. Most ill pilgrims suffered from upper RTI, but pneumonia and severe respiratory infections are also frequent [33]. Using molecular techniques (PCR), previous studies addressing the carriage of respiratory pathogens before, during and after the Hajj, showed a significant acquisition of micro-organisms, especially rhinoviruses, common human coronaviruses and influenza virus [11]. *H. influenzae, S. pneumoniae* and

S. aureus accounted for the most common acquired bacteria, particularly among ill French pilgrims [14, 15]. Multinational studies conducted on larger cohorts of pilgrims corroborated these results [29, 34, 35]. In this study, 84.1% of ill participants sampled at the onset of symptoms were positive for at least one respiratory pathogen, and human rhinovirus and human coronaviruses were the most frequent respiratory pathogens identified. It is notable that 64.3% of pilgrims were positive for at least one respiratory bacteria. In a large retrospective study conducted between 2004 and 2013 in over 1,000 hospitalised pilgrims with pneumonia, 36% were positive for *S. aureus*, 30% for *K. pneumoniae* and 25% for *H. influenzae*. *S. pneumoniae* was also identified among 18% of pilgrims with confirmed community-acquired pneumonia [36]. Studies conducted among outpatients have generally shown a lower rate of bacterial respiratory infections. Specifically, in a five-year study of nearly 255,000 Iranian pilgrims recruited at 1,352 Hajj caravans, only 357 samples tested positive for respiratory bacteria [37, 38].

Our results showed that 25% of pilgrims infected with respiratory bacteria were not treated with antibiotics. To date, the rationality of the use of antibiotics for pilgrims has been rarely studied. In one previous study, antibiotic consumption was higher in French pilgrims with symptoms of upper RTI (usually caused by viruses) than in those with lower respiratory infection or pulmonary involvement [39]. According to French recommendations on antibiotic use, 28.8% of pilgrims who had an indication for treatment with antibiotics did not receive them. In contrast, only 40% of pilgrims who were treated with antibiotics had an indication for this treatment [39]. Improper antibiotic treatment may represent a condition leading to the development of antibiotic-resistance bacteria. Indeed, Hajj pilgrims have a high prevalence of multidrug-resistant bacteria carriage on return [7].

One of the reasons for the inappropriate use of antibiotics is the frequency of self-medication among pilgrims. Although by law antibiotics can only be purchased in Saudi Arabia using a prescription, it is still possible for pilgrims to access antibiotics without a prescription. In one 2015 study, 39.2% of pilgrims reported that they had acquired non-prescribed antibiotics in Saudi Arabia [40]. Pilgrims may also bring antibiotics from their home country before joining the pilgrimage or share these medications with other pilgrims.

Another cause for inappropriate antibiotic use is the lack of access to microbiological laboratory facilities in some medical missions during the Hajj, including for French pilgrims. This is combined with the tendency to prescribe broad spectrum antibiotics for patients with respiratory symptoms without a microbiological diagnosis. In the context of the Hajj with more than two million pilgrims and a high incidence of RTIs, most symptomatic participants, however, receive treatment in outpatient clinics or from the accompanying medical staff without microbiological diagnosis.

In the context of the Hajj pilgrimage, it is important to detect infections that can be easily cured with symptomatic treatment or antibiotic treatment, and those that can affect prognosis, requiring hospitalisation. Large medical missions may have diagnostic facilities, and microbiology laboratories are available in hospitals and primary healthcare structures. Small Hajj medical missions, however, may lack these facilities, which in turn can affect patient management. Therefore, POC rapid molecular diagnostic tools that can be performed on-site by doctors and nurses at small Hajj medical missions can optimise rapid diagnosis. Indeed, it is designed to be easy to use and interpret, and can provide a quick diagnosis (within an hour) using simple laboratory facilities. POC rapid molecular diagnostic tools can be used in medical missions during the Hajj [41]. New pathogens of interest can also be added to the detection panels of these POC rapid molecular diagnostic tools, making them very useful for detecting and managing potential COVID-19 cases during Hajj.

Our study has some limitations. First, it was conducted on a small sample of French pilgrims and its results cannot be extrapolated to all pilgrims. Because the study looked at ill participants who consulted the accompanying doctor, a chest x-ray and other subclinical laboratory tests could not be performed. Bacterial cultures could not be performed due to the study design. qPCR used to detect respiratory pathogens does not distinguish between dead and living microorganisms. The study looked at only a small number of organisms, and illnesses could have been caused by other pathogens which were not tested. Furthermore, the detection of a particular organism does not mean it is the causative agent. However, our study identified the potential causative agent of RTIs in pilgrims from Marseille and showed a high prevalence of inappropriate antibiotic use. POC rapid molecular diagnostic tools could be used for patient management and the rationalisation of antibiotic consumption among Hajj pilgrims.

Conflict of interest: The authors declare that they have no conflict of interest.

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