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Review Article

MIDDLE EAST RESPIRATORY SYNDROME CORONAVIRUS (MERS-COV): THREAT TO GLOBAL PUBLIC HEALTH & CHALLENGES

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ABSTRACT

Middle East respiratory syndrome coronavirus (MERS-CoV), a novel human coronavirus that caused outbreaks of a SARS-like illness in theMiddle East, is now considered a threat to global public health. As of 11 June 2014, 699 laboratory-confirmed cases of human infection with Middle East respiratory syndrome coronavirus (MERS-CoV) have been reported to WHO including at least 209 deaths.This review discusses the symptoms, complications, prevention and challenges in developing effective and safe anti-MERS vaccines and treatment in order to control its spread and to combat any future pandemic.

Keywords: MERS, Coronavirus, WHO, symptoms, vaccine, therapy.

INTRODUCTION

Middle East Respiratory Syndrome (MERS) is an illness caused by a virus (more specifically, acoronavirus) called Middle East Respiratory Syndrome Coronavirus (MERS-CoV). MERS affects the respiratory system (lungs and breathing tubes). Most MERS patients developed severe acute respiratory illness with symptoms of fever, cough and shortness of breath. About 3-4 out of every 10 patients reported with MERS have died.Health officials first reported the disease in Saudi Arabia in September 2012. Through retrospective investigations, health officials later identified that the first known cases of MERS occurred in Jordan in April 2012. So far, all cases of MERS have been linked to countries in and near the Arabian Peninsula.MERS-CoV has spread from ill people to others through close contact, such as caring for or living with an infected person. However, there is no evidence of sustained spreading in community settings.MERS can affect anyone. MERS patients have ranged in age from younger than 1 to 99 years old.[1]

Coronavirus

Coronaviruses are common viruses that most people get some time in their life. Human coronaviruses usually cause mild to moderate upper-respiratory tract illnesses.Coronaviruses are named for the crown-like spikes on their surface. There are four main sub-groupings of coronaviruses, known as alpha, beta, gamma, and delta.Human coronaviruses were first identified in the mid-1960s. The six coronaviruses that can infect people are: alpha coronaviruses 229E and NL63, and beta coronaviruses OC43, HKU1, SARS-CoV (the coronavirus that causes severe acute respiratory syndrome, or SARS), and MERS-CoV (the coronavirus that causes Middle East Respiratory Syndrome, or MERS).There are many coronaviruses that naturally infect animals. Most of these usually infect only one animal species or, at most, a small number of closely related species, but not people. However, SARS-CoV can infect people and animals, including monkeys, Himalayan palm civets, raccoon dogs, cats, dogs, and rodents. MERS-CoV has also been found to infect

people and animals, including camels and bats.[1]

Symptoms & Complications

Most people confirmed to have MERS-CoV infection have had severe acute respiratory illness with symptoms of

- fever
- cough
- shortness of breath

Some people also had gastrointestinal symptoms including diarrhea and nausea/vomiting. For many people with MERS, more severe complications followed, such as pneumonia and kidney failure. About 3-4 out of every 10 people reported with MERS have died. Most of the people who died had an underlying medical condition. Some infected people had mild symptoms (such as cold-like symptoms) or no symptoms at all; they recovered.Based on what researchers know so far, people with pre-existing medical conditions (also called comorbidities) may be more likely to become infected with MERS-CoV, or have a severe case. Pre-existing conditions from reported cases like diabetes; cancer; and chronic lung, heart, and kidney disease. Individuals with weakened immune systems are also at higher risk for getting MERS or having a severe case.

Based on information to date, the incubation period for MERS (time between when a person is exposed to MERS-CoV and when they start to have symptoms) is usually about 5 or 6 days, but can range from 2-14 days.[1]

Prevention

Currently, there is no vaccine to prevent MERS-CoV infection. The U.S. National Institutes of Health is exploring the possibility of developing one.

People protect themselves from respiratory illnesses by taking everyday preventive actions:

- Wash hands often with soap and water for 20 seconds, and help young children do the same. If soap and water are not available, use an alcohol-based hand sanitizer.
- Cover nose and mouth with a tissue when you cough or sneeze and then throw the tissue in the trash.
- Avoid touching eyes, nose and mouth with unwashed hands.
- Avoid personal contact, such as kissing, or sharing cups or eating utensils, with sick people.
- Clean and disinfect frequently touched surfaces such as toys and doorknobs.[1]

Treatment

There is no specific antiviral treatment recommended for MERS-CoV infection. Individuals with MERS can seek medical care to help relieve symptoms. For severe cases, current treatment includes care to support vital organ functions.[1]

WHO Reports

As of 11 June 2014, 699 laboratory-confirmed cases of human infection with Middle East respiratory syndrome coronavirus (MERS-CoV) have been reported to WHO, including at least 209 deaths.Overall, 63.5% of cases reporting sex (n=677) are male and the median age is 47 years old (range 9 months-94 years old; n=695). An additional 113 cases occurring between 2012 and 2014 were reported by the Saudi Arabian Ministry of Health on 3 June 2014. These cases are not reflected in the current case count as investigation into these cases is currently ongoing with Saudi officials.To date, the affected countries in the Middle East include Iran, Jordan, Kuwait, Lebanon, Oman, Qatar, Saudi Arabia (KSA), United Arab Emirates (UAE) and Yemen; in Africa: Algeria, Egypt and Tunisia; in Europe: France, Germany, Greece, Italy, the Netherlands and the United Kingdom; in Asia: Malaysia and Philippines; and in North America: the United States of America (USA). Since the last update of 8 May 2014, four newly affected countries reported MERS-CoV cases: Algeria, Iran, Lebanon and the Netherlands.

Since the last update of 8 May 2014, 163 laboratory-confirmed cases, including 38 deaths, were reported to WHO. These include 138 cases reported by KSA (including cases from Riyadh, Jeddah, Medina, Mecca, Qunfudhah, Al Jawf, Al Taif, Damman, Dilam, Hafar Al Batin, Kharj and Rumah), 13 cases reported by UAE (all from Abu Dhabi), 3 cases reported by Jordan, 3 cases by Iran, 2 cases by the Netherlands, 1 case by the US and 1 case by Lebanon. The number of laboratory-confirmed MERS-CoV cases in KSA and UAE, where several healthcare-associated outbreaks were occurring, decreased sharply in May.

Summary of KSA Cases reported between 11 April and 9 June 2014

This summary covers cases reported form KSA between 11 April and 9 June, including 138 cases of reported to WHO by KSA since the last update on 8 May. In total, between 11 April and 9 June 2014, 402 laboratory-confirmed cases of MERS-CoV, including at least 114 deaths, from KSA were officially

reported to WHO (Figure 2). All of these cases are currently reflected in the WHO case count. Thirty-five cases were reported from Madina, 132 from Riyadh, 208 from Mecca Province (including 154 from Jeddah, 39 from Mecca, 8 from Qunfudhah and 7 from Al Taif), 10 from Tabuk, 6 from Al Jawf, 3 from Najran, and 3 from Ash Sharqiyah (5 cases did not have their location within KSA specified). The nationality of cases was provided for 223 of the 402 cases. Among these 138 were Saudi nationals.[2]

The median age of the 402 cases is 46.0 years old (range 9 months-94 years old) and 58.3% of those with information on sex (n=388) are male. Almost half (44.5%) of the cases with reported information (n=398) experienced severe disease including 114 cases who died; 114 cases (28.6%) were reported to be asymptomatic or have mild disease. Of 149 cases for which information was provided, 140 reported to have at least one underlying medical condition.

More than 25% of the reported cases are health care workers (109/402). Among the 109 health care workers, 63 were reported as asymptomatic or developing mild symptoms, 35 with moderate symptoms (requiring hospitalization but not admission to an intensive care unit), 7 were reported as having severe disease and 4 were fatal[2].

Newly affected countries: Algeria, Iran, Lebanon and the Netherlands

Algeria has reported its first laboratory-confirmed cases on 1 June 2014. Both cases had separately travelled to Saudi Arabia for pilgrimage in May and sought treatment upon returning to Algeria. It is unknown whether these two cases had contact with a known MERS-CoV case, visited a health care health care facility or had contact with animals while in KSA. Investigations among contacts of the two cases while in Saudi Arabia and in Algeria are currently ongoing.

Iran reported its first laboratory-confirmed MERS-CoV cases on 26 May 2014. The first two cases were sisters who had no history of travel, or contact with camels, but who had close contact with an individual with influenza-like-symptoms who had recently travelled to KSA to perform Umrah. Investigations are currently ongoing in Iran to determine if the close contact has been tested for MERS-CoV. One additional case, a 35 year old female health care worker caring for the first reported Iran case, was identified on 4 June. Lebanon reported its first case on 8 May 2014 in a health care worker who no reported contact with a known MERS-CoV case, had not travelled to the Middle East within the 14 days prior to symptom onset and did not have contact with animals or animal products. The patient is known to travel to several countries in the Gulf region, but his most recent travel was five weeks prior to symptom onset. Investigations are ongoing in the source of his infection.The Netherlands reported two MERS-CoV cases 1 among siblings who travelled to Medina and Mecca KSA between 26 April and 10 May 2014. Investigations are ongoing to identify the source of exposure, however it is known that the male patient, 70 years-old, visited medical care facilities in Medina or Mecca while in KSA. The sister, 73 years-old, was identified as a case through contact tracing investigation. Both cases had underlying conditions that have been shown to pre dispose to severe disease.2 A total of 78 close contacts (among which were the travel group, relatives and flight contacts) were monitored for a period of 14 days, and no additional cases of MERS-CoV infection were identified during this period.Follow up of contacts of exported cases in April-June 2014 has continued since the last summary. No additional cases have been identified in Algeria, Egypt, Greece, Lebanon, Malaysia, the Philippines or the USA from the recent exported cases to those countries. However, Jordan reported further transmission from a case exported from KSA. Limited human-to-human transmission was reported in Iran in a health care worker caring for one of the exported cases.[2]

CHALLENGES

Challenge in designing MERS vaccines

To control MERS, we must develop an effective and safe vaccine, which constitutes a second challenge to researchers. However, the problems encountered in the development of SARS vaccines should be revisited before the MERS vaccines are designed. Some of the inactivated virus-based, DNA-based and viral vector-based vaccine candidates could induce Th2- mediated immunopathology or immunoenhancing pathology[3-7] raising concerns about the safety of the SARS vaccines. previous studies have shown that the SARS vaccinecandidates based on the receptor-binding domain (RBD) in the S1 subunit of the SARS-CoVspike protein is more effective and safer than the above-mentioned vaccine candidates.[08-10] By comparing the sequences of spike proteins of SARS-CoV and MERS-CoV, we predicted that a 286-amino acid fragment (residues 377-662) in the S1 subunit of MERS-CoV contains its RBD.[11] We strongly believe that the RBD in the MERS-

CoV spike protein is therefore an important target for developing MERS vaccines. Most recently, Chan et al. reported that the sera of some convalescent SARS patients contained antibodies that could cross-react or cross-neutralize MERS-CoV.[12] This raises a hope that people with histories of SARS-CoV infection might not be susceptible to MERS-CoV infection. However, our study demonstrated that the epitopes eliciting the cross-reactive antibodies may not be located in the RBD of SARS-CoV S protein.[13] Thus, it is doubtful whether these antibodies really have a role in cross-protection against MERS-CoV.

Challenge in developing anti-MERS therapy

To date, no effective antiviral therapeutics against MERSCoVhave been discovered. Clinical management is mainly supportive, placing emphasis on organ support for respiratory and renal failure. In cases of acute respiratory failure, the use of extracorporeal membrane oxygenation (ECMO) is expected to improve survival rates significantly.

Several nonspecific antiviral drugs, such as ribavirin, lopinavir, and type I IFN, have been used for treating SARS, although their actual efficacy in these patients is still unclear. IFN-a was shown to inhibit in vitro MERS-CoVreplication in cells, but it is unknown whether it works*in vivo*.It has been thought that cytokine storm, a potentially fatal immune reaction characterized by the massive release of proinflammatory cytokines, is responsible for the deaths of patients infected by highly pathogenic avian influenza A (H5N1) virus or SARS-CoV. Therefore, immunosuppressant or immunomodulatory drugs, which diminish inflammation during infection, are expected to have therapeutic benefit. However, whether or not the immunosuppressant

drugs should be used for treating MERS patients is debatable. First, no report has yet shown that cytokine storms are indeed responsible for the deaths of MERS patients. Second, cell host response to infection with MERS-CoV is much different from that to SARS-CoV infection. Yuen and colleagues believed that corticosteroid should not be considered for treating MERS, particularly since patients with severe pneumonia and respiratory failure could be supported

by ECMO until the cytokine storm is over.MERS-CoVfusion inhibitor-based therapy would only require aregimen of a few days at the onset of MERS-CoV infection tosave patients' lives.[14]

CONCLUSION

In conclusion, MERS-CoV, which caused health alertof a SARS-like illness in the Middle East mainly in Saudi Arabia, is nowconsidered a threat to global public health. While it's human to human transmission and animal to human transmission have been detected. To avoid its serious concerns over its pandemic potential researchers must take immediate steps to identify the source of this fatal virus and develop effective and safe anti-MERS-CoVvaccines and therapeutics in order to control its spread and to combat any future pandemic.

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Conflict of interest statement

We declare that we have no conflict of interest.

REFERENCES

1. Centers for disease control & prevention, Middle east respiratory syndrome Coronavirus (23-3-2015) at http://www.cdc.gov/coronavirus/mers/about/index.html
2. World Health Organization, Middle east respiratory syndrome Coronavirus (23-3-2015) at http://www.who.int/csr/disease/coronavirus_infections/en/
3. Deming D, Sheahan T, Heise M, Yount B, Davis N, Sims A, Suthar M, Harkema J, Whitmore A, Pickles R, West A, Donaldson E, Curtis K, Johnston R and Baric R. Vaccine efficacy in senescent mice challenged withrecombinant SARS-CoV bearing epidemic and zoonotic spike variants. PLoS Med. 2006;3:525.
4. Yasuiet F. Prior immunization with severe acute respiratory syndrome(SARS)-associated coronavirus (SARS-CoV) nucleocapsid protein causessevere pneumonia in mice infected with SARS-CoV. J Immunol. 2008;181:6337- 6348.
5. Bolles M, Deming D, Long K, Agnihothram S, Whitmore A, Ferris M, Funkhouser W, Gralinski L, Totura A, Heise M and Baric RS. A double inactivated SARS-CoV vaccine provides incomplete protection in

miceand induces increased eosinophilic pro-inflammatory pulmonary responseupon challenge. J Virol. 2011;85(23):12201- 12215.
6. Tseng CT, Sbrana E, Iwata-Yoshikawa N, Newman PC, Garron T, Atmar RL, Peters CJ and Couch RB. Immunization with SARS coronavirusvaccines leads to pulmonary immunopathology on challenge with the SARS virus. PLoS One. 2012;7:35421.
7. Jaume M, Yip MS, Kam YW, Cheung CY, Kien F, Roberts A, Li PH, Dutry I, Escriou N, Daeron M, Bruzzone R, Subbarao K, Peiris JS, Nal B and Altmeyer R. SARS CoV subunit vaccine: antibody-mediated neutralization and enhancement. Hong Kong Med J. 2012;18 (2) :31-36.
8. Du L, He Y, Zhou Y, Liu S, Zheng BJ and Jiang S. The spike protein ofSARS-CoV: a target for vaccine and therapeutic development. Nat Rev Microbiol. 2009;7:226-236.
9. He Y, Lu H, Siddiqui P, Zhou Y and Jiang S. Receptor-binding domain ofsevere acute respiratory syndrome coronavirus spike protein containsmultiple conformation-dependent epitopes that induce highly potentneutralizing antibodies. J Immunol. 2005;174:4908-4915.
10. Jiang S, Bottazzi ME, Du L, Lustigman S, Tseng CT, Curti E, Jones K, Zhan B and Hotez PJ. Roadmap to developing a recombinantcoronavirus S protein receptor-binding domain vaccine for severe acuterespiratory syndrome. Expert Rev Vaccines. 2012;11:1405-1413.
11. Jiang S, Lu L, Du L and Debnath AK. A predicted receptor-binding andcritical neutralizing domain in S protein of the novel human coronavirusHCoV-EMC. J Infect. 2013;66:464-466.
12. Chan KH. Cross-reactive antibodies in convalescent SARS patients' sera against theemerging novel human coronavirus EMC (2012) by both immunofluorescentand neutralizing antibody tests, (22-03-2015) at http://dx.doi.org/10.1016/j.jinf.2013.03.015.
13. Du L, Ma C and Jiang S. Antibodies induced by receptor-binding domain inspike protein of SARS-CoV do not cross-neutralize the novel humancoronavirus hCoV-EMC. J Infect. 2013; 66:464-466.
14. Lu Lu and Shibo Jiang. Middle East respiratory syndrome coronavirus (MERS-CoV): challenges in identifying its source and controlling its spread. J microbes and infection. 2013; 15:625-629.