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Title:

Middle East Respiratory Syndrome Coronavirus –Risk Factors and Determinants of Primary, Household, and Nosocomial Transmission

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Search Strategy

We searched publications in English on the MEDLINE, EMBASE and GOOGLE SCHOLAR for the period January 1, 2012 to January 16th, 2018 using the search terms “Middle East Respiratory Syndrome” or “MERS-CoV” or “MERS” in combination with the terms “Epidemiology”, or “Transmission” or “Infection control” or “outbreak” or “risk factors” or “Prevention” or “Management” or “Hospital” or “Household” or “Community” or “Nosocomial” or “Healthcare setting” or “camels”. We also searched CIDRAP and ProMed websites for news, latest postings and articles on MERS and MERS-CoV. We also searched websites of global and national public health agencies such as WHO, US-Centers for Disease Control, UK-Public Health England, European Center for Disease Prevention and Control (ECDC), the Saudi Arabia Ministry of Health and South Korea Centers for Disease Control and Prevention portals. We selected publications relevant to clinical features, MERS-CoV viral load and shedding, epidemiology, transmission, outbreak management, infection control, and prevention. We also searched the reference lists of articles and reviews identified by this search strategy and selected those we judged relevant to inform readers of more references.

ABSTRACT

Middle East respiratory syndrome coronavirus (MERS-CoV) is a lethal zoonosis that causes death in 35·7% of cases. As of Feb 28, 2018, 2182 cases of MERS-CoV infection (with 779 deaths) in 27 countries were reported to WHO worldwide, with most being reported in Saudi Arabia (1807 cases with 705 deaths). MERS-CoV features prominently in the WHO blueprint list of priority pathogens that threaten global health security. Although primary transmission of MERS-CoV to human beings is linked to exposure to dromedary camels (Camelus dromedarius), the exact mode by which MERS-CoV infection is acquired remains undefined. Up to 50% of MERS-CoV cases in Saudi Arabia have been classified as secondary, occurring from human-to-human transmission through contact with asymptomatic or symptomatic individuals infected with MERS-CoV. Hospital outbreaks of MERS-CoV are a hallmark of MERS-CoV infection. The clinical features associated with MERS-CoV infection are not MERS-specific and are similar to other respiratory tract infections. Thus, the diagnosis of MERS can easily be missed, unless the doctor or health-care worker has a high degree of clinical awareness and the patient undergoes specific testing for MERS-CoV. The largest outbreak of MERS-CoV outside the Arabian Peninsula occurred in South Korea in May, 2015, resulting in 186 cases with 38 deaths. This outbreak was caused by a traveller with undiagnosed MERS-CoV infection who became ill after returning to Seoul from a trip to the Middle East. The traveller visited several health facilities in South Korea, transmitting the virus to many other individuals long before a diagnosis was made. With 10 million pilgrims visiting Saudi Arabia each year from 182 countries, watchful surveillance by public health systems, and a high degree of clinical awareness of the possibility of MERS-CoV infection is essential. In this Review, we provide a comprehensive update and synthesis of the latest available data on the epidemiology, determinants, and risk factors of primary, household, and nosocomial transmission of MERS-CoV, and suggest measures to reduce risk of transmission.

Introduction

The past 15 years have witnessed two new deadly zoonotic coronaviruses with epidemic potential which have focused attention of global public health authorities: The Severe Acute Respiratory Syndrome coronavirus (SARS-CoV)[1-3] and The Middle East Respiratory Syndrome coronavirus (MERS-CoV).[4,5] Since the last MERS review in The Lancet in 2015,[5] MERS-CoV cases have continued to be reported from the community and hospitals across the Arabian Peninsula, with occasional cases in travelers resulting in other continents leading to non-sustained outbreaks in health care settings.[4] We review current knowledge on the determinants and risk factors regarding primary, household, and nosocomial transmission of MERS-CoV.

Epidemiology

Nosocomial and household outbreaks are a hallmark of MERS-CoV infection and account for about 40% of MERS-CoV cases globally. Large health care associated outbreaks of MERS-CoV have occurred in Saudi Arabia, United Arab Emirates, and South Korea. Two and a half years ago, from 20 May to 13 July 2015, MERS-CoV caused the largest outbreak outside the Arabian Peninsula in the South Korea resulting in 186 confirmed MERS cases with 38 deaths (20.4% mortality rate).[4,7-9] The outbreak occurred when a Korean traveler returning from a trip to Qatar, UAE, Saudi Arabia and Bahrain became ill and had been to several health facilities before finally being diagnosed as having MERS-CoV infection on May 20, 2015 at Samsung Medical Center[7,9]. Human to human transmission linked to healthcare facilities led to a total of 186 people (of which 25 were healthcare workers) with MERS-CoV infection within a few weeks. 181 out of 186 cases were associated with hospitals.[9]

This outbreak clearly illustrated how MERS-CoV can spread from person to person in hospitals in a well-resourced developed country setting outside the Middle East. Following this unprecedented outbreak, the tenth meeting of the WHO MERS Emergency Committee[10] was convened by the Director-General under the International Health Regulations (IHR 2005) on 2 September 2015. Since then intermittent sporadic cases, community clusters and nosocomial outbreaks of MERS-CoV have continued to occur in Saudi Arabia[4] MERS-CoV remains on the WHO Blueprint list of priority pathogens[11] (**Box 1**) since it remains a persistent threat to global health security [http://www.who.int/blueprint/priority-diseases/en/].

The number of MERS-CoV cases reported to the WHO[4] has steadily increased since the first isolation of MERS-CoV in September 2012 from the sputum of a 60-year old male patient in Saudi Arabia who had succumbed in June 2012 to severe pneumonia and multisystem disease.[12] Between September 2012 and 16th January 2018, 2,123 laboratory-confirmed cases of MERS-CoV infection have been reported from 27 countries (**Figure 1**) of which there have been 740 deaths (35% mortality rate). The majority of MERS-CoV infections of humans have occurred in Saudi Arabia (n=1,775), of which there have been 723 deaths, 40.5% mortality rate).[4,13] Up to 49% of human MERS-CoV cases in Saudi Arabia have been classified as primary infections, 11% as Household transmission, 24% related to healthcare facilities and 3% of cases were not classifiable.[13]

Source of Primary Human MERS-CoV infections

'Primary' MERS-CoV infection refers to human infection acquired in the community. Despite extensive investigations, the specific source and mode of transmission of primary human MERS-CoV infections remains an enigma.[5,6] Whilst bats have been implicated, there are no definitive data on the epidemiological link between human MERS-CoV infections and bats so far. Based on a study of 1,100 bat samples, only one fragment of MERS CoV was found in one Taphozous bat which matched closely to a human isolate of MERS-CoV.[14] Epidemiological, genetic, and exposure linkages between dromedary camels and human MERS cases seem to indicate that dromedary camels are the main intermediary animal reservoirs of MERS-CoV.[15] (**Table 1**). A study from Qatar in April 2014, reported antibodies to MERS-CoV in serum and milk of camels. Evidence for active virus shedding in nasal secretions and/or faeces was observed in 7 out of 12 camels while viral RNA was detected in milk in 5 of these 7 camels.[15] In a systematic, active surveillance study in Egypt, among 2,541 camels tested, 1,808 (71.2%) were seropositive by microneutralization assay and out of 2,825 nasal swabs, MERS-CoV RNA was detected in 435 (15.4%) by RT-PCR. In addition, RT-PCR was also positive 18 of

114 rectal swabs (15.4%), 12 of 187 milk samples (6.4%) and 0 of 26 urine samples from camels. Antibody was detected in 38 of milk samples (20.3%) at low titers. Juvenile camels had a significantly lower sero-provalence than adult camels (37% vs. 82%) but had similar RT-PCR detection rates (16% vs. 15%). MERS-CoV survives for prolonged periods in camel's milk but viable virus becomes undetectable after pasteurization at 63C for 30 min.[16]

Risk factors for primary MERS-CoV infection

Table 1 outlines the risk factors for Primary and Household transmission of MERS-CoV. A case controlled study from Saudi Arabia[17] found several independent risk factors for increased susceptibility to acquiring primary MERS-CoV infections: a) direct dromedary exposure in the fortnight before illness onset (adjusted OR 7.45, 95% CI 1.57–35.28); b) diabetes mellitus (adjusted OR 6.99, 95% CI 1.89–25.86); c) heart disease (adjusted OR 6.87, 95% CI 1.81–25.99); d) currently smoking tobacco (adjusted OR 6.84, 95% CI 1.68–27.94) and, e) direct physical contact with dromedary camels during the previous 6 months (adjusted OR 14.59, 95% CI 2.38–89.55). Compared with the general population in Saudi Arabia (0.2%) in 2012-13, the sero-prevalence of MERS-CoV antibody increased by 15-fold in camel shepherds (2 [2.3%] of 87, p=0.0004) and by 23-fold in slaughter-house workers (five [3.6%] of 140; p<0.0001).[18] In a study from Qatar,[19] the following significant risk factors identified for primary MERS-CoV infection among camel workers: involvement in animal training, milking camels, workers with respiratory symptoms requiring overnight stay in hospital, contact with camels' waste, and poor hand hygiene before and after animal tasks.

Transmission from camels to humans

People in close contact with dromedary camels, patients with MERS-CoV infection and healthcare workers (HCWs) taking care of MERS-CoV patients are at an increased risk of acquiring the infection.

MERS-CoV transmission from camels to humans, is currently thought to be via direct contact with camels via respiratory droplets or saliva or through consumption of camel products such as milk or undercooked camel meat.[15,19-21] Camel to human cross species transmission of MERS-CoV has been confirmed by viral RNA sequencing from samples obtained from infected dromedary camels and from symptomatic[20,21] and asymptomatic patients[22] after known exposure to the infected camels. A study of animal herds associated with patients with MERS-CoV infection from Saudi Arabia[23] found that 75/584 dromedary camels were positive on nasal swabs for MERS-CoV RNA for about 2 weeks, whereas the nasal swabs were negative in other animals including goats, sheep, and cattle. Interestingly 70.9% of camels related to human cases had antibodies to MERS-CoV by ELISA assays while full genome sequences of ten MERS-CoV camel isolates were identical to their corresponding patients.[23] Nevertheless, testing of serum from 191 persons with various degrees of exposure to an infected dromedary herd found no serologic evidence of infection.[24] The data suggest that whilst MERS-CoV is widespread among dromedary camels, zoonotic transmission of MERS-CoV from camels to humans is relatively uncommon, and human disease is not directly proportional to potential exposure to camels.[24]

Furthermore, although dromedary camels are a known host species for the MERS-CoV, less than half of the primary cases have had history of exposure to dromedary camels.[4-6] Based on existing MERS-CoV sequence data to examine the phylodynamics in camels and humans with structured coalescent model, Dudas et al[25] have shown that long-term evolution of MERS-CoV occurs exclusively in camels while humans serve as a transient and terminal host ultimately. In addition, the study has shown that human outbreaks in the Arabian Peninsula have been driven by seasonally varying zoonotic transfer of viruses from camels.[25]

Non-specific clinical features

Making a diagnosis of MERS requires a high degree of clinical awareness of the possibility of MERS. The clinical features, laboratory, and radiological abnormalities associated with MERS-CoV infection are not MERS-specific and are similar to other respiratory tract infections.[4-6,26-32] Thus the diagnosis of MERS can easily be missed when the patient presents to point of healthcare with an acute respiratory illness, and the patient places all those in contact with him/her (family, patients and healthcare workers) at the risk of acquiring MERS-CoV infection.

Adults acquiring MERS-CoV infection can develop a spectrum of illness, from asymptomatic, mild, moderate to severe disease.[5-7,26-32] The incubation period is between 2 to 14 days. Mild cases can have low-grade fever, runny nose, dry cough, sore throat, and myalgia. Severe cases have pneumonia progressing to acute respiratory distress syndrome, multisystem disease and organ failure. Oh MD, et al[33] measured progression of pneumonia in severe cases by scoring the infiltrates on chest radiographs, and showed that pneumonia progressed abruptly around day 7 of illness and reached a peak at approximately day 14. MERS-CoV viral load in lower respiratory tract samples are higher than those from the upper respiratory tract.[33,34] Extrapulmonary features including myalgia are common.[5-7,25-32] Up to half of cases have acute kidney injury and one third of critically ill patients have gastrointestinal symptoms such as abdominal pain, nausea, vomiting, and diarrhea.[27] MERS-CoV has been detected in stool specimens.[35] Ahmed et al[36] collected daily information on MERS-CoV cases posted by the Saudi Arabian Ministry of Health (MOH) between Dec 2, 2014, and Nov 12, 2016, on 660 confirmed cases of MERS-CoV. The study found that 3-day, 30-day, and overall mortality were 13.8%, 28.3%, and 29.8%. Patients over the age of 60 were more likely to die (45.2% mortality) from their infections than were younger patients (20%).

Risk factors for severe disease and death

Patients with pre-existing medical co-morbidities have more severe disease and higher mortality rates.[5-7,26-31] Risk factors for poor outcome (severe disease or death) in MERS-CoV infection include advanced age, male gender, comorbid illness (eg: obesity, diabetes mellitus, heart and lung diseases, and immuno-compromised states), low serum albumin, concomitant infections, positive plasma MERS-CoV RNA, being non-HCWs, altered mentation, high pneumonia severity index score on hospitalization, signs of severe inflammation at initial presentation (elevated inducible protein-10, monocyte chemoattractant protein-1 and interleukin 6 concentrations), and high viral load at hospital days 5–10 with low antibody titres at hospital days 11–16 during the clinical course of disease.[31,36-39] The MERS-CoV dipeptidyl-peptidase 4 receptor has been shown to be upregulated in the lungs of smokers and patients with COPD and this may explain why patients with comorbid lung diseases are prone to severe illness.[40]

Person to person transmission

MERS-CoV has been identified in clinical specimens such as sputum, endotracheal aspirate, bronchoalveolar lavage; nasal or nasopharyngeal swabs, urine, faeces, blood and lung tissue.[5-7,31,35,41] When available, it is important to take serial specimens from both the upper and the lower respiratory tract. While MERS-CoV may also be detected in serum/blood, it is uncommonly detected in urine and stool. The precise modes of MERS-CoV transmission through direct or indirect contact, airborne, droplet or ingestion have yet to be defined. MERS-CoV does not seem to transmit easily from person to person unless there is close contact with MERS-CoV infected patients.[41-43] Human-to-human transmission has been described within communities and households[30,43-45] but has been more striking within healthcare settings.[26-29,46-50] Health care associated outbreaks have occurred in several countries, with the largest outbreaks seen in Saudi Arabia, United Arab Emirates, and South Korea.[26-29,46-50] Persons in close contact with dromedary camels and healthcare workers (HCWs) taking care of patients with MERS-CoV infection are at an increased risk of acquiring the infection while healthy adults may develop mild illness or even asymptomatic infection. Whilst there is no clear evidence of sustained, human-to-human transmission, the South Korea outbreak involved within hospital and hospital-to-hospital transmission.[9,51-54]

Household transmission

Several reports from Saudi Arabia describe transmission between persons in the community or those living in large households and family compounds.[22,30,44,45] An investigation of 280 household contacts of 26 index MERS-CoV-infected Saudi Arabian patients,[43] with follow-up serologic analysis in 44 contacts performed in 2014 to determine the rate of 'silent or subclinical' secondary infection after exposure to primary cases of MERS-CoV infection, found there were 12 probable cases of secondary transmission (4%; 95% CI, 2 to 7%). Seven apparently healthy household contacts carried MERS-CoV in their upper respiratory tract. This, together with the finding of low levels of MERS-CoV RNA in asymptomatic persons from MERS-CoV outbreaks in a Jeddah hospital[47] indicates MERS-CoV -shedding after exposure to infected patients.

Of 79 relatives that were investigated after MERS-CoV infections affected an extended family in Saudi Arabia in 2014, 19 (24%) were MERS-CoV positive; 11 were hospitalized, and 2 died. Eleven (58%) tested positive by real time reverse transcription polymerase chain reaction (rRTPCR) but 8 (42%) who tested negative by rRTPCR were positive by serology with confirmatory immunofluorescence assay and microneutralization.[45] Compared with MERS-CoV–negative adult relatives, MERS-CoV–positive adult relatives were older and more likely to be male [Risk ratio 4.8 (1.6–15.0)] and to have chronic comorbid illness [RR 2.8 (1.4–5.7)]. Risk factors for household transmission included sleeping in an index patient's room [RR 4.1 (1.5–11.2)], removing patient's waste [RR 3.2 (1.2–8.4)], and touching respiratory secretions from an index patient [RR 4.0 (1.6–9.8)] (**Table 1**). Proximity to the patient and casual contact were not associated with transmission. This study also clearly demonstrated that serology was more sensitive than standard rRTPCR for identifying relatives who were infected.[45]

Nosocomial transmission

Nosocomial outbreaks have been a hallmark of MERS-CoV infection and account for approximately a third of MERS-CoV cases reported globally.[4] MERS-CoV was found to be more stable in aerosol at low temperature/low humidity conditions (20°C/40% relative humidity) than influenza virus and could still be recovered from plastic or steel surfaces after 48 hrs.[16] This property may explain why

MER-CoV transmitted easily in healthcare facilities equipped with central air-conditioning leading to major nosocomial outbreaks and super-spreading events, especially in the presence of aerosol-generating procedures (AGPs).

A retrospective study of clusters of hospital cases of MERS-CoV infection in Jordan[26] dated back to Apr 2012 showed that poor compliance with infection control measures among healthcare workers and lack of proper isolation rooms were risk factors leading to the nosocomial outbreak. Another nosocomial outbreak of MERS-CoV infection in Al Hasa in 2013 involving 23 patients in 3 different healthcare facilities was caused by poor infection control practices and possibly some contribution by AGPs including use of continuous positive airway pressure, nebulized medications, and cardiopulmonary resuscitation. Following enhancement of infection control measures (**Table 2**), the nosocomial outbreaks settled down.[27]

The nosocomial outbreaks in Abu Dhabi[49] in 2014 were due to spread of MERS-CoV in healthcare settings predominantly occurring well before MERS-CoV infection was recognized and diagnosed. The rapid spread was attributed to poor compliance among HCWs with wearing personal protection equipment while interacting with the patients and application of AGPs including intubation, manual ventilation before intubation, use of nebulized medications and oxygen therapy. These data underscore the importance of increasing awareness and infection control measures at first points of entry to healthcare facilities.[55]

In Jeddah in 2014, major nosocomial outbreaks of MERS-CoV infection occurred involving 3 healthcare facilities where existing in-patients, clinic patients, and visitors became infected following exposure to contaminated healthcare facilities.[47] Emergency departments (ED) with overcrowding and poor infection control were the major location of exposure leading to nosocomial outbreaks in hospitals in Saudi Arabia[48] and South Korea.[8,9,56]

Two unlinked clusters of MERS-CoV infection[13,57] occurred at the same hospital in Wadi Aldwaser city, Riyadh Region occurred in early 2017. A cluster of 10 cases in March 2017 where the primary case was in the dialysis unit, and a cluster of 5 cases in April 2017. Both involved household contacts, HCWs and patients. In June 2017 an outbreak of 34 MERS-CoV cases occurred in a hospital in Riyadh City, Riyadh.[57] The primary case was a 47-year-old male admitted to the ED for intubation who at that time was not identified as infected with MERS-CoV. Prior to diagnosis, 220 HCWs, patients and visitors had contact with this patient. Contact tracing, identified an additional 33 MERS cases during this outbreak. 50% the cases associated with this outbreak were HCWs. Eleven patients were classified as having severe disease, of whom 7 died, and 22 were asymptomatic. One case from this cluster then sought treatment for renal dialysis at another health-care facility in Riyadh City where 5 additional cases were identified -three household contacts, one patient contact in the hospital, and one HCW. Unrelated to this cluster, in June 2017, another MERS cluster of nine cases occurred at a hospital in Riyadh City: a butcher who reported direct contact to dromedary camels and eight HCW contacts (4 asymptomatic and 4 with mild disease).[57]

Healthcare workers and transmission

Among HCWs who treated MERS-CoV patients at King Faisal Specialist Hospital in Jeddah[58] in March-July 2014, the attack rate was 8% (20/250) and differed by hospital units: Medical ICU, 11.7% (15/128); ED, 4.1% (5/122). Among the HCWs, radiographers had the highest infection risk (29.4% [5/17]), followed by nurses (9.4% [13/138]), respiratory therapists (3.2% [1/31]), and physicians (2.4% [1/41]). HCWs who always covered their nose and mouth with medical mask or N95 mask were less likely to be infected compared to those who sometimes/never covered their nose and mouth during AGPs [8/133(6%) vs 6/32(18.8%), RR 0.32(0.12-0.86), p=0.03].[58]

MERS-CoV viral load and transmission

Analysis of spreaders in South Korea showed that they could transmit MERS-CoV from Day 1 to 11 of their illness (median, 7 days; IQR, 5 to 8 days) and the number of patients infected by each spreader ranged from 1 to 84 (IQR, 1 to 12).[53] MERS-CoV viral loads (sputum, throat swabs, or tracheal aspirates) peaked during the second week of illness while the lower respiratory tract specimens had higher and more prolonged levels of MERS-CoV RNA as detected by rRTPCR.[33] Nosocomial transmission in South Korea was independently associated with the cycle threshold ([OR], 0.84; 95%CI, 0.75–0.96) and pre-isolation hospitalization or ED visits (OR, 6.82; 95% CI, 2.06–22.84). The super-spreading events (defined as ≥ 5 transmissions) were associated with a higher number of pre-isolation contacts (n=777 vs n=78), more frequent pre-isolation ED visits by the index patients (100% vs 35.3%), and more 'doctor shopping' (seeking medical attention in different healthcare facilities) (100% vs 47.1%) in comparisons to non-super-spreading events.[51]

Severity of illness and transmission

Analysis of data in South Korea suggested that patients who died from MERS-CoV infection were more likely to cause secondary infections than those that survived while direct, human-to-human transmission associated with clinical progression of the fatal cases (eg lower respiratory tract involvement with higher viral load, need for AGPs), and indirect transmission via environmental contamination (e.g., fomites and indoor ventilation systems) may account for nosocomial amplification of MERS-CoV in South Korea.[59] The reproduction number for nosocomial outbreaks in Saudi Arabia and South Korea was estimated to be in the range of 2 to 5.[60] The risk factors for nosocomial MERS-CoV outbreaks are summarized in **Table 3**.[26-29,34,46-48,51,55]

Environmental contamination in hospitals

Environmental contamination by MERS-CoV in patients' rooms has been reported in South Korea, with positive RT-PCR and culture from environmental swabs taken from bed sheets, bed rails, intravenous fluid hangers, computer tomography cassette, and anteroom tables while viable virus could still be isolated in 3 of the 4 enrolled patients on day 18 to day 25 after symptom onset.[52] Another study detected the presence of MERS-CoV by RTPCR of viral cultures of 4 of 7 air samples from 2 patients' rooms, 1 patient's restroom, and 1 common corridor. MERS-CoV was also detected in

15 of 68 surface swabs by viral cultures. Immunofluorescence assays on the cultures of the air and swab samples revealed the presence of MERS-CoV while electron microscopy images revealed intact particles of MERS-CoV in viral cultures of the air and swab samples.[56] A third study showed weakly positive RTPCR from environmental swabs taken from bed guardrail and monitors. Even after cleaning the monitors with 70% alcohol-based disinfectant, RTPCR remained weakly positive, and converted to negative only after wiping with diluted sodium chlorite.[61]

Transmission of MERS-CoV by asymptomatic individuals

MERS-CoV has been detected in asymptomatic individuals during screening of HCWs in nosocomial outbreaks in Saudi Arabia and South Korea. The MERS-CoV positivity of upper airway specimens of the HCWs usually turned negative on PCR testing within 2-3 days[21] although a case of prolonged PCR positivity up to 35 days has been reported in a HCW with subclinical infection.[42] Prolonged PCR positivity has been noted in some patients with MERS-CoV infection in the recovery phase with negative viral culture.[34,61,62] While the prolonged PCR positivity may be due to slow turnover of damaged respiratory epithelium with non-viable RNA fragments in some patients, it remains unclear if asymptomatic persons (especially HCWs) may transmit MERS-CoV infection to high risk patients such as the immunocompromised and those with chronic renal and lung disease. In a Korean study, 591 HCWs participated in MERS patients care with proper personal protective equipment were later screened for MERS-CoV after finishing the patient care and three asymptomatic individuals (0.5%) were found. Another follow up study of an asymptomatic person in South Korea showed no transmission to 82 contacts[63] while another study speculated that a family cluster of MERS-CoV infection in Saudi Arabia was probably related to exposure to an unrecognized asymptomatic or sub-clinical mild case in the hospital setting.[44] Four generations of transmission among HCWs in the hospital and the home environment have been observed in Saudi Arabia following investigation of an index case (a nurse with MERS-CoV and pulmonary tuberculosis) and her 73 contacts. While the illness was mostly mild, transient or asymptomatic among the HCWs, this study has shown that

HCWs could transmit MERS-CoV to other HCWs despite being asymptomatic.[50]

Decreasing risk of transmission

With no effective vaccine available, rapid case identification, isolation, infection prevention and control measures are critical to prevent the spread of MERS-CoV within households, the community and in health care facilities. Guidelines and recommendations from global public health bodies are given in **Appendix 1**. Since symptoms and signs of respiratory tract infections (RTIs) are non-specific and are common to all microbial aetiologies of RTIs, it is difficult to diagnose primary cases of patients with MERS-CoV infection early and accurately. Investment in development of rapid point of care testing for MERS-CoV would be of huge value to the global public health community. The upsurge in the number of human infections due to MERS-CoV over the past few years in healthcare facilities in the Middle East and South Korea were attributed to several preventable factors. The low level of HCW awareness of the possibility of MERS-CoV with consequential poor implementation of infection control procedures resulted in nosocomial outbreaks. These involved transmission to existing hospitalized patients, outpatients, visitors and HCWs within healthcare facilities. Transmission was associated with over-crowding, lack of isolation room facilities and environmental contamination without significant genetic change in the transmissibility of the virus.[57]

Infection prevention and control measures

The SARS epidemic led to important infection prevention and control recommendations for managing patients with suspected CoV infection and these are applicable to MERS-CoV.[3] A high degree of awareness of the possibility of MERS-CoV infection and early isolation of suspected or confirmed MERS cases with proactive surveillance are critical to preventing nosocomial spread. To decrease MERS-CoV human-to-human spread and environmental contamination, aerosolizing procedures should be avoided in crowded hospital accident and emergency departments and in inpatient medical wards without adequate infection control measures, Droplet precautions are required for managing patients with confirmed MERS-CoV infection. Wearing a surgical mask within 1-2 m of the patient, and wearing gown, gloves, mask, eye protection on entering the room and removing them upon leaving, are important infection control measures .[64] Airborne precautions should be applied when performing AGPs such as open suctioning or aspiration of respiratory tract, intubation, bronchoscopy or cardiopulmonary resuscitation. These include wearing a half-mask air purifying respirator like a US NIOSH-approved N95 filtering facepiece respirator [FFR] or a European EN-approved FFP2 or FFP3 filtering facepiece respirator. The respirator should fit properly, and all HCWs should undergo in-depth training in proper use, donning, doffing, and performing a user seal check every time the respirator is used.[64]

To reduce room contamination in the hospital setting, the application of a minimum room ventilation rate of six air changes per hour in an existing facility is recommended, A higher ventilation rate of 12 air changes per hour is required for new or renovated constructions, especially when caring for patients receiving mechanical ventilation and during AGPs.[65] Cleaning environmental surfaces with water and detergent and applying commonly used disinfectants (such as hypochlorite) is an effective and sufficient procedure.[64]

Unprotected or inadvertant exposure of HCWs to MERS patients should prompt rapid quarantine and testing of the exposed HCWs. MERS-CoV-positive HCWs should only be allowed to return to work when at least 2 upper respiratory tract samples taken at least 24 hrs apart proven to be negative spanning the full incubation period of 14 days.[50,66]

Education of communities and travellers

In MERS-CoV endemic countries where MERS-CoV cases are suspected or diagnosed in the community and households, educational awareness of MERS-CoV and MERS prevention measures within the home may reduce further transmission and prevent outbreaks of community clusters. Persons with co-morbidties such as diabetes, kidney disease, chronic lung disease, cancer or those on immunosuppressive treatments are at high risk of developing severe MERS-CoV disease, thus they should avoid close contact with camels and bats. Patients with chronic renal failure and patients with chronic heart disease can have misleading clinical presentations when they have MERS-CoV infection as these patients may also have fluid retention from their underlying disease causing lung infiltrates and dyspnoea. Regular hand washing before and after touching camels and avoiding contact with sick camels is advised. People should avoid drinking raw camel milk or camel urine, or eating camel meat that has not been properly cooked. WHO does not advise special screening for MERS-CoV at points of entry after return from the Middle East nor does it currently recommend the application of any travel or trade restrictions. Persons with a history of travel from or to the Arabian Peninsula within 10 days of developing symptoms of an acute respiratory infection involving fever of 38°C or more, cough with radiologic pulmonary changes presentation should alert the physician to the possibility of MERS-CoV infection.[67]

Unanswered questions

It has been 5 years since its first discovery and many unanswered questions remain (**Table 4**). Exposure to dromedary camels and related contact activities are risk factors for primary MERS-CoV infection, the exact mechanisms of transmission require urgent investigation. Genomic studies indicate that MERS-CoV causing infections in humans is indistinguishable from the virus found in dromedary camels in the Middle East. A surveillance study for MERS-CoV in dromedaries in Africa and Central Asia by MERS-CoV spike pseudoparticle neutralization assay has shown that camel serum samples from African countries have high prevalence of MERS-CoV antibodies.[68] Using quantitative RT-PCR, positive specimens for MERS-CoV were detected in camel nasal swabs from all different African countries from which samples were collected. In contrast, dromedary serum and swab samples from Kazakhstan in Central Asia were negative for MERS-CoV by these assays.[69] Phylogenetic analysis of the spike gene revealed that MERS-CoVs from Africa formed a cluster closely related to, but distinct from, the viruses in the Arabian Peninsula. These findings indicate that

MERS-CoV is actively circulating in dromedary populations in Africa but the MERS-CoV virus in Africa is phylogenetically distinct from that in the Middle East.[68] The findings that MERS-CoV is not universally endemic in dromedaries raises the hypothesis that certain species of bats or some other animal, the environment, or both, may constitute a maintenance community and be the true natural reservoir of MERS-CoV and that the virus spills over to camels and is maintained within camels for varying periods of time.[69] This needs to be studied further.

The role of unpasteurized milk, meat, secretions (saliva, urine, sweat and stool) of dromedary camels in the transmission of MERS-CoV requires further study. The risk factors for household transmission include sleeping in same room and contact with patient's secretions, and the role of asymptomatic persons in nosocomial transmission of MERS-CoV infection to high risk patients need to be clarified. While AGPs such as intubation, manual ventilation before intubation, tracheotomy and non-invasive ventilation appeared to have played a significant role in nosocomial outbreaks of SARS-CoV infection[70], the precise role of these procedures in the transmission of MERS-CoV infection in the healthcare settings requires further investigation. Meanwhile improved compliance with infection prevention and control protocols and adherence to standard precautions, (**Appendix 1**) is required to decrease the risk of number of human-to-human transmission of MERS-CoV and outbreaks in healthcare facilities.

CONCLUSIONS

MERS-CoV remains an important public health risk and further international spread through travellers[71] can be anticipated in view of the observed patterns of nosocomial outbreaks and transmission within healthcare facilities in the Middle East and in South Korea.[72] With 10 million pilgrims visiting Saudi Arabia each year from 182 countries to perform the Hajj and Umrah pilgrimages,[73] watchful surveillance by public health systems, and a high degree of clinical awareness of the possibility of MERS-CoV infection is essential, especially for countries with weak public health systems.[74] Nosocomial transmission is often due to a delayed diagnosis of MERS-CoV infection in a patient shedding MERS-CoV in a crowded healthcare setting such as an inpatient ward, emergency department or renal dialysis unit.[26-29,34,46-48,51,55] Early recognition of cases, improved compliance with internationally recommended infection control protocols and rapid implementation of infection control measures are required to prevent health care facility-associated outbreaks of MERS-CoV.[75] There is a dire need for the establishment of robust public health infrastructures, and effective global consortia to enable rapid and effective detection, definition and surveillance of new infectious diseases threats, and for prioritizing research, preparedness, response and control efforts. Five years after first identification of MERS-CoV many important questions remain. With no specific treatments[76] available and the high mortality rate, advancing priority research remains a priority.[77]

AUTHOR DECLARATIONS

All authors have an academic interest in coronaviruses. Professors Hui, Azhar, Memish and Zumla are members of the Global Centre for Mass Gatherings Medicine. Professor Zumla is co-lead of the PANDORA-ID-NET collaboration. Authors declare no other conflicts of interests.

AUTHOR ROLES

Professors Hui and Zumla conceived the concept of the review and performed the literature search and developed the first drafts of the manuscript. All authors contributed equally to subsequent drafts. Professors Hui and Zumla finalised the manuscript.

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LEGENDS TO BOXES, TABLES, FIGURES AND APPENDIX

Box 1: WHO Revised list of priority diseases, January 2017

Table 1. Risk factors for Primary and Household transmission

Table 2. Enhanced Infection-control measures that were effective in controlling nosocomial outbreaks

Table 3. Risk factors for nosocomial MERS-CoV outbreaks

Table 4. Unanswered questions – MERS-CoV determinants, risk and transmission

Supplemental table 1. Selected publications of dromedary camels as the source of MERS-CoV infection in humans

Appendix 1: Additional information: Guidelines and Infection Control Recommendations on MERS-CoV by global public health bodies

Box 1:

WHO Revised list of priority diseases, January 2017[11]

- Crimean Congo haemorrhagic fever
- Ebola virus disease and Marburg virus disease
- Lassa fever
- Middle East respiratory syndrome coronavirus
- Severe acute respiratory syndrome
- Nipah virus infection and related henipaviral diseases
- Rift valley fever
- Zika virus disease
- Disease X (pathogen unknown)

Source: http://www.who.int/blueprint/priority-diseases/en/

Table 1. Risk factors for Primary and Household transmission

1. **Risk factors for primary MERS-CoV infection**.[19]

   a) Significant risk factors were involvement in:

   - camel training
   - milking camels
   - workers with respiratory symptoms requiring overnight stay in hospital
   - contact with camels' waste
   - poor hand hygiene before and after animal task

   b) Independent factors associated with primary MERS-CoV illness (Saudi Arabia):[17]

   - Direct dromedary exposure in the 2 weeks before illness onset (adjusted OR 7.45, 95% CI 1.57–35.28),
   - Diabetes (adjusted OR 6.99, 95% CI 1.89–25.86)
   - Heart disease (adjusted OR 6.87, 95% CI 1.81–25.99) or currently smoking tobacco (adjusted OR 6.84, 95% CI 1.68–27.94).
   - Direct physical contact with dromedaries in the previous 6 months (adjusted OR 14.59, 95% CI 2.38–89.55).

2. **Risk factors for household transmission**.[45]

   a) Sleeping in an index patient's room [RR 4.1 (1.5–11.2)]

   b) Removing patient's waste (urine, stool and sputum) [RR 3.2 (1.2–8.4)]

   c) Touching respiratory secretions from an index patient [RR 4.0 (1.6–9.8)]

Table 2.

Enhanced Infection-control measures that were effective in controlling nosocomial outbreaks:[27]

a) Hand hygiene, droplet & contact precautions for febrile patients & testing these patients for MERS-CoV, b) Putting surgical masks on all patients undergoing hemodialysis & N95 respirator for HCWs managing any patient with confirmed MERS-CoV undergoing an aerosol-generating procedure, c) Not allowing patients with suspected MERS-CoV infection into the dialysis unit & the ICUs, d) Augmenting environmental cleaning, & excluding non-essential staff & visitors.

Table 3. Risk factors for nosocomial MERS-CoV outbreaks[26-29,34,46,48, 51,55]

- Exposure of patients, HCWs and visitors to contaminated and overcrowded healthcare facilities especially Emergency Departments, inpatient wards and dialyses units

- Exposure to symptomatic MERS patients or Healthcare workers caring for them

- Poor compliance with MERS-specific infection control guidelines

- Poor compliance with appropriate Personal Protective Equipment when assessing patients with febrile respiratory illness

- Application of potential aerosol-generating procedures (eg, resuscitation, continuous positive airways (CPAP) ventilation, nebulised drugs)

- Lack of proper isolation room facilities, bed distance <1metre

- Frequent shifting of healthcare seeking behaviour from hospital to hospital /emergency department to another

- Friends & family members staying as caregivers in overcrowded healthcare facilities.

Table 4. Unanswered questions – MERS-CoV determinants, risk and transmission

• Whilst camels are known reservoirs, what is/are the exact animal or environmental source(s) of MERS-CoV? • What is/are the mode(s) of primary transmission to humans in sporadic cases? • Why do children have low MERS-CoV infection/disease rates? • Are there other risk factors for transmission between camels and humans? • What are the seasonal trends in transmission and disease patterns? • What is the role of asymptomatic or mild infections in human to human transmission in the community and in nosocomial settings? • What are the drivers of transmission and exact modes of transmission in healthcare settings? • What are the specific exposures which put healthcare workers at most risk? • What roles so asymptomatic MERS-CoV PCR-positive HCWs play in nosocomial transmission and outbreaks? • To what extent does environmental contamination within hospitals play in nosocomial spread of MERS-CoV? • What are the MERS-CoV viral shedding patterns in different bodily fluids during illness • What are the roles of non-respiratory specimens (eg. faeces, urine, saliva, semen, sweat, blood and tears in transmission of MERS-CoV? • Why MERS-CoV has persisted longer than SARS-CoV? • What is the specific pathogenesis of MERS-CoV infection? • Why there are lack of autopsy or pathological studies and why the specific pathology of MERS-CoV remains undefined? • What are the innate and adaptive immune protective immune mechanisms? • Are protective immune mechanisms deleterious? • What MERS-CoV mutations and evolutionary changes are taking place over time? • Do Host genetics play a role in susceptibility and pathogenesis of MERS-CoV? • Do animal models of MERS-CoV accurately reflect the situation in humans?

Figure 1 Global cases of MERS-CoV infection reported to WHO

(Courtesy of WHO)

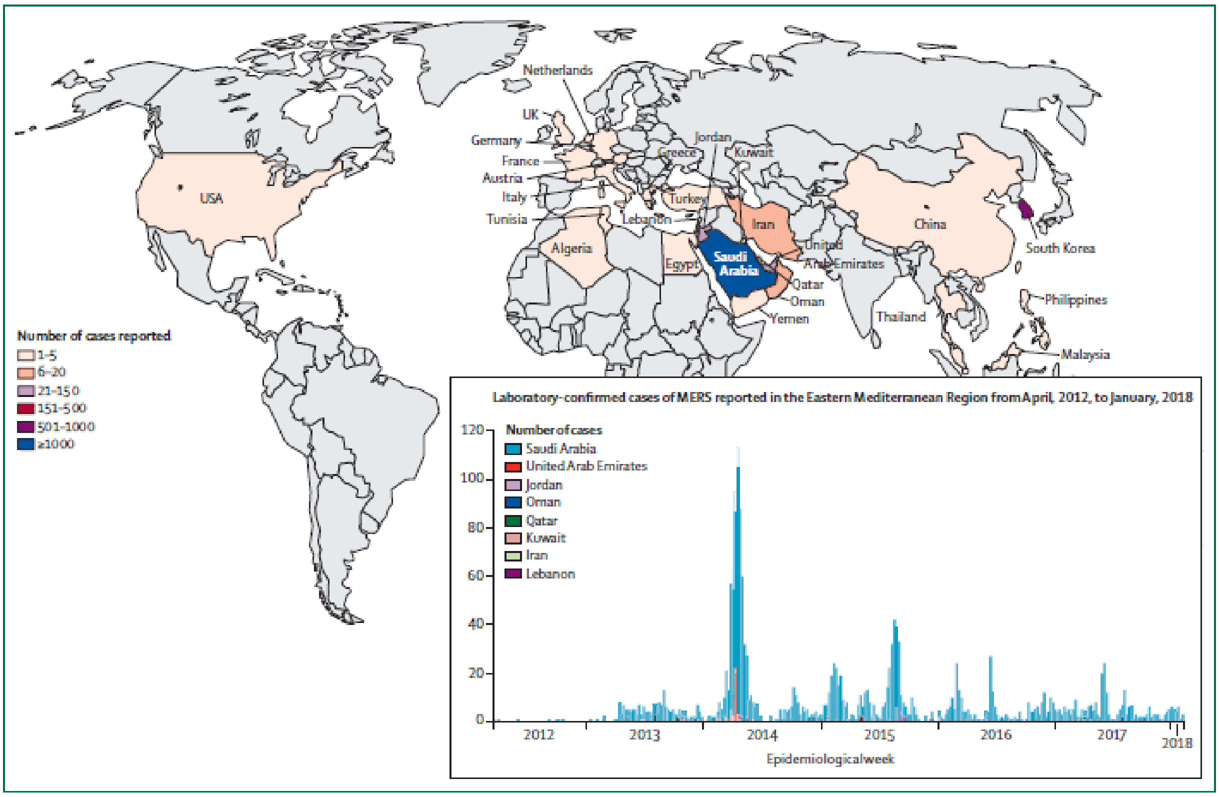

Figure: Global cases of MERS-CoV infection reported to WHO
Reproduced from WHO[4] by permission of World Health Organization. MERS CoV=Middle East respiratory syndrome coronavirus.

Approximately 80% of human cases have been reported by Saudi Arabia. Since 2012, 27 countries have reported cases of MERS including Algeria, Austria, Bahrain, China, Egypt, France, Germany, Greece, Islamic Republic of Iran, Italy, Jordan, Kuwait, Lebanon, Malaysia, the Netherlands, Oman, Philippines, Qatar, Republic of Korea, Kingdom of Saudi Arabia, Thailand, Tunisia, Turkey, United Arab Emirates, United Kingdom, United States, and Yemen. Cases identified outside the Middle East are usually travellers who were infected in the Middle East.

Appendix 1

Additional information, Guidelines and Infection Control Recommendations on MERS-CoV by global public health bodies

US-CDC	**MERS-CoV- prevention and treatment** https://www.cdc.gov/coronavirus/mers/about/prevention.html **Preventing MERS-CoV from Spreading to Others in Homes and Communities** https://www.cdc.gov/coronavirus/mers/hcp/home-care-patient.html https://www.cdc.gov/coronavirus/mers/risk.html **People Who May Be at Increased Risk for MERS** https://www.cdc.gov/coronavirus/mers/infection-prevention-control.html
UK-PHE	**Interim Infection Prevention and Control Recommendations for Hospitalized Patients with Middle East Respiratory Syndrome Coronavirus (MERS-CoV)** https://www.gov.uk/government/publications/merscov-infection-control-for-possible-or-confirmed-cases **MERS-CoV: advice for travellers returning from the Middle East** https://www.gov.uk/government/publications/mers-cov-infographics-for-travellers-from-the-middle-east
WHO	**MERS-CoV Daily updates, facts and figures** http://www.who.int/emergencies/mers-cov/en/ **MERS-CoV factsheet** http://www.who.int/mediacentre/factsheets/mers-cov/en/ **MERS-CoV: infection control for possible or confirmed cases** http://www.who.int/csr/disease/coronavirus_infections/ipc-mers-cov/en/ **Travel advice for pilgrims** http://www.who.int/ith/updates/20170601/en/ **Management of asymptomatic persons who are RTPCR positive for MERS-CoV. Interim Guidance. Updated 3 Jan 2018.** http://apps.who.int/iris/bitstream/10665/180973/1/WHO_MERS_IPC_15.2_eng.pdf?ua=1&ua=**1**
Saudi Arabia MoH	**FAQs coronavirus (MERS-CoV)** https://www.moh.gov.sa/en/CCC/FAQs/Corona/Pages/default.aspx **Infection prevention and control guidelines for the Middle East respiratory Syndrome Coronavirus (MERS-CoV) – Moh, Command and Control centre, 4th Edition January 2017.** https://www.moh.gov.sa/endepts/Infection/Documents/Guidelines-for-MERS-CoV.PDF
ECDC	https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/ MERS-rapid-risk-assessment-update-october-2015.pdf https://ecdc.europa.eu/en/middle-east-respiratory-syndrome-coronavirus/factsheet

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Appendix 1a

Selected publications of dromedary camels as the source of MERS-CoV infection in humans

Authors	Main findings
Dudas G, et al. 2018	Based on existing MERS-CoV sequence data to examine the phylo-dynamics in camels and humans with structured coalescent model, Dudas et al have shown that long-term evolution of MERS-CoV occurs exclusively in camels while humans serve as a transient and terminal host ultimately. In addition, the study has shown that human outbreaks in the Arabian Peninsula have been driven by seasonally varying zoonotic transf of viruses from camels.
Kasem S, et al. 2017	An investigation of animal herds associated with MERS-infected patients in Saudi Arabia, during 2014-2016. Seventy-five dromedary camels positive for MERS-CoV RNA; the virus was not detected in sheep, goats, and cattle. MERS-CoV RNA from infected camels was not detected beyond 2 weeks after the first positive result was detected in nasal swabs obtained from infected camels. Anti-MERS ELISA assays showed that 70.9% of camels related to human cases had antibodies to MERS-CoV. The full genome sequences of the ten MERS-CoV camel isolates were identical to their corresponding patients and were grouped together within the larger MERS-CoV sequences cluster for human and camel isolates reported form the Arabian Peninsula.
Lau SK, et al. 2017	219 camel and human MERS-CoV genome sequences available in GenBank were analyzed. Phylogenetic analysis showed that 5 and 214 strains belong to clade A and B, respectively, with clade A further divided into lineage A1 (3 human strains) and lineage A2 (2 camel strains), and clade B divided into B1 to B6 (each containing both human and camel strains). Recombination analysis showed potential recombination events in five strains from dromedaries in Saudi Arabia, with recombination between lineage B5 and B3 in four strains, and between lineage B3 and B4 in one strain. The spike protein showed the highest number of amino acid substitutions, especially between A2 and other lineages, and contained positively selected codons. Notably, codon 1020 was positively selected among B and B5 strains, and can distinguish between clade A (Q1020) and B (R1020/H1020) strains, suggesting that this residue may play a role in the evolution of S protein during divergence of different lineages. The time of the most recent common ancestor of all MERS-CoV was dated to approximately 2010.

Muhairi SA, et al. 2016	Nasal swabs from 1113 dromedary camels (39 farms) and 34 sheep (1 farm) and sputum samples from 2 MERS-CoV infected camel farm owners and 1 MERS-CoV-infected sheep farm owner were collected in Abu Dhabi. Samples from camels and humans underwent real-time quantitative RTPCR screening to detect MERS-CoV. In addition, sequencing and phylogenetic analysis of partially characterized MERS-CoV genome fragments obtained from camels were performed. Among the 40 farms, 6 camel farms were positive for MERS-CoV; the virus was not detected in the single sheep farm. The maximum duration of viral shedding from infected camels was 2 weeks after the first positive test result as detected in nasal swabs and in rectal swabs obtained from infected calves. Three partial camel sequences characterized in this study (ORF 1a and 1ab, Spike1, Spike2, and ORF4b) together with the corresponding regions of previously reported MERS-CoV sequence obtained from one farm owner were clustering together within the larger MERS-CoV sequences cluster containing human and camel isolates reported for the Arabian Peninsula.
Farag EA, et al. 2015	A high proportion of camels presenting for slaughter in Qatar showed evidence for nasal MERS-CoV shedding (62/105). Sequence analysis showed the circulation of at least five different virus strains at these premises, suggesting that this location is a driver of MERS-CoV circulation and a high-risk area for human exposure. No correlation between RNA loads and levels of neutralizing antibodies was observed, suggesting limited immune protection and potential for reinfection despite previous exposure.
Reusken CB, et al. 2015	The investigators determined the presence of neutralizing antibodies to MERS-CoV in persons in Qatar with and without dromedary contact in 2013-2014. Antibodies were only detected in those with contact, suggesting dromedary exposure as a risk factor for infection. The study also showed evidence for substantial underestimation of the infection in populations at risk in Qatar.
Haagmans BL, et al. 2014	Samples taken from 14 camels on Oct 17, 2013 in an outbreak investigation in a farm in Qatar. MERS-CoV detected in nose swabs from three camels by three independent RT-PCRs and sequencing. The nucleotide sequence of an ORF1a fragment (940 nucleotides) and a 4·2 kb concatenated fragment were very similar to the MERS-CoV from two human cases on the same farm and a MERS-CoV isolate from Hafr-Al-Batin. Eight additional camel nose swabs were positive on one

	or more RT-PCRs, but could not be confirmed by sequencing. All camels had MERS-CoV spike-binding antibodies that correlated well with the presence of neutralising antibodies to MERS-CoV.

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Appendix 1b:

Additional information: Situation update guidelines and infection control recommendations on MERS-CoV by global public health bodies

WHO	**MERS-CoV Daily updates, facts and figures** http://www.who.int/emergencies/mers-cov/en/ **MERS-CoV factsheet** http://www.who.int/mediacentre/factsheets/mers-cov/en/ **MERS-CoV: infection control for possible or confirmed cases** http://www.who.int/csr/disease/coronavirus_infections/ipc-mers-cov/en/ **Travel advice for pilgrims** http://www.who.int/ith/updates/20170601/en/ **Management of asymptomatic persons who are RTPCR positive for MERS-CoV. Interim Guidance. Updated 3 Jan 2018.** http://apps.who.int/iris/bitstream/10665/180973/1/WHO_MERS_IPC_15.2_eng.pdf?ua=1&ua=1
FAO	**MERS-CoV situation update** **http://www.fao.org/ag/againfo/programmes/en/empres/mers/situation_update.html**
US-CDC	**MERS-CoV- prevention and treatment** https://www.cdc.gov/coronavirus/mers/about/prevention.html **Preventing MERS-CoV from Spreading to Others in Homes and Communities** https://www.cdc.gov/coronavirus/mers/hcp/home-care-patient.html https://www.cdc.gov/coronavirus/mers/risk.html **People Who May Be at Increased Risk for MERS** https://www.cdc.gov/coronavirus/mers/infection-prevention-control.html
UK-PHE	**Interim Infection Prevention and Control Recommendations for Hospitalized Patients with Middle East Respiratory Syndrome Coronavirus (MERS-CoV)** https://www.gov.uk/government/publications/merscov-infection-control-for-possible-or-confirmed-cases **MERS-CoV: advice for travellers returning from the Middle East** https://www.gov.uk/government/publications/mers-cov-infographics-for-travellers-from-the-middle-east
Saudi Arabia MoH	**FAQs coronavirus (MERS-CoV)** https://www.moh.gov.sa/en/CCC/FAQs/Corona/Pages/default.aspx **Infection prevention and control guidelines for the Middle East respiratory Syndrome Coronavirus (MERS-CoV) – Moh, Command and Control Centre, 4th Edition January 2017.** https://www.moh.gov.sa/endepts/Infection/Documents/Guidelines-for-MERS-CoV.PDF **Middle East respiratory Syndrome Coronavirus; Guidelines for health care professionals. April, 2018 -v. 5.0 pdf. Saudi Arabia Ministry of health, Command and Control Centre.** **MERS-CoV Health guidelines** https://www.moh.gov.sa/en/CCC/InformationCenter/Pages/default.aspx
ECDC	**ECDC Middle East respiratory Syndrome Coronavirus (MERS-CoV)** https://ecdc.europa.eu/en/middle-east-respiratory-syndrome-coronavirus https://ecdc.europa.eu/en/middle-east-respiratory-syndrome-coronavirus/factsheet