Oman Medical Journal (2014) Vol. 29, No. 3:169-171
DOI 10.5001/omj.2014.43

Editorial

MERS-CoV: Bridging the Knowledge Gaps

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Received: 5 Mar 2014 / Accepted: 5 May 2014

Since its emergence in September 2012 and as of 30 April 2014, there have been 424 cases of the Middle East Respiratory Syndrome-Coronavirus (MERS-CoV) reported to public health authorities worldwide (15 countries). This tally includes 95 healthcare workers (22%) and 131 deaths (mortality rate of 31%).[1] To date, only two laboratory confirmed cases have been reported in Oman. The number of cases reported globally in April 2014 alone were nearly equal to all reported cases since the emergence of MERS-CoV. The cause of this rapid increase in cases is currently unknown but justifiably concerning. Increase zoonotic transmission, increase transmission in healthcare setting and change in the virus resulting in more effective human-to-human transmission are among some of the most plausible explanations.

The majority of the cases now reported have likely acquired the infection through human to human transmission and only about a quarter are considered as primary cases. The occurrence of new cases seems to follow a seasonal pattern, with increasing incidence from March-April onwards.[2] Recent MERS-CoV cases comprise a significant proportion of healthcare workers and asymptomatic cases or cases presenting with mild symptoms. Up to now, extensive search to identify the possible source of MERS-CoV has resulted in identifying camels and bats as probable sources with camels being most likely the intermediate host. Deep genome sequencing of MERS-CoV from a patient's sample revealed its close relatedness to European bat coronaviruses.[3] The first hint of involvement of camels came from serological studies which identified neutralizing antibodies against MERS-CoV spike protein in camels.[4] Subsequent serological and molecular work confirmed this finding in camels connected to human cases in Qatar, which were positive for MERS-CoV by real time reverse transcription polymerase chain reaction (rRT-PCR) from nasal swabs.[5] A recent study from United Arab Emirates revealed that this virus has been circulating in camels since at least 2003, long before the first human cases were identified.[6] In addition, recent research suggested that MERS-CoV can survive for prolonged periods when it was introduced into camel milk, goat milk and cow milk.

Comprehensive laboratory preparedness plan is paramount to the public health contingency plan for diagnosis and control of novel organisms. As a response to the emergence of MERS-CoV, nucleic acid detection and serological assays were rapidly developed.[7,8] These assays were internationally released for early identification and to reduce ongoing transmission. Molecular testing, which is a real time reverse transcription polymerase chain reaction (rRT-PCR), has been considered to be the cornerstone for diagnosis.[9] WHO recommends a two step-approach, a screening and a confirmatory nucleic acid detection tests. This approach ensures the use of two different targets in MERS-CoV genome.[9] The screening rRT-PCR targets the upstream of E protein gene *(upE)*.[7,8] Any positive reaction on the screening PCR must be confirmed by a highly specific PCR which targets the opening reading frame 1b *(ORF 1b)* of the MERS-CoV genome.[10] Multiple respiratory samples from different sites should be collected for nucleic acid detection tests,[11] and this is to increase the probability of detecting MERS-CoV. Moreover, MERS-CoV has been detected using rRT-PCR from blood, urine, and stool, but the usefulness of these specimens for diagnosing MERS-CoV infection is uncertain.[12] The use of antibody detection assays has been limited since the emergence of MERS-CoV.[10] Immunofluorescence antibody assay (IFA) was the first serological test described. It is based on the detection of IgM and IgG.[11] A positive result on IFA will be followed by serological confirmatory tests such as micro neutralization test.[11] The limitations of the serological assays are lack of validation and cross reaction with other coronaviruses. As a result, a protein microarray technology has been developed for a specific detection of IgM and IgG which has showed promising results.[13] Recent studies have shown the ability of this virus to grow in animal and human cell lines.[14]

Development of effective therapeutics and vaccines is not only critical but is urgently needed to curb and mitigate the alarmingly high mortality rate and the feared far-reaching global spread of MERS-CoV infection. General supportive care continues to be the basis of management of patients with MERS-CoV infection today as current treatment recommendations do not support any specific therapies. In view of the phylogenetic relatedness of MERS-CoV to SARS-coronavirus, it is comprehensibly assumed that therapeutic agents that worked on SARS-coronavirus may also work for MERS-CoV. This hypothesis forms the basis for current research. An extensive systematic review of treatments

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used for patients infected with the phylogenetically related virus (SARS- coronavirus) identified the following agents as potential therapeutic options: ribavirin, corticosteroids, lopinavir and ritonavir (LPV/r), interferon (IFN-α and IFN-β), intravenous immunoglobulin (IVIG), and SARS convalescent plasma. However, it was not possible to determine whether treatments benefited SARS infected patients, and this was largely due to the variation in treatment regimens.[15] A more recent systematic review exploring therapeutic options for MERS-CoV infection based on therapies used on SARS-coronavirus infected patients identified four therapeutic agents (ribavirin, peg-interferon α, lopinavir/ritonavir, and convalescent plasma) for MERS-CoV infection and proposed specific dosages.[16] According to a clinical decision making tool for treatment of MERS-CoV produced by the International Severe Acute Respiratory & Emerging Infection Consortium (ISARIC), the strongest evidence (based on experience from SARS coronavirus) for intervention exists for use of convalescent plasma that possess neutralizing antibodies with limited, and in some cases, no support existing for the use of the remaining agents.[17] Whether convalescent plasma would be effective in the treatment of MERS-CoV infection is yet to be proven. In a recent observational study of five MERS-CoV patients treated with a combination of interferon and ribavirin, none of the patients responded to the supportive or therapeutic interventions and all died of their illness. All patients received therapy late (median of 19 days).[18]

With the recent discovery and identification of dipeptidyl peptidase 4 (DPP4; also known as CD26) in human bronchial lung tissue as a functional receptor for MERS-CoV,[19] this suggests that inhibition of MERS-CoV binding to this cell receptor may show promise for therapy of MERS-CoV. This was demonstrated in a recent study where a humanized anti-CD26 monoclonal antibody was shown to have an inhibitory effect on MERS-CoV.[20] Cyclophilin inhibitors (such as mycophenolic acid and cyclosporine A) have shown strong inhibition of MERS-CoV replication in vitro. Whether these agents will offer therapeutic options is yet to be answered. It is evident from this review that there is an urgent need for clinical trials to define the most effective regimens for the treatment of this truly concerning novel infection.

The increasing number of MERS-CoV cases and its associated high mortality rate emphasizes the importance of developing an effective and safe vaccine to control its further spread. To date, there is no approved vaccine for MERS-CoV; however, there are efforts to produce such a vaccine. The dipeptidyl peptidase 4 (DPP4) has been identified as the receptor for the virus. The spike (S) protein of the virus interacts with the DPP4, enabling its fusion and entry into the host cell. The S protein is divided into two subunits; S1 and S2 which are responsible for binding and fusion with the cellular membrane, respectively. The receptor binding domain (RBD) is located on the S1 region and found to be immunogenic and induces a strong neutralizing antibody response.[21] In one promising study on mice, which were vaccinated with a recombinant protein containing RBD of MERS-CoV fused with fragment crystallizable region (Fc) of human IgG, it was shown that administering this vaccine intranasally had induced a strong systemic neutralizing antibody and high local mucosal immune responses.[22] Until MERS-CoV vaccine is made available, basic infection prevention and control strategies will continue to be the foremost public health measure for battling this deadly virus.

The risk MERS-CoV poses on public health is not yet entirely understood; however, the continued outbreak of new cases - particularly with the sharp increase in number of reported cases in last month accounting for nearly half of all reported cases since the emergence of this novel virus, the ongoing risk of transmission to humans with fear of increasing transmissibility, the recent reports of increasing nosocomial outbreaks with transmission to healthcare personnel, and the increasing reports of cases imported outside Saudi Arabia - currently 15 countries, all justifiably raise public concern. Whether MERS-CoV has the potential to cause a pandemic is elusive at present. The fact that our current knowledge on this virus is sparse should not induce unnecessary panic or fear, instead it should promote vigilance and a state of preparedness.[23] Over reaction to the current situation may lead to significant clinical, economic and epidemiological impacts among others.

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