HUMAN VACCINES & IMMUNOTHERAPEUTICS
2020, VOL. 16, NO. 12, 2938–2943
https://doi.org/10.1080/21645515.2020.1842683

Taylor & Francis
Taylor & Francis Group

COMMENTARY

COVID-19 in the elderly people and advances in vaccination approaches

Kuldeep Dhama[a], Shailesh Kumar Patel[a], Senthilkumar Natesan[b], Kranti Suresh Vora[b,c], Mohd Iqbal Yatoo[d], Ruchi Tiwari[e], Shailendra K Saxena[f], Karam Pal Singh[a], Rajendra Singh[a], and Yashpal Singh Malik[g]

[a]Division of Pathology, ICAR-Indian Veterinary Research Institute, Bareilly, Uttar Pradesh, India; [b]Department of Infectious Diseases, Indian Institute of Public Health Gandhinagar, Ganghinagar, Gujarat, India; [c]Health Research Institut, University of Canberra, ACT, Australia; [d]Division of Veterinary Clinical Complex, Faculty of Veterinary Sciences and Animal Husbandry, Shuhama, Alusteng Srinagar, Sher-E-Kashmir University of Agricultural Sciences and Technology of Kashmir, Srinagar, Jammu and Kashmir, India; [e]Department of Veterinary Microbiology and Immunology, College of Veterinary Sciences, Uttar Pradesh Pandit Deen Dayal Upadhyaya Pashu Chikitsa Vigyan Vishwavidyalaya Evam Go Anusandhan Sansthan (DUVASU), Mathura, India; [f]Centre for Advanced Research (CFAR), Faculty of Medicine, King George's Medical University (KGMU), Lucknow, India; [g]Division of Biological Standardization, ICAR–Indian Veterinary Research Institute, Bareilly, Uttar Pradesh, India

ABSTRACT

The rapid worldwide spread of the COVID-19 pandemic, caused by the newly emerged severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in tens of millions of infections and over one million deaths. SARS-CoV-2 infection affects all age groups; however, those over 60 years old are affected more severely. Moreover, pre-existing co-morbidities result in higher COVID-19-associated mortality in the geriatric population. This article highlights the associated risk factors of SARS-CoV-2 infection in older people and progress in developing COVID-19 vaccines, especially for efficient vaccination of the older population. There is also a summary of immunomodulatory and immunotherapeutic approaches to ameliorate the outcome of COVID-19 in older individuals.

ARTICLE HISTORY
Received 8 August 2020
Revised 19 October 2020
Accepted 21 October 2020

KEYWORDS
SARS-CoV-2; covid-19; elderly people; vaccine

Coronavirus disease 2019 (COVID-19) is a newly emerged severe contagious disease, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] The rapid worldwide spread of the virus has resulted in tens of millions of infections and over one million deaths. Although the respiratory system is primarily affected, leading to severe pneumonitis and even death,[2] involvement of the gastrointestinal system, heart, kidneys, and nervous system is also being reported.[3] Individuals of all age groups, sexes, races, and physiological conditions are equally susceptible to the virus, and it is assumed that most of the world population will be exposed in the near future[4] if a vaccine does not become available soon. Moreover, elderly and immunocompromised individuals with other comorbidities such as diabetes, hypertension, cancer, asthma, and cardiovascular abnormalities are more severely affected with a higher rate of case mortality.[5–8] Notably, higher prevalence of the disease is reported in individuals above 60 y of age.[5,9] Additionally, a retrospective study conducted on 85 fatal SARS-CoV-2 cases reported a median age of 65.8 y for diabetes, cardiopulmonary diseases, and hypertension comorbidities.[10] Furthermore, a study including 1625 fatal cases of COVID-19 was reported, and of those, 139, 578, and 850 patients were 60–69, 70–79, and 80 y of age or above, respectively,[11] supporting the higher COVID-19-associated mortality in the geriatric population.

Older age (60 y or above) is identified as the major risk factor for COVID-19.[5,9] Accordingly, waning health and weakening physiological functioning of vital organs, including the respiratory system, lead to impaired mucociliary clearance of foreign particles or micro-organisms in aged individuals.[12,13] Likewise, both innate and adaptive immune systems are reportedly weakened, and the possibility of underlying chronic diseases upsurges as age advances, leading to the higher acquisition of infections.[14] Acute respiratory distress syndrome (ARDS) is the main clinical outcome of COVID-19, which is attributed to acute lung injury due to pneumonitis, primarily leading to the death of older individuals. In addition, intravascular coagulation and pulmonary embolism are also the leading causes of COVID-19-associated mortality, irrespective of the occurrence of severe pneumonitis. It is evident that elderly patients develop coagulation abnormalities leading to disseminated intravascular coagulation during the late stage of COVID-19, prompting stroke, heart attack, pulmonary embolism, and gangrene formation in various parts of the body.[15–18] Intravascular coagulation is a life-threatening condition that is currently managed using anticoagulants such as low molecular heparin while monitoring the risk of bleeding.[19,20] Autopsy studies showed the presence of thrombus and congestion in the lungs and various other organs, indicating abnormal coagulation leading to death.[21,22] The addition of prophylactic anticoagulants increases the survival rate and recovery from the disease in elderly patients, and is one of the reasons for reduced mortality related to COVID-19 now in July 2020 compared to February 2020. Host proteases such as TMPRSS2 and TMPRSS4 are required for cleavage of the

CONTACT Kuldeep Dhama kdhama@rediffmail.com Division of Pathology, ICAR –Indian Veterinary Research Institute, Bareilly, Uttar Pradesh 243122, India; Yashpal Singh Malik malikyps@gmail.com Division of Biological Standardization, ICAR–Indian Veterinary Research Institute, Izatnagar, Bareilly, Uttar Pradesh 243122, India.

spike protein for the virus to enter the host cell successfully. In elderly patients, protease levels were elevated, therefore enhancing successful virus entry and establishment of the virus infection.[23–25] Furthermore, poor nutrition, dehydration, and dementia, along with many other clinical complications, are also risk factors, especially in bedridden and frail patients.[26] Reduced immunity and organ function and age-related pathophysiological susceptibility also add to the vulnerability, infectivity, and attack rate of SARS-CoV-2 in the elderly population.[27] Furthermore, the expression of angiotensin-converting enzyme-2 (ACE2) receptor decreases with age, resulting in restricted protective effects of ACE2.[27] Negligence in this age group in timely diagnosis, therapeutic management, and adequate preventive measures might further widen the sphere of risk.

Based on clinical presentation, COVID-19 is divided into asymptomatic, mild, severe, and critical forms, among which asymptomatic and mild forms are very prevalent.[28] Fever is reported as the most common symptom of SARS-CoV-2 infection; however, a case series of 56 patients revealed that only a small number of elderly patients (older than 60 y) manifested fever, suggesting that fever is not common in SARS-CoV-2 infection in geriatric patients.[5] Moreover, other respiratory symptoms such as cough, dyspnea, sore throat, and rhinorrhea, along with anorexia, headache, myalgia, anosmia, ageusia, and diarrhea, were also evident in COVID-19.[8,29] Although comprehensive analysis of age-specific COVID-19 clinical symptoms is lacking, the possibility of atypical and nonspecific symptoms in geriatric patients is highly expected, similar to that in other diseases.[30] Furthermore, a higher frequency of the severe form of COVID-19 with increased mortality is expected, necessitating the intensive care unit (ICU) for affected elderly patients. The laboratory hematological finding, severe lymphocytopenia, also seems to be more pronounced in older COVID-19 patients.[5] In addition, elevated levels of lactate dehydrogenase (a marker for tissue damage), D-dimer (a marker for blood clots), and C-reactive protein (a marker for excessive inflammation or myocardial damage), and decreased platelet count were also observed in elderly COVID-19 patients.[31,32]

The unavailability of specific treatments and vaccines raises concerns about the protection of immunocompromised older adults. However, multiple efforts made worldwide and the rapid pace of vaccine development ensure the availability of an effective COVID-19 vaccine soon.[33] In this context, many vaccine platforms are being explored globally, including non-replicating vectors, DNA, RNA, subunit structures, inactivated virus-like particles, and live-attenuated vaccines.[34] Moreover, as of September 28, 2020, 40 vaccine candidates were under clinical evaluation and 151 under preclinical evaluation.[35] Among these vaccine candidates, ChAdOx1-S (Oxford/AstraZeneca), inactivated vaccines of Sinovac, Wuhan Institute of Biological Products/Sinopharm, Beijing Institute of Biological Products/Sinopharm, LNP encapsulated mRNA vaccine of Moderna/NIAID and BioNTech/Fosun Pharma/Pfizer, protein subunit vaccine of Novavax and non-replicating viral vector adenovirus type 5 vector of CanSino Biological Inc./Beijing Institute of Biotechnology (Adenovirus Type 5 Vector), Gamaleya Research Institute (Adeno-based (rAd26-S+ rAd5-S), Janssen Pharmaceutical Companies (Ad26COVS1), and adenovector vaccine of Johnson and Johnson have reached Phase 3 clinical evaluation, while the adjuvanted recombinant protein (RBD-Dimer), a subunit vaccine (Anhui Zhifei Longcom Biopharmaceutical/Institute of Microbiology, Chinese Academy of Sciences) and mRNA vaccine of Curevac, are at stage 2 of clinical evaluation.[35–37] All these vaccines were administered through the intramuscular route and evaluated for 14–21 d (inactivated vaccines) or 28 d (mRNA vaccines), whereas information about the non-replicating viral vector vaccines (ChAdOx1-S, adenovirus type 5 vector) is not available.[35] The evaluation of immune response against these vaccines must have special considerations for older age people who are at increased risk and suffer severely due to COVID-19.[38–40] Immunosenescence or altered immune response in older ages may affect vaccine performance.[39,41] It is believed that inactivated vaccines might be effective in generating sufficient immune responses, but the risks in older age groups need to be evaluated.[34,41] Similarly, to ensure adequacy of the immune response against subunit vaccines, which is generally low, additional boosters might be required.[34,41] Non-replicating viral vector-based vaccines, which are novel platforms and yet to be evaluated, may also require special considerations in geriatric patients.[34,41] Nevertheless, little knowledge has been harnessed on vaccinal immunity and responses thereto using SARS-CoV-2 in older adults. To gain further insights on vaccine-generated immune responses and before taking any policy decision on implementing vaccine use in the older population, experimentation results based on older laboratory animal studies on SARS-CoV-1 infection must be revisited.[42] In Russia, a few vaccine candidates have been explored, including inactivated, recombinant proteins, subunit vaccines (S protein), mRNA-based, and vectored vaccines.[41] Russia-based Gamaleya National Research Center for Epidemiology and Microbiology has also completed Phase 2 clinical evaluations in June 2020 and human trials of two forms of COVID-19 vaccines at Sechenov University and Burdenko Military Hospital.[43] Sputnik V became the first registered vaccine against COVID-19 and its public use has been started.[44,45] In India, a few vaccine trials are underway, and the first indigenous coronavirus vaccine, COVAXIN, which is an inactivated vaccine, is undergoing phase II human clinical trials across the country.[46] This vaccine was developed by Bharat Biotech in collaboration with the Indian Council of Medical Research-National Institute of Virology.[46] It has received the approval of the Drug Controller General of India for phase I and II human clinical trials[46] and has produced strong immunogenicity without side effects, thus its Phase III trial is likely to start in India.[45] In addition to the ongoing efforts in developing effective vaccines, there is also a need to evaluate other available immunotherapeutic approaches, including monoclonal antibodies with a high neutralizing index, which are devoid of any side effects associated with live or inactivated vaccines.[47]

Each of the vaccine candidates under clinical evaluation has advantages and disadvantages. Moreover, although live-attenuated or inactivated vaccines are potent, reinfection can occur. Similarly, a subunit vaccine candidate may be safe, but

its potency is always a matter of concern.[34] Hence, while considering a vaccine candidate for older people, safety issues must be adequately addressed. Moreover, the weaker immune system of older individuals might not recognize and attack the SARS-CoV-2, requiring regular boosters/doses that amplify the strength of the vaccine, which may have serious side-effects.[48,49] Hence, when a vaccine is developed, it must be evaluated for its safety and efficacy against SARS-CoV-2 by clinical trials that include older people.[49] In this context, clinical trials such as NCT04475302, NCT04470609, NCT04417335, NCT04441047, NCT04383574, which are specially dedicated for evaluation of safety and immunogenicity of SARS-CoV-2 vaccine in people 60 y or older are very encouraging and may prove crucial for the prevention of the disease and related mortalities in this age group.

Studies have highlighted the age-related decrease in vaccine efficacy, which is due to a decline in the adaptive and inherent immune response. As the aging population is increasing globally, especially in developed countries, vaccine efforts must take into consideration age-related issues to ensure effective control of infectious diseases, including COVID-19. These efforts are necessary to ensure a healthier life for the elderly as life expectancy is increasing.[50] An effective vaccine must stimulate a broad T and B cell response, potentially overcoming the reduced immune function in the older population.[39] All possible efforts are being made to develop a safe and effective vaccine against SARS-CoV-2, but the global panic created by the prevailing situation of increasing disease occurrence hastens the evaluation process many folds. In this context, the vaccines against SARS-CoV-2 entered clinical trials within a remarkable time of just 6 months as compared to the typical 3 to 9 y required for other vaccines.[51] However, the speed should neither affect the quality of released vaccines nor encourage the utilization of improper entities, as a substandard commercialized vaccine may result in severe health hazards or vaccine failure.

Enhancing immunity especially in elderly can be beneficial in overcoming respiratory infections including COVID-19.[52,53] Immune-enhancing strategies in the elderly need to be well taken care of so as to boost immunity which could aid in ameliorating the severity of COVID-19 disease development as well as to avoid SARS-CoV-2 infection. These include dietary intake of balanced and nutritious foods, nutraceuticals, probiotics, medicinal herbs, traditional medicines, and Ayurvedic products along with supplementation of zinc and vitamins (A, C, D, E, B_6 and B12).[54–61] Physical exercises including adopting Yoga in routine life also aid to maintain and improve proper biological functions of the body and enhance the immunity.

Various other immune potentiating and immunotherapeutic approaches such as convalescent plasma therapy,[47,62–64] antibodies (neutralizing antibodies, monoclonal antibodies), intravenous immunoglobulins (IVIg);[47,65–67] T cells and Natural killer (NK) cells based immunotherapies,[68–71] Toll-like receptors (TLRs),[72,73] cytokine therapies,[74] and various immunomodulatory drugs,[75–77] have all revealed promising results to safeguard health of COVID-19 patients.

Monoclonal antibodies (MAbs) have been produced that act specifically against SARS-CoV-2.[47,67] MAbs such as B38, H4, 47D11 have been found effective in producing higher neutralizing antibody titers in elderly thus can effectively protect from COVID-19.[78] They bind to RBD of S protein in SARS-CoV-2 thus inhibit binding of RBD and ACE receptor.[79,80] In one study, itolizumab (humanized anti-CD6 MAb) has been shown to be well tolerated in elderly people, reducing IL-6 levels, and producing favorable clinical outcome in COVID-19 patients.[81] It has shown prospects for minimizing cytokine storm in elderly during COVID-19, even in those with multiple comorbidity and critically and severely ill patients.[82] Similarly, MAbs LY-CoV555 of Eli Lilly and REGN-COV-2 of Regeneron Pharmaceuticals are under trials for use in COVID-19 patients.[83]In the present scenario, self-isolation and self-quarantine have been enforced by many countries to mitigate this pandemic. Moreover, regular use of personal protective equipment (PPE), adoption of physical distancing, respiration etiquette, and hand hygiene are highly recommended for older people.[84] Furthermore, regular disinfection of the surroundings of geriatric people with effective disinfectants must be ensured to prevent contamination of surfaces by SARS-CoV -2 to reduce the chances of infection.[84] Mental health issues in the elderly are exacerbated because of social isolation, loneliness, financial issues due to an increase in online scams, and dependency on caregivers during COVID-19.[85] It is essential to ensure the protection of the elderly not only from COVID-19 but other physical and mental health issues related to the pandemic. Governments must implement alert systems and provide information through telehealth helplines to the elderly.

In conclusion, older people are being disproportionately affected by COVID-19. The severity of the disease is greater, and the mortality among this age group is higher than in other age groups. The high mortality level is due to higher proportions of comorbidities such as diabetes, heart issues, and lung problems along with compromised immunity. Vaccine development efforts should include older people in clinical trials to ensure the efficacy and safety of the vaccine in this increasing segment of the population, and to evaluate associated risks in older age groups along with assessing requirement of booster doses for amplifying immunity. To win the fight against COVID-19, the world must ensure that the elderly are well protected and supported.

Acknowledgments

All the authors acknowledge and thank their respective Institutes and Universities.

Author contributions

All the authors substantially contributed to the conception, compilation of data, checking, and approving the final version of the manuscript, and agree to be accountable for its contents.

Disclosure statement

All authors declare that there exist no commercial or financial relationships that could, in any way, lead to a potential conflict of interest.

Funding

This compilation is a review article written by its authors and required no substantial funding to be stated.

ORCID

Kuldeep Dhama http://orcid.org/0000-0001-7469-4752
Kranti Suresh Vora http://orcid.org/0000-0001-5999-1118
Mohd Iqbal Yatoo http://orcid.org/0000-0002-4501-7354
Ruchi Tiwari http://orcid.org/0000-0001-6897-3472
Shailendra K Saxena http://orcid.org/0000-0003-2856-4185
Rajendra Singh http://orcid.org/0000-0003-3127-3346
Yashpal Singh Malik http://orcid.org/0000-0002-2832-4854

References

1. Dhama K, Khan S, Tiwari R, Sircar S, Bhat S, Malik YS, Singh KP, Chaicumpa W, Bonilla-Aldana DK, Rodriguez-Morales AJ. Coronavirus Disease 2019-COVID-19. Clin Microbiol Rev. 2020a;33:e00028–20.
2. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, Liu S, Zhao P, Liu H, Zhu L, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020;8(4):420–22. doi:10.1016/S2213-2600(20)30076-X.
3. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. J Am Med Ass. 2020a;323(11):1061–69. doi:10.1001/jama.2020.1585.
4. Giesecke J. The invisible pandemic. Lancet. 2020;395(10238):e98. doi:10.1016/S0140-6736(20)31035-7.
5. Liu K, Chen Y, Lin R, Han K. Clinical features of COVID-19 in elderly patients: a comparison with young and middle-aged patients. J Infect. 2020;80(6):e14–e18. doi:10.1016/j.jinf.2020.03.005.
6. Tian S, Hu W, Niu L. Pulmonary pathology of early phase 2019 novel coronavirus (COVID-19) pneumonia in two patients with lung cancer. J Thorac Oncol. 2020;15:700–04. pii: S1556-0864(20)30132-5. doi:10.1016/j.jtho.2020.02.010.
7. Wang L, He W, Yu X, Hu D, Bao M, Liu H, Zhou J, Jiang H. Coronavirus disease 2019 in elderly patients: characteristics and prognostic factors based on 4-week follow-up. J Infect. 2020b Jun;80(6):639–45. doi:10.1016/j.jinf.2020.03.019.
8. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507–13. doi:10.1016/S0140-6736(20)30211-7.
9. Yang Y, Lu QB, Liu MJ, Wang Y, Zhang A, Jalali N, Dean N, Longini I, Halloran ME, Xu B, et al. Epidemiological and clinical features of the 2019 novel coronavirus outbreak in China. Med Rxiv. 2020. doi:10.1101/2020.02.10.20021675.
10. Du Y, Tu L, Zhu P, Mu M, Wang R, Yang P, Wang X, Hu C, Ping R, Hu P, et al. Clinical features of 85 fatal cases of COVID-19 from wuhan: a retrospective observational study. Am J Respir Crit Care Med. 2020;201(11):1372–79. doi:10.1164/rccm.202003-0543OC.
11. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. J Am Med Ass. 2020;323(18):1775–76. doi:10.1001/jama.2020.4683.
12. Dent E, Martin FC, Bergman H, Woo J, Romero-Ortuno R, Walston JD. Management of frailty: opportunities, challenges, and future directions. Lancet. 2019;394(10206):1376–86. doi:10.1016/S0140-6736(19)31785-4.
13. Skloot GS. The effects of aging on lung structure and function. Clin Geriatr Med. 2017;33(4):447–57. doi:10.1016/j.cger.2017.06.001.
14. Oh SJ, Lee JK, Shin OS. Aging and the immune system: the impact of immunosenescence on viral infection, immunity and vaccine immunogenicity. Immune Netw. 2019;19(6):e37. doi:10.4110/in.2019.19.e3.
15. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. Blood. 2020 Jun 4;135(23):2033–40. doi:10.1182/blood.2020006000.
16. Becker RC. COVID-19 update: covid-19-associated coagulopathy. J Thromb Thrombolysis. 2020 Jul;50(1):54–67. doi:10.1007/s11239-020-02134-3.
17. Belen-Apak FB, Sarıalioğlu F. Pulmonary intravascular coagulation in COVID-19: possible pathogenesis and recommendations on anticoagulant/thrombolytic therapy. J Thromb Thrombolysis. 2020 Aug;50(2):278–80. doi:10.1007/s11239-020-02129-0.
18. Lillicrap D. Disseminated intravascular coagulation in patients with 2019-nCoV pneumonia. J Thromb Haemost. 2020 Apr;18(4):786–87. doi:10.1111/jth.14781.
19. Asakura H, Ogawa H. Potential of heparin and nafamostat combination therapy for COVID-19. J Thromb Haemost. 2020 Jun;18(6):1521–22. doi:10.1111/jth.14858.
20. Hippensteel JA, LaRiviere WB, Colbert JF, Langouët-Astrié CJ, Schmidt EP. Heparin as a therapy for COVID-19: current evidence and future possibilities. Am J Physiol Lung Cell Mol Physiol. 2020 Aug 1;319(2):L211–L217. doi:10.1152/ajplung.00199.2020.
21. Lax SF, Skok K, Zechner P, Kessler HH, Kaufmann N, Koelblinger C, Vander K, Bargfrieder U, Trauner M. Pulmonary arterial thrombosis in COVID-19 with fatal outcome: results from a prospective, single-center, clinicopathologic case series. Ann Intern Med. 2020;173(5):350–61. doi:10.7326/M20-2566.
22. Rapkiewicz AV, Mai X, Carsons SE, Pittaluga S, Kleiner DE, Berger JS, Thomas S, Adler NM, Charytan DM, Gasmi B, et al. Megakaryocytes and platelet-fibrin thrombi characterize multi-organ thrombosis at autopsy in COVID-19: a case series. EClinicalMedicine. 2020 Jun 25;24:100434. doi:10.1016/j.eclinm.2020.100434.
23. Paczek L, Michalska W, Bartlomiejczyk I. Proteolytic enzyme activity as a result of aging. Aging Clin Exp Res. 2009 Feb;21(1):9–13. doi:10.1007/BF03324892.
24. Matsuyama S, Nao N, Shirato K, Kawase M, Saito S, Takayama I, Nagata N, Sekizuka T, Katoh H, Kato F, et al. Enhanced isolation of SARS-CoV-2 by TMPRSS2-expressing cells. Proc Natl Acad Sci U S A. 2020 Mar 31;117(13):7001–03. doi:10.1073/pnas.2002589117.
25. Shirato K, Kawase M, Matsuyama S. Wild-type human coronaviruses prefer cell-surface TMPRSS2 to endosomal cathepsins for cell entry. Virology. 2018 Apr;517:9–15. doi:10.1016/j.virol.2017.11.012.
26. Isaia G, Marinello R, Tibaldi V, Tamone C, Bo M. Atypical presentation of COVID-19 in an older adult with severe alzheimer disease. Am J Geriatr Psychiatry. 2020;28:790–91. doi:10.1016/j.jagp.2020.04.018. S1064-7481(20)30319-5.
27. Dhochak N, Singhal T, Kabra SK, Lodha R. Pathophysiology of COVID-19: why children fare better than adults? Indian J Pediatr. 2020;87(7):537–46. doi:10.1007/s12098-020-03322-y.
28. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in china: summary of a report of 72 314 cases from the Chinese center for disease control and prevention. JAMA. 2020;323:1239. doi:10.1001/jama.2020.2648.
29. Dhama K, Patel SK, Pathak M, Yatoo MI, Tiwari R, Malik YS, Singh R, Sah R, Rabaan AA, Bonilla-Aldana DK, et al. An update on SARS-CoV-2/COVID-19 with particular reference to its clinical pathology, pathogenesis, immunopathology and mitigation strategies. Travel Med Infect Dis. 2020b;37:101755. doi:10.1016/j.tmaid.2020.101755.
30. Bonanad C, García-Blas S, Tarazona-Santabalbina FJ, Díez-Villanueva P, Ayesta A, Sanchis Forés J, Vidán-Austiz MT, Formiga F, Ariza-Solé A, Martínez-Sellés M. Scientific societies of the authors. The contributing authors are members of the following scientific bodies. Coronavirus: the geriatric emergency of 2020. Joint document of the section on geriatric cardiology of the Spanish society of cardiology and the Spanish society of geriatrics and gerontology. Rev Esp Cardiol (Engl Ed). 2020. doi:10.1016/j.rec.2020.05.001. S1885-5857(20)30178-X.

31. Frater JL, Zini G, d'Onofrio G, Rogers HJ. COVID-19 and the clinical hematology laboratory. Int J Lab Hematol. 2020 Jun;42 (Suppl 1):11–18. doi:10.1111/ijlh.13229.
32. Mardani R, Ahmadi Vasmehjani A, Zali F, Gholami A, Mousavi Nasab SD, Kaghazian H, Kaviani M, Ahmadi N. Laboratory parameters in detection of COVID-19 patients with positive RT-PCR; a diagnostic accuracy study. Arch Acad Emerg Med. 2020 Apr 4;8 (1):e43.
33. Patel SK, Pathak M, Tiwari R, Yatoo MI, Malik YS, Sah R, Rabaan AA, Sharun K, Dhama K, Bonilla-Aldana DK, et al. A vaccine is not too far for COVID-19. J Infect Dev Ctries. 2020;14(5):450–53. doi:10.3855/jidc.12744.
34. Yatoo MI, Hamid Z, Parray OR, Wani AH, Wani A, Saxena A, Patel SK, Pathak M, Tiwari R, Malik YS, et al. COVID-19 - Recent advancements in identifying novel vaccine candidates and current status of upcoming SARS-CoV-2 vaccines. Hum Vaccin Immunother. 2020 Jul 23;1–14. doi:10.1080/21645515.2020.1788310.
35. WHO. DRAFT landscape of COVID-19 candidate vaccines – 28 September 2020; 2020 [accessed 2020 Sep 30]. https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines.
36. Johnson and Johnson. Developing a vaccine and identifying therapies for COVID-19; 2020 [accessed 2020 Sep 30]. https://www.jnj.com/coronavirus/prevention-and-treatment.
37. Tse LV, Meganck RM, Graham RL, Baric RS. The current and future state of vaccines, antivirals and gene therapies against emerging coronaviruses. Front Microbiol. 2020;11:658. doi:10.3389/fmicb.2020.00658.
38. Koirala A, Joo YJ, Khatami A, Chiu C, Britton PN. Vaccines for COVID-19: the current state of play. Paediatr Respir Rev. 2020 Jun 18. doi:10.1016/j.prrv.2020.06.010. S1526-0542(20) 30095-6.
39. Pawelec G, Weng NP. Can an effective SARS-CoV-2 vaccine be developed for the older population? Immun Ageing. 2020 Apr 11;17:8. doi:10.1186/s12979-020-00180-2.
40. Le TT, Andreadakis Z, Kumar A, Gómez Román R, Tollefsen S, Saville M, Mayhew S. The COVID-19 vaccine development landscape. Nat Rev Drug Discov. 2020;19(5):305–06. doi:10.1038/d41573-020-00073-5.
41. Calina D, Docea AO, Petrakis D, Egorov AM, Ishmukhametov AA, Gabibov AG, Shtilman MI, Kostoff R, Carvalho F, Vinceti M, et al. Towards effective COVID-19 vaccines: updates, perspectives and challenges (Review). Int J Mol Med. 2020 Jul;46(1):3–16. doi:10.3892/ijmm.2020.4596.
42. Clay CC, Donart N, Fomukong N, Knight JB, Overheim K, Tipper J, Van Westrienen J, Hahn F, Harrod KS. Severe acute respiratory syndrome-coronavirus infection in aged nonhuman primates is associated with modulated pulmonary and systemic immune responses. Immun Ageing. 2014;11(1):4. doi:10.1186/1742-4933-11-4.
43. [accessed 2020 Aug 6]. https://health.economictimes.indiatimes.com/news/industry/russia-1st-nation-to-finish-human-trials-for-covid-19-vaccine/76938659.
44. Sputnik V. The first registered vaccine against COVID-19; 2020 [accessed 2020 Sep 30]. https://sputnikvaccine.com/.
45. TOI. Coronavirus vaccine: from covaxin to Russian vaccine roll out, here are all the updates regarding COVID-19 vaccine development; 2020 [accessed 2020 Sep 30]. https://timesofindia.indiatimes.com/life-style/health-fitness/health-news/coronavirus-vaccine-from-covaxin-to-russian-vaccine-roll-out-here-are-all-the-updates-regarding-covid-19-vaccine-development/photostory/78362614.cms?picid=78362622.
46. [accessed 2020 Oct 10]. https://www.bharatbiotech.com/covaxin.html.
47. Sharun K, Tiwari R, Iqbal Yatoo M, Patel SK, Natesan S, Dhama J, Malik YS, Harapan H, Singh RK, Dhama K. Antibody-based immunotherapeutics and use of convalescent plasma to counter COVID-19: advances and prospects. Expert Opin Biol Ther. 2020;20(9):1033–46. doi:10.1080/14712598.2020.1796963.
48. Gates B. What you need to know about the COVID-19 vaccine; 2020 [accessed 2020 May 27]. https://www.gatesnotes.com/Health/What-you-need-to-know-about-the-COVID-19-vaccine.
49. [accessed 2020 Aug 6]. https://www.statnews.com/2020/04/25/success-covid-19-vaccine-hinge-on-delivery/.
50. Koff WC, Williams MA. Covid-19 and immunity in aging populations-A new research agenda. Perspective. New Eng J Med. 2020;383:804–05. doi:10.1056/NEJMp2006761.
51. Heaton PM. The COVID-19 vaccine-development multiverse. N Engl J Med. 2020. doi:10.1056/NEJMe2025111.
52. Jayawardena R, Sooriyaarachchi P, Chourdakis M, Jeewandara C, Ranasinghe P. Enhancing immunity in viral infections, with special emphasis on COVID-19: A review. Diabetes Metab Syndr. 2020;14 (4):367–82. doi:10.1016/j.dsx.2020.04.015.
53. de Almeida Brasiel PG. The key role of zinc in elderly immunity: a possible approach in the COVID-19 crisis. Clin Nutr ESPEN. 2020;38:65–66. doi:10.1016/j.clnesp.2020.06.003.
54. Chen L, Hu C, Hood M, Zhang X, Zhang L, Kan J, Du J. A novel combination of vitamin C, curcumin and glycyrrhizic acid potentially regulates immune and inflammatory response associated with coronavirus infections: a perspective from system biology analysis. Nutrients. 2020a;12(4):1193. doi:10.3390/nu12041193.
55. Galanakis CM. The food systems in the era of the coronavirus (COVID-19) pandemic crisis. Foods. 2020;4:523. doi:10.3390/foods9040523.
56. Infusino F, Marazzato M, Mancone M, Fedele F, Mastroianni CM, Severino P, Ceccarelli G, Santinelli L, Cavarretta E, Marullo AGM, et al. Diet supplementation, probiotics, and nutraceuticals in SARS-CoV-2 infection: a scoping review. Nutrients. 2020;12(6): E1718. doi:10.3390/nu12061718.
57. Jahan I, Onay A. Potentials of plant-based substance to inhabit and probable cure for the COVID-19. Turk J Biol. 2020;44(3):228–41. doi:10.3906/biy-2005-114.
58. Morais AHA, Passos TS, Maciel BLL, da Silva-maia JK. Can probiotics and diet promote beneficial immune modulation and purine control in coronavirus infection? Nutrients. 2020;12(6):E1737. doi:10.3390/nu12061737.
59. Panyod S, Ho CT, Sheen LY. Dietary therapy and herbal medicine for COVID-19 prevention: a review and perspective. J Trad Complement Med. 2020;10(4):420–27. doi:10.1016/j.jtcme.2020.05.004.
60. Rastogi S, Pandey DN, Singh RH. COVID-19 pandemic: A pragmatic plan for ayurveda intervention. J Ayurveda Integr Med. 2020. doi:10.1016/j.jaim.2020.04.002.
61. Vellingiri B, Jayaramayya K, Iyer M, Narayanasamy A, Govindasamy V, Giridharan B, Ganesan S, Venugopal A, Venkatesan D, Ganesan H, et al. COVID-19: a promising cure for the global panic. Sci Total Environ. 2020;725:138277. doi:10.1016/j.scitotenv.2020.138277.
62. Bloch EM, Shoham S, Casadevall A, Sachais BS, Shaz B, Winters JL, van Buskirk C, Grossman BJ, Joyner M, Henderson JP, et al. Deployment of convalescent plasma for the prevention and treatment of COVID-19. J Clin Invest. 2020;130(6):2757–65. doi:10.1172/JCI138745.
63. Chen L, Xiong J, Bao L, Shi Y. Convalescent plasma as a potential therapy for COVID-19. Lancet. 2020b;20(4):398–400. doi:10.1016/S1473-3099(20)30141-9.
64. Selvi V. Convalescent Plasma: a challenging tool to treat COVID-19 patients-A lesson from the past and new perspectives. Biomed Res Int. 2020 Sep 22;2020:2606058. doi:10.1155/2020/2606058.
65. Gupta A, Karki R, Dandu HR, Dhama K, Bhatt ML, Saxena SK. COVID-19: benefits and risks of passive immunotherapeutics. Hum Vaccin Immunother. 2020:1–10. doi:10.1080/21645515.2020.1808410.
66. Kumar GV, Jeyanthi V, Ramakrishnan S. A short review on antibody therapy for COVID-19. New Microbes New Infec. 2020;35:100682. doi:10.1016/j.nmni.2020.100682.
67. Shanmugaraj B, Siriwattananon K, Wangkanont K, Phoolcharoen W. Perspectives on monoclonal antibody therapy as potential therapeutic intervention for Coronavirus disease-19

(COVID-19). Asian Pac J Allergy Immunol. 2020:1. doi:10.12932/AP-200220-0773.
68. Bachanova V, Bishop MR, Dahi P, Dholaria B, Grupp SA, Hayes-Lattin B, Janakiram M, Maziarz RT, McGuirk JP, Nastoupil LJ, et al. CAR T-cell consortium. chimeric antigen receptor t cell therapy during the COVID-19 pandemic. Biol Blood Marrow Transplant. 2020;26(7):1239–46. doi:10.1016/j.bbmt.2020.04.008.
69. Hu Y, Tan Su Yin E, Yang Y, Wu H, Wei G, Su J, Cui Q, Jin A, Yang L, Fu S, et al. CAR T-cell treatment during the COVID-19 pandemic: management strategies and challenges. Curr Res Transl Med. 2020;68(3):111–18. doi:10.1016/j.retram.2020.06.003.
70. Khoury M, Cuenca J, Cruz FF, Figueroa FE, Rocco PRM, Weiss DJ. Current status of cell-based therapies for respiratory virus infections: applicability to COVID-19. Eur Respir J. 2020;55:2000858. doi:10.1183/13993003.00858-2020.
71. Market M, Angka L, Martel AB, Bastin D, Olanubi O, Tennakoon G, Boucher DM, Ng J, Ardolino M, Auer RC. Flattening the COVID-19 curve with natural killer cell based immunotherapies. Front Immunol. 2020;11:1512. doi:10.3389/fimmu.2020.01512.
72. Angelopoulou A, Alexandris N, Konstantinou E, Mesiakaris K, Zanidis C, Farsalinos K, Poulas K. Imiquimod - A toll like receptor 7 agonist - Is an ideal option for management of COVID 19. Environ Res. 2020;188:109858. doi:10.1016/j.envres.2020.109858.
73. Poulas K, Farsalinos K, Zanidis C. Activation of TLR7 and innate immunity as an efficient method against COVID-19 pandemic: imiquimod as a potential therapy. Front Immunol. 2020;11:1373. doi:10.3389/fimmu.2020.01373.
74. Rahmati M, Moosavi MA. Cytokine-targeted therapy in severely ill COVID-19 patients: options and cautions. EJMO. 2020;4(2):179–81. doi:10.14744/ejmo.2020.72142.
75. Alijotas-Reig J, Esteve-Valverde E, Belizna C, Selva-O'Callaghan A, Pardos-Gea J, Quintana A, Mekinian A, Anunciacion-Llunell A, Miró-Mur F. Immunomodulatory therapy for the management of severe COVID-19. Beyond the anti-viral therapy: A comprehensive review. Autoimmun Rev. 2020;19(7):102569. doi:10.1016/j.autrev.2020.102569.
76. Burrage DR, Koushesh S, Sofat N. Immunomodulatory drugs in the management of SARS-CoV-2. Front Immunol. 2020;11:1844. doi:10.3389/fimmu.2020.01844.
77. Golonka RM, Saha P, Yeoh BS, Chattopadhyay S, Gewirtz AT, Joe B, Vijay-Kumar M. Harnessing innate immunity to eliminate SARS-CoV-2 and ameliorate COVID-19 disease. Physiol Genom. 2020;52(5):217–21. doi:10.1152/physiolgenomics.00033.2020.
78. Jahanshahlu L, Rezaei N. Monoclonal antibody as a potential anti-COVID-19. Biomed Pharmacother. 2020;129:110337. doi:10.1016/j.biopha.2020.110337.
79. Wang C, Li W, Drabek D, Okba NM, van Haperen R, Osterhaus AD. A human monoclonal antibody blocking SARS-CoV-2 infection. Nat Commun. 2020;11:1–6.
80. Wu Y, Wang F, Shen C, Peng W, Li D, Zhao C, Li Z, Li S, Bi Y, Yang Y, et al. A noncompeting pair of human neutralizing antibodies block COVID-19 virus binding to its receptor ACE2. Science. 2020;368(6496):1274–78. doi:10.1126/science.abc2241.
81. Ramos-Suzarte M, Diaz Y, Martin Y, Calderon NA, Santiago W, Vinet O, La YO, Perez J, Oyarzabal A, Perez Y, et al. Use of a humanized anti-CD6 monoclonal antibody (itolizumab) in elderly patients with moderate COVID-19. Preprint medRxiv. 2020. doi:10.1101/2020.07.24.20153833.
82. Saavedra D, Añé-Kourí AL, Sánchez N, Filgueira LM, Betancourt J, Herrera C, Manso L, Chavez E, Caballero A, Hidalgo C, et al. An anti-CD6 monoclonal antibody (Itolizumab) reduces circulating IL-6 in severe covid-19 elderly patients. Immunity Ageing. 2020. doi:10.21203/rs.3.rs-32335/v1.
83. NJH. Clinical trials of monoclonal antibodies to prevent COVID-19 now enrolling; 2020. [accessed 2020 Sep 30]. https://www.nih.gov/news-events/news-releases/clinical-trials-monoclonal-antibodies-prevent-covid-19-now-enrolling.
84. Rios P, Radhakrishnan A, Thomas SM, Darvesh N, Straus SE, Tricco AC. Guidelines for preventing respiratory illness in older adults aged 60 years and above living in long-term care. Preprint medRxiv. 2020. doi:10.1101/2020.03.19.20039180.
85. WHO Policy Brief. Preventing and managing COVID-19 across long-term care services: policy brief; 2020b 2020 Jul 24 [accessed 2020 Jul 27]. https://www.who.int/publications/i/item/WHO-2019-nCoV-Policy_Brief-Long-term_Care-2020.1.