Front. Med. 2016, 10(4): 377–382
DOI 10.1007/s11684-016-0466-7

REVIEW

From SARS to MERS: evidence and speculation

Hainv Gao, Hangping Yao, Shigui Yang, Lanjuan Li (✉)

State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou 310003, China; Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, Hangzhou 310003, China

Abstract **The Middle East respiratory syndrome coronavirus (MERS-CoV) is a novel zoonotic pathogen. In 2012, the infectious outbreak caused by MERS-CoV in Saudi Arabia has spread to more than 1600 patients in 26 countries, resulting in over 600 deaths. Without a travel history, few clinical and radiological features can reliably differentiate MERS from SARS. But in real world, comparing with SARS, MERS presents more vaguely defined epidemiology, more severe symptoms, and higher case fatality rate. In this review, we summarize the recent findings in the field of MERS-CoV, especially its molecular virology, interspecies mechanisms, clinical features, antiviral therapies, and the further investigation into this disease. As a newly emerging virus, many questions are not fully answered, including the exact mode of transmission chain, geographical distribution, and animal origins. Furthermore, a new protocol needs to be launched to rapidly evaluate the effects of unproven antiviral drugs and vaccine to fasten the clinical application of new drugs.**

Keywords middle east respiratory syndrome; animal origin; cross-species transmission; monoclonal antibody

Introduction

The world witnessed the devastating outbreak of severe acute respiratory syndrome coronavirus (SARS-CoV) in 2003, resulting in up to 8000 cases and 700 deaths worldwide [1]. SARS-CoV is a novel zoonotic pathogen, causing typical fever and respiratory symptoms. No specific antiviral drugs and vaccines were available for SARS-CoV. Fortunately, SARS-CoV remained in the population for only 8 months and vanished without a trace. In 2012, a new interspecies coronavirus outbreak occurred in Saudi Arabia, and this infection has spread to 26 countries across the globe, infecting 1698 patients, and resulting in 609 deaths as of March 23, 2016 [2]. The virus was initially designated HCoV-EMC [3]. All individuals diagnosed with Middle East respiratory syndrome (MERS) have been linked directly or indirectly to one of four countries in the Middle East. Therefore, the virus was renamed Middle East respiratory syndrome coronavirus (MERS-CoV). Compared with SARS, the novel coronavirus emerged with a more vaguely defined epidemiology, more severe symptoms, higher case fatality rate, absence of prophylactic or therapeutic measures, and most importantly, circulation in humans with mixed features of both epidemic and sporadic nature [4]. The largest outbreak of MERS-CoV outside of Saudi Arabia occurred in South Korea with 185 confirmed cases and 36 deaths [5], including the fourth-generation descendants of MERS cases, which emerged sporadically but later as an epidemic. In this review, we summarize the recent findings in the field of MERS-CoV, especially its molecular virology, interspecies mechanism, clinical features, and antiviral therapies, as well as our speculations.

Received August 9, 2015; accepted June 12, 2016
Correspondence: ljli@zju.edu.cn

Virology

MERS-CoV belongs to lineage C of the genus *Betacoronavirus* in the family *Coronaviridae* under the order *Nidovirales*. SARS-CoV belongs to *Betacoronavirus* lineage B. Similar to SARS-CoV, MERS-CoV is a positive-sense, enveloped, single-stranded RNA virus, which is spherical with a diameter of approximately 125 nm; MERS-CoV also represents one of the largest identified RNA genomes, with up to 30 kilobases (kb) [6]. MERS-CoV is the sixth CoV known to cause human infection and is closely related to bat coronaviruses HKU4 and HKU5, compared with SARS [7]. The genome of MERS-CoV

contains a 5′ cap structure along with a 3′ poly (A) tail and comprises four main structural proteins, namely, spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins; all these proteins are encoded within the 3′ end of the viral genome. The viral genome is organized in the following order: 5′UTR-ORF1a/1b-S-E-M-N-3′UTR-poly (A) tail. The 5′ cap structure and 3′ poly (A) tail play a vital role in the replication and transcription of the viral genome. The ORF1a/1b occupies 2/3 of the genome and encodes a series of non-structural proteins. Most of these proteins are involved in the formation of the viral replication/transcription complex. The S glycoprotein mediates receptor recognition and membrane fusion and is also the focus of most immunization strategies against MERS-CoV. The S glycoprotein is cleaved into two subunits: S1 and S2. The S1 subunit contains the receptor-binding domain (RBD), which mediates viral attachment to its host receptor. When S1 binds to its receptor, the S2 subunit changes its conformation and partially inserts into the target cell, drawing viral and host cell surfaces closer to facilitate plasma membrane fusion. This conformational change requires the formation of a fusion core by two heptad repeats (HR1 and HR2) of the S2 subunit. Interference with either HR1 or HR2 blocks the viral entry. The three other structural proteins relate to virion assembly and release. MERS-CoV contains five accessory proteins, namely, 3, 4a, 4b, 5, and 8b (Fig. 1) [8], which present no homology with other coronaviruses. The accessory protein 4a exhibits a potent antagonistic activity against interferon response through both cytoplasmic and nuclear targets. The functions of the other accessory proteins have yet to be clarified.

Animal origin

Accumulating evidence suggests that the dromedary camel is the animal reservoir of MERS-CoV. Serologic studies have shown the presence of cross-reactive antibodies to MERS-CoV in dromedary camels in Oman, Qatar, and Mongolia [9–11]. Live MERS-CoV was isolated directly from infected camels and confirmed in camel-to-human transmission. However, the exact mode of transmission remains largely under investigation. The effects of raw meat consumption, intake of camel milk, or exposure to other infections remain unclear. To date, studies have not found any regularity in MERS-CoV transmission from the existing cases. A comparative analysis indicated that the virus isolated from camels shows more genetic variation, with few genomic variants not infectious to humans [12]; this finding partially explained the lower infection rate in humans than in camels. Therefore, camels serve as an important reservoir for the maintenance and diversification of MERS-CoVs.

The existence of an intermediate host between camels and humans has yet to be established. During the SARS epidemic, virus transmission from bats to humans was intermediate via civet (*Paguma larvata*) and spread by raccoon. We speculated whether MERS-CoV was transmitted similarly, given the evidence that MERS-CoV replicated in cell lines of other animals, including goat, pig, rabbit, horse, and civet [13–15]. However, no evidence of other intermediate hosts was found mediating MERS transmission from camels to humans.

The origin of MERS-CoV infection in camel remains unclear. The transmission from bats is supported by the following evidence: (1) MERS-CoV is phylogenetically and closely related to *Tylonycteris* bat CoV HKU4 (Ty-BatCoV-HKU4) and *Pipistrellus* bat CoV HKU5 (Pi-BatCoV-HKU5), which were discovered in *Tylonycteris pachypus* and *Pipistrellus abramus*, respectively, in Hong Kong in 2006, revealing the MERS-CoV genomic origins in bats [16]; (2) the MERS-CoV receptor is also the receptor for HKU4 but not HKU5, hence showing functional identity [17]; and (3) viral gene fragments identical or quite similar to those of MERS-CoV have also been recovered in bats. However, an infectious virus was not isolated directly from bats [18]. If MERS-CoV originated directly from bats, the spread from the bats to humans cannot be explained. The exact mode of transmission, geographical distribution, and origins cannot also be explained.

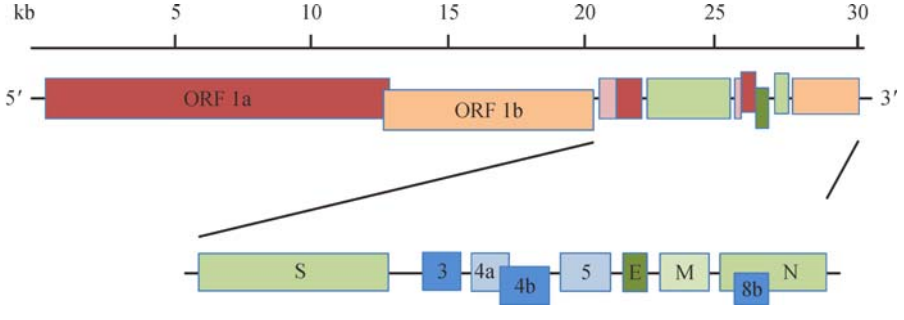

Fig. 1 Genomic organization of MERS-CoV.

Cross-species transmission mechanism

The initial entry of the virus into human cells is mediated by specific receptors. Scientists have identified dipeptidyl peptidase 4 (DPP4; also known as CD26) as a functional receptor for MERS-CoV, whereas SARS enters the target cells via angiotensin converting enzyme 2 (ACE2). DPP4 is a membrane-bound peptidase with a type II topology and forms homodimers on the cell surface. DPP4 contributes critically to our understanding of the pathogenesis and epidemiology of this newly emerging human coronavirus and may facilitate the development of antiviral therapies and vaccines [19]. Patients with chronic obstructive pulmonary disease and cystic fibrosis demonstrate increased DPP4 immunostaining in alveolar epithelia and alveolar macrophages. This finding suggests that a preexisting pulmonary disease increases MERS-CoV receptor abundance and predisposes individuals to MERS morbidity and mortality, which is consistent with current clinical observations [20].

When MERS-CoV enters the body, it will impair the innate immune response of cells, including the RIG-I-like receptor signaling and MDA-5, which are associated with the expression of interferon α. Additionally, type I and II major histocompatibility (MHC) genes are affected, thereby decreasing the expression levels of the major cytokines involved in the activation of lymphocytes [21–23].

The host-viral interaction suggests that the interspecies transmission of MERS-CoV might be associated with the following two elements for efficient infection and replication: (1) vira l adsorption capacity on the surface of human cells, particularly respiratory epithelial cells; and (2) inhibition of innate immunity of subsequent viral entry into the human cells and attenuation of the activation of adaptive immune response to take over the host metabolic apparatus and replicate efficiently.

Clinical presentation

The severity and outcome of MERS are related to gender, older age, and underlying diseases. Majority of the MERS patients are elderly males with median age of 56 years. A study involving 47 patients showed an increase in case-fatality rates with age, from 39% (seven of 18) in those younger than 50 years, to 48% (13 of 27) in the group aged under 60 years, and 75% (15 of 20) in patients aged 60 years or older [24]. A study involving 70 consecutive patients found the age of 65 years associated with increased mortality (OR 4.39, 95% CI 2.13−9.05; $P < 0.001$) [25]. Most patients present underlying co-morbid medical disorders, such as diabetes and hypertension [26].

Patients with MERS present with symptoms of influenza-like illness (ILI). Clinically, MERS and SARS show few similar features, including fever, cough (predominantly dry), and even renal failure. The majority of MERS patients are reported to suffer from multiple co-morbid conditions. However, few MERS patients show no fever or cough at all and present with walking pneumonia at early stages, which can progress rapidly. A quarter to a third of all the patients shows digestive tract symptoms. More than half of the patients develop acute renal impairment at a median time of around 11 days after symptom onset, with most cases requiring renal replacement therapy [24,27,28–31]. However, about 6.6% of patients with SARS show acute renal failure occurring at 20 days after the onset of symptoms, and only 5% need replacement therapy [24]. The possible factors contributing to the common presentation of acute renal failure in MERS patients include (1) increased number of chronic renal diseases in MERS patients, with progressive respiratory failure; and (2) direct renal injury; DPP4 is present in the renal cells, and MERS-CoV was detected in urine.

Without a travel history, linking the patient to the Arabian Peninsula, or a known MERS case, few clinical and radiological features can reliably differentiate MERS from acute pneumonia caused by other microbial agents. Asymptomatic cases have been reported among female healthcare workers and children [28]. MERS-CoV incidence in children is less frequent and seems to be associated with less mortality in patients without underlying comorbidities [32]. Low mortality in children with MERS-CoV was also reported in SARS-CoV infections, in which symptoms were milder, without any mortality, and with few hospitalizations [33].

MERS-CoV shedding was further clarified during the new epidemic in Korea, at the hospital from the first week up to 18 days to 25 days after the onset of symptoms. The viable virus can shed through respiratory secretion from clinically fully recovered patients [34]. The SARS “viral load” in upper respiratory tract secretions was low in the first 5 days of illness, and then increased progressively, peaking early in the second week [35]. These results emphasize the need for sufficient isolation based on laboratory results rather than solely on clinical symptoms in patients with coronavirus infection.

Antiviral therapy

To date, no approved antiviral therapy is available for MERS-CoV, indicating a much slower response to this potential pandemic than to the avian H7N9 flu. Candidate antiviral agents are identified using three general approaches. First, broad-spectrum antiviral drugs, such as interferon, ribavirin, and cyclophilin inhibitors, which were effective in SARS patients, were determined to test

the activity to MERS-CoV [36–38]. *In vitro* studies suggest that the type I interferon exerted an antiviral effect against several cell lines. MERS-CoV was 50 times to 100 times more sensitive to interferon α (IFN α) treatment than SARS-CoV [36,37]. *In vitro* studies also showed significant antiviral effects of ribavirin and interferon α-2b combination therapy [37]. In a retrospective study, ribavirin and interferon α-2a therapy were significantly associated with improved survival at 14 days but not at 28 days [38]. The clinical significance of cyclosporine for MERS treatment is likely limited, as the drug's peak serum level at clinical dosages was below its EC50 for MERS-CoV [36].

The second approach to identify candidate antivirals targeting MERS involves screening of chemical libraries comprising numerous existing drugs. The advantages of this approach include the commercial availability, known pharmacokinetics, and established safety reports. The first drug identified by this approach was mycophenolic acid, which is an antirejection drug used in transplantation and a broad-spectrum antiviral drug. The EC50 of this drug against MERS-CoV was very low. Therefore, a low dosage may be effective without inducing significant immunosuppression, but this assumption warrants further preclinical evaluation in animal studies [39]. The other drugs, including lopinavir and chloroquine, still remain in the *in vitro* stage.

The third approach to antiviral drug developments is based on the knowledge of genome and structural biology of MERS-CoV. Compared with the drugs identified by the first and second approaches, those identified by this approach were most effective against MERS-CoV. However, this novel drug development needs time and investment. The therapeutic potential of antibodies targeting coronaviruses was well recognized during the SARS outbreak [40–42]. To date, monoclonal antibodies targeting different epitopes on the RBD in the S1 subunit of the MERS-CoV S protein have been identified. These monoclonal antibodies bind to RBD with 10-fold to 450-fold higher affinity than the RBD binding affinity to the human DPP4, conferring broader and higher neutralizing activity [43–46]. One of the antibodies, m336, neutralizes the virus with exceptional potency and therefore represents a potential drug and vaccine candidate [47]. HR2P, a synthetic peptide derived from the HR2 domain of MERS-CoV spike protein, specifically binds to the HR1 domain of the viral spike protein and blocks viral fusion, resulting in the inhibition of MERS-CoV replication and its spike protein-mediated cell fusion [48]. Nevertheless, a major obstacle relates to the difficulty in generating highly potent neutralizing mAbs in a relatively short time during an epidemic. The other challenge relates to the emergence of possible escape mutants.

Conclusions

The outbreak of MERS-CoV poses a serious threat to global public health and highlights the imperative for further investigation into the viral epidemiology and pathogenesis, as well as the development of effective therapeutic and prophylactic agents against MERS-CoV infection. First, well-designed large-scale case-control studies are needed to define the transmission chain of MERS-CoV and to enable appropriate intervention by the government. Second, retrospective serum antibody detection should be continued to define its true distribution in humans and animals. Third, systematic surveillance for signs of host adaptation and viral genome variations is very important. Fourth, a randomized control study should be conducted to evaluate the effects of the available antiviral drugs. Finally, animal vaccines limit the animal-to-human transmission [49], which will alter our approach to drug development against newly emerging infectious diseases. However, with regard to clinical trials, we should note that a traditional sequence of studies in animals followed by phased clinical trials may be very slow during public health emergencies. A common protocol should be launched to rapidly evaluate the promising but unproven therapies in the current fatal emerging infectious disease outbreaks and future epidemics [50].

Acknowledgements

This work was partially supported by the National Natural Science Foundation of China (No. 31500138) (to H.G.) and the Major Program of National Natural Science Foundation of China (No. 81590763) (to H.Y.)

Compliance with ethics guidelines

Hainv Gao, Hangping Yao, Shigui Yang, and Lanjuan Li declare that they have no conflict of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

References

1. World Health Organization. Summary of probable SARS cases with onset of illness from 1 November 2002 to 31 July 2003[EB/OL]. 2004–04–21.http://www.who.int/csr/sars/country/table2004_04_21/en/ (Acessed July 27, 2015)
2. World Health Organization. Middel East respiratory syndrome coronavirus (MERS-CoV) Saudi Arabia. http://www.who.int/csr/don/23-march-2016-mers-saudi-arabia/en/(Acessed August 6, 2016)
3. Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA. Isolation of a novel coronavirus from a man with

pneumonia in Saudi Arabia. N Engl J Med 2012; 367(19): 1814–1820

4. World Health Organization. Background and summary of novel coronavirus infection—as of 22 November 2013. 2013. http:// www. who. int/ csr/ disease/ coronavirus_ infections/ Update12_ MERS-CoV_ update_ 22Nov13. Pdf (Acessed August 6, 2016)
5. World Health Organization. Middle East respiratory syndrome coronavirus (MERS-CoV)— Republic of Korea. Geneva: WHO. 24 May 2015. http://www.who.int/csr/don/14-july-2015-mers-korea/en/ (Accessed July 15 2015)
6. Zumla A, Hui DS,Perlman S. Middle East respiratory syndrome. Lancet 2015; 386 (9997):995–1007
7. Lau SK, Li KS, Tsang AK, Lam CS, Ahmed S, Chen H, Chan KH, Woo PC, Yuen KY. Genetic characterization of Betacoronavirus lineage C viruses in bats reveals marked sequence divergence in the spike protein of pipistrellus bat coronavirus HKU5 in Japanese pipistrelle: implications for the origin of the novel Middle East respiratory syndrome coronavirus. J Virol 2013; 87(15): 8638–8650
8. Fehr AR, Perlman S. Coronaviruses: an overview of their replication and pathogenesis. Methods Mol Biol 2015; 1282: 1–23
9. Azhar EI, El-Kafrawy SA, Farraj SA, Hassan AM, Al-Saeed MS, Hashem AM, Madani TA. Evidence for camel-to-human transmission of MERS coronavirus. N Engl J Med 2014; 370(26): 2499–2505
10. Farag EA, Reusken CB, Haagmans BL, Mohran KA, Stalin Raj V, Pas SD, Voermans J, Smits SL, Godeke GJ, Al-Hajri MM, Alhajri FH, Al-Romaihi HE, Ghobashy H, El-Maghraby MM, El-Sayed AM, Al Thani MH, Al-Marri S, Koopmans MP. High proportion of MERS-CoV shedding dromedaries at slaughterhouse with a potential epidemiological link to human cases, Qatar 2014. Infect Ecol Epidemiol 2015; 5(0): 28305
11. Chan SM, Damdinjav B, Perera RA, Chu DK, Khishgee B, Enkhbold B, Poon LL, Peiris M. Absence of MERS-Coronavirus in Bactrian Camels, Southern Mongolia, November 2014. Emerg Infect Dis 2015; 21(7): 1269–1271
12. Briese T, Mishra N, Jain K, Zalmout IS, Jabado OJ, Karesh WB, Daszak P, Mohammed OB, Alagaili AN, Lipkin WI. Middle East respiratory syndrome coronavirus quasispecies that include homologues of human isolates revealed through whole-genome analysis and virus cultured from dromedary camels in Saudi Arabia. MBio 2014; 5(3): e01146–e14
13. Haagmans BL, van den Brand JM, Provacia LB, Raj VS, Stittelaar KJ, Getu S, de Waal L, Bestebroer TM, van Amerongen G, Verjans GM, Fouchier RA, Smits SL, Kuiken T, Osterhaus AD. Asymptomatic Middle East respiratory syndrome coronavirus infection in rabbits. J Virol 2015; 89(11): 6131–6135
14. van Doremalen N, Miazgowicz KL, Milne-Price S, Bushmaker T, Robertson S, Scott D, Kinne J, McLellan JS, Zhu J, Munster VJ. Host species restriction of Middle East respiratory syndrome coronavirus through its receptor, dipeptidyl peptidase 4. J Virol 2014; 88(16): 9220–9232
15. Barlan A, Zhao J, Sarkar MK, Li K, McCray PB Jr, Perlman S, Gallagher T. Receptor variation and susceptibility to Middle East respiratory syndrome coronavirus infection. J Virol 2014; 88(9): 4953–4961
16. Annan A, Baldwin HJ, Corman VM, Klose SM, Owusu M, Nkrumah EE, Badu EK, Anti P, Agbenyega O, Meyer B, Oppong S, Sarkodie YA, Kalko EK, Lina PH, Godlevska EV, Reusken C, Seebens A, Gloza-Rausch F, Vallo P, Tschapka M, Drosten C, Drexler JF. Human betacoronavirus 2c EMC/2012-related viruses in bats, Ghana and Europe. Emerg Infect Dis 2013; 19(3): 456–459
17. Yang Y, Du L, Liu C, Wang L, Ma C, Tang J, Baric RS, Jiang S, Li F. Receptor usage and cell entry of bat coronavirus HKU4 provide insight into bat-to-human transmission of MERS coronavirus. Proc Natl Acad Sci USA 2014; 111(34): 12516–12521
18. Memish ZA, Mishra N, Olival KJ, Fagbo SF, Kapoor V, Epstein JH, Alhakeem R, Durosinloun A, Al Asmari M, Islam A, Kapoor A, Briese T, Daszak P, Al Rabeeah AA, Lipkin WI. Middle East respiratory syndrome coronavirus in bats, Saudi Arabia. Emerg Infect Dis 2013; 19(11): 1819–1823
19. Raj VS, Mou H, Smits SL, Dekkers DH, Müller MA, Dijkman R, Muth D, Demmers JA, Zaki A, Fouchier RA, Thiel V, Drosten C, Rottier PJ, Osterhaus AD, Bosch BJ, Haagmans BL. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. Nature 2013; 495(7440): 251–254
20. Meyerholz DK, Lambertz AM, McCray PB Jr. Dipeptidyl peptidase 4 distribution in the human respiratory tract: implications for the middle east respiratory syndrome. Am J Pathol 2015; 186(1):78–86
21. Siu KL, Yeung ML, Kok KH, Yuen KS, Kew C, Lui PY, Chan CP, Tse H, Woo PC, Yuen KY, Jin DY. Middle East respiratory syndrome coronavirus 4a protein is a double-stranded RNA-binding protein that suppresses PACT-induced activation of RIG-I and MDA5 in the innate antiviral response. J Virol 2014; 88(9): 4866–4876
22. Faure E, Poissy J, Goffard A, Fournier C, Kipnis E, Titecat M, Bortolotti P, Martinez L, Dubucquoi S, Dessein R, Gosset P, Mathieu D, Guery B. Distinct immune response in two MERS-CoV-infected patients: can we go from bench to bedside? PLoS ONE 2014; 9(2): e88716
23. Josset L, Menachery VD, Gralinski LE, Agnihothram S, Sova P, Carter VS, Yount BL, Graham RL, Baric RS, Katze MG. Cell host response to infection with novel human coronavirus EMC predicts potential antivirals and important differences with SARS coronavirus. MBio 2013; 4(3): e00165–e13
24. Assiri A, Al-Tawfiq JA, Al-Rabeeah AA, Al-Rabiah FA, Al-Hajjar S, Al-Barrak A, Flemban H, Al-Nassir WN, Balkhy HH, Al-Hakeem RF, Makhdoom HQ, Zumla AI, Memish ZA. Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study. Lancet Infect Dis 2013; 13(9): 752–761
25. Eckerle I, Müller MA, Kallies S, Gotthardt DN, Drosten C. *In-vitro* renal epithelial cell infection reveals a viral kidney tropism as a potential mechanism for acute renal failure during Middle East respiratory syndrome (MERS) coronavirus infection. Virol J 2013, 23;10:359
26. Saad M, Omrani AS, Baig K, Bahloul A, Elzein F, Matin MA, Selim MA, Al Mutairi M, Al Nakhli D, Al Aidaroos AY, Al Sherbeeni N, Al-Khashan HI, Memish ZA, Albarrak AM. Clinical aspects and outcomes of 70 patients with Middle East respiratory syndrome coronavirus infection: a single-center experience in Saudi Arabia. Int J Infect Dis 2014; 29: 301–306
27. Memish ZA, Al-Tawfiq JA, Makhdoom HQ, Al-Rabeeah AA, Assiri A, Alhakeem RF, AlRabiah FA, Al Hajjar S, Albarrak A, Flemban H, Balkhy H, Barry M, Alhassan S, Alsubaie S, Zumla A. Screening for Middle East respiratory syndrome coronavirus infection in hospital patients and their healthcare worker and family

contacts: a prospective descriptive study. Clin Microbiol Infect 2014; 20(5): 469–474

28. Al-Abdallat MM, Payne DC, Alqasrawi S, Rha B, Tohme RA, Abedi GR, Al Nsour M, Iblan I, Jarour N, Farag NH, Haddadin A, Al-Sanouri T, Tamin A, Harcourt JL, Kuhar DT, Swerdlow DL, Erdman DD, Pallansch MA, Haynes LM, Gerber SI, Sabri N, Al Azhari M, Khazali H, Al Maayah M, Bilbeisi A, Dawood N, Al Zubi B, Meflih J, Mounds T, Fitzner J, Eltom A, Mafi A, Miao C, Caidi H, Trivedi S, Kamili S, Hall AJ, Curns A, Moore J, Pham H, Zimmerman C, Farnon E, Giorgi G, Gerber R. Hospital-associated outbreak of Middle East respiratory syndrome coronavirus: a serologic, epidemiologic, and clinical description. Clin Infect Dis 2014; 59(9): 1225–1233
29. Assiri A, McGeer A, Perl TM, Price CS, Al Rabeeah AA, Cummings DA, Alabdullatif ZN, Assad M, Almulhim A, Makhdoom H, Madani H, Alhakeem R, Al-Tawfiq JA, Cotten M, Watson SJ, Kellam P, Zumla AI, Memish ZA; KSA MERS-CoV Investigation Team. Hospital outbreak of Middle East respiratory syndrome coronavirus. N Engl J Med 2013; 369(5): 407–416
30. Al-Tawfiq JA, Hinedi K, Ghandour J, Khairalla H, Musleh S, Ujayli A, Memish ZA. Middle East respiratory syndrome coronavirus: a case-control study of hospitalized patients. Clin Infect Dis 2014; 59 (2): 160–165
31. Arabi YM, Arifi AA, Balkhy HH, Najm H, Aldawood AS, Ghabashi A, Hawa H, Alothman A, Khaldi A, Al Raiy B. Clinical course and outcomes of critically ill patients with Middle East respiratory syndrome coronavirus infection. Ann Intern Med 2014; 160(6): 389–397
32. Thabet F, Chehab M, Bafaqih H, Al Mohaimeed S. Middle East respiratory syndrome coronavirus in children. Saudi Med J 2015; 36 (4): 484–486
33. Denison MR. Severe acute respiratory syndrome coronavirus pathogenesis, disease and vaccines: an update. Pediatr Infect Dis J 2004; 23(11 Suppl): S207–S214
34. Bin Seo Y, Heo JY, Song MS, Lee J, Kim EH, Park SJ, Kwon HI, Kim SM, Kim YI, Si YJ, Lee IW, Baek YH, Choi WS, Min J, Jeong HW, Choi YK. Environmental contamination and viral shedding in MERS patients during MERS-CoV Outbreak in South Korea. Clin Infect Dis 2016; 62(6):755–760
35. Hui DS, Memish ZA, Zumla A. Severe acute respiratory syndrome vs. the Middle East respiratory syndrome. Curr Opin Pulm Med 2014; 20(3): 233–241
36. de Wilde AH, Raj VS, Oudshoorn D, Bestebroer TM, van Nieuwkoop S, Limpens RW, Posthuma CC, van der Meer Y, Bárcena M, Haagmans BL, Snijder EJ, van den Hoogen BG. MERS-coronavirus replication induces severe *in vitro* cytopathology and is strongly inhibited by cyclosporin A or interferon-α treatment. J Gen Virol 2013; 94(Pt 8): 1749–1760
37. Falzarano D, de Wit E, Martellaro C, Callison J, Munster VJ, Feldmann H. Inhibition of novel β coronavirus replication by a combination of interferon-α2b and ribavirin. Sci Rep 2013; 3: 1686
38. Omrani AS, Saad MM, Baig K, Bahloul A, Abdul-Matin M, Alaidaroos AY, Almakhlafi GA, Albarrak MM, Memish ZA, Albarrak AM. Ribavirin and interferon α-2a for severe Middle East respiratory syndrome coronavirus infection: a retrospective cohort study. Lancet Infect Dis 2014; 14(11): 1090–1095
39. Chan JF, Chan KH, Kao RY, To KK, Zheng BJ, Li CP, Li PT, Dai J, Mok FK, Chen H, Hayden FG, Yuen KY. Broad-spectrum antivirals for the emerging Middle East respiratory syndrome coronavirus. J Infect 2013; 67(6): 606–616
40. Sui J, Li W, Murakami A, Tamin A, Matthews LJ, Wong SK, Moore MJ, Tallarico AS, Olurinde M, Choe H, Anderson LJ, Bellini WJ, Farzan M, Marasco WA. Potent neutralization of severe acute respiratory syndrome (SARS) coronavirus by a human mAb to S1 protein that blocks receptor association. Proc Natl Acad Sci U S A 2004; 101(8):2536–2541
41. ter Meulen J, Bakker AB, van den Brink EN, Weverling GJ, Martina BE, Haagmans BL, Kuiken T, de Kruif J, Preiser W, Spaan W, Gelderblom HR,Goudsmit J , Osterhaus AD. Human monoclonal antibody as prophylaxis for SARS coronavirus infection in ferrets. Lancet 2004; 363(9427):2139–2141
42. Traggiai E, Becker S, Subbarao K, Kolesnikova L, Uematsu Y, Gismondo MR, Murphy BR, Rappuoli R, Lanzavecchia A. An efficient method to make human monoclonal antibodies from memory B cells: potent neutralization of SARS coronavirus. Nat Med 2004; 10(8):871–875
43. Du L, Zhao G, Yang Y, Qiu H, Wang L, Kou Z, Tao X, Yu H, Sun S, Tseng CT, Jiang S, Li F, Zhou Y. A conformation-dependent neutralizing monoclonal antibody specifically targeting receptor-binding domain in Middle East respiratory syndrome coronavirus spike protein. J Virol 2014; 88(12): 7045–7053
44. Ying T, Du L, Ju TW, Prabakaran P, Lau CC, Lu L, Liu Q, Wang L, Feng Y, Wang Y, Zheng BJ, Yuen KY, Jiang S, Dimitrov DS. Exceptionally potent neutralization of Middle East respiratory syndrome coronavirus by human monoclonal antibodies. J Virol 2014; 88(14): 7796–7805
45. Jiang L, Wang N, Zuo T, Shi X, Poon KM, Wu Y, Gao F, Li D, Wang R, Guo J, Fu L, Yuen KY, Zheng BJ, Wang X, Zhang L. Potent neutralization of MERS-CoV by human neutralizing monoclonal antibodies to the viral spike glycoprotein. Sci Transl Med 2014; 6(234): 234ra59
46. Tang XC, Agnihothram SS, Jiao Y, Stanhope J, Graham RL, Peterson EC, Avnir Y, Tallarico AS, Sheehan J, Zhu Q, Baric RS, Marasco WA. Identification of human neutralizing antibodies against MERS-CoV and their role in virus adaptive evolution. Proc Natl Acad Sci USA 2014; 111(19): E2018–E2026
47. Ying T, Li H, Lu L, Dimitrov DS, Jiang S. Development of human neutralizing monoclonal antibodies for prevention and therapy of MERS-CoV infections. Microbes Infect 2015;17(2):142–148.
48. Lu L, Liu Q, Zhu Y, Chan KH, Qin L, Li Y, Wang Q, Chan JF, Du L, Yu F, Ma C, Ye S, Yuen KY, Zhang R, Jiang S. Structure-based discovery of Middle East respiratory syndrome coronavirus fusion inhibitor. Nat Commun 2014; 5: 3067
49. Borio L, Cox E, Lurie N. Combating emerging threats—accelerating the availability of medical therapies. N Engl J Med 2015; 373 (11): 993–995
50. .Haagmans BL, van den Brand JM, Raj VS, Volz A, Wohlsein P, Smits SL, Schipper D, Bestebroer TM, Okba N, Fux R, Bensaid A, Solanes Foz D, Kuiken T, Baumgärtner W, Segalés J, Sutter G, Osterhaus AD. An orthopoxvirus-based vaccine reduces virus excretion after MERS-CoV infection in dromedary camels. Science 2016; 351(6268): 77–81