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REVIEW

What Have We Learned About Middle East Respiratory Syndrome Coronavirus Emergence in Humans? A Systematic Literature Review

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Abstract

Background: Middle East respiratory syndrome coronavirus (MERS-CoV) was first identified in humans in 2012. A systematic literature review was conducted to synthesize current knowledge and identify critical knowledge gaps.
Materials and Methods: We conducted a systematic review on MERS-CoV using PRISMA guidelines. We identified 407 relevant, peer-reviewed publications and selected 208 of these based on their contributions to four key areas: virology; clinical characteristics, outcomes, therapeutic and preventive options; epidemiology and transmission; and animal interface and the search for natural hosts of MERS-CoV.
Results: Dipeptidyl peptidase 4 (DPP4/CD26) was identified as the human receptor for MERS-CoV, and a variety of molecular and serological assays developed. Dromedary camels remain the only documented zoonotic source of human infection, but MERS-like CoVs have been detected in bat species globally, as well as in dromedary camels throughout the Middle East and Africa. However, despite evidence of camel-to-human MERS-CoV transmission and cases apparently related to camel contact, the source of many primary cases remains unknown. There have been sustained health care-associated human outbreaks in Saudi Arabia and South Korea, the latter originating from one traveler returning from the Middle East. Transmission mechanisms are poorly understood; for health care, this may include environmental contamination. Various potential therapeutics have been identified, but not yet evaluated in human clinical trials. At least one candidate vaccine has progressed to Phase I trials.
Conclusions: There has been substantial MERS-CoV research since 2012, but significant knowledge gaps persist, especially in epidemiology and natural history of the infection. There have been few rigorous studies of baseline prevalence, transmission, and spectrum of disease. Terms such as ''camel exposure'' and the epidemiological relationships of cases should be clearly defined and standardized. We strongly recommend a shared and accessible registry or database. Coronaviruses will likely continue to emerge, arguing for a unified ''One Health'' approach.

Keywords: MERS, MERS-CoV, coronaviruses, zoonotic disease, severe acute respiratory infection (SARI), MERS epidemiology

Introduction

September 2012 saw the identification of a novel human coronavirus, now known as Middle East respiratory syndrome coronavirus (MERS-CoV) (ProMED-mail 2012, Zaki et al. 2012). MERS-CoV is a beta-coronavirus distinct from but genetically related to the SARS (severe acute respiratory syndrome) coronavirus (Hilgenfeld and Peiris 2013, de Wit et al. 2016).

As MERS was identified a few years after the 2003 SARS outbreak, which spread across continents and raised pandemic concerns, there has been continuing concern about the

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pandemic potential of MERS-CoV (Hilgenfeld and Peiris 2013, de Wit et al. 2016). To assess and anticipate potential epidemic spread of MERS-CoV, it is essential to better understand the virology; human clinical characteristics, possible therapeutic and preventive options; epidemiology and transmission; and animal interfaces and possible origins and natural hosts.

MERS was first identified in a patient with lower respiratory disease by a physician in Saudi Arabia, and subsequently, the virus was identified and characterized from this patient's sputum sample by researchers in Saudi Arabia and at Erasmus Medical Center in the Netherlands. Since then (to December 2018), 2266 laboratory-confirmed MERS-CoV cases and 804 deaths across 27 countries (35.5% crude case

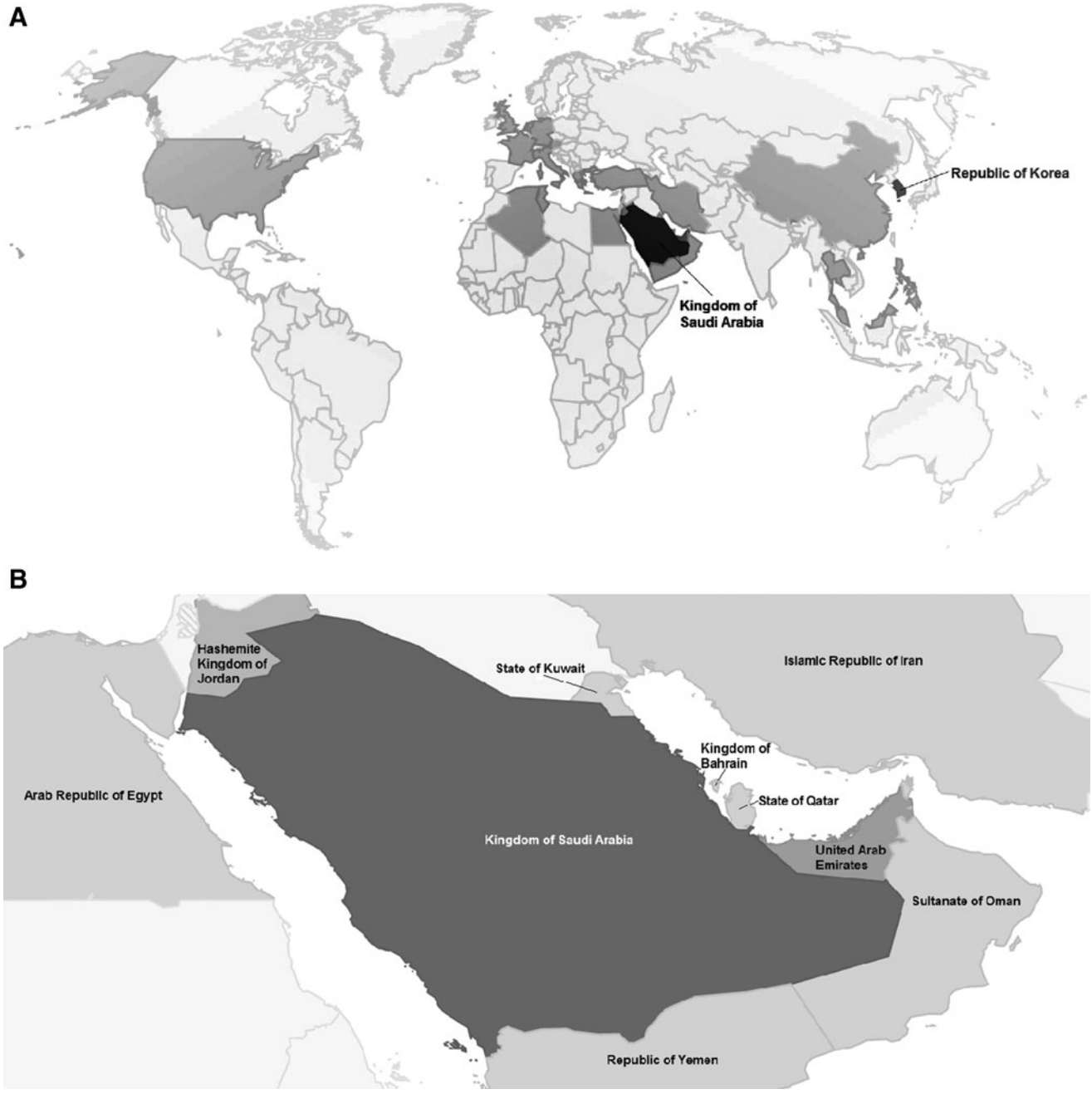

FIG. 1. **(A)** Map of countries having at least one laboratory-confirmed human MERS-CoV case, 2012–2016. *Darker shades* indicate greater numbers of laboratory-confirmed cases. **(B)** *Inset* of Fig. 1A showing Gulf countries having at least one laboratory-confirmed human MERS-CoV case. *Darker shades* indicate greater numbers of laboratory-confirmed cases. Data Source: World Health Organization (www.who.int/emergencies/mers-cov/en *and* www.who.int/emergencies/mers-cov/risk-assessment-july-2017.pdf). This map was generated using R software (*R Foundation* for Statistical Computing, Vienna, Austria) and the ''googleVis'' package (Gesmann et al. 2017). MERS-CoV, Middle East respiratory syndrome coronavirus.

fatality rate [CFR]) have been reported to the WHO (Fig. 1), with the majority of cases (1888) and deaths (730) reported from Saudi Arabia (World Health Organization 2018a, World Health Organization/EMRO 2018). Cases continue to occur (World Health Organization/EMRO 2018).

Although the first known MERS-CoV cases were from Jordan (confirmed retrospectively, and the source is still unknown) (Hijawi et al. 2013), about 80% of MERS-CoV cases originate from or passed through Saudi Arabia. The infection is likely zoonotic; although origins and transmission are poorly understood, the dromedary camel is the one documented source of human zoonotic infection (Memish et al. 2014e).

A systematic review of MERS-CoV research was conducted to survey our current understanding of MERS-CoV and to identify research gaps in four major areas: (1) virology; (2) clinical characteristics, outcomes, and therapeutic and preventive options; (3) epidemiology and transmission; and (4) animal interface and the search for natural hosts of MERS-CoV.

Materials and Methods

We conducted a systematic literature review, using Embase, Google Scholar, MEDLINE/PubMed, supplemented by Thomson-Reuters ''Web of Science''™ (all databases), to identify peer-reviewed published articles on MERS-CoV available by July 14, 2017. All searches were for articles published from 2012 onward, since MERS was first identified in 2012. The following search terms were used in all the databases for matches in title only (Google Scholar), title or abstract (Embase and MEDLINE/PubMed), or topic (''Web of Science''): ''novel coronavirus,'' ''novel coronavirus EMC,'' ''novel coronavirus Erasmus,'' ''hCoV-EMC,'' ''MERS-CoV'' (a PubMed ''MeSH'' term), ''MERS coronavirus,'' ''Middle East Respiratory Syndrome,'' and ''Middle East Respiratory Syndrome Coronavirus'' (a PubMed MeSH term).

We reviewed the titles and abstracts of all resulting citations to identify relevant articles for this systematic review, following PRISMA guidelines (Fig. 2) (Moher et al. 2009). For all nonduplicate articles, excluding opinion and editorial pieces, on MERS-CoV or a related topic, we retrieved the full-text version and indexed the citation. Inclusion criteria were peer-reviewed primary research articles about MERS-CoV published between 2012 and mid-July 2017 (inclusive, with periodic updates to 2018) and adding unique information about MERS-CoV to the knowledge base within at least one of the four key themes: (1) virology; (2) clinical characteristics, outcomes, and therapeutic and preventive options; (3) epidemiology and transmission; and (4) animal interface and search for natural hosts of MERS-CoV.

Only English language publications (or with an English-language abstract available) were included. Of the 3364 titles retrieved, 407 were unique (nonduplicate), scientific research works relevant to MERS-CoV, and of these, 208 were originally included in the review based on the inclusion criteria (some interim updates have been made during article preparation).

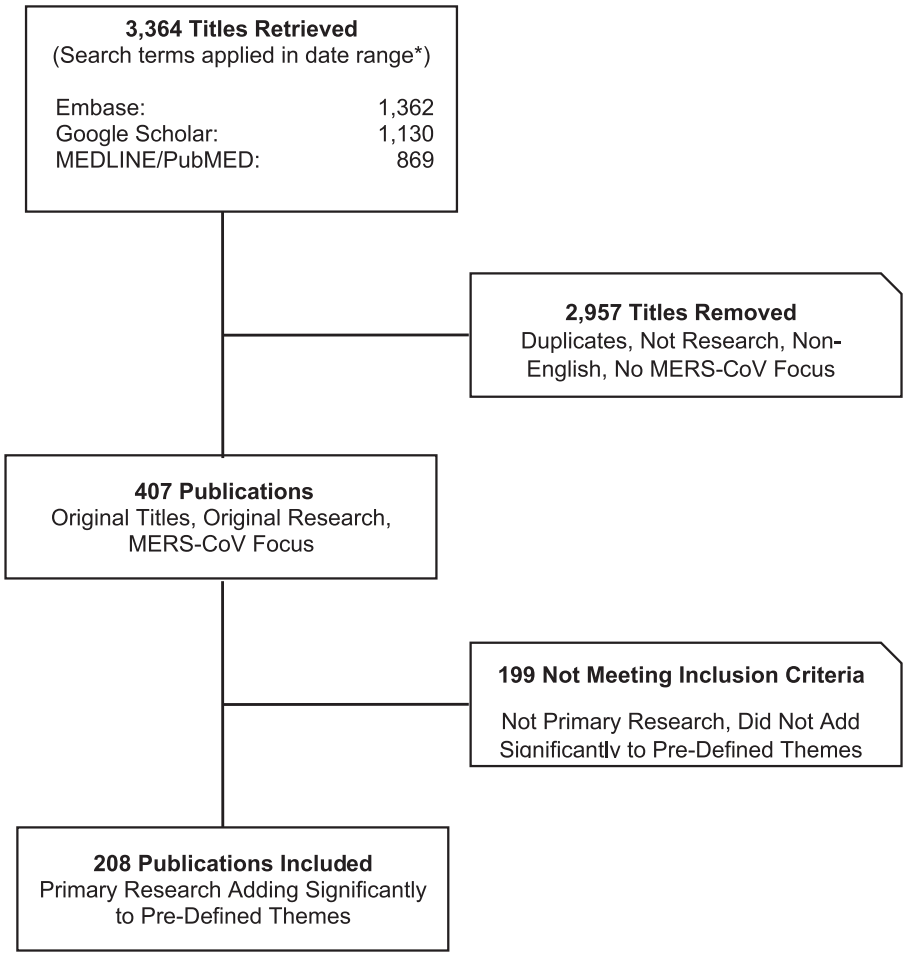

FIG. 2. Study selection diagram for systematic literature review on MERS-CoV (*For complete search terms and applicable date ranges, see the Materials and Methods section.).

Results

Virology

The pathogen causing MERS has been identified as a coronavirus, now named MERS-CoV, classified in the family *Coronaviridae* (subfamily *Coronavirinae*) (ICTV 2016). Coronaviruses are a family of enveloped, approximately spherical, positive-sense, single-stranded RNA viruses with genome length 26–32 kilobases (kb). Of the four described coronavirus genera, alpha- and beta-coronaviruses are believed to originate from bat species, whereas gamma- and delta-coronaviruses are believed to be of avian origin (Woo et al. 2012).

Within the beta-coronavirus genus, four lineages have been described: A, B (which includes SARS-CoV), C, and D. MERS-CoV is a beta-coronavirus of lineage C (Cotten et al. 2013), the first of this lineage known to infect humans. There are two main recognized clades (genetic sublineages) of MERS-CoV, clade A, which includes the earliest known MERS-CoV strains (EMC/2012 and Jordan-N3/2012), and clade B, which includes newer cases (Cotten et al. 2013), although additional genotypes are revealed by genomic sequencing (Chu et al. 2015), suggesting the existence of additional clades.

The genome of MERS-CoV is ~30 kb and encodes 10 proteins: 2 replicase polyproteins (ORFs 1a and 1b), including the RNA-dependent RNA polymerase (RdRp); 4 structural proteins: envelope (E), M (membrane), N (nucleocapsid), and S (surface spike glycoprotein), and 4 nonstructural proteins (ORFs 3, 4a, 4b, and 5) (Kim et al. 2015; review: de Wit et al. 2016).

Particular attention has understandably focused on the S (spike) surface protein, which confers receptor specificity (Qian et al. 2013) and is considered the major determinant of coronavirus host range (Graham and Baric 2010, Hulswit et al. 2016). The main route of entry for MERS-CoV is dipeptidyl peptidase 4 (DPP4, also known as CD26) on the host cell surface (Raj et al. 2013), which is utilized by the receptor-binding domain of the MERS-CoV spike protein (Chen et al. 2013, Raj et al. 2013, 2014).

The virus readily replicates in A549 (human lung), Huh-7 (human liver), and the widely used Vero E6 (African green monkey kidney) cell lines (Raj et al. 2013, Eckerle et al. 2014), among others. Culture, *in vitro* and *ex vivo*, has also been used to help determine cell tropism and identify potential natural hosts of the virus. MERS-CoV can infect a variety of human cell types and tissues in culture, including macrophages, fibroblasts, and endothelial cells (Scobey et al. 2013, Tao et al. 2013, Hin et al. 2016). In an *ex vivo* study using human lung explants, MERS-CoV infected both alveolar epithelial cells and macrophages (Type II pneumocytes), with resulting alveolar damage (Hocke et al. 2013).

Interestingly, although kidney failure is frequently described in fatal cases and the virus grows well in a number of kidney and liver cell lines, in the one autopsy report that has been published, viral antigen was detected by immunohistochemical staining only in pneumocytes and lung interstitial epithelial cells, and not in the kidney or other extrapulmonary sites (Ng et al. 2016).

Replication was demonstrated in goat, camel (Eckerle et al. 2014), and equid origin cell lines (Meyer et al. 2015), but was not detected in cattle, sheep, or rodent cell lines tested (Eckerle et al. 2014).

Given the interest in bats as a natural host for many coronaviruses, especially since SARS, and the currently unknown origin of MERS-CoV, several bat cell lines have been tested to determine if they could support MERS-CoV replication (Müller et al. 2012, Cai et al. 2014, Eckerle et al. 2014).

As a broad generalization, the virus was reported to replicate well (roughly comparable with growth in Vero E6 cells) in kidney and lung cells from *Rousettus aegyptiacus* and other Old World pteropid (fruit) bats (Müller et al. 2012, Cai et al. 2014), to a lesser degree in cell lines from Old World insectivorous bats (Müller et al. 2012, Eckerle et al. 2014), and very little, if at all, in lung cells from several New World bats (Müller et al. 2012, Cai et al. 2014). However, as a caveat, no replication was found in the *Rousettus aegyptiacus* embryo cell lines tested (Cai et al. 2014).

Adaptation to cells from other bat species that are normally refractory to infection because of having a somewhat different DPP4 protein was recently demonstrated *in vitro* (Letko et al. 2018), resulting from selection of spike protein mutations that permitted binding to the new DPP4. A similar change, from bat to human-type receptor, was observed with SARS in 2003 (Letko et al. 2018).

Animal models for MERS-CoV include transgenic mice expressing human DPP4 (Cockrell et al. 2014, Zhao et al. 2014, Agrawal et al. 2015), which develop respiratory disease and are the most widely used model; marmosets (Falzarano et al. 2014); rhesus macaques (de Wit et al. 2013, Munster et al. 2013, Yao et al. 2014); camels (Barlan et al. 2014); horses (Barlan et al. 2014), and alpacas (Adney et al. 2016). However, there is no animal model that clearly mimics human clinical MERS (review: Baseler et al. 2016).

Diagnostic assays. The main laboratory assays for MERS-CoV are molecular tests to detect viral RNA, and serology (for prior infection) (CDC 2014, World Health Organization 2018b).

Reverse transcription PCR either real time or conventional, is now standard. For diagnostic screening, PCR primer sets to regions upstream of the E gene (''up-E'') are most frequently used, with ORF1a or ORF1b for confirmation (Corman et al. 2012a, 2012b). Sensitivity was reported as ~3.4 viral gene copies/25 μL reaction for up-E and ~64 copies for ORF1b, with specificity approaching 100% using a test panel of other known coronaviruses and clinical respiratory samples (Corman et al. 2012a). ORF1a PCR was reported to have comparable sensitivity and specificity to up-E (Corman et al. 2012b). Commercial kits are available, with comparable results reported (Corman et al. 2014c, Seong et al. 2016, Mohamed et al. 2017).

For sequencing, tests have been developed that may be better suited for strain differentiation, targeting regions of the RdRp (RNA polymerase) or N (nucleocapsid) genes (Corman et al. 2012b); there are a number of publications reporting on their use (Corman et al. 2012b; CDC 2014, Lu et al. 2014).

Another PCR test, targeting the S (spike) region, was developed to monitor circulation of MERS-CoV variants (Abd et al. 2013, Smits et al. 2015). Other types of nucleic acid tests have also been used (Shirato et al. 2014), as has immunohistochemistry (Ng et al. 2016).

Serologic samples are usually screened using enzyme-linked immunosorbent assay (ELISA) (Reusken et al. 2013a). If the sample is ELISA positive, CDC and other agencies formerly recommended confirmatory testing, first

by immunofluorescence assay (IFA) and then by the gold standard plaque-reduction neutralization test or microneutralization (CDC 2014), but now recommend going directly to microneutralization assay (CDC 2014, revised). Other serological tests such as pseudoparticle neutralization (Perera et al. 2013) and array-based serology (Reusken et al. 2013a) have also been developed.

Unfortunately, there are pitfalls in serology, including cross-reactivity and false negatives. In 2014, CDC preliminarily reported a MERS-CoV case with a positive ELISA and IFA, but later retracted the case report due to a negative microneutralization result (Breakwell et al. 2015). Consequently, CDC no longer recommends IFA but instead now recommends using two different ELISA tests, with microneutralization for confirmation (CDC 2014, revised). Conversely, low or waning antibody response after infection, which would yield false negatives, has also been reported (Alshukairi et al. 2016, Choe et al. 2017). False negatives are further discussed below in the section on Host Response.

Clinical characteristics and outcomes

Clinical findings have been described and reviewed in detail (Assiri et al. 2013a, Saad et al. 2014, Rasmussen et al. 2015, World Health Organization 2015). The incubation period is ~5–7 days (in some cases up to 12 days) (Assiri et al. 2013a, 2013b). Fever, cough, shortness of breath, and pneumonia (with abnormal chest radiography) are the most frequently noted signs; myalgia, diarrhea, vomiting, abdominal pain, chills or rigors, or malaise are also seen (Assiri et al. 2013a, Drosten et al. 2013, Eckerle et al. 2013, Guery et al. 2013, Ajlan et al. 2014, Arabi et al. 2014, Faure et al. 2014, Kapoor et al. 2014, Scheuplein et al. 2015, Hunter et al. 2016). Renal failure or pulmonary failure and shock were commonly described in severe and fatal cases. Overall CFR is ~35.5% (World Health Organization 2018a).

Viral excretion from the respiratory tract has been documented through the first month of illness (Memish et al. 2014d, Poissy et al. 2014, Spanakis et al. 2014), with greater viral loads detected in lower respiratory tract specimens compared with upper respiratory tract (Drosten et al. 2013, Guery et al. 2013, Kapoor et al. 2014). Viral excretion for short periods was reported in urine and stool, although viral loads were low (Drosten et al. 2013). There was at least one report that MERS-CoV secondary cases (individuals infected by a primary case) clear infection earlier than primary cases (Memish et al. 2014d).

Disease outcomes differed by age and comorbidities (Assiri et al. 2013a, 2013b, Khalid et al. 2014, Saad et al. 2014, Alsahafi and Cheng 2016). Most cases in Saudi Arabia have occurred among men, ages 45 or older, and those living in areas of lower relative humidity and high temperature (Alghamdi et al. 2014). A review of 939 cases in Saudi Arabia found that CFR increases with age, from 12.5% among those 19 years or younger to 86.2% among those 80 years or older (Alsahafi and Cheng 2016). Mortality was more frequent and rapid in individuals with comorbidities such as diabetes, chronic renal disease, and, in one study, higher body mass index (Assiri et al. 2013a, 2013b, Al-Tawfiq et al. 2014, Khalid et al. 2014, Saad et al. 2014, Alsahafi and Cheng 2016). More severe disease has been associated with higher viral load (Feikin et al. 2015).

There are a handful of case reports on MERS outcomes in other vulnerable populations, including three cases in pregnant women and one in an HIV-positive individual.

In the three documented cases of pregnant women with MERS-CoV infection, one woman in her second trimester of pregnancy (~5 months) experienced a stillbirth; the mother survived (Payne et al. 2014). The two other women were reported to be in their third trimester (32 weeks) when they presented with MERS. A healthy infant was delivered in each of these cases, although one mother died despite interferon (IFN) treatment (Malik et al. 2016), and one recovered despite the severity of her symptoms (Alserehi et al. 2016). Both were apparently healthy before infection and in their 30s. It is therefore possible that infection during the third trimester may be associated with better fetal outcomes, while other factors may be more critical for maternal outcome, but the numbers are too small to generalize.

There has been at least one published case of an individual with HIV/AIDS acquiring MERS-CoV (Shalhoub et al. 2015). This patient was probably infected with MERS-CoV during a hospital stay and subsequently shed virus for 38 days. The patient recovered after treatment (Shalhoub et al. 2015).

Host response

There have been a number of studies on immune function (Corman et al. 2016, Zhao et al. 2017). Neutralizing antibodies were detected in many patients, but several studies suggested that neutralizing antibodies induced during infection did not appear to be protective (Corman et al. 2016, Zhao et al. 2017), and it has been suggested that higher antibody titers may be more closely correlated with greater viral load and consequently worse prognosis (Zhao et al. 2017).

Kinetics of response may also be important. An antibody kinetics study with 17 patients in South Korea (from the same research group that later reported waning antibody titers in patients over a 1-year follow-up) found that most patients produced a robust neutralizing IgG antibody response beginning at about 2 weeks and peaking by about 3 weeks; delayed response was generally correlated with a less favorable prognosis (Park et al. 2015).

Persistence of antibody generally seems to follow a similar pattern. Detectable neutralizing antibody titers (≥20) have been reported in some patients up to 34 months (Payne et al. 2016). However, results varied considerably even within this group, and most reports indicate that duration of antibody response, as well as its magnitude, seemed most closely correlated with disease severity and that antibodies could be low or even absent in mild or asymptomatic infection (Alshukairi et al. 2016, Choe et al. 2017). These reports of low or waning antibody titers, especially in asymptomatic or mildly symptomatic individuals, may make serology problematic as a marker of population prevalence.

There is evidence that innate immunity, including IFNs and cytokines, and cellular immunity by $CD8^+$ (presumably ''killer'') T cells may play important roles in host defense and recovery (Faure et al. 2014, Zhao et al. 2017). Zhao et al. (2017) compared the role of antibodies and T cells in human MERS cases, and found that survivors mounted a vigorous $CD8^+$ T cell response even in the absence of a detectable antibody response.

Macrophages also appear to play an important role, but there are limited and somewhat ambiguous data from the mouse model (Coleman et al. 2017), human cells (Zhou et al. 2014), and patients (Faure et al. 2014). With a number of viruses, it is not unusual for resting macrophages to be permissive for replication but for macrophages to show antiviral activity after activation (such as by IFN-γ) (Morse and Morahan 1981). Dendritic cells have been reported to produce IFN in response to infection (Scheuplein et al. 2015).

One challenge to overcome is the effect of the virus on host defenses. A caveat is that much of this research (although not all) has been done *in vitro* and may not necessarily be comparable with the immunological results described above in patients. MERS-CoV has been reported to inhibit host innate immunity (Lau et al. 2013). Impaired IFN and cytokine responses may mediate some of these effects, based on assays on cells from MERS patients (Faure et al. 2014, Scheuplein et al. 2015), although the numbers of patients were small. *In vitro* studies have shown that MERS-CoV could downregulate expression of IFN-stimulated gene subsets (Yang et al. 2013), chemokines (Mielech et al. 2014), and IFN-β. Another study found that MERS-CoV may cause delayed induction of proinflammatory cytokines together with suppression of the host's innate antiviral response (Lau et al. 2013).

Virus replication in human monocyte-derived macrophages has been described, with increased expression of tumor necrosis factor α (up to a 3-fold increase over normal levels), interleukin 6 (up to almost a 6-fold increase), interleukin 12, IFN-γ, and chemokines (some at a 10-fold or more increase and even more prominently than with SARS-CoV) being reported (Zhou et al. 2014).

Therapeutic and preventive options

Currently, the main treatment strategy is symptomatic supportive care; mechanical ventilation and ICU admission are usually required for severe cases.

Published data on applied therapeutic regimens for MERS-CoV patients are scarce, but there have been efforts to develop interventions.

Two case reports have documented the use of a combination of ribavirin and IFN α2b as a therapy for MERS-CoV patients, with divergent results. In one report, this therapy was given to five patients but all five died. However, all five patients had comorbidities and were diagnosed late in the course of their illness, suggesting the therapy may have been delivered too late to prove effective (Al-Tawfiq et al. 2014). In another report, this therapy was given to one patient who eventually recovered (Khalid et al. 2015).

In a retrospective cohort study of 44 patients with severe MERS (requiring ventilatory support), treatment with ribavirin and pegylated IFN α2a (note, not 2b) appeared to increase short-term survival (14 days), although by 28 days only 10 of the patients were still living (6/20 survivors in treated group compared with 4/24 surviving in the comparison group) (Omrani et al. 2014).

Among promising studies evaluating therapies in animal models, one *in vivo* study found that the combination of ribavirin and IFN α2b therapy significantly improved outcomes among MERS-CoV-infected rhesus monkeys (Falzarano et al. 2013). In another study, using the common marmoset model, lopinavir/ritonavir and IFN α1b (separately and in combination) also proved promising (Chan et al. 2015).

Although neutralizing antibodies induced during infection did not appear to be protective during natural infection (Corman et al. 2016, Zhao et al. 2017), human convalescent sera containing neutralizing antibodies conferred dose-dependent protection in a mouse model (Zhao et al. 2017). The readily available sera from MERS-immune camels apparently were also an effective treatment for MERS-infected mice and reduced the severity of pathological changes in murine lung tissue (Zhao et al. 2015). Several monoclonal antibodies (mAbs) (Mou et al. 2013, Ohnuma et al. 2013, Du et al. 2014, Jiang et al. 2014, Tang et al. 2014, Ying et al. 2014, Houser et al. 2016) and conventional antibodies (Zhao et al. 2013) have demonstrated effective neutralization of MERS-CoV, and could serve as potential therapeutic agents, at least in the interim.

High-throughput screening and other methods have identified additional promising compounds in several classes (Chan et al. 2013, de Wilde et al. 2013, 2014, Gao et al. 2013, Shirato et al. 2013, Adedeji et al. 2014, Dyall et al. 2014, Hart et al. 2014, Lu et al. 2014, Lundin et al. 2014, Tao et al. 2014, Wrensch et al. 2014, Corti et al. 2015, Liu et al. 2015). These include inhibitors against both viral (Kilianski et al. 2013, Lei et al. 2014, Kumar et al. 2017) and host (Gierer et al. 2015) proteases needed to process the virus. However, it was reported that inhibiting proprotein convertases inhibits host cell processing of the spike protein but did not affect viral infectivity or cell-to-cell spread (Gierer et al. 2015).

Other targets studied have included viral entry inhibitors (Zhao et al. 2013, Du et al. 2015) and protein 4a, which the researchers found suppressed innate antiviral response (Siu et al. 2014).

Vaccine development. Development of a human (and possibly camel) vaccine for MERS-CoV should be a key priority, given concerns about its spread and pandemic potential, but vaccine development can be a long process that is often driven by economics (Modjarrad 2016).

Much of the focus thus far has centered on the identification of the residues within the receptor-binding domain of the spike protein, conferring the best chance of protection (Du et al. 2013a, 2013b, Lan et al. 2014, Ma et al. 2014a, 2014b). A number of other antigens, some in viral vectors, have been tested in the laboratory (Song et al. 2013, Kim et al. 2014).

A replication defective full-length cDNA clone of the MERS-CoV genome has been developed for identifying future vaccine candidates (Almazán et al. 2013). Vaccine candidates for dromedary camels have also been investigated, and have been reported to elicit protective responses (using the MERS-CoV spike protein in a poxvirus vector) (Haagmans et al. 2016).

There are special challenges to developing a MERS vaccine. The sporadic nature of human MERS-CoV infection and the difficulty of identifying suitable animal models for challenge studies make controlled trials difficult. Disease in camels usually appears mild (Adney et al. 2014), reducing the economic incentive for immunization. A camel vaccine could also be given in combination with a required vaccine, e.g., rabies, as suggested by Wirblich et al. (2017), or camelpox, as suggested by Haagmans et al. (2016).

Correlates of protection and duration of immunity are also uncertain. There are reports of strong antibody responses (Haagmans et al. 2016), but it has been suggested that the presence of neutralizing antibodies may not be protective in camels (Hemida et al. 2014) or humans (Corman et al. 2016, Zhao et al. 2017), and waning antibody titers have been reported in humans who have recovered from MERS-CoV infection (Choe et al. 2017). On the contrary, the reports of protection of mice by passive transfer of neutralizing antibodies suggest that this might be overcome by optimizing timing and dose (Zhao et al. 2017).

Research on MERS-CoV vaccine candidates is ongoing, and at least one candidate vaccine has now progressed to a Phase I human clinical trial (Modjarrad 2016, CEPI 2017). In a promising development, the recently launched Coalition for Epidemic Preparedness Innovations (CEPI) has listed MERS vaccine as one of its initial targets.

Epidemiology and transmission

The source of infection for most primary cases (the first known human case in a potential or putative chain of transmission) remains unknown. Baseline incidence and prevalence are unknown as only clinical cases or those found through contact tracing are generally identified. The few population-based studies that have been done appear to show low prevalence in the general population. A serological study of 10,009 individuals in Saudi Arabia found 15 seropositive for MERS-CoV, 7 of whom were occupationally camel-exposed (shepherds and slaughterhouse workers) (Müller et al. 2015), although the occupational samples were collected for a separate study and therefore may not be representative. In another study of 57,363 persons with suspected MERS-CoV infection tested by Saudi Arabia from April 2015 to February 2016, only 384 (0.7%) tested positive (Bin Saeed et al. 2017).

Most work has been done on symptomatic MERS patients because they are most likely to be detected and identified. Even so, one analysis suggested that at least 62% of even symptomatic cases were undetected (Cauchemez et al. 2014), and a study using data from travelers suggested that there may have been as many as 3250 severe cases from September 2012 to January 2016, about 2.3 times the number of cases confirmed (O'Hagan et al. 2016).

Determination of primary versus secondary cases is also challenging. One estimate is that 61% of MERS-CoV are primary cases, who tend to be mostly middle-aged males, compared with secondary cases who tend to be younger and distributed more evenly by sex (Gossner et al. 2016). The official overall CFR stands at ~35.5% (World Health Organization 2018a). However, it has been suggested that the CFR among primary cases, estimated to be 74%, is likely inflated due to detection bias; CFR among secondary cases is estimated to be 20% (Cauchemez et al. 2014).

The main known exposures are health care-associated infections and contact with camels. Aside from the health care setting, the mechanisms for the introduction of the virus into human populations are poorly understood. Occupational exposure risks are also poorly characterized, both in health care and for those who work with camels.

As with SARS, many cases have been health care facility-associated (Drosten et al. 2015), but the mechanism of infection is unclear for many individuals (Fanoy et al. 2014). Active case finding, typically among perceived risk groups or those hospitalized with pneumonia, has been used with varying success to identify cases (Gierer et al. 2013, Aburizaiza et al. 2014, Memish et al. 2014a).

Nosocomial transmission due to inadequate infection control is well established as a significant driver of MERS-CoV infections in humans (Al-Abdallat et al. 2014, Maltezou and Tsiodras 2014, Oboho et al. 2015, Alraddadi et al. 2016, Assiri et al. 2016, Hastings et al. 2016), notably during the spring 2014 outbreak in Saudi Arabia and the late spring 2015 outbreak in South Korea. A review (Maltezou and Tsiodras 2014) of 536 known MERS-CoV cases at the time of the review using publicly available data found 11 possible or confirmed health care-associated transmission events leading to substantial morbidity and mortality, often involving patients having comorbidities.

Infection control lapses were apparently responsible for virtually all reported health care transmission events, highlighting the need for strengthened infection control capacity worldwide. However, specific breaches in infection control were usually not identified and probably varied (Maltezou and Tsiodras 2014). Some high-risk procedures were identified, usually aerosol generating procedures, including hemodialysis and respiratory intensive care (Assiri et al. 2013b).

Secondarily infected health care workers tended to have milder symptoms and better prognoses. In the 2014 outbreak in Saudi Arabia, one study analyzed 191 symptomatic cases of MERS-CoV and found that 20.9% were health care workers (additional infected health care workers were asymptomatic, so that 30.6% of the 255 total cases analyzed were health care workers), and most patients had contact with a health care facility (Oboho et al. 2015). In a cluster of 9 MERS-CoV cases in Jordan, 6 were health care workers at the outbreak hospital, and no MERS-CoV transmission was detected at 2 transfer hospitals with adequate infection control (Al-Abdallat et al. 2014).

A health care-associated outbreak occurred in South Korea in the late spring of 2015 through July 2015, arising from one infected individual returning from the Gulf states (Cowling et al. 2015, Hui et al. 2015, Park et al. 2015). An analysis of 185 South Korean MERS-CoV cases using publicly available data delineated three generations of secondary infections (more than half of the cases were from the second generation) (Lee and Wong 2015). Overall, 154 cases were hospital-associated (Lee and Wong 2015), primarily affecting non-health care workers, spread by conditions such as close contact with the patients in crowded hospital or emergency rooms (Lee 2015b) and patients switching facilities (Lee 2015a, 2015b).

Direct contact could be inferred in only about 10% of the cases, and some authors suggested that fomite transmission could be important (Lee and Wong 2015, Seo et al. 2016, also reviewed in Otter et al. 2016). Earlier reports demonstrated that MERS-CoV is relatively stable in the environment, reported recoverable on surfaces after 48 h at 20°C and 48% relative humidity and for at least 12 h at 30°C with 30% humidity (van Doremalen et al. 2013), or in liquid at 25°C after 2 h (Leclercq et al. 2014). In a study of four laboratory-confirmed MERS-CoV patient rooms in two South Korean hospitals, MERS-CoV viral RNA was found on environmental

surfaces, including bedsheets and medical equipment, up to 5 days after a patient's last PCR-positive respiratory specimen; viable virus was also detected (Seo et al. 2016).

However, there were apparently few reports of infections in hospital laundry or maintenance workers, contrary to what would be expected for environmental transmission. It is possible that they were not identified or reported. We could find only two publications specifically mentioning infection in hospital cleaners (Hastings et al. 2016, Liu et al. 2016). Hastings et al. (2016) investigated a 2014 outbreak in King Fahd General Hospital and reported 1 MERS-CoV case among 1295 maintenance or housekeeping personnel. However, it appears that only symptomatic cases were tested, and specific details on this case were not provided.

Many reports from contact tracing identified family members, friends, coworkers, and other persons who had close contact with the patient. These include reports from Saudi Arabia (Memish et al. 2013b, Omrani et al. 2013, Drosten et al. 2014), as well as the United Kingdom (Pebody et al. 2012, Health Protection Agency (HPA) UK Novel Coronavirus Investigation Team 2013, Thomas et al. 2014), Iran (Yavarian et al. 2015), Tunisia (Abroug et al. 2014), China (Wu et al. 2015), Greece (Tsiodras et al. 2014), Germany (Buchholz et al. 2013, Reuss et al. 2014), Malaysia (Premila Devi et al. 2014), France (Mailles et al. 2013), and Italy (Puzelli et al. 2013).

Family clusters were identified in a number of these reports, but at most only a small percentage of contacts became cases, suggesting that close contact is not as important a risk factor as health care-associated transmission, and direct human-to-human transmission appears limited. Although the outbreak in South Korea also involved close contact among family members and other patients in hospital rooms, this may be more appropriately categorized as health care-associated transmission (Kang et al. 2017).

However, there is relatively little information on asymptomatic individuals, most of whom are detected by contact tracing. In one study, an asymptomatic health care worker excreted MERS-CoV for over 5 weeks (Al-Gethamy et al. 2015). In the spring 2014 outbreak in Saudi Arabia, an estimated 25.1% of laboratory-confirmed MERS-CoV was asymptomatic (Oboho et al. 2015). An analysis of 65 MERS-CoV patients in United Arab Emirates found that 35% were asymptomatic, and 1 individual yielded positive lower respiratory tract specimens for more than 2 weeks (Hosani et al. 2016). Al Hammadi et al. reported two asymptomatic men who had contact with infected camels; infection was confirmed by PCR in both men, and in all eight camels in the group (Al Hammadi et al. 2015). However, the actual frequency of asymptomatic individuals compared with symptomatic individuals is largely unknown.

Parameters for transmission dynamics are important for mathematical modeling of spread. Due to the heterogeneity in transmission, an important characteristic of infection dynamics, R_0 (the basic reproductive rate in a susceptible population), has been difficult to pinpoint. Estimates have ranged from 0.50 to 0.69 (Breban et al. 2013, Poletto et al. 2014) to between 0.8 and 1.3 (Cauchemez et al. 2014). $R_0 > 1$ is required for an outbreak to be self-sustaining (Anderson and May 1991). For specific locations, one model suggested an R_0 of 3.5–6.7 in Jeddah and 2.0–2.8 in Riyadh (Majumder et al. 2014), but these likely did not correct for effect of superspreading in health care settings (Kucharski and Althaus 2015). One mathematical model suggested the risk of secondary transmission following an imported MERS-CoV case is 22.7% (95% CI: 19.2–25.1%), with the risks of generations 2, 3, and 4 estimated to be 10.5%, 6.1%, and 3.9%, respectively (Nishiura et al. 2015).

Travel-related cases. Despite the mass gathering of individuals at the annual Hajj pilgrimage (Khan et al. 2013), to date it has not resulted in any known MERS-CoV transmission events (Barasheed et al. 2014, Benkouiten et al. 2014, Gautret et al. 2014, Memish et al. 2014b, 2014c, Aberle et al. 2015, Annan et al. 2015), confirming modeling estimates for the 2014 Hajj (Lessler et al. 2014). Two travelers returning to the Netherlands from a separate pilgrimage (Umrah) in May 2014 were found to have MERS-CoV (Kraaij-Dirkzwager et al. 2014). Many of the travel-related cases have been tabulated (Pavli et al. 2014, Sridhar et al. 2015, Carias et al. 2016). In all these cases, casual transmission (outside of family and health care settings) has not been observed.

The animal interface and search for natural and reservoir hosts of MERS-CoV

Dromedary camels are the only documented zoonotic source of human infection, and there is considerable circumstantial evidence supporting camel-to-human transmission, including evidence of camels and humans becoming infected with an identical MERS-CoV (Azhar et al. 2014, Ferguson and Kerkhove 2014, Memish et al. 2014e). Identical genomic sequences of MERS-CoV were isolated from a camel owner who died from MERS-CoV and his camel who had rhinorrhea at that time; identical MERS-CoV RNA fragments were later detected in the air at the camel barn (Azhar et al. 2014). Serology suggested that the camel was infected before the owner (Azhar et al. 2014). Critics have suggested that the identical sequences may be due to cross-contamination (Drosten et al. 2014), but the authors maintain that the isolates were collected on different days and processed in different facilities. Other epidemiologic investigations have found similar evidence, but directionality was not implied (Ferguson and Kerkhove 2014, Memish et al. 2014e).

In outbreak sites, viral genomic sequences from camels have matched those published for humans, and one analysis of MERS-CoV among camels showed that many of the camel viruses can be classified into clades that correlate with human outbreaks (Alagaili et al. 2014). Interestingly, three dromedary camel strains of MERS-CoV had similar viral replication competence to human strains in Vero-E6 cells and human respiratory tract explants (Chan et al. 2014).

This evidence suggests that camels would appear involved in cross-species transmission of MERS-CoV, although the precise mechanism and frequency remain uncertain.

Occupational exposure to camels would seem a particularly strong risk factor for infection, but its relative importance and relative risk of different exposures are not well documented (Hemida et al. 2015). As camels are widely used in the region for a variety of purposes, many people have contact with camels, and exposure is often invoked in non-occupational primary cases. Assessment of camel exposure is further complicated by the varying and sometimes vague

Table 1. Location, Methods, and Results of Recent Middle East Respiratory Syndrome Coronavirus Camel Seroprevalence Studies

Countries (reference)	*Year(s)*	*Test(s) used*[a]	*No. of samples*	*No. of positives (%)*
Egypt (Perera et al. 2013)	2013	ppNT	110	108 (98.2)
Egypt, Somalia, Sudan (Müller et al. 2014)	1983–1997	rELISA	189	159 (84.1)
		MNT		153 (81.0)
Egypt, Sudan, others (Ali et al. 2017a)	2015–2016	MNT	1031	871 (84.5)[b]
Ethiopia (Reusken et al. 2014b)	2010–2011	S1 microarray	188	181 (96.3)[c]
Jordan (Reusken et al. 2013b)	2013	Nt	11	11 (100.0)
Kenya (Corman et al. 2014b)	1992–2013	rELISA	774	228 (29.5)
		IFA		213 (27.5)
		MNT		133 (17.2)
Nigeria (Reusken et al. 2014b)	2010–2011	S1 microarray	358	337 (94.1)[c]
Oman (Reusken et al. 2013c)	2013	PRNT	50	50 (100.0)
Saudi Arabia (Alagaili et al. 2014)	1992–2010	ELISA	264	230 (87.1)
	2013	ELISA	203	150 (73.9)
Saudi Arabia (Hemida et al. 2014)	1993	ppNT	131	118 (90.1)
Saudi Arabia (Hemida et al. 2013)	2012–2013	ppNT	310	280 (90.3)
Tunisia (Reusken et al. 2014b)	2009	S1 microarray	204	99 (48.5)[c]
United Arab Emirates (Meyer et al. 2014)	2003, 2013	rIFA	651	632 (97.1)
		Nt		509 (80.5)
United Arab Emirates (Alexandersen et al. 2014)	2005	Nt	11	9 (81.8)

[a]ppNT, pseudoparticle neutralization; rELISA, recombinant enzyme-linked immunosorbent assay; MNT, microneutralization; PRNT, plaque reduction neutralization test; rIFA, recombinant immunofluorescence assay; Nt, serum neutralization.
[b]Seroprevalence reported higher in camels imported from Sudan (543/594; 88.7%) and East Africa (71/98; 72.4%) than resident (257/339; 5.8%); total 41/1078 nasal swabs reported PCR positive, 35/41 from Sudan.
[c]The exact number was not reported, and has been imputed from the reported percentages.

definitions used to classify camel exposure, and the multiple types of possible exposures. Even so, it has been hypothesized that camel exposure is commonly underreported (Gossner et al. 2016). There is a critical need for clearer definitions and measurements of ''camel exposure,'' and to standardize methodology.

Evidence to date indicates that MERS-like coronaviruses have been circulating in camels since at least the 1980s, before the first detection of MERS-CoV in humans (Müller et al. 2014). Seropositivity has been found consistently in African and Middle Eastern camels since 1983 (Table 1). There is virologic evidence of MERS-CoV infection in camels in Qatar (Ferguson and Kerkhove 2014, Haagmans et al. 2014, Raj et al. 2014), Egypt (Chu et al. 2014, Ali et al. 2017a, 2017b), Oman (Nowotny and Kolodziejek 2014), Saudi Arabia (Hemida et al. 2014), Sudan, and elsewhere (Chu et al. 2015, Ali et al. 2017a).

Increasing genomic evidence suggests a diversity of coronaviruses in camels throughout the Middle East and Africa, including in major source countries for camel imports to the Middle East, cross-neutralizing with MERS-CoV but having divergent sequences and probably not human pathogens (Chu et al. 2015, 2018). This may explain the high apparent seropositivity in camels in Africa in the absence of known human cases of MERS.

Maintenance of the virus in the camel population remains an open question. Symptomatic MERS-CoV infection has been documented in both calves and adult camels (Adney et al. 2014), and viral shedding was detected in nasal secretions up to 7 days postinoculation with MERS-CoV (Adney et al. 2014), as well as in milk and possibly feces (Hemida et al. 2014, Reusken et al. 2014a). Camel milk has been suggested as a possible source of infection for both humans and camel foals (Hemida et al. 2014, Reusken et al. 2014a, van Doremalen et al. 2014). One study demonstrated that added MERS-CoV can survive in milk for at least 48 h at both 4°C and 22°C, although not detected after pasteurization (van Doremalen et al. 2014).

Other possible livestock hosts for MERS-CoV have been investigated, and have generally been negative (Hemida et al. 2013, Perera et al. 2013, Reusken et al. 2013b, 2013c, Alagaili et al. 2014, Alexandersen et al. 2014, van Doremalen et al. 2014, Meyer et al. 2015). One study found 15 seropositive alpacas, which are members of the camelid family, in Qatar (Reusken et al. 2016). Experimentally infected alpacas in one study demonstrated upper respiratory tract infection, viral shedding, and transmission to other alpacas (Adney et al. 2016).

The search for the origins and natural hosts of MERS-CoV continues. Bat species across the world are known to host a wide variety of coronaviruses, including beta-coronaviruses (the genus to which MERS-CoV belongs) (Anthony et al. 2013, Corman et al. 2013, Lelli et al. 2013, Memish et al. 2013a), and bats tend to show greater coronavirus diversity than other mammals (Drexler et al. 2014, Anthony et al. 2017). Consequently, much research has focused on the possible origin of MERS-CoV in bats. Possibly further supporting this hypothesis, in bat cell lines MERS-CoV has been reported to replicate only in those cell lines that express DPP4, the functional human receptor for the virus, and not in bat cell lines lacking DPP4 expression (Raj et al. 2013, Cai et al. 2014).

It is possible that MERS-CoV itself may be a relatively new introduction in humans. A phylogenetic analysis utilizing 65 complete or partially complete MERS-CoV genomic sequences (32 from Saudi Arabian cases in 2013) estimated that the most recent common ancestor was in March 2012 (95% CI: December 2011–June 2012) (Cotten et al. 2014).

One study, from analysis of an S1 subunit in its spike gene, suggested that MERS-CoV may have arisen from intraspike

recombination between two ancestral coronaviruses (Corman et al. 2014).

The virus has not been isolated from a bat, although a portion of MERS-CoV RNA sequence apparently was identified in a bat (the insectivorous bat *Taphozous perforatus*, the Egyptian tomb bat) in Saudi Arabia in the same site as an early human case (100% nucleotide match, although this was only ~180 nucleotides in the relatively well-conserved RdRp region) (Memish et al. 2013a). MERS-like coronaviruses, including the closely related HKU4, which also uses a DPP4 receptor, and HKU5, first identified by Woo et al. in 2006 (Woo et al. 2006, Lau et al. 2013, Matthews et al. 2014, Wang et al. 2014), and others have been identified in bat species in China (Matthews et al. 2014, Yang et al. 2014), Mexico (Anthony et al. 2013), South Africa (Ithete et al. 2013, Corman et al. 2014a), and Uganda (Anthony et al. 2017).

Discussion and Conclusions

Since the detection of MERS-CoV in 2012, a large body of research has been amassed, as evidenced by the hundreds of unique results from our database searches. The virus has rapidly been characterized, and its functional human receptor swiftly identified. Species and cellular tropism studies have complemented clinical investigations, and laboratory work has provided further insights on MERS-CoV pathogenesis.

Observational research from outbreaks in the Middle East and South Korea has generated a growing repository of clinical data, basic epidemiology, and genome sequences. Other studies have evaluated the roles of human/animal interfaces, health care settings, family clusters, and travel in MERS-CoV transmission. Furthermore, bats have been implicated as the possible origin of MERS-CoV, while dromedary camels have been shown to be likely sources of many human infections. There has been progress in developing therapeutics and vaccines. Although these have not yet progressed to full clinical trials, they could in the foreseeable future.

A major reason we undertook this review was to determine what gaps still exist. Of the publications we originally identified, the largest category (80 publications) was in laboratory or basic science studies, followed by surveillance (59), animal interfaces (55), clinical aspects and health care (50), therapeutics and vaccines (42), while human transmission and epidemiology was one of the sparsest (35, including investigations of hospital outbreaks and travel-related cases), noting that these categories are not necessarily exclusive and there is overlap.

In general, continued surveillance for MERS-CoV in affected countries should continue, prioritizing surveillance in humans, camels, and bats, given their apparent importance. As serology may not be reliable, due to cross-reactions and possibly waning antibodies, virologic surveillance and sequencing should also be attempted on selected specimens whenever feasible.

Although the role of bats is yet to be fully elucidated, and evidence is lacking that bats are a source of human infection, the diversity of coronaviruses, including MERS-like coronaviruses, in bat species across the globe indicates that continued research and ongoing surveillance of coronaviruses in bats are justified (Lau et al. 2013, Lelli et al. 2013, Yang et al. 2014).

A number of key gaps remain in epidemiology, including transmission, population-based incidence or prevalence rates, and geographic and demographic distributions of infections. Based on the limited human seroprevalence data so far, it seems likely that population prevalence is low, but the baseline should be established. It is also not clear whether seropositivity is a reliable indicator of prior infection. The finding of variable low antibody titers at 1 year postinfection (Choe et al. 2017) indicates that methods other than traditional serosurveys may be required (Reusken et al. 2013a, Malik et al. 2016). If serology is not reliable, this raises the question of how to screen populations. There are methods that are both more sensitive and more specific for antibody detection (Mishra et al. 2018), as well as assays of cellular immunity (Zhao et al. 2017), but are costlier and more difficult for population screening.

Contact tracing has identified asymptomatic infections, but studies of their frequency and transmissibility have been limited. Many of those infected are health care workers in whom these questions could be systematically studied. Relatively little is known about the natural history of human asymptomatic infections. Further studies of virus shedding, seroconversion, and transmission in asymptomatic infections are needed. Some evidence suggests that secondary cases have lower average CFRs and that subsequent links in the chain of MERS-CoV infection may decrease in severity.

Exposure in most primary cases is still largely inferential at best. While camels are apparently often the likely source, the definitions of camel exposure are varied, preventing clear epidemiological inferences. Definitions of the exposures and the methodology and metrics for determining exposure should be clarified and standardized. Even if camels are a principal source of human infections, this would still not explain a substantial portion of primary human cases that did not have apparent camel exposure before infection. This raises questions about how and where these other primary cases acquired MERS-CoV infection, whether through other animal species, unidentified zoonotic exposure, unrecognized infectious persons (such as asymptomatic infectious individuals), or environmental contamination.

Consequently, clarifying the routes of transmission remains crucial and should receive emphasis. To date, there is no compelling evidence of direct human-to-human transmission, such as through droplets, but secondary infection has been reported. It is often unclear how health care workers become infected. There is possible evidence of environmental contamination (fomites) in health care settings (nosocomial transmission) and close contact with an active MERS-CoV case.

Various infection control lapses have been documented, but rarely a specific event or route (Ben Embarek and Van Kerkhove 2015, Alraddadi et al. 2016, Van Kerkhove et al. 2016). Rigorous infection control therefore remains essential and could prevent many secondary cases. In the interim, better documentation or identification of the specific lapses that led to infection would be of great value in understanding mechanisms of transmission and is one of the greatest knowledge gaps. Much of the evidence for fomite transmission, for example, remains anecdotal (Van Kerkhove et al. 2016).

The mechanisms supporting chains of human MERS-CoV transmission need to be more fully evaluated. These gaps indicate a need for additional research, and also for consistent

terminology and clear definitions. Although the epidemiological literature on MERS-CoV is large, much of it is fragmented and inconsistently reported. It is often difficult to deduce the sequence of infections, relationships between cases, or specific exposures. A comprehensive and consistent database or registry should be a priority.

Genome sequencing has proved useful in several respects. Genome sequencing was used to help determine viral circulation and ancestry (Cotten et al. 2014), and to differentiate apparently similar and serologically cross-reacting coronaviruses in camels, addressing the (still unresolved) question of why MERS seems regionally limited, while many camels are imported from other places (Chu et al. 2015, 2018). It has also been used to reconstruct the transmission events and help to establish chains of infection (Assiri et al. 2013b, Cotten et al. 2013), but it must be noted that there is a pressing need for more rigorous conventional epidemiology as well to validate the methodologies. These approaches might well serve a complementary function in advancing our understanding.

There remains a need for effective therapeutics and vaccines. Treatment remains symptomatic, with insufficient clinical data on other therapeutic options. These options will always be limited in number, but their development should be approached more systematically with shared protocols and critical comparison of results. As a number of drug and vaccine candidates have been identified, there may be more options available for future clinical trials. There appear to be efforts underway to develop some clinical trials based on standardized protocols. This is needed, despite the challenges presented by the sporadic nature of the cases, and the relative rarity of clinical MERS.

There were several limitations in this systematic review of MERS-CoV. Only publications in English or with English language abstracts were eligible for inclusion, although most of the cases have been in Arabic-speaking areas and Korea. However, hundreds of English language reports were available from countries around the world, including the Middle East and South Korea, minimizing this concern. Second, this review contains publications indexed by these databases by July 2017, so it is possible that some publications, especially recently published articles or manuscripts still in production, were unintentionally excluded from the review. We updated our literature review periodically during the preparation of this article to minimize the number of missed publications. Third, ''gray literature'' was not included, such as government reports and technical documents, and most meeting abstracts, although it is likely that important findings would have been submitted for journal publication.

As an emerging infection of zoonotic origin (Morse 1995), a unified One Health approach that engages the human health, livestock and companion animal, wildlife, and environment sectors will be crucial in dealing with MERS (Morse 2012, Morse et al. 2012). It could serve as an excellent case study for epidemiology and response to a new zoonotic, or emerging, infection.

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