Advancing Priority Research on the Middle East Respiratory Syndrome Coronavirus

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(See the brief report by Aburizaiza et al on pages 243–6, and the major article by Yao et al on pages 236–42.)

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Over a year since its first discovery, a new human disease, the Middle East Respiratory Syndrome (MERS), continues to be of major international concern due to its high fatality rate and lack of knowledge regarding its primary source and mode of transmission. It is caused by a novel coronavirus (CoV) MERS-CoV, initially named 2cEMC/2012 (HCoV-EMC) [1] and subsequently renamed as MERS-CoV [2] after international consensus [3]. It presents as a spectrum of respiratory diseases and is associated with a high case-fatality rate in persons with comorbid medical conditions [4, 5]. The first MERS case report was from Jeddah, Kingdom of Saudi Arabia (KSA), in September 2012 when MERS-CoV was isolated from a Saudi Arabian patient who died from a severe respiratory illness and multiorgan failure [2]. As of 15 November 2013, there have been 153 laboratory-confirmed cases of MERS, with 64 deaths (42% case-fatality rate), reported from 10 countries to the World Health Organization (WHO) [6, 7]. All cases were linked directly or indirectly to 1 of 6 countries in the Middle East: KSA, Qatar, Jordan, United Arab Emirates (UAE), Oman and Tunisia. Five countries outside the Middle East—the United Kingdom, France, Italy, Germany, and Tunisia—have reported patients who were either transferred for care or returned from a visit to the Middle East and subsequently became ill. Four of these countries—Italy, France, Tunisia, and the United Kingdom—have had secondary cases linked to the initial imported case [6, 7]. The majority of MERS-CoV cases to date (127 out of 153 cases) have been reported from KSA, occurring as family [8] or hospital [5] clusters, sporadic community cases, or detected with mild disease or asymptomatic infection on screening of healthcare workers who were in contact with MERS cases [9]. Human-to-human transmission of MERS-CoV has been well documented in KSA [5, 10], England [11], France [12], Tunisia, and Italy [6, 12]. The clusters detected so far are mostly small and there have been no reports of sustained transmission of MERS-CoV within the community.

Despite several multicountry collaborative research efforts with the government of KSA to define the demographic, clinical features, mode of transmission, and epidemiology of family and hospital clusters [4–10], several important priority research questions remain unanswered. It is unclear what the primary source and primary mode of transmission of MERS-CoV to humans is—critical information that is essential for developing interventions for reducing the risk of transmission, defining the epidemiology, and developing effective control measures. The cellular receptor for MERS-CoV has been identified as dipeptidyl peptidase 4 (DPP-4 or CD26) [11], and the structure of the receptor-binding domain of the virus spike protein complexed with DPP-4 was rapidly identified [13]. The receptor is conserved across mammals, suggesting several animal hosts, although no definitive animal reservoir for MERS-CoV has been identified. Studies of MERS-CoV genomes from MERS cases suggest the existence of a direct animal reservoir for MERS-CoV [10].

Bats are usual suspects for transmission of coronaviruses. A recent study [14] identified a small 190-nucleotide sequence of MERS-CoV, with maximum possibility of identity, in a fecal sample from an Egyptian tomb bat. Serological studies in animals have detected antibodies against the spike protein of betacoronaviruses [15], and this finding has led...
Aburizazaiza and colleagues [19] in this local populations. The article by Asad have not shown widespread infection in tions in the Middle East, human studies presence of anti-MERS-CoV antibodies transmission to humans.

mate food source, and the mode of mediate animal host(s) or other inani- reservoir of MERS-CoV, any other inter- ductions for MERS-CoV are not available and for developing effective therapies. In this issue of The Journal, Tanfeng Yao and colleagues [23] describe an animal model of MERS which they produced by using intratracheal infection of Rhesus macaque monkeys with MERS-CoV, resulting in the development of pneumonia, and showed MERS-CoV replication was largely restricted to the lower-respiratory tract. The infected monkeys showed clinical signs of disease, virus replication, histological changes, and neutralizing antib- production. Another recent study of a Rhesus macaque monkey model of MERS-CoV infection has shown similar findings [24]. Using a combination of intratracheal, ocular, oral, and intranasal inoculation with \(7 \times 10^6\) 50% tissue culture infectious dose of the MERS-CoV isolate HCoV-EMC/2012, the monkeys developed a transient lower-respiratory-tract infection. Clinical signs, virus shedding, virus replication in respiratory tissues, gene expression, and cytokine and chemokine profiles peaked early in infection and decreased over time. MERS-CoV caused a mild to marked multifocal interstitial pneumonia, with MERS-CoV replication occurring mainly in alveolar pneumocytes. This tropism of MERS- CoV for the lower-respiratory tract may explain the severity of the disease observed in humans and the limited human-to-human transmission.

The MERS-CoV rhesus macaque mod- el will be instrumental in developing and testing vaccine and treatment options for an emerging viral pathogen with pandem- ic potential. Specific therapeutic interven- tions for MERS-CoV are not available and have not been clinically evaluated. Cur- rent patient management relies exclusively on supportive care, which, given the high case-fatality rate recorded so far [4], is not highly effective. Empiric treatment with antiviral drugs or drug regimens, or
immune therapies (which were used for severe acute respiratory syndrome [SARS]) [25] require clinical evaluation. A recent study [26] indicates that a 2-drug combination may be effective against MERS-CoV. Using small compound-based forward chemical genetics to screen known drugs against influenza, and also interferons, nelfinavir, lopinavir, and nitazoxanide because of their reported anticoxsavirus effects, the authors identified mycophenolic acid, ribavirin, and interferons as exhibiting in vitro anti-MERS-CoV activity, and showed that the antiviral effect of interferon-β-1b was stronger than that of ribavirin. Using the Rhesus macaque monkey model for MERS-CoV infection, Falzarano et al [27] showed that treatment with IFN-α2b and ribavirin reduced virus replication, moderated the host response, and improved clinical outcome. Clinical evaluation of IFN-α2b and ribavirin should be considered for severe cases of MERS. Other treatment options for MERS-CoV that require further investigation include the cyclophilin inhibitors [28, 29] and convalescent plasma [30] from patients who have fully recovered from MERS-CoV. Convalescent plasma and related hyperimmune globulin may have had some apparent success during SARS [31] and during the influenza pandemic due to the 2009 influenza A (H1N1) virus [32].

With the current knowledge gaps, it is unknown whether MERS-CoV will remain a disease restricted to the Middle East with intermittent, sporadic outbreaks; progress to becoming a global pandemic; or burn out with time. Many priority research questions remain to be answered before the true pandemic potential and global impact of MERS-CoV can be accurately determined. Almost all patients who died or those who have been hospitalized with severe disease had other co-morbid medical conditions [4]. The mortality rate and severity of disease are exaggerated to some degree by detection of such cases. The case-fatality rate has fallen in recent months due to the detection of milder and asymptomatic cases [7]. Determining the true spectrum of MERS-CoV infection and disease severity requires widespread viral testing, collection of clinical data, and serologic studies. Case-control studies are essential for defining the MERS-CoV outbreak, and validated accurate serological tests, which are sensitive and specific, are required to facilitate these. The most ominous characteristic of pandemic MERS-CoV strains would be progression to efficient human-to-human transmission. The number of sporadic MERS cases being reported has been small and indicates that the virus appears not readily capable of rapid human-to-human transmission. Despite extensive investigation and testing of hundreds of contacts by the KSA Ministry of health, only a few instances of transmission to healthcare workers or family contacts were identified [6, 7, 9]. Sequencing studies of all MERS-CoV genomes may reveal genetic features that will tell us if MERS-CoV has the ability to mutate and spread efficiently. The rapid sharing of genetic sequence information [10, 33] will provide valuable insights into the understanding of the molecular characteristics and transmission dynamics, which will assist in defining species specificity, ascertaining mutation rates and virulence, and also enabling discovery of drug targets, novel drugs, diagnostics, and vaccines.

Two million pilgrims from over 180 countries, and 1 million local KSA pilgrims, have recently visited Makkah and Madinah, KSA, to perform the 2013 annual Haj pilgrimage, and have returned home after stays of between 2 and 8 weeks. Millions of others will visit KSA throughout the year for the mini-pilgrimage Umrah. While answers to priority research on MERS-CoV are being sought, the need for more coordinated surveillance and improved effective international cooperation between WHO, Middle Eastern governments, academic stakeholders, and pharmaceutical companies remains critical to tackling this ominous threat [34]. It is rather disconcerting that major knowledge gaps remain for the current MERS-CoV outbreak over a year after its first discovery. Once again, this illustrates that there remains a dire need for the establishment of robust public health and clinical infrastructures, effective global consortia, and a stable funding source for rapid and effective development of new infectious diseases outbreaks and threats, and for prioritizing research, preparedness, and response efforts.

Note

Potential conflicts of interest. All authors: No reported conflicts.

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