Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and Hajj Gatherings

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Abstract

Hajj, the Pilgrimage to the Holy City of Makkah, Saudi Arabia, is one of the largest mass gatherings in the World. Due to the overcrowding, there is a risk of the transmission of infectious diseases from person to person, especially the risk

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of respiratory diseases. Since the emergence of Middle East Respiratory Syndrome Coronavirus, there was a significant interest in the risk that this posed to the Hajj. So far, there had been systematic surveillance of the virus among returning Pilgrims and no cases were identified in relation to the Hajj. However, there were two reported MERS-CoV cases related to the mini-Hajj, Umrah, in May 2014. Continued surveillance and vigilance are required to monitor and evaluate the risk in the future.

Keywords
Hajj · Pilgrimage · Mass gathering · MERS-CoV · Middle east respiratory syndrome coronavirus

Introduction

Hajj, the pilgrimage to the holy city of Makkah, Saudi Arabia, is one of the largest mass gatherings in the world. Due to the overcrowding, there is a risk of the transmission of infectious diseases from person-to-person, contaminated food or water, respiratory droplet, airborne transmission, and vector-borne transmission (Al-Tawfiq and Memish 2012a, 2015a; Gautret et al. 2016a). The potential for outbreaks due to person-to-person transmission, food and waterborne disease outbreak, fast and wide geographic spread of diseases, and the introduction of non-endemic diseases are all fearful events during mass gathering. Possible communicable diseases pattern during mass gathering include endemic diseases and imported and exported diseases.

The Hajj draws 3 million Muslims annually, and of these pilgrims, there are 2 million non-Saudis. The majority of 89% travel by air (Al-Tawfiq and Memish 2012a) from more than 180 countries. The Hajj journey is well described (Memish et al. 2014a). Pilgrims visit the Holy mosque in Makkah, the Plain of Arafat, Muzdaliffah and Mina where pilgrims stay in tents made particularly for pilgrims (Memish et al. 2014a).

The Saudi Ministry of Health pays particular attention to the Hajj with multiple committees. The preventive medicine committee oversees all public health and preventative matters during the Hajj (Memish et al. 2014a; Al-Tawfiq and Memish 2014a). The Kingdom of Saudi Arabia deploys a large number of public health officers to ensure compliance with health requirements. Those healthcare workers ensure compliance with required immunization and administer mandatory prophylactic medications (Memish 2010). There are strong public health teams who diligently monitor the occurrence of communicable diseases using an electronic surveillance (Al-Tawfiq and Memish 2012b). The surveillance particularly monitor influenza, influenza-like illness, meningococcal disease, food poisoning, viral hemorrhagic fevers, yellow fever, cholera, polio, and plague (Memish 2010; Al-Tawfiq and Memish 2012b). With the emergence of Middle East respiratory syndrome coronavirus (MERS-CoV), the disease became also a focus of surveillance especially during the Hajj. Coronaviruses other than MERS-CoV were detected in

0.6–0.8% of the tested population in regard to the Hajj seasons (Al-Tawfiq and Memish 2012b).

Middle East Respiratory Syndrome Coronavirus (MERS-CoV): The Virus

Human coronaviruses cause acute respiratory illness in humans and include Alpha- and Betacoronavirus genera. Betacoronaviruses are divided into four clades (A–D). MERS-CoV is a member of the human betacoronaviruses MERS-CoV and is classified in Clade C (lineage 3). Similar to the severe acute respiratory syndrome (SARS)-CoV, MERS-CoV is a positive-strand RNA virus. MERS-CoV genome has more than 30,000 nucleotides with 7 predicted open reading frames (ORFs) and 4 structural genes expressing 4 proteins, namely the spike (S) protein, nucleocapsid (N), membrane (M), and envelope (E) proteins (Cotten et al. 2013, 2014). The closest coronavirus to MERS-CoV are Clade C betacoronaviruses, Tylonycteris bat virus HKU4, Neoromicia zuluensis bat in South Africa, and Pipistrellus bat HKU5 virus (Corman et al. 2014; Ithete et al. 2013; van Boheemen et al. 2012).

Clinical Presentation

MERS-CoV causes a range of respiratory illness from a mild disease to a severe and life threatening infection. In one study, a three-phase illness was described and included the initial phase of fever and clinical stability probably representing viral replication, followed by an immunologic phase with clinical and radiographic deterioration and subsequent improvement (Al-Tawfiq and Hinedi 2018). In addition, asymptomatic cases had been described. Asymptomatic cases were reported in 12.5% of 144 confirmed MERS-CoV cases in 2012, and this rate was 25.1% among 255 confirmed cases (Al-Tawfiq and Gautret 2018). In children, the rate of asymptomatic cases ranged between 41.9% and 81.8% (Al-Tawfiq and Gautret 2018; Alfaraj et al. 2018; Al-Tawfiq et al. 2016a; Thabet et al. 2015; Memish et al. 2014b). There are three patterns of MERS-CoV infection: isolated sporadic cases, intra-family clusters, and healthcare-associated infections (Al-Tawfiq and Auwaerter 2018). The clinical presentation of most cases is consistent with respiratory illness and 33% of patients may have nausea, vomiting, or diarrhea (Al-Tawfiq et al. 2016b). Early symptoms are mild and nonspecific which last several days prior to progressing to severe pneumonia. There are no predictive signs or symptoms to differentiate MERS-CoV from community acquired pneumonia in hospitalized patients (World Health Organization 2015). There is an apparent heterogeneity in transmission. Severe disease is usually seen in primary or index cases, immunocompromised, and people with underlying comorbidities. Mild or asymptomatic disease usually occurs in secondary cases and was initially thought to be only in the young and previously healthy individuals. However, mortalities and severe cases were seen among primary cases and among young individuals (Corman et al. 2014). Although person-to-person transmission is definite, the route of transmission is still

not clear. The median incubation period was 5.2 days (95% CI, 1.9–14.7), and the serial interval was 7.6 days (95% CI, 2.5–23.1) (Assiri et al. 2013b).

There are few studies describing co-infection of MERS-CoV with influenza A, parainfluenza, herpes simplex, and *Streptococcus pneumonia* and tuberculosis (Alfaraj et al. 2017a, b; World Health Organization 2013).

MERS-CoV infection carries a case fatality rate of 40–60% (Al-Tawfiq and Memish 2014b; Assiri et al. 2013a, b; Penttinen et al. 2013). Lower case-fatality rates of 20% were reported in two studies from Saudi Arabia and South Korea. The current study included a larger number of patients spanning a longer duration and the case fatality rate was only 20% (Al-Tawfiq et al. 2017; Ki 2015). Variable laboratory findings were reported among MERS-CoV patients. Lymphopenia was described in 44–92% of patients (Assiri et al. 2013a, b; Zaki et al. 2012; Al-Tawfiq et al. 2014a; Hijawi et al. 2013; Guery et al. 2013; Memish et al. 2013a; Arabi et al. 2014). In addition, thrombocytopenia was also described in different studies (Assiri et al. 2013a, b; Arabi et al. 2014; Al-Tawfiq and Memish 2015b).

The main diagnostic test for MERS-CoV is based on real-time reverse-transcription polymerase chain reaction (PCR). The samples are either Dacron-flocked nasopharyngeal swabs or sputum samples (Assiri et al. 2013b). The PCR test amplifies both the upstream E protein (upE gene) and ORF1a for MERS-CoV. The best samples for the diagnosis of MERS-CoV is lower respiratory samples as these samples have lower Ct values (higher viral load) and were present later in the course of the disease (Assiri et al. 2013b; Memish et al. 2014c). This also in line with WHO recommendations (World Health Organization 2015).

History of MERS-CoV in Relation to the Hajj

In the recent years, two novel corona viruses emerged and posed a global threat. These are SARS-CoV in 2003 and MERS-CoV in 2013. It was shown that there were no cases of SARS linked to the Hajj (Al-Tawfiq et al. 2014b). The first two MERS-CoV infections occurred weeks before the 2012 annual Muslim Hajj season. The first MERS case was in a Saudi Arabian patient (Zaki et al. 2012) and the second was in a patient from Qatar who was transferred to London (Pebody et al. 2012). The initial 2012 Hajj season started few weeks after the first case of MERS-CoV infection was reported (Memish et al. 2014d). However, there were no reported cases among pilgrims in 2012 (Kandeel et al. 2011; Rashid et al. 2008; Al-Tawfiq et al. 2013; Memish et al. 2013b). Thus, the Saudi Ministry of Health (MoH) utilized the MERS-CoV case definition for monitoring any occurrence of the disease during Hajj for early detection of cases among pilgrims (Al-Tawfiq and Memish 2014a). An enhanced surveillance system was established for the detection of MERS-CoV cases. The disease remains limited to the Middle East with the exception of sporadic travel-associated infections and the large outbreak in South Korea (Sridhar et al. 2015; Kim et al. 2016; Korea Centers for Disease Control and Prevention 2015; Pavli et al. 2014). In one study conducted during September 2012–October 2013, 77 travelers from the Middle East met the possible case definition for MERS and 2

of them tested positive for MERS (Sridhar et al. 2015). In a small study of 14 retuning pilgrims, all patients were hospitalized for respiratory symptoms and none of them tested positive for MERS-CoV in Marseille France in October 2013 (Gautret et al. 2014). Furthermore, nasopharyngeal swabs were collected from suspected cases and all samples tested negative for MERS-COV (Memish et al. 2014d). Another small study of seven pilgrims was conducted in 2014 in Austria, and none had MERS-CoV (Aberle et al. 2015).

Systematic Screening for MERS-CoV Among Attendees of the Annual Hajj

Following that, there were systematic screening of pilgrims for MERS-CoV, and none of the studies showed positive cases (Al-Tawfiq et al. 2013; Aberle et al. 2015; Gautret et al. 2013; Barasheed et al. 2014; Baharoon et al. 2009; Memish et al. 2014e, 2015; Annan et al. 2015; Refaey et al. 2016; Atabani et al. 2016; ProMed 2013; Griffiths et al. 2016; Benkouiten et al. 2014; Ma et al. 2017; Al-Abdallat et al. 2017; Koul et al. 2017). Mathematical models estimated the risk of MERS-CoV among pilgrims to be 1–7 cases per Hajj and 3–10 per Umrah per year (Gardner et al. 2014). Early in the history of MERS-CoV, it was estimated that 6.2 pilgrims may develop MERS-CoV symptoms during the Hajj, and 4 pilgrims may become infected and return home before symptoms development (Lessler et al. 2014). Systematic surveillance of returning pilgrims was done in several studies in Egypt, Iran, France, and Ghana as well as studies in Saudi Arabia (Gautret et al. 2013, 2014; Memish et al. 2014e; Annan et al. 2015). The prevalence of non-MERS coronavirus was detected in 1–21% of pilgrims (Gautret et al. 2013, 2014, 2016a, b; Al-Tawfiq and Memish 2014a; Memish et al. 2012, 2014d, e, 2015; Kandeel et al. 2011; Al-Tawfiq et al. 2013, 2016c; Aberle et al. 2015; Barasheed et al. 2014; Baharoon et al. 2009; Annan et al. 2015; Refaey et al. 2016; Atabani et al. 2016; ProMed 2013; Griffiths et al. 2016; Benkouiten et al. 2014; Ma et al. 2017; Al-Abdallat et al. 2017; Koul et al. 2017) (Table 1). Despite the extensive surveillance and since the emergence of MERS-CoV, only four cases have been linked to Umrah (Mini-Hajj) (Kraaij-Dirkzwager et al. 2014; Fanoy et al. 2014; ProMed 2014a, b, n.d.). In addition, few studies examined MERS-CoV among symptomatic pilgrims, and none was positive for MERS-CoV (Table 2, Fig. 1) (Memish et al. 2014d; Al-Tawfiq et al. 2013; Aberle et al. 2015).

Recommendations for Pilgrims in Relation to MERS-CoV

As MERS-CoV emerged in 2012, there were no specific recommendations targeting the newly emerging virus. In October 2012, updated recommendations on health hazards and recommendations for Hajj 2012 were published (Al-Tawfiq and Memish 2012b). The 2012 Hajj season was concluded with no cases of MERS-CoV among pilgrims. More 300 ill pilgrims were tested for MERS-CoV and all were negative

Table 1 Systematic screening of MERS-CoV among pilgrims

Reference	Year of the study	Study population	Method	Number screened	N (%) positive
Gautret et al. 2013	2012	French cohort	Nasopharyngeal swab	154	0
Gautret et al. 2014	2013	Departing pilgrims	Nasal swabs	129	0
Barasheed et al. 2014	2013	Pilgrims from Saudi Arabia, Australia, and Qatar	Nasal swabs	1038	0
Refaey et al. 2016	2012–2015	Egyptian	Nasopharyngeal and oropharyngeal swabs	484	0
Annan et al. 2015	2013	Adult African Hajj pilgrims returning to Ghana, West Africa	Nasopharyngeal swab	839	0
Memish et al. 2015	2013	Departing pilgrims, paired, and non-paired cohort	Nasal swabs	692 (paired cohort), 514 (non-paired arriving cohorts); and 470 (non-paired departing cohort)	0
Gautret et al. 2014; Benkouiten et al. 2014	2013	French pilgrims	Nasal and throat swab	129	0
Memish et al. 2014e	2013	Multiple nationalities	Nasopharyngeal swab	3210 pre-Hajj	0
Memish et al. 2014e	2013	Multiple nationalities	Nasopharyngeal swab	2025 post-Hajj	0
Atabani et al. 2016	2013–2015	Symptomatic British pilgrims	Upper and lower respiratory tract	202	0
Griffiths et al. 2016	2013–2015	Ill French travelers	Not indicated	33	0
Ma et al. 2017	2013–2015	Chinese	Lower respiratory tract sputum, washes, and upper respiratory tract oropharyngeal swab	847	0

(*continued*)

Table 1 (continued)

Reference	Year of the study	Study population	Method	Number screened	N (%) positive
Al-Abdallat et al. 2017	2015	Jordanian	Nasopharyngeal and oropharyngeal	125	0
Koul et al. 2017	2014–2015	Kashmir, north India	Nasopharyngeal and throat swabs	300	0

Table 2 Screening of symptomatic pilgrims for MERS-CoV

Reference	Year of the study	Study population	Method	Number screened	N (%) positive
Al-Tawfiq et al. 2013	2012	Symptomatic French	Nasopharyngeal swab	300	0
Memish et al. 2014d	2013	Admitted pilgrims with pneumonia	Sputum	38	0
Aberle et al. 2015	2014	Symptomatic pilgrims returning to Austria	Sputum, throat swab, or bronchoalveolar lavage	7	0

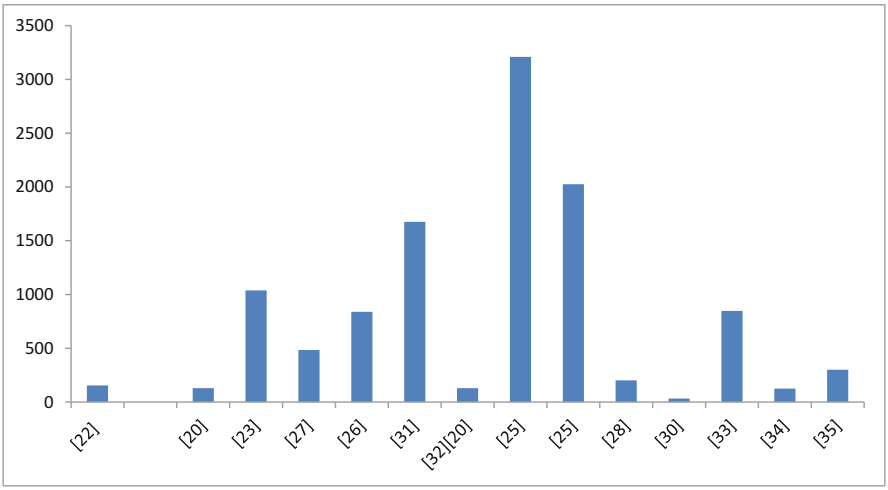

Fig. 1 Histogram shows the number of systematic screened pilgrims for MERS-CoV and none of them tested positive

(Al-Tawfiq et al. 2013). There are no special recommendations for pilgrims in regard to MERS-CoV infection. Pilgrims are advised to practice proper hand hygiene, protective behaviors, and cough etiquette. It is also recommended that pilgrims avoid contacts with camels (Al-Tawfiq and Memish 2012b). In addition, in 2015,

Saudi Arabia banned the sacrifice of camels for Hajj and discouraged visits by pilgrims to camel barns during Hajj activities (Gautret et al. 2016b).

Conclusion

MERS-CoV infection remains very rare among pilgrims. There were extensive surveillance of pilgrims for the existence of MERS-CoV, but all were negative. However, two cases were detected among returning travelers after performing Umrah (mini-Hajj). Continued surveillance and vigilance are required to further enhance public awareness and inform evidence-based practices.

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