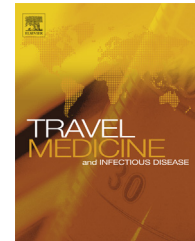




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REVIEW

Middle East respiratory syndrome coronavirus (MERS-CoV): Prevention in travelers



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Summary Middle East respiratory syndrome coronavirus (MERS-CoV), a novel coronavirus that causes a severe lower respiratory tract infection in humans, emerged in the Middle East in 2012. Since then, MERS-CoV has caused an ongoing epidemic in the Arabian Peninsula with sporadic cases imported in Europe, North Africa, Southeast Asia, and the United States of America. As of 28th May 2014, 636 laboratory-confirmed cases of infection with MERS-CoV have been reported to World Health Organization including 14 cases imported by travelers. The epicenter of the current MERS-CoV epidemic is located in Saudi Arabia, where millions of pilgrims travel for two mass gatherings annually. In this review we summarize MERS-CoV cases in relation to travel with focus on the epidemiology and prevention in travelers. It is important to increase awareness of travelers about the risks and appropriate preventive measures and for health professionals to be on alert if a patient with severe respiratory symptoms reports a recent history of travel to the region affected with MERS-CoV. Measures should be taken by local health authorities of the affected countries in order to improve hospital hygiene. Finally, it is crucial to investigate the reasons for travelers' poor compliance with rules and recommendations issued by Saudi officials and to take appropriate measures in order to improve them.
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1. Introduction

International travel has increased dramatically over the past six decades; from 25 million in 1950, to 528 million in 1995, 1035 million in 2012 and is expected to reach 1.8 billion in 2030. In 2012, international tourist arrivals in the Middle East were estimated at 52 million [1]. Travelers can be exposed to various infectious agents and may facilitate their spread across borders. The importance of travel in the dissemination of respiratory diseases [2] has been demonstrated by the rapid worldwide spread of Severe Acute Respiratory Syndrome (SARS) outbreak in 2003 and the recent pandemic of influenza A (H1N1) in 2009 [3,4].

The Middle East respiratory syndrome coronavirus (MERS-CoV) was isolated for the first time from a Saudi patient with severe pneumonia and a fatal outcome in September 2012. Since then, MERS-CoV has caused an ongoing outbreak in the Arabian Peninsula [5–8] with sporadic cases imported in European, North African, Southeast Asian countries and USA [9–17]. Coronaviruses are positive-sense RNA viruses. MERS-CoV belongs to *Betacoronavirus* phylogenetic lineage C that, in addition to MERS-CoV, contains 2 distinct bat-associated CoV species (HKU4 and HKU5) [7]. As of 15th May 2014, globally, 572 laboratory-confirmed cases of infection with MERS-CoV have officially been reported to WHO, including 173 deaths [6]. We summarize travel-related cases of MERS-CoV with focus on the epidemiology and prevention in travelers.

2. Source for human infection

Patterns of transmission of MERS CoV remain unclear. Hypotheses include frequent zoonotic infections with limited subsequent human-to-human transmission chains with self-sustained epidemic in humans [16,11]. There is growing evidence that the dromedary camel is a reservoir for the MERS-CoV and is playing an important role in the transmission to humans [15,18,19]. Although bats have been the ultimate progenitor virus, epidemiologically appears more likely that camels would be the source of infection in humans [6]. The ways of human-to-human transmission include direct transmission through droplets produced during coughing or sneezing, indirect transmission through contact with contaminated surfaces and devices [6]. A recent study showed that when MERS-CoV is added to unpasteurized camel milk stored at 4 °C, the virus remains infectious beyond 72 h but that infectious viruses could not be found after pasteurization [7].

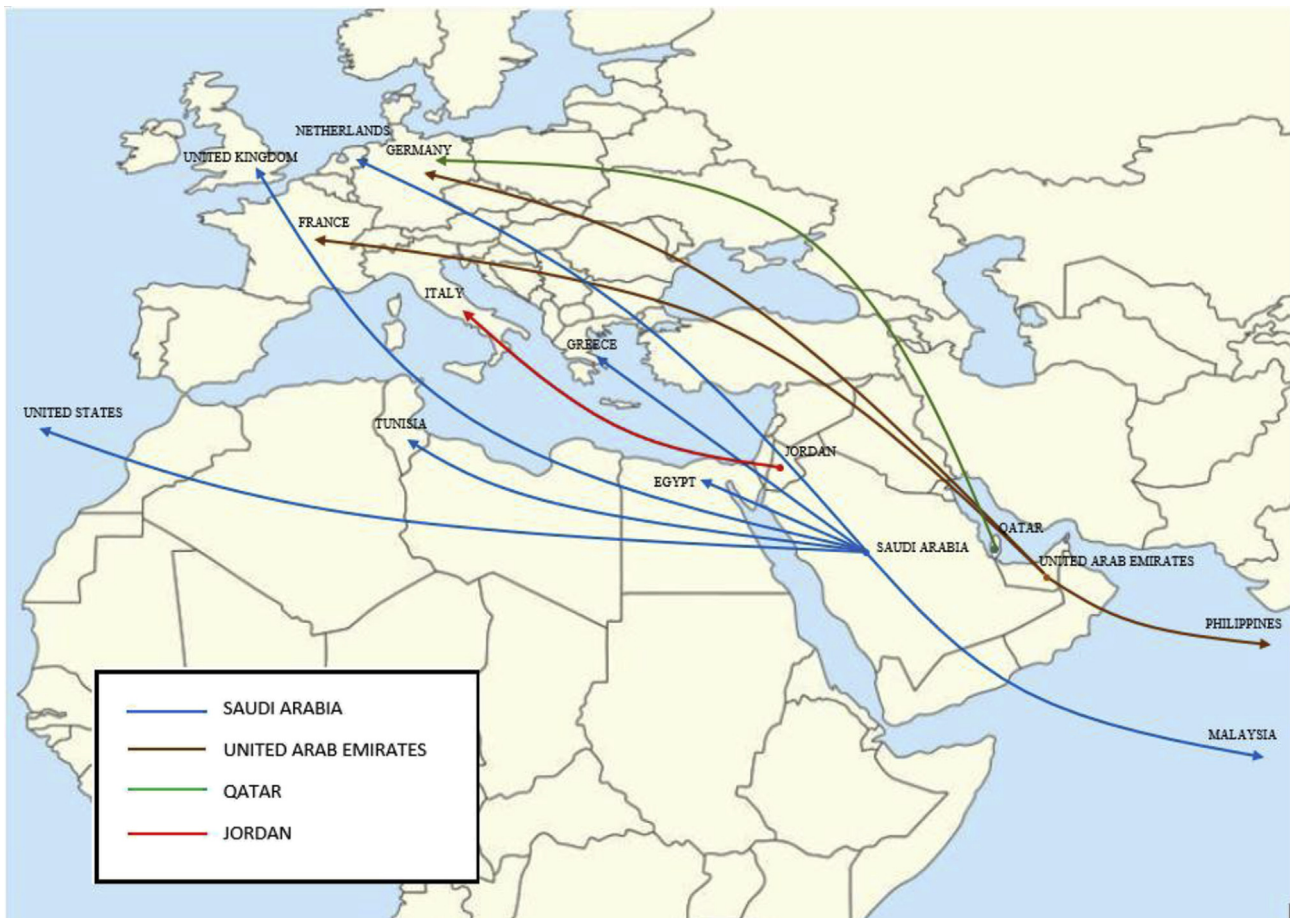
3. Epidemiology and risk for travelers

The number of reported cases of MERS-CoV increased markedly since mid March 2014. In particular, the number of cases reported in April 2014 account for more than 50% of the total cases which have been reported seen June 2012 [5]. The travel-associated MERS-CoV cases reported by countries outside the Arabian Peninsula in 2014 occurred in persons with residence in or travel to countries of the Middle East. The first imported case in Greece [11] increased to six the number European countries with confirmed cases of MERS-CoV infection amongst travelers,

namely Germany, Greece, France, Italy, Netherlands and the United Kingdom (UK) [6]. Furthermore, imported primary cases have been reported by other countries outside Europe such as Egypt, Tunisia, Malaysia and the Philippines (Fig. 1) [6]. Characteristics of MERS-CoV infection cases in travelers are presented in Table 1. The majority of them were male (92.8%), and between 27 and 73 years of age, with a case fatality rate of 28.5%. Most common destination was Saudi Arabia (64.2%). Travel related cases have been associated with secondary cases in close contacts of index cases without a travel history suggesting person-to-person, although limited, transmission; a total of seven secondary cases have been reported in the literature [9,12,13,16]. Family clusters have been described in relation to the imported cases in Tunisia and the UK [9,16] as well as in health-care settings [13,17,20].

Work is one of the common reasons for travel to the Middle East. A recent Greek airport based survey which was conducted from 2011 to 2013 showed that 46.8% of business travelers who visited tropical and subtropical areas traveled to the Middle East [21]. Many Middle Eastern countries are home to large foreign-born populations including migrant workers. Five of all MERS CoV cases amongst travelers concerned expatriates who resided in Saudi Arabia [11,16,17]; three of them were health-care workers [16,17]; this highlights the importance of adherence to recommended infection-control measures, such as standard, contact, and airborne precautions (including eye protection), for health-care workers working in health care settings in the affected countries, while managing patients under investigation or who have probable or confirmed MERS-CoV infections [16]. Contact with animals, in particular visiting, or working in a camel farm is considered a risk factor for acquiring the disease; the Malaysian pilgrim, the first UK and the two German imported cases reported contact with camels during their stay in the Arabian Peninsula (35.7% of all cases) [10,14,22]. This information was not known in 50% of the cases (Table 1).

Hajj, the largest religious mass gathering takes place every year in Saudi Arabia; it has become the epicenter of mass migration of millions of Muslims of large ethnic diversity. Communicable disease outbreaks of various infectious diseases have been reported repeatedly, during and following the Hajj [23]. Several studies have been carried out for the surveillance of MERS-CoV in pilgrims [24–27]. A rapid acquisition of respiratory viruses, mainly rhinovirus was found in 39% of French pilgrims who suffered from respiratory symptoms soon after commencing the 2012 Hajj, with 11% returning infected to France with potential spreading of these respiratory viruses [25]. No case of MERS-CoV nasal carriage was evidenced in this cohort, despite high rates of respiratory symptoms [26]. Similarly, there was no evidence of MERS-CoV nasal carriage among Hajj pilgrims in another study which was performed on pilgrims from 22 countries attending the 2013 Hajj [27]. This study revealed that rates of compulsory vaccinations uptake were high, whereas uptake of pneumococcal and flu seasonal vaccinations were low, including among the high-risk population showing pilgrims' poor compliance with vaccine recommendations [27]; this may explain the increased prevalence of influenza in pilgrims [28]. Although there was no evidence of MERS-CoV nasal carriage during



***United States and United Kingdom reported 2 cases from Saudi Arabia, respectively**

Fig. 1 Geographical distribution of travel-related MERS-CoV cases and places of probable infections worldwide, as of 28 of May ($n = 14$)*.

screening of Hajj pilgrims, three of the cases amongst travelers concerned pilgrims returning from Mecca to the country where they reside (Malaysia, Netherlands and United Kingdom, respectively) [9,16]. The patient from Malaysia, a 54 year-old man with underlying health conditions traveled to Saudi Arabia with a pilgrimage group of 18 and visited a camel farm, during which he consumed camel milk. There was no human-to-human transmission observed amongst close contacts and in health-care facilities in Malaysia [16]. The case from the Netherlands which concerned a 70 year old man reported no contact with animals or consumption of raw animal products. Identification of close contacts, including flight contacts was also initiated [16]. Cluster cases were reported during contact tracing of the third case which concerned an adult middle-aged male in the United Kingdom who visited Mecca and Medina on pilgrimage. No direct contact with animals or with people with severe respiratory illness was reported in the 10 days before the onset of his illness. Contact tracing, including aircraft passengers identified two secondary cases among family members without a history recent travel: one developed a severe respiratory illness and died and the other influenza-like illness; no other severe cases were identified or CoV detected in respiratory samples among 135 contacts for the following 10 days [9].

MERS-CoV has emerged in the Middle East where religious mass gatherings take place in Saudi Arabia every year and potentially may cause severe, life-threatening respiratory disease which may contribute to the international spread of MERS-CoV. Religious mass gatherings in Saudi Arabia draw millions of travelers and Muslim pilgrims from predominantly resource poor countries with limited medical and public health capacity for the detection and response to imported cases. This may lead to domestic transmission and the onset of an outbreak at [29]. Based on the predicted population movements out of Saudi Arabia, a potential for a global spread of MERS-CoV can not be excluded according to Kahn and colleagues [29]. Breban and colleagues calculated that the risk for MERS-CoV to have a pandemic potential is less than 5%; however the influence of Hajj mass gathering was not taken into account [30].

According to a recent French study, despite the Saudi Arabia Ministry of Health recommendation for people at highest risk of the complications of MERS (Co-V) to refrain from the 2013 Hajj for their own safety, 48% of pilgrims preparing for Hajj from France did not comply [31,32]. Knowledge, attitudes and practices of Hajj pilgrims about MERS (Co-V) may be influenced by cultural and religious beliefs; although they may be aware about the Saudi

Table 1 Characteristics of published MERS (Co-V) cases among travelers.

Country of importation	Ref	Age	Gender	Destination	Duration of travel (days)	Purpose of travel	Past history	Animal contact	Laboratory confirmation	Outcome	Secondary cases
1. Egypt	16	27	M	SA	Expatriate	NA	NA	NA	YES	Survived	—
2. France	13	64	M	UAE	8	NA	Renal transplantation	NA	YES	Died	1
3. Germany	14	73	M	UAE	Local citizen	NA	Multiple Myeloma	YES Camel Breeder	YES	Died	—
4. Germany	15,22	~49	M	Qatar	Local citizen	NA	Heavy Smoker	YES Camel, goat	YES	Survived	—
5. Greece	11	69	M	SA	Expatriate	Work	NA	YES Indirect with bats	YES	Survived	—
6. Italy	12	45	M	Jordan	40	Tourist	Nil	NA	YES	Survived	2
7. Malaysia	16	54	M	SA	13	Pilgrim	Underlying health conditions	YES	YES	Died	—
8. Netherlands	16	70	M	SA	14	Pilgrim	NA	NO	YES	Survived	—
9. Philippines	16	34	F	UAE	Expatriate	Work	Nil	NA	YES	Survived	—
10. Tunisia	16	65	M	SA	NA	NA	NA	NA	YES	Died	2
11. UK	10	49	M	SA	<30	Tourist	Nil	YES	YES	Survived	—
12. UK	9	middle aged	M	SA/Pakistan	8/35	Pilgrim	Nil	NO	YES	Survived	2
13. USA	17	≥60	M	SA	Expatriate	Work	NA	NA	YES	Survived	—
14. USA	17	≥40	M	SA	Expatriate	Work	NA	NA	YES	Survived	—

Abbreviations: UAE: United Arab Emirates, UK: United Kingdom, USA: United States America, SA: Saudi Arabia, NA: Not available.

Table 2 MERS CoV preventive advice for travelers to the Middle East.^a

1. Wash your hands with soap and water or apply an alcohol solution.
2. Cover your mouth and nose with a tissue while coughing or sneezing.
3. Avoid hand shaking or touching your mouth, nose and eyes with your hands.
4. Avoid contact with patients with respiratory symptoms.
5. Avoid contact with domestic or wild animals (e.g. camels).
6. Avoid contact with animal secretions (e.g. urine, faeces).
7. Avoid consumption of unpasteurized milk (in particular from camels), or meat inadequately cooked.
8. Avoid consumption of fruit and vegetables which are not washed or peeled by yourself.
9. If you develop any respiratory symptoms during your trip seek medical attention immediately, report your recent trip and postpone your return until you have fully recovered.
10. After returning from countries of the Middle East, if within 14 days you develop fever 38 °C or more and respiratory symptoms (cough, shortness of breath, etc) you should seek medical attention immediately and inform your doctor about your recent trip.
11. If you are a pilgrim traveling for Hajj and Umrah and above 65 years of age, or if you suffer from chronic diseases (e.g. heart, kidney or respiratory disease, diabetes, congenital or acquired immune deficiency, malignancy or terminal illness, or if you are a pregnant women or a child (<12 years of age), you should postpone the performance of the Hajj and Umrah for your own safety^b

^a In accordance with WHO, CDC, ECDC and the Hellenic Centre for Disease Control and Prevention guidelines.

^b The Saudi Ministry of Health (MoH) recommendations.

Ministry of Health recommendations and may be informed about the risks during a pre-travel consultation there is a need for communication strategies for this high risk group of travelers in order to improve their risk perception and attitudes towards prevention [33].

4. Prevention of MERS-CoV in travelers

The current epidemiology of MERS-CoV on the Arabian Peninsula may lead to travel implications and it is likely that more cases will be imported and detected globally [34]. Furthermore, MERS CoV cases may be imported to other regions of the world by pilgrims who visit Saudi Arabia for Hajj and Umrah. WHO travel advice does not impose any travel or trade restrictions with regard to MERS-CoV and does not advise special screening at points of entry [6].

Further vigilance in assessing patients with travel history to the affected region is warranted. Travel health consultants should have access to updated information in regards to the epidemiology of the disease and preventive measures and they could contribute to the surveillance of imported cases. Although the source of the virus and the mechanism of transmission is unknown, it would be important to take all possible preventive measures in order to reduce the general risk of infection while traveling [5–7]. Thus Public Health Authorities should develop strategies in order to increase awareness about MERS (CoV) in travelers, health and tourism industry professionals.

Non-pharmaceutical interventions are known to reduce the spread of respiratory viruses from person to person [35]. Therefore, people visiting the Middle East at all times of the year and in particular pilgrims of Hajj and Umrah should take precautions such as: avoiding close contact with people suffering from acute respiratory infections, take personal hygiene measures (frequent hand-washing, cough and sneeze etiquette), adhering to food safety and hygiene rules (avoiding unsafe water, undercooked meats, raw fruits and vegetables unless they have been peeled).

Raw camel milk consumption in the Middle East may be associated with several zoonotic infections; therefore it is advisable for Hajj pilgrims to avoid unpasteurized milk. It is also recommended to avoid close contact with live farm or wild animals in particular camels [36]. Travelers to the Middle East who develop respiratory symptoms either during travel or within 14 days after their return should seek medical attention. A history about their recent trip should be given. Furthermore they should practice cough etiquette (cover coughs and sneezes with disposable tissues, maintain distance, and wash hands) and to postpone their travel until they are no longer symptomatic (Table 2) [5–7,37,38].

Based on current information, it is prudent for people at high risk for severe disease due to MERS-CoV (e.g. those with diabetes, immunosuppression, chronic lung disease, pre-existing renal failure) to take appropriate precautions when visiting farms, barn areas or market environments where camels are present such as avoiding contact with camels, personal hygiene measures, and avoiding drinking raw milk or eating food that may be contaminated with animal secretions or products unless they are properly washed, peeled, or cooked [5–7,37,38].

The Saudi Ministry of Health (MoH) recommendations include that elderly people, above 65 years of age, and those with chronic diseases e.g. heart disease, kidney disease, respiratory disease and diabetes and pilgrims with immune deficiency such as congenital and acquired, malignancies and terminal illnesses, pregnant women and children (under 12) coming for Hajj and Umrah, should postpone the performance of the Hajj and Umrah for their own safety [31].

5. Conclusion

MERS-CoV infection is an emerging disease with pandemic potential originating from Saudi Arabia, where millions of pilgrims travel for two mass gatherings annually. The majority of MERS-CoV cases are reported in Saudi Arabia with a

significant rate of hospital transmission. The possibility of airborne transmission is very low and secondary cases are only likely after close contact and due to severe symptoms there is only little likelihood of unregistered clinical cases. Countries should focus on increasing awareness of travelers visiting friends and relatives and of health professionals about patients with severe respiratory symptoms who report a recent history of travel to the region affected with MERS-CoV. Travel medicine practitioners should not discourage travelers to visit these countries as long as they follow the basic hygienic measures. Travelers should be advised to avoid local hospitals if medical help is needed and to be visited by a doctor instead. Measures should be taken by local health authorities of the affected countries in order to improve hospital hygiene. In addition, it is crucial to investigate the reasons for travelers' poor compliance with rules and recommendations issued by Saudi officials and to take appropriate measures in order to improve them.

An internationally coordinated effort to better understand global population movements in this area and the most probable pathways for international spread of MERS-CoV could help direct anticipatory MERS-CoV surveillance and public health preparedness to mitigate its potential global health and economic impacts.

Conflict of interest

None.

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