aJava

Asian Journal of Animal and Veterinary Advances

Academic
Journals Inc.

www.academicjournals.com

Asian Journal of Animal and Veterinary Advances 10 (12): 843-851, 2015
ISSN 1683-9919 / DOI: 10.3923/ajava.2015.843.851

Middle East Respiratory Syndrome (MERS): The Emerging Zoonoses

[1]Najimaana Wani, [1]Z.H. Munshi and [2]Aafreen Wahid Ganai
[1]Division of Veterinary Public Health and Epidemiology, Faculty of Veterinary Sciences and Animal Husbandry, Shuhama, SKUAST-K, 190006, Kashmir
[2]Division of Veterinary Public Health and Epidemiology, Faculty of Veterinary Sciences and Animal Husbandry, SKUAST-J, R.S. Pura, Jammu, 181102, Kashmir

Corresponding Author: Najimaana Wani, Division of Veterinary Public Health and Epidemiology, Faculty of Veterinary Sciences and Animal Husbandry, SKUAST-K, Shuhama, Alustang, Srinagar, 190006, Kashmir Tel: +91-9906489343 Fax: 01942262210

ABSTRACT

Middle East Respiratory Syndrome (MERS), also known as camel flu, is a zoonotic viral respiratory infection caused by the MERS-coronavirus (MERS-CoV). Symptoms may range from mild to severe. The MERS-CoV was first identified in September, 2012 among individuals with severe acute respiratory illness in Kingdom of Saudi Arabia. All primary cases of MERS are epidemiologically linked to the Middle East. The disease is especially severe in elderly men with comorbidities. Between 2012 and 7 July, 2015, 1368 laboratory-confirmed cases of human infection with (MERS-CoV) have been reported to WHO, including at least 487 deaths. The MERS-CoV has entered the human population in the Arabian Peninsula on multiple occasions from direct or indirect contact with infected dromedary camels or camel related products (e.g., raw camel milk). Twenty six countries have been affected since, 2012 by this virus. As of today, there is no vaccine available for MERS-CoV and there are no specific drugs or treatment regimens available. Medical care is supportive and aimed at to help relieve symptoms and treat complications. Reverse transcription-PCR on respiratory or extra pulmonary specimens rapidly establishes diagnosis. Supportive treatment with extra corporeal membrane oxygenation and dialysis is often required in patients with organ failure. Anti-virals with potent *in vitro* activities include neutralizing monoclonal antibodies, antiviral peptides, interferons, mycophenolic acid and lopinavir.

Key words: Coronavirus, Middle East, WHO, zoonotic, MERS-CoV

INTRODUCTION

Coronaviruses are found worldwide and causing a range of illnesses in humans, animals and rodents. In humans, coronaviruses can cause mild to severe illness like common cold as well as Severe Acute Respiratory Syndrome (SARS). The new strain of Coronavirus MERS-CoV (formerly called "Novel coronavirus") was first isolated and identified by Egyptian virologist Dr. Ali Mohamed Zaki from previously unknown coronavirus from the man's lungs in Kingdom of Saudi Arabia (Zaki *et al*., 2012). The isolated cells showed cytopathic effects (CPE) in the form of rounding and syncytia formation. The infected individuals developed severe acute respiratory illness with symptoms of fever, cough and shortness of breath. A second case was found in a 49 year old male living in Qatar who presented with similar flu symptoms and a sequence of the virus was nearly identical to that of the first case. The MERS-CoV appears similar to coronaviruses found in bats however; genetic sequence analyses have shown that the new virus is

different from other known human coronaviruses, including SARS (Ksiazek *et al*., 2003). In humans, the virus has a strong tropism for non-ciliated bronchial epithelial cells and it has been shown to effectively evade the innate immune responses and antagonize interferon (IFN) production in these cells. This tropism is unique in that most respiratory viruses target ciliated cells (Kindler *et al*., 2013; Raj *et al*., 2013). No vaccines and specific antivirals have been developed as yet and therefore, the supportive treatment remains the mainstay of case management (Spanakis *et al*., 2014).

DISTRIBUTION

As of July 2015, MERS-CoV cases have been reported in over 21 countries, including Saudi Arabia, Jordan, Qatar, Egypt, the United Arab Emirates, Kuwait, Turkey, Oman, Algeria, Bangladesh, Indonesia, Austria, the United Kingdom, South Korea, the United States, Mainland China, Thailand and the Philippines (Fig. 1 and 2).

ETIOLOGY

The MERS-CoV or EMC/2012 (HCoV-EMC/2012) is a novel positive-sense, single-stranded RNA virus of the genus Betacoronavirus. Initially called novel coronavirus 2012 or simply novel coronavirus. This is a new strain of coronavirus that has not been previously identified in humans. In humans, this large family of viruses is known to cause illness ranging from the common cold to Severe Acute Respiratory Syndrome (SARS) (Perlman and Netland, 2009). The MERS-CoV is

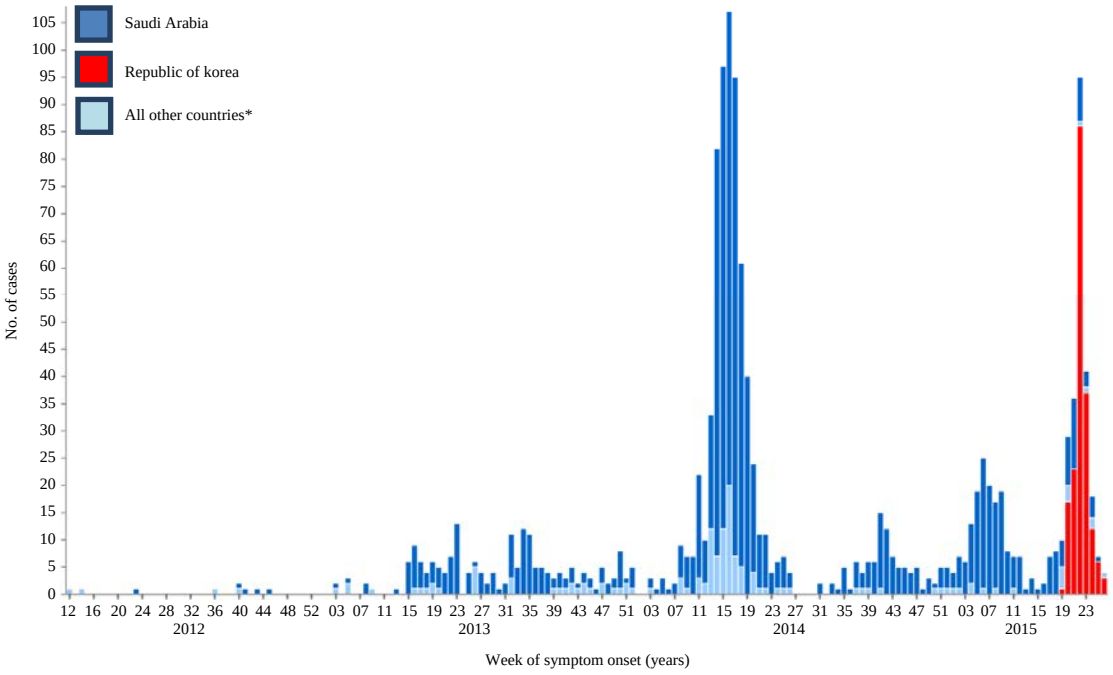

Fig. 1: Epidemic curve of MERS-CoV cases (n = 1368) (as of 7 July, 2015) (WHO., 2015), *All other countries reporting cases to date: Egypt, Iran, Jordan, Kuwait, Lebanon, Oman, Qatar, United Arab Emirates, Yemen, Algeria, Tunisia, Austria, France, Germany, Greece, Italy, the Netherlands, Turkey, United Kingdom, Malaysia, Philippines, Thailand, and United States of America

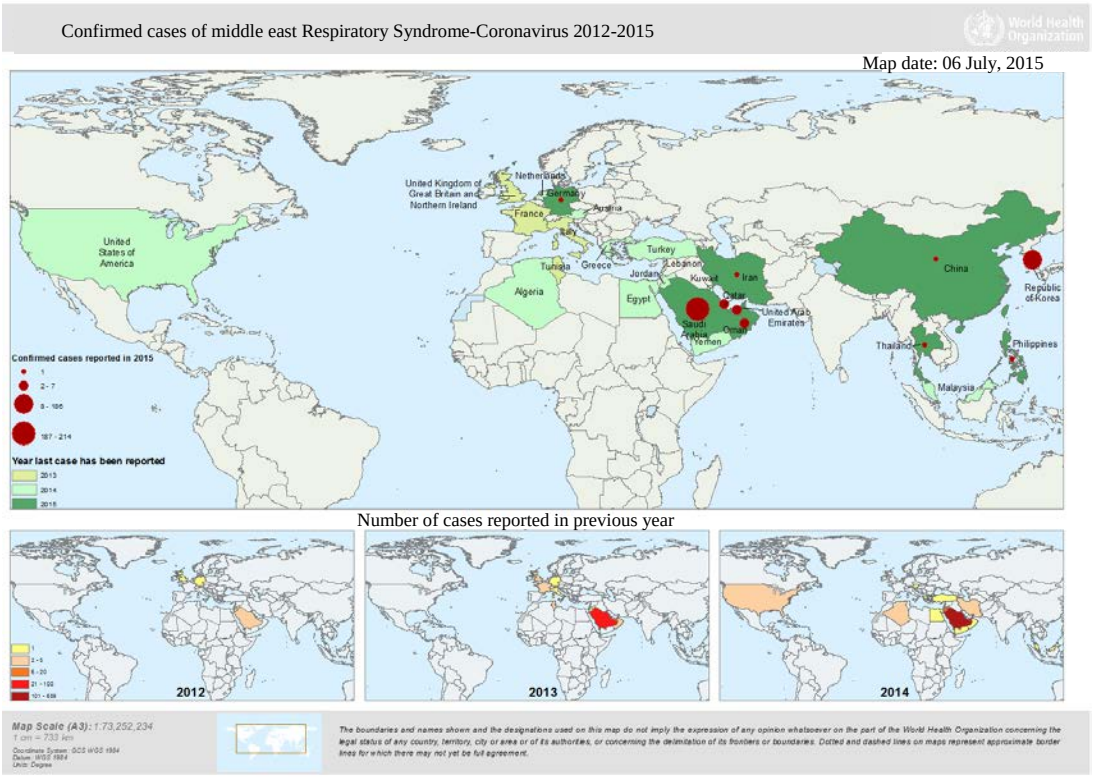

Fig. 2: Number of laboratory-confirmed MERS-CoV cases reported by countries by year since 2012 WHO (2015)

distinct from SARS coronavirus and distinct from the common-cold coronavirus and known endemic human Betacoronaviruses HCoV-OC43 and HCoV-HKU1 (Zeng *et al*., 2008). The MERS-CoV had frequently been referred to as a SARS-like virus or simply the novel coronavirus and early it was referred to as the "Saudi SARS". The virus appears to have originated in bats (Corman *et al*., 2014). The virus itself has been isolated from a bat (Memish *et al*., 2013). Thus, bats are thought to be natural hosts of this virus. This virusis closely related to the Tylonycteris bat coronavirus HKU4 and Pipistrellus bat coronavirus HKU5 and therefore considered to belong to the same species by the International Committee on Taxonomy of Viruses (ICTV) (Annan *et al*., 2013). Its genomes are phylogenetically classified into two clades, Clades A and B. Early cases of MERS were of Clade A clusters (EMC/2012 and Jordan-N3/2012) while new cases are genetically different in general (Clade B) (Woo *et al*., 2009). The virus grows readily on Vero cells and LLC-MK2 cells (Eckerle *et al*., 2014).

TRANSMISSION

Like SARS, the MERS-CoV spreads between people via close contact, shared medical instruments and coughing. The MERS-Co-V has proved difficult to control even in the most advanced, well-funded hospitals, with clusters of infections being reported in health-care facilities in Saudi Arabia, Jordan and France. This was highlighted in an epidemiological study of 23 cases in Al-Hasa (Assiri *et al*., 2013). The study demonstrates that 21 of the 23 cases were acquired by person-to-person transmission in hemodialysis units, intensive care units or in-patient units in three different health care facilities. Camels from the Middle East may be a source of

MERS-Co V infection spread to the humans. The MERS has also been transmitted to other countries through travelers infected in Arabian Peninsula and neighboring countries. Human-to-human transmission has been observed to a limited extent in households and healthcare workers (Cauchemez *et al*., 2014).

ZOONOTIC SIGNIFICANCE

The MERS-CoV infection is a global public health concern. Considering that direct contact of humans with bats or their secreta may be rare, intermediate hosts that are susceptible to MERS-CoV may be involved in transmitting this virus to humans. As a consequence, upon detection of MERS-CoV emergence, different animal species commonly found in the Middle East, such as camels and goats, are considered as potential intermediate hosts in the MERS-CoV outbreak (CDC., 2013).

INCUBATION PERIOD

Although the exact timing and nature of exposures that result in infection is usually unknown for those cases for which exposure is known or strongly suspected, the incubation period for laboratory confirmed cases of MERS-CoV is generally less than one week.

CLINICAL PRESENTATION

Common symptoms are:

- Acute, serious respiratory illness with fever
- Cough and shortness of breath
- Breathing difficulties
- Pneumonia
- Gastrointestinal symptoms, including diarrhoea
- Kidney failure

DIAGNOSIS

According to World Health Organization, the interim case definition is that a confirmed case is identified in a person with a positive lab test by "molecular diagnostics including either a positive PCR on at least two specific genomic targets or a single positive target with sequencing on a second (WHO., 2013a).

Radiology: Chest X-ray findings tend to show bilateral patchy infiltrates consistent with viral pneumonitis and ARDS. Lower lobes tend to be more involved. The CT scans show interstitial in filtrates.

Laboratory diagnosis: The MERS cases have been reported to have low white blood cell countand in particular low lymphocytes. For PCR testing, the WHO recommends obtaining samples from the lower respiratory tract via bronchoalveolar lavage (BAL), sputum sample or tracheal aspirate as these have the highest viral loads. There have also been studies utilizing upper respiratory sampling via nasopharyngeal swab (WHO., 2013b). Several highly sensitive, confirmatory real-time RT-PCR assays exist for rapid identification of MERS-CoV from patient-derived samples. These assays attempt to amplify up E (targets elements upstream of the E gene), open reading frame 1B (targets the ORF1b gene) and open reading frame 1A (targets the ORF1a gene) (Corman *et al*., 2012). The WHO recommends the upE target for screening assays as it is highly sensitive. In

addition, hemi-nested sequencing amplicons targeting RdRp (present in all coronaviruses) and nucleocapsid (N) gene (specific to MERS-CoV) fragments can be generated for confirmation via sequencing (Lu *et al*., 2014). Reports of potential polymorphisms in the N gene between isolates highlight the necessity for sequence-based characterization. The WHO recommended testing algorithm is to start with an upE RT-PCR and if positive confirm with ORF 1A assay or RdRp or N gene sequence assay for confirmation. If both an upE and secondary assay are positive it is considered a confirmed case.

Immunofluorescence assays (IFA) and protein-microarray based assay have also been developed for diagnosis (Reusken *et al*., 2013). Due to the limited validation done so far with serological assays, WHO guidance is that "cases where the testing laboratory has reported positive serological test results in the absence of PCR testing or sequencing, are considered probable cases of MERS-CoV infection, if they meet the other conditions of that case definition" (WHO., 2013a).

DIFFERENTIAL DIAGNOSES

The MERS-CoV is to be differentiated with SARS-CoV. Both SARS-CoV and MERS-CoV may cause severe respiratory failure and extra pulmonary features such as diarrhoea, whereas mild or asymptomatic cases also occur in both conditions. In comparison with SARS, patients with MERS are older withmale predominance, more comorbid illness and relatively lower human-to-human transmission potential. Although, the viral kinetics of MERS-CoV remain unknown, nosocomial infections of MERS occur early within the first week of illness of the index case, whereas those of SARS occurred mainly in the second week of illness when the patient's upper airway viral load peaks on day 10 of illness. The MERS progresses to respiratory failure much more rapidly than SARS. *In-vitro* data suggest that interferon (IFN) with or without ribavirin and mycophenolic acid may inhibit MERS-CoV, whereas protease inhibitors and IFN have inhibitory activity against SARS-CoV (Hui *et al*., 2014).

TREATMENT

As of 2015 there is no specific vaccine or treatment for the disease (WHO., 2015). However, a number of antiviral medications are currently being studied (Zumla *et al*., 2015). Although, MERS-CoV has been shown to antagonize endogenous interferon (IFN) production, treatment with exogenous types I and III IFN (IFN-α and IFN-λ, respectively) have effectively reduced viral replication *in vitro*.When rhesus macaques were given interferon-α2b and ribavirin and exposed to MERS, they developed less pneumonia than control animals (Falzarano *et al*., 2013). Researchers are investigating a number of ways to combat the outbreak of Middle East respiratory syndrome coronavirus, including using interferon, chloroquine, chlorpromazine, loperamide and lopinavir as well as other agents such as mycophenolic acid and camostat (Chan *et al*., 2015; Cheng *et al*., 2015).

CONTROL AND PREVENTION

A suspected patient should be managed as potentially infected by following recommended biosafety precautions. Currently there is no vaccine or antiviralfor the treatment of the disease. Only supportive treatment is given and these include:

- Supplemental oxygen
- Empiric antimicrobials for community-acquired pathogens
- Conservative fluid management

Use of systemic high-dose corticosteroids can result in serious adverse events in patients including opportunistic infection, avascular necrosis, new health-care-associated bacterial infection and possibly prolonged viral replication. Therefore, corticosteroids should be avoided unless they are indicated for another reason.

- Standard precautions should always be applied in all health-care settings for all patients

Standard precautions include hand hygiene and use of Personal Protective Equipment (PPE) to avoid direct contact with patient's blood, body fluids, secretions (including respiratory secretions) and non-intact skin:

- Wear a particulate respiratorwhen putting on a disposable particulate respirator (e.g., N95mask)
- Wear eye protection (i.e., Goggles or a face shield)
- Wear a clean, non-sterile, long-sleeved gown
- Wear an impermeable apron with expected high fluid volumes that might penetrate the gown
- Perform procedures in an adequately ventilated room perform hand hygiene (hand washing or antisepting hand rub) before and after contactwith the patient and his or her surroundings and after PPE removal (WHO., 2013b)

ADVOCACY AND COMMUNICATION

Message for middle east travelers

Before travel: Persons with pre-existing major medical conditions (e.g., chronic diseases such as diabetes, chronic lung disease and immunodeficiency) are more likely to develop severe infection for MERS if they are exposed to the virus.

Consult a health care provider before travelling to review the risk and assess whether making the traveling is advisable.

At middle east (During your stay at middle east countries):

- Avoid close contact with sick people, especially with those suffering from acute respiratory infections
- Avoid close contact with camels, do not visit farms
- Adhere good food-safety practices, avoid undercooked meat, do not consume unpasteurized camel milk and properly wash fruits and vegetables before eating them
- Maintain good personal hygiene
- If you develop a significant acute respiratory illness with fever and cough (severe enough to interfere with usual daily activities) during your stay at middle east countries you should:
- Report to the local health facilities
- Cover your mouth and nose when coughing or sneezing, if this is not possible, cough or sneeze into upper sleeves of your clothe
- Wash your hands by water and soap regularly afterwards
- Avoid attending crowded places and preferably isolate yourself until the end of the respiratory symptoms and if isolation is not possible, use a tissue for covering nose and mouth or a surgical mask when you are in crowded places

After returning from middle east: If you develop a significant acute respiratory illness with fever and cough within two weeks after you return, you should:

- Seek medical attention, inform health workers about your travel
- Immediately notify your local health authority
- Take precautions when coughing or sneezing
- Minimize your contact with others to keep them away from infection

CONCLUSIONS

Until now, 1368 confirmed MERS cases have been reported. The clinical symptoms caused by MERS-CoV infection mainly relate to the acute respiratory disease that is induced by the virus. In contrast to the SARS epidemic that rapidly was controlled, MERS-CoV is emerging zoonoses, 3 years after it was first detected. Therefore there is an urgent need to clarify whether the virus is introduced multiple times through zoonotic transmission or that human to human transmission is the main driver of the spread of the virus. A further understanding of the emergence and spread of this novel human CoV may halt it's emergence and establishment in the human population. Developing an effective camel MERS-CoV vaccine and implementing appropriate infection control measures may control the continuing epidemic threat. Diagnosis needs help from state health departments, CDC and some international labs. WHO is continuing to work with ministries of health in all affected countries and with international partners to better understand transmission patterns and risk factors for infection and severe outcomes, as well as to develop mitigation measures to prevent human infections and to support the timely release of research findings.

ACKNOWLEDGMENTS

The authors are grateful to Prof. (Dr) Shakil Ahmed Wani, H.O.D Div of Microbiology and Immunology and Prof. (Dr) Sarfaraz Ahmed Wani, Dean FVSc and A.H Shuhama for guidance, critical appreciation in execution of this work.

REFERENCES

Annan, A., H.J. Baldwin, V.M. Corman, S.M. Klose and M. Owusu *et al*., 2013. Human betacoronavirus 2c EMC/2012-related viruses in bats, Ghana and Europe. Emerg. Infect. Dis., 19: 456-459.

Assiri, A., A. McGeer, T.M. Perl, C.S. Price and A.A. Al Rabeeah *et al*., 2013. Hospital outbreak of middle east respiratory syndrome coronavirus. N. Engl. J. Med., 369: 407-416.

CDC., 2013. Update: Severe respiratory illness associated with Middle East Respiratory Syndrome Coronavirus (MERS-CoV)-worldwide, 2012-2013. Morbidity Mortality Weekly Rep., 62: 480-483.

Cauchemez, S., C. Fraser, M.D. van Kerkhove, C.A. Donnelly and S. Riley *et al*.,, 2014. Middle east respiratory syndrome coronavirus: Quantification of the extent of the epidemic, surveillance biases and transmissibility. Lancet Infect. Dis., 14: 50-56.

Chan, J.F.W., S.K.P. Lau, K.K.W. To, V.C.C. Cheng, P.C.Y. Woo and K.Y. Yuen, 2015. Middle east respiratory syndrome coronavirus: Another zoonotic betacoronavirus causing SARS-like disease. Clin. Microbiol. Rev., 28: 465-522.

Cheng, K.W., S.C. Cheng, W.Y. Chen, M.H. Lin and S.J. Chuang *et al*., 2015. Thiopurine analogs and mycophenolic acid synergistically inhibit the papain-like protease of Middle East respiratory syndrome coronavirus. Antiviral Res., 115: 9-16.

Corman, V.M., I. Eckerle, T. Bleicker, A. Zaki and O. Landt, 2012. Detection of a novel human coronavirus by real-time reverse-transcription polymerase chain reaction. Eurosurveillance, Vol. 17, No. 39.

Corman, V.M., N.L. Ithete, L.R. Richards, M.C. Schoeman, W. Preiser, C. Drosten and J.F. Drexler, 2014. Rooting the phylogenetic tree of middle east respiratory syndrome coronavirus by characterization of a conspecific virus from an African Bat. J. Virol., 88: 11297-11303.

Eckerle, I., V.M. Corman, M.A. Muller, M. Lenk, R.G. Ulrich and C. Drosten, 2014. Replicative capacity of MERS coronavirus in livestock cell lines. Emerg. Infect. Dis., 20: 276-279.

Falzarano, D., E. de Wit, A.L. Rasmussen, F. Feldmann and A. Okumura *et al*., 2013. Treatment with interferon-*a*2b and ribavirin improves outcome in MERS-CoV-infected rhesus macaques. Nature Med., 19: 1313-1317.

Hui, D.S., Z.A. Memish and A. Zumla, 2014. Severe acute respiratory syndrome vs. the Middle East respiratory syndrome. Curr. Opin. Pulm. Med., 20: 233-241.

Kindler, E., H.R. Jonsdottir, D. Muth, O.J. Hamming and R. Hartmann *et al*., 2013. Efficient replication of the novel human betacoronavirus EMC on primary human epithelium highlights its zoonotic potential. mBio, Vol. 4, No. 1. 10.1128/mBio.00611-12

Ksiazek, T.G., D. Erdman, C.S. Goldsmith, S.R. Zaki and T. Peret *et al*., 2003. A novel coronavirus associated with severe acute respiratory syndrome. N. Engl. J. Med., 348: 1953-1966.

Lu, X., B. Whitaker, S.K.K. Sakthivel, S. Kamili and L.E. Rose *et al*., 2014. Real-time reverse transcription-PCR assay panel for middle east respiratory syndrome coronavirus. J. Clin. Microbiol., 52: 67-75.

Memish, Z.A., N. Mishra, K.J. Olival, S.F. Fagbo and V. Kapoor *et al*., 2013. Middle East respiratory syndrome coronavirus in bats, Saudi Arabia. Emerg. Infect. Dis., 19: 1819-1823.

Perlman, S. and J. Netland, 2009. Coronaviruses post-SARS: Update on replication and pathogenesis. Nat. Rev. Microbiol., 7: 439-450.

Raj, V.S., H. Mou, S.L. Smits, D.H.W. Dekkers and M.A. Muller *et al*., 2013. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. Nature, 495: 251-254.

Reusken, C.B.E.M., B.L. Haagmans, M.A. Muller, C. Gutierrez and G.J. Godeke *et al*., 2013. Middle East respiratory syndrome coronavirus neutralising serum antibodies in dromedary camels: A comparative serological study. Lancet Infect. Dis., 13: 859-866.

Spanakis, N., S. Tsiodras, B.L. Haagmans, V.S. Raj and K. Pontikis *et al*., 2014. Virological and serological analysis of a recent Middle East respiratory syndrome coronavirus infection case on a triple combination antiviral regimen. Int. J. Antimicrob. Agents, 44: 528-532.

WHO., 2013a. Laboratory testing for middle east respiratory syndrome coronavirus. WHO, Geneva, Switzerland, September 2013. http://www.who.int/csr/disease/coronavirus_infections/MERS_ Lab_recos_16_Sept_2013.pdf.

WHO., 2013b. Revised interim case definition for reporting to WHO-Middle East respiratory syndrome coronavirus (MERS-CoV). WHO, Geneva, Switzerland, July 2013. http://www.who.int/csr/disease/coronavirus_infections/case_definition_03_07_2014/en/.

WHO., 2015. Middle East respiratory syndrome coronavirus (MERS-CoV). Fact Sheet No. 401, WHO, Geneva, Switzerland, June 2015. http://www.who.int/mediacentre/factsheets/mers-cov/en/.

Woo, P.C.Y., S.K.P. Lau, Y. Huang and K.Y. Yuen, 2009. Coronavirus diversity, phylogeny and interspecies jumping. Exp. Biol. Med., 234: 1117-1127.

Zaki, A.M., S. van Boheemen, T.M. Bestebroer, D.M.E. Albert, D.V.M. Osterhaus and R.A.M. Fouchier, 2012. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N. Engl. J. Med., 367: 1814-1820.

Zeng, Q., M.A. Langereis, A.L.W. van Vliet, E.G. Huizinga and R.J. de Groot, 2008. Structure of coronavirus hemagglutinin-esterase offers insight into corona and influenza virus evolution. Proc. Natl. Acad. Sci. USA., 105: 9065-9069.

Zumla, A., D.S. Hui and S. Perlman, 2015. Middle East respiratory syndrome. Lancet, 386: 995-1007.