Middle East Respiratory Syndrome: Emergence of a Pathogenic Human Coronavirus

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Abstract

In 2012, a zoonotic coronavirus was identified as the causative agent of Middle East respiratory syndrome and was named MERS coronavirus (MERS-CoV). As of August 11, 2016, the virus has infected 1,791 patients, with a mortality rate of 35.6%. Although MERS-CoV generally causes subclinical or mild disease, infection can result in serious outcomes, including acute respiratory distress syndrome and multi-organ failure in patients with comorbidities. The virus is endemic in camels in the Arabian Peninsula and Africa and thus poses a consistent threat of frequent reintroduction into human populations. Disease prevalence will increase substantially if the virus mutates to increase human-to-human transmissibility. No therapeutics or vaccines are approved for MERS; thus, development of novel therapies is needed. Further, since many MERS cases are acquired in healthcare settings, public health measures and scrupulous attention to infection control are required to prevent additional MERS outbreaks.

THE OUTBREAKS

In June of 2012 a man in Jeddah, Saudi Arabia, was admitted to a hospital with severe pneumonia. A novel coronavirus (CoV) related to the severe acute respiratory syndrome (SARS) CoV was isolated from this patient and shown to be the etiological agent (1). Further studies showed that it was related to several bat CoVs, including HKU4 and HKU5, and it was named the Middle East respiratory syndrome CoV (MERS-CoV) (2). Retrospective studies showed that the same virus was also responsible for an outbreak of respiratory disease in Zarqa, Jordan, in April of 2012. As of August 11, 2016, MERS-CoV infection has been identified in 1,791 patients, with 640 associated deaths (**http://www.who.int/emergencies/mers-cov/en/**). All of the cases were geographically linked to the Middle East, and cases that occurred outside of the Middle East involved travelers from this region. Many MERS cases occurred in hospitals on the Arabian Peninsula, usually in the setting of inadequate infection-control practices. In the summer of 2015, an outbreak of 186 MERS cases occurred in South Korea. This outbreak stemmed from a single patient who had returned from the Middle East. Diagnosis of MERS was delayed, as he sought treatment at multiple medical facilities, which facilitated virus spread to susceptible individuals at these facilities (3). As was the case for the Middle East patients, a majority of severely ill patients had underlying diseases, as described below. Fortunately, increased surveillance for MERS-CoV and improved infection-control measures in hospitals have slowed the spread of this highly pathogenic virus (**Figure 1**).

THE VIRUS

MERS-CoV is a member of the family Coronaviridae, which is divided into four genera—alpha, beta, gamma, and delta—based on phylogenetic clustering. These genera are further subdivided into distinct lineages. Both MERS and SARS are caused by β-CoVs, but MERS-CoV belongs to lineage C whereas SARS-CoV belongs to lineage B (2). CoVs cause a variety of diseases in mammals, including respiratory, hepatic, enteric, and neurologic pathologies of differing severity in species ranging from humans to domesticated and companion animals (4).

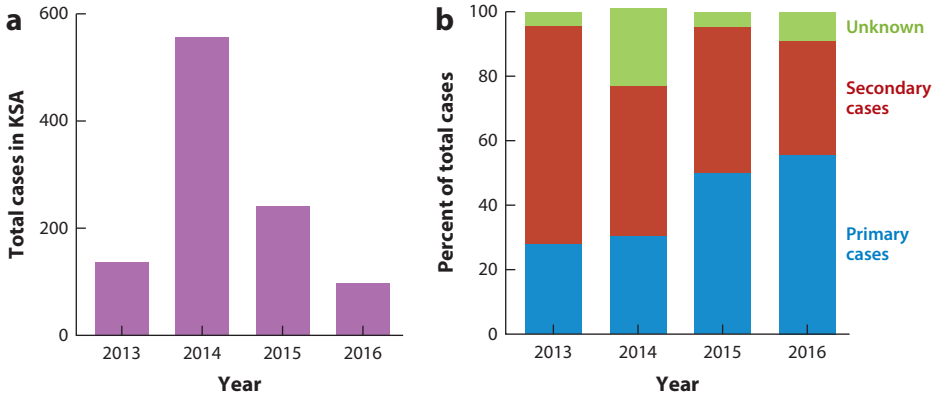

Figure 1

Case distribution of Middle East respiratory syndrome coronavirus (MERS-CoV) in the Kingdom of Saudi Arabia (KSA), 2013–2016. The total (*a*) and percentage (*b*) of primary, secondary, or unknown MERS cases are plotted per year. Although secondary cases of MERS predominated during the early stages of the outbreak, improved infection-control practices have significantly reduced the number and percentage of secondary cases in the last two years (12; **http://www.moh.gov.sa/en/CCC/Pages/Weekly-Monitor.aspx**).

The members of Coronaviridae are enveloped, positive-sense, single-stranded RNA viruses. CoVs are the largest known RNA viruses to date, with genomes of ~30 kb. All CoVs have a highly conserved genome organization with a single large 5′ open reading frame (ORF) encoding a replicase polyprotein followed by several additional ORFs that encode structural and accessory genes interspersed through the 3′ end of the genome (4). The polyprotein is cleaved by viral proteases into 16 nonstructural proteins largely mediating virus replication. Genes at the 3′ end of the genome encode several virion structural proteins, including the nucleocapsid (N), matrix (M), and envelope (E) proteins, as well as the spike (S) protein. The S protein mediates binding of the virus to the host cell receptor and is a major determinant of virulence. Finally, accessory proteins are largely involved in modulating the innate immune response to CoVs. The MERS-CoV genome encodes five unique accessory proteins, of which at least two, 4A and 4B, modulate interferon (IFN) production when expressed in isolation (5).

Soon after the discovery of MERS-CoV, the receptor that mediates cell entry was identified as dipeptidyl peptidase 4 (DPP4), a large ectopeptidase present at the surface of many different cell types (6). The use of DPP4 distinguishes MERS-CoV from SARS-CoV, which uses angiotensin-converting enzyme 2 (ACE2), another large ectopeptidase, as its receptor (7). Although there has been extensive recombination of MERS-CoV in camels (8), and genetic changes in the virus have been noted since 2012, there is no evidence that the virus has mutated to enhance binding to DPP4. Rather, in one instance, a virus with diminished affinity for the receptor was described (9). This suggests that adaptation of MERS-CoV spike protein to human DPP4 is not occurring. In contrast, SARS-CoV underwent extensive mutation to adapt to the human ACE2 protein (10).

EPIDEMIOLOGY

Since 2012, MERS cases have been identified in 27 countries, although most occur in the Kingdom of Saudi Arabia and other countries on the Arabian Peninsula. Furthermore, all cases outside of the Middle East can be traced to patients who had recently traveled from this region. The largest series of outbreaks occurred in the spring of 2014 in Saudi Arabia, when ~500 hospital-acquired cases appeared throughout the country within a few months due to breaches in infection control. These outbreaks were terminated by increased awareness and reporting and by scrupulous attention to infection-control measures. The 2015 MERS outbreak in South Korea was halted by placing ~17,000 individuals under quarantine. In that outbreak, 36 patients succumbed to the infection, with a case fatality rate of 19%, substantially lower than the case fatality rate of 42% reported in Saudi Arabia (11). This lower case fatality rate likely reflects careful screening to identify all infected patients, including those with subclinical disease. This outbreak was alarming because it was the first time MERS-CoV infected a large number of patients outside of the Middle East.

As described below, camels are the probable source for zoonotic transmission of the virus, but the source for infection in many patients with primary (i.e., not associated with MERS patient contact) disease remains undetermined. Several epidemiologic studies demonstrated that secondary cases occur in healthcare settings and, to a lesser extent, in households (12). Human-to-human spread requires close contact and is likely through large droplets, although aerosol or fomite transmission has not been ruled out. MERS-CoV's ability to persist in the environment for up to 24 h may also be a source for human infection (13). Sequences from MERS-CoV isolated from single outbreaks are very similar, if not identical, an observation consistent with interhuman transmission (14). Sequence analyses of virus isolated from patients who were infected at different times and places revealed little evidence for directed mutation, suggesting that the virus is not

adapting to human populations as SARS-CoV did (14). MERS-CoV is transmitted inefficiently among humans. For example, one study found that the transmission rate of infected patients to household contacts was only 4% (12, 15). Many of these household contacts were asymptomatic or had mild disease. The R_0 factor for MERS-CoV has been estimated to be less than 0.7 and likely closer to 0.5, significantly lower than an R_0 of 1, a mark of epidemic potential (16). Other studies, based on serologic measurements with extrapolation to the entire populations, suggested that roughly 45,000 people in Saudi Arabia were infected (17). Although not clinically ill, these individuals may play a role in spreading MERS-CoV.

To date, almost two-thirds of all MERS cases have been males; however, males and females have similar case fatality rates (12). This sex-based difference in case numbers is believed to reflect difference in MERS-CoV exposure. Age is also a risk factor for developing severe MERS, as the average MERS patient is ~50 years old. Primary cases and secondary hospital-acquired cases tend to be older, whereas infected secondary household members and healthcare personnel are generally younger. Elderly patients have a much greater likelihood of dying from the disease, with a fatality rate of nearly 90% for patients over 80 years of age compared to ~10% for those under the age of 20 (12).

Perhaps the most consistently described risk factor for MERS disease is the presence of underlying comorbidities such as diabetes (68%), chronic renal disease (49%), obesity, hypertension (34%), chronic cardiac diseases (28%), and lung diseases such as asthma and chronic obstructive pulmonary disease (12, 18). In total, ~75% of all documented cases occurred in patients with comorbidities.

PATHOGENESIS

MERS pathogenesis begins with entry of virus via the respiratory tract, where the spike (S) protein interacts with its cellular receptor DPP4. DPP4 is expressed in the respiratory tract on type I and II pneumocytes, nonciliated bronchial epithelial cells, endothelial cells, and some hematopoietic cells (6, 19). DPP4 is less abundant on the surface of upper-airway (nasal cavity to conducting airways) epithelia but is highly expressed on the epithelial cells of distal airways and alveoli (20). Relatively low abundance of DPP4 in the upper respiratory tract may limit human-to-human transmission. DPP4 is also widely expressed on the epithelial cells of several other organs and tissues such as kidneys, intestine, liver, thymus, and bone marrow (21). Immunohistochemical examination of lungs from patients with chronic lung disease, such as chronic obstructive pulmonary disease, revealed increased DPP4 expression on alveolar epithelia (type I and II cells) and alveolar macrophages compared to controls (19). These findings suggest that preexisting pulmonary disease results in augmented DPP4 expression, which may predispose individuals to more severe MERS.

Lack of patient autopsy or surgical pathology samples from the Middle East outbreaks or the Korean outbreak has limited studies of MERS-CoV pathogenesis. So far, understanding of MERS-CoV pathogenesis is based on in vitro studies, infection of human lung explants and laboratory animals, and description of a single autopsy (22). In vitro studies revealed robust MERS-CoV replication in nondifferentiated and differentiated human primary epithelial cells and several tissue culture cell lines (23–25). MERS-CoV antigen was detected in type I and type II pneumocytes and in nonciliated and possibly ciliated bronchial and bronchiolar epithelial cells, endothelial cells, and alveolar macrophages in infected human lung explants (26, 27). Ex vivo infection of lung tissues corroborated findings observed in the single MERS autopsy case, where immunohistochemical examination of lungs revealed MERS-CoV antigen in pneumocytes (type I and II), airway epithelial cells, endothelial cells, and (rarely) macrophages (22, 26).

HOST IMMUNE RESPONSE

A rapid and well-coordinated innate immune response is the first line of defense against viral infections; dysregulated and exuberant innate immune responses may cause immunopathology. MERS-CoV infection of human epithelial cells induced significant but delayed type I, II, and III IFN responses (28). Similarly, proinflammatory cytokines and chemokines such as interleukin (IL)-1β, IL-6, and IL-8 showed delayed but marked induction upon MERS-CoV infection (29). In vitro studies show that in addition to infecting epithelial cells, MERS-CoV infects hematopoietic cells such as monocyte-macrophages, dendritic cells, and activated T cells (30–32). This is in contrast to SARS-CoV, which abortively infects monocyte-macrophages and dendritic cells (33, 34). Similar to the situation in epithelial cells, MERS-CoV infection of human peripheral blood monocyte–derived macrophages and dendritic cells induced delayed but elevated levels of proinflammatory cytokines and chemokines such as CCL-2, CCL-3, RANTES, IL-2, and IL-8 (29, 31). However, induction of type I IFN by monocyte-macrophages and dendritic cells was not substantial except for plasmacytoid dendritic cells, which produced high amounts of type I and III IFN upon infection (30, 31, 35). MERS-CoV infection of activated T cells induced apoptosis via both intrinsic and extrinsic pathways (32), which could contribute to the lymphopenia observed in MERS patients with poor outcomes. Limited data available from MERS patients with poor outcome show elevated CXCL-10, IL-17, and IL-23 expression, with a paucity of IFN-α and IFN-γ expression (36). At this point, it is difficult to determine factors contributing to protective versus pathologic immune responses because of insufficient clinical data and limited autopsy samples.

CLINICAL FEATURES IN HUMANS

MERS-CoV infection causes a wide range of clinical manifestations in humans. The infection can be asymptomatic, and clinical symptoms of MERS disease range from mild respiratory illness to severe acute pneumonia, which rapidly progresses to acute lung injury and acute respiratory distress syndrome, multi-organ failure, and death (18, 37–41).

Incubation Period

Studies of human-to-human MERS-CoV transmission from clusters of MERS patients revealed a median incubation period of 5–7 days, with a range of 2–14 days (18, 42). In MERS patients, the median time from the onset of illness to hospitalization is approximately four days and the median time from onset of symptoms to intensive care unit admission is approximately five days (18, 38).

Clinical Manifestations

In hospitalized patients, the most common manifestations include flu-like symptoms such as fever, sore throat, nonproductive cough, chills/rigors, chest pain, headache, myalgia, shortness of breath, and dyspnea, which rapidly progress to pneumonia in those who develop severe disease. MERS in humans often causes gastrointestinal symptoms such as abdominal pain, vomiting, and diarrhea (18, 38–41). Patients with milder disease often present with disease manifestations confined to the upper respiratory tract.

Laboratory Findings

Samples obtained from the upper respiratory tract of MERS patients showed lower virus titers and RNA copy numbers than those collected from the lower respiratory tract. In some patients,

low levels of MERS-CoV genomic RNA were detected in blood, urine, and stool (43, 44). Hematological analysis of MERS patients revealed lymphocytopenia and thrombocytopenia. Other laboratory findings include elevated creatinine, lactate dehydrogenase, and alanine and aspartate aminotransferase suggestive of renal and liver disease (18). Chest radiographic and computerized tomography findings demonstrated minor to extensive unilateral and bilateral abnormalities including enhanced bronchovascular markings, airspace opacities, patchy infiltrates, and airspace consolidations. Airspace opacities were either nodular or reticular with reticulonodular shadowing and pleural effusions (45).

Gross and Histopathological Findings

Despite numerous deaths related to MERS-CoV infection in humans in Saudi Arabia, South Korea, and other parts of the world, only one autopsy report of MERS in humans is available (22). Gross examination revealed extensive lung consolidation with generalized congestion and edema. The most prominent histological findings were exudative-type diffuse alveolar damage, necrosis of alveolar epithelial cells, hyperplasia of type II pneumocytes, sloughing of bronchiolar epithelium, alveolar edema, alveolar fibrin deposition, hyaline membrane formation, thickening of alveolar septa, and inflammatory cell infiltration (monocyte-macrophages, neutrophils, and lymphocytes). Pathologic changes were also observed in the kidney, heart, liver, bone marrow, and lymphoid organs, but it is not known whether these findings directly reflected virus infection or occurred nonspecifically in the context of terminal disease.

THE CAMEL CONNECTION

MERS-CoV is most closely related to the *Tylonycteris* and *Pipistrellus* bat CoVs HKU4 and HKU5, respectively, suggesting that bats could have been the ultimate source for the virus. In support of this, a single CoV isolate from an adult female *Neormocia* cf. *zuluensis* bat from South Africa was found to harbor a β-CoV that was highly related to MERS-CoV. This virus was shown to root the phylogenetic tree of MERS-CoV (46), suggesting that MERS-CoV distantly originated in African bats.

Bats were considered an unlikely source of repeated direct transmission to humans because of the lack of contact between bats and humans. Thus, many other animals found in the Arabian Peninsula, such as goats, horses, chickens, sheep, poultry, and camels, were tested for MERS-CoV seropositivity. Only dromedary camels were found to be positive for anti-MERS-CoV antibody. Dromedary camels are present throughout Africa and the Arabian Peninsula, and camels at these sites were shown to be seropositive with rates as high as 80% in some populations (reviewed in 47). Surprisingly, serum samples from as far back as 1982 in Africa and 1992 in Saudi Arabia were positive for MERS-CoV antibodies. This suggests that MERS-CoV has infected camels for an extended period of time and raises the question of why MERS was not detected in patients in Saudi Arabia before 2012. Of note, camels from Australia, Canada, the United States, Germany, the Netherlands, and Japan are seronegative for MERS-CoV (47). These data all point to a likely transmission of MERS-CoV from bats to camels in Africa many years ago with subsequent spread to the Middle East. Although the majority of primary human cases are not associated with camel exposure, transmission from camels has been documented in several cases. Sequence analysis of virus collected from two humans and at least three camels at a barn in Qatar found them to be infected with the same strain of virus. Other studies found that a prominent risk factor for MERS disease was contact with camels, and in Saudi Arabia and Qatar, those who worked with camels were much more likely to be seropositive for MERS-CoV (~3.6–6.4%) than the general

population (0.15%) (17; reviewed in 48). Another study reported that camels in 2014–2015 in Saudi Arabia harbored at least five different lineages of MERS-CoVs, as well as β-CoV 1-HKU23 and camelid CoVs related to the human CoV 229E (8). Some of the MERS-CoV strains were recombinants between different camel isolates. These camel isolates were very similar to those circulating in human populations at that time, providing strong support for the link between camel and human infection.

Although camels are clearly the primary zoonotic intermediate for MERS-CoV infection, the route of transmission into the human population is not entirely clear and is likely multifactorial. In contrast to humans, camels transmit the virus to each other relatively easily because DPP4 is highly expressed in their upper respiratory tract (20). The highest levels of virus are found in nasal discharge from camels (49), suggesting that direct contact with a sick animal may lead to human transmission (48). Although there is an increased rate of seropositivity for MERS-CoV among slaughterhouse workers (17), smaller prospective studies found no evidence for MERS-CoV infection for others with occupational exposure (50), indicating that transmission from camels to humans is inefficient. In addition to respiratory spread, the virus may also be transmitted through contaminated camel milk and even meat. Camel milk is not pasteurized in many parts of the Middle East, and MERS-CoV RNA has been detected in raw milk collected in a marketplace in Qatar (51). Virus may be naturally present in milk or meat or may be introduced by poor hygienic conditions. Prevention of camel-to-human transmission will require extensive implementation of precautionary measures such as the use of personal protective equipment as well as increased awareness of the likelihood of infection. Because camels are important in many aspects of Arab culture, eliminating the threat of MERS-CoV will be difficult and will require changing local customs.

WHAT IS BEING DONE TO COMBAT THE VIRUS?

Diagnosis

Patients with MERS-CoV present with clinical manifestations similar to those of other respiratory virus infections, making it difficult to diagnose MERS on clinical grounds. Formal guidelines have been established to diagnose MERS. During the acute phase of the illness, MERS-CoV may be detected in respiratory tract specimens by detection of either infectious virus or viral RNA. Diagnosis of MERS-CoV infection by viral RNA detection requires two positive qRT-PCR tests on two different specific genomic segments or a single positive qRT-PCR result with a sequence of another positive genomic segment. qRT-PCR detection of MERS-CoV genomic mRNA in upper and lower airway samples by targeting a gene segment upstream of E gene (UpE) and in ORF1ab is recommended (52). Efforts should be made to collect samples from the lower respiratory tract because viral loads are higher at this site (20). MERS can also be diagnosed by detecting virus-specific antibodies in serum samples collected at least 2–3 weeks after disease onset. A positive enzyme-linked immunosorbent assay (ELISA) followed by a positive immunofluorescence and/or microneutralization test is required for diagnosis (53). MERS-CoV antibody titers appear to wane with time, especially in patients with mild disease (54).

Vaccine Development

No MERS-CoV-specific vaccines are currently approved for use in humans. Inactivated virus vaccines, live attenuated virus vaccines, viral vector vaccines, subunit vaccines, and DNA vaccines have all been developed, but none have reached clinical trials (reviewed in 55, 56). Live attenuated

vaccines induce both antibody and T cell responses, which tend to persist for long times, but these vaccines are not likely to be clinically useful because of the concern that they could recombine with circulating CoV, generating new pathogenic CoV strains. Vaccinating camels is also a potential strategy to prevent MERS-CoV transmission to humans (57).

Therapies

Currently there is no specific approved therapeutic agent available to treat MERS. Supportive care is the mainstay of treatment. Because type I IFNs effectively inhibit MERS-CoV replication in vitro (23, 58), the timely administration of IFNα2 with another agent such as ribavirin may reduce lung viral load and diminish lung injury. Early (8 h post infection) administration of IFNα2 and ribavirin reduced MERS-CoV titers and lung immunopathology in experimentally infected rhesus macaques (59). In one clinical study, administration of IFNα2 and ribavirin showed enhanced survival in critically ill patients at 14 days but not at 28 days (60). However, in another study, late administration of IFNα2 and ribavirin in critically ill patients had no effect on mortality (61). Early administration, which is critical for therapeutic efficacy, is difficult to achieve in a clinical setting, probably explaining the disparity in results.

Passive immunotherapy with convalescent patient plasma or MERS-CoV-specific antibodies represents a promising approach to treat MERS patients (62). Plasma from MERS survivors with high titers of neutralizing antibodies could be used for passive immunotherapy, although this approach is hindered by the lack of MERS survivors with high-titer antibodies. Substantial progress has been made in producing neutralizing antibodies specific to MERS-CoV. In one study, investigators isolated a potent MERS-CoV neutralizing antibody from memory B cells of a MERS patient and showed that treatment with this antibody inhibited MERS-CoV replication in a mouse model (63). Similarly, MERS-CoV neutralizing antibodies developed using naïve human antibody-phage display libraries effectively inhibited MERS-CoV replication and reduced lung pathology in MERS-CoV-challenged rhesus macaques (64, 65). In another approach, polyclonal antibodies produced from transchromosomic bovines effectively inhibited MERS-CoV replication both in vitro and in vivo in a mouse model (66). All of these antibodies target the receptor-binding domain of the MERS-CoV S protein. Use of neutralizing antibodies for therapeutic purposes relies on rapid identification of patients and administration soon after disease onset. These antibodies may be most useful for prophylaxis in high-risk hospital and healthcare settings.

In addition to IFN and neutralizing antibodies, several antiviral drugs are under investigation for clinical use (67, 68). MERS-CoV-specific peptide fusion inhibitors function by efficiently inhibiting virus entry and replication in vitro and were shown to reduce lung viral loads when used as prophylactic or therapeutic agents in mouse and macaque models (69, 70). Drugs targeting viral enzymes (papain-like protease and 3C-like protease) inhibit CoV replication and may be useful for reducing viral loads in patients. Lopinavir, a drug with anti-HIV protease activity, has been used in SARS and MERS patients, although efficacy has not been proven. Additionally, several antiviral drugs, such as chloroquine, chlorpromazine, mycophenolic acid, and nitazoxanide, have been identified in broad drug screens, but these drugs need further investigation before they can be used in MERS patients.

Animal Models of Infection

Suitable animal models are necessary to screen antiviral therapeutics and vaccines and to study pathogenesis. Small laboratory animals, particularly rodents, do not support MERS-CoV replication because MERS-CoV S protein cannot bind to DPP4 orthologs in these animals. The first

MERS-CoV mouse model was generated by sensitizing mice to infection by intranasal transduction of human DPP4 (71). These transduced mice developed mild to moderate pneumonia after MERS-CoV challenge. Subsequently, several human DPP4 transgenic mouse models were developed. These mice generally developed a fatal encephalitis (72, 73), providing a platform for stringent evaluation of vaccines and anti-MERS-CoV drugs. MERS-CoV-challenged rabbits displayed subclinical disease (74, 75), and rhesus macaques displayed mild to moderate respiratory disease. Marmosets are also susceptible to infection and have been reported to develop severe disease (76), although these results are controversial (77). The basis for these differences is not clear, but they may reflect differences in virus stocks, routes of administration, and sources and ages of marmosets. Experimentally infected camels develop mild rhinitis without overt pneumonia and are useful for studies of camel-to-camel and camel-to-human transmission (49).

Control of Transmission

MERS-CoV transmission in healthcare settings accounts for many MERS cases, although it has diminished as infection-control measures have been rigorously applied (78, 79). Because the early signs of MERS-CoV resemble those of other respiratory infections, healthcare workers in the Middle East and elsewhere should follow standard procedure consistently in all patients. Droplet and contact precautions should be practiced when treating probable or confirmed cases of MERS-CoV infection. Given that people with diabetes, renal failure, chronic lung disease, or compromised immune systems are at high risk of developing severe disease after MERS-CoV infection, these people should avoid close contact with camels when visiting farms or markets where the virus is known to be potentially circulating. Following general hygiene measures, such as regular hand washing after touching animals and avoiding contact with sick animals, will reduce the risk of contracting MERS-CoV. As stated above, other hygiene practices should be adopted, such as avoiding raw camel milk or camel urine (used medicinally) and eating only well-cooked meat. In combination, these and other World Health Organization recommendations appear to be having a positive effect, as the number of secondary cases of MERS in Saudi Arabia is dropping (**Figure 1**).

CONCLUSIONS AND FUTURE DIRECTIONS

In the years since MERS-CoV appeared as a novel virus with potential epidemic threat, several advances have been made and many questions answered. For instance, we now are reasonably certain that the zoonotic source of the virus is the dromedary camel. However, many questions and issues remain to be addressed.

In order to prevent future outbreaks, it is critical to continue to increase surveillance for MERS. It is important to closely monitor circulating MERS-CoV for mutations that enhance its transmission or virulence: CoVs are known to have high rates of recombination (4), and thus MERS could adapt to become more transmissible in humans. Furthermore, physicians must be aware of MERS as a possible diagnosis if a patient with a febrile respiratory disease has recently returned from the Middle East. Finally, stringent infection-control measures are critical to control the spread of this virus in healthcare settings.

As with all other CoVs, there are currently no therapeutics or vaccines available to control the infection. In order to develop therapeutics and vaccines, new small-animal models that more closely resemble lethal human disease are required. Using these models, we will be able to better evaluate repurposed and new drugs, vaccines, and antibodies for their efficacy. Determining novel host and viral determinants of pathogenesis will help to identify additional drug targets as well as aid in vaccine development.

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The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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