BOLETÍN BIBLIOGRÁFICO BIBLIOTECA DE SALUD
DR. BOGOSLAV JURICIC TURINA

Boletín Bibliográfico Nº2/ 2015

La Biblioteca de Salud "Dr. Bogoslav Juricic Turina, dependiente de la División de Planificación Sanitaria del Ministerio de Salud, tiene el agrado de enviar a usted, el Boletín Bibliográfico Nº2/2015. (Seguir el vínculo para acceder al texto completo).

MERS CoV (Síndrome Respiratorio del Medio Oriente Coronavirus)

1. **Identification of new respiratory viruses in the new millennium.**
Berry M, Gamieldien J, Fielding BC.
Viruses. 2015 Mar 6; 7(3):996-1019. Review.

2. **Middle East respiratory syndrome coronavirus: epidemiology and disease control measures.**
Al-Tawfiq JA, Memish ZA.
Infect Drug Resist. 2014 Nov 3; 7:281-7. Review.

3. **Molecular pathology of emerging coronavirus infections.**
Gralinski LE, Baric RS.
J Pathol. 2015 Jan; 235(2):185-95. Review.

4. **The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis.**
Mair-Jenkins J, Saavedra-Campos M, Baillie JK, Cleary P, Khaw FM, Lim WS, Makki S, Rooney KD, Beck CR; Convalescent Plasma Study Group.
J Infect Dis. 2015 Jan 1; 211(1):80-90. Review.

5. **Systems approaches to Coronavirus pathogenesis.**
Schäfer A, Baric RS, Ferris MT.
Curr Opin Virol. 2014 Jun; 6:61-9. Review.

6. **Current advancements and potential strategies in the development of MERS-CoV vaccines.**
Zhang N, Jiang S, Du L.
Expert Rev Vaccines. 2014 Jun; 13(6):761-74.

7. **Membrane ectopeptidases targeted by human coronaviruses.**
Bosch BJ, Smits SL, Haagmans BL.
Curr Opin Virol. 2014 Jun; 6:55-60. Review.

8. **Coronaviruses: important emerging human pathogens.**
Coleman CM, Frieman MB.
J Virol. 2014 May; 88(10):5209-12. Review.

9. **MERS: emergence of a novel human coronavirus.**
Raj VS, Osterhaus AD, Fouchier RA, Haagmans BL.
Curr Opin Virol. 2014 Apr;5:58-62. Review.

10. **Middle East respiratory syndrome coronavirus antibody reactors among camels in Dubai, United Arab Emirates, in 2005.**
Alexandersen S, Kobinger GP, Soule G, Wernery U.
Transbound Emerg Dis. 2014 Apr; 61(2):105-8. Review.

11. **Cell-based antiviral screening against coronaviruses: developing virus-specific and broad-spectrum inhibitors.**
Kilianski A, Baker SC.
Antiviral Res. 2014 Jan; 101:105-12. Review.

12. **The Middle East respiratory syndrome--how worried should we be?**
Perlman S.
MBio. 2013 Aug 20;4(4). 531. Review.

BASE DE DATOS UpToDate

All topics are updated as new evidence becomes available and our peer review process is complete.
Literature review current through: May 2015. | **This topic last updated:** Jun 15, 2015.

INTRODUCTION — In September 2012, a case of novel coronavirus infection was reported involving a man in Saudi Arabia who was admitted to a hospital with pneumonia and acute kidney injury in June 2012 [1]. Only a few days later, a separate report appeared of an almost identical virus detected in a second patient with acute respiratory syndrome and acute kidney injury [2,3]. The second patient initially developed symptoms in Qatar but had traveled to Saudi Arabia before he became ill and then sought care in the United Kingdom [4]. Many subsequent cases and clusters of infections have been reported, as discussed below. (See 'Epidemiology' below.)

This novel coronavirus, initially termed human coronavirus-EMC (for Erasmus Medical Center), has been named Middle East respiratory syndrome coronavirus (MERS-CoV) [5].

Updated information about MERS-CoV can be found on the World Health Organization website and the United States Centers for Disease Control and Prevention website.

The virology, epidemiology, clinical manifestations, diagnosis, treatment, and prevention of MERS-CoV are discussed here. Community-acquired coronaviruses and severe acute respiratory syndrome coronavirus are reviewed separately. (See "Coronaviruses" and "Severe acute respiratory syndrome (SARS)".)

VIROLOGY — Middle East respiratory syndrome coronavirus (MERS-CoV) is a lineage C betacoronavirus, different from the other human betacoronaviruses (severe acute respiratory syndrome coronavirus, OC43, and HKU1) but closely related to several bat coronaviruses [4,6-11]. (See 'Bats' below.)

Dipeptidyl peptidase 4 (DPP4; also known as CD26), which is present on the surfaces of human nonciliated bronchial epithelial cells, is a functional receptor for MERS-CoV [12,13]. Expression of human and bat DPP4 in nonsusceptible cells enables infection by MERS-CoV. The DPP4 protein displays high amino acid sequence conservation across different species, including the sequence that was obtained from bat cells.

In a cell line susceptibility study, MERS-CoV infected several human cell lines, including lower (but not upper) respiratory, kidney, intestinal, and liver cells, as well as histiocytes [14]. The range of tissue tropism in vitro was broader than that for any other known human coronavirus. In another study, human bronchial epithelial cells were susceptible to infection [15]. MERS-CoV can also infect nonhuman primate, porcine, bat, civet, rabbit, and horse cell lines [14,16,17]. Further study is necessary to determine whether these in vitro findings will translate to broader species susceptibility during in vivo infections [18].

Because of a large increase in cases in Saudi Arabia in the spring of 2014, there was concern that MERS-CoV might have mutated to become more transmissible or virulent. However, cell culture experiments of viruses isolated during these outbreaks showed no evidence of changes in viral

replication rate, immune escape, interferon sensitivity, or serum neutralization kinetics compared with a contemporaneous but phylogenetically different virus recovered in Riyadh or the original MERS-CoV isolate from 2012 [19].

Genetic analysis — In an analysis of the full or partial genomes of MERS-CoV obtained from 21 patients with MERS-CoV infection in Saudi Arabia between June 2012 and June 2013, there was sufficient heterogeneity to support multiple separate animal-to-human transfers [20]. Moreover, even within a hospital outbreak in Al-Hasa, Saudi Arabia, there was evidence of more than one virus introduction. By estimating the evolutionary rate of the virus, the authors concluded that MERS-CoV emerged around July 2011 (95 percent highest posterior density July 2007 to June 2012).

Phylogenetic analysis during the spring of 2014 showed that viruses from patients in Jeddah, Saudi Arabia, were genetically similar, suggesting that the outbreak in Jeddah was caused by human-to-human transmission [19]. Of 168 specimens that were positive for MERS-CoV during the outbreak in Jeddah, 49 percent came from a single hospital, King Fahd Hospital. Isolates from patients in Riyadh, Saudi Arabia, during the spring of 2014 belonged to six different clades, suggesting that these infections resulted from increased zoonotic activity or transmission from humans in other regions. One cluster of infections observed in a single hospital in Riyadh was associated with a single clade, suggesting nosocomial transmission.

EPIDEMIOLOGY — In September 2012, a novel coronavirus infection was reported in ProMed Mail, an internet-based reporting system that helps disseminate information about infectious disease outbreaks worldwide [1]. The virus was isolated from the sputum of a man in Jeddah, Saudi Arabia, who was admitted to a hospital with pneumonia and acute kidney injury in June 2012. Shortly thereafter, a report appeared of an almost identical virus detected in a patient in Qatar with acute respiratory syndrome and acute kidney injury; the patient had traveled recently to Saudi Arabia [2-4].

Subsequent cases and clusters of infections have been reported, as discussed below (figure 1). Since April 2012, more than 1280 cases of MERS-CoV infection have been reported (see 'Geographic distribution' below). The actual number of cases is likely to be higher [21]. The median age is 48 years (range 9 months to 94 years) and 64 percent of cases have been male [22].

The number of cases in the Middle East increased dramatically in March and April 2014 then declined sharply in mid-May 2014 [22,23]. An increase in cases also occurred during March and April 2013.

Geographic distribution — Since April 2012, more than 1280 laboratory-confirmed human infections with Middle East respiratory syndrome coronavirus (MERS-CoV) have been reported to the World Health Organization (WHO), occurring in several countries in the Arabian Peninsula, including Jordan, Kuwait, Lebanon, Oman, Qatar, Saudi Arabia, the United Arab Emirates, and Yemen (figure 2); the majority of cases have occurred in Saudi Arabia, including some case clusters [23-25]. A limited number of cases have also been reported from Algeria, Austria, China, Egypt, France, Germany, Greece, Iran, Italy, South Korea, Malaysia, the Netherlands, the Philippines, Tunisia, Turkey, the United Kingdom, and the United States. In the European and Asian countries as well as in Algeria, Egypt, Tunisia, and the United States, patients developed illness after

returning from the Arabian Peninsula. In the United Kingdom, France, Italy, and Tunisia, limited human-to-human transmission occurred among close contacts of the index cases.

Cases and clusters — Some notable cases and clusters are summarized as follows:

- The index case was a man in Jeddah, Saudi Arabia, who was hospitalized with pneumonia in June 2012 [4]. He developed acute respiratory distress syndrome (ARDS) and acute kidney injury and died; MERS-CoV was isolated from his sputum.
- In September 2012, a nearly identical coronavirus was detected in a man who also had an acute respiratory distress syndrome and acute kidney injury requiring admission to the intensive care unit [2,26,27]. He initially developed symptoms in Qatar but had recently traveled to Saudi Arabia and sought care in the United Kingdom [4].
- A cluster occurred in October and November 2012 in four men in one family in Riyadh, Saudi Arabia, two of whom died [28]. None of the 24 other family members who lived with the infected patients or 124 healthcare workers who had contact with them became ill.
- The two earliest confirmed cases were subsequently reported from Jordan [29,30]. Both patients died during a cluster of acute respiratory illness in April 2012, which included 10 healthcare workers. Serologic testing suggested that seven surviving hospital contacts had MERS-CoV infection.
- In January 2013, a resident of the United Kingdom who had traveled to Saudi Arabia and Pakistan developed a severe respiratory illness, and diagnostic tests of respiratory specimens were positive for both MERS-CoV and H1N1 influenza A; he died in March 2013 [31]. In February 2013, the patient's son, who had underlying medical conditions, died from MERS-CoV infection after being in close contact with his father [32,33]. Another family member developed a mild illness and was also found to have MERS-CoV [32]. Neither of these individuals traveled to the Middle East, strongly suggesting that they acquired the virus via person-to-person spread.
- In April 2013, a cluster of 23 confirmed cases and 11 probable cases of MERS-CoV was detected in Al-Hasa in the Eastern Province of Saudi Arabia [34]. Almost all cases were directly linked to person-to-person exposure, most of them in the hemodialysis (nine cases) or intensive care (four cases) units of a single hospital. There were only two proven cases in healthcare workers, and only three family members (all of whom had visited the hospital) were proven infected despite a survey of over 200 household contacts.
- In May 2013, a patient in France developed MERS-CoV infection after returning to France from a vacation to the United Arab Emirates [33]. A second patient was diagnosed with MERS-CoV after sharing a hospital room with the first patient [33,35]. The first patient died and the second patient was critically ill. Both patients were immunocompromised, one a renal transplant recipient and the second on daily glucocorticoids. No cases of secondary transmission were detected in more than 100 healthcare workers, despite the lack of use of personal protective equipment [35].
- A sharp increase in the number of cases was reported in Saudi Arabia and the United Arab Emirates in March and April 2014 [22,36,37]. Of the over 500 cases reported, the majority represented hospital-based outbreaks in the Saudi Arabian cities of Jeddah (255 cases), Riyadh, Tabuk, and Madinah and in Al Ain City, Abu Dhabi, United Arab Emirates, and included cases in healthcare workers, patients admitted for other medical problems, visitors, and ambulance staff. Up to 75 percent of cases during this period appeared to be acquired from exposure to persons known to be infected [38]. Nevertheless, there has been no clear evidence of sustained

human-to-human transmission of MERS-CoV in community settings. Many of the secondary infections that occurred in healthcare workers were either mildly symptomatic or asymptomatic, but 15 percent of healthcare workers presented with severe disease or died [37].

- The first case in the United States occurred in an American healthcare worker in his sixties who lived and worked in Riyadh, Saudi Arabia, but traveled to Indiana in April 2014, where he presented for care [39-41]. A second imported case in the United States was confirmed in May 2014 in Florida in an individual who was visiting from Saudi Arabia [39,42,43].
- The first cases in South Korea occurred in May 2015; the index case was a man who had recently traveled to Bahrain, the United Arab Emirates, Saudi Arabia, and Qatar [44]. As of mid-June 2015, 149 secondary cases have been reported among household and hospital contacts; 15 deaths have been reported [45-49]. One case occurred in a man who traveled to China following exposure to two relatives with MERS-CoV infection; this patient is the first reported case in China [47].

Possible sources and modes of transmission — It seems likely that dromedary camels are the primary animal host for MERS-CoV (see 'Camels' below). The presence of case clusters strongly suggests that human-to-human transmission occurs [33-35,50].

Serologic studies have shown low prevalence of MERS-CoV antibodies in humans in Saudi Arabia [51,52]. A broad antibody survey of 10,009 individuals representative of the general population of Saudi Arabia found seropositivity in 15 (0.15 percent), all but one of whom resided in five interior provinces (of 13 total provinces) [53]. In a separate survey included in the same report, 87 camel shepherds and 140 slaughterhouse workers were tested, of whom 7 (3.1 percent) were seropositive.

Among 5235 adult pilgrims from 22 countries who visited Mecca, Saudi Arabia, for Hajj in 2013, none had a positive MERS-CoV polymerase chain reaction (PCR) from the nasopharynx; 3210 individuals were screened pre-Hajj, and 2025 were screened post-Hajj [54].

Bats — Studies performed in Europe, Africa, and Asia, including the Middle East, have shown that coronavirus RNA sequences are found frequently in bat fecal samples and that some of these sequences are closely related to MERS-CoV sequences [8-10]. In a study from Saudi Arabia, 823 fecal and rectal swab samples were collected from bats, and, using a PCR assay, many coronavirus sequences were found [10]. Most were unrelated to MERS-CoV, but, notably, one 190 nucleotide sequence in the RNA-dependent RNA polymerase (RdRp) gene was amplified that had 100 percent identity with a MERS-CoV isolate cloned from the index patient with MERS-CoV infection; the sequence was detected from a fecal pellet of a *Taphozous perforatus* bat captured from a site near the home of the patient. MERS-CoV grows readily in several bat-derived cell lines [16].

Although bats might be a reservoir of MERS-CoV, it is unlikely that they are the immediate source for most human cases because human contact with bats is uncommon [55].

Camels — As noted above, it is likely that camels serve as hosts for MERS-CoV. The strongest evidence of camel-to-human transmission of MERS-CoV comes from a study in Saudi Arabia in which MERS-CoV was isolated from a man with fatal infection and from one of his camels; full-

genome sequencing demonstrated that the viruses isolated from the man and his camel were identical [56]. The study had the following findings:

- A previously healthy 44-year-old man was admitted to the intensive care unit of a hospital in Jeddah, Saudi Arabia, with severe dyspnea. He initially developed fever, rhinorrhea, cough, and malaise eight days prior to admission, and he became dyspneic three days prior to admission. He owned a herd of nine dromedary camels; he had visited the camels daily until three days before admission. Four of the camels had been ill with nasal discharge during the week before the onset of the man's illness. The man had applied a topical medicine to the nose of one of the ill camels seven days before he became ill. The patient died 15 days after hospital admission.
- Nasal swabs collected from the patient on hospital days 1, 4, 14, and 16 were all positive for MERS-CoV by real-time reverse-transcriptase polymerase chain reaction (rRT-PCR). The first nasal specimen collected from one symptomatic camel was also positive by rRT-PCR; a repeat nasal specimen collected 28 days later was negative. Nasal specimens that were collected from the other camels on day 1 (seven camels) and day 28 (eight camels) were negative by rRT-PCR. Milk, urine, and rectal specimens collected from all camels were negative by rRT-PCR.
- Separate Vero cell cultures inoculated with the first specimens obtained from the patient and from the PCR-positive camel both grew MERS-CoV strains, which, on full-genome sequencing, were identical.
- A serum specimen collected from the patient on day 1 was negative for MERS-CoV antibodies (<1:10) by immunofluorescence assay, whereas the specimen collected on day 14 had an antibody titer of 1:1280. Paired serum specimens from the infected camel also showed a >4-fold increase in the antibody titer. Four other camels had increases in antibody, and the remaining four camels had high, stable antibody titers to MERS-CoV.

These results suggest that MERS-CoV can infect dromedary camels and can be transmitted from them to humans by close contact.

Other phylogenetic analyses comparing portions of the MERS-CoV genome obtained from camels to MERS-CoV obtained from humans with epidemiologic links to the camels have demonstrated that the viruses were similar [57-60].

Serologic studies have also suggested that camels are an important source of MERS-CoV:

- Of 203 serum samples from dromedary camels in various regions of Saudi Arabia collected in 2013, 150 (74 percent) had antibodies to MERS-CoV by enzyme-linked immunosorbent assay [58]. The rate of seropositivity was higher in adult than juvenile camels (>95 percent among camels >2 years of age versus 55 percent in camels ≤2 years of age). Using stored serum samples from 1992 to 2010, antibodies to MERS-CoV were detected as early as 1992. No MERS-CoV–specific antibodies were detected in domestic sheep or goats in Saudi Arabia.
- Almost all adult camels (>90 percent) from countries in the Arabian Peninsula, Jordan, Egypt, Nigeria, and Ethiopia show antibody evidence of prior MERS-CoV infection; adult camels in other countries of the region (Kenya, Tunisia, Spain, Canary Islands) are also MERS-CoV antibody positive but at a lower prevalence [57,59-68]. Camels in other parts of Europe and in the Americas do not have MERS-CoV antibodies, and no other domestic animals tested have shown evidence of infection [17,68].

In another study, three dromedary camels inoculated with MERS-CoV intratracheally, intranasally, and conjunctivally shed large quantities of virus from the upper respiratory tract [69]. Infectious virus was detected in nasal secretions for 7 days postinoculation and viral RNA for up to 35 days postinoculation.

Human-to-human transmission — Case clusters in the United Kingdom, Tunisia, Italy, and in healthcare facilities in Saudi Arabia, France, Iran, and South Korea strongly suggest that human-to-human transmission occurs (figure 3) [19,22,33-35,70-72]. The number of contacts infected by individuals with confirmed infections, however, appears to be limited [73-76]. Secondary cases have tended to be milder than primary cases, and many secondary cases have been reported to be asymptomatic [38,76]. Possible modes of transmission include droplet and contact transmission [77].

More than half of all laboratory-confirmed secondary cases have been associated with healthcare settings [78]. The majority of cases in the spring of 2014 in Saudi Arabia were acquired through human-to-human transmission in healthcare settings, likely due at least in part to systemic weaknesses in infection control [22,36,79]. A phylogenetic analysis of viruses isolated during the outbreaks in Saudi Arabia in the spring of 2014 is discussed above. (See 'Genetic analysis' above.)

Secondary transmission has also occurred in the household setting. Among 280 household contacts of 26 index patients with MERS-CoV infection, 12 probable cases of secondary transmission were detected by PCR of a pharyngeal swab and/or serology (4 percent, 95% CI 2 to 7 percent) [76]. However, it is possible that some of the index cases and probable secondary cases may have acquired MERS-CoV from a common source, particularly since three of seven contacts tested positive for MERS-CoV by PCR only four days after illness onset in the index cases. Another limitation of this study is that some secondary cases may have been missed since only 108 of 280 contacts had samples available for serologic testing >3 weeks after onset of symptoms in the index case.

Virus is found most easily in lower respiratory tract samples (tracheal aspirates, sputum, or bronchoalveolar lavage fluid) of symptomatic patients, and this shedding may persist for as long as two weeks [56]. Of perhaps greater concern, prolonged shedding was also detected by PCR in an asymptomatic healthcare worker [80]. The individual was initially tested following occupational exposure to MERS-CoV. Serial PCR testing revealed ongoing shedding for six weeks. These findings raise concerns that asymptomatic individuals could unknowingly transmit infection to others.

In a study that evaluated the transmissibility and epidemic potential of MERS-CoV based upon 55 laboratory-confirmed cases detected by late June 2013, the reproduction number (R_0; defined as the average number of infections caused by one infected individual in a fully susceptible population) was estimated to be between 0.60 and 0.69 [81,82]. The finding of an $R_0 < 1$ suggests that MERS-CoV does not yet have pandemic potential. Others have pointed out that the R_0 might be higher in the absence of infection control measures [21].

CASE DEFINITIONS — For epidemiologic purposes, the following Middle East respiratory syndrome coronavirus (MERS-CoV) infection case definitions have been proposed by the World Health Organization (WHO) [83]:

- **Confirmed case** – A person with laboratory confirmation of infection with MERS-CoV irrespective of clinical signs and symptoms
- **Probable case** – A probable case is defined by the following criteria:
  - A febrile acute respiratory illness with clinical, radiographic, or histopathologic evidence of pulmonary parenchymal disease (eg, pneumonia or acute respiratory distress syndrome) **and**
  - A direct epidemiologic link with a confirmed MERS-CoV case **and**
  - Testing for MERS-CoV is unavailable, negative on a single inadequate specimen, or inconclusive

OR

  - A febrile acute respiratory illness with clinical, radiographic, or histopathologic evidence of pulmonary parenchymal disease (eg, pneumonia or acute respiratory distress syndrome) **and**
  - The person resides in or traveled to the Middle East or countries where MERS-CoV is known to be circulating in dromedary camels or where human infections have recently occurred **and**
  - Testing for MERS-CoV is inconclusive

OR

  - An acute febrile respiratory illness of any severity **and**
  - Direct epidemiologic link with a confirmed MERS-CoV case **and**
  - Testing for MERS-CoV is inconclusive

WHO criteria for laboratory confirmation require detection of viral nucleic acid or acute and convalescent serology. The presence of nucleic acid can be confirmed by positive results from at least two sequence-specific real-time reverse-transcriptase polymerase chain reactions (rRT-PCRs) or a single sequence-specific rRT-PCR test and direct sequencing from a separate genomic target [84]. A case confirmed by serology requires demonstration of seroconversion in two samples ideally collected at least 14 days apart using at least one screening assay (enzyme-linked immunoassay, immunofluorescence assay) and a neutralization assay. Specific criteria and additional definitions can be found on the WHO's website. PCR testing is discussed in detail below. (See 'Polymerase chain reaction and sequencing' below.)

The United States Centers for Disease Control and Prevention's (CDC's) case definitions can be found on the CDC's website.

CLINICAL MANIFESTATIONS

Incubation period — In an outbreak of Middle East respiratory syndrome coronavirus (MERS-CoV) infection in Saudi Arabia that resulted in laboratory-confirmed MERS-CoV in 23 individuals, the median incubation period was 5.2 days (95% CI 1.9-14.7 days) [34]. In one secondary case that occurred in a patient in France who shared a room with an infected patient, the incubation period was estimated at 9 to 12 days [35].

The World Health Organization (WHO) and the United States Centers for Disease Control and Prevention (CDC) recommend that an evaluation for MERS-CoV be considered in individuals with a syndrome of MERS who returned from travel to the Arabian peninsula or neighboring countries within the past 14 days [85]. Countries in or neighboring the Arabian Peninsula are defined below. (See 'In the United States' below.)

Clinical features — Most patients with MERS-CoV infection have been severely ill with pneumonia and acute respiratory distress syndrome, and some have had acute kidney injury [4,28,33-35,75,86,87]. Many patients have required mechanical ventilation, and some have required extracorporeal membrane oxygenation. Other clinical manifestations that have been reported are gastrointestinal symptoms (anorexia, nausea, vomiting, abdominal pain, diarrhea), pericarditis, and disseminated intravascular coagulation [28,33,35,87,88]. Among 12 critically ill patients, 11 had extrapulmonary manifestations including shock (in 11) and acute kidney injury (in 7) [75]. One immunocompromised patient presented with fever, diarrhea, and abdominal pain but without early respiratory symptoms; pneumonia was identified incidentally on a chest radiograph [33,35].

It remains unclear whether persons with specific conditions are disproportionately infected with MERS-CoV or have more severe disease [73]. In a study of 47 patients with MERS-CoV infection in Saudi Arabia, 45 (96 percent) had underlying comorbidities, including diabetes mellitus (68 percent), hypertension (34 percent), chronic cardiac disease (28 percent), and chronic kidney disease (49 percent) [87]. One patient was receiving long-term immunosuppressive therapy with glucocorticoids. In a study of 12 critically ill patients with MERS-CoV infection, each individual had at least one comorbid condition; the median number of comorbid conditions was 3 (range 1 to 6) [75]. In a case-control study that included 17 case patients with MERS-CoV infection and 82 controls, case patients were more likely than controls to be overweight, have diabetes mellitus, and to have end-stage renal disease [89].

The high rate of comorbidities reported must be interpreted with caution, since diabetes mellitus was frequently observed in a study of more than 6000 patients presenting to an outpatient clinic in Riyadh, Saudi Arabia, and because approximately half of the 47 patients described in the first study were part of an outbreak in a hemodialysis unit [87], where rates of chronic kidney disease and hypertension would be expected to be high [90].

The following clinical findings were observed among 47 patients with MERS-CoV infection in Saudi Arabia [87]:

- Fever (>38°C) – 46 patients (98 percent)
- Fever with chills or rigors – 41 patients (87 percent)
- Cough – 39 patients (83 percent)
- Shortness of breath – 34 patients (72 percent)
- Hemoptysis – 8 patients (17 percent)
- Sore throat – 10 patients (21 percent)
- Myalgias – 15 patients (32 percent)
- Diarrhea – 12 patients (26 percent)
- Vomiting – 10 patients (21 percent)
- Abdominal pain – 8 patients (17 percent)
- Abnormal chest radiograph – 47 patients (100 percent)

Of these 47 patients, 42 (89 percent) required intensive care and 34 (72 percent) required mechanical ventilation [87]. The median time from presentation for medical care to mechanical ventilation was 7 days (range 3 to 11 days) and to death was 14 days (range 5 to 36 days).

Mild and asymptomatic infections — Although many patients have had severe disease, some reports have described individuals with a mild respiratory illness not requiring hospitalization [85,91]. In one report, a patient developed a dry cough on the tenth day of illness followed by dyspnea and hypoxia on the eleventh day of illness; prior to that, he had only nonspecific signs and symptoms (malaise, myalgias, low-grade fever) [41].

Several individuals with asymptomatic infection have been identified among contacts of patients with symptomatic infection [22,36,76,91]. As an example, the Saudi Arabian Ministry of Health screened more than 3000 close contacts of patients using real-time reverse-transcriptase polymerase chain reaction of nasopharyngeal swabs and identified seven healthcare workers with MERS-CoV infection, two of whom were asymptomatic and five of whom had mild upper respiratory tract symptoms [91].

It appears that many individuals who have been reported to be asymptomatic have in fact had signs and symptoms of illness. In a study of a healthcare facility–associated outbreak in Jeddah, Saudi Arabia, in the spring of 2014, there were 255 laboratory-confirmed cases of MERS-CoV infection [36]. Of 64 patients who were initially identified as being asymptomatic, 33 of the 64 individuals (52 percent) were available for a telephone survey. Of these 33 people, 79 percent reported at least one symptom during the month before testing and 70 percent reported more than one symptom. Unexpectedly, 36 percent of the individuals reported the presence of signs and symptoms as the reason for undergoing MERS-CoV testing, even though they had been identified as being asymptomatic.

Children — There is only one published description of MERS-CoV infection in children [92]. Of 11 infections, 9 were asymptomatic, all discovered during contact investigations of older patients. Both symptomatic cases were in children with underlying conditions (cystic fibrosis and Down syndrome).

Effect on fetuses — One stillbirth at five months' gestation has been reported in a woman with MERS-CoV infection [93]. The woman developed vaginal bleeding and abdominal pain on the seventh day of illness with MERS-CoV, and she spontaneously delivered a stillborn infant. In another MERS-CoV infection in pregnancy occurring near term, a woman in the United Arab Emirates gave birth to an apparently healthy baby; the mother died after delivery [78].

Clinical findings in animal models — Several studies have shown that nonhuman primates develop MERS-CoV infection after inoculation with MERS-CoV and can therefore be used as animal models for studying MERS-CoV infection [94-96]. In contrast, mice, ferrets, and guinea pigs do not appear to be susceptible to MERS-CoV infection [96]. In one study, six rhesus macaques were inoculated with MERS-CoV through a combination of intratracheal, intranasal, oral, and ocular routes [94]. Within 24 hours, all animals developed anorexia, fever, tachypnea, cough, piloerection, and hunched posture. Chest radiographs showed localized infiltrates and increased interstitial markings. After the animals were euthanized, postmortem examinations showed multifocal to coalescent lesions throughout the lungs. Histopathology demonstrated infiltrates of neutrophils and macrophages, compatible with acute interstitial pneumonia.

In another study by the same group, following inoculation with MERS-CoV, rhesus macaques developed a transient lower respiratory tract infection [95]. Clinical signs, virus shedding, virus replication in respiratory tissues, gene expression, inflammatory changes on histology, and

cytokine and chemokine profiles peaked one day after infection and decreased rapidly over time. In nasal swabs and bronchoalveolar lavage fluid specimens, viral loads were also highest on day 1 postinfection and decreased rapidly. Two of three animals were still shedding virus from the respiratory tract on day 6 (the same day they were euthanized). MERS-CoV caused a multifocal, mild to marked interstitial pneumonia, with virus replication occurring primarily in type I and II alveolar pneumocytes.

Laboratory abnormalities — Among 47 cases of MERS-CoV infection in Saudi Arabia, laboratory abnormalities included leukopenia (14 percent), lymphopenia (34 percent), lymphocytosis (11 percent), thrombocytopenia (36 percent), elevated aspartate aminotransferase (15 percent), elevated alanine aminotransferase (11 percent), and elevated lactate dehydrogenase (49 percent) [87]. Other reports have described lymphocytopenia (with or without neutropenia), anemia, and/or thrombocytopenia [28,35,75,86]. Some patients have shown progressive renal failure, with rising blood urea nitrogen and creatinine [4,28,31,35,75]. Disseminated intravascular coagulation and hemolysis have also been reported [33,86].

Imaging findings — As noted above, among 47 cases of MERS-CoV disease in Saudi Arabia, abnormalities on chest radiography were noted in all 47 cases [87]. Imaging findings ranged from minimal to extensive abnormalities, including increased bronchovascular markings, airspace opacities, patchy infiltrates, interstitial changes, patchy to confluent airspace consolidations, nodular opacities, reticular opacities, reticulonodular shadowing, pleural effusions, and total opacification of lung segments and lobes; abnormalities were either unilateral or bilateral (image 1). In patients with MERS-CoV who underwent computed tomography scanning, the most common findings were bilateral predominantly peripheral and basilar airspace changes with more extensive ground-glass opacities than consolidation [97,98].

DIAGNOSIS — The World Health Organization (WHO) has developed a questionnaire to be used for the initial investigation of cases; it can be found on the WHO's website [99].

Preferred tests and specimen types — Lower respiratory tract specimens should be the first priority for collection and real-time reverse-transcriptase polymerase chain reaction (rRT-PCR) testing, since rRT-PCR testing of lower respiratory specimens appears to be more sensitive for detection of Middle East respiratory syndrome coronavirus (MERS-CoV) than testing of upper respiratory tract specimens [84,85,100,101]. (See 'Polymerase chain reaction and sequencing' below.)

Given the potential severity of MERS-CoV infections, the risk for human-to-human transmission, and the limited data about the sensitivity of each diagnostic test, we suggest that multiple specimens be collected from different sites and at different times to increase the likelihood of detecting MERS-CoV [84,100]. Priority should be given to respiratory specimens (lower tract if obtainable and in all cases of severe disease; upper tract if disease is mild and lower tract specimens cannot be obtained). Serum samples (acute and convalescent samples 14 to 21 days later) should also be obtained for serologic testing [84,101].

We recommend the following diagnostic approach, which has been adapted from guidelines issued by the United States Centers for Disease Control and Prevention (CDC) and the WHO [39,84,100,101]:

- Lower respiratory tract specimens such as sputum, endotracheal aspirate, or bronchoalveolar lavage (BAL) fluid should be obtained for rRT-PCR testing from all cases of severe disease and from milder cases when possible.
- Upper respiratory tract specimens should be obtained for rRT-PCR testing and should be either a combined nasopharyngeal and oropharyngeal swab specimen (two synthetic fiber swabs with plastic shafts, combined in a single collection container) **or** a 2 to 3 mL nasopharyngeal aspirate. Obtaining upper respiratory tract specimens is especially important if the patient does not have signs or symptoms of lower respiratory tract disease or if the collection of lower respiratory tract specimens is not possible.
- If initial testing of respiratory specimens is negative in a patient who is strongly suspected of having MERS-CoV infection, additional respiratory specimens should be obtained from multiple respiratory sites. Possible reasons for false-negative results include that the specimen was of poor quality, that it was collected late or very early in the illness, that it was not handled and shipped appropriately, or that there were technical problems with the test.
- Acute and convalescent (14 to 21 days later) sera should be obtained for serologic testing. If only a single sample is to be obtained, it should be collected at least 14 days after onset of symptoms.
- In certain cases, the diagnosis should be confirmed by nucleic acid sequencing [84].
- When good quality respiratory tract specimens are not available or when the clinician wishes to monitor the presence of virus in different body compartments, blood, urine, and/or stool specimens can be collected. Virus has been detected from these specimens but usually at lower concentrations than in respiratory tract specimens.

Repeat testing is helpful for confirming clearance of the virus. Respiratory specimens should be tested every two to four days until there are two consecutive negative results. If the discharge of the patient from an isolation ward requires negative PCR results, specimens can be obtained daily.

Laboratories with limited experience testing for MERS-CoV are encouraged to have their results confirmed by laboratories with greater experience (particularly negative specimens from patients in whom MERS-CoV infection is thought to be likely) [84].

Additional information about diagnostic testing can be found in a WHO document and in a CDC document [84,101].

Polymerase chain reaction and sequencing — Data from the cases sampled to date indicate that lower respiratory tract specimens (sputum, tracheal aspirates, BAL fluid) are more sensitive for detection of MERS-CoV by rRT-PCR testing than those from the upper respiratory tract (combined nasopharyngeal and throat swab, nasopharyngeal aspirates) [27,28,33,35,84,86,100,102]. However, upper respiratory tract specimens are still useful for diagnosing MERS-CoV. As an example, in a series of 47 patients with MERS-CoV, the majority of patients were diagnosed using nasopharyngeal swabs [87].

In a detailed analysis of a patient with multiple myeloma and MERS-CoV infection who succumbed after developing acute respiratory distress syndrome (ARDS) and septic shock, high concentrations of MERS-CoV were detected by rRT-PCR from respiratory specimens (BAL fluid or tracheobronchial secretions), peaking at 1.2 $x10^6$ copies/mL [86]. MERS-CoV was also detectable from oronasal secretions, stool, and urine but at low concentrations. Only one of two oronasal specimens was

positive by rRT-PCR (5370 copies/mL). No virus was detected from the blood of this patient, but it has been detected from the blood of another reported patient [35]. (See "Severe acute respiratory syndrome (SARS)", section on 'Polymerase chain reaction'.)

Three rRT-PCR assays for routine detection of MERS-CoV have been developed [84]. Currently described tests are an assay targeting a region upstream of the E protein gene (upE) [27] and assays targeting the open reading frame 1b (ORF 1b) [27] and the open reading frame 1a (ORF 1a) [103]. In some cases, sequencing should be performed for confirmation.

An emergency use authorization was issued by the US Food and Drug Administration in 2013 for the rRT-PCR assay developed by the CDC on clinical respiratory, blood, and stool samples [104].

Serology — Several serology assays have been developed for the detection of MERS-CoV antibodies, including immunofluorescence assays and a protein microarray assay [84,103,105-107]. The CDC has developed a two-stage approach, which uses an enzyme-linked immunosorbent assay (ELISA) for screening followed by an indirect immunofluorescence test or microneutralization test for confirmation [84]. Any positive test by a single serologic assay should be confirmed with a neutralization assay. There are limited data on the sensitivity and specificity of antibody tests for MERS-CoV.

According to the WHO, cases with a positive serologic test in the absence of PCR testing or sequencing are considered probable cases if they meet the other elements comprising the case definition of a probable case [84]. (See 'Case definitions' above.)

Whom to test — The WHO and the CDC have developed recommendations regarding whom to test. Clinicians in countries other than the United States should use the WHO's recommendations and consult with their ministry of health for further guidance regarding the evaluation of possible new cases of MERS-CoV infection.

Outside the United States — Based upon guidelines from the WHO, we recommend that, outside the United States, the following individuals be tested for MERS-CoV [100]:

- A person with an acute respiratory infection, which may include history of fever and cough and evidence of pulmonary parenchymal disease (eg, pneumonia or ARDS), based upon clinical or radiographic evidence of consolidation, who requires admission to hospital, with no other etiology that fully explains the clinical presentation. Testing should be performed according to local guidance for the evaluation of community-acquired pneumonia (CAP). Examples of other etiologies of CAP include *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, *Legionella pneumophila*, other recognized causes of bacterial pneumonia, influenza, and respiratory syncytial virus. Clinicians should be alert to the possibility of atypical presentations in patients who are immunocompromised.

  AND any of the following:

  - The person resides in the Middle East, particularly in regions where human MERS-CoV infections have been reported or in countries where MERS-CoV is known to be circulating in dromedary camels.
  - The disease is in a cluster that occurs within a 14-day period, without regard to place of residence or history of travel. A cluster is defined as two or more persons with onset of

symptoms within the same 14-day period associated with a specific setting, such as a classroom, workplace, household, extended family, hospital, other residential institution, military barracks, or recreational camp. (See "Diagnostic approach to community-acquired pneumonia in adults".)

- The disease occurs in a healthcare worker who has been working in an environment where patients with severe acute respiratory infections are being cared for, particularly patients requiring intensive care, without regard to place of residence or history of travel.
- The person has history of travel within 14 days before onset of illness to the Middle East or to countries where MERS-CoV is known to be circulating in dromedary camels or to regions where human cases have recently occurred.
- The person has an unusual or unexpected clinical course, especially sudden deterioration despite appropriate treatment, without regard to place of residence or history of travel, even if another etiology has been identified that fully explains the clinical presentation.

- An individual with an acute respiratory illness of any severity who, within 14 days of onset of illness, had any of the following exposures:
  - Close physical contact with a confirmed or probable case of MERS-CoV infection while that patient was ill. (See 'Case definitions' above.)
  - Exposure to a healthcare facility in a country where hospital-associated MERS-CoV infections have been reported.
  - Direct contact with dromedary camels or consumption or exposure to dromedary camel products (raw meat, unpasteurized milk, urine) in countries where MERS-CoV is known to be circulating in dromedary camel populations or where human infections occurred as a result of presumed zoonotic transmission.
- Countries in the Middle East are strongly encouraged to consider adding testing for MERS-CoV to testing algorithms as part of routine sentinel respiratory disease surveillance and diagnostic panels for pneumonia.

Routine testing of asymptomatic contacts of cases is not recommended [84].

In the United States — The following discussion has been adapted from recommendations issued by the CDC for the investigation of possible cases in the United States [39].

Healthcare providers should evaluate individuals for MERS-CoV infection if they meet the following criteria for being a **patient under investigation** [108]:

- Fever and pneumonia or acute respiratory distress syndrome (based on clinical or radiographic evidence) and **either**:
  - A history of travel from countries in or near the Arabian Peninsula (countries considered in or neighboring the Arabian Peninsula include Bahrain, Iraq, Iran, Israel, Jordan, Kuwait, Lebanon, Oman, Palestinian territories, Qatar, Saudi Arabia, Syria, the United Arab Emirates, and Yemen) within 14 days before symptom onset **or**
  - Close contact with a symptomatic traveler who developed fever and acute respiratory illness (not necessarily pneumonia) within 14 days after traveling from countries in or near the Arabian Peninsula **or**
  - Is a member of a cluster of patients with severe acute respiratory illness (eg, fever and pneumonia requiring hospitalization) of unknown etiology in which MERS-CoV is being evaluated in consultation with state and local health departments

OR

●Fever and symptoms of respiratory illness (eg, cough, shortness of breath) and being in a healthcare facility (as a patient, healthcare worker, or visitor) within 14 days before symptom onset in a country in or near the Arabian Peninsula in which recent healthcare-associated cases of MERS-CoV have been identified

OR

●Fever **or** symptoms of respiratory illness (eg, cough, shortness of breath) and close contact with a confirmed MERS-CoV case while the affected person was ill

A **close contact** is defined as [108]:

●Being within approximately 6 feet (2 meters) or within the room or care area for a prolonged period of time (eg, healthcare personnel, household members) while not wearing recommended personal protective equipment (ie, gowns, gloves, respirator, eye protection)

OR

●Having direct contact with infectious secretions (eg, being coughed on) while not wearing recommended personal protective equipment (ie, gowns, gloves, respirator, eye protection)

Additional information can be found on the CDC's website.

The CDC requests that state and local health departments immediately report patients under investigation for MERS-CoV infection to the CDC.

Specimen handling — Specimens should reach the laboratory as soon as possible after collection [84]. When there is likely to be a delay of more than 72 hours in the laboratory receiving respiratory tract specimens, specimens should be frozen at -80°C and shipped on dry ice. It is important to avoid repeated freezing and thawing of specimens. Serum should be separated from whole blood and can be stored and shipped at 4°C or frozen and shipped on dry ice or liquid nitrogen. Storage of respiratory and serum specimens in domestic frost-free freezers should be avoided, given their wide temperature fluctuations.

Where to ship specimens — For patients in the United States, clinicians seeking information about shipping or testing should contact the CDC Emergency Operations Center at 770-488-7100. Additional information can be found on the CDC's website.

For patients in countries other than the United States, clinicians should follow the recommendations of their ministry of health regarding diagnostic testing.

Reporting cases — The WHO recommends that probable and confirmed cases be reported within 24 hours of classification through the Regional Contact Point for International Health Regulations at the appropriate WHO Regional Office [100]. (See 'Case definitions' above.)

Additional recommendations regarding reporting of MERS-CoV infections can be found on the WHO's website and the CDC's website.

TREATMENT — As with other coronaviruses, no antiviral agents are recommended for the treatment of Middle East respiratory syndrome coronavirus (MERS-CoV) infection. The World Health Organization (WHO) has issued recommendations for the management of severe respiratory infections suspected to be caused by MERS-CoV [109]. (See "Coronaviruses", section on 'Treatment and prevention'.)

In cell culture and animal experiments, combination therapy with interferon (IFN)-alpha-2b and ribavirin appears promising [110,111]. In a study in which MERS-CoV was grown in two different cell lines, high concentrations of IFN-alpha-2b or ribavirin were required to inhibit viral replication [110]. However, when used in combination at lower concentrations, IFN-alpha-2b and ribavirin resulted in a comparable reduction in viral replication as high concentrations of either agent alone.

In a study of rhesus macaques, two groups of three monkeys were inoculated with MERS-CoV through a combination of intratracheal, intranasal, oral, and ocular routes; one group was treated with subcutaneous IFN-alpha-2b plus intramuscular ribavirin beginning eight hours after inoculation and the other group was not treated [111]. In contrast with untreated macaques, treated animals did not develop breathing abnormalities and showed no or very mild radiographic evidence of pneumonia. Treated animals had lower concentrations of serum and lung proinflammatory markers, fewer viral genome copies, and fewer severe histopathologic changes in the lungs.

In a retrospective cohort study in patients with severe MERS-CoV infection, combination therapy with ribavirin and IFN-alpha-2a, started a median of three days after diagnosis (20 patients), was associated with significantly improved survival at 14 days compared with 24 patients who received only supportive care (70 versus 29 percent survival), but not at 28 days (30 versus 17 percent survival, a nonsignificant difference) [112]. There were greater declines in hemoglobin in the ribavirin-interferon group than in the controls (4.32 versus 2.14 g/L). In other retrospective studies, combination therapy with ribavirin plus IFN-alpha-2a, IFN-alpha-2b, or IFN-beta-1a has not been associated with a mortality benefit [113,114]. It is difficult to interpret the results of these retrospective studies, and further evaluation in randomized trials is needed before treatment recommendations can be made.

Glucocorticoids have been administered sporadically to MERS-CoV infected patients with no clear criteria for use and no clear conclusions regarding their effect [75,113]. Glucocorticoids were extensively prescribed for patients with severe acute respiratory syndrome (SARS), but review of this experience suggests overall harm rather than benefit [115]. Their use is not recommended for MERS-CoV infections. Other experimental therapies being investigated include convalescent plasma, monoclonal antibodies, an inhibitor of the main viral protease, and entry/fusion inhibitors targeting the MERS-CoV spike protein [116-124].

PREVENTION

Infection control — The World Health Organization (WHO) and the United States Centers for Disease Control and Prevention (CDC) have issued recommendations for the prevention and control of Middle East respiratory syndrome coronavirus (MERS-CoV) infections in healthcare settings [37,125-127]. An increased level of infection control precautions is recommended when caring for patients with probable or confirmed MERS-CoV infection compared with that used for

patients with community-acquired coronaviruses or other community-acquired respiratory viruses.

The WHO recommends that standard and droplet precautions be used when caring for patients with acute respiratory tract infections [37]. Contact precautions and eye protection should be added when caring for probable or confirmed cases of MERS-CoV infection. Airborne precautions should be used when performing aerosol-generating procedures.

The CDC recommends the use of standard, contact, and airborne precautions for the management of hospitalized patients with known or suspected MERS-CoV infection [73,127,128].

Additional information can be found on the WHO's website and the CDC's website.

Interim home care and isolation — The CDC recommends that ill individuals who are being evaluated for MERS-CoV infection and do not require hospitalization may be cared for and isolated in their home [39]. Healthcare providers should contact their state or local health department to determine whether home isolation or additional measures are indicated because recommendations might be modified as more data become available. Isolation is defined as the separation or restriction of activities of an ill person with a contagious disease from those who are well. Additional information on home care and isolation guidance is available on the CDC's website.

Avoiding camels — The WHO recommends that individuals at high risk of severe disease, such as immunocompromised hosts and those with diabetes, chronic lung disease, or preexisting renal failure, take precautions when visiting farms, barn areas, camel pens, or market environments where camels are present [129]. These measures include avoiding contact with camels, practicing good hand hygiene, avoiding drinking raw camel milk or camel urine, avoiding eating meat that has not been cooked thoroughly, and avoiding eating food that may be contaminated with animal secretions or products unless they are properly washed, peeled, or cooked.

The WHO recommends that when visiting a farm or barn, members of the general public adhere to general hygiene measures, including regular hand washing before and after touching animals, avoiding contact with sick animals, and following food hygiene practices [38]. Unless wearing a face mask and protective clothing, individuals should avoid contact with any camel that has tested positive for MERS-CoV until subsequent tests have confirmed that the animal is free of virus [129].

Specific recommendations for camel farm and slaughterhouse workers can be found on the WHO's website.

Travel recommendations — Detailed information for travelers to Mecca, Saudi Arabia, for Hajj and/or Umrah can be found on the WHO's website [130]. The WHO does not recommend either special screening for MERS-CoV at points of entry or the application of any travel or trade restrictions. However, the WHO recommends that countries outside the affected region maintain a high level of vigilance, especially countries with large numbers of travelers or guest workers returning from the Middle East [37].

The Ministry of Health of Saudi Arabia recommended that, in 2014, the following individuals postpone their plans to travel to Mecca, Saudi Arabia, for Hajj and/or Umrah due to the outbreak of MERS-CoV infection [131,132]:

- Older individuals (>65 years of age)
- Individuals with chronic diseases (eg, heart disease, kidney disease, respiratory disease, nervous system disorders, diabetes)
- Individuals with immunodeficiency (congenital or acquired)
- Patients with malignancy
- Patients with a terminal illness
- Pregnant women
- Children

No cases of MERS-CoV infection were detected during Hajj in 2012 or 2013 [133].

In May 2014, the CDC's travel notice was upgraded to a Level 2 Alert, which includes enhanced precautions for travelers to countries in or near the Arabian Peninsula who plan to work in healthcare settings [39]. Such individuals should review the CDC's recommendations for infection control for confirmed or suspected MERS patients before they depart, practice these precautions while in the area, and monitor their health closely during and after their travel.

The CDC recommends that all United States travelers to countries in or near the Arabian Peninsula protect themselves from respiratory diseases, including MERS-CoV, by washing their hands often and avoiding contact with persons who are ill [39]. If travelers to the region have onset of fever with cough or shortness of breath during their trip or within 14 days of returning to the United States, they should seek medical care. They should call ahead to their healthcare provider and mention their recent travel so that appropriate isolation measures can be taken in the healthcare setting. More detailed travel recommendations related to MERS are available on the CDC's website.

Vaccine development — There is no licensed vaccine for MERS-CoV, although one manufacturer has developed an experimental candidate MERS-CoV vaccine based on the major surface spike protein using recombinant nanoparticle technology [134]. Other candidate vaccines that are being studied include a full-length infectious cDNA clone of the MERS-CoV genome in a bacterial artificial chromosome, a recombinant modified vaccine Ankara (MVA) vaccine expressing full-length MERS-CoV spike protein, and vaccines encoding the full-length MERS-CoV S protein and the S1 extracellular domain of S protein using adenovirus vectors [135-137].

OUTCOMES — As of June 12, 2015, 455 of 1289 patients (35 percent) with laboratory-confirmed Middle East respiratory syndrome coronavirus (MERS-CoV) infection reported to the World Health Organization (WHO) have died [25]. Because individuals with mild symptoms are less likely to be evaluated than patients with severe disease, those with MERS-CoV and mild disease might be underrepresented in published reports and reports from the WHO [138]. The reported case-fatality rate might therefore be an overestimate. This hypothesis is supported by an analysis pointing out that 14 of 19 (74 percent) patients with infection detected through routine surveillance died compared with 5 of 24 (21 percent) of secondary cases [21].

In a study of 47 patients with MERS-CoV infection in Saudi Arabia, case-fatality rates rose with increasing age, from 39 percent in those younger than 50 years of age, to 48 percent in those younger than 60 years of age, to 75 percent in those aged 60 years or older [87]. A separate analysis has shown similar findings [21].

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient information: Middle East respiratory syndrome coronavirus (The Basics)")

SUMMARY AND RECOMMENDATIONS

- A novel coronavirus, Middle East respiratory syndrome coronavirus (MERS-CoV) causing severe respiratory illness emerged in 2012 in Saudi Arabia. Many additional cases and clusters of MERS-CoV infections have been detected subsequently in the Arabian Peninsula, particularly in Saudi Arabia (figure 1 and figure 2). Isolated cases have also occurred in North Africa, Europe, Asia, and the United States. The number of cases in the Arabian Peninsula increased dramatically in March and April 2014 then declined sharply in ensuing months. However, cases continue to be detected. (See 'Introduction' above and 'Epidemiology' above.)
- MERS-CoV is closely related to coronaviruses found in bats, suggesting that bats might be a reservoir of MERS-CoV. Camels likely serve as hosts for MERS-CoV. The presence of case clusters strongly suggests that human-to-human transmission occurs. (See 'Possible sources and modes of transmission' above.)
- Real-time reverse-transcriptase polymerase chain reaction (rRT-PCR) testing applied to respiratory secretions is the diagnostic assay of choice. Lower respiratory tract specimens should be a priority for collection and testing. To increase the likelihood of detecting MERS-CoV, we suggest collection of multiple specimens from different sites and at different times. Obtaining acute and convalescent serum is also important. Other specimen types and diagnostic tests are discussed above. (See 'Diagnosis' above and 'Preferred tests and specimen types' above.)
- Individuals with an acute respiratory infection who have an epidemiologic link to MERS-CoV or who have had an unusual or unexpected clinical course (especially sudden deterioration despite appropriate treatment) should be tested for MERS-CoV. Certain other patients may also require evaluation for MERS-CoV infection. Specific recommendations regarding whom to test are presented above. (See 'Whom to test' above.)

- There is currently no treatment recommended for coronavirus infections except for supportive care as needed. (See 'Treatment' above.)
- An increased level of infection control precautions is recommended when caring for patients with probable or confirmed MERS-CoV infection compared with that used for patients with community-acquired coronaviruses or other community-acquired respiratory viruses. The United States Centers for Disease Control and Prevention (CDC) recommends the use of standard, contact, and airborne precautions for the management of hospitalized patients with known or suspected MERS-CoV infection. (See 'Infection control' above.)
- There is no licensed vaccine for MERS-CoV. (See 'Vaccine development' above.)
- The World Health Organization (WHO) does not recommend either special screening for MERS-CoV at points of entry or the application of any travel or trade restrictions. The Ministry of Health of Saudi Arabia recommended that, in 2014, older adults, those with chronic diseases, immunocompromised patients, pregnant women, and children postpone their plans to travel to Mecca, Saudi Arabia, for Hajj and/or Umrah. (See 'Travel recommendations' above.)
- Additional information about MERS-CoV can be found on the WHO's website and the CDC's website.

REFERENCES

1. ProMed Mail: Novel coronavirus - Saudi Arabia: human isolate; Archive Number: 20120920.1302733 http://www.promedmail.org/direct.php?id=20120920.1302733 (Accessed on April 22, 2013).
2. World Health Organization. Novel coronavirus infection in the United Kingdom. http://www.who.int/csr/don/2012_09_23/en/index.html (Accessed on September 25, 2012).
3. Wise J. Patient with new strain of coronavirus is treated in intensive care at London hospital. BMJ 2012; 345:e6455.
4. Zaki AM, van Boheemen S, Bestebroer TM, et al. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N Engl J Med 2012; 367:1814.
5. de Groot RJ, Baker SC, Baric RS, et al. Middle East respiratory syndrome coronavirus (MERS-CoV): announcement of the Coronavirus Study Group. J Virol 2013; 87:7790.
6. United Kingdom Health Protection Agency. Partial genetic sequence information for scientists about the novel coronavirus 2012. http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/RespiratoryViruses/NovelCoronavirus/respPartialgeneticsequenceofnovelcoronavirus/ (Accessed on September 27, 2012).
7. Cotten M, Lam TT, Watson SJ, et al. Full-genome deep sequencing and phylogenetic analysis of novel human betacoronavirus. Emerg Infect Dis 2013; 19:736.
8. Annan A, Baldwin HJ, Corman VM, et al. Human betacoronavirus 2c EMC/2012-related viruses in bats, Ghana and Europe. Emerg Infect Dis 2013; 19:456.
9. Ithete NL, Stoffberg S, Corman VM, et al. Close relative of human Middle East respiratory syndrome coronavirus in bat, South Africa. Emerg Infect Dis 2013; 19:1697.
10. Memish ZA, Mishra N, Olival KJ, et al. Middle East respiratory syndrome coronavirus in bats, Saudi Arabia. Emerg Infect Dis 2013; 19:1819.
11. Chan JF, Lau SK, To KK, et al. Middle East respiratory syndrome coronavirus: another zoonotic betacoronavirus causing SARS-like disease. Clin Microbiol Rev 2015; 28:465.

12 Raj VS, Mou H, Smits SL, et al. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. Nature 2013; 495:251.

13 Lu G, Hu Y, Wang Q, et al. Molecular basis of binding between novel human coronavirus MERS-CoV and its receptor CD26. Nature 2013; 500:227.

14 Chan JF, Chan KH, Choi GK, et al. Differential cell line susceptibility to the emerging novel human betacoronavirus 2c EMC/2012: implications for disease pathogenesis and clinical manifestation. J Infect Dis 2013; 207:1743.

15 Kindler E, Jónsdóttir HR, Muth D, et al. Efficient replication of the novel human betacoronavirus EMC on primary human epithelium highlights its zoonotic potential. MBio 2013; 4:e00611.

16 Müller MA, Raj VS, Muth D, et al. Human coronavirus EMC does not require the SARS-coronavirus receptor and maintains broad replicative capability in mammalian cell lines. MBio 2012; 3.

17 Meyer B, García-Bocanegra I, Wernery U, et al. Serologic assessment of possibility for MERS-CoV infection in equids. Emerg Infect Dis 2015; 21:181.

18 McIntosh K. A new virulent human coronavirus: how much does tissue culture tropism tell us? J Infect Dis 2013; 207:1630.

19 Drosten C, Muth D, Corman VM, et al. An observational, laboratory-based study of outbreaks of middle East respiratory syndrome coronavirus in Jeddah and Riyadh, kingdom of Saudi Arabia, 2014. Clin Infect Dis 2015; 60:369.

20 Cotten M, Watson SJ, Kellam P, et al. Transmission and evolution of the Middle East respiratory syndrome coronavirus in Saudi Arabia: a descriptive genomic study. Lancet 2013; 382:1993.

21 Cauchemez S, Fraser C, Van Kerkhove MD, et al. Middle East respiratory syndrome coronavirus: quantification of the extent of the epidemic, surveillance biases, and transmissibility. Lancet Infect Dis 2014; 14:50.

22 World Health Organization. Middle East respiratory syndrome coronavirus (MERS-CoV): Summary of current situation, literature update and risk assessment–as of 5 February 2015. http://www.who.int/csr/disease/coronavirus_infections/mers-5-february-2015.pdf?ua=1 (Accessed on March 04, 2015).

23 Rha B, Rudd J, Feikin D, et al. Update on the epidemiology of Middle East respiratory syndrome coronavirus (MERS-CoV) infection, and guidance for the public, clinicians, and public health authorities - January 2015. MMWR Morb Mortal Wkly Rep 2015; 64:61.

24 Zumla A, Hui DS, Perlman S. Middle East respiratory syndrome. Lancet 2015.

25 World Health Organization. Middle East respiratory syndrome coronavirus (MERS-CoV) – Republic of Korea. http://www.who.int/csr/don/12-june-2015-mers-korea/en/ (Accessed on June 15, 2015).

26 Centers for Disease Control and Prevention (CDC). Severe respiratory illness associated with a novel coronavirus--Saudi Arabia and Qatar, 2012. MMWR Morb Mortal Wkly Rep 2012; 61:820.

27 Corman VM, Eckerle I, Bleicker T, et al. Detection of a novel human coronavirus by real-time reverse-transcription polymerase chain reaction. Euro Surveill 2012; 17.

28 Memish ZA, Zumla AI, Al-Hakeem RF, et al. Family cluster of Middle East respiratory syndrome coronavirus infections. N Engl J Med 2013; 368:2487.

29 World Health Organization. Global Alert and Response. Background and summary of novel coronavirus infection – as of 30 November 2012.

http://www.who.int/csr/disease/coronavirus_infections/update_20121130/en/index.html (Accessed on December 06, 2012).

30 Al-Abdallat MM, Payne DC, Alqasrawi S, et al. Hospital-associated outbreak of Middle East respiratory syndrome coronavirus: a serologic, epidemiologic, and clinical description. Clin Infect Dis 2014; 59:1225.

31 Bermingham A, Chand MA, Brown CS, et al. Severe respiratory illness caused by a novel coronavirus, in a patient transferred to the United Kingdom from the Middle East, September 2012. Euro Surveill 2012; 17:20290.

32 World Health Organization. Global alert and response. Novel coronavirus infection – update. http://www.who.int/csr/don/2013_02_16/en/index.html (Accessed on February 17, 2013).

33 World Health Organization. Global alert and response. Novel coronavirus summary and literature update – as of 17 May 2013. http://www.who.int/csr/disease/coronavirus_infections/update_20130517/en/index.html# (Accessed on May 17, 2013).

34 Assiri A, McGeer A, Perl TM, et al. Hospital outbreak of Middle East respiratory syndrome coronavirus. N Engl J Med 2013; 369:407.

35 Guery B, Poissy J, el Mansouf L, et al. Clinical features and viral diagnosis of two cases of infection with Middle East Respiratory Syndrome coronavirus: a report of nosocomial transmission. Lancet 2013; 381:2265.

36 Oboho IK, Tomczyk SM, Al-Asmari AM, et al. 2014 MERS-CoV outbreak in Jeddah--a link to health care facilities. N Engl J Med 2015; 372:846.

37 World Health Organization. Middle East respiratory syndrome coronavirus (MERS-CoV) summary and literature update – as of 9 May 2014. http://www.who.int/csr/disease/coronavirus_infections/MERS_CoV_Update_09_May_2014.pdf?ua=1 (Accessed on May 12, 2014).

38 World Health Organization. WHO risk assessment. Middle East respiratory syndrome coronavirus (MERS-CoV). http://www.who.int/csr/disease/coronavirus_infections/MERS_CoV_RA_20140424.pdf?ua=1 (Accessed on April 24, 2014).

39 Bialek SR, Allen D, Alvarado-Ramy F, et al. First confirmed cases of Middle East respiratory syndrome coronavirus (MERS-CoV) infection in the United States, updated information on the epidemiology of MERS-CoV infection, and guidance for the public, clinicians, and public health authorities - May 2014. MMWR Morb Mortal Wkly Rep 2014; 63:431.

40 Centers for Disease Control and Prevention. CDC announces first case of Middle East respiratory syndrome coronavirus infection (MERS) in the United States. http://www.cdc.gov/media/releases/2014/p0502-US-MERS.html (Accessed on May 02, 2014).

41 Kapoor M, Pringle K, Kumar A, et al. Clinical and laboratory findings of the first imported case of Middle East respiratory syndrome coronavirus to the United States. Clin Infect Dis 2014; 59:1511.

42 Centers for Disease Control and Prevention. Middle East respiratory syndrome (MERS). http://www.cdc.gov/CORONAVIRUS/MERS/INDEX.HTML (Accessed on May 13, 2014).

43 Florida Health. Health officials confirm first MERS-CoV case in Florida http://newsroom.doh.state.fl.us/wp-content/uploads/newsroom/2014/01/051214-MERS-CoV-Case-Confirmed-in-Florida.pdf (Accessed on May 13, 2014).

44 World Health Organization. Middle East respiratory syndrome coronavirus (MERS-CoV) – Republic of Korea. http://www.who.int/csr/don/24-may-2015-mers-korea/en/ (Accessed on May 26, 2015).

45 World Health Organization. Summary and risk assessment of current situation in Republic of Korea and China. http://www.who.int/csr/disease/coronavirus_infections/risk-assessment-3june2015/en/ (Accessed on June 04, 2015).

46 World Health Organization. Middle East respiratory syndrome coronavirus (MERS-CoV) – Republic of Korea. http://www.who.int/csr/don/09-june-2015-mers-korea/en/ (Accessed on June 10, 2015).

47 World Health Organization. Middle East respiratory syndrome coronavirus (MERS-CoV) – China. http://www.who.int/csr/don/30-may-2015-mers-china/en/ (Accessed on June 01, 2015).

48 World Health Organization. Middle East Respiratory Syndrome (MERS) in the Republic of Korea - MERS situation assessment. http://www.who.int/mediacentre/news/situation-assessments/2-june-2015-south-korea/en/ (Accessed on June 03, 2015).

49 World Health Organization. MERS-CoV in the Republic of Korea at a glance. http://www.wpro.who.int/outbreaks_emergencies/wpro_coronavirus/en/ (Accessed on June 15, 2015).

50 Gulland A. Two cases of novel coronavirus are confirmed in France. BMJ 2013; 346:f3114.

51 Aburizaiza AS, Mattes FM, Azhar EI, et al. Investigation of anti-middle East respiratory syndrome antibodies in blood donors and slaughterhouse workers in Jeddah and Makkah, Saudi Arabia, fall 2012. J Infect Dis 2014; 209:243.

52 Gierer S, Hofmann-Winkler H, Albuali WH, et al. Lack of MERS coronavirus neutralizing antibodies in humans, eastern province, Saudi Arabia. Emerg Infect Dis 2013; 19:2034.

53 Müller MA, Meyer B, Corman VM, et al. Presence of Middle East respiratory syndrome coronavirus antibodies in Saudi Arabia: a nationwide, cross-sectional, serological study. Lancet Infect Dis 2015; 15:559.

54 Memish ZA, Assiri A, Almasri M, et al. Prevalence of MERS-CoV nasal carriage and compliance with the Saudi health recommendations among pilgrims attending the 2013 Hajj. J Infect Dis 2014; 210:1067.

55 The Lancet Infectious Diseases. Need for global cooperation in control of MERS-CoV. Lancet Infect Dis 2013; 13:639.

56 Azhar EI, El-Kafrawy SA, Farraj SA, et al. Evidence for camel-to-human transmission of MERS coronavirus. N Engl J Med 2014; 370:2499.

57 Haagmans BL, Al Dhahiry SH, Reusken CB, et al. Middle East respiratory syndrome coronavirus in dromedary camels: an outbreak investigation. Lancet Infect Dis 2014; 14:140.

58 Alagaili AN, Briese T, Mishra N, et al. Middle East respiratory syndrome coronavirus infection in dromedary camels in Saudi Arabia. MBio 2014; 5:e00884.

59 Chu DK, Poon LL, Gomaa MM, et al. MERS coronaviruses in dromedary camels, Egypt. Emerg Infect Dis 2014; 20:1049.

60 Memish ZA, Cotten M, Meyer B, et al. Human infection with MERS coronavirus after exposure to infected camels, Saudi Arabia, 2013. Emerg Infect Dis 2014; 20:1012.

61 Perera RA, Wang P, Gomaa MR, et al. Seroepidemiology for MERS coronavirus using microneutralisation and pseudoparticle virus neutralisation assays reveal a high prevalence of

antibody in dromedary camels in Egypt, June 2013. Euro Surveill 2013; 18:pii=20574.

62 Meyer B, Müller MA, Corman VM, et al. Antibodies against MERS coronavirus in dromedary camels, United Arab Emirates, 2003 and 2013. Emerg Infect Dis 2014; 20:552.

63 Hemida MG, Perera RA, Wang P, et al. Middle East Respiratory Syndrome (MERS) coronavirus seroprevalence in domestic livestock in Saudi Arabia, 2010 to 2013. Euro Surveill 2013; 18:20659.

64 Reusken CB, Ababneh M, Raj VS, et al. Middle East Respiratory Syndrome coronavirus (MERS-CoV) serology in major livestock species in an affected region in Jordan, June to September 2013. Euro Surveill 2013; 18:20662.

65 Reusken CB, Messadi L, Feyisa A, et al. Geographic distribution of MERS coronavirus among dromedary camels, Africa. Emerg Infect Dis 2014; 20:1370.

66 Corman VM, Jores J, Meyer B, et al. Antibodies against MERS coronavirus in dromedary camels, Kenya, 1992-2013. Emerg Infect Dis 2014; 20:1319.

67 Müller MA, Corman VM, Jores J, et al. MERS coronavirus neutralizing antibodies in camels, Eastern Africa, 1983-1997. Emerg Infect Dis 2014; 20:2093.

68 Reusken CB, Haagmans BL, Müller MA, et al. Middle East respiratory syndrome coronavirus neutralising serum antibodies in dromedary camels: a comparative serological study. Lancet Infect Dis 2013; 13:859.

69 Adney DR, van Doremalen N, Brown VR, et al. Replication and shedding of MERS-CoV in upper respiratory tract of inoculated dromedary camels. Emerg Infect Dis 2014; 20:1999.

70 Abroug F, Slim A, Ouanes-Besbes L, et al. Family cluster of Middle East respiratory syndrome coronavirus infections, Tunisia, 2013. Emerg Infect Dis 2014; 20:1527.

71 Raj VS, Farag EA, Reusken CB, et al. Isolation of MERS coronavirus from a dromedary camel, Qatar, 2014. Emerg Infect Dis 2014; 20:1339.

72 Hui DS, Perlman S, Zumla A. Spread of MERS to South Korea and China. Lancet Respir Med 2015.

73 Centers for Disease Control and Prevention (CDC). Updated information on the epidemiology of Middle East respiratory syndrome coronavirus (MERS-CoV) infection and guidance for the public, clinicians, and public health authorities, 2012-2013. MMWR Morb Mortal Wkly Rep 2013; 62:793.

74 Reuss A, Litterst A, Drosten C, et al. Contact investigation for imported case of Middle East respiratory syndrome, Germany. Emerg Infect Dis 2014; 20:620.

75 Arabi YM, Arifi AA, Balkhy HH, et al. Clinical course and outcomes of critically ill patients with Middle East respiratory syndrome coronavirus infection. Ann Intern Med 2014; 160:389.

76 Drosten C, Meyer B, Müller MA, et al. Transmission of MERS-coronavirus in household contacts. N Engl J Med 2014; 371:828.

77 Centers for Disease Control and Prevention. Health Alert Network. Notice to health care providers: updated Guidelines for Evaluation of Severe Respiratory Illness Associated with Middle East respiratory syndrome coronavirus (MERS-CoV). http://emergency.cdc.gov/HAN/han00348.asp (Accessed on June 13, 2013).

78 World Health Organization. Middle East respiratory syndrome coronavirus (MERS-CoV) summary and literature update – as of 20 January 2014. http://www.who.int/csr/disease/coronavirus_infections/MERS_CoV_Update_20_Jan_2014.pdf (Accessed on January 29, 2014).

World Health Organization. WHO statement on the eighth meeting of the IHR Emergency Committee regarding MERS-CoV. http://www.who.int/mediacentre/news/statements/2015/8th-mers-emergency-committee/en/ (Accessed on March 10, 2015).

Al-Gethamy M, Corman VM, Hussain R, et al. A case of long-term excretion and subclinical infection with Middle East respiratory syndrome coronavirus in a healthcare worker. Clin Infect Dis 2015; 60:973.

Breban R, Riou J, Fontanet A. Interhuman transmissibility of Middle East respiratory syndrome coronavirus: estimation of pandemic risk. Lancet 2013; 382:694.

Bauch CT, Oraby T. Assessing the pandemic potential of MERS-CoV. Lancet 2013; 382:662.

World Health Organization. Revised case definition for reporting to WHO – Middle East respiratory syndrome coronavirus - Interim case definition as of 14 July 2014. http://www.who.int/csr/disease/coronavirus_infections/case_definition/en/ (Accessed on March 06, 2015).

World Health Organization. Laboratory testing for Middle East respiratory syndrome coronavirus - Interim recommendations (revised), September 2014. http://www.who.int/csr/disease/coronavirus_infections/WHO_interim_recommendations_lab_detection_MERSCoV_092014.pdf?ua=1 (Accessed on March 06, 2015).

Centers for Disease Control and Prevention (CDC). Update: Severe respiratory illness associated with Middle East Respiratory Syndrome Coronavirus (MERS-CoV)--worldwide, 2012-2013. MMWR Morb Mortal Wkly Rep 2013; 62:480.

Drosten C, Seilmaier M, Corman VM, et al. Clinical features and virological analysis of a case of Middle East respiratory syndrome coronavirus infection. Lancet Infect Dis 2013; 13:745.

Assiri A, Al-Tawfiq JA, Al-Rabeeah AA, et al. Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study. Lancet Infect Dis 2013; 13:752.

World Health Organization. Global alert and response. Background and summary of novel coronavirus infection – as of 21 December 2012. http://www.who.int/csr/disease/coronavirus_infections/update_20121221/en/index.html (Accessed on February 12, 2013).

Al-Tawfiq JA, Hinedi K, Ghandour J, et al. Middle East respiratory syndrome coronavirus: a case-control study of hospitalized patients. Clin Infect Dis 2014; 59:160.

Drosten C. Is MERS another SARS? Lancet Infect Dis 2013; 13:727.

Memish ZA, Zumla AI, Assiri A. Middle East respiratory syndrome coronavirus infections in health care workers. N Engl J Med 2013; 369:884.

Memish ZA, Al-Tawfiq JA, Assiri A, et al. Middle East respiratory syndrome coronavirus disease in children. Pediatr Infect Dis J 2014; 33:904.

Payne DC, Iblan I, Alqasrawi S, et al. Stillbirth during infection with Middle East respiratory syndrome coronavirus. J Infect Dis 2014; 209:1870.

Munster VJ, de Wit E, Feldmann H. Pneumonia from human coronavirus in a macaque model. N Engl J Med 2013; 368:1560.

de Wit E, Rasmussen AL, Falzarano D, et al. Middle East respiratory syndrome coronavirus

(MERS-CoV) causes transient lower respiratory tract infection in rhesus macaques. Proc Natl Acad Sci U S A 2013; 110:16598.

Yao Y, Bao L, Deng W, et al. An animal model of MERS produced by infection of rhesus macaques with MERS coronavirus. J Infect Dis 2014; 209:236.

Ajlan AM, Ahyad RA, Jamjoom LG, et al. Middle East respiratory syndrome coronavirus (MERS-CoV) infection: chest CT findings. AJR Am J Roentgenol 2014; 203:782.

Das KM, Lee EY, Enani MA, et al. CT correlation with outcomes in 15 patients with acute Middle East respiratory syndrome coronavirus. AJR Am J Roentgenol 2015; 204:736.

World Health Organization. Middle East respiratory syndrome coronavirus (MERS-CoV). Initial interview questionnaire of cases. http://www.who.int/csr/disease/coronavirus_infections/MERS_case_investigation_questionnaire.pdf (Accessed on August 13, 2013).

World Health Organization. Interim surveillance recommendations for human infection with Middle East respiratory syndrome coronavirus. http://www.who.int/csr/disease/coronavirus_infections/InterimRevisedSurveillanceRecommendations_nCoVinfection_14July2014.pdf?ua=1 (Accessed on March 23, 2015).

Centers for Disease Control and Prevention. Interim guidelines for collecting, handling, and testing clinical specimens from patients under investigation (PUIs) for Middle East respiratory syndrome coronavirus (MERS-CoV) – Version 2. http://www.cdc.gov/coronavirus/mers/guidelines-clinical-specimens.html (Accessed on April 03, 2015).

Memish ZA, Al-Tawfiq JA, Makhdoom HQ, et al. Respiratory tract samples, viral load, and genome fraction yield in patients with Middle East respiratory syndrome. J Infect Dis 2014; 210:1590.

Corman VM, Müller MA, Costabel U, et al. Assays for laboratory confirmation of novel human coronavirus (hCoV-EMC) infections. Euro Surveill 2012; 17.

US Food and Drug Administration. Letter of authorization: CDC novel coronavirus 2012 real-time RT-PCR assay. http://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm355529.htm (Accessed on June 13, 2013).

Chan KH, Chan JF, Tse H, et al. Cross-reactive antibodies in convalescent SARS patients' sera against the emerging novel human coronavirus EMC (2012) by both immunofluorescent and neutralizing antibody tests. J Infect 2013; 67:130.

Buchholz U, Müller MA, Nitsche A, et al. Contact investigation of a case of human novel coronavirus infection treated in a German hospital, October-November 2012. Euro Surveill 2013; 18.

Reusken C, Mou H, Godeke GJ, et al. Specific serology for emerging human coronaviruses by protein microarray. Euro Surveill 2013; 18:20441.

Centers for Disease Control and Prevention. Interim guidance for healthcare professionals. http://www.cdc.gov/coronavirus/mers/interim-guidance.html (Accessed on April 06, 2015).

World Health Organization. Interim guidance document. Clinical management of severe acute respiratory infections when novel coronavirus is suspected: What to do and what not to do.

9 http://www.who.int/csr/disease/coronavirus_infections/InterimGuidance_ClinicalManagement_NovelCoronavirus_11Feb13.pdf (Accessed on April 09, 2013).

10 Falzarano D, de Wit E, Martellaro C, et al. Inhibition of novel β coronavirus replication by a combination of interferon-α2b and ribavirin. Sci Rep 2013; 3:1686.

11 Falzarano D, de Wit E, Rasmussen AL, et al. Treatment with interferon-α2b and ribavirin improves outcome in MERS-CoV-infected rhesus macaques. Nat Med 2013; 19:1313.

12 Omrani AS, Saad MM, Baig K, et al. Ribavirin and interferon alfa-2a for severe Middle East respiratory syndrome coronavirus infection: a retrospective cohort study. Lancet Infect Dis 2014; 14:1090.

13 Al-Tawfiq JA, Momattin H, Dib J, Memish ZA. Ribavirin and interferon therapy in patients infected with the Middle East respiratory syndrome coronavirus: an observational study. Int J Infect Dis 2014; 20:42.

14 Shalhoub S, Farahat F, Al-Jiffri A, et al. IFN-α2a or IFN-β1a in combination with ribavirin to treat Middle East respiratory syndrome coronavirus pneumonia: a retrospective study. J Antimicrob Chemother 2015.

15 Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. PLoS Med 2006; 3:e343.

16 Guery B, van der Werf S. Coronavirus: need for a therapeutic approach. Lancet Infect Dis 2013; 13:726.

17 Ren Z, Yan L, Zhang N, et al. The newly emerged SARS-like coronavirus HCoV-EMC also has an "Achilles' heel": current effective inhibitor targeting a 3C-like protease. Protein Cell 2013; 4:248.

18 World Health Organization. WHO-ISARIC joint MERS-CoV Outbreak Readiness Workshop: Clinical management and potential use of convalescent plasma. http://www.who.int/csr/disease/coronavirus_infections/MERS_outbreak_readiness_workshop.pdf (Accessed on December 30, 2013).

19 Tang XC, Agnihothram SS, Jiao Y, et al. Identification of human neutralizing antibodies against MERS-CoV and their role in virus adaptive evolution. Proc Natl Acad Sci U S A 2014; 111:E2018.

20 Jiang L, Wang N, Zuo T, et al. Potent neutralization of MERS-CoV by human neutralizing monoclonal antibodies to the viral spike glycoprotein. Sci Transl Med 2014; 6:234ra59.

21 Ying T, Du L, Ju TW, et al. Exceptionally potent neutralization of Middle East respiratory syndrome coronavirus by human monoclonal antibodies. J Virol 2014; 88:7796.

22 Du L, Zhao G, Yang Y, et al. A conformation-dependent neutralizing monoclonal antibody specifically targeting receptor-binding domain in Middle East respiratory syndrome coronavirus spike protein. J Virol 2014; 88:7045.

23 Lu L, Liu Q, Zhu Y, et al. Structure-based discovery of Middle East respiratory syndrome coronavirus fusion inhibitor. Nat Commun 2014; 5:3067.

Zhao J, Perera RA, Kayali G, et al. Passive immunotherapy with dromedary immune serum in an experimental animal model for middle East respiratory syndrome coronavirus infection. J Virol 2015; 89:6117.

World Health Organization. Infection prevention and control of epidemic-and pandemic prone acute respiratory infections in health care - WHO guidelines. http://apps.who.int/iris/bitstream/10665/112656/1/9789241507134_eng.pdf?ua=1 (Accessed on May 13, 2014).

Rasmussen SA, Gerber SI, Swerdlow DL. Middle East respiratory syndrome coronavirus: update for clinicians. Clin Infect Dis 2015; 60:1686.

Centers for Disease Control and Prevention. Interim infection prevention and control recommendations for hospitalized patients with Middle East respiratory syndrome coronavirus (MERS-CoV). http://www.cdc.gov/coronavirus/mers/infection-prevention-control.html (Accessed on June 12, 2015).

Harriman K, Brosseau L, Trivedi K. Hospital-associated Middle East respiratory syndrome coronavirus infections. N Engl J Med 2013; 369:1761.

World Health Organization. Middle East respiratory syndrome coronavirus (MERS-CoV) – 13 June 2014. Update on MERS-CoV transmission from animals to humans, and interim recommendations for at-risk groups. http://www.who.int/csr/disease/coronavirus_infections/MERS_CoV_RA_20140613.pdf?ua=1 (Accessed on June 17, 2014).

World Health Organization. World - travel advice on MERS-CoV for pilgrimages. http://www.who.int/ith/updates/20140603/en/ (Accessed on June 17, 2014).

Kingdom of Saudi Arabia - Ministry of Health. Health regulations for travelers to Saudi Arabia for Umrah & pilgrimage (Hajj)- 1435 (2014) http://www.moh.gov.sa/en/Hajj/Pages/HealthRegulations.aspx (Accessed on September 17, 2014).

Kingdom of Saudi Arabia - Ministry of Health. MOH announces the health requirements to be met by this year's Hajj pilgrims. http://www.moh.gov.sa/en/Hajj/News/Pages/News-2014-09-02-001.aspx (Accessed on September 17, 2014).

Memish ZA, Zumla A, Alhakeem RF, et al. Hajj: infectious disease surveillance and control. Lancet 2014; 383:2073.

Novavax. Novavax produces MERS-CoV vaccine candidate. http://www.novavax.com/download/releases/2013-06-06%20CoronaV%20FINAL%20PR.pdf (Accessed on June 13, 2013).

Almazán F, DeDiego ML, Sola I, et al. Engineering a replication-competent, propagation-defective Middle East respiratory syndrome coronavirus as a vaccine candidate. MBio 2013; 4:e00650.

Song F, Fux R, Provacia LB, et al. Middle East respiratory syndrome coronavirus spike protein delivered by modified vaccinia virus Ankara efficiently induces virus-neutralizing antibodies. J Virol 2013; 87:11950.

Kim E, Okada K, Kenniston T, et al. Immunogenicity of an adenoviral-based Middle East

37 Respiratory Syndrome coronavirus vaccine in BALB/c mice. Vaccine 2014; 32:5975.

138 Gomersall CD, Joynt GM. Middle East respiratory syndrome: new disease, old lessons. Lancet 2013; 381:2229.

Le invitamos a consultar UpToDate en la Biblioteca Virtual Minsal: http://www.bibliotecaminsal.cl/