Coronaviruses: severe acute respiratory syndrome coronavirus and Middle East respiratory syndrome coronavirus in travelers

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Purpose of review
Middle East respiratory syndrome coronavirus (MERS-CoV) is currently the focus of global attention. In this review, we describe virological, clinical, epidemiological features and interim travel advice and guidelines regarding MERS-CoV. We compare and contrast these with the severe acute respiratory syndrome coronavirus (SARS-CoV).

Recent findings
MERS-CoV is a novel β CoV that causes a spectrum of clinical illness from asymptomatic to the rapidly fatal disease mainly in those with comorbid conditions. Epidemiological and genomic studies show zoonotic transmission to humans from camels and possibly bats. In contrast to the SARS-CoV pandemic, very limited global spread of fatal MERS-CoV has occurred outside the Arabian Peninsula. Although mainly currently restricted to Middle Eastern countries, MERS-CoV was reported from at least 10 other countries in Europe, Asia and the United States. All primary cases have been linked to travel to the Middle East. Nosocomial transmission of MERS-CoV has occurred because of poor infection control measures. Specific molecular diagnostic tests are available. Currently, there are no specific drugs for prevention or treatment for MERS-CoV and vaccine development is in the early stages. Advice and guidance for travelers to the Middle East are updated regularly by the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC).

Summary
Like SARS-CoV, MERS-CoV threatens global health security. All physicians and travelers to the Middle East should be aware of the new threat caused by MERS-CoV and follow CDC and WHO guidelines. Those who develop ill health during their trip or soon after their return should seek medical care.

Keywords
coronaviruses, MERS-CoV, Middle East, SARS-CoV, travel

INTRODUCTION

Coronaviruses (CoVs) are a group of viruses known to cause mild to severe diseases in humans. The group consists of alpha, beta, gamma, and delta subgroups. Six human CoVs (HCoVs) are known to cause disease in humans: HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, severe acute respiratory syndrome coronavirus (SARS-CoV), and most recently the Middle East respiratory syndrome coronavirus (MERS-CoV) [1]. Both SARS-CoV and MERS-CoV belong to the beta CoVs. SARS-CoV initially emerged in 2003 in China [2] and MERS-CoV was first identified in the Kingdom of Saudi Arabia in 2012 [3]. Whilst MERS-CoV and SARS-CoV share some common virological and clinical features there are several important differences [4▪▪]. Here, we describe virological, clinical, epidemiological features, and interim travel advice and guidelines for the MERS-CoV, a new threat to travelers to the Middle East. It was first detected in Saudi Arabia in

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KEY POINTS

- Similarities exist between SARS and MERS in relation to the clinical and laboratory data.
- Case fatality rate of MERS was 60% initially and now approaches 30% as more asymptomatic cases are recognized.
- Travel-associated infections with SARS and MERS have occurred, but it seems these are lower with MERS-CoV.

September 2012, and is currently the focus of global attention because of its epidemic potential. We compare and contrast these with the SARS-CoV first detected at the end of 2002 in China and which spread globally via travelers.

INITIAL CASES

SARS-CoV was first reported in 2003 from China, Guangdong Province, and later spread to 37 countries and resulted in 8273 confirmed cases with a case fatality rate of 9% [5]. Outbreaks of atypical pneumonia were reported in Vietnam, Hong Kong, Canada, and Singapore in February–March 2003 [2,6–9]. It was reported that these cases were linked to index patients who stayed on the ninth floor of a hotel in Hong Kong on 21–22 February 2003 [10]. Most of the reported cases occurred in Southeast Asia (China, Hong Kong, Taiwan, Singapore, and Vietnam). In North America, 27 cases were imported into the United States and 251 cases were recorded in Canada [11].

MERS-CoV was first reported from a Saudi Arabian patient in September, 2012, who died from severe respiratory illness in June 2012 [3,12]. The virus was originally known as HCoV-EMC [3], and was subsequently designated as MERS-CoV [13▪]. Retrospectively, the first known outbreak was identified in a hospital in Zarqa, Jordan [14▪,15]. This outbreak was recognized after the identification of the MERS-CoV in September 2012, as two specimens from deceased patients were retrospectively tested positive for MERS-CoV by real-time polymerase chain reaction [15].

Intrafamilial clusters of MERS-CoV infection showed that MERS-CoV infection usually causes mild or asymptomatic infection in these contacts [16,17]. Subsequent studies documented severe disease in family contacts [18▪]. Since the emergence of MERS-CoV in 2012, there has been a recent increase in number of cases. In April 2014, there were a total of 145 cases, or 56% of the total cases reported from Saudi Arabia and United Arab Emirates [19].

WHAT ARE THE VIRAL RECEPTORS?

The target of the virus seems to be different between SARS-CoV and MERS-CoV. Although angiotensin-converting enzyme 2 is the host receptor of SARS-CoV [20], dipeptidyl peptidase 4 (DPP4, otherwise known asCD26) was identified as the cellular receptor for MERS-CoV [21,22]. DPP4 homologues are present in a variety of cell lines [23,24].

RISK OF IN-FLIGHT TRANSMISSION

The risk of in-flight transmission of MERS-CoV was calculated to be one new infection in a 5-hour flight in first class, and 15 infections from a 'super-spreader' traveling 13 h in an economy class [25]. So far, there has been no confirmed in-flight transmission of MERS-CoV. Two cases of MERS-CoV were reported to be introduced to United States from patients who traveled from Saudi Arabia with no documented in-flight transmission [26▪].

The in-flight transmission of SARS was studied in a few reports. In one study of a flight carrying a symptomatic SARS patient, laboratory-confirmed SARS developed in 16 of 119 (13.4%) passengers. Development of SARS was related to the physical proximity to the index patient, SARS was reported in eight of 23 persons seated in the three rows in front of the index patient, and in 10 of the 88 persons seated elsewhere [27]. In a second flight with four symptomatic persons, only one passenger developed illness and no illness was documented in passengers on a third flight with presymptomatic SARS passenger [27]. Two patients were exposed to a SARS patient in flight from Hanoi to Paris [28] and in other instances [29]. Other studies failed to show in-flight transmission [30–32].

CLINICAL PRESENTATIONS, LABORATORY FINDINGS, AND RADIOGRAPHIC PRESENTATION

The incubation period of SARS was calculated to be 4.6 days [33], and that of MERS-CoV to be 5–14 days [34▪▪]. The median time from symptom onset of MERS-CoV patients to hospitalization was 3–4 days and the median time from admission to an ICU and to death was 5 and 11.5 days, respectively [34▪▪,35▪▪]. In MERS-CoV, there is a male predominance dissimilar from SRAS [2,36,37,38▪▪,39▪]. There is a huge overlap in the clinical presentations between SARS-CoV and MERS-CoV infections [2,36,37,38▪▪, 39▪]. Common presenting symptoms include: fever, cough, dyspnea, chills, rigor, headache, myalgia, and malaise [2,9,33,40–44]. Atypical initial symptoms of diarrhea and vomiting were reported in patients with MERS and SARS [34▪▪,35▪▪,38▪▪]. The initial cases of

MERS-CoV infection showed relatively different findings from SARS. In patients with SARS, preexisting chronic illnesses were less common: diabetes, 24 vs. 68%; renal disease, 2.6 vs. 49%, and heart disease, 10 vs. 28% [35▪▪]. SARS cases were mainly seen in young healthy individuals; this is in contrast to the fact that more than half of the cases of MERS-CoV infection occurred in individuals older than 50 years [34▪▪,35▪▪,38▪▪,45▪]. The mortality rate of the initial cases of MERS-CoV was about 70% of severe disease and later the case-fatality rate was much lower [34▪▪,35▪▪,38▪▪,39▪,46].

In patients with SARS-CoV and MERS-CoV infections, patients typically have lymphopenia and may have increased activated prothrombin time [34▪▪,35▪▪,38▪▪]. However, lymphopenia was not different in cases and control of MERS-CoV [38▪▪]. The viral loads in the lower respiratory tract were higher than in the upper respiratory tract and the yield of genomic fraction was higher as well in lower respiratory tract samples [47▪▪]. Tracheal aspirates produced higher MERS-CoV viral load compared with nasopharyngeal swabs ($P = 0.005$) and to sputum ($P = 0.0001$) and tracheal aspirates had a similar viral load compared with bronchoalveolar lavage ($P = 0.3079$) [47▪▪]. In both SARS-CoV and MERS-CoV, there is a predominance of peripheral and lower zone pulmonary infiltrate, then the progressive development of multifocal or bilateral pulmonary infiltrates with more rapid progression in MERS-CoV than SARS-CoV infection [2,3,36,37,38▪▪,39▪].

SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS AND MIDDLE EAST RESPIRATORY SYNDROME CORONAVIRUS ANIMAL RESERVOIRS

Since the initial description of both SARS and MERS, it was speculated that these viruses were linked to bats [3]. Bats in general and specially the horseshoe bats (*Rhinolophus* genus) exhibited detectable antibodies to SARS-CoV and carried CoVs that were phylogenetically related to SARS-CoV, SARS-CoV-like coronaviruses [48,49]. SARS-CoV-like CoVs had 88–92% sequence homology with human or civet isolates and bats could be the natural reservoir [50]. Although the findings were questioned, there was evidence pointing to a link between SARS-CoV and masked palm civets [50,51].

For MERS-CoV, bats were thought to be responsible for the transmission of the virus. A closely related bat CoVs, BtCoV-HKU4 and BtCoV-HKU5 were found to be phylogenetically linked to MERS-CoV [52]. Beta CoVs closely related to MERS-CoV were shown to be present in 24.9% of Nycteris bats and 14.7% of Pipistrellus bats in Ghana and four European countries [53]. One fragment of MERS-CoV was found in one Taphozous bat out of 1100 bat samples, with close matching to a human isolate of MERS-CoV [54▪]. Recent studies point toward camels as a possible source of MERS-CoV infection. Neutralizing antibody levels against MERS-CoV were found in camels from the Spanish Canary Islands, Oman, and Egypt [55▪]. Avirological confirmation of an outbreak of MERS-CoV involving three camels and two humans in Qatar showed that the isolated MERS-CoV was very similar to the MERS-CoV from two human cases on the same farm and a MERS-CoV isolate from Hafr Al-Batin [56▪]. In Oman, five (6.5%) of 76 dromedary camels tested positive for MERS-CoV, and the MERS-CoV sequences (3754 nucleotides) from Oman and Qatar were closely related to human MERS-CoV sequences [57▪]. Complete MERS-CoV genome sequences were obtained from nasal swabs of dromedary camels in Saudi Arabia and the dromedary MERS-CoV genome sequences were identical to human MERS-CoV sequences [58▪]. There was more than one genomic variant in individual dromedaries [58▪]. Although a high percentage of dromedary camels had circulating MERS-CoV-neutralizing antibodies, sheep, goats, and cows were negative for MERS-CoV-neutralizing antibodies [59,60]. These data link camels to MERS-CoV, although another source of an intermediate host that is yet to be identified must exist, as only a portion of index cases reported contact with camels.

TRAVEL-RELATED MIDDLE EAST RESPIRATORY SYNDROME CORONAVIRUS

MERS-CoV is currently restricted to Middle Eastern countries and was reported from Saudi Arabia, United Arab Emirates, Qatar, Oman, Jordan, Kuwait, Yemen, and Lebanon. MERS-CoV has been reported from at least 10 other countries in Europe and Asia and the first two cases have been reported recently from the United States [61]. Countries with travel-associated cases include: United Kingdom, France, Tunisia, Italy, Malaysia, Philippines, Greece, Egypt, United States, and the Netherlands [61]. The first imported MERS-CoV infection was found in a 49-year-old Qatari who was treated in the United Kingdom [62]. The first imported case into United States was announced on 2 May 2014 [63]. The patient traveled from Saudi Arabia to Indiana, via London and Chicago. The patient is a healthcare worker who lives and works in Saudi Arabia [63]. The second case was announced on 11 May 2014, in a traveler who also came to the United States from

Saudi Arabia and is also a healthcare worker who traveled from Saudi Arabia to Orlando via London, Boston, and Atlanta [63]. On 17 May 2014, the first locally acquired MERS-CoV was announced in the United States where the first case likely passed the infection to a colleague in Indiana after two business meetings in which they were in close proximity [64]. However, subsequent testing of this contact proved that he was negative for MERS-CoV by serology (see: http://www.cdc.gov/media/releases/2014/p0528-mers.html, accessed 2 July 2014). In the Netherlands, two imported cases were reported on 13 and 15 May 2014 by National Institute for Public Health and the Environment (RIVM) [65]. A man and woman shared a hotel room for 2 weeks and both suffer from underlying conditions [65]. Other imported cases were reported in: UK (4 cases/3 deaths), Germany (2 cases/1 death), France (2 cases/1 death), Italy (1 case/0 deaths), Greece (1 case/0 deaths), Tunisia (3 cases/1 death), Malaysia (1 case/1 death), Philippines (1 case/0 deaths) [66]. Local secondary transmission following importation was reported from the United Kingdom, France, Tunisia, and United States [66] after a primary case was imported. The transmission resulted in the infection of one healthcare worker in France, to one close contact of a primary case in Tunisia, and a second close contact who traveled to Saudi Arabia developed confirmed infection and to two family contacts in the UK.

The US CDC recommends the following for travelers to prevent MERS-CoV infection [67]:

(1) Wash hands often with soap and water. If soap and water are not available, use an alcohol-based hand sanitizer.
(2) Avoid touching your eyes, nose, and mouth.
(3) Avoid close contact with sick people.

MIDDLE EAST RESPIRATORY SYNDROME CORONAVIRUS AND THE ANNUAL HAJJ

Annual Hajj attracts pilgrims from 184 countries [68,69]. There is always the concern of potential occurrence of outbreaks during mass gatherings such as the Hajj. The 2012 annual Hajj season had no reported MERS-CoV cases among four million pilgrims [70], and MERS-CoV test was negative among 300 symptomatic pilgrims with upper respiratory symptoms [71] and among a cohort of 154 French pilgrims, [72]. For the annual 2013 Hajj, MERS-CoV was not detected in 3210 pre-Hajj and 2025 post-Hajj samples obtained from pilgrims from 22 different countries [73▪▪]. The Saudi Ministry of Health recommendations regarding the annual Hajj advise the following people to postpone the Hajj: 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), malignancy, and terminal illnesses, pregnant women and children under 12 years [74].

TREATMENT FOR SEVERE ACUTE RESPIRATORY SYNDROME AND MIDDLE EAST RESPIRATORY SYNDROME

There is no approved therapy for SARS and MERS infections. Recent publications summarized the therapeutic options [75–77]. These studies discussed the different options: interferon alpha, lopinavir/ritonavir, ribavarin, inhibitors of virus replication such as cylcophilin inhibitors, inhibition of MERS-CoV cell receptors (DPP4, also known as CD26), and MERS-CoV neutralization antibodies. None of these agents were shown to be conclusively effective. An observational study used interferon and ribavarin for the therapy of five MERS-CoV patients [75,76]. The study did not reveal a survival advantage, as these agents were used late in the course of the disease. Recently, three human monoclonal antibodies, m336, m337, and m338, targeting the receptor (CD26/DPP4)-binding domain of the MERS-CoV spike glycoprotein neutralized MERS-CoV [78]. Also, a panel of neutralizing antibodies offered the possibility of developing human monoclonal antibody-based immunotherapy [79]. More recent in-vitro studies from 231 screening activities showed a list of 66 compounds that were active against SARS-CoV, 232 MERS-CoV, or both [80]. Of these, six drugs were active against SARS-CoV only, 33 drugs were active against MERS-CoV only, and 27 drugs were active against both SARS-CoV and MERS-CoV, and these drugs were grouped in 13 different therapeutic classes [80]. In-vitro studies also showed that chloroquine, chlorpromazine, loperamide, and lopinavir inhibited MERS-CoV replication and the replication of SARS-CoV and human CoV 229E [81]. Inhibition of SARS-CoV and MERS-CoV helicase was accomplished by SSYA10–001 [82].

VACCINES FOR SEVERE ACUTE RESPIRATORY SYNDROME AND MIDDLE EAST RESPIRATORY SYNDROME

In general, there is no vaccination for CoVs. With the emergence of SARS-CoV in 2003, vaccines for SARS were being developed and were based on whole or inactivated SARS-CoV, spike subunits, recombinant viruses or DNA plasmids expressing SARS-CoV proteins, or virus-like particles. In mice, a modified vaccinia virus and spike subunit vaccines induced MERS-CoV-neutralizing antibodies [83,84].

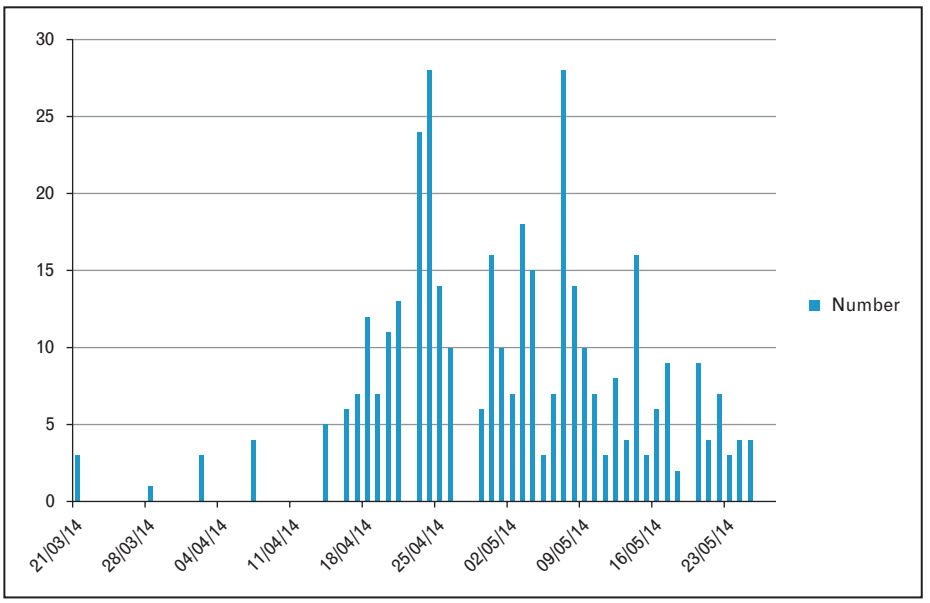

FIGURE 1. Number of reported Middle East respiratory syndrome coronavirus cases in Saudi Arabia from 21 March 2014 to 27 May 2014 [92].

It was speculated that the use of MERS-CoV-neutralizing monoclonal antibody in exposed individuals such as a patient's family member or a healthcare worker before or after exposure to MERS-CoV may prevent or inhibit MERS-CoV infection [85]. Intranasal vaccination of MERS-CoV receptor-binding protein (RBD)-Fc induced systemic humoral immune responses comparable with subcutaneous vaccination. Intranasal vaccination also produced more robust systemic cellular immune responses and higher local mucosal immune responses in mouse [86]. A truncated RBD protein showed promise for the development of an effective and well tolerated vaccine [87]. An rMERS-CoV deletion mutant with the E gene deleted showed a replication-competent, propagation-defective virus that could only be grown in the laboratory by providing E protein in Trans, whereas it would only survive a single virus infection cycle *in vivo* and may be a vaccine candidate [88].

INFECTION CONTROL

There is a clear but limited human-to-human transmission of MERS-CoV. Outside the hospital setting, the transmission of MERS-CoV seems to be infrequent and intermittent. In a study of 130 blood donors in Jeddah in 2012 and 226 abattoir workers in Jeddah and Makkah in October 2012, eight showed reactive sera by immunofluoresence testing and were not specific for MERS-CoV [89]. Non-MERS-CoV-neutralizing antibodies were detected in 268 samples obtained from persons from the Eastern province of Saudi Arabia [90].

The recent increase in the number of MERS-COV cases reported primarily from Jeddah in April 2014, were mainly related to poor infection control measures at hospitals. The total reported number of MERS-CoV cases since the initial description of the disease to 28 May 2014 by Saudi Arabia was 562 with increasing numbers of cases since March 2014 (Fig. 1) [91,92]. Two recent commentaries emphasize the need to adhere to recommended infection control measures [64,92]. The World Health Organization recommendations of airborne infection precautions to be used in aerosol-generating procedures [93] and the US and European Centers for Disease Control and Prevention (CDC) recommendations of airborne infection isolations for all MERS-CoV patients [94].

CONCLUSION

Like SARS-CoV, MERS-CoV threatens global health security. All physicians and travelers to the Middle East should be aware of the new threat caused by MERS-CoV and follow CDC and WHO guidelines. Those who develop ill health during their trip or soon after their return should seek medical care, and all physicians must take a travel history. Appropriate isolation measures should be undertaken in all suspected and confirmed cases.

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Conflicts of interest

All authors have no conflict of interest to declare.

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