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EC MICROBIOLOGY
Review Article

Middle East Respiratory Syndrome Coronavirus (MERS-CoV): Transmission Dynamics and Prospects for Vaccine Development

Bandar Alosaimi[1,2]*, Maaweya E Hamed[3] and Asif Naeem[1]

[1]*Research Center, King Fahad Medical City, Riyadh, Saudi Arabia*

[2]*College of Medicine, King Fahad Medical City, Riyadh, Saudi Arabia*

[3]*College of Science, King Saud University, Department of Botany and Microbiology, Riyadh, Saudi Arabia*

***Corresponding Author:** Bandar Alosaimi, College of Medicine, King Fahad Medical City, Riyadh, Saudi Arabia.

Received: September 03, 2019; **Published:** October 18, 2019

Abstract

Middle East respiratory syndrome coronavirus (MERS-CoV) has infected more than 2200 people with case fatality rate of 35%, mainly in the Middle East. The primary source of infection in humans is suspected to be contact with dromedary camels. Although human-to-human transmission is not common, it continues to cause large outbreaks, especially in health-care settings. MERS-CoV's transmission mainly occurs by droplets or contact through aerosol. Other contributing factors are lack of personal hygiene and implementation of infection control methods. The fatal outcome of cases is usually associated with other underlying medical conditions. There is no specific treatment available and the treatment relies mainly on supportive therapies along with use of various antimicrobial agents. The viral spike (S) protein is immunogenic and therefore, used as a key target antigen for vaccine development. It has the potential to elicit sufficient immunity both humoral and cellular against MERS-CoV; therefore, it is likely to be developed as a vaccine against MERS-CoV infection.

Keywords: *Middle East Respiratory Syndrome Coronavirus (MERS-CoV); Transmission; Treatment; Vaccines; Saudi Arabia*

Abbreviations

CoVs: Coronaviruses; DPP4: Receptor Dipeptidyl Peptidase 4; RBD: Receptor Binding Domain; MERS-CoV: Middle East Respiratory Syndrome Coronavirus; HCWs: Health Care Workers; CDC: Centers for Disease Control and Prevention; NTD: N-terminal Domain; CTD: C-terminal Domain; RBD: Receptor-binding Domain; DPP4: Dipeptidyl Peptidase 4; sDPP4: Soluble Dipeptidyl Peptidase 4; IFN: Interferon; ExoN: Exoribonuclease; MVA: Modified Vaccinia Virus Ankara; rRBD: recombinant Receptor Binding Domain

Background

Middle East Respiratory Syndrome Coronavirus (MERS-CoV) was first isolated in 2012 from a 60-year-old patient in Saudi Arabia. It was associated with symptoms of fever, expectoration, and shortness of breath leading to death of the patient due to respiratory and renal failure [4]. Initial laboratory investigations for common respiratory viruses, like respiratory syncytial virus, influenza A and B, parainfluenza virus types 1 to 3, and adenovirus were negative. However, virus-specific cytopathological changes were observed after inoculation of sputum sample in Vero and LLC-MK2 cell lines [4]. Most of the cases have been reported from the Middle East. At present, 82% of human cases of MERS-CoV infection have been reported by Kingdom of Saudi Arabia alone. WHO has been notified about 806 deaths related to MERS-CoV, and 27 countries have reported cases of MERS-CoV [1]. Genetically similar strains have imported to most of the countries [5]. Clinical manifestations of MERS-CoV are similar to those of SARS, nevertheless, MERS-CoV patients mostly develop rapid respiratory failure [5]. MERS-CoV has a wide species tropism as the virus can replicate in a variety of mammalian cells of different origins [6].

MERS-CoV causes severe health complications with a high fatality rate. Specific antiviral therapies for the treatment of MERS infection do not exist at the moment. However, several potential drugs identified during *in vitro* studies are in clinical use that could be used to treat MERS infection [2]. The spike (S) protein of MERS-CoV has a crucial role in virus host interaction and pathogenesis. The S1 subunit in the receptor binding domain (RBD) mediates the binding of virus to the cellular host by a receptor protein called dipeptidyl peptidase 4 (DPP4). The S2 subunit then mediates the fusion of viral and host cell membranes [3]. The viral spike (S) protein is immunogenic and therefore, used as a key target antigen for vaccine development [3].

The presence of MERS-CoV specific antibodies in dromedary camels suggests the zoonotic nature of MERS-CoV infections among humans [7]. However, the dynamics of transmission of MERS-CoV from animal to humans interface are not fully understood. At the same time, dromedary camels experimentally infected with MERS-CoV have shown to secrete high amounts of infectious virus in the nasal discharge [10]. Bats as likely origin of MERS-CoV interms of transmission and reservoir have also been discussed [8]. Human to human transmission of MERS-CoV has been reported and confirmed recently [13]. Most of the major outbreaks of MERS-CoV are associated with the health-care facilities leading to human-to-human transmission [14]. However, it is still unclear whether the inter-human transmission is similar to SARS occurring by means of large respiratory droplets, coughing and sneezing, or via fomites [12]. Moreover, the episodes of transmission usually take place during both the symptomatic and the incubation phases of the infection [5].

Transmission dynamics of MERS-CoV

The MERS-CoV transmission occurs mainly due to nosocomial infections, but risk factors in healthcare settings are not well defined [15]. The MERS-CoV is transmitted directly by droplets and contact might convert spread through aerosol under certain conditions [17]. The high risk group for MERS-CoV transmission are the infected health care workers (HCWs) [17].

The assessment of the knowledge and attitudes of HCWs in Saudi Arabia to MERS-CoV has revealed that the poor usage of mask, hand hygiene, lack of training and awareness about infection control, implementation of policies and procedures are associated with high risk of transmission of MERS-CoV [18]. Therefore, knowledge deficits, unrecognized disease, insufficient infection control guidelines, poor commitment, and great numbers of patient cases during outbreaks increase the nosocomial transmission [14].

Majority of severe MERS cases have been observed among patients with additional chronic conditions, such as obesity, diabetes, cardiovascular diseases, respiratory distress, renal disease, cancer or immunocompromised, and in elderly patients [18]. Moreover, obesity, diabetes, and renal disease are also the risk factors for nosocomial transmission of MERS-CoV as compared to the negative controls of hospital-based cases with respiratory illnesses [12]. Increased number of smokers among healthcare workers reflected that HCW smokers have a threefold higher risk for infection as compared to nonsmokers [16].

MERS-CoV prevalence may indicate Middle East social norms, which increase the probability of exposure in males relative to females, or elderly men at a higher rate of underlying medical conditions [20]. Confirmed cases of MERS-CoV in Saudi Arabia has shown that male-to-female case ratio is 1.6:1. [21]. The source of primary infection in humans is suspected from animal transmission of MERS-CoV, with high evidence supporting the importance of dromedary camels in Saudi Arabia [52].

A cross sectional study investigated large number of camels from Burkina Faso, Ethiopia, and Morocco [22]. The results showed that the risk of infection among camel was related to sex. Female milking camels had the highest titer of antibodies against MERS-CoV, ensued by male camels used for meat consumption. Camels used for transportation activities had the lowest seroprevalence however, milking camels were associated with MERS-CoV illness [22]. People having contact with camels in countries like Saudi Arabia, Qatar, and United Arab Emirates, are at great risk of MERS-CoV infection [1]. Better understanding of potential ramifications of MERS-CoV helps to improve the infection prevention and control awareness, and implementation of proper measures to prevent the spread of MERS-CoV in environmental and health care settings [1].

The global public health authorities have called for implementation of infection-control and surveillance measures, since the outbreak of MERS-CoV [60]. Challenge in controlling of emerging infectious diseases requires constant re-evaluation and intelligence in the management besides the treatment and prevention methods. Furthermore, majority of MERS cases reported were due to the lack of infection control measures in community and healthcare settings [13]. Healthcare-related clusters of MERS-CoV have caused the sustained and continued emergence of outbreaks involving human to human transmission. However, the possibility of MERS-CoV epidemic remains limited at present [23].

The primary animal reservoir is currently recognized in camels with dominant cases of MERS-CoV [20]. The infected camels with MERS-CoV may show nasal discharge or no signs at all. They may transmit MERS-CoV through various body secretions like nasal, eye discharge, faeces, and raw milk. MERS-CoV could be stable in camel's milk for long periods of time; and for that, pasteurization or cooking is recommended before consumption. In surveys conducted to create MERS awareness among the Saudi Arabian population, less than half of the participants were aware that camels might be the primary source of MERS-CoV [59].

One of the potential ways to prevent these zoonotic infections in the endemic areas is to avoid direct contact or dairy products with camels [24]. A good hand hygiene practice can reduce the risk of community transmission. Basic infection control measures include wearing of a mask outdoors, which has been found with 70% risk reduction. Frequently washing hands after returning home has resulted in a smaller risk reduction. Ministry of Health in Saudi Arabia put regular updates through social media and on its website, regarding details of ongoing MERS-CoV cases [24]. Multiple superspreading events related to an index case was associated with two health-care associated outbreaks [58]. Secondary transmission occurred due to delays in identification of cases and failure to implement the control measures. Implementation of infection control prevention precautions, contact tracing, repeat testing for suspected cases eventually stopped transmission [58].

Healthcare workers are more susceptible to MERS-CoV; up to 75% infections in the healthcare environment are secondary infections, which are acquired from infected patients through airborne transmission, droplet contact, or through direct and indirect contact [25]. In fact, large outbreaks have been reported in healthcare settings compared to the transmission in community settings. Recent health-care-associated outbreaks in Saudi Arabia and South Korea were due to poor compliance with infection control practices thus resulting in person-to person transmission of MERS-CoV [26]. In the perspective of human to human transmission, particularly in health care facilities there is an urgent need of effective preventative measures. Further, In Saudi Arabia and Korea it is recommended to implement effective and consistent application of basic and advanced infection control procedures to reduce the number of hospital-associated cases [27]. Comorbidities and complicated clinical presentation have been associated with a delay in the identification of MERS-CoV infected individuals [61]. Therefore, systematic and efficient testing for MERS-CoV in hospital setting for patients with known risk factors and deteriorating respiratory symptoms might help in timely identification of MERS-CoV cases.

Standard contact precautions are recommended by United States' Centers for Disease Control and Prevention (CDC), when caring for an infected patient and airborne precaution involving N-95 mask. In addition, before and after every patient contact; hand hygiene should be performed, on any occasion, especially handling patient's blood, body fluids. Isolation rooms fitted with ventilated system should be used to isolate the patient, when patient is suspected or confirmed with the infection in healthcare settings. Furthermore, use of gloves and a gown while attending the infected or suspect patients, and their disposal before exit could be useful [56]. Nevertheless, awareness among healthcare providers can limit the outbreak and control MERS in rapid isolation. Strict infection control practices may also limit the spreading of the disease. The outbreak of MERS has been exaggerated in healthcare facilities due to massive spreading events. Therefore, staff education, basic personal prevention measures, and advanced procedures for the handling of infected patients could be affective prevention and control measures [57].

The possibility of MERS spreading to all nations comes with the ease of international travelling. MERS endemic countries could lead to importation of virus due to travelers from MERS free countries. CDC recommended that frequent hand-washing and avoiding close contact with ill persons could be very useful for travelers. Especially from contact with persons with acute respiratory symptoms or suspected animals, maintain personal hygiene, and avoid eating uncooked food or drink unpasteurized milk, peculiarly from camels [20]. Travelers from the region that developed respiratory symptoms or onset of fever during their trip or within 14 days of leaving the region should get medical care [28]. South Korean experience determined an adequate assessment of patients who had a recently travelled to ensure early application of suitable control measures and speed up laboratory confirmation and relevant clinical management [23]. Furthermore, in countries other than Middle East, travel history should be recorded for patients presenting with symptoms similar to MERS-CoV infection. Meanwhile, US citizens travelling to Middle East need to follow the guidlines, recommended by Centers for Disease Control and Prevention regarding MERS-CoV, including particular information for those traveling for Hajj and Umrah [28].

MERS-CoV transmission becomes a great concern during the annual Hajj pilgrimage. However, the surveillance studies since 2013 have not showed any MERS-CoV cases among Hajj pilgrims [19,23]. Suitable infection control measures can easily be impaired in the crowded living quarters during Hajj. Therefore, the visiting pilgrims are recommended by health agencies to wash their hands, consume hygienic foods, and isolate themselves if they are infected. The Saudi Ministry of Health in 2013, recommended that elderly people with chronic diseases, the immunocompromised patients, pregnant women, and children less than 12 years old need to abstain from performing the Hajj and Umrah [19,24]. The awareness, early detection, and application of appropriate infection control measures are the most effective tools.

Treatment of MERS-CoV

The cases of MERS-CoV occur periodically in the form of clusters or as health-care associated outbreaks and vary from asymptomatic to rapidly progressive and deadly disease [53,54]. MERS-CoV is classified into lineage-C beta-coronavirus, infecting humans [30]. Like SARS (severe acute respiratory syndrome) coronavirus infection, MERS-CoV infection can cause an acute respiratory distress syndrome with multi-organ dysfunction [4]. Finding suitable treatment for MERS-CoV is of primary importance as there is currently no specific therapy or vaccine for its prevention and cure [31]. The serologic testing for detection of unidentified infections in asymptomatic or mildly symptomatic individuals remains inadequate [62]. The case management of MERS-CoV infections depends on a combination of supportive measures and antiviral therapy for any associated viral infections, along with strict implementation of infection control safeguards [1]. At present, no approved antiviral therapy for the treatment of patients with MERS-CoV infection is available. The existing information about treatment options for MERS-CoV is based on the experience from SARS-CoV and from *in vitro* studies [13]. Mechanism of action of therapeutic agents available for MERS-CoV could be classified as the agents that block the entry of virus, inhibit virus growth, interfere with the host immune system, and a combination treatment [13].

MERS-CoV spike (S) protein belongs to the family of type I transmembrane glycoproteins, which is located at the viral envelope surface in a trimer state [32]. The first phase of viral entry could be blocked by targeting the binding site between the RBD and the receptor and provide superior pharmacological action to suppress MERS-CoV infection [67]. Experimental MERS-CoV infection in ferrets showed that adenosine deaminase, a DPP4 binding protein, competes for virus binding and appear to be a natural antagonist for MERS-CoV infection [68]. The soluble form of DPP4 (sDPP4) can also inhibit the entry of MERS-CoV into host cells [69]. The antiviral action and pharmacological properties of sDPP4 might be enhanced by the chemical modification or addition of some protein fragments [32]. Alternatively, cellular DPP4 interaction with viral RBD could also be blocked by using anti-DPP4 antibodies leading to the inhibition of MERS-CoV infection. However, it is difficult to adopt this experimental strategy *in vivo* because DPP4 has crucial roles in several distinct signaling pathways and regulation of many peptides [33].

Similar to enfu-virutide (HIV fusion inhibitor T20), the peptides originating from the MERS-CoV S2 subunit of spike protein in the HR2 domain bind specifically to HR1 domain leading to blockage of viral fusion core synthesis. It eventually causes the prevention of viral envelope protein and host cell membrane interaction [35]. Further characterization of these peptides could have great potential in terms of effective treatment and prevention of MERS-CoV infections. A decrease in the degradation of metabolic enzymes and reduced protein immunogenicity prolongs half-life of the conjugated complex of PEG to a peptide drug. All of these strategies could potentially be useful for induction of changes in the fusion inhibitory peptides of MERS-CoV, thus, enhancing their antiviral properties for treatment purposes.

A combination of Ribavirin and interferon-a2b has shown promising results in the animal models. It lead to a reduction in viral replication, improved the healing of infected lung tissue, and enhanced the recovery of MERS-CoV infected rhesus macaques. Furthermore, the prophylactic dose of the combination was observed to reduce disease severity [37]. MERS-CoV infection results in the elevated levels of IL-8 and an attenuated IFN-b response. Different treatment regimes of interferon separately or combined with ribavirin have been known to cause inhibition of SARS-CoV [38]. In case of MERS-CoV, both IFN-a and IFN-l caused more efficient inhibition as compared to SARS-CoV. The addition of IFN-b caused a further reduction of 3-log in viral titer. MERS-CoV was more susceptible to a combination of different interferon products including IFN-a2b, IFN-g, IFN-universal and IFN-a2a, IFN-b. The strongest *in vitro* inhibition of MERS-CoV was caused by IFN-b treatment. Pegylated IFN-a was 50 to 100 times more effective *in vitro* for MERS-CoV as compared to SARS- CoV [39]. Convalescent plasma has also been used for MERS-CoV neutralization, as a treatment option [13]. This approach can only be used when convalescent plasma from recovered patients is available. However, significant neutralizing activity has not been observed in recovering MERS-CoV patients with mild pneumonia >1 year after being successfully treated with antiviral agents [9]. Other virus replication inhibitors such as cylcophilin inhibitors were also investigated as a possible therapy for MERS-CoV infection. Immunosuppressant agents like mycophenolic acid inhibits the proliferation of lymphocytes and prevents viral RNA replication [13]. Replication of all coronavirus genera, including SARS-CoV is blocked by cyclosporine A. Its *in vitro* inhibitory role has also been recognized against MERS-CoV. Despite invitro activities, the question remains regarding the ability of these agents to give better treatment outcomes. Exoribonuclease (ExoN) has been revealed as a promising target for inhibition, and together with ribavirin these nano-molecule inhibitors of ExoN activity may be presented as potential pan-CoV treatment [41].

MERS-CoV vaccine candidate development

Continous efforts have been carried out since the emergence of MERS-CoV in 2012 for the preparation of vaccine against MERS-CoV. Vaccine trials were delayed due to the absence of suitable animal models of MERS-CoV disease [63]. Different vaccine candidates have been tested on different animal models (Table 1) to evaluate their immunogenicity, such as recombinant modified vaccinia virus Ankara (MVA) by expression of full-length MERS-CoV spike protein (MVA-MERS-S), or DNA vaccine encoding S protein [42].

Different recombinant plasmids, expressing MERS-CoV spike protein: pcDNA3.1-S, pcDNA3.1-SDCD, and pcDNA3.1-S1 can induce immunity against MERS-CoV infection in BALB/c mice [42]. Among those pcDNA3.1-S1 showed the highest antibody titer reaching end point of 1:1280 and could elicit a potent and strong protective immune response against MERS-CoV infection [42].

DNA vaccine immunization expressing full-length Spike protein followed by the S1 subunit protein caused a neutralizing antibody against both receptor binding domain (RBD) and non-RBD portions of S1 and S2 subunit, and vaccinated Rhesus macaques demonstrated a significantly better radiological finding as compared to the unvaccinated subunits [43]. Another study evaluated the efficacy of synthetic consensus anti–spike protein DNA vaccine to induce immunity against MERS-CoV infection. The vaccine had elicited considerable cellular immunity and neutralizing antibodies against Spike protein in all animal models. However, rhesus masques seroconverted rapidly after only single immunization and demonstrated high levels of neutralizing antibodies [44].

However, there are challenges for vaccine development and could delay its availability for human use. The cost-effectiveness of vaccine is the most important factor since pharmaceutical companies would not benefit due to the high cost of the clinical trial, low targeted population, and time duration.

Development of MERS-CoV neutralizing antibodies

Neutralizing antibodies against MERS-CoV infection were isolated from memory B cell from an infected individual in London and named as LCA60 [46]. BALB/c mice transduced with adenoviral vectors expressing human CD26 were used in intranasal infection with EMC and London strains of MERS-CoV. The LCA 60 was confirmed to neutralize MERS-CoV from London (London1/2012), Saudi Arabia (EMC/2012), and Jordan (Jordan-N3/2012) [46].

In order to test cross neutralization, four recombinant receptor binding domain (rRBD) proteins from different human MERS-CoV strains and one (rRBD) protein from camel MERS-CoV strain were developed [47]. These rRBD proteins elicited S-protein specific antibodies in immunized mice inducing cross neutralization of 17 MERS-CoV pseudoviruses. This resulted in the expression of S proteins of variant human and camel MERS-CoV isolates. The RBD-based MERS vaccines were able to protect against present and future strains due its ability to elicit sufficient cross neutralizing antibodies [47].

rRBD vaccine in rhesus macaques can provide partial immunity against MERS-CoV infection [48]. Vaccinated rhesus macaques were challenged with MERS-CoV and displayed mild symptoms of pneumonia. However, the pathological examination showed that rRBD vaccine had alleviated the pneumonia compared to the control group.

MERS-CoV S protein expressing vaccine using measles virus as a vector have also been employed [49]. The vaccine expressed MERS-CoV S protein in full length (MERS-CoV S) or a soluble variant of MERS-CoV S in truncated form (MERS-CoV-solS). The vaccine was tested on type I interferon receptor-deficient (IFNAR-/-) - CD46Ge mice. The viral neutralizing test revealed that both vaccines had elicited neutralizing antibodies against measles virus and MERS-CoV. Further splenocyte analysis revealed that both vaccines can induce antigen-specific CD8+ CTLs that are capable of lysing cells expressing MERS-CoV S. Recombinant MV encoded various forms of the MERS-CoV S glycoprotein, which can elicit humoral and cellular immunity and provide protective immunity against MERS-CoV infection [49].

A modified Vaccinia Virus Ankara (MVA) vaccine [64] expressing MERS-CoV spike protein (MVA-S) elicited Nab and CD8+ T cell responses in mice and conferred protection against MERS-CoV infection in mice transduced with adenovirus hDPP4 before challenge [65]. Another additional feature of this vaccine has been less inflammation and hyperplasia of lymph node at the injection site [66]. This vaccine was given to reduce virus excretion in dromedary camels after MERS-CoV infection. The vaccinated camels were challenged with MERS-CoV, which showed mild clinical signs compared to the control group. The testing of samples of nasal respiratory tract revealed high titers of MERS-CoV in control groups. While, vaccinated camel showed significant reduction in excretion of MERS-CoV [42]. A Phase I clinical trial is going on at present (https://clinicaltrials.gov/ct2/show/ NCT03615911).

Inhibitory activities of Anti-MERS-CoV fusion inhibitor on cellular level

The neutralizing activity against MERS-CoV pseudo virus infection showed that there is correspondence between the neutralizing antibodies and the ones tested by pseudo virus inhibition assay. This clearly confirmed reliability of established pseudo virus-based inhibition assay to conduct the evaluation of neutralizing antibodies. The vaccines against MERS-CoV are induced against these antibodies [50].

Protective effect of MERS-HR2P-M2

In the cell culture, the IFN-β is associated with the inhibition of MERS-CoV infection. The kinetics of virus clearance is likely to be accelerated if an individual is provided with IFN-β treatment before or after having MERS-CoV infection [51].

Conclusion

MERS-CoV is a fatal zoonotic virus that originated in the Middle East and continued outbreaks remains a challenge for public health. There is no specific therapy or vaccine available for humans or animals. The anti-viral peptides, monoclonal antibodies and protease

inhibitors are among the treatment options that have shown some success *in vitro* and *in vivo*. Various treatment options could only be used at early stages of infection by disruption of viral replication, dissemination and limiting immune responses. Therefore, further studies are needed to understand the pathogenesis of the disease and transmission dynamics of MERS. The latest ongoing outbreak at Wadi Addawasir in Saudi Arabia (at the time of submission of this manuscript) underlines the importance of intrupting the transmission of virus and further strengthening of infection control measures at health-care facilities. The pathogenesis and immune responses of MERS-CoV are not fully understood, which is important for effective vaccine development. Additionally, the duration of immune responses after the vaccination have not been assessed for MERS-CoV vaccine candidates. Nevertheless, the completion of ongoing clinical trials based on the expression of S protein in DNA plasmid early next year might prove to be a desicive step to prevent future outbreaks and help in better treatment. GLS-5300, a DNA plasmid vaccine expressing MERS-CoV spike (S) glycoprotein is the first potential MERS-CoV vaccine to have entered human trials. This vaccine is currently being evaluated for safety, tolerability and immunogenicity after intradermal administration. The vaccination is followed by electroporation at 0.3 and 0.6 mg/dose for determination of 2 and 3-dose regimens. A Phase I/IIa clinical trial is underway (https://clinicaltrials.gov/ct2/show/NCT03721718).

Declarations

The author declares no conflict of interest.

Ethical Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author upon request.

Competing Interest

The author declares no competing interest.

Funding

This research is not funded by any source.

Author Contribution

BA was responsible to completely conclude and correspond this review.

Acknowledgement

The authors thank the Research Center at King Fahad Medical City for their continues support.

Bibliography

1. WHO. WHO Middle East respiratory syndrome coronavirus. WHO MERS-CoV (2019).
2. Kaech SM., *et al.* "Effector and memory T-cell differentiation: implications for vaccine development". *Nature Reviews Immunology* 2 (2002): 251-262.
3. Choi J., *et al.* "Progress of Middle East respiratory syndrome coronavirus vaccines: a patent review". *Expert Opinion on Therapeutic Patents* 27 (2017): 721-731.

4. Zaki AM., *et al.* "Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia". *The New England Journal of Medicine* 367 (2012):1814-1820.

5. Chung YS., *et al.* "Genetic Characterization of Middle East Respiratory Syndrome Coronavirus, South Korea, 2018". *Emerging Infectious Diseases* 25.5 (2019).

6. Chan JF., *et al.* "Broad-spectrum antivirals for the emerging Middle East respiratory syndrome coronavirus". *Journal of Infection* 67 (2013): 606-616.

7. Al-Tawfiq JA and Memish ZA. "Middle East respiratory syndrome coronavirus: transmission and phylogenetic evolution". *Trends in Microbiology* 22 (2014): 573-579.

8. Corman V., *et al.* "Detection of a novel human coronavirus by real-time reverse-transcription polymerase chain reaction". *Euro surveillance* (2012): 17.

9. Choi JY., *et al.* "Absence of neutralizing activity in serum 1 year after successful treatment with antivirals and recovery from MERS in South Korea". *Clinical and Experimental Vaccine Research* 8.1 (2019): 86-88.

10. Adney DR., *et al.* "Replication and shedding of MERS-CoV in upper respiratory tract of inoculated dromedary camels". *Emerging Infectious Diseases* 20 (2014): 1999.

11. Alagaili AN., *et al.* "Middle East respiratory syndrome coronavirus infection in dromedary camels in Saudi Arabia". *MBio* 5 (2014): e00884-e00814.

12. Hui DS and Zumla A. "Advancing priority research on the Middle East respiratory syndrome coronavirus". *The Journal of Infectious Disease* 209.2 (2014):173-176.

13. Al-Tawfiq JA and Memish ZA. "Drivers of MERS-CoV transmission: what do we know?". *Expert Review of Respiratory Medicine* 10 (2016): 331-338.

14. Oboho IK., *et al.* "MERS-CoV outbreak in Jeddah—a link to health care facilities". *The New England Journal of Medicine* 372 (2014): 846-854.

15. Kang CK., *et al.* "Clinical and Epidemiologic Characteristics of Spreaders of Middle East Respiratory Syndrome Coronavirus during the 2015 Outbreak in Korea". *Journal of Korean Medical Science* 32 (2017): 744-749.

16. Alraddadi BM., *et al.* "Risk factors for Middle East respiratory syndrome coronavirus infection among healthcare personnel". *Emerging Infectious Diseases* 22 (2016): 1915.

17. Kim JY., *et al.* "Middle East respiratory syndrome infection control and prevention guideline for healthcare facilities". *Infection and Chemotherapy* 47 (2015): 278-302.

18. Alsahafi AJ and Cheng AC. "Knowledge, Attitudes and Behaviours of Healthcare Workers in the Kingdom of Saudi Arabia to MERS Coronavirus and Other Emerging Infectious Diseases". *International Journal of Environmental Research and Public Health* 13 (2016): 1214.

19. Hashem AM., *et al.* "MERS-CoV, influenza and other respiratory viruses among symptomatic pilgrims during 2014 Hajj season". *Journal of Medical Virology* (2019).

20. Shapiro M., *et al.* "Middle East respiratory syndrome coronavirus: review of the current situation in the world". *Disaster and Military Medicine* 2 (2016): 9.

21. Aleanizy FS., *et al.* "Outbreak of Middle East respiratory syndrome coronavirus in Saudi Arabia: a retrospective study". *BMC Infectious Diseases* 17 (2017): 23.

22. Miguel E., *et al.* "Risk factors for MERS coronavirus infection in dromedary camels in Burkina Faso, Ethiopia, and Morocco, 2015". *Eurosurveillance* (2017): 22.

23. Omrani AS and Shalhoub S. "Middle East respiratory syndrome coronavirus (MERS-CoV): what lessons can we learn?". *Journal of Hospital Infection* 91 (2015): 188-196.

24. Gautret P., *et al.* "Viral respiratory tract infections-environmental risk factors and transmission". *The Lancet Infectious Diseases* 14 (2014): 1113-1122.

25. Mirza MB., *et al.* "Middle East respiratory syndrome and precautions to be taken by dental surgeons". *Journal of Health Specialties* 4 (2016): 105.

26. Zumla A., *et al.* "Infectious diseases epidemic threats and mass gatherings: refocusing global attention on the continuing spread of the Middle East Respiratory syndrome coronavirus (MERS-CoV)". *BMC Medicine* 14 (2016): 132.

27. Rabaan A., *et al.* "Dynamics of scientific publications on the MERS-CoV outbreaks in Saudi Arabia". *Journal of Infection and Public Health* 10.6 (2017): 702-710.

28. Rasmussen SA., *et al.* "Middle East respiratory syndrome coronavirus: update for clinicians". *Clinical Infectious Diseases* 60 (2015): 1686-1689.

29. Sharif-Yakan A and Kanj SS. "Emergence of MERS-CoV in the Middle East: origins, transmission, treatment, and perspectives". *Plos Pathogens* 10 (2014): e1004457.

30. van Boheemen S., *et al.* "Genomic characterization of a newly discovered coronavirus associated with acute respiratory distress syndrome in humans". *MBio* 3.6 (2012): e00473-e00412.

31. Falzarano D., *et al.* "Inhibition of novel β coronavirus replication by a combination of interferon-α2b and ribavirin". *Scientific Reports* 3 (2013): 1686.

32. Xia S., *et al.* "Middle East respiratory syndrome coronavirus (MERS-CoV) entry inhibitors targeting spike protein". *Virus Research* 194 (2014): 200-210.

33. Zhong J., *et al.* "An emerging role of dipeptidyl peptidase 4 (DPP4) beyond glucose control: potential implications in cardiovascular disease". *Atherosclerosis* 226 (2013): 305-314.

34. Ying T., *et al.* "Exceptionally potent neutralization of Middle East respiratory syndrome coronavirus by human monoclonal antibodies". *Journal of Virology* 88 (2014): 7796-7805.

35. Lu L., *et al.* "Structure-based discovery of Middle East respiratory syndrome coronavirus fusion inhibitor". *Nature Communications* 5 (2014): 3067.

36. Guery B and van der Werf S. "Coronavirus: need for a therapeutic approach". *The Lancet Infectious Diseases* 13 (2013): 726-727.

37. Khalid M., *et al.* "Case report Ribavirin and interferon-α2b as primary and preventive treatment for Middle East respiratory syndrome coronavirus: a preliminary report of two cases". *Antiviral Therapy* 20 (2015): 87-91.

38. Momattin H., *et al.* "Therapeutic options for Middle East respiratory syndrome coronavirus (MERS-CoV)–possible lessons from a systematic review of SARS-CoV therapy". *International Journal of Infectious Disease* 17 (2013): e792-e798.

39. Hart BJ., *et al.* "Interferon-β and mycophenolic acid are potent inhibitors of Middle East respiratory syndrome coronavirus in cell-based assays". *Journal of General Virology* 95 (2014): 571-577.

40. Buchholz U., *et al.* "Contact investigation of a case of human novel coronavirus infection treated in a German hospital, October-November 2012". *Euro Surveillance* 18.8 (2013).

41. Smith EC., *et al.* "Coronaviruses lacking exoribonuclease activity are susceptible to lethal mutagenesis: evidence for proofreading and potential therapeutics". *Plos Pathogens* 9 (2013): e1003565.

42. Haagmans BL., *et al.* "An orthopoxvirus-based vaccine reduces virus excretion after MERS-CoV infection in dromedary camels". *Science* 351 (2016): 77-81.

43. Wang Q., *et al.* "Bat origins of MERS-CoV supported by bat coronavirus HKU4 usage of human receptor CD26". *Cell Host and Microbe* 16 (2014): 328-337.

44. Muthumani K., *et al.* "A synthetic consensus anti–spike protein DNA vaccine induces protective immunity against Middle East respiratory syndrome coronavirus in nonhuman primates". *Science Translational Medicine* 7 (2015): 301-132.

45. Shi J., *et al.* "Epitope-based vaccine target screening against highly pathogenic MERS-CoV: an in silico approach applied to emerging infectious diseases". *PloS one* 10 (2015): e0144475.

46. Corti D., *et al.* "Prophylactic and postexposure efficacy of a potent human monoclonal antibody against MERS coronavirus". *Proceedings of the National Academy of Sciences* 112 (2015): 10473-10478.

47. Tai W., *et al.* "Recombinant receptor-binding domains of multiple MERS-coronaviruses induce cross-neutralizing antibodies against divergent human and camel MERS-coronaviruses and antibody-escape mutants". *Journal of Virology* (2017): e01651-e01616.

48. Lan J., *et al.* "Recombinant receptor binding domain protein induces partial protective immunity in rhesus macaques against Middle East respiratory syndrome coronavirus challenge". *EBio Medicine* 2 (2015): 1438-1446.

49. Malczyk AH., *et al.* "A highly immunogenic and protective Middle East respiratory syndrome coronavirus vaccine based on a recombinant measles virus vaccine platform". *Journal of Virology* 89 (2015): 11654-11667.

50. Zhao G., *et al.* "A safe and convenient pseudovirus-based inhibition assay to detect neutralizing antibodies and screen for viral entry inhibitors against the novel human coronavirus MERS-CoV". *Virology Journal* 10.1 (2013): 266.

51. Channappanavar R., *et al.* "Protective effect of intranasal regimens containing peptide Middle East respiratory syndrome coronavirus fusion inhibitor against MERS-CoV infection". *The Journal of Infectious Diseases* 212.12 (2015): 1894-1903.

52. Reusken CB., *et al.* "Middle East respiratory syndrome coronavirus (MERS-CoV) RNA and neutralizing antibodies in milk collected according to local customs from dromedary camels, Qatar, April 2014". *Eurosurveillance* 19 (2014): 20829.

53. Al-Tawfiq JA and Auwaerter PG. "Healthcare-associated infections: the hallmark of the Middle East respiratory syndrome coronavirus (MERS-CoV) with review of the literature". *Journal of Hospital Infection* 101.1 (2019): 20-29.

54. Alfaraj SH., *et al.* "Middle East respiratory syndrome coronavirus transmission among health care workers: implication for infection control". *American Journal of Infection Control* 46 (2018): 165-168.

55. Channappanavar R., *et al.* "Protective Effect of Intranasal Regimens Containing Peptidic Middle East Respiratory Syndrome Coronavirus Fusion Inhibitor Against MERS-CoV Infection". *The Journal of Infectious Diseases* 212.12 (2015): 1894-1903.

56. Madani TA. "Case definition and management of patients with MERS coronavirus in Saudi Arabia". *The Lancet Infectious Diseases* 14 (2014): 911-913.

57. Hui DS. "Super-spreading events of MERS-CoV infection". *Lancet* 388 (2016): 942-943.

58. Alanazi K., *et al.* "Scope and extent of healthcare-associated Middle East respiratory syndrome coronavirus transmission during two contemporaneous outbreaks in Riyadh, Saudi Arabia, 2017". *Infection Control and Hospital Epidemiology* 40.1 (2019): 79-88.

59. Althobaity HM., *et al.* "Knowledge and awareness of Middle East respiratory syndrome coronavirus among Saudi and Non-Saudi Arabian pilgrims". *International Journal of Health Sciences (Qassim).* 11.5 (2017): 20-25.

60. Al-Abdely HM., *et al.* "Infection Prevention and Control Guidelines for the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) Infection, 4th edition. Riyadh, Saudi Arabia: Ministry of Health (2017).

61. Amer H., *et al.* "Unusual presentation of Middle East respiratory syndrome coronavirus leading to a large outbreak in Riyadh during 2017". *American Journal of Infection Control* 46 (2018): 1022-1025.

62. Payne DC., *et al.* "Multihospital Outbreak of a Middle East Respiratory Syndrome Coronavirus Deletion Variant, Jordan: A Molecular, Serologic, and Epidemiologic Investigation". *In Open Forum Infectious Diseases* 5.5 (2018).

63. Vergara-Alert J Vidal., *et al.* "Searching for animal models and potential target species for emerging pathogens: Experience gained from Middle East respiratory syndrome (MERS) coronavirus". *One Health* 3 (2017): 34-40.

64. Sutter G and Moss B. "Nonreplicating vaccinia vector efficiently expresses recombinant genes". *Proceedings of the National Academy of Sciences of the United States of America* 89 (1992): 10847-10851.

65. Volz A Kupke., *et al.* "Protective Efficacy of Recombinant Modified Vaccinia Virus Ankara Delivering Middle East Respiratory Syndrome Coronavirus Spike Glycoprotein". *Journal of Virology* 89 (2015): 8651-8656.

66. Langenmayer MC., *et al.* "Distribution and absence of generalized lesions in mice following single dose intramuscular inoculation of the vaccine candidate MVA-MERS-S". *Biologicals* 54 (2018): 58-62.

67. Lu G., *et al.* "Molecular basis of binding between novel human coronavirus MERS-CoV and its receptor CD26". *Nature* 500.7461 (2013): 227-231.

68. Gao J., *et al.* "Structure of the fusion core and inhibition of fusion by a heptad-repeat peptide derived from the S protein of MERS-CoV". *Journal of Virology* 87 (2013):13134-3140.

69. Raj VS., *et al.* "Adenosine deaminase acts as a natural antagonist for dipeptidyl peptidase 4-mediated entry of the Middle East respiratory syndrome coronavirus". *Journal of Virology* 88.3 (2014): 1834-1838.

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