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Review Article

Insights to the epidemiology, diagnosis and treatments of SARS-CoV-2

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ABSTRACT

The novel coronavirus disease 2019 (COVID-19) is a huge global public health threat which affected millions of people and have been causing high mortalities. Coronaviruses have the largest genomes for RNA viruses, enveloped and single-stranded. They mainly cause respiratory disease with incidences of enteric problems and affecting the liver and neurological system in animals and humans. The rapid diagnosis of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection is required for better control of spread of evolving mutant viruses. This review article aims to gather insights on the epidemiology, diagnosis and treatment of SARS-CoV-2 infection. In conclusion, apart from the COVID-19 disease epidemiology, a better understanding of the available effective, rapid and sensitive tests for SARS-CoV-2 diagnosis and the novel drugs for treatment both prophylactically and therapeutically are necessary to mitigate any future risks of infection.

1. Introduction

Coronavirus disease 2019 (COVID-19) which was first demonstrated in Wuhan city of China in December 2019, is a very contagious disease occured by severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2) (CDC, 2021; Huang et al., 2020; Rahman et al., 2021; WHO, 2021a) and was declared a global pandemic by the World Health Organization (WHO) in March 11, 2020 (WHO, 2021b). Coronaviruses are the members of the family Coronaviridae in the order Nidovirales (Schoeman and Fielding, 2019; Woo et al., 2010). The virus contains the largest genome for RNA viruses, single-stranded with a large-envelope (Maurya et al., 2022; Schoeman and Fielding, 2019; Woo et al., 2010). COVID-19 causes mainly respiratory disease with incidences of enteric problems and affect the liver and neurological system in animals and humans (Tang et al., 2020). The rapid diagnosis of SARS-CoV-2 infection leads to better control of its spread. There are several criteria including case history, clinical symptoms, serological and molecular diagnosis, and radiological diagnosis

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including computed tomography (CT) imaging are required (Rahman et al., 2021). Although several drugs and neutralizing monoclonal antibodies have been utilised for the treatment of COVID-19, the impact of the antiviral agents have still been investigated (Beigel et al., 2020).

In this review, we aim to analyse the epidemiology, diagnosis and treatment of SARS-CoV-2 infection.

2. Epidemiology

Daily reports of increased number of infections and associated deaths due to COVID-19 have been dramatic, therefore understanding its epidemiology is important (Uddin et al., 2020). COVID-19 cases were first reported from Wuhan, Hubei Province, China, towards the end of 2019 where most patients suffering from pneumonia of unknown origin had a history of visit to Huanan seafood market (Jiang et al., 2020). According to the WHO, over 108 million laboratories have reported cases of COVID-19 worldwide with more than 2.4 million mortality by February 16, 2021 (https://covid19.who.int/). However, the actual number of COVID-19 cases could be significantly higher as a large proportion of infected individuals are asymptomatic and undiagnosed (Yanes-Lane et al., 2020).

The causative agent, SARS-CoV-2, and the transmission occurred via respiratory route during close contacts of individuals (Meyerowitz et al., 2020). Initially, the WHO had indicated *R* value 2 (the number of people that one infected person will pass on) for SARS-CoV-2, but subsequent studies have suggested it to be highly variable and greater than 2 (Callaway et al., 2020; Liu et al., 2020a; Katul et al., 2020; Manriquez et al., 2020). This superfast spreading nature of one infected individual transmitting to large number of secondary contacts is the major drivers of COVID-19 pandemic (Chang et al., 2021). This suggests that as the virus pass through the people, over a period of time its ability to transmit to susceptible people has been increasing, but may not be associated with the disease severity. These data shows the highly transmissible nature of this unknown virus.

Most of those who died from COVID-19 have underlying comorbidities including diabetes, hypertension, or cardiovascular disease, which could compromise their immune system (Ssentongo et al., 2020). COVID-19 associated severe outcomes (hospitalizations, intensive care unit admissions and deaths) are greater in men than women worldwide (Gebhard et al., 2020; Klein et al., 2020). SARS-CoV-2 is considered causing milder disease in children, and up to one fourth of infants born to infected mothers are affected (Chen et al., 2020a). However, there is unfortunately limited data on the demographic and clinical characteristics of the SARS-CoV-2 infection in children (Lu et al., 2020). According to a study performed on pediatric COVID-19 patients, of the 2914 patients with available data, 56% were male between the age of 1 day and 17 years and 79% were demonstrated to have no comorbidities in the United States (Patel, 2020). In the United States, 22% of the infected population consists of children under the age of 18 years (Patel, 2020). However, as per records of the Center for Disease Control (CDC), 1.7% cases occurred in pediatric patients are under the age of 18 among COVID-19 cases whose age was reported to be known. While the rate of hospitalization in pediatric patients is 20% whose hospitalization status is known, it is estimated to be 33% in all adults aged 18-64 years (CDC, 2020). Overall, the disease trend suggested that the severity of disease is high in immune compromised and aged people with comorbid conditions compared to the infected young and female healthy population.

The effects of prior Bacillus Calmette-Guérin (BCG) vaccination on COVID-19 pandemic is a matter of curiosity. There were reports suggesting that countries with national mandatory BCG vaccination policies had lower rate of COVID-19 spread and mortality, but other studies have shown no such relationship exist (Chimoyi et al., 2020; Gopalaswamy et al., 2020). The data pertaining to BCG vaccination and COVID-19 outcomes are affected by several confounding factors including vaccination policy, population structure, ethnicity/race and healthcare facilities, demanding for clinical trials to better understand this relationship which is currently ongoing in many countries (Gopalaswamy et al., 2020). These findings suggest that there are anecdotal beneficial anti-viral effects in individuals with prior history of BCG vaccination and now exposed to SARS-CoV2 infection.

3. Diagnosis

COVID-19 has been described as a disease that can be transmitted from human to human via nasal and oral droplets, and the virus uses angiotensin-converting enzyme 2 (ACE2) receptor to attach to susceptible cells. Infection with SARS-CoV-2 causes highly variable clinical outcomes than SARS, MERS and common cold (Chen, 2020; Patel, 2020). ACE2 receptor is expressed mainly by airway epithelial cells and distributed widely at low levels in human body including lung, kidney, intestines, blood vessels and oral mucosa (Hamming et al., 2004; Xu et al., 2020). The value of integrated diagnostics for the management of the current pandemic or the possible future pandemic of corona viruses outbreaks is very much needed for the molecular identification of the virus and quantification of quality of the immunological response. Detection of viral genetic material by polymerase chain reaction (PCR) in a nasopharyngeal swab or sputum sample is used for the diagnosis of COVID-19 infection (Uddin et al., 2020; Wang et al., 2020a), indicating that the virus mainly infects and resides in the respiratory tract causing major damage to the lungs hence nasopharyngeal swab and sputum samples are considered as reliable source for SARS-CoV-2 diagnosis.

Over the past few months currently available molecular technologies have been exploited to develop a rapid, highly specific and sensitive assays for the detection of SARS-CoV-2 and COVID-19. Rapid antigen detection tests were implemented to detect the SARS-CoV-2 antigen in addition to RT-PCR, but this test was lacking specificity and had increased risk of false-negative results (Mak et al., 2020). The need to implement next-generation sequencing has been previously highlighted in literature to detect mutated viruses and identify the viral genome for specific mutations. It has been stated that "synthesis sequencing" technique and "long reading sequence" have been utilized to detect viral genomes at single-base resolution levels (Andersen et al., 2020; Kim et al., 2020; Tang et al., 2020). Due to potential higher error rate, nanopore sequencing technology should be adapted to supplement other sequencing techniques such as synthesis sequencing. In addition, it has been emphasized that the technology of nanopore sequencing with its small and compact size have an advantage over other sequencing techniques, and it will provide RNA sequencing flexibility in the far regions where there are no full-fledged reference laboratories (Uddin et al., 2020).

Another diagnostic approach which has been reported for SARS-CoV-2 is by serological tests which detect antibodies generated by the host immune system against the virus, and it has been emphasized that the scores of these "antibody" tests are clear (Li et al., 2020). Immune based assays were employed for the detection of human IgA/IgM or IgG antibodies (van Elslande et al., 2020). The antibody-related tests have been reported to be faster, but the procedure takes over two days. Further, it usually takes up to two weeks post exposure to virus infection to detect elicited antibodies. However, it has been underlined the usefulness of antibody-based tests in community-based evaluation to measure the herd immunity and to identify susceptible individuals, though its utility for diagnosing early stage of COVID-19 is limited (Stadlbauer et al., 2020). Sero surveillance for SARS-CoV-2 antibody analysis is beneficial for detecting naïve individuals and the level of immunity in immune compromised people.

During this COVID-19 pandemic, various molecular based diagnostic tests were employed for epidemiology, global pandemic research, point of care tests, populations screens, and hospital-based tests. Some of them are Nucleic Acid Amplification Tests (NAAT) based on isothermal amplification, Loop mediated isothermal amplifications, CRISPR based detection, which were adopted at the point of care units, exploited for the visual read outs of the assay using PH sensitive dyes and to generate multiplex panels to differentiate SARS-CoV-2 from other coronaviruses. These tests are rapid (<1 hr) having comparable sensitivity to RT-PCR with minimal processing requirements (Metsky et al., 2020; Notomi et al., 2020; Yu et al., 2020; Zhang et al., 2020).

Symptoms of COVID-19 range from asymptomatic infections to lethal form which include severe pneumonia and acute respiratory distress (Uddin et al., 2020). In a study of adult patients with an average age of 70 (range, 43-92 years, 52% male), chronic kidney disease and congestive heart failure were found most common (86%) comorbidity, with the early symptoms identified being shortness of breath

(76%), fever (52%) and cough (48%) (Ong et al., 2020). The average number of days to onset of symptoms is 3.5 days and in a study 81% of inpatients were admitted to the intensive care unit 24 hours after initial hospitalization (Ong et al., 2020). The most common comorbidities were emphasized to be asthma, diabetes, immunosuppression and cardiovascular disease. Of pediatric patients testing positive for COVID-19, 14.9% were asymptomatic (Patel, 2020). It has been reported that patients have presented with cough (48%), fever (47%), sore throat/pharyngitis (28.6%), upper respiratory symptoms, rhinorrhea, sneezing, nasal congestion (13.7%), diarrhea (10.1%) and vomiting/nausea (7.8%) (Patel, 2020). According to the results of computed tomography (CT), in the same study, 36% of the cases reported unilateral CT findings, and 64% had bilateral CT imaging findings. Unlike adults, most infected children experience milder disease and generally have faster recovery. Additional care may be required for accompanying children and young children (Patel, 2020).

It is concluded that preexisting ailments in multiple organs especially heart, lung and kidney have been found to be the precipitating factor for the severity of COVID-19 in patients.

4. Treatment

An effective treatment for SARS-CoV-2 infection is still largely unknown in the USA. However, the first COVID-19 patient reported to have been treated with supportive care and intravenous Remdesivir showed improvement in overall health condition (Holshue et al., 2020). Drugs such as Lopinavir-Ritonavir, Oseltamivir, Umifenovir, Azithromycin, Hydroxychloroquine, Interferon alpha, and IV gamma globulin have also been tested for COVID-19 treatment (Eghbali et al., 2020; Qiu et al., 2020; Shen et al., 2020; Wang et al., 2020b; Zheng et al., 2020). A large multinational clinical trial, referred as the Solidarity trial, investigated on four repurposed antiviral drugs for COVID-19 such as hydroxychloroquine, remdesivir, lopinavir, and interferon beta-1a which had little or no effect on many hospitalized COVID-19 patients (Pan et al., 2021). However, results from other studies showed beneficial effect of remdesivir treatment on COVID-19 (Beigel et al., 2020). The European Union, United Kingdom, and the United States provided emergency use authorization to remdesivir (Dyer, 2020). There are several treatment strategies have been proposed to treat COVID-19 patients globally using repurposed drugs and supportive therapies. Among all Remdesivir has been found beneficial in many countries if administered early within the first couple of days of the onset of infection.

Severity of COVID-19 in patients have been attributed to cytokine storm, leading to large scale infiltration of immune cells into the lungs resulting in alveolar damage, lung function reduction, and death. The drug Ruxolitinib a oral bioavailable Janus-associated kinase (JAK) inhibitor has been shown to lower cytokine levels and improve outcomes (Yeleswaram et al., 2020). It has been emphasized that Baricitinib has high anti-inflammatory properties and help in alleviating chronic inflammation in interferonopathies (Sanchez et al., 2018). The availability of these advantageous pharmacokinetic properties have made it special among approved drugs. However, at tolerated doses the drugs have no effect on reducing viral infectivity (Stebbing et al., 2020). Baricitinib, which can reduce viral infectivity, viral replication and abnormal host inflammatory response likely considered along with other antivirals (lopinavir or ritonavir and remdesivir) and used widely in COVID-19 patients (Stebbing et al., 2020). To dampen the severity of disease several proinflammatory cytokines blocking drugs were found beneficial along with corticosteroids when used wisely.

After over one year of the onset of disease the convalescent plasma or immunoglobulins have been in use as a last resort to increase the survival rate of COVID-19 patients (Chen et al., 2020b). During the onset of pandemic, several studies conducted in rhesus macaques using convalescent plasma from COVID-19 survivors (CCP) have highlighted the pre-requisite to have sufficiently higher titer of neutralizing antibodies in CCP to treat COVID-19 patients (ShaanLakshmanappa et al., 2021), and CCP infused animals had detectable level of antiviral antibodies with significantly reduced interstitial pneumonia (Van Rompay et al., 2022). Collectively these studies proved therapeutic value of the CCP and further clinical use during early COVID-19 infection.

Convalescent plasma therapy in COVID-19 is safe and reduces mortality if the treatment is initiated very early with enough quantity of virus neutralizing antibodies present in the serum (Casadevall et al., 2020). The neutralizing monoclonal antibodies were used in the early days of COVID-19 as therapeutic interventions against the new variants. The combination of two potent monoclonal antibodies C-135 LS and C-144 LS were tested therapeutically in rhesus macaques have significantly reduced the virus replication in the respiratory system (Van Rompay et al., 2021) and same monoclonal antibody cocktail was tested prophylactically in aged rhesus macaques with comorbidity conditions have shown the dramatic improvement in preventing COVID-19 infection (Verma et al., 2021). These studies indicated that several treatment approaches like use of CCP, monoclonal antibodies both prophylactically and therapeutically were tried to control the SARS-COV-2 infection using human and animal studies. These approaches were given proof of concept to try different treatment strategies in clinical studies against emerging new variants of SARS-CoV-2. Timely and appropriate administration of methylprednisolone in severe and critically ill patients with COVID-19 may develop positive outcomes by alleviating the lung function with no apparent negative effects on the production of specific IgG to SARS-CoV-2 (Liu et al., 2020b).

Conclusion

In conclusion, Further Artificial Intelligence (AI) and machine learning tools needs to be developed and applied for data interpretation for effective diagnostics, vaccines and treatments against the constantly appearing new variants of SARS CoV-2. The effective epidemiological data monitoring and surveillance should lead to the development of advanced diagnostic tests which further guides the effective treatment choices and follow-ups for successful therapy against COVID-19 pandemic.

Conflict of interest

The authors declare that they have no conflict of interest.

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Refereces

Andersen, K.G., Rambaut, A., Lipkin, W.I., et al. (2020) The proximal origin of SARS-CoV-2. Nat. Med. 26: 450-2.

Beigel, J.H., Tomashek, K.M., Dodd, L.E., et al. (2020) Remdesivir for the treatment of Covid-19 - final report. N. Engl. J. Med. 383: 1813-26.

Callaway, E., Cyranoski, D., Mallapaty, S., et al. (2020) The coronavirus pandemic in five powerful charts. Nature [Internet]. http://www.nature.com/articles/d41586-020-00758-2

Casadevall, A., Grossman, B.J., Henderson, J.P., et al. (2020) The assessment of convalescent plasma efficacy against COVID-19. Med. (NY) 1: 66-77.

CDC COVID-19 Response Team (2020) Coronavirus Disease 2019 in Children - United States, February 12 - April 2, 2020. MMWR Morb Mortal Wkly Rep 69: 422-6.

Chang, S., Pierson, E., Koh PW, et al. (2021) Mobility network models of COVID-19 explain inequities and inform reopening. Nature 589:82-87.

Chen, Y., Peng, H., Wang, L., et al. (2020a) Infants born to mothers with a new coronavirus (COVID-19). Front. Pediatr. 8:104.

Chen, L., Xiong, J., Bao, L., Shi, Y. (2020b) Convalescent plasma as a potential therapy for COVID-19. Lancet Infect. Dis. 20: 398-400.

Chimoyi, L., Velen, K., Churchyard, G.J., et al. (2020) An ecological study to evaluate the association of Bacillus Calmette-Guerin (BCG) vaccination on cases of SARS-CoV2 infection and mortality from COVID-19. PLoS ONE 15: e0243707.

Dyer, O. (2020) Covid-19: Remdesivir has little or no impact on survival, WHO trial shows. Br. Med. J. 371: m4057.

Eghbali, A., Shokrollahi, S., Mahdavi, N.S., et al. (2020) COVID-19 in pediatric

patients: A case series. J. Cell. Mol. Anesth. 5:3-5.

Gebhard, C., Regitz-Zagrosek, V., Neuhauser, H.K., et al. (2020) Impact of sex and gender on COVID-19 outcomes in Europe. Biol. Sex. Differ. 11:29.

Gopalaswamy, R., Ganesan, N., Velmurugan, K., et al. (2020) The strange case of BCG and COVID-19: The verdict is still up in the air. Vaccines (Basel) 8: 612.

Hamming, I., Timens, W., Bulthuis, M.L.C., et al. (2004) Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J. Pathol.* 203: 631-7.

Holshue, M.L., DeBolt, C., Lindquist, S., et al. (2020) First case of 2019 novel Coronavirus in the United States. N. Engl. J. Med. 382: 929-36.

Huang, C., Wang, Y., Li, X., et al. (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395: 497-506.

Jiang, S., Du, L., Shi, Z. (2020) An emerging coronavirus causing pneumonia outbreak in Wuhan, China: calling for developing therapeutic and prophylactic strategies. Emerg. *Microbes* Infect. 9:27 5-277.

Katul, G.G., Mrad, A., Bonetti, S., et al. (2020) Global convergence of COVID19 basic reproduction number and estimation from early-time SIR dynamics. PLoS ONE 15: e0239800.

Kim, D., Lee, J.-Y., Yang, J.-S., et al. (2020) The architecture of SARS-CoV-2 transcriptome. Cell 181: 914-21.e910.

Klein, S.L., Dhakal, S., Ursin, R.L., et al. (2020) Biological sex impacts COVID-19 outcomes. PLoS Pathog. 16: e1008570.

Li, Z., Yi, Y., Luo, X., et al. (2020) Development and clinical application of a rapid IgM-IgG combined antibody test for SARS-CoV-2 infection diagnosis. J. Med. Virol. 92: 1518-24.

Liu, Y., Gayle, A.A., Wilder-Smith, A., Rocklöv, J. (2020a) The reproductive number of COVID-19 is higher compared to SARS coronavirus. J. Travel Med. 27: taaa021.

Liu, J., Zheng, X., Huang, Y., et al. (2020b) Successful use of methylprednisolone for treating severe COVID-19. J. Allergy Clin. Immunol. 146: 325-7.

Lu, X., Zhang, L., Du, H., et al. (2020) SARS-CoV-2 infection in children. N. Engl. J. Med. 382: 1663-5.

Mak, G.C., Cheng, P.K., Lau, S.S., et al. (2020) Evaluation of rapid antigen test for detection of SARS-CoV-2 virus. J. Clin. Virol. 129: 104500.

Metsky, H.C., Freije, C.A., Kosoko-Thoroddsen, T.-S.F., et al. (2020) CRISPR-based surveillance for COVID-19 using genomically-comprehensive machine learning design. bioRxiv [Preprint]. doi: 10.1101/2020.02.26.967026

Meyerowitz, E.A., Richterman, A., Gandhi, R.T., Sax, P.E. (2021) Transmission of SARS-CoV-2: A review of viral, host, and environmental factors. Ann. Intern. Med. 174: 69-79.

Notomi, T., Okayama, H., Masubuchi, H., et al. (2000) Loop-mediated isothermal amplification of DNA. Nucleic Acids Res. 28: E63.

Ong, S.W.X., Tan, Y.K., Chia, P.Y., et al. (2020) Air, surface environmental, and personal protective equipment contamination by severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) from a symptomatic patient. JAMA 323: 1610-2.

Pan, H., Peto, R., Karim, Q.A., et al. (2021) Repurposed antiviral drugs for COVID-19 – interim WHO SOLIDARITY trial results. N. Engl. J. Med. 384: 497-511.

Patel, N.A. (2020) Pediatric COVID-19: Systematic review of the literature. Am. J. Otolaryngol. 41: 102573.

Qiu, H., Wu, J., Hong, L., et al. (2020) Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. Lancet Infect. Dis. 20: 689-96.

Rahman, S., Montero, M.T.V., Rowe, K., et al. (2021) Epidemiology, pathogenesis, clinical presentations, diagnosis and treatment of COVID-19: a review of current evidence. Expert Rev. Clin. Pharmacol. 14: 601-21.

Ruiz-Manriquez, J., León-Lara, X., Campos-Murguía, A. et al. (2020) Knowledge of Latin American gastroenterologists and

endoscopists regarding SARS-CoV-2 infection. Revista de Gastroenterología de México. 85: 288-94.

Sanchez, G.A.M., Reinhardt, A., Ramsey, S., et al. (2018) JAK1/2 inhibition with baricitinib in the treatment of autoinflammatory interferonopathies. J. Clin. Invest. 128: 3041-52.

Shaan Lakshmanappa, Y., Elizaldi, S.R., Roh, J.W., et al. (2021) SARS-CoV-2 infection induces robust germinal center CD4 T follicular helper cell responses in rhesus macaques. Nat. Commun. 12: 541.

Shen, Q., Guo, W., Guo, T., et al. (2020) Novel coronavirus infection in children outside of Wuhan, China. *Pediatr. Pulmonol.* 55: 1424-9.

Ssentongo, P., Ssentongo, A.E., Heilbrunn, E.S., et al. (2020) Association of cardiovascular disease and 10 other pre-existing comorbidities with COVID-19 mortality: A systematic review and meta-analysis. PLoS One 15: e0238215.

Stadlbauer, D., Amanat, F., Chromikova, V., et al. (2020) SARS-CoV-2 seroconversion in humans: A detailed protocol for a serological assay, antigen production, and test setup. *Curr. Protoc. Microbiol.* 57: e100.

Stebbing, J., Phelan, A., Griffin, I., et al. (2020) COVID-19: combining antiviral and anti-inflammatory treatments. Lancet Infect. Dis. 20: 400-2.

Tang, X., Wu, C., Li, X., et al. (2020) On the origin and continuing evolution of SARS-CoV-2. Natl. Sci. Rev. 7: 1012-23.

Uddin, M., Mustafa, F., Rizvi, T.A., et al. (2020) SARS-CoV-2/COVID-19: Viral genomics, epidemiology, vaccines, and therapeutic interventions. Viruses 12: 526.

van Elslande, J., Houben, E., Depypere, M., et al. (2020) Diagnostic performance of seven rapid IgG/IgM antibody tests and the Euroimmun IgA/IgG ELISA in COVID-19 patients. Clin. Microbiol. Infect. 26: 1082-7.

Van Rompay, K.K.A., Olstad, K.J., Sammak, R.L., et al. (2021) Early treatment with a combination of two potent neutralizing antibodies improves clinical outcomes and reduces virus replication and lung inflammation in SARS-CoV-2 infected macaques. PLoS Pathog. 17(7): e1009688.

Van Rompay, K.K.A., Olstad, K.J., Sammak, R.L., et al. (2022) Early post-infection treatment of SARS-CoV-2 infected macaques with human convalescent plasma with high neutralizing activity had no antiviral effects but moderately reduced lung inflammation. PLoS Pathog. 18: e1009925.

Verma, A., Hawes, C.E., Shaan Lakshmanappa, Y., et al. (2021) Monoclonal antibodies protect aged rhesus macaques from SARS-CoV-2 associated immune activation. Cell Rep. 37: 109942

Wang, Y., Kang, H., Liu, X., Tong, Z. (2020a) Combination of RT-qPCR testing and clinical features for diagnosis of COVID-19 facilitates management of SARS-CoV-2 outbreak. J. Med. Virol. 92: 538-9.

Wang, D., Ju, X.L., Xie, F., et al. (2020b) Clinical analysis of 31 cases of 2019 novel coronavirus infection in children from six provinces (autonomous region) of northern China. Zhonghua Er Ke Za Zhi 58: 269-74.

WHO (2021a). Coronavirus disease (COVID-19) pandemic. [Cited 2021 March 19]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019

WHO (2021b). WHO Director-General's opening remarks at the media briefing on COVID19. [Cited 2021 March 19]. Available from: https://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/news/news/2020/3/who-announces-covid-19-outbreak-a-pandemic

Xu, H., Zhong, L., Deng, J., et al. (2020) High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int. J. Oral Sci. 12: 8.

Yanes-Lane, M., Winters, N., Fregonese, F., et al. (2020) Proportion of asymptomatic infection among COVID-19 positive persons and their transmission potential: A systematic review and meta-analysis. PLoS ONE 5: e0241536.

Yeleswaram, S., Smith, P., Burn, T., et al. (2020) Inhibition of cytokine signaling by ruxolitinib and implications for COVID-19 treatment. Clin. Immunol. 218: 108517.

Yu, L., Wu, S., Hao, X., et al. (2020) Rapid detection of COVID-19 coronavirus using a reverse transcriptional loop-mediated isothermal amplification (RT-LAMP) diagnostic platform. *Clin. Chem.* 66: 975-7.

Zhang, Y., Odiwuor, N., Xiong, J., et al. (2020) Rapid molecular detection of SARS-CoV2 (COVID-19) virus RNA using colorimetric LAMP. medRxiv [Preprint]. doi: 10.1101/2020.02.26 .20028373

Zheng, F., Liao, C., Fan, Q.H., et al. (2020) Clinical characteristics of children with coronavirus disease 2019 in Hubei, China. *Curr. Med. Sci.* 40: 275-80