EDITORIAL

The Covid-19, Epidemiology, Clinic and Prevention

Alessandro Antonelli[1,*], Giusy Elia[1], Silvia Martina Ferrari[1], Rudy Foddis[2], Salvatore De Marco[3], Alfonso Cristaudo[2] and Poupak Fallahi[2]

[1]Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy; [2]Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy; [3]U.O. 5th Medicine, AOUP, Pisa, Italy

1. BACKGROUND

In December 2019, a cluster of pneumonia cases, due to a newly identified β-coronavirus, occurred in Wuhan, China (Covid-19, or SARS-CoV-2). This was a zoonotic coronavirus breakout, that allowing human-to-human transmission, raised global health concerns [1]. On 26 February 2020, the rate of new cases begin to decline in China, but the tendency changed outside China, where new cases occurred, such as in Italy, South Korea and Iran; and for the first time the number of new cases outside China surmounted those reported in China [2]. After China, Italy had the second largest number of Covid-19 case-fatality rate [3]. Unfortunately, the infection spread also to all other European countries. Covid-19 is also spreading in US, mainly a high concentration in New York City, with a higher fatality rate. Other countries such as Iran, Turkey, Canada, South Korea, Brazil, Israel, have also unfortunately experienced a large spread of the infection. African countries are at particular risk because of the density of the communities and insufficient diagnostic and therapeutic capacities [4]. According to the European Centre for Disease Prevention and Control (ECDC), since December 31, 2019 and as of April 3, 2020, >1 000 000 cases of Covid-19 have been reported, including 51,515 deaths, and the number is increasing every day.

2. VIROLOGY

SARS-CoV-2 is strictly related to SARS-CoV [5]. It is believed to have a zoonotic origin. Coronavirus genetically clusters with the genus Betacoronavirus, in subgenus Sarbecovirus (lineage B), together with two bat-derived strains. At the whole genome level, it is 96% identical to other bat coronavirus samples (BatCov RaTG13) [6, 7]. Similar to other viruses, SARS-CoV-2 infects lung alveolar epithelial cells through receptor-mediated endocytosis *via* the angiotensin-converting enzyme II (ACE2) as an entry receptor [4]. Also, the DPP4 receptor is implicated in viral entry [8].

3. TRANSMISSION

The disease is believed to spread mainly with close contacts (within 1 to 2 meters), and through small droplets originating by people during sneeze, cough, or talk [9]. The contagion can also occur by first touching a contaminated surface and then touching eyes, nose, or mouth [9]. The virus survives for hours to days on surfaces [10, 11]. The aerosol dispersion is also responsible for diffusion of the disease. Virus spread may happen before symptoms appear, however if people are symptomatic, the virus is most contagious [12]. As stated by the ECDC, it is still not known the ease of spreading of this disease; generally, one person is able to infect from two to three others [10].

4. CLINIC OF COVID-19

Within the subset of patients admitted to hospital, the most common symptoms at onset of illness were fever (90-98%), cough (70-80%), dyspnoea (60-50%) and myalgia or fatigue (40-50%). Notably, 20-30% of patients had upper respiratory tract symptoms such as coryza, or gastrointestinal symptoms such as nausea, vomiting, and diarrhoea. Other clinical features included sputum production, headache (8%) and haemoptysis. The median time from onset of symptoms to first hospital admission was 4-8 days. About 20-30% required intensive treatment unit (ITU) admission for respiratory support:70-80% of patients are male and 30-50% had pre-existing comorbidities, such as hypertension (15-25%), diabetes (20-25%), obesity, and cardiovascular diseases (10-15%), or Chronic obstructive pulmonary disease (COPD). Laboratory features include leukopenia (20-40%), lymphopenia (20-45%) and raised aspartate aminotransferase (40%). Abnormalities on computed tomography (CT) of the chest were seen in all patients [13].

*Address correspondence to this author at the Department of Clinical and Experimental Medicine, University of Pisa, School of Medicine, *Via* Savi, 10, I-56126, Pisa, Italy; Tel: +39-050-992318; Cell: +39-335-8119294 or +39-335-344701; Fax: +39-050-993472 or +39-050-500841;
E-mail: alessandro.antonelli@med.unipi.it

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5. DIAGNOSIS

Two risk factors for Covid-19 are: having traveled to an area with community infection in the 14 preceding days, or having had tight relationships with infected people.

5.1. Imaging

In symptomatic patients, absent pleural effusions and asymmetric peripheral ground glass opacities represent some of the clinical features that can be observed on radiographs and CT [14]. As shown by a Chinese study that compared CT and polymerase chain reaction (PCR), CT imaging is more sensitive and faster than PCR, but less specific [15].

5.2. Viral Testing

The first diagnosis of Covid-19 can be made based on the symptoms. Subsequently, CT imaging or reverse transcription PCR (RT-PCR) performed on infected secretions have to provide definitive confirmation [15, 16]. Different RNA testing protocols exist for SARS-CoV-2 [17] that can be performed on respiratory or blood samples [18].

6. COMPLICATIONS

ITU patients had raised PCR, prothrombin and D-dimer levels on admission relative to non-ITU patients. A raised troponin [hypersensitive-troponin I (hs-cTnI)] was detected in about 10-20% of patients, possibly suggestive of virus-associated myocarditis. Systemic manifestations are frequent in Covid-19 infection, similar to other viral diseases [13, 19]. Complications included acute respiratory distress syndrome (20-30%) and secondary infection (10-20%). The overall mortality rate is 5-15% of hospitalized patients with a preponderance of older males (aged > 60 years) with comorbidities (obesity, diabetes, hypertension, cardiovascular diseases, or COPD) [13]. Furthermore, in coronavirus infection the coagulopathy is associated with high mortality and high D-dimers that are a particularly important marker for the coagulopathy [20]. The disease progression is associated with a decrease in lymphocytes. A better result of the disease can be given by a higher cell count of total lymphocytes, and in the early stage of novel-coronavirus (2019-nCoV) infection, a vital factor directing disease progression may be immune response [21]. A study shows that in patients with SARS-CoV-2 infection distinct host inflammatory cytokine profiles are present, and it reveals that there is an association between Covid-19 pathogenesis and excessive cytokine releases (in Bronchoalveolar Lavage Fluid and Peripheral Blood Mononuclear Cells), such as CCL2/MCP-1, CXCL10/IP-10, CCL3/MIP-1A, and CCL4/MIP1B [22]. According to different data, severe patients have mild or severe cytokine storms, which is also an important cause of death. Therefore, to save patients with critical conditions, the treatment of cytokine storm is important. Interleukin-6 (IL-6) has a key role in cytokine release syndrome (CRS). A novel strategy to treat severe patients could be to block the signal transduction pathway of IL-6 [23].

7. THERAPIES

For the moment, concrete antiviral medications approved for Covid-19 do not exist, and studies that are testing the existing medications are going on. Oxygen therapy, intravenous fluids, and breathing support are necessary depending on the severity [24]. The use of steroids may decrease results, and it is controversial [25]. However, steroids are used in the ITU setting in patients with Acute Respiratory Distress Syndrome (ARDS).

7.1. Virally Targeted Agents

In a large spectrum of RNA viruses, viral RNA synthesis is blocked from nucleoside analogues. Favipiravir (T-705) is a guanine analogue approved for the treatment of influenza, able to inhibit viral RNA-dependent RNA polymerase (*i.e*. influenza, Ebola, *etc*.) and its activity against SARS-CoV-2 was reported from a recent study (see randomized trials evaluating the effectiveness of favipiravir plus interferon-α or baloxavir marboxil) [26]. Remdesivir (GS-5734) inhibits HIV reverse transcriptase. It has several activities against RNA viruses, including SARS and MERS, in cell cultures and animal models, and it has been investigated in a clinical trial for Ebola. Intravenous remdesivir (200 mg on day 1 and 100 mg once daily for 9 days) has been evaluated by two phase III trials started in early February 2020 in patients with SARS-CoV-2 (NCT04252664 and NCT04257656) [26]. Protease inhibitors such as disulfiram, lopinavir and ritonavir have shown some activities against SARS [26] and MERS and clinical trials designed to evaluate these compounds on Covid-19 patients are currently underway (for example, ChiCTR2000029539). In recent times, one of these trials did not show any benefit beyond standard care from lopinavir-ritonavir treatment among hospitalized adult patients with severe Covid-19 [27].

7.2. Host-targeted Agents

Pegylated interferon alfa-2a and -2b, which can boost the innate immune responses against HBV and HCV, may play a role also against SARS-CoV-2 (see clinical trial, ChiCTR2000029387). Many other compounds are under investigation for their potential activity against SARS-CoV-2. Chloroquine, which has been used classically to treat malaria and autoimmune disorders (*i.e*. rheumatoid arthritis and systemic lupus erythematosus), has shown *in vitro* antiviral activity also against SARS-CoV-2 and it is now under evaluation in an open-label trial (ChiCTR2000029609) [26]. Tocilizumab is a humanized monoclonal antibody against IL-6 receptor (IL-6R), and it prevents the binding with IL-6, which can trigger the cytokine storm in patients

with severe Covid-19 [23]. Artificial intelligence has suggested AP2-associated protein kinase 1 (AAK1) disrupting drugs as potential inhibitors of viral entry into the target cells. For these reasons, Baricitinib, approved for rheumatoid arthritis [4], and ruloxitinib, an approved anti-inflammatory JAK1/2/TYK2 inhibitor, are under clinical evaluation for Covid-19 (in combination with mesenchymal stem cell infusion) [28].

Moreover, attempts to impair the binding of Sars-Cov-2 with its receptor on targeted cells, ACE2, and to block other spike proteins are under investigation. However, there is no indication to stop antihypertensive drugs in these patients [29]. Different degrees of coagulopathy have been described among patients who died from severe Covid-19 and high D-dimer levels emerged as a poor prognostic factor. Therefore LMWH, such as enoxaparin, are proposed by several scientific societies in the treatment of Covid-19 patients [30]. A small French study reported that Covid-19 patients treated with hydroxychloroquine have significant lower viral load or even complete viral clearance in the subsequent nasopharyngeal samples, especially if co-administered with azithromycin [31]. However, there are several limitations of these data and discordant results have been more recently described on this association [32]. Ivermectin has also been suggested to inhibit Covid-19 replication [33].

7.3. Passive Antibody Therapy

Convalescent plasma from recovered individuals represents a historical method to transfer neutralizing antibodies against this virus into affected and ill patients. For this reason, it has also been suggested for SARS and, lastly, for Covid-19 [34]. Further forms of passive immunization (*e.g*. using manufactured monoclonal antibodies) are under investigation [34].

8. PREVENTION

To prevent the diffusion of the infection, some measures have been recommended: people should stay at home, avoid gatherings, frequently wash hands with water and soap (at least for 20 seconds), and avoid touching the face, nose, eyes and mouth with unclean hands [35]. Social activities have been reduced by closing schools, reducing travel and public events, adopting distancing strategies on all occasions, including at least six feet distance (2 meters) between people [36]. The use of masks initially was recommended by World Health Organization (WHO) only in people with respiratory symptoms or taking care of patients with a suspect of infection [35]. Now wearing mask is a recommendation to all the population worldwide [37].

8.1. Personal Protective Equipment

The primary objective is to minimise the risk of diffusion of the virus, so precautions are to be taken, in healthcare personnel caring people with Covid-19, who perform procedures generating aerosol (*e.g*. intubation, or hand ventilations). The CDC recommends placing patients in Airborne infection isolation room (AIIR), besides standard precautions [38].

8.2. Vaccine

Different agencies have undertaken researches for the development of a vaccine, that is not available at the moment. Three vaccination strategies are under investigation. The first strategy aims to build a whole virus vaccine with inactive or dead virus, producing an immune response to an induced infection with Covid-19. The second strategy is to produce a vaccine with subunits of virus, sensitizing the immune system. SARS-CoV-2 and SARS-CoV to enter human cells use the ACE2 receptor [39]. The S-spike protein helps the virus introduction to the ACE2 receptor, being the focus of these researches. The third strategy is the use of a novel technique that creates nucleic acid vaccines (DNA or RNA) [40]. The first clinical trial, which started in March 2020 in Seattle, involving four volunteers, uses a vaccine containing a genetic code copied of the virus that is harmless [41].

CONCLUSION

The novel coronavirus 2019, which started as an outbreak in China in December 2019 has rapidly spread all over the world, such that on March 11, 2020, WHO declared this disease as pandemic. Given the fragile health systems in many countries, they may have serious difficulties to afford primary healthcare requirements for the current Covid-19 epidemic. The emergency that the world faces today demands that we develop urgent and effective measures to protect people at high risk of transmission. WHO has accelerated research in diagnostics, vaccines and therapeutics for this novel coronavirus [42].

REFERENCES

[1] Xie, M.; Chen, Q. Insight into 2019 novel coronavirus - an updated interim review and lessons from SARS-CoV and MERS-CoV. *Int. J. Infect. Dis.*, **2020**, *94*, 119-124.

[2] World Health Organization: WHO Director-General's opening remarks at the mission briefing on COVID-19-26 February 2020. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-mission-briefing-on-covid-19---26-february-2020 (Accessed April 2020).

[3] Onder, G.; Rezza, G.; Brusaferro, S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. *JAMA*, **2020**, [Epub ahead of print].

[4] Velavan, T.P.; Meyer, C.G. The COVID-19 epidemic. *Trop. Med. Int. Health,* **2020**, *25*(3), 278-280.

[5] Zhu, N.; Zhang, D.; Wang, W.; Li, X.; Yang, B.; Song, J.; Zhao, X.; Huang, B.; Shi, W.; Lu, R.; Niu, P.; Zhan, F.; Ma, X.; Wang, D.; Xu, W.; Wu, G.; Gao, G.F.; Tan, W. China novel coronavirus investigating and research team. A novel coronavirus from patients with pneumonia in China, 2019. *N. Engl. J. Med.,* **2020**, *382*(8), 727-733.

[6] Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19) (16-24 February 2020). Available from: https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf (Accessed April **2020**).

[7] Zhou, P.; Yang, X.L.; Wang, X.G.; Hu, B.; Zhang, L.; Zhang, W.; Si, H.R.; Zhu, Y.; Li, B.; Huang, C.L.; Chen, H.D.; Chen, J.; Luo, Y.; Guo, H.; Jiang, R.D.; Liu, M.Q.; Chen, Y.; Shen, X.R.; Wang, X.; Zheng, X.S.; Zhao, K.; Chen, Q.J.; Deng, F.; Liu, L.L.; Yan, B.; Zhan, F.X.; Wang, Y.Y.; Xiao, G.F.; Shi, Z.L. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*, **2020**, *579*(7798), 270-273.

[8] Iacobellis, G. COVID-19 and diabetes: can DPP4 inhibition play a role*? Diabetes Res. Clin. Pract*., **2020**, *162*, 108125.

[9] World Health Organization: Q&A on coronaviruses (COVID-19), 2020. Available from: https://www.who.int/news-room/q-a-detail/q-a-coronaviruses (Accessed April **2020**).

[10] European Centre for Disease Prevention and Control: Q&A on COVID-19. Available from: https://www.ecdc.europa.eu/en/covid-19/questions-answers (Accessed April **2020**).

[11] Centers for Disease Control and Prevention: Coronavirus Disease 2019 (COVID-19). Environmental Cleaning and Disinfection Recommendations. Available from: https://www.cdc.gov/coronavirus/2019-ncov/community/organizations/cleaning-disinfection.html (Accessed April **2020**).

[12] World Health Organization: Coronavirus disease 2019 (COVID-19) Situation Report 73. Available from: https://www.google.com/search?channel=crow2&client= firefox-b-d&q=Coronavirus+disease+2019+(COVID-19)+Situation+Report+–+73(Accessed April 2020).

[13] Lake, M.A. What we know so far: COVID-19 current clinical knowledge and research. *Clin. Med. (Lond).,* **2020**, *20*(2), 124-127.

[14] Li, Y.; Xia, L. Coronavirus Disease 2019 (COVID-19): role of chest CT in diagnosis and management. *AJR. Am. J. Roentgenol.,* **2020**, *4*, 1-7.

[15] Ai, T.; Yang, Z.; Hou, H.; Zhan, C.; Chen, C.; Lv, W.; Tao, Q.; Sun, Z.; Xia, L. Correlation of chest CT and RT-PCR testing in coronavirus disease 2019 (COVID-19) in China: a report of 1014 cases. *Radiology,* **2020**, 200642.

[16] Radiological Society of North America. Science Daily: CT provides best diagnosis for COVID-19. Available from: www.sciencedaily.com/releases/2020/02/200226151951.htm **(**Accessed April, **2020**).

[17] World Health Organization: Coronavirus disease (COVID-19) technical guidance: laboratory testing for 2019-nCoV in humans. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/laboratory-guidance (Accessed April, **2020**).

[18] Centers for Disease Control and Prevention: Real-Time RT-PCR Panel for Detection 2019-Novel Coronavirus. Available from: https://www.cdc.gov/coronavirus/2019-ncov/downloads/rt-pcr-panel-for-detection-instructions.pdf (Accessed April, **2020**).

[19] Ferrari, S.M.; Fallahi, P.; Mancusi, C.; Colaci, M.; Manfredi, A.; Ferri, C.; Antonelli, A. HCV-related autoimmune disorders in HCV chronic infection. *Clin. Ter.,* **2013**, *164*(4), e305-e312.

[20] Thachil, J. The versatile heparin in COVID-19. *J. Thromb. Haemost.,* **2020**, *18*(5), 1020-1022.

[21] Zhou, Y.; Zhang, Z.; Tian, J.; Xiong, S. Risk factors associated with disease progression in a cohort of patients infected with the 2019 novel coronavirus. *Ann. Palliat. Med.*, **2020**, *9*(2), 428-436.

[22] Xiong, Y.; Liu, Y.; Cao, L.; Wang, D.; Guo, M.; Jiang, A.; Guo, D.; Hu, W.; Yang, J.; Tang, Z.; Wu, H.; Lin, Y.; Zhang, M.; Zhang, Q.; Shi, M.; Liu, Y.; Zhou, Y.; Lan, K.; Chen, Y. Transcriptomic characteristics of bronchoalveolar lavage fluid and peripheral blood mononuclear cells in COVID-19 patients. *Emerg. Microbes. Infect.*, **2020**, *9*(1), 761-770.

[23] Zhang, C.; Wu, Z.; Li, J.W.; Zhao, H.; Wang, G.Q. The cytokine release syndrome (CRS) of severe COVID-19 and interleukin-6 receptor (IL-6R) antagonist Tocilizumab may be the key to reduce the mortality. *Int. J. Antimicrob. Agents.*, **2020**, 105954. [Epub ahead of print].

[24] BMJ Best Practice: Overview of coronaviruses. Available from: https://bestpractice.bmj.com/topics/en-gb/3000165?q=Coronavirus,%202019%20novel&c=suggested (Accessed, April 2020).

[25] Giwa, A.L.; Desai, A.; Duca, A. Novel 2019 coronavirus SARS-CoV-2 (COVID-19): an updated overview for emergency clinicians. *Emerg. Med. Pract.,* **2020**, *22*(5), 1-28.

[26] Li, G.; De Clercq, E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). *Nat. Rev. Drug. Discov.*, **2020**, *19*(3), 149-150.

[27] Cao B.; Wang, Y.; Wen, D.; Liu, W.; Wang, J.; Fan, G.; Ruan, L.; Song, B.; Cai, Y.; Wei, M.; Li, X.; Xia, J.; Chen, N.; Xiang, J.; Yu, T.; Bai, T.; Xie, X.; Zhang, L.; Li, C.; Yuan, Y.; Chen, H.; Li, H.; Huang, H.; Tu, S.; Gong, F.; Liu, Y.; Wei, Y.; Dong, C.; Zhou, F.; Gu, X.; Xu, J.; Liu, Z.; Zhang, Y.; Li, H.; Shang, L.; Wang, K.; Li, K.; Zhou, X.; Dong, X.; Qu, Z.; Lu, S.; Hu, X.; Ruan, S.; Luo, S.; Wu, J.; Peng, L.; Cheng, F.; Pan, L.; Zou, J.; Jia, C.; Wang, J.; Liu, X.; Wang, S.; Wu, X.; Ge, Q.; He, J.; Zhan, H.; Qiu, F.; Guo, L.; Huang, C.; Jaki, T.; Hayden, F.G.; Horby, P.W.; Zhang, D.; Wang, C.A Trial of lopinavir-ritonavir in adults hospitalized with severe covid-19. *N. Engl. J. Med.*, **2020**, *382*(19), 1787-1799.

[28] Md Insiat Islam Rabby. Current drugs with potential for treatment of COVID-19: a literature review. *J. Pharm. Pharm. Sci.,* **2020**, *23*(1), 58-64.

[29] Tignanelli, C.J.; Ingraham, N.E.; Sparks, M.A.; Reilkoff, R.; Bezdicek, T.; Benson, B.; Schacker, T.; Chipman, J.G.; Puskarich, M.A. Antihypertensive drugs and risk of COVID-19? *Lancet Respir. Med.,* **2020**, *8*(5), e29.

[30] Tang, N.; Bai, H.; Chen, X.; Gong, J.; Li, D.; Sun, Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J. Thromb. Haemost.,* **2020**, *18*(5), 1094-1099.

[31] Gautret, P.; Lagier, J.C.; Parola, P.; Hoang, V.T.; Meddeb, L.; Mailhe, M.; Doudier, B.; Courjon, J.; Giordanengo, V.; Vieira, V.E.; Dupont, H.T.; Honoré, S.; Colson, P.; Chabrière, E.; La Scola, B.; Rolain, J.M.; Brouqui, P.; Raoult, D. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int. J. Antimicrob. Agents.,* **2020**, 105949. [Epub ahead of print].

[32] Molina, J.M.; Delaugerre, C.; Goff, J.L.; Mela-Lima, B.; Ponscarme, D.; Goldwirt, L.; de Castro, N. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. *Med. Mal. Infect.*, **2020**, *50*(4), 384.

[33] Caly, L.; Druce, J.D.; Catton, M.G.; Jans, D.A.; Wagstaff, K.M. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 *in vitro*. *Antiviral Res.*, **2020**, *178*. [Epub ahead of print].

[34] Casadevall, A.; Pirofski, L.A. The convalescent sera option for containing COVID-19. *J. Clin. Invest.* **2020***, 130*(4), 1545-1548.

[35] World Health Organization: Coronavirus disease (COVID-19) advice for the public. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/advice-for-public (Accessed April **2020**).

[36] Centers for Disease Control and Prevention: Coronavirus Disease 2019 (COVID-19). Travel-Associated Exposures. Available from: https://www.cdc.gov/coronavirus/2019-ncov/php/risk-assessment.html (Accessed April **2020**).

[37] Steps to help prevent the spread of COVID-19 if you are sick. Available from: https://www.cdc.gov/coronavirus/2019-ncov/downloads/sick-with-2019-nCoV-fact-sheet.pdf (Accessed April 2020).

[38] Centers for Disease Control and Prevention: What healthcare personnel should know about caring for patients with confirmed or possible coronavirus disease 2019 (COVID-19). Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/caring-for-patients-H.pdf (Accessed April **2020**).

[39] Cascella, M.; Rajnik. M.; Cuomo, A.; Dulebohn, S.C.; Di Napoli, R. Features, evaluation and treatment coronavirus (COVID-19). Treasure Island (FL): StatPearls Publishing; **2020**.

[40] Chen, W.H.; Strych, U.; Hotez, P.J.; Bottazzi, M.E. The SARS-CoV-2 vaccine pipeline: an overview. *Curr. Trop. Med. Rep*., **2020**, 1-4.

[41] Roberts, M. BBC News: Coronavirus: US volunteers test first vaccine. Available from: https://www.bbc.com/news/health-51906604 (Accessed April **2020**).

[42] Agrawal, S.; Goel, A.D.; Gupta, N. Emerging prophylaxis strategies against COVID-19. *Monaldi Arch. Chest. Dis.,* **2020**, *90*(1).