

LEADING ARTICLE

Coronavirus-2019 (COVID-19): A Novel Pandemic Disease with Global Health Care Burden

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Coronavirus is an ancient virus with a worldwide distribution [1]. This virus group is the second common cause of common cold after Rhinoviruses [2]. Both human and animals are infected by Coronaviruses and induced mild respiratory infections with rare case severity. Bats, cats and camels are the reservoirs of coronaviruses and the viruses may be transmitted from animals to human and thus included in zoonotic infectious diseases. During the period from the 1st human coronavirus isolation, the virus without medical interest as they mostly induced mild upper respiratory infections [3]. Coronaviruses are present for at least 500-800 years in human and all originated in bats [4,5]. Additionally, this virus group is responsible for infections induction in mammals and birds [6]. In medical history, only 3 global pandemics were reported, plague pandemic in 1720, Cholera pandemic in 1820, and Spanish influenza pandemic in 1920 [7]. However, the COVID-19 pandemic differs from the previous 3 pandemics in its transmission in an exponential manner (Exponential equation). COVID-19 caused by SARS-CoV-2 which was naturally evolves in animal and transmitted to human [7].

Before the outbreak of COVID-19, only six coronaviruses reported that are with the ability to infect human: MERS-CoV, SARS-CoV, HCoV-HKU1, HCoV-229E, HCoV-NL63, HCoV-OC43 [8-10].

The last four are endemic locally and associated mainly with the mild, self-limiting disease, while the first two can cause severe illness [11-13]. Genetic diversity of Coronaviruses, genome frequent recombination, high prevalence rate, unavailability of an effective vaccine and antiviral agents, and high prevalence rate and animal-human interface increasing activity form a continuous threat to human health [14,15]. The health threat became obvious in December 2019 and early 2020 as the novel coronavirus (SARS-CoV-2) was identified as the aetiology of rapidly and large outbreaks of respiratory disease, including potentially fatal pneumonia, in Wuhan, China [16]. In a short period the COVID-19 transmitted from China to about all worlds.

COVID-19 mortality was lower than that of Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) [17,18]. Both SARS and MERS were spread between people with close contact. MERS outbreak still occurring and spread outside the Middle East region such as South Korea [19].

The respiratory viral diseases are the common viral infections that are spread frequently among people through droplets of coughing, sneezing and maybe talking [2]. In the last two decades, three coronavirus strains that induced respiratory diseases outbreaks [20]. SARS-CoV-2 was different from SARS-CoV and MERS-CoV as it leads to pandemics, while the other two were epidemic .

The sequence databases indicated that all human coronaviruses were of animal origin [21,22]. Previous studies documented the spillover of coronaviruses from animal to animal and from animal to human [23-58]. The natural course of the disease indicated that immune and inflammatory responses form the effective arm that controls the outcome of the infection. However, the disease severity and mortality may be a side effect to both immune and inflammatory responses [2]. In literature, the virus-host interaction was studied and multiple scenarios were proposed for the effectiveness of immune responses in disease control and outcome and immunity-inflammatory influence on disease mortality [59-137].

Although there are a global research works that evaluate the effectiveness of drugs/compound as a therapeutic approach for COVID-19, however, to date none found to be with promising effect. The Russian researcher formulated an effective antiviral agent

(Favipiravir] against SARS-CoV-2 and introduced to the market for their use. Additionally, the vaccine evaluation takes a long period until the development of the novel potential vaccine. The research efforts to find effective antiviral agents panel and effective vaccines take a long time to introduce promising results. The best approach to find an effective drug against SARS-CoV-2 infection is to test new compounds, not to rely on the testing of that used in another virus's treatment. The novel drugs are that which prevent viral attachment with the host cell to get rid of immune and inflammatory harmful responses [138].

COVID-19 is the first disease that takes the attention of WHO; national, regional and global health authorities; all worldwide political directors; non-governmental organization; human rights organization, and social leaders. The COVID-19 pandemic illustrated the following outcomes:

1. Globally there is no perfect health care system that deals effectively with COVID-19 pandemic in both developed and developing countries.
2. To date, the only antiviral agent that assumed to be effective in the treatment of COVID-19 is Avifavir (Favipiravir) and may be Remdesivir.
3. The main common methods of disease transmission are through droplets of coughing, sneezing or maybe talking.
4. The most effective preventive measures are social distancing, mask-wearing, personal hygiene (frequent hand washing), wandering prevention, quarantine of contact and isolation of the infected individual.
5. Area isolation is essential for disease control.
6. Social and personal compliance with orders of wandering prevention, social distancing, personal hygiene and none attendance to crowded places for the risk factors that leads to the exponential increase in COVID-19 cases.
7. Forman et al [139] addressed key lessons which include: Transparency, solidarity, coordination, decisiveness, clarity, accountability, refocusing and increased funding to ensure the WHO is capable of coordinating global responses to major health challenges, Existing global insurance institutions and policies are inadequate, and these require significant changes and improvements, Efforts to develop COVID-19 vaccines and

treatments are commendable, but there is still much more to do, We need to test the responsiveness and resilience of health systems and make changes and improvements based on the results, Effective communication must occur at the highest political levels, and There are opportunities to introduce novel approaches, such as using robots and artificial intelligence (AI), in this – and in future – pandemic response .

8. Attention for human rights and health education are needed globally.
9. We noticed the spread of SARS-CoV-2 to individuals working in the hospital management department, operation theatre, X-ray section, and the wards that are away from those dealing in the management of COVID-19 patients. This suggests that mechanical ventilation and air conditioning system may play a role in virus transmission. Thus this must be taken into consideration at the time of hospital building design or to go back to our previous infectious disease hospitals.
10. The infrastructure of the ministry of health needs urgent SWOT evaluation and actions must be taken to improve the health care system and MOH budget reform.
11. The disease pandemic not led efficiently as there is misconduct and conflict or opposition between the political leaders and healthcare leader's actions. In the current situation, the leadership must be operated by healthcare personnel.
12. The pandemics uncontrolled and characterized by a steady increase in cases with time due to political orders not to close border as early as possible. i. e. the disease focus is from Iran.
13. A contradictory opinion released from WHO.
14. The government did not cover the needs of the self-employed workers and thus they forced not to comply with orders of wandering movement with subsequent exposure to disease focuses.
15. Lack of infection control measures in MOH hospitals and primary care centers.
16. Lack of health care personnel training on the control of infections.
17. No role for an epidemiologist, virologist and immunologist in the control and preventive measures.

18. The pandemic clarifies the importance of medical colleges, Health technical colleges and laboratory technical college's curriculum reform.
19. The cases mainly managed by a physician specialized in internal medicine, which is not the sound approach. Thus sub-specialty post-graduate establishment in Iraqi Board of Medical Specialization and Arab Board of Medical Specialization or medical colleges is required urgently .
20. MOH financial support from the central government is not enough to provide 15% of health care services.
21. There is no global agreement on the origin of the virus. Is the virus mutated naturally in its animal host or is it a human-induced strain? No dogmatic answer yet, the future will explore that fact.
22. Herd immunity approach would not solve the COVID-19 problem.
23. MOH not provided enough personal protective equipment for all health care workers.
24. There are non-ethical research working as reported by retraction of two large scale research works by Lancet and New England Journal.
25. To date, the most effective treatment as antiviral agent is the use of plasma from previously infected individuals. However, the reduction if IgG and neutralizing antibody levels in the early convalescent phase might have implications for immunity strategy and serological survey [140].
26. Vaccine production trials may be promising.
27. There is a wide gap between expected incidence and MOH daily cases reporting and this mostly due to low screening coverage [1.33% of total Iraqi population, 29/6/2020].
28. Although the Iraqi Health Care System is with many deficits, the health care providers working properly and influence pandemic outcomes.
29. Recent study [141] indicated a 3p21.31 gene cluster as genetic susceptibility locus in patients with COVID-19 with respiratory failure. Additionally, ABO blood group system also involved in the influence of individual susceptibility to COVID-19 infections. Blood group A was with higher risk, while group O was with lower risk for SARS-CoV-2 infection.

30. One social problem that challenges COVID-19 management in Iraqi community is the believe that the disease is STIGMA.
31. The disease mortality rate was 4.766% (28/7/2020) and the prevalence rate was 0.287% for Iraqi population (115332/40138387). The recovery rate was 70.3%.
32. The cases incidence increased dramatically during the period from 5/6/2020 to 28/7/2020 (54 days) as compared to the period of 98 days from 24/2/2020 to 4/6/2020. The cases at 28/7/2020 12 times (106492) that that at 4/6/2020 (8840). This cases incidence increase may indicate that COVID-19 may be out of control. The increase in COVID-19 incidence was mostly attributed to the personal behavior as they not apply the recommendation of WHO and national and local crises committees. Nosocomial infection especially in healthcare providers increased due to none availability of protection equipments and this may play another was for disease transmission. Disease stigma in community prevent many of infected individuals from healthcare consultation and thus play a focus of infection in their communities. Recently, the heresy of typhoid fever classification of moderate number of cases provide another focus for infection in the community.

In conclusion, SARS-CoV-2 pandemic infection indicated the needs for global health care systems reform. In addition, the pandemic illustrated the need for health education and establishment of infectious disease subspecialty in medical institutes and warranted building of infectious disease isolated hospitals with a special design that overcome nosocomial infections.

References

1. Beaudette FR, Hudson CB. Cultivation of the virus of infectious bronchitis. Journal of the American Veterinary Medical Association, 1937; 90: 51-6.
2. Alsamarai AGM, Alobaidi AHA, Alsamarai MAM. Coronavirus 2019 (COVID-19): A Novel Pandemic Disease. Aalborg Academy J Med Sci 2020;3(2):151-184.
3. Almeida JD, Tyrrell D. The morphology of three previously uncharacterized human respiratory viruses that grow in organ culture. J Gen Virol 1967;1:175-8.
4. Chan PK, Chan MC. Tracing the SARS-coronavirus. J Thorac Dis 2013, 5(Suppl. 2):S118.

5. Berry M, Gamiieldien J, Fielding BC. Identification of new respiratory viruses in the new millennium. *Viruses* 2015, 7(3): 996.
6. Cavanagh D. Coronaviridae: a review of coronaviruses and toroviruses. *Coronaviruses with Special Emphasis on First Insights Concerning SARS*. 2005:1–54.
7. Aljubory NH. Corona: The Century Pandemic. *Aalborg Academy J Med Sci* 2020;3(2):1-45.
8. Bonilla-Aldana DK, Holguin-Rivera Y, Cortes-Bonilla I, Cardona-Trujillo MC, García-Barco A, Bedoya-Arias HA, Rabaan AA, Sah R, Rodriguez-Morales AJ. Coronavirus infections reported by ProMED, February 2000-January 2020. *Travel Med Infect Dis*. 2020 Feb 6:101575. doi: 10.1016/j.tmaid.2020.101575. Epub ahead of print. PMID: 32036011; PMCID: PMC7102564.
9. Skariyachan S, Challapilli SB, Packirisamy S, Kumargowda ST, Sridhar VS. Recent aspects on the pathogenesis mechanism, animal models and novel therapeutic interventions for Middle East respiratory syndrome coronavirus infections. *Front Microbiol* 2019;10: 569.
10. Aleanizy FS, Mohamed N, Alqahtani FY, El Hadi Mohamed RA. Outbreak of Middle East respiratory syndrome coronavirus in Saudi Arabia: a retrospective study. *BMC infectious Dis* 2017;17:23.
11. WHO 2003 <https://www.who.int/ith/diseases/sars/en/>
12. Song Z, Xu Y, Bao L, Zhang L, Yu P, Qu Y, Zhu H, Zhao W, Han Y, Qin C. From SARS to MERS, Thrusting Coronaviruses into the Spotlight. *Viruses*. 2019;11(1):59.
13. Paules CI, Marston HD, Fauci AS. Coronavirus infections-More than just the common cold. *JAMA (J Am Med Assoc)* 2020;323(8):707-708.
14. Hui DS, Azhar E, Madani TA. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health - The latest 2019 novel coronavirus outbreak in Wuhan, China. *Int J Infect Dis* 2020;91: 264-266.
15. Zhu N, Zhang D, Wang W, Xingwang Li, M.D., Bo Yang, M.S., Jingdong Song, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med* 2020;382(8):727-733.

16. WHO. WHO statement regarding cluster of pneumonia cases in Wuhan, China (World Health Organization, January 9, 2020); Emergencies: Novel coronavirus 2019, WHO.
17. WHO. Summary of probable SARS cases with onset of illness from 1 November 2002 to 31 July 2003. Dec 31, 2003. https://www.who.int/csr/sars/country/table2004_04_21/en/.
18. WHO. Middle East Respiratory Syndrome Coronavirus (MERS-CoV). November, 2019. <http://www.who.int/emergencies/mers-cov/en/>].
19. Fauci AS. COVID-19 is an emerging, rapidly evolving situation. National Institute of Allergy and Infectious Diseases. <https://www.niaid.nih.gov/about/director>.
20. Guarner J. Three Emerging Coronaviruses in Two Decades: The Story of SARS, MERS, and Now COVID-19, *Am J Clin Pathol* 2020;153(4):420–421.
21. Su S, Wong G, Shi W, Liu J, Lai ACK, Zhou J, et al. Epidemiology, genetic recombination, and pathogenesis of coronaviruses. *Trends Microbiol.*2016;24: 490–502.
22. Forni D, Cagliani R, Clerici M, Sironi M. Molecular evolution of human coronavirus genomes. *Trends Microbiol.* 2017;25:35–48.
23. Huang, YW, Dickerman AW, Piñeyro P, Li L, Fang L, Kiehne R, et al. Origin, evolution, and genotyping of emergent porcine epidemic diarrhea virus strains in the United States. *MBio* 2013;4:e00737–00713.
24. Liu C, Tang J, Ma Y, Liang X, Yang Y, Peng G, et al. Receptor usage and cell entry of porcine epidemic diarrhea coronavirus. *J. Virol.*2015;89:6121–6125.
25. Simas PV, Barnabé AC, Durães-Carvalho R, Neto DF, Caserta LC, Artacho L, et al. Bat coronavirus in Brazil related to appalachian ridge and porcine epidemic diarrhea viruses. *Emerg. Infect. Dis.* 2015;21:729–731.
26. Lacroix A, Duong V, Hul V, San S, Davun H, Omaliss K, et al. Genetic diversity of coronaviruses in bats in Lao PDR and Cambodia. *Infect. Genet. Evol.*2017;48: 10–18.
27. Song HD, Tu CC, Zhang GW, Wang SY, Zheng K, Lei LC, et al. Cross- host evolution of severe acute respiratory syndrome coronavirus in palm civet and human. *Proc. Natl Acad. Sci. USA* 2005;102:2430–2435.

28. Paden CR, Yusof MFBM, Al Hammadi ZM, Queen K, Tao Y, Eltahir YM, et al. Zoonotic origin and transmission of Middle East respiratory syndrome coronavirus in the UAE. *Zoo Pub Health* 2018;65:322–333.
29. Haagmans BL, Al Dhahiry SH, Reusken CB, Raj VS, Galiano M, Myers R, Godeke GJ, et al. Middle East respiratory syndrome coronavirus in dromedary camels: an outbreak investigation. *Lancet Infect Dis* 2014;14:140–145.
30. Azhar EI, El-Kafrawy SA, Farraj SA, Hassan AM, Al-Saeed MS, Hashem AM, et al. Evidence for camel- to-human transmission of MERS coronavirus. *N Eng J Med* 2014; 370:2499–2505.
31. Raj VS, Farag EABA, Reusken CBEM, Lamers MM, Pas SD, Voermans J, et al. Isolation of MERS coronavirus from a dromedary camel, Qatar, 2014. *Emerg Infect Dis* 2014;20:1339–1342.
32. Sabir JS, Lam TT, Ahmed MM, Li L, Shen Y, Abo-Aba SE, et al. Co- circulation of three camel coronavirus species and recombination of MERS- CoVs in Saudi Arabia. *Science* 2016;351:81–84.
33. Chu DKW, Hui KPY, Perera RAPM, Miguel E, Niemeyer D, Zhao J, et al. MERS coronaviruses from camels in Africa exhibit region- dependent genetic diversity. *Proc Natl Acad Sci.,USA* 2018;115:3144–3149.
34. Lau SK, Li KS, Tsang AK, Lam CS, Ahmed S, Chen H, et al. 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;87:8638–8650.
35. Cui J, Li F, Shi ZL. Origin and evolution of pathogenic coronaviruses. *Nature Review Microbiology* 2019;17:181-192.
36. Montecino-Latorre D, Goldstein T, Gilardi K, Wolking D, Wormer EV, Kazwala R, et al. Reproduction of East-African bats may guide risk mitigation for coronavirus Spillover. *One Health Outlook* 2020;2:2.
37. Yin Y, Wunderink RG. MERS, SARS and other coronaviruses as causes of pneumonia. *Respirology*. 2018;23(2):130–7.
38. Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, Jin HJ, et al. The origin, transmission and clinical therapies on coronavirus disease

- 2019 (COVID-19) outbreak – an update on the status. *Military Medical Research* 2020;7:11
39. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*. 2020; <https://doi.org/10.1038/s41586-020-2012-7>.
40. Angeletti S, Benvenuto D, Bianchi M, Giovanetti M, Pascarella S, Ciccozzi M. COVID-2019: the role of the nsp2 and nsp3 in its pathogenesis. *J Med Virol*. 2020;92(6).<https://doi.org/10.1002/jmv.25719>.
41. Zhang L, Shen FM, Chen F, Lin Z. Origin and evolution of the 2019 novel coronavirus. *Clin Infect Dis*. 2020. <https://doi.org/10.1093/cid/ciaa112> [Epub ahead of print].
42. Wu D, Zou S, Bai T, Li J, Zhao X, Yang L, et al. Poultry farms as a source of avian influenza a (H7N9) virus re-assortment and human infection. *Sci Rep*. 2015;5:7630.
43. Tang X, Wu C, Li X, Song Y, Yao X, Wu X, et al. On the origin and continuing evolution of SARS-CoV-2. *Natl Sci Rev*. 2020. <https://doi.org/10.1093/nsr/nwaa036>.
44. Jia HP, Look DC, Shi L, Hickey M, Pewe L, Netland J, et al. ACE2 receptor expression and severe acute respiratory syndrome coronavirus infection depend on differentiation of human airway epithelia. *J Virol*. 2005;79(23):14614–21.
45. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS. *J Virol*. 2020. <https://doi.org/10.1128/JVI.00127-20> [Epub ahead of print].
46. Tortorici MA, Veesler D. Structural insights into coronavirus entry. *Adv Virus Res*. 2019;105:93–116.
47. Zhang N, Jiang S, Du L. Current advancements and potential strategies in the development of MERS-CoV vaccines. *Expert Rev Vaccines*. 2014;13(6):761–74.
48. Xia S, Zhu Y, Liu M, Lan Q, Xu W, Wu Y, et al. Fusion mechanism of 2019-nCoV and fusion inhibitors targeting HR1 domain in spike protein. *Cell Mol Immunol*. 2020. <https://doi.org/10.1038/s41423-020-0374-2>.
49. Yu F, Du L, Ojcius DM, Pan C, Jiang S. Measures for diagnosing and treating infections by a novel coronavirus responsible for a pneumonia outbreak originating in Wuhan, China. *Microbes*

- Infect. 2020. <https://doi.org/10.1016/j.micinf.2020.01.003> [Epub ahead of print].
50. de Wilde AH, Snijder EJ, Kikkert M, van Hemert MJ. Host factors in coronavirus replication. *Curr Top Microbiol Immunol*. 2018;419:1–42.
51. Sawicki SG, Sawicki DL. Coronavirus transcription: a perspective. *Curr Top Microbiol Immunol*. 2005;287:31–55.
52. Hussain S, Pan J, Chen Y, Yang Y, Xu J, Peng Y, et al. Identification of novel subgenomic RNAs and noncanonical transcription initiation signals of severe acute respiratory syndrome coronavirus. *J Virol*. 2005;79(9):5288–95.
53. Perrier A, Bonnin A, Desmarests L, Danneels A, Goffard A, Rouille Y, et al. The C-terminal domain of the MERS coronavirus M protein contains a trans-Golgi network localization signal. *J Biol Chem*. 2019;294(39):14406–21.
54. Letko M, Marzi A, Munster V. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. *Nat Microbiol*. 2020. <https://doi.org/10.1038/s41564-020-0688-y>.
55. Song W, Gui M, Wang X, Xiang Y. Cryo-EM structure of the SARS coronavirus spike glycoprotein in complex with its host cell receptor ACE2. *PLoS Pathog*. 2018;14(8):e1007236.
56. Millet JK, Whittaker GR. Host cell proteases: critical determinants of coronavirus tropism and pathogenesis. *Virus Res*. 2015;202:120–34.
57. Simmons G, Gosalia DN, Rennekamp AJ, Reeves JD, Diamond SL, Bates P. Inhibitors of cathepsin L prevent severe acute respiratory syndrome coronavirus entry. *P Natl Acad Sci USA*. 2005;102(33):11876–81.
58. Andersen KG, Rambaut A, Lipkin WI, Holmes EC, Garry RF. The proximal origin of SARS-CoV-2. *Nature Medicine* www.nature.com/naturemedicine.
59. Ryzhakov G, Randow F. SINTBAD, a novel component of innate antiviral immunity, shares a TBK1-binding domain with NAP1 and TANK. *EMBO J* 2007;26:3180–3190.
60. Ramasamy, S, Saez B, Mukhopadhyay S, Ding D, Ahmed AA, Chen X, et al. Tle1 tumor suppressor negatively regulates inflammation in vivo and modulates NF- κ B inflammatory pathway. *Proc Natl Acad Sci. USA*. 2016;113:1871–1876.

61. Zhang X, Li X, Ning F, Shang Y, Hu, X. TLE4 acts as a corepressor of Hes1 to inhibit inflammatory responses in macrophages. *Protein Cell* 2019;10:300–305.
62. Tetsuka T, Uranishi H, Imani H, Ono T, Sonta S, Takahasi N, et al. Inhibition of nuclear factor-kappaB-mediated transcription by association with the aminoterminal enhancer of split, a Groucho-related protein lacking WD40 repeats. *J Biol Chem* 2000; 275: 4383–4390.
63. Wang C, Chen T, Zhang J, Yang M, Li N, Xu X, Cao X. et al. The E3 ubiquitin ligase Nrdp1 ‘preferentially’ promotes TLR-mediated production of type I interferon. *Nat Immunol* 2009;10:744–752.
64. Kondo, T., Watanabe, M. & Hatakeyama, S. TRIM59 interacts with ECSIT and negatively regulates NF- κ B and IRF-3/7-mediated signal pathways. *Biochem Biophys Res Commun.*2012; 422:501–507.
65. Li S, Wang L, Berman M, Kong YY, Dorf ME. Mapping a dynamic innate immunity protein interaction network regulating type I interferon production. *Immunity* 2011;35:426–440.
66. Xia X, Cui J, Wang HY, Zhu L, Matsueda S, Wang Q, et al. NLRX1 negatively regulates TLR-induced NF- κ B signaling by targeting TRAF6 and IKK. *Immunity* 2011;34:843–853.
67. Kanke T, MacFarlane SR, Seatter MJ, Davenport EL, Paul A, McKenzie RC, Plevin RJ. et al. Proteinase-activated receptor-2-mediated activation of stress-activated protein kinases and inhibitory kappa B kinases in NCTC 2544 keratinocytes. *J Biol Chem*2001; 276:31657–31666.
68. Matsuda A, Suzuki Y, Honda G, Muramatsu S, Matsuzaki O, Nagano Y, et al. Large-scale identification and characterization of human genes that activate NF-kappaB and MAPK signaling pathways. *Oncogene* 2003;22:3307–3318.
69. Liu, XY, Wei B, Shi HX, Shan YF, Wang C. Tom70 mediates activation of interferon regulatory factor 3 on mitochondria. *Cell Res.* 2010;20:994–1011.
70. Reineke LC, Lloyd RE. The stress granule protein G3BP1 recruits protein kinase R to promote multiple innate immune antiviral responses. *J Virol.* 2015;89:2575–2589.

71. Yang W, Yang W, Ru Y, Ren J, Bai J, Wei J, et al. G3BP1 inhibits RNA virus replication by positively regulating RIG-I-mediated cellular antiviral response. *Cell Death Dis.* 2019;10:946.
72. Kim SSY, Sze L, Liu C, Lam KP. The stress granule protein G3BP1 binds viral dsRNA and RIG-I to enhance interferon- β response. *J. Biol. Chem.* 2019; 294: 6430–6438.
73. Raaben M, Groot Koerkamp MJA, Rottier PJM, de Haan CAM. Mouse hepatitis coronavirus replication induces host translational shutoff and mRNA decay, with concomitant formation of stress granules and processing bodies. *Cell Microbiol.* 2007;9:2218–2229.
74. Nakagawa K, Narayanan K, Wada M, Makino S. Inhibition of Stress Granule Formation by Middle East Respiratory Syndrome Coronavirus 4a Accessory Protein Facilitates Viral Translation, Leading to Efficient Virus Replication. *J Virol.* 2018; 92 (20). pii: e00902-18.
75. Ivanov P, Kedersha N, Anderson P. Stress Granules and Processing Bodies in Translational Control. *Cold Spring Harb Perspect Biol.* 2019; 11 (5). pii: a032813.
76. Slaine PD, Kleer M, Smith NK, Khaperskyy DA, McCormick C. Stress Granule-Inducing Eukaryotic Translation Initiation Factor 4A Inhibitors Block Influenza A Virus Replication. *Viruses* 2017; 9 (12). pii: E388.
77. Thompson P, Eam A, NP Young, Fish S, Chen J, Barrera M, et al. Abstract 2698: eFT226, a potent and selective inhibitor of eIF4A, is efficacious in preclinical models of lymphoma. *Experimental and Molecular Therapeutics* 2019.
78. Reineke LC, Tsai WC, Jain A, Kaelber JT, Jung SY, Lloyd RE, et al. Casein Kinase 2 Is Linked to Stress Granule Dynamics through Phosphorylation of the Stress Granule Nucleating Protein G3BP1. *Mol Cell Biol* 2017;37 (4). pii: e00596-16.
79. Fonseca BD, Jia JJ, Hollensen AK, Pointet R, Hoang HD, Niklaus MR, et al. LARP1 is a major phosphorylation substrate of mTORC1. *BioRxiv*, 2018; 491274.
80. Kindrachuk J, Ork B, Hart BJ, Mazur S, Holbrook MR, Frieman MB, et al. Antiviral potential of ERK/MAPK and PI3K/AKT/mTOR signaling modulation for Middle East respiratory syndrome coronavirus infection as identified by

- temporal kinome analysis. *Antimicrob Agents Chemother.* 2015;59(2):1088-99.
81. Frieman M, Yount B, Heise M, Kopecky-Bromberg SA, Palese P, Baric RS. Severe acute respiratory syndrome coronavirus ORF6 antagonizes STAT1 function by sequestering nuclear import factors on the rough endoplasmic reticulum/Golgi membrane. *J Virol.* 2007;81(18):9812-24.
 82. Faria PA, Chakraborty P, Levay A, Barber GN, Ezelle HJ, Enninga J, et al. VSV disrupts the Rae1/mrnp41 mRNA nuclear export pathway. *Mol Cell* 2005;17:93–102.
 83. Timms RT, Zhang Z, Rhee DY, Harper JW, Koren I, Elledge SJ. A glycine-specific N-degron pathway mediates the quality control of protein N-myristoylation. *Science.* 2019;365(6448):eaaw4912.
 84. Quan B, Seo HS, Blobel G, Ren Y. Vesiculoviral matrix (M) protein occupies nucleic acid binding site at nucleoporin pair (Rae1 • Nup98). *Proc Natl Acad Sci USA.* 2014; 111:9127–9132.
 85. Li G, Fan Y, Lai Y, Han T, Li Z, Zhou P, et al. Coronavirus infections and immune responses. *J Med Virol.* 2020; 92 (4) : 424- 432.
 86. Baruah V, Bose S. Immunoinformatics-aided identification of T cell and B cell epitopes in the surface glycoprotein of 2019-nCoV. *J Med Virol* 2020;92(5):495-500.
 87. Zhang B, Zhou X, Qiu Y, Feng F, Feng J, Jia J, et al. Clinical characteristics of 82 death cases with COVID-19. *medRxiv.* 2020. 02.26.20028191.
 88. Wong CK, Lam CW, Wu AK, Ip WK, Lee NL, Chan IH, Lit LC, Hui DS, Chan MH, Chung SS, Sung JJ. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. *Clin Exp Immunol.* 2004;136(1):95-103.
 89. Conti P, Ronconi G, Caraffa A, Gallenga CE, Ross R, Frydas I, et al. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by COVID-19: anti-inflammatory strategies. *J. Biol. Regul. Homeostatic Agents.* 2020; 34(2).
 90. Jiang F, Deng L, Zhang L, Cai Y, Cheung CW, Xia Z. Review of the clinical characteristics of coronavirus disease 2019 (COVID-19). *J Gen Intern Med.* 2020:1-5.

91. de Wit E, van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. *Nat Rev Microbiol.* 2016; 14(8): 523- 534.
92. Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. *Semin Immunopathol.* 2017; 39(5): 529- 539.
93. Rokni M, Ghasemi V, Tavakoli Z. Immune responses and pathogenesis of SARS-CoV-2 during an outbreak in Iran: Comparison with SARS and MERS. *Reviews Med Virol* 2020;1-6.
94. Deng X, van Geelen A, Buckley AC, et al. Coronavirus Endoribonuclease activity in porcine epidemic diarrhea virus suppresses type I and type III interferon responses. *J Virol.* 2019; 93(8):e02000-18.
95. Yang CH, Li K, Pfeffer SR, Pfeffer LM. The type I IFN-induced miRNA, miR-21. *Pharmaceuticals.* 2015; 8(4): 836- 847.
96. Prompetchara E, Ketloy C, Palaga T. Immune responses in COVID-19 and potential vaccines: lessons learned from SARS and MERS epidemic. *Asian Pac J Allergy Immunol.* 2020; 38:1-9.
97. Gorse GJ, Donovan MM, Patel GB. Antibodies to coronaviruses are higher in older compared with younger adults and binding antibodies are more sensitive than neutralizing antibodies in identifying coronavirus-associated illnesses. *J Med Virol.* 2020; 92(5): 512- 517.
98. Liu W, Fontanet A, Zhang PH, Zhan L, Xin ZT, Baril L, et al. Two-year prospective study of the humoral immune response of patients with severe acute respiratory syndrome. *J Infect Dis.* 2006; 193(6): 792- 795.
99. Hsueh PR, Huang LM, Chen PJ, Kao CL, Yang PC. Chronological evolution of IgM, IgA, IgG and neutralisation antibodies after infection with SARS-associated coronavirus. *Clin Microbiol Infect.* 2004; 10(12): 1062- 1066.
100. Tang F, Quan Y, Xin Z-T, Wrammert J, Ma MJ, Lv H, et al. Lack of peripheral memory B cell responses in recovered patients with severe acute respiratory syndrome: a six-year follow-up study. *J Immunol.* 2011; 186(12): 7264- 7268.

101. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*. 2020; 579(7798):270-273.
102. Gu J, Gong E, Zhang B, Zheng J, Gao Z, Zhong Y, et al. Multiple organ infection and the pathogenesis of SARS. *J Exp Med*. 2005;202(3):415-24.
103. Li CK, Wu H, Yan H, Ma S, Wang L, Zhang M, Tang X, et al. T cell responses to whole SARS coronavirus in humans. *J Immunol*. 2008; 181(8): 5490- 5500.
104. Fan YY, Huang ZT, Li L, Wu MH, Yu T, Koup RA, et al. Characterization of SARS-CoV-specific memory T cells from recovered individuals 4 years after infection. *Arch Virol*. 2009; 154(7): 1093- 1099.
105. Peng H, Yang LT, Wang LY, Li J, Huang J, Lu ZQ, et al. Long-lived memory T lymphocyte responses against SARS coronavirus nucleocapsid protein in SARS-recovered patients. *Virology*. 2006; 351(2): 466- 475.
106. Guan WD, Mok CK, Chen ZL, Feng LQ, Li ZT, Huang JC, et al. Characteristics of traveler with Middle East respiratory syndrome, China, 2015. *Emerg Infect Dis*. 2015; 21(12): 2278- 2280.
107. Ng OW, Chia A, Tan AT, Jadi RS, Leong HN, Bertoletti A, et al. Memory T cell responses targeting the SARS coronavirus persist up to 11 years post-infection. *Vaccine*. 2016; 34(17): 2008- 2014.
108. Oh HL, Chia A, Chang CX, Leong HN, Ling KL, Grotenbreg GM, et al. Engineering T cells specific for a dominant severe acute respiratory syndrome coronavirus CD8 T cell epitope. *J Virol*. 2011; 85(20): 10464- 10471.
109. Wu F, Wang A, Liu M, Wang Q, Chen J, Xia S, et al. Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implications. <https://doi.org/10.1101/2020.03.30.20047365>
110. Shi Y, Wang Y, Shao C, Huang J, Gan J, Huang X, et al. COVID-19 infection: the perspectives on immune responses. *Cell Death & Differentiation*. 2020; <https://doi.org/10.1038/s41418-020-0530-3>

111. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao y, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. *Clin Infect Dis* 2020; March, pii: ciaa248. doi: 10.1093/cid/ciaa248.
112. Min CK, Cheon S, Ha NY, Sohn KM, Kim Y, Aigerim A, et al. Comparative and kinetic analysis of viral shedding and immunological responses in MERS patients representing a broad spectrum of disease severity. *Sci Rep* 2016; 6: 25359.
113. Shaw AC, Goldstein DR, Montgomery RR. Age-dependent dysregulation of innate immunity. *Nat Rev Immunol* 2013; 13(12): 875-87.
114. Hotez PJ, Bottazzi ME, Corry D. The Potential Role of Th17 Immune Responses in Coronavirus Immunopathology and Vaccine-induced Immune Enhancement. *Preprints* 2020, 2020040159.
115. Wu D, Yang XO. TH17 responses in cytokine storm of COVID-19: An emerging target of JAK2 inhibitor Fedratinib. *J Microbiol Immunol Infect* 2020; pii: S1684-1182(20)30065-7.
116. Hoe E, Anderson J, Nathanielsz J, Toh ZQ, Marimla R, Balloch A, Licciardi PV. The contrasting roles of Th17 immunity in human health and disease. *Microbiol Immunol* 2017;61: 49-56
117. Murdock BJ, Falkowski NR, Shreiner AB, Sadighi Akha AA, McDonald RA, White ES, et al. Interleukin-17 drives pulmonary eosinophilia following repeated exposure to *Aspergillus fumigatus* conidia. *Infect Imm* 2012;80: 1424-36
118. Cheung PF, Wong CK, Lam CW. Molecular mechanisms of cytokine and chemokine release from eosinophils activated by IL-17A, IL-17F, and IL-23: implication for Th17 lymphocytes mediated allergic inflammation. *J Immunol* 2008;180: 5625-35
119. Al-Ramli W, Prefontaine D, Chouiali F, Martin JG, Olivenstein R, Lemiere C, Hamid Q. T(H)17-associated cytokines (IL-17A and IL-17F) in severe asthma. *J Allergy Clin Immunol* 2009;123: 1185-7
120. Zhang Y, Li J, Zhan Y, Wu L, Yu X, Zhang W, et al. Analysis of serum cytokines in patients with severe acute respiratory syndrome. *Infect Imm* 2004; 72: 4410-5
121. Kimura A, Kishimoto T. IL-6: regulator of Treg/Th17 balance. *Eur J Immunol* 2010; 40: 1830-5168.

122. Zhang X, Wu K, Wang D, Yue X, Song D, Zhu Y, Wu J. Nucleocapsid protein of SARS-CoV activates interleukin-6 expression through cellular transcription factor NF-kappaB. *Virology* 2007;365: 324-35.
123. Zhang X, Song K, Tong F, Fei M, Guo H, Lu Z, et al. First case of COVID-19 in a patient with multiple myeloma successfully treated with tocilizumab. *Blood Adv* 2020;4: 1307-10.
124. Gasch M, Goroll T, Bauer M, Hinz D, Schutze N, Polte T, et al. Generation of IL-8 and IL-9 producing CD4(+) T cells is affected by Th17 polarizing conditions and AHR ligands. *Mediators Inflamm* 2014: 182549.
125. Groeneveld ABJ. A Central Role of Interleukin-8 in the Pathogenesis of ARDS. In: Vincent JL. (eds) *Yearbook of Intensive Care and Emergency Medicine* 1998. *Yearbook of Intensive Care and Emergency Medicine*, Vol 1998. Springer, Berlin, Heidelberg.
126. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497–506.
127. Chen C, Zhang XR, Ju ZY, He WF. Advances in the research of cytokine storm mechanism induced by Corona Virus Disease 2019 and the corresponding immunotherapies. *Zhonghua Shaoshang Zazhi*. 2020;36(0):E005.
128. Liu Y, Zhang C, Huang F, Yang Y, Wang F, Yuan J, et al. 2019-novel coronavirus (2019-nCoV) infections trigger an exaggerated cytokine response aggravating lung injury. 2020. <http://www.chinaxiv.org/abs/202002.00018>.
129. Lin L, Lu L, Cao W, Li T. Hypothesis for potential pathogenesis of SARS-CoV-2 infection—a review of immune changes in patients with viral pneumonia. *Emerging Microbes Infections*, 2020;9(1):727-732.
130. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of 2019 novel coronavirus infection in China. *N Engl J Med*. 2020;undefined:undefined. doi:10.1056/NEJMoa2002032.
131. Dan H, Maureen G, Richard B, Clark KL. Quantitative mRNA expression profiling of ACE 2, a novel homologue of angiotensin converting enzyme. *FEBS*. 2002.

132. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients With 2019 novel coronavirus- infected pneumonia in Wuhan, China. *JAMA*. 2020; 323(11): 1061–1069.
133. Wan SX, Yi QJ, Fan SB, Lv G, Zhang X, Guo L, et al. Characteristics of lymphocyte subsets and cytokines in peripheral blood of 123 hospitalized patients with 2019 novel coronavirus pneumonia (NCP). *medRxiv*. 2020;undefined:undefined, doi:10.1101/2020.02.10.20021832.
134. Liu Q, Zhou YH, Yang ZQ. The cytokine storm of severe influenza and development of immunomodulatory therapy. *Cell Mol Immunol*. 2016;13 (1):3–10.
135. Ho J, Wu A, Lam B, Ooi GC, Khong PL, Ho PL, et al. Pentaglobin in steroid-resistant severe acute respiratory syndrome. *Int J Tuberc Lung Dis*. 2004;8(10):1173–1179.
136. Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *J Thromb Haemost*. 2020;18(6):1421-1424.
137. Liu G, Li H. COVID-19: Attacks the 1-Beta Chain of Hemoglobin and Captures the Porphyrin to Inhibit Human Heme Metabolism. *ChemRxiv*. Preprint. 2020. <https://doi.org/10.26434/chemrxiv.11938173.v7>.
138. Alsamarai AGM, Alobaidi AHA, Alsamarai MAM. SARS-CoV-2: Treatment and Therapeutic Approaches. *Aalborg Academy J Med Sci* 2020;3(3):1-32: Online First.
139. Forman R, Atun R, McKee M, Mossialoss E. 12 Lessons learned from the management of the coronavirus pandemic. *Health Policy* (2020), <https://doi.org/10.1016/j.healthpo>
140. Long QX, Tang X, Shi Q, Li Q, Deng H, Yuan J, et al. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. *Letters, Nature Medicine* 2020. www.nature.com/naturemedicine.
141. Ellinghaus D, Degenhardt F, Bujanda L, Buti M, Albillos A, Prati PI, et al. Genomewide association of severe COVID-19 with respiratory failure. *New Eng J Med.org* 2020.