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Travel implications of emerging coronaviruses: SARS and MERS-CoV

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Summary The emergence of Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and of the Middle East Syndrome Cornavirus (MERS-CoV) caused widespread fear and concern for their potential threat to global health security. There are similarities and differences in the epidemiology and clinical features between these two diseases. The origin of SARS-COV and MERS-CoV is thought to be an animal source with subsequent transmission to humans. The identification of both the intermediate host and the exact route of transmission of MERS-CoV is crucial for the subsequent prevention of the introduction of the virus into the human population. So far MERS-CoV had resulted in a limited travel-associated human cases with no major events related to the Hajj.

1. Introduction

The emergence of Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) in 2003 in China [1] and of the Middle East Syndrome Coronavirus (MERS-CoV) in the Kingdom of Saudi Arabia (KSA) in 2012 [2] aroused widespread fear and concern for their potential threat to global health security. Several similarities and differences in the epidemiology, clinical features and management of SARS and MERS have been identified [3]. Both SARS-CoV and MERS-CoV viruses are enveloped positive strand RNA betacoronaviruses. SARS-CoV and MERS-CoV isolated from bats share sequence homology with isolates from humans or civet cat isolates suggest that bats are reservoirs [4—8]. In contrast to MERS-CoV where the Hajj and Umrah (mini-

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Hajj) continued to occur without any reported cases, whereas SARS had a significant economical impact. The estimated global economic cost of 100 billion; $US 48 billion in China alone [9,10].

2. SARS and MERS — the initial events

In 27 November 2002, non-official report was issued pointing the presence of an outbreak of respiratory illness in Guangdong Province, China [11]. This was followed in February 2003 by the notification of WHO by the Chinese Ministry of Health of an outbreak of acute respiratory syndrome with 305 cases and 5 deaths [12]. In February—March 2003, there were clusters of atypical pneumonia reported in Vietnam, Hong Kong, Canada, and Singapore [1,13—16]. All these clusters were linked to index patients who stayed on the ninth floor of a hotel in Hong Kong on February 21—22, 2003 [17]. Subsequently, SARS-CoV spread across 30 countries in 6 continents and resulted in a cumulative 8098 cases and 774 deaths (9.5%) [18] with a high rate (21%) of involvement of healthcare workers [19].

With regards to MERS-CoV, the first case of MERS was reported from a patient from Jeddah, Saudi Arabia. The patient had a fulminant disease and he died in September 2012 [2]. Subsequently, MERS-CoV was reported to cause sporadic, intrafamilial or healthcare associated outbreaks infection in Saudi Arabia [20—23], Qatar [24], Jordan [25,26], United Kingdom [27,28], Germany [29], France [30], Tunisia [31], United Arab Emirates [32], and Italy [33]. As of June 26, 2014, there are a total of 707 laboratory-confirmed MERS-CoV infection, including 252 deaths [34].

3. Epidemiology, clinical features and transmission of SARS and MERS

The epidemiology, viral kinetics and transmission patterns of SARS-CoV are well documented [35,36]. SARS-CoV caused higher rates of infections in healthcare settings, and affected healthier and younger persons [37]. The mean age was 56 (range 14—94) compared to 39.9 (range 1—91) years and the male to female ratio was 3.3:1 and 1:1.3; for MERS and SARS respectively [21]. The estimated mean incubation period of SARS was 4.6 days [95% confidence interval (CI) 3.8—5.8 days] [20,38] and the incubation period of MERS was 5.2 days (95% CI 2.2 to 12.4 days) [20].

SARS was found to spread by droplet transmission or direct person-to-person through close contact [36,39—42]. It was estimated that 42% of the early SARS cases in Guandong where among people involved in animal trade or in food preparation [43]. SARS-CoV antibodies were found in 13% of the animal traders with no diagnosis of SARS compared with 1%—3% of persons in three control groups [44].

The clinical picture of SARS and MERS seems to be similar [3]. In an early comparison between the two diseases, the mortality rate of MERS-CoV was 55% compared to 0—40% for SARS [21], and case-fatality rate for patients with comorbidities of 60% compared to 1—2%, and a mean time from onset to death (days) 16.5 compared to 23.7 for MERS and SARS, respectively [21]. Haemoptysis was more common in MERS (17%) compared to SARS (1%) [21].

Whilst the clinical presentation and transmission characteristics of MERS-CoV infection appear similar to SARS-CoV the geographical distribution indicates that all primary cases of MERS confirmed so far had a link with the Middle East [42] and no global spread outside the Middle East has occurred despite millions of pilgrims who have visited KSA during the past 2 years from 184 countries [43]. This finding indicates that transmission between humans of MERS-Cov is lower than that of SARS-CoV.

4. Animal reservoirs

Both SARS-CoV and MERS-CoV are most likely of zoonotic origin, and the potential animal reservoirs seem to be bats. SARS-CoV-like viruses were isolated from Himalayan palm civets (*Paguma larvata*) in Guangdong Province, China; from raccoon dogs (*Nyctereutes procyonoides*); and from a Chinese ferret badger (*Melogale moschata*) [45]. Seroprevalence of SARS-CoV antibodies among wild animal trader in Guangdong Province was higher than among workers in other parts of the market or in controls [44,45]. The highest prevalence of antibody (72.7%) was noted among those who traded primarily in palm civets [44].

In vitro studies revealed possible intermediate host for MERS-CoV. Cell lines from goats and camels exhibited efficient replication of the virus [46]. The highest production of virus particles was in goat lung and kidney cells and was comparable to human lung and Vero E6 cells 9 (interferon-deficient primate kidney cells) [46]. MERS-CoV binds to the dipeptidyl peptidase-4 (DPP4s) of camel, goat, cow and sheep [47]. Thus, camels, goats, sheep and cows may be MERS-CV intermediate host reservoir species. In the search of serologic evidence for MERS-CoV infection, neutralising antibodies were not found in sera from goats and cattle [48]. In Saudi Arabia including regions of Riyadh and Al Ahsa, pseudoparticle neutralisation (ppNT) and microneutralisation (MNT) tests detected no antibodies to MERS-CoV in sheep ($n = 100$), goats ($n = 45$), cattle ($n = 50$) and chickens ($n = 240$) [49].

In a patient with MERS-CoV infection, the patient owned a farm with camels and goats [29]. There were reports of illness affecting the goats and the patient had no direct contact with animals but he ate goat meat and was in contact with an animal caretaker who had respiratory tract disease [29]. One patient had direct contact with a diseased camel shortly before onset of his symptoms [32], and one patient treated a sick camel [50,51]. MERS-CoV from one patient and from the camel were identical [50,51].

Both SARS and MERS caused pulmonary lesions in experimentally challenged cynomolgus macaque monkeys (*Macaca fascicularis*) [52] and in rhesus macaques, respectively [53]. MERS-CoV has a genetic similarity to bat coronaviruses and thus suggesting an origin in flying mammals [8,54]. In Saudi Arabia, one bat (*Taphozous perforates*) had a short nucleotide segment identical to the homologous segment of the MERS-CoV virus isolated from an index-case [8]. SARS-related CoVs were identified in *Rhinolophus* spp. bats in China [55] and Europe [56], and MERS-related CoVs in *Pipistrellus* bats in Europe [57].

The primary source of MERS-CoV remains unknown but an intermediary animal source other than bats or other animal product is suspected [8,21]. There is increasing evidence of

the presence of MERS antibodies in camels pointing them as possible reservoir or an intermediate host. In an initial study from 50 sera of dromedary camels (*Camelus dromedaries*) from Oman showed a high-titre of neutralizing antibodies against MERS-CoV [58]. Later on, multiple studies showed positive antibodies in camels from many countries including Spain (Canary Islands), Egypt, Qatar, KSA, UAE, and Jordan [48,50,58—65]. In addition, MERS-CoV was detected by PCR in 2 of 9 (22.2%) camels from the farm of a patient in Jeddah, KSA [50,51], and from 3 of the 14 tested dromedary camels in Qatar [59]. More than one genomic variant was found in dromedary camels which is different from humans where one variant exist and thus the finding suggests interspecies transmission of MERS-CoV of specific genotypes [66]. Currently, the route of animal-to-human transmission is not clearly known [67]. However, MERS-CoV was found in camel milk in 41.7% of 12 tested camel milk [68].

Human to human transmission occurred in the Al-Hasa hospital cluster outbreak [20] via droplet route and possible transmission via contaminated fomites. Whilst initial reports were of hospitalized patients who experienced severe respiratory disease resulting in a high mortality in those with comorbidities [9] subsequent proactive screening of all family and health worker contacts of MERS patients have revealed a spectrum of clinical illness from asymptomatic, mild, moderate to severe disease [44]. MERS had caused higher mortality (60% of patients with coexisting chronic illnesses) than the low mortality of 0—40% for SARS [21].

The concern of in flight transmission of MERS-CoV was evaluated in a mathematical model. The modeling suggests if within-flight transmission of MERS-CoV occurs, one infectious case may result in multiple simultaneous outbreaks in different countries [69]. However, there was no Hajj related MERS-CoV cases [70]. Initial screening for MERS-CoV was positive in a returning woman to Spain but the test was not confirmed [70,71]. A few cases of MERS-CoV related to Umrah were reported.

5. Global concern of MERS-CoV and the impact on the Hajj

The Kingdom of Saudi Arabia had the largest number of reported MERS-CoV patients and the Kingdom hosts one of the largest mass gathering in the world. Thus, the potential for the Hajj to cause a global epidemic was of a great concern. During the Hajj, pilgrims gather in a small area in crowded conditions [72,73]. Annually the Saudi Ministry of Health publishes the Hajj requirement including required vaccines, yellow fever for individuals arriving from countries or areas at risk of yellow fever, poliomyelitis vaccine for travellers arriving from Polio-endemic countries, and Polio-reinfected countries; and quadrivalent (ACYW135) meningococcal vaccine for all visitors arriving for Umra or pilgrimage (Hajj) [74]. In addition, the Saudi Ministry of Health recommends seasonal influenza vaccine for all international pilgrims [74].

The first case of MERS-CoV infection was identified from a patient in Jeddah, Saudi Arabia and the patient died in June 2012 [2,75,76]. Public knowledge of MERS-CoV infection was known only few weeks before the 2012 pilgrimage (Fig. 1) [77]. In 2012 with the emergence of MERS-CoV, the Saudi Ministry of Health, based on available data at that time and in accordance with the WHO advice, did not recommend any travel restrictions [77,78]. The Saudi MoH recommendations also promoted the use of good hand hygiene and cough etiquette [78]. On October 10—31, 2012, the 2012 annual Hajj season was uneventful with no reported MERS-CoV cases among four million pilgrims [79]. Among 300 symptomatic pilgrims with upper respiratory symptoms, none of them tested positive for MERS-CoV [80]. In a cohort of 154 French pilgrims, 83.4% had respiratory symptoms, but none was tested positive for MERS-CoV [81]. A number of sporadic cases and cluster of MERS-CoV occurred in 2012 and 2013 in Saudi Arabia as discussed earlier with clear evidence of human to human transmission among close contacts. As the season for the 2013 Hajj approached, the Saudi MoH further strengthened the recommendations based on the available data. The recommendations stated that people 65 years and older, and those with chronic diseases (such as: heart disease, kidney disease, respiratory disease and diabetes) and pilgrims with immune deficiency (congenital and acquired), malignant and terminal illnesses, pregnant women and children aged under 12 years should postpone the performance of the Hajj and Umrah [74].

An optimistic estimate of MERS-CoV R0 was calculated to be 0.69 compared to the prepandemic R0 for severe acute

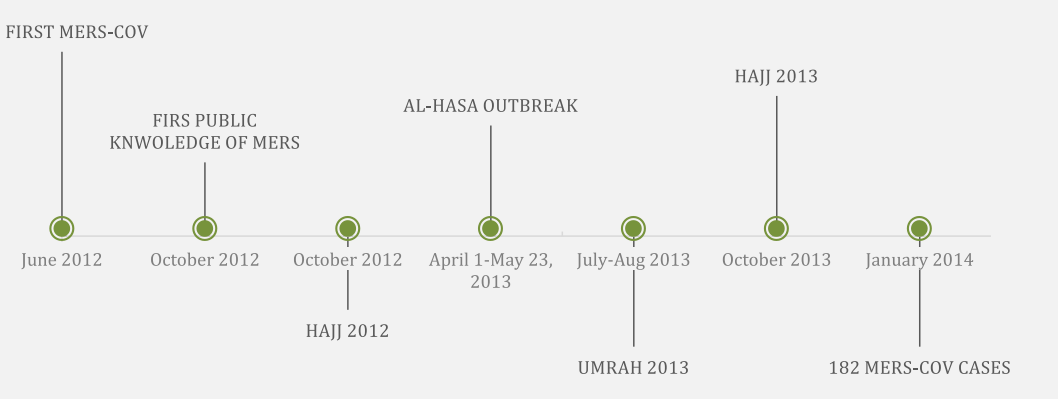

Figure 1 Tome line of MERS-CoV cases in Relation to annual Muslim pilgrimage (Hajj) and mini-Hajj (Umrah) in the Kingdom of Saudi Arabia.

respiratory syndrome coronavirus (SARS-CoV) of 0.7—0.80 [82]. indicating that MERS-CoV in its current status was unlikely to cause a pandemic [83]. In the event that the next an index patient would infect eight or more individuals then the R0 could be above 1 indicating a pandemic potential [83,84]. The 2012 and 2013 Hajj was completed with no evidence of MERS-CoV [70,85].

6. Advice to travellers to the Middle East

There are no vaccines available which can prevent SARS-CoV or MERS-coV infection. The UK PHE and the US CDC does not recommend that anyone change their travel plans to the Middle East because of MERS-CoV threat [86]. This CDC travel notice is a Watch (Level 1) which means travellers to the Arabian Peninsula are advised to follow standard precautions, such as hand washing and avoiding contact with people who are ill. It also recommends that all travellers intending to go on the Hajj or Umrah should follow the KSA MoH special recommendations [85]. Because of the risk of MERS, Saudi Arabia recommends that the following groups should postpone their plans for Hajj and Umrah in 2012—2013 and 2013—2014:

- People over 65 years old
- Children under 12 years old
- Pregnant women
- People with chronic diseases (such as heart disease, kidney disease, diabetes, or respiratory disease)
- People with weakened immune systems
- People with cancer or terminal illnesses.
- Travellers are advised to follow routine measures that can help prevent the spread of infections (Table 1).

7. Screening travellers for SARS-CoV or MERS-CoV

Screening travellers for emerging respiratory viruses such as SARS-CoV was recognized as important in 2003 due to its pandemic potential. The basis of such screening to reduce the potential risks of international spread of infectious disease was controversial [87—91]. In an analysis of the effectiveness of non-contact infrared thermometers (NCIT), the calculated positive predictive value (PPV) was 0.9—76.0% and negative predictive value (NPV) was 86.1—99.7% based on fever prevalence of 1.2—16.9% [87]. In a small study of airline travellers, 3 (0.8%) of 359 met the influenza-like illness case definition [89]. Pitman et al. [90] concluded that "entry screening is unlikely to be effective in preventing the importation of either SARS or influenza". Identifying a maximum of 9% of SARS infected individuals has no significant impact on the course of any subsequent SARS epidemic [90]. In Canada, the use of thermal scanning to detect fever, only 191 (0.025%) of 763,082 screened persons had an initial temperature of >38 °C [91]. The estimated cost of such screening was Can$7.55 million in 4 months [91].

Table 1 Routine Measures for to travellers to help preventing the spread of viruses.

Measure	Advices
Hand Washing	Washing hands often with soap and water. If soap and water are not available, an alcohol-based hand sanitizer may be used
Personal Hygiene	Avoid touching one's eyes, nose, and mouth
Contacts with Sick People	Avoid close contact with people having colds, coughs and sneezes
Contacts with Animals	Avoid contacts with sick animals
Cough Etiquette	Cover one's mouth with a tissue when coughing or sneezing, and dispose properly the used tissue

8. Travellers returning from the Middle East

Travellers to the Arabian Peninsula upon return should seek health care if they develop fever, cough or shortness of breath within 14 days of travel. They should volunteer their travel history so it can alert their physician to the possibility of an imported infectious disease. **Health care providers should have a** high degree of awareness to the possibility of MERS-CoV infection in patients who develop severe acute lower respiratory illness and proactively ask for a history of travel to the Middle East or contact with sick friends or relatives who have been to the Middle East.

9. Conclusion

The origin of SARS-COV and MERS-CoV is thought to be an animal source with subsequent transmission to humans. The identification of both the intermediate host and the exact route of transmission of MERS-CoV is crucial for the subsequent prevention of the introduction of the virus into the human population. Appropriate initial isolation of MERS-CoV patients would prevent the transmission in the healthcare setting.

Conflict of interest

Authors have no conflict of interest to declare.

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