Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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EDITORIAL

The search for therapeutic options for Middle East Respiratory Syndrome (MERS)

More than three years after the first case was described, Middle East Respiratory Syndrome (MERS) coronavirus continues to cause sporadic cases in the community as well as intermittent major hospital outbreaks. Poor infection control practices, hospital overcrowding and delayed diagnoses have been identified as root causes for healthcare-associated transmission. The case fatality rate is approximately 35% [1]. However, the mortality rate for patients hospitalized with lower respiratory tract illness is higher, and for those who require intensive care admission, the reported mortality rate reaches 65—90% [2]. So far, no therapy has been proven to be effective, and our understanding of the disease pathogenesis in humans remains incomplete. An autopsy of a patient with MERS that has been published identified significant parenchymal involvement of the lower respiratory tract [3]. In a review of 37 patients, Corman et al. identified high and protracted viral replication in the lower respiratory tract of seriously ill MERS patients [4]. These findings suggest that the early use of sufficiently potent antiviral regimens may benefit patients by reducing viral activity, preventing lung damage and decreasing the load of viral shedding among these patients. Delayed diagnoses and a lack of well-defined animal models have not allowed for quick progress on drug development for MERS [5]. Nevertheless, some progress has been made in developing therapeutics and is discussed in this article. Further work is still needed.

Immunotherapy with viral-specific antibodies represents a promising avenue of therapy for MERS and has been considered to be a high priority for clinical testing [6,7]. A research protocol for collecting and testing convalescent plasma from previously infected patients and infected patients, with the goal of transfusing protective antibodies to MERS patients, has been formulated [8]. This protocol has led to the establishment of a network of investigators, the characterization of patients with MERS and the screening of previously or potentially exposed individuals. Recent data suggest that neutralizing antibodies develop in most survivors [9]. These individuals could donate plasma for the clinical study or production of hyperimmune globulins. The work is still in progress to determine whether this is a feasible large-scale therapy.

Substantial progress has been made on the production of MERS-CoV-specific neutralizing antibodies in humans as well as ''humanized'' MERS-CoV neutralizing antibodies that show antiviral activity in animal models [10—12]. A human polyclonal antibody product has been generated from cows using molecular technologies in which bovine Ig genes were knocked out and human immunoglobulin-producing genes were inserted into the genome. In addition, mice were genetically modified to produce human monoclonal antibodies when they were exposed to and challenged with the MERS-CoV antigen [13]. Antibodies produced in large quantities were then purified, and the neutralizing activity was measured and made available for testing in MERS animal models. These technologies are currently in various stages of development and represent a promising and potential intervention that may be tested in future clinical trials.

Repurposed medications are another category of potential therapeutics that is of great interest [14]. Public Health England, in collaboration with the International Severe Acute and Emerging Respiratory Infection Consortium (ISARIC), identified interferons (+/— ribavirin), lopinavir, nitazoxanide and chloroquine and as potential therapeutics that have sufficient promise for future investigation. Both interferon-beta and ritonavir-boosted

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lopinavir have shown to have antiviral effects in the common marmoset model of MERS [15]. However, none of these potential therapies have sufficient clinical data to suggest that they be used routinely in clinical care; instead, they were tested in the context of an appropriately designed clinical trial. There have been several observational reports evaluating the efficacy of interferons, which are often used in conjunction with ribavirin [16]. However, it is difficult to identify the true efficacy from these studies because of the small sample size and need to adequately address the indication bias. Systemic corticosteroids, ribavirin monotherapy, intravenous immunoglobulin and mycophenolic acid/myophenolate mofetil appear to be associated with a greater likelihood of causing harm rather than having potential benefits and have not been prioritized for evaluation. Evolving and new evidence should be continually reassessed. There are also ongoing screening efforts to identify novel inhibitors: a nucleotide prodrug called GS-5734 inhibits Ebola in macaques and has been used to treat several Ebola patients. GS-5734 is a potent inhibitor of coronaviruses, including MERS-CoV *in vitro* (Travis Warren, Presented at ICAAC 2015). Studies in animal models are in progress.

The episodic nature of MERS-CoV infections and the relatively low numbers of reported cases at any given hospital or region present a practical challenge for conducting clinical trials. Therefore, collaboration among investigators and centers will be critical for conducting adequately powered therapeutic clinical trials. Scientifically valid clinical evidence regarding safety and efficacy must drive and inform the incorporation of new therapeutics into clinical practice. Acknowledging that most potential therapies will not ultimately be effective, the research infrastructure should consider an adaptive design that allows the comparison of multiple treatment regimens to an identified concurrent control group.

Collaborative national and international intellectual, scientific, logistical, regulatory and financial support has already begun in KSA [17,18]. National and international investigators have developed draft protocols of observational studies to help identify risk factors for acquiring MERS to better characterize the clinical illness, identify risk factors for illness progression and clarify the mortality rate among all patients fulfilling the case definition of MERS (much of this work has already been performed in KSA and internationally) [19,20]. On the other hand, protocols for therapeutic trial(s) of the most promising potential therapies need to be developed. These protocols must be ready and approved by the ethics committees in different hospitals and must be utilized to enroll sporadic patients as well as cases during outbreaks. There should also be a coordinating center with a mandate to support protocol development, prepare potential study sites, and ensure that all needed elements are in place for clinical trials, such as IRB approvals, consent forms, data management ability, and research coordinators. Eventually, mechanisms to share data and specimens throughout the national and international scientific communities need to be established. This research infrastructure, including the investigative staff, needs to be present or mobile to sites, quickly in the hopes of enrolling patients. In addition to treatment-based evaluations, non-treatment based research priorities and gaps should be addressed.

The journey toward an effective therapy for MERS could be a long one, but it is certainly going to be exiting. The articles presented in the issue of the *Journal of Infection and Public Health* reflects on the significant developments and milestones of this journey.

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