Middle East Respiratory Syndrome (MERS)

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INTRODUCTION

The first patient identified with Middle East respiratory syndrome (MERS) was a 60-year-old male who presented in June of 2012 with fever, cough, and shortness of breath in Jeddah, Kingdom of Saudi Arabia (Saudi Arabia). The patient developed acute respiratory distress syndrome and subsequently died of respiratory and renal failure after being hospitalized for 11 days (1). After tests for other more common respiratory viruses were negative, a novel coronavirus was identified, which was initially called HCoV-EMC (human coronavirus-Erasmus Medical Center, referring to where the virologic studies had been performed) and later became known as Middle East respiratory syndrome coronavirus (MERS-CoV) (1). After information about this newly identified coronavirus was posted on the Program for Monitoring Emerging Diseases (ProMED) website by Dr. Ali Mohamed Zaki (2), a second patient with MERS-CoV was identified. This patient was a 49-year-old male with a history of travel to Saudi Arabia who presented to a hospital in Qatar with bilateral pneumonia in September 2012 and was later transported to the United Kingdom for intensive care, where he was determined to have the same novel coronavirus (3). Via genetic analysis, the cases from Saudi Arabia and Qatar were found to be 99.5% identical (4). Later, two deceased patients who

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TABLE 1 Comparison of characteristics of SARS and MERS$^{a,b}$

| Characteristic                          | SARS                          | MERS                          |
|----------------------------------------|-------------------------------|-------------------------------|
| First patients reported                | Guangdong, China, in November 2002 | Zarqa, Jordan, in April 2012  |
| Virus                                  | SARS-CoV                       | MERS-CoV                       |
| Type of coronavirus                    | Lineage b betacoronavirus      | Lineage c betacoronavirus      |
| Host cell receptor                     | Angiotensin converting enzyme 2 | Dipeptidyl peptidase 4        |
| Animal hosts                           | Chinese horseshoe bats, palm civets | Not yet confirmed, but camel is likely host |
| Incubation period                      |                               |                               |
| Mean (95% CI; days)                    | 4.6 (3.8–5.8)                 | 5.2 (1.9–14.7)                |
| Range (days)                           | 2–14                          | 2–13                          |
| Serial interval (days)                 | 8.4                           | 7.6                           |
| Basic reproduction number              | 2–3                           | <1                            |
| Patient characteristics                |                               |                               |
| Adults                                 | 93%                           | 98%                           |
| Children                               | 5–7%                          | 2%                            |
| Age range (years)                      | 1–91                          | 1–94                          |
| Average age (years)                    | Mean 39.9                     | Median 50                     |
| Sex ratio (M:F)                        | 43%:57%                       | 64.5%:35.5%                   |
| Mortality                              |                               |                               |
| Case fatality rate overall             | 9.6%                          | 40%                           |
| Case fatality rate with comorbidities  | 46%                           | 60%                           |
| Time (days) from symptom onset         | 2–8                           | 0–16                          |
| to hospitalization                     |                               |                               |
| Time (days) from symptom onset         | 21                            | 12                            |
| to death                               |                               |                               |
| Comorbidities                          | 10–30%                        | 76%                           |
| Clinical manifestations                |                               |                               |
| Fever                                  | 99–100%                       | 98%                           |
| Chills/rigors                           | 15–73%                        | 87%                           |
| Cough                                  | 62–100%                       | 83%                           |
| Hemoptysis                             | 0–1%                          | 17%                           |
| Headache                               | 20–56%                        | 11%                           |
| Myalgia                                | 45–61%                        | 32%                           |
| Malaise                                | 31–45%                        | 38%                           |
| Shortness of breath                    | 40–42%                        | 72%                           |
| Nausea                                 | 20–35%                        | 21%                           |
| Vomiting                               | 20–35%                        | 21%                           |
| Diarrhea                               | 20–25%                        | 26%                           |
| Sore throat                            | 13–25%                        | 14%                           |
| Rhinorrhea                             | 2–24%                         | 6%                            |
| Laboratory results                     |                               |                               |
| Radiographic abnormalities             | 94–100%                       | 90–100%                       |
| Leukopenia                             | 25–35%                        | 14%                           |
| Lymphopenia                            | 68–85%                        | 32%                           |
| Thrombocytopenia                       | 40–45%                        | 36%                           |
| Elevated LDH                           | 50–71%                        | 48%                           |
| Elevated ALT                           | 20–30%                        | 11%                           |
| Elevated AST                           | 20–30%                        | 14%                           |
| Respiratory failure requiring          | 14–20%                        | 80%                           |
| mechanical ventilation                 |                               |                               |

$^a$Modified from references 26, 159, and 160.

$^b$Abbreviations: SARS, severe acute respiratory syndrome; MERS, Middle East respiratory syndrome; CoV, coronavirus; LDH, lactate dehydrogenase; ALT, alanine aminotransferase; AST, aspartate transaminase.
were part of a cluster of 13 cases of suspected pneumonia among health care personnel at a hospital in Jordan that had occurred in April 2012 were diagnosed retrospectively as having MERS-CoV infection (5).

Many of the clinical features of MERS were similar to those seen in severe acute respiratory syndrome (SARS), which is caused by another coronavirus, SARS-coronavirus (SARS-CoV) (see Table 1 for characteristics of SARS compared to MERS), and because of these similarities, a high level of concern was raised (6, 7). SARS had caused an epidemic in 2002-2003 after it rapidly spread from China, where it originated, to over 8,000 people in 27 countries, with a case-fatality rate of nearly

**TABLE 2 Chronology of key events**

| Date                  | Key events                                                                                                                                 |
|-----------------------|-------------------------------------------------------------------------------------------------------------------------------------------|
| April 2012            | Cluster of 13 patients in a hospital in Jordan with acute respiratory illness; two deceased patients of this cluster were retrospectively diagnosed (in September 2012) through study of stored specimens with MERS-CoV (5, 90) |
| 13 June 2012          | 60-year-old man admitted to hospital in Saudi Arabia with a 7-day history of fever, cough, and dyspnea (1)                                      |
| 20 September 2012     | Isolation of MERS-CoV from June case in Saudi Arabia reported on Program for Monitoring Emerging Diseases (ProMED) website by Dr. Ali Mohamed Zaki (1, 2) |
| September 2012        | Diagnostic RT-PCR assay for MERS-CoV developed and used by Health Protection Agency in United Kingdom to identify second case of MERS in a patient who had been transferred from Qatar (4, 126) |
| 25 September 2012     | WHO releases case definition for MERS (162)                                                                                               |
| November 2012         | Full genome of MERS-CoV characterized by Erasmus Medical Center (25)                                                                     |
| February 2013         | Definitive evidence of human-to-human transmission observed in family cluster in the United Kingdom (59)                                 |
| March 2013            | Dipeptidyl peptidase 4 determined to be host-cell receptor for MERS-CoV (27)                                                             |
| April 2013            | Study in rhesus macaque animal model shows that MERS-CoV fulfills Koch's postulates (115)                                                |
| April 2013            | Largest cluster of MERS to date (as of April 2013) (23 cases) occurs in eastern Saudi Arabia (55)                                        |
| 3 June 2013           | CDC activates its Emergency Operations Center to strengthen preparedness for MERS (deactivated on 13 August 2013) (23)                    |
| 11 June 2013          | Interim infection prevention and control recommendations for hospitalized patients with known or suspected MERS-CoV infection for U.S. hospitals issued by CDC (163) |
| 9 and 17 July 2013    | 10 meetings of the International Health Regulations Emergency Health Committee convened by the WHO between July 2013 and December 2015: situation serious and of great concern, but conditions for Public Health Emergency of International Concern not met (http://www.who.int/iae/ihr_ec_2013/en/) |
| 14 May 2014           | MERS-CoV neutralizing antibodies identified in Omani camels (73)                                                                        |
| 17 June 2014          | Full genome sequence analysis of 21 MERS-CoV genomes identifies multiple zoonotic introductions, suggesting lower reproduction number (164) |
| 5 February 2015       | MERS-CoV detected in three camels and epidemiologically linked to two human cases (85)                                                   |
| 17 June 2015          | Rapid increase in the numbers of MERS cases reported in Arabian Peninsula (22)                                                           |
| 3 September 2015      | CDC confirms first and second (19) cases of MERS in the United States in Indiana and Florida, respectively. CDC activates its Emergency Operations Center on 2 May to respond to domestic case (deactivated on 12 June 2014) |
| 20 May 2015           | First patient with MERS reported in Republic of Korea (64); outbreak affecting >180 people ensues; largest outbreak outside of Saudi Arabia (165) |

Adapted in part from reference 161.

Abbreviations: MERS-CoV, Middle East respiratory syndrome coronavirus; RT-PCR, reverse transcription PCR; WHO, World Health Organization.
10% and an estimated cost of tens of billions of dollars (8, 9). Genomic analysis of SARS-CoV showed that the virus evolved early on in the outbreak to become better adapted to humans, which permitted more efficient human-to-human transmission (10–13). The basic reproduction number for SARS (the expected number of secondary infections resulting from one infected person in a susceptible population) was estimated to be 2 to 4 (14, 15). However, SARS was characterized by superspreading events, in which a few cases were responsible for a large number of secondary cases; the majority of SARS cases did not transmit to others. The outbreak was brought under control in July 2003 after implementation of public health interventions, although additional cases related to laboratory or animal market exposures were seen later in 2003 and in 2004 (13). Since 2004, no additional SARS cases have been reported.

Since its discovery in 2012, MERS-CoV has been referred to by several different names, including HCoV-EMC, human betacoronavirus 2c EMC, HCoV-EMC/2012, human betacoronavirus 2c England-Qatar, human betacoronavirus 2C Jordan-N3, betacoronavirus England 1, and novel coronavirus, among others. Because of the confusion that these different names caused in the scientific literature, the Coronavirus Study Group of the International Committee on Taxonomy of Viruses met in 2013 and agreed to name the new coronavirus Middle East respiratory syndrome coronavirus (MERS-CoV) (16).

The outbreak of MERS has continued (see Table 2 for key events in the outbreak). As of 5 February 2016, 1,638 laboratory-confirmed cases (see Fig. 1 for epidemic curve) and 587 (36%) deaths had been reported to the World Health Organization (17). Strong evidence supports the role of the dromedary camel as

![Graph](image-url)
the animal reservoir for MERS-CoV, but how the virus is transmitted to humans is not well understood (18). The vast majority of cases have been reported from Saudi Arabia, and all cases thus far recognized have direct or indirect links through travel or residence to countries in or near the Arabian Peninsula (Saudi Arabia, United Arab Emirates, Qatar, Oman, Jordan, Kuwait, Iran, Lebanon, and Yemen). Currently, the country with the second highest number of cases is the Republic of Korea, with an outbreak of more than 180 cases in 2015 following introduction into the country by a single patient who had traveled from the Middle East. As of 5 February 2016, 26 countries have reported cases of MERS to the World Health Organization (Fig. 2), with two patients with MERS reported in the United States, one in Indiana and the other in Florida, both in May of 2014 (19). Despite extensive evaluation and testing of contacts of these two patients in their households, communities, and health care settings, no additional people infected with MERS were identified (20).

The Emergency Committee convened by the World Health Organization Director-General under the International Health Regulations (2005) met 10 times regarding MERS between July 2013 and December 2015, most recently on 2 September 2015. The Committee has continued to state that MERS does not currently constitute a Public Health Emergency of International Concern but noted a continued heightened sense of concern about the overall MERS situation. At the most recent meeting, the Emergency Committee emphasized the following (21):

- National authorities should ensure that all health care facilities have the capacity, knowledge, and training to implement and maintain good practices, especially infection prevention and control measures and early identification of cases.

![Global map of countries with confirmed cases of Middle East respiratory syndrome coronavirus (MERS-CoV), 2012 to 2016, as reported by the World Health Organization (data as of 5 February 2016) (http://www.who.int/emergencies/mers-cov/en/).](http://www.who.int/emergencies/mers-cov/en/)
• Appropriate authorities should collaboratively address deeper systemic issues that are impeding control of MERS, both in animals and humans.
• National authorities should ensure the rapid and timely sharing of information of public health importance, including epidemiological investigations, viral genetic sequence information, and findings from research studies.
• International collaboration to develop human and animal vaccines and therapeutics should be accelerated.
• In view of the evidence that camels are the main source of community-acquired infections, public health, animal health, and agricultural sectors must improve their collaboration to address the public health risk of MERS.
• National leadership is essential to ensure a flexible, efficient, and well-coordinated whole-of-government response to the challenges posed by MERS.

Although much has been learned about MERS-CoV since its emergence in 2012, many questions remain. Human-to-human transmission occurs, usually in health care settings, but sustained and efficient human-to-human transmission has not been observed. However, vigilance is needed, because MERS-CoV could develop the ability to transmit efficiently from person to person, as was seen with SARS-CoV during the outbreak of 2002-2003. For countries without active transmission of MERS-CoV, such as the United States, preparedness efforts are essential. These include efforts toward prevention of travelers becoming infected with MERS-CoV (by providing information to travelers on avoidance of high-risk settings for MERS transmission), enhancement of the ability to rapidly identify and isolate patients with MERS (by educating clinicians regarding patients that should be tested for MERS-CoV and ensuring laboratory capacity for MERS-CoV diagnostic testing), and prevention of MERS-CoV transmission should an imported case occur (by developing and disseminating infection control guidelines for prevention of MERS-CoV transmission in health care settings) (22, 23).

**MERS-COV**

Coronaviruses are large single-stranded, positive-sense RNA viruses capable of infecting humans and many animal species. A high degree of diversity has been observed in coronaviruses, related to their high rate of mutation and the large size of their genomes. Four coronavirus genera have been identified based on genomic and serologic characteristics: Alpha-, Beta-, Gamma-, and Delta-coronavirus. A total of six coronaviruses that infect humans have been identified in two of these genera: Alphacoronavirus (NL63 and HCoV-229E) and Betacoronavirus (HCoV-OC43, HCoV-HKU1, MERS-CoV, and SARS-CoV) (24). MERS-CoV is in lineage c of the genus Betacoronavirus; this lineage also includes two bat coronavirus species, *Tylonycteris* bat coronavirus HKU4 and *Pipistrellus* bat coronavirus HKU5 (16). SARS-CoV is a lineage b Betacoronavirus. SARS-CoV and MERS-CoV both cause severe respiratory infections in humans, whereas the other coronaviruses that infect humans generally cause mild, self-limited respiratory infections, similar to the common cold.

The MERS-CoV genome is ~30 kb in length and contains at least 10 open reading frames (ORFs) (25). The MERS-CoV genome encodes four structural proteins: the spike (S) protein, the envelope (E) protein, the membrane (M) protein, and the nucleocapsid (N) protein (26). Virions are made up of a core (composed of viral RNA and multiple copies of the N protein) and a viral membrane, made up of the E, M, and S proteins (Fig. 3). The S proteins are distributed throughout the envelope and give the virus a crown-like (corona) appearance (Fig. 4). Dipeptidyl peptidase 4 (DPP4) is the host cell receptor for MERS-CoV (27). DPP4 attaches to the
receptor binding domain of the MERS-CoV S protein, which results in S protein cleavage, fusion of the virus and host cell, and release of the viral RNA into the cytoplasm (28). The S protein has two subunits: S1 mediates virus binding through the receptor binding domain, and S2 mediates virus entry by fusing the virus and host cell membranes. For membrane fusion to occur, the S protein must be cleaved at the S1/S2 boundary by human proteases. The use of DPP4 as a receptor in MERS is in contrast to SARS-CoV, which uses angiotensin-converting enzyme 2 as its receptor (29). DPP4 is necessary for the virus to enter cells, explaining the ability of MERS-CoV to infect cells from some animals (e.g., nonhuman primates, bats, and camels) but not others (e.g., hamsters, mice, dogs, and cats) (30). DPP4 is also expressed on many types of human tissues, including lung, kidney, small intestine, liver, and prostate (27, 30, 31), and might be responsible for some of the extrapulmonary manifestations (e.g., renal failure) seen in MERS. In the respiratory tract, DPP4 receptors are localized to the alveolar regions, which might explain why MERS is primarily a lower respiratory tract disease. Further, the fact that DPP4 receptors are minimally expressed in the nasal cavity and conducting airways might explain why efficient human-to-human transmission has not been seen (32).

Recent comparison of the genomic sequences of spike proteins from MERS-CoV, a virus with the ability to enter human cells, to those from a related bat coronavirus HKU4, a virus that is unable to enter human cells, identified two sequence differences that allowed the spike protein to interact with human proteases, genetic changes that gave MERS-CoV the ability to enter human cells (33). The authors suggested that these mutations were critical to the evolution of a bat coronavirus to one that could infect humans, either directly or through an intermediate host.

Whole-genome sequencing of 65 MERS-CoV specimens in 2013 showed the presence of four phylogenetic clades, three of which were no longer circulating. The authors hypothesized that the disappearance of
these clades could be due to implementation of improved infection control measures, along with a basic reproduction number of less than 1, or possibly to transmission from people who were asymptomatic and undiagnosed (34). The differences observed in the genomic sequences suggested that the infections were not the result of a continuous chain of human-to-human transmission, but were more likely related to the virus being intermittently reintroduced into humans from an animal reservoir. Continued genomic analysis of MERS-CoV is needed to determine if mutations are occurring that allow for better adaptation to humans and more efficient human-to-human transmission.

**RISK FACTORS**

Risk factors for MERS appear to have changed as the spread of MERS has progressed. Early patients identified with MERS were much more likely to have comorbidities such as diabetes, heart disease, and chronic renal disease (33) and to be older males (10). However, the predominance of males has become less impressive as the outbreak has continued (11), including in the recent outbreak in the Republic of Korea, in which 61% of infected patients were male (35). Several possible reasons for the male predominance have been hypothesized including that males have a higher level of exposure to camels (although this would not explain the male predominance in the Republic of Korea, where all cases were secondary), males are more likely to seek health care (although this seems the opposite of what is typically observed in Korea), males are more likely to be tested for MERS-CoV or reported to the WHO, or males are more susceptible to MERS.

In an analysis of the first 144 laboratory-confirmed and 17 probable MERS-CoV cases reported to the WHO (36), cases were divided into those that were sporadic or index cases and cases that were secondary (ones with epidemiological links to known MERS-CoV cases). Among the 146 cases that could be classified, 51 (35%) were sporadic or index cases and 95 (65%) were secondary. Sporadic/index cases were more likely to have severe disease (defined as admission to an intensive care unit; use of extracorporeal membrane oxygenation, mechanical ventilation, or vasopressors; reported as “critical” or “severe”; or who died) than secondary cases (90.2% for sporadic/index and 49.5% for secondary). Median age was 59 and 43 years among sporadic/index and secondary cases, respectively. Among the sporadic/index cases, 70.6% were over 50 years of age and 72.6% were male, compared to 37.4% over 50 years of age and 60.0% male in the secondary group of cases. Underlying conditions were reported in 80.9% of sporadic/index cases and 67.2% of secondary cases. These results suggest that sporadic and index cases are more likely to be detected when people are severely ill; as more infections are identified through contact investigations, patients are more likely to be mildly affected or asymptomatic and to be younger and less likely to have underlying conditions.

A case-control study was performed during an outbreak in Saudi Arabia in 2014 to identify risk factors for primary MERS-CoV illness (37). To identify patients with primary MERS-CoV, those with a history of exposure to other MERS-CoV cases or to people with acute respiratory illness of unknown cause or with a history of exposure to health care settings during the 14 days before symptom onset were excluded. Multivariable analysis identified direct exposure to dromedary camels during the 2 weeks before onset of illness, diabetes mellitus, heart disease, and smoking as independent risk factors for primary MERS-CoV illness. Milking dromedary camels was the only specific camel-related exposure that was significantly associated with MERS-CoV illness. However, even among these cases classified as primary, only about a third reported exposure to dromedary camels during the 2 weeks before
illness onset. Living in the same household as people who reported working on or visiting a farm with dromedary camels was also a risk factor, suggesting that indirect exposure might be important. A male predominance was noted among the primary case patients; only 1 of 30 primary case patients in this study was female; however, sex was used to match cases and controls and thus could not be analyzed in the case-control study.

In addition to identifying risk factors for becoming ill with MERS-CoV, other studies have analyzed possible risk factors for dying of MERS. Underlying health conditions and older age have been identified as risk factors for death from MERS in several studies (38–42). For example, in a study from the recent outbreak in the Republic of Korea (42), the authors used a multivariate logistic regression model to identify risk factors for death and found that the odds of dying for persons with underlying health conditions were 7 times higher than for persons without underlying conditions. In that study, for every 1-year increase in a patient’s age, the odds of dying increased by 12%. Viral load also might play a role; a recent study, which used multiple logistic regression analysis, showed that patients who were older (>60 years of age), who had an underlying condition, and who had a higher viral load of MERS-CoV in the upper respiratory tract were at increased risk of death (43). The length of the incubation period might also play a role in the likelihood of a person dying of MERS. Data from an analysis of cases from the Republic of Korea suggest that a longer incubation period is associated with a lower rate of death (44), similar to what has been seen in SARS (45).

MERS has been diagnosed in children, although it appears to be rare (98% of people infected with MERS-CoV have been adults) (26). In a study of 11 cases in children diagnosed with MERS in Saudi Arabia, 9 were asymptomatic (identified as part of contact investigations) and 2 were symptomatic (46). Both children who were symptomatic had underlying illnesses; one was a 2-year-old with cystic fibrosis and the other was a 14-year-old with Down syndrome.

We are aware of only one report of a pregnant woman with MERS. This woman was identified as part of a follow-up investigation of the April 2012 outbreak in Jordan conducted in May 2013. The 39-year-old woman reported respiratory symptoms consistent with MERS during the outbreak period and was subsequently positive for MERS-CoV antibody, suggesting that she had been infected during the outbreak (because she was antibody-positive on a single specimen and she had been symptomatic, she met the WHO case definition for “probable MERS”). During her illness, she delivered a stillborn infant at around 5 months gestation (47). Based on only this one report, we are unable to determine the risks to the pregnant woman or her fetus associated with MERS. However, data from SARS suggest that pregnant women with MERS and their fetuses might be at increased risk of adverse pregnancy outcomes (48).

Data suggest that time of year could be a risk factor for MERS; although MERS illnesses appear throughout the year, the first cases of MERS (identified retrospectively) occurred in April of 2012, and significant increases in numbers of cases have occurred in the spring of the following years (2013, 2014, and 2015). The reason for the seasonal pattern is not known; however, links to the timing of the camel calving season have been made (camels are typically born between late October and late February) (49, 50). Some authors have noted an association between the timing of weaning of camel calves and of diarrhea in these calves with increased numbers of MERS cases (50). Others have hypothesized that the seasonal pattern might occur because young camels are more likely to become ill and shed virus than older camels that are already seropositive for MERS-CoV (49, 51). In a recent study of over 800 dromedary camels of different ages (52), acute MERS-CoV infection was seen in calves but not in older camels, supportive of
this hypothesis. These authors suggest that camel-to-human transmission of MERS-CoV could be prevented if humans avoided young camels (<2 years of age) (52).

Serologic studies have been used to identify occupational risk factors for MERS-CoV infection; in a recent seroprevalence study, shepherds and slaughterhouse workers (persons with occupational camel exposure) were 15 and 23 times more likely to be seropositive for MERS-CoV antibodies than members of the general population (53). In another study, 10 of 294 people with occupational exposure to camels (slaughterhouse workers, barn workers at a camel racing track, and camel farm workers) were seropositive for MERS-CoV antibody, compared with none of 204 without dromedary camel exposure (54).

TRANSMISSION

Cases of MERS can be categorized as primary (sporadic or index cases in a cluster) or secondary (epidemiologically linked to an index case). Among the first 161 confirmed or likely cases reported to the WHO between September 2012 and October 2013, 95 (59%) were believed to be secondary cases, in which person-to-person transmission had occurred (36). Person-to-person transmission of MERS-CoV has occurred in both household and hospital settings (55–57). Household transmission was first suspected in November of 2012 in a family cluster in Saudi Arabia in which there were three confirmed and one probable case (an elderly male, his two sons, and his grandson) (58). Although person-to-person transmission seemed likely, a common source of infection could not be ruled out. Definitive evidence of person-to-person transmission was observed in February of 2013 in the United Kingdom. Two secondary cases among family members (without history of travel) were identified among contacts of an adult male with MERS who had traveled to the Arabian Peninsula 10 days before symptom onset. Among the two secondary cases, one was believed to have been infected in the household setting, while the other was believed to be infected while visiting the patient when he was hospitalized. This cluster provided strong evidence for human-to-human transmission, but it appeared that transmission was infrequent: only two cases of MERS were identified among the 135 persons who had been in contact with the patients (59). These data are consistent with later studies of household contacts. In a study of 26 index patients and their 280 household contacts, only 12 cases (4%, 95% CI 2-7) of probable secondary transmission were identified (56). Low likelihood of transmission has also been seen in other situations; for example, in an analysis of 61 contacts of the first patient with MERS in the United States (all those who had a face-to-face contact with the patient or who entered the patient’s room without recommended personal protective equipment before airborne and contact precautions were instituted), all had negative test results for MERS-CoV (20).

The majority of secondary cases have been observed in hospital settings (5, 55, 60–62). Among 74 secondary cases reported to the WHO between September 2012 and October 2013 for whom setting of transmission was reported, 13 (18%) had been infected in household settings, 60 (81%) were infected in health care settings, and one was infected in a workplace other than a health care setting. Among those infected in a health care setting, 30 were health care personnel who had treated MERS patients, 19 were patients receiving treatment in hospitals, and 6 were visitors (36).

In the spring of 2014, a large outbreak of MERS occurred in Saudi Arabia, with more cases reported during April and May of 2014 than all cases reported previously. Concern was raised regarding whether the virus had evolved to allow for more efficient human-to-human transmission. In a study from a health care facility in Jeddah, Saudi Arabia, that was
involved in the outbreak (62). 255 patients with laboratory-confirmed MERS-CoV infection were identified. Of those, 64 patients (25.1%) were asymptomatic or mildly symptomatic. Among the symptomatic patients, 40 (20.9%) were health care personnel. Of the non–health care personnel who had data that could be assessed, nearly all (109/112 or 97.3%) had an epidemiological link to a health care facility, a person with confirmed MERS-CoV infection, or a person with severe respiratory illness in the 14 days before symptom onset. Only three patients reported no such contacts. Based on these data and subsequent genomic analyses that showed no significant changes in the MERS-CoV genome, it appears that person-to-person spread in the health care setting was the basis for this outbreak (63).

The recent outbreak in the Republic of Korea in which one person with MERS who traveled from the Arabian Peninsula resulted in 186 cases in less than two months is further illustrative of the impact of transmission in health care facilities. In this outbreak, 181 (97%) of the cases had exposures to health care facilities, and 82% of these cases occurred in four hospitals (64). Among the 186 cases, 25 (13.4%) were health care personnel, 82 (44.1%) were patients who were exposed in the health care setting, and 61 (32.8%) were caregivers (65).

This outbreak was fueled in part by superspreading events, in which a single patient transmits infection to a large number of others. Superspreading events were critical for the transmission of SARS (66) but had not been previously described for MERS. However, in the outbreak in Korea, over 80% of transmission events were linked to five patients, and most cases (91.3%) resulted in no transmission. Genomic analysis showed no evidence of mutations in MERS-CoV that might have modified its transmissibility. The patients who transmitted MERS-CoV to the highest numbers of people were ones with a severe cough, but they were otherwise similar to other patients. The reasons hypothe-

sized for the superspreading events seen in this outbreak were a delay in diagnosis and isolation of MERS patients, the fact that many patients sought health care at multiple facilities, frequent transfers between hospitals, significant numbers of paid caregivers in hospitals, and high numbers of contacts (including other patients, paid caregivers, and family members and friends, who typically accompany patients in hospitals in Korea) with MERS patients in large, crowded health care facilities (65).

Based on data from secondary cases, the MERS incubation period is approximately 5 to 6 days, with a range of 2 to 14 days (36, 39, 65). Transmission of MERS is not well understood. Possible transmission routes include (i) droplet (in which droplets >5 μm in diameter with the ability to travel approximately 6 feet contain infectious virus and make contact with mucous membranes), (ii) airborne (in which droplet nuclei <5 μm in diameter with the ability to travel >6 feet are inhaled into a susceptible person’s respiratory tract), (iii) direct contact transmission (contact without a contaminated intermediate object or person), and (iv) indirect contact transmission (involving transfer through an intermediate contaminated object or person) (http://www.cdc.gov/hicpac/2007IP/2007ip_part1.html). Experimental data show that MERS-CoV is able to survive on contaminated surfaces for 48 hours and to maintain stability when aerosolized, suggesting that aerosol, droplet, and contact (direct and indirect) transmission all might play a role (67).

The most likely source of virus when transmission occurs in health care settings appears to be from the lower respiratory tract. In a study of 37 hospitalized patients with MERS, the highest level of MERS-CoV viral load was in specimens from the lower respiratory tract (average viral load from the lower respiratory tract was $5.0 \times 10^6$ copies per ml, compared to $1.9 \times 10^6$ copies per ml from the upper respiratory tract) (68). Viral RNA was detected in 33% of sera, 14.6% of
stool, and 2.4% of urine specimens. Attempts to isolate infectious virus from sera and stool failed, suggesting that these sources are unlikely to contribute substantially to health care–associated infections.\(^{(68)}\)

The basic reproduction number can be used to assess the likelihood that an infectious disease will develop sustained transmission. Several analyses have attempted to estimate the basic reproduction number for MERS. The first, based on data collected before 21 June 2013, estimated a reproduction number ranging from 0.60 to 0.69 \(^{(69)}\). In an analysis that used data from human clusters through 8 August 2013, the authors concluded that transmission was not sustained when infection control measures were utilized, but in the absence of these measures, the reproduction number was estimated to be 0.8 to 1.3 \(^{(70)}\). The most recent analysis, based on data from two large health care–associated outbreaks in Saudi Arabia in the spring of 2014, estimated much higher reproduction numbers, with a reproduction number of 3.5 to 6.7 for the Jeddah outbreak and 2.0 to 2.8 for the Riyadh outbreak \(^{(71)}\). However, these estimates were obtained during specific outbreaks with high levels of transmission and are unlikely to reflect the overall reproduction number.

**ANIMAL RESERVOIR**

For primary cases (cases without an epideimiologic link to a known MERS case), the source of MERS-CoV is unknown. Some of these primary cases might have been exposed to a person infected with MERS-CoV who was mildly affected or asymptomatic and thus not known to have MERS. Another source might be an animal reservoir for MERS-CoV.

Based on the similarity of MERS-CoV’s genetic sequence to those of bat coronaviruses, MERS-CoV is assumed to have a bat-related ancestral origin. Analysis of specimens from bats living in close proximity to the household of a human patient with MERS identified one specimen (from a bat fecal pellet) with 100% genetic identity, based on analysis of a fragment, to the MERS-CoV obtained from the patient, supporting involvement of bats in transmission of MERS to humans \(^{(72)}\). However, the lack of exposure to bats for most MERS patients and the finding that MERS-CoV has only rarely been identified in bats \(^{(72)}\) suggested that an intermediate host species is likely to be involved.

Several pieces of evidence suggest that dromedary camels are important in the transmission of MERS-CoV. Studies have identified anti-MERS-CoV antibodies in dromedary camels, but not in other animals such as cows, goats, or sheep \(^{(73–77)}\). These antibodies were seen in camels from the Middle East, but also from other countries such as Spain, Nigeria, Tunisia, and Ethiopia \(^{(73, 75)}\). Stored serum samples from camels from Saudi Arabia from as early as 1992 \(^{(78, 79)}\), from the United Arab Emirates in 2003 \(^{(80)}\), and from Africa as early as 1983 \(^{(81, 82)}\) were positive for MERS-CoV antibodies. This suggests that MERS-CoV has circulated widely in dromedary camel populations for decades. However, transmission to humans appears to be a recent and infrequent phenomenon; MERS-CoV antibodies were not seen in serum samples collected in the fall of 2012 from 130 blood donors and 226 workers in slaughterhouses for camels, cattle, and sheep in Saudi Arabia \(^{(83)}\). A more recent cross-sectional serological survey of healthy people over 15 years of age in Saudi Arabia between 1 December 2012 and 1 December 2013 showed a low frequency of MERS-CoV antibody seropositivity (seen in 15 of 10,009 individuals or about 0.15%). However, rates were significantly higher among people with exposure to camels; shepherds were 15 times more likely and slaughterhouse workers were 23 times more likely to be seropositive for MERS-CoV antibodies \(^{(53)}\).

In addition to the finding of MERS-CoV antibodies, MERS-CoV viruses have also
been found in camels, including ones that are genetically identical (84) or closely related (85, 86) to those identified in patients ill with MERS. For example, MERS-CoV was isolated from nasal swabs from a patient who died of MERS and from one of his nine camels who previously had rhinorrhea and with whom the patient had close contact. Of note, only nasal swabs from the camel tested positive for MERS-CoV; milk, urine, and rectal samples tested negative. Full genome sequencing showed that the MERS-CoV culture isolates from the patient and his camel were 100% identical. Based on serologic analysis, it appeared that the camel had transmitted the virus to his owner; the first serum sample from the camel showed high levels of MERS-CoV antibodies, while the patient’s first serum sample was negative for MERS-CoV antibody, with high antibody levels measured in the patient’s sample collected two weeks later (84). In addition, MERS-CoV that was identical in sequence to that obtained from the patient and his camel was later identified in an air sample from the camel barn (87).

As discussed previously, a case-control study conducted during the 2014 outbreak in Saudi Arabia (37) evaluated animal exposures as potential risk factors for contracting MERS-CoV infection among patients with primary MERS-CoV infection. No associations were observed between primary MERS-CoV infection and exposures to bats, goats, horses, sheep, or the products of these animals. Direct cattle exposure was more likely among cases than controls (OR 6.00, 95% CI 1.02 to 48.44). No significant differences were noted in exposures to animal products, including uncooked meat, unpasteurized animal milk, or dromedary urine. Direct exposure to dromedary camels within the 2 weeks before onset of illness was significantly associated with primary MERS-CoV infection on multivariable analysis (adjusted OR 7.45, 95% CI 1.57 to 35.28). However, not all case-patients reported direct exposure to dromedary camels during the 2 weeks before illness onset. Living in a household with a person who had direct contact with dromedary camels was also a risk factor.

Although transmission from dromedary camels to humans appears likely, many patients with MERS-CoV have no history of camel exposure, and the frequency of transmission from infected camels to exposed humans appears to be low (88). Reasons for the lack of exposure to camels among some people with MERS-CoV could be that exposures occurred through consumption of unpasteurized camel milk, undercooked camel meat, or medicinal use of camel urine (50). Viral RNA has been detected in camel milk (74) and can be detected up to 72 hours when stored at 4°C and 22°C (89), suggesting that transmission through consumption of camel milk could be possible. After camel milk spiked with MERS-CoV was heat-treated for 30 minutes, no infectious virus could be recovered (89). However, no epidemiologic data support these other modes of transmission. Another possibility is that some patients might be infected by people with MERS-CoV infection who are asymptomatic and thus not identified as infected (58). When serologic studies were performed in outbreak settings, a significant proportion of people with evidence of past infection with MERS-CoV were not symptomatic (25% in one study) (62).

INFECTION CONTROL RECOMMENDATIONS FOR HEALTH CARE FACILITIES

Infections in health care settings have played a major role in the transmission of MERS-CoV (35, 57, 62, 90). The modality of transmission in health care settings is not fully understood. However, data from SARS (91) and MERS (5) suggest that implementation of health care infection control measures is effective in preventing transmission. An important question with regard to infection
control measures is whether airborne precautions are required. MERS-CoV RNA fragments were detected in an air sample from a barn that housed a camel with MERS-CoV that was owned by an infected patient; these fragments were identical to those from the camel and patient, suggesting that airborne transmission might be possible (87). However, questions have been raised about the methods used in this study (92).

Screening and triage procedures to ensure early identification of patients potentially infected with MERS-CoV in health care settings are essential. Once a patient is suspected of having MERS, infection control measures should be immediately implemented. The U.S. Centers for Disease Control and Prevention has provided interim recommendations for infection control when patients are suspected of or confirmed to have MERS-CoV infection. The CDC acknowledged that the modes of transmission of MERS-CoV are incompletely defined, but given the absence of a vaccine or chemoprophylaxis and a possible high rate of morbidity and mortality, the recommendations include adherence to standard, contact, and airborne precautions. Airborne precautions include patient placement in an airborne infection isolation room, when feasible, and use of respiratory protection (e.g., a National Institute for Occupational Safety and Health–certified, fit-tested N95 filtering face-piece respirator) by health care workers entering the care area or room. Eye protection with goggles or a face shield is also recommended. Aerosol-generating procedures (including cough-generating procedures, bronchoscopy, sputum induction, intubation and extubation, cardiopulmonary resuscitation, and open suctioning of airways) appear to present particularly high risk of MERS-CoV transmission to health care workers (61, 63, 93). Thus, the CDC recommends conducting these procedures only when medically necessary and in an airborne infection isolation room if possible, limiting the number of health care personnel present during these procedures to the minimum number needed for patient care, prohibiting health care personnel without appropriate personal protective equipment from entering the room until sufficient time has elapsed for infectious particles to be cleared, and conducting environmental surface cleaning after the procedures are completed. These recommendations will be updated when additional information becomes available (http://www.cdc.gov/coronavirus/mers/infection-prevention-control.html).

WHO recommendations for MERS-CoV standard, contact, and droplet precautions are similar to those from the CDC; however, airborne precautions are reserved for situations where aerosol-generating procedures might be performed. The latest infection control guidelines from the WHO can be obtained at http://www.who.int/csr/disease/coronavirus_infections/ipc-mers-cov/en/.

PREVENTION OF TRAVEL-ASSOCIATED TRANSMISSION

All cases identified thus far with MERS-CoV infection have been directly or indirectly linked to the Arabian Peninsula. These include cases associated with travel (94) and with spread of MERS to 17 countries outside those in or near the Arabian Peninsula (http://www.cdc.gov/coronavirus/mers/). Strategies to prevent travel-associated transmission have been recommended by the CDC and the WHO. No travel restrictions to or from the Arabian Peninsula have been recommended. For travelers to the Arabian Peninsula to work as health care workers are directed to become familiar with infection control guidelines for patients with confirmed and suspected MERS. CDC travel recommendations will be updated as additional
information becomes available: http://wwwnc.cdc.gov/travel/.

Specific recommendations have also been made by the CDC and WHO regarding exposure to camels, given the increasing evidence that camels play a critical role in transmission in primary cases. Travelers who will be visiting farms, markets, barns, or other settings where they might be in contact with animals, should practice general hygiene measures, including hand-washing before and after touching animals and avoiding contact with ill animals. Eating raw or undercooked animal products should be avoided. The WHO recommends additional precautions for people at risk for developing severe MERS illness (people with diabetes, renal failure, or chronic lung disease and immunocompromised people), including avoiding contact with camels and avoiding consumption of raw camel milk, urine, and undercooked meat, especially camel meat. The latest information from the WHO is available at http://www.who.int/csr/disease/coronavirus_infections/faq/en/ and http://www.who.int/csr/disease/coronavirus_infections/MERS_CoV_RA_20140613.pdf?ua=1.

Travelers to regions with MERS transmission should be instructed that if they develop symptoms of MERS, they should seek medical care. In addition, travelers should make the health care facility aware of their recent travel before presenting for care so that appropriate infection control measures can be put in place (22, 95). Although clinicians caring for patients with signs and symptoms consistent with MERS-CoV following travel to countries affected by MERS need to consider the possibility of MERS, studies have shown that these patients frequently have other (non-MERS) respiratory illnesses, usually influenza (96, 97).

A high level of concern has been raised about transmission during the Hajj, in which more than 2 million Muslim visitors from around the world travel to Saudi Arabia during one week each year as part of a religious pilgrimage (98, 99). In addition to the close contact with other pilgrims, visitors are likely to have contact with animals, including some that might be infected with MERS. However, despite increased surveillance following the Hajj, no Hajj-associated cases of MERS have been confirmed (98, 100–103), but several travel-associated cases have been observed among people returning after Umrah, a Muslim pilgrimage in which ∼6 million pilgrims participate in each year; this pilgrimage can occur at any time during the calendar year (104, 105).

**ANIMAL MODELS**

The availability of animal models for a novel infectious pathogen such as MERS-CoV allows for more rapid advances in research (106). Small animals typically used for experimental studies (e.g., Syrian hamsters, mice, and ferrets) cannot be used as animal models without modification because MERS-CoV is unable to replicate in these species (107–109) due to differences in the DPP4 host cell receptor. Rabbits can be infected with MERS-CoV but are asymptomatic (110); because of this, rabbit models can be used for studies of disease transmission but not for studies of illness or response to therapeutics.

Although mice, which are preferred for experimental studies over larger animals because they are less resource intensive, cannot become naturally infected with MERS-CoV because murine DPP4 does not serve as a receptor, researchers have recently developed mouse models for MERS, either by sensitizing mice to MERS-CoV with an adenovirus that expresses human DPP4 (111) or by creating transgenic mouse lines that express human DPP4 (112–114). Mice that are intranasally inoculated with a human DPP4-expressing adenovirus and then infected with MERS develop pneumonia, similar to that in humans, and can be helpful in studying immune response and to evaluate MERS-CoV therapeutics and vaccines. Transgenic mouse lines that have been...
modified to express human DPP4 become infected with MERS-CoV and have major effects on the lungs and the brain, often resulting in death, limiting the ability to study host response to the virus; however, severity of disease appears to be related to the dose of virus provided (112–114). These models show promise for the study of the pathogenesis of MERS as well as assessment of potential vaccines and therapeutics.

Two species of nonhuman primates have been used as animal models for MERS-CoV: the rhesus macaque and the common marmoset (106). In these species, inoculation with MERS-CoV results in viral replication and clinical illness. The rhesus macaque was the first animal model to be used for MERS-CoV. Inoculation of these animals with MERS-CoV resulted in transient disease that was mild to moderate in severity, including fever, increased respiratory rate, and decreased appetite. This animal model was used to fulfill Koch’s postulates for MERS-CoV, confirming the virus as the causative agent for the clinical illness seen in patients with MERS (115). After studies of the DPP4 receptor showed that the common marmoset’s receptor was similar to the human receptor (27), the common marmoset was pursued as an animal model for MERS. Following inoculation with MERS-CoV, the common marmoset develops moderate to severe illness, with increased respiratory rate, loss of appetite, and decreased activity, and severe interstitial pneumonia, sometimes resulting in death. These nonhuman primate models can be seen as complementary, with the macaque developing mild to moderate disease and the marmoset developing disease at the more severe end of the spectrum (116).

Dromedary camels also have been experimentally inoculated with MERS-CoV, and when infected, they develop mild symptoms, including rhinorrhea and temperature elevations, and shed high quantities of virus from the upper respiratory tract (117). These animals could be used to better understand the ecology and transmission of MERS-CoV (106).

**CLINICAL FINDINGS**

People infected with MERS-CoV can present with a wide range of clinical findings, ranging from asymptomatic to severe illness and death. Cases with mild or no symptoms often have been identified as part of contact investigations (36, 46, 62). People who are asymptomatic or who have only mild symptoms are frequently identified when serologic testing is performed; a quarter of patients with MERS-CoV infection identified in an outbreak at a health care facility in Jeddah, Saudi Arabia, were asymptomatic (62). Clinical manifestations are often nonspecific and indistinguishable from more common illnesses such as influenza; thus, travel and exposure histories are critical.

Most symptomatic patients with MERS have had fever, chills or rigors, cough, and shortness of breath (26, 38, 39, 41, 55). Other findings commonly seen include malaise, myalgia, sore throat, and headache. Gastrointestinal symptoms (nausea, vomiting, and diarrhea) are also often seen (Table 2). The respiratory illness often progresses to pneumonia and subsequently to acute respiratory distress syndrome. Abnormalities on chest radiographs range from minor to interstitial infiltrates to total opacification of lung segments and lobes (39, 55, 60). Abnormal laboratory findings seen in some patients include leukopenia, lymphopenia, thrombocytopenia, and elevated lactate dehydrogenase, alanine aminotransferase, and aspartate aminotransferase (26, 39, 118).

Kidney failure has been described in some patients with MERS. Based on a systematic review performed in 2013, MERS patients developed acute renal failure more often and earlier than patients with SARS (119). Whether this is due to direct infection of the kidney or related to critical illness (68) is unknown. MERS-CoV RNA was detected in a small proportion (2.4%) of urine specimens from infected patients in a recent study (68).

A recent report of three patients with MERS-CoV who developed a severe
neurological syndrome has raised the question of whether the central nervous system might be another target of MERS-CoV (120). All three patients had severe neurologic symptoms including altered level of consciousness, ataxia, and focal motor deficit. Brain MRIs showed widespread, bilateral hyperintense lesions within the white matter on T-2 weighted imaging. Cerebrospinal fluid was obtained from two of the three patients and MERS-CoV reverse transcription PCR (RT-PCR) was negative for both; findings were remarkable only for an increased protein level.

Limited information is available on the pathology of MERS, given the rarity of autopsy examinations for cultural and religious reasons among many affected patients (121). Based on data from chest CT scans, respiratory features appear to be consistent with an organizing pneumonia, based on the findings of ground-glass opacities with a distribution in the subpleural and peribronchovascular regions (122). These findings differ from those seen in patients with SARS, in which a bronchiolitis obliterans organizing pneumonia-like pattern and fibrosis tend to occur in late stages of the disease (123). A recent report of an autopsy on a single patient provides additional insight (124): diffuse alveolar damage was observed in the lungs, with localization to type 2 pneumocytes and epithelial syncytial cells. Despite the patient having renal failure requiring dialysis, MERS-CoV antigens were not detected outside of the lungs, including in the kidneys, suggesting that the renal failure was due to factors other than direct MER-CoV infection of the kidney. Additional pathologic examination of materials from autopsies will be needed to confirm these findings.

**CASE DEFINITION**

Both the CDC and the WHO have developed case definitions for diagnosis of confirmed and probable cases of MERS (Tables 3 and 4). In addition, the CDC has a case definition for “patients under investigation” to assist health care personnel in determining which patients warrant testing for MERS-CoV (Table 3). As more information is learned about MERS-CoV, these case definitions will be updated. For the latest information, the CDC (http://www.cdc.gov/coronavirus/mers/case-def.html) and WHO (http://www.who.int/csr/disease/coronavirus_infections/case_definition/en/) websites should be consulted.

An important consideration when determining which patients to test for MERS-CoV is that coinfection with other respiratory pathogens has been reported (38, 125). Thus, identification of another respiratory pathogen does not rule out the possibility that a patient has MERS-CoV.

**VIROLOGIC DIAGNOSIS**

Shortly after description of the first patient with MERS, real-time RT-PCR assays were developed to allow for rapid laboratory diagnosis of MERS (126, 127). These assays targeted regions upstream of the E gene (upE), within open reading frame 1b (ORF1b) and within ORF1a. These authors recommended use of the two highly sensitive assays upE and ORF1a for diagnostic purposes (ORF1b was found to be of lower sensitivity than ORF1a) (127). The authors also described two RT-PCR assays for sequencing, which targeted the RNA-dependent RNA polymerase (RdRp) and nucleocapsid genes (RdRpSeq and NSeq assays, respectively) (127).

The CDC developed an assay that incorporates additional RT-PCR targets focused on the MERS-CoV nucleocapsid gene (N2 and N3); this assay uses upE and N2 targets for screening of specimens and the N3 target for positive test confirmation (128). On 5 June 2013, this CDC Novel Coronavirus 2012 Real-time RT-PCR Assay was approved for use by the U.S. Food and Drug Administration through an emergency use authorization (http://www.fda.gov/MedicalDevices/
Safety/EmergencySituations/ucm161496.htm). Reagent kits for this assay were subsequently distributed through the CDC Laboratory Response Network to state health departments as well as to international public health laboratories (128).

The WHO has developed interim guidance for laboratory testing for MERS, most recently updated in June 2015 (129). For the WHO to consider a case of MERS confirmed by RT-PCR, one of the following criteria must be met: (i) a positive RT-PCR result for at least two specific targets on the MERS-CoV genome using a validated assay or (ii) one positive RT-PCR result for a specific target on the MERS-CoV genome and MERS-CoV sequence confirmation from a separate viral genomic target (127). The WHO considers cases with positive RT-PCR results at only a single target but with signs consistent

### TABLE 3 Middle East Respiratory Syndrome Coronavirus (MERS-CoV) definitions from the CDC<sup>a,b</sup>

| Clinical features                        | Epidemiologic risk                                                                 |
|------------------------------------------|-----------------------------------------------------------------------------------|
| Patient under investigation              |                                                                                   |
| Severe illness: Fever<sup>c</sup> and pneumonia or acute respiratory distress syndrome (based on clinical or radiological evidence) | And A history of travel from countries in or near the Arabian Peninsula<sup>d</sup> within 14 days before symptom onset or close contact<sup>e</sup> with a symptomatic traveler who developed fever<sup>c</sup> and acute respiratory illness (not necessarily pneumonia) within 14 days after traveling from countries in or near the Arabian Peninsula<sup>d</sup>Or A member of a cluster of patients with severe acute respiratory illness (e.g., fever<sup>c</sup> and pneumonia requiring hospitalization) of unknown etiology in which MERS-CoV is being evaluated, in consultation with state and local health departments in the United States |
| Milder illness: Fever<sup>c</sup> and symptoms of respiratory illness (not necessarily pneumonia; e.g., cough, shortness of breath) | And A history of being in a health care facility (as a patient, worker, or visitor) within 14 days before symptom onset in a country or territory in or near the Arabian Peninsula<sup>d</sup>in which recent health care–associated cases of MERS have been identified |
| Fever<sup>c</sup> or symptoms of respiratory illness (not necessarily pneumonia; e.g., cough, shortness of breath) | And Close contact<sup>e</sup> with a confirmed MERS patient while the patient was ill |
| Confirmed case                           | A person with laboratory confirmation of MERS-CoV infection; confirmatory laboratory testing requires a positive PCR on at least two specific genomic targets or a single positive target with sequencing on a second |
| Probable case                            | A patient under investigation with absent or inconclusive laboratory results for MERS-CoV infection who is a close contact<sup>e</sup> of a laboratory-confirmed MERS-CoV patient; examples of laboratory results that may be considered inconclusive include a positive test on a single PCR target, a positive test with an assay that has limited performance data available, or a negative test on an inadequate specimen |

<sup>a</sup>From http://www.cdc.gov/coronavirus/mers/case-def.html#modalIdString_CDCTable_0 (see CDC website for up-to-date information).

<sup>b</sup>These criteria serve as guidance for testing; however, patients should be evaluated and discussed with public health departments on a case-by-case basis if their clinical presentation or exposure history is equivocal (e.g., uncertain history of health care exposure).

<sup>c</sup>Fever may not be present in some patients, such as those who are very young, elderly, immunosuppressed, or taking certain medications. Clinical judgment should be used to guide testing of patients in such situations.

<sup>d</sup>Countries considered in the Arabian Peninsula and neighboring include Bahrain; Iraq; Iran; Israel, the West Bank, and Gaza; Jordan; Kuwait; Lebanon; Oman; Qatar; Saudi Arabia; Syria; the United Arab Emirates; and Yemen.

<sup>e</sup>Close contact is defined as (i) being within approximately 6 feet (2 meters) or within the room or care area for a prolonged period of time (e.g., health care personnel, household members) while not wearing recommended personal protective equipment (i.e., gowns, gloves, respirator, eye protection) or (ii) having direct contact with infectious secretions (e.g., being coughed on) while not wearing recommended personal protective equipment (i.e., gowns, gloves, respirator, eye protection). Data to inform the definition of close contact are limited. At this time, brief interactions such as walking by a person are considered low risk and do not constitute close contact.
TABLE 4 Middle East respiratory syndrome coronavirus (MERS-CoV) case definition for reporting to the WHO

| Confirmed case | | | |
|----------------|-----------------|-----------------|-----------------|
| A person with laboratory confirmation of MERS-CoV infection\(^b\), irrespective of clinical signs and symptoms | And | Direct epidemiologic link\(^c\) with a confirmed MERS-CoV case | And | Testing for MERS-CoV is unavailable, negative on a single inadequate specimen\(^d\), or inconclusive\(^e\) |

| Probable case | | | |
|----------------|-----------------|-----------------|-----------------|
| A febrile acute respiratory illness with clinical, radiological, or histopathological evidence of pulmonary parenchymal disease (e.g., pneumonia or acute respiratory distress syndrome) | And | Direct epidemiologic link\(^b\) with a confirmed MERS-CoV case | And | Testing for MERS-CoV is unavailable, negative on a single inadequate specimen\(^d\), or inconclusive\(^e\) |

| Definition 1: | | | |
|----------------|-----------------|-----------------|-----------------|
| A febrile acute respiratory illness with clinical, radiological, or histopathological evidence of pulmonary parenchymal disease (e.g., pneumonia or acute respiratory distress syndrome) | And | The person resides or travelled in the Middle East or in 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\(^e\) |

| Definition 2: | | | |
|----------------|-----------------|-----------------|-----------------|
| An acute febrile respiratory illness of any severity | And | Direct epidemiologic link\(^b\) with a confirmed MERS-CoV case | And | Testing for MERS-CoV is inconclusive\(^e\) |

\(^a\)From http://www.who.int/csr/disease/coronavirus_infections/case_definition/en/ (see WHO website for up-to-date information).  
\(^b\)A case may be laboratory confirmed by detection of viral nucleic acid or serology. The presence of viral nucleic acid can be confirmed by either a positive reverse transcription PCR result on at least two specific genomic targets or a single positive target with sequencing of a second target. A case confirmed by serology requires demonstration of seroconversion in two samples, ideally taken at least 14 days apart, by a screening (enzyme-linked immunosorbent assay [ELISA], indirect fluorescent antibody [IFA]), and by a neutralization assay. However, the interim recommendations for laboratory testing for MERS-CoV should be consulted for the most recent standard for laboratory confirmation.  
\(^c\)A direct epidemiological link with a confirmed MERS-CoV patient may include (i) health care–associated exposure, including providing direct care for MERS-CoV patients, working with health care workers infected with MERS-CoV, visiting patients, or staying in the same close environment of individuals infected with MERS-CoV; (ii) working in close proximity or sharing the same classroom environment with individuals infected with MERS-CoV; (iii) traveling with individuals infected with MERS-CoV in any kind of conveyance; (iv) living in the same household as individuals infected with MERS-CoV; (v) the epidemiological link may have occurred within a 14-day period before or after the onset of illness in the case under consideration.  
\(^d\)An inadequate specimen would include a nasopharyngeal swab without an accompanying lower respiratory specimen, a specimen that has had improper handling, is judged to be of poor quality by the testing laboratory, or was taken too late in the course of illness.  
\(^e\)Inconclusive tests may include (i) a positive screening test on a single real-time reverse transcription PCR target without further confirmation and (ii) evidence of sero-reactivity by a single convalescent serum sample, ideally taken at least 14 days after exposure by a screening assay (ELISA or IFA) and a neutralization assay in the absence of molecular confirmation from respiratory specimens.

Collection of specimens from symptomatic patients can include lower respiratory tract specimens (i.e., sputum, bronchoalveolar lavage, tracheal aspirates), upper respiratory tract specimens (i.e., oropharyngeal swabs, nasopharyngeal swabs, aspirate, or wash), and serum (especially if lower respiratory tract specimens are unavailable) (129). Lower respiratory tract specimens have the highest MERS-CoV viral load (130–132) and thus should be collected whenever possible (129). MERS-CoV has sometimes been detected in lower respiratory tract specimens or in serum when upper respiratory tract specimens previously tested negative (19, 133). MERS-CoV has been detected in serum, urine, and stool, although at lower concentrations than in the lower respiratory tract (68, 134). In cases with confirmed MERS-CoV, WHO guidance recommends sequential sampling of specimens with MERS and a history of potential exposure as “probable.”
from multiple sites (including urine and stool) to improve understanding of virus shedding and to guide infection control measures (129).

To confirm MERS-CoV clearance in clinically recovered patients, the WHO recommends two consecutive negative PCR results from respiratory specimens collected at least every 2 to 4 days. Samples can be collected daily if a patient’s discharge from isolation requires consecutive negative results (129).

Development of serological assays for MERS-CoV has been challenging because of problems with cross-reactivity with other coronaviruses and has been further complicated by the limited availability of MERS-CoV convalescent sera to allow for protocol validation (135). Methods for different types of serological tests for MERS have been published, including enzyme-linked immunosorbent assay (ELISA), indirect fluorescent antibody (IFA), and virus neutralization assays, among others (127, 136–138). Virus neutralization assays are considered the “gold standard” but require live virus and thus must be performed under biosafety lab 3 conditions. Therefore, laboratories often initially use less specific assays (e.g., ELISA) and then when those studies are positive, proceed to more definitive tests such as IFA or virus neutralization assays (56). For example, the CDC used a two-stage approach for detecting MERS-CoV antibodies that included testing using ELISA, followed by confirmation with either an IFA or a microneutralization test (5).

The WHO guidance includes recommendations for the use of serologic testing to make a diagnosis of MERS-CoV infection for reporting to the WHO under international health regulations (129). For a patient to be considered a confirmed case by the WHO, seroconversion must be documented by at least one screening assay—ELISA or IFA—and a positive result for a neutralization assay) on only a single specimen is considered a probable case, in the absence of a positive RT-PCR test for MERS-CoV. A person who is asymptomatic with positive results of antibody testing on a single specimen does not meet WHO criteria for either a confirmed or probable case (129).

**IMMUNE RESPONSE**

Information on the immune response to MERS-CoV infection is limited. In a recent analysis of 37 hospitalized MERS patients (68), viral load and antibody response were followed longitudinally beginning at the time of diagnosis through the course of their hospitalization. Antibodies were detected in most patients in the second week after diagnosis (estimated to be 2 to 3 weeks after illness onset). An inverse correlation was noted between the level of antibodies and viral load in the sera. In some cases, antibodies to MERS-CoV and viral RNA were detected in the same serum specimens. Even in the presence of neutralizing antibodies, virus was not cleared from the lower respiratory tract, leading the authors to suggest that vaccine strategies should not rely solely on the production of neutralizing antibodies (68).

Limited information is available on the contribution of T-cells to the MERS-CoV immune response (139). Using the mouse model that has been sensitized to MERS-CoV with an adenovirus that expresses human DPP4, mice that were T-cell deficient were compared to control mice following infection with MERS-CoV; the T-cell-deficient mice had viral persistence in the lungs, whereas control mice were able to clear the MERS-CoV from the lungs (111). These data suggest that T-cells are likely to be important in the immune response to MERS-CoV.
CLINICAL MANAGEMENT AND ANTIVIRALS

No specific antiviral treatment for MERS is available. Treatment of severely ill patients is primarily supportive, including mechanical ventilation, lung protective ventilation strategies, extracorporeal membrane oxygenation, inotropic support, antimicrobial therapy for secondary infections, and hemodialysis, as indicated (4, 131, 140).

Screening of potential therapeutics using cell culture has been used to identify treatment options that might be effective against MERS-CoV, including interferons, mycophenolate mofetil, cyclosporine A, ribavirin, nitazoxanide, lopinavir, and monoclonal antibodies (141–146); a few of these have shown anti-coronavirus activity and thus have potential as therapeutic options. In addition, animal models have been used to study possible therapeutics for MERS. Treatment with ribavirin and interferon-α2b was shown to improve clinical outcomes in rhesus macaques (147). Better outcomes were observed in the common marmoset animal model following treatment with lopinavir/ritonavir or interferon-β1b, while animals treated with mycophenolate mofetil had worse outcomes (148).

Based on studies of the utility of convalescent plasma among patients with SARS-CoV or influenza, MERS convalescent plasma has been proposed as a possible treatment for MERS patients (149). A protocol for a study of feasibility, safety, and clinical and laboratory endpoints of treatment with convalescent plasma was recently published, and this study is anticipated as a precursor to a randomized controlled trial (150). A systematic review of treatments used for patients with SARS showed that systemic steroids might be harmful (151); thus, steroids should not be used in MERS patients. Certain medications have been studied in MERS patients; for example, in a small retrospective cohort study (20 treated compared to 24 untreated patients), survival was improved after treatment with ribavirin and interferon-α2a after 14 days, but at 28 days, the results were not statistically significant (30% survival among treated versus 17% among those untreated, \( p = 0.54 \)) (152). Randomized controlled trials will be required to determine whether these therapeutics have clinical benefit.

VACCINES

Currently no vaccine is available to protect humans or animals from developing MERS, but efforts are ongoing to develop a MERS vaccine. Based on the current epidemiology of MERS, in which most illness appears to occur in certain groups, widespread vaccination with a MERS vaccine is unlikely to be recommended. Instead, targeting patients at high risk of infection (those with occupational exposure to camels or people working in health care settings in locations with MERS transmission) or those at high risk of severe illness (people with underlying conditions) might be warranted. Another approach that has been considered is vaccination of camels to prevent illness in humans by decreasing the introduction of the virus into the human population (153).

Much has been learned about coronavirus vaccines as part of the efforts to develop a SARS vaccine, and this information can be used in the development of a safe and effective MERS vaccine. For example, a full-length S-protein-based SARS vaccine has been shown to produce neutralizing antibodies in vaccinated ferrets following infection with SARS-CoV, but inflammation of the liver was also seen, suggesting that enhancement of disease can occur following vaccination (154), which raises concerns about using this vaccine approach for MERS-CoV. As another example, data from SARS suggest that intranasal vaccination might be advantageous compared to other modes of vaccine administration because it can produce a mucosal response, thus blocking viral repli-
cation in the respiratory tract, in addition to inducing a systemic humoral response (155). Results from studies of intranasal versus other modes of administration of MERS vaccines are comparable (156).

Several different types of MERS vaccines are under development, including vaccines based on viral vectors, recombinant viral proteins, DNAs, nanoparticles, and recombinant virus (157, 158). These vaccines are currently undergoing testing in cell culture and in animal models (mice, rabbits, camels, and nonhuman primates). Many of these vaccines target part or all of the S protein, its subunit, or the receptor-binding domain, and in some cases immunogenicity has been demonstrated in animal models (31). Clinical trials will be required to test these vaccines in humans, and planning is under way for trials of some of the more promising vaccine candidates (157).

**CONCLUSIONS**

The first patients with novel coronavirus infection, now known as Middle East respiratory syndrome coronavirus (MERS-CoV), were reported in 2012. In the ensuing years, over 1,600 cases have been reported, as of February 2016. Most of these have occurred in Saudi Arabia or in other countries on or near the Arabian Peninsula, but travel-associated cases have also occurred. In 2015, in the Republic of Korea, a single travel-associated case led to a significant outbreak of over 180 cases. MERS-CoV causes a severe respiratory illness in many patients, although when contacts are investigated, a significant proportion of patients are asymptomatic or only have mild symptoms. The case fatality rate may be as high as 40%, although this estimate is likely to have been based on cases in which mildly affected and asymptomatic cases were missed. At this time, no vaccines or treatments are available. Based on genomic data, MERS-CoV is likely of bat ancestral origin; however, epidemiological and other data suggest that the source of most primary cases is exposure to camels. Person-to-person spread occurs, both in household and health care settings, although sustained and efficient person-to-person transmission has not been observed. Strict adherence to infection control recommendations has been associated with control of previous outbreaks. Based on the experience with SARS, it is recognized that genomic changes in MERS-CoV could result in increased transmissibility; thus, vigilance is needed.

Given the frequency of air travel, all countries are at risk for patients with MERS, and preparedness efforts are critical. These include prevention of travelers becoming infected with MERS-CoV, enhancement of the ability to rapidly identify and isolate patients with MERS, and prevention of MERS-CoV transmission in health care settings should an imported case occur.

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