



The Overall Effects Of Covid-19 On The Basis Of Management And Treatment In Pediatric Patients: A Complete Review

Shruti Soni^{1*}, Adarsh S Bhadoria², Dr. Pragnesh Patani³

¹*Student, Khyati College of Pharmacy, Palodia, Ahmedabad

²Assistant Professor, Khyati College of Pharmacy, Palodia, Ahmedabad

³Principal, Khyati College of Pharmacy, Palodia, Ahmedabad

***Corresponding Author: Shruti Soni**

*Student, Khyati College of Pharmacy, Palodia, Ahmedabad

Article History	Abstract:
<p>Received: 6 Jan 2024 Revised: 30 Jan 2024 Accepted: 10 Feb 2024</p>	<p>COVID-19 is a disease that is caused by a novel coronavirus known as SARS-COV-2 that has been spreading around the world. Controlling COVID-19 is more difficult due to the highly infectious nature of the disease and clinical complications in patients. Everyone worldwide has struggled with it since it was first introduced in Wuhan, in the Chinese state of Hubei. It reaches every corner, infecting individuals from any walk of life. Everybody has been affected in some way, with the majority usually negatively. Fortunately, they have not yet experienced the direct health effects of COVID-19, but this emergency has had a major effect on their overall health. The viral infection may stay in the atmosphere for a long time, and it mostly spreads through the air. It affects the mucous membranes of the mouth, nose, and eyes. Children's health, social, and financial well-being are all negatively impacted by the COVID-19 epidemic, with the poorest children, such as those who are homeless and those who are detained, being most negatively impacted. School closings, social isolation, and loneliness enhance children's risk of nutritional deficiency, increase their exposure to domestic abuse, build their level of anxiety and stress, and decrease their access to essential family and child care services. According to research, the virus is continually changing and spreading through asymptomatic carriers, which indicates a serious threat to global health. This paper provides an overview of the most recent data on the overall effects of COVID-19 on the basis of management and treatment in pediatric patients.</p>
<p>CC License CC-BY-NC-SA 4.0</p>	<p>Keywords: SARS-COV-2, management in children, overall effects, prevention</p>

Introduction:

According to the present time, the novel coronavirus disease (COVID-19) has affected 1,600,000 people worldwide, killed approximately 100,000 people, and been found in 215 different countries, zones, or states¹. While appearing to be less at risk for infection, children as well as teenagers might nevertheless have the COVID-19 disease². Studies about severe COVID-19 of different kinds in children of all ages are also very common³. Due to the crown-shaped spikes on the outside of the virus that can be observed when examined under an electron microscope, coronaviruses were given their name from the Latin word corona, which means crown or halo⁴. The biggest known RNA virus genome is that of the coronavirus, an enclosed virus with a non-segmented, single-stranded, positive-sense RNA genome of about 32 kilobases⁵. Coronaviruses are members of the nidovirales order's coronavirinae subfamily of the coronaviridae family. Alphacoronavirus,

betacoronavirus, deltacoronavirus, and gammacoronavirus are the four categories that together make up the Coronavirinae subfamily. The SARS-CoV-2 variant belongs to the betacoronavirus genus, according to genome examination of sequences^{6,7}. As a result, the coronavirus genome is known to have a 50-cap and a 30-poly (A) tail, and it functions as an mRNA for translation of the replicase polyproteins that are necessary for viral replication when it infects the host cell⁵. According to reports, animal reservoirs such as bats, mice, rats, chickens, dogs, cats, horses, and camels are where most coronaviruses have been found to live^{8,9}. Few research studies have explored SARS-CoV-2 infections in younger age groups, given mild infections and comparable transmissibility^{10,11}. One percent of children (under 10 years old) were found to be positive out of 44,762 confirmed COVID-19 cases, according to a study carried out in China¹². In another study, out of 32,437 verified tests at public health laboratories in the US, only 0.5% (0–4 years) and 1.3% (5–17 years) among those with lower age groups were tested positive¹³. According to these studies, youngsters experience typical symptoms less frequently and more mildly than older people. There is currently only in vitro evidence that children have a small quantity of SARS-CoV-2-specific ACE2 receptors^{14,15}, whereas a bunch of studies have revealed that innate immunity plays an important role and that naive T-cell responses are capable of reducing the severity of the SARS-CoV-2 infection in children^{16,17}. The SARS-CoV-2 virus is shown to be actively defeated by primary responder immune cells, particularly monocytes, natural killer cells (NK), and dendritic cells¹⁶. Asymptomatic children, however, can be passive carriers of health problems since they are unable to describe their medical condition or history of interaction with COVID-19-positive patients¹⁸.

Although COVID-19 (Corona Virus Disease-2019) can cause a variety of clinical signs, from minor flu-like symptoms to disorders that might be fatal, the biggest problem is locating asymptomatic cases, mostly in children and elderly people. As an example, once infected with SARS-CoV-2, pediatricians either experience moderate or asymptomatic sickness; this results in a reduced risk of the infection in pediatricians, as has been observed. The RTPCR test for symptomatic children with SARS-CoV-2-specific antibodies was, however, negative in a small number of cases¹⁹. The likelihood of a functioning immune system and already existing antibodies against other viral illnesses, such as pediatric pneumonia, might indicate it. The SARS-CoV-2 sample collection procedure and the kind of specimens taken from children are additional issues because the viral load might vary greatly. In addition, the etiology and risk of transmission of COVID-19 may differ in younger and older people, and the following are the contributing variables²⁰:

(1) Children have fewer ACE2 receptors than adults, and a less developed enzyme defends against SARS-CoV-2 variations.

(2) Low levels of cytokines from inflammation, which alter significantly as people get older. However, children who tested positive for COVID-19 had high levels of procalcitonin and interleukin-6²¹.

(3) Variable Th2 immune cell protection and related eosinophilia.

Although the precise pathophysiology of SARS-CoV-2 is uncertain, children can experience varying degrees of severity. Due to the lack of information on the transmission of SARS-CoV-2 in children right now as well as the difficulty in recognizing asymptomatic signs of infections, clinical characteristics are unknown. In addition, severe suitability in children is caused by recently discovered SARS-CoV-2 variants, including B.1.1.7, B.1.526.2, B.1.151, and N501Y.V1^{22,23}. Therefore, it is necessary to establish and validate adequate, accurate, and reliable detection systems all around the world. It was discovered that over 50% of patients had interactions with another sick person. The symptoms that were most common were fever, cold, rhinorea, cough, sore throat, headache, nausea, vomiting, diarrhoea, abdominal pain, fatigue, conjunctivitis, skin rashes, and myalgia. There was zero vertical transmission of virus observed in the cases studied²⁴.

Effects of COVID-19 on children at a certain age:

Positive effects:

1. Nature: It is helpful because it reduces noise and pollution from transportation. This, according to personal experiences, has modified our natural environment and given children greater opportunities to observe and recognize the conservation of biodiversity.

2. Enhanced awareness: The ability UNICEF, the World Health Organization (WHO), and medical authorities have advised parents to explain the epidemic to their children in detail. For instance, UNICEF has developed eight top suggestions for supporting and soothing kids during the pandemic. In addition to reassuring their children and outlining the concrete steps they may take towards their own and others' safety, parents need to be genuine and forthright with them²⁵.

3. Improving a relationship: Spending time with family members might help some kids develop stronger relationships with them, and learning about the pandemic's effects can help kids develop morals and compassion as they become more aware of other people's suffering²⁶.

4. Growth and development of children: It is believed that school closings harm children's education. Solutions for distance educational programs, such as the use of e-learning aids, have strong support from UNESCO. Children who are directly exposed to that could be able to master instructional techniques that will benefit them in the future. They could also engage in a range of creative, intellectual, and physical activities that may help in the development of their talents during this time²⁷.

Negative effects:

1. Psychiatric effects: The fear associated with developing a disease is on an entirely new level. A high level of annoyance, anxiety, distractions, and fear of the global epidemic, all of which have a negative effect on mental health, was found in preliminary research on 320 children in China. In classrooms, psychological conditions are rarely discussed²⁸. In these uncertain times, stress can permanently harm a child and cause irreversible damage. A lack of social interaction, extended cell phone use while schools and colleges are closed as a result of non-pharmaceutical therapies, and possibly compromised study and employment prospects all contribute to a rise in negative thinking²⁹.

2. sleep disorders: It is concerning how common sleep issues are in kids and teenagers in the COVID-19 pandemic³⁰. The current COVID-19 outbreak appears to have been linked to numerous sleep problems. It has also been demonstrated that sleep problems are associated with higher degrees of psychological distress³¹. During the COVID-19 epidemic, 55.5% of schoolchildren aged 6 to 12 reported having problems falling asleep³².

3. Maintaining and being healthy: Children have so far been significantly less affected by the direct effects of the COVID-19 infection than other age groups. Unlike the immediate effects of COVID-19, low-income families will need to reduce their basic food and medical expenses as a result of decreased family income. It is possible to estimate that hundreds of thousands more children expired in 2020 than would have occurred in a realistic pre-pandemic scenario using the IMF's prediction for worldwide economic growth and the past relationship between GDP (gross domestic product) and infant mortality in the developing world³³. This would basically reverse the decrease in newborn mortality that has happened over the previous two to three years in a single year³⁴.

4. The act of violence: the COVID-19 pandemic may have had a significant impact on many children and their families, not only due to the lockdown, strict regulations, social exclusion, changing demographics, and reduction in health care services³⁵, but also due to the abrupt rise in childhood poverty and the potential for long-lasting family instability³⁶. The pandemic is a global problem that affects not only our health and economy but also the well-being of our families through a sliding process of factors that could originate, induce, or magnify possible pressures. Children and adolescents face a significant risk of victimization as a result of the unprecedented nature of the COVID-19 issue³⁷.

Pathophysiology:

Specifically, two cell membrane proteins are the primary targets required for the angiotensin-converting enzyme 2 (ACE2) receptor, and transmembrane serine protease 2 (TMPRSS2) is involved in SARS-CoV-2 invasion³⁸. Although the extent of expression is unknown, both proteins can be expressed in the CNS. Animal studies have proven that glial cells and neurons both express ACE2 and that some glial cells also express TMPRSS2³⁹. The human brain's diverse areas have low but constant transcriptomic expression⁴⁰. Both the olfactory neuroepithelium and the vascular pericytes in the olfactory bulb have been shown to contain ACE2^{41,42}. Human data are currently inadequate, generally. Extrapolating from this research on animals and in basic science has resulted in theories about how COVID-19 can cause neurological symptoms, including direct nervous system infection⁴³. inflammatory reactions brought on by local and/or systemic infection, as well as the vasculature^{44,45}. Additional suggested pathways include brain hypoxia brought on by respiratory failure⁴⁶ and more indirect impacts via cardiovascular problems⁴². We would want to emphasize that each of these systems is presently only a theory and largely untested; therefore, it is unknown which one predominates in children.

Management of COVID-19 in pediatric patients:

Children are not included in these therapeutic clinical studies; recommendations for COVID-19 therapy in children are typically derived from data on adults. Almost no trials for acute COVID-19 therapy included individuals younger than 18 years old at the time of writing, despite the fact that more than 300 randomized experiments managing COVID-19 research have been published and more than 3000 have been registered⁴⁷. Regulatory regulations, extrapolation of efficacy data from adult research, and pediatric-specific safety and dose information, which may be restricted, must all be taken into account when considering repurposed or innovative medicinal medicines in children.

Strong clinical confidence allows doctors to advise supportive care just for the great majority of youngsters with moderate disease and those who don't need extra oxygen. Based on efficacy results from adult trials, several guidelines for the treatment of pediatric patients with acute COVID-19 include taking into account antiviral medication via remdesivir along with immunomodulatory medical care using corticosteroids (dexamethasone) and biological substance medicines (tocilizumab)⁴⁸. While there is less information available on remdesivir and tocilizumab, dexamethasone and steroids are frequently used in children for different disorders and have a widely accepted safety and toxicity profile. Other developing medicines should only be used in clinical trials and should be carefully examined if information regarding safety and effectiveness for children is available⁴⁸. Other medications should not be utilized because they have failed to effectively treat the COVID-19 infection. These include aspirin, colchicine, hydroxychloroquine, azithromycin, and convalescent plasma⁴⁸. The monoclonal antibody treatment Sotrovimab has been given the green light by the Food and Drug Administration (FDA) for use in children 12 years of age and older with severe COVID-19 disease risk factors⁴⁹. Sotrovimab use should be considered on an individual basis because of the lack of safety evidence for the medication in children and the short-term progression of the COVID-19 infection in the majority of children⁴⁸.

Prevent pediatric patients from COVID-19:

1. Safety: Most children associate their homes with a place of safety and protection. Unfortunately, for a minority, the situation is the opposite. The most common form of violence that children experience is violence committed by caregivers. When families are stressed out and cooped up at home, such violent acts are more likely to occur. 60% of all children worldwide live in countries that are either totally or partially on lockdown⁵⁰. Unfortunately, lockdowns give child abusers the opportunity to harm children. Children are rarely in an environment to discuss such horrible acts. Patients during COVID have no longer a means of communicating with teachers to report concerns at home at a time when there had been a greater need, despite social service organizations and other pertinent legal and safety measures for children being discontinued or curtailed^{51,52,53}.

2. Sanitization: Hands need to be often cleansed through soap and water. If water and soap are not easily found, use a hand sanitizer with an alcohol component that contains at least 60% alcohol. Wash your hands with soap and water if they appear to be noticeably impure. Make sure that there is access to clean, accessible latrines and drinking water at home. Make sure that garbage is properly collected, kept, and disposed of. Cough and sneeze into a piece of tissue as well as your elbow to prevent injuring the skin around your eyes and nose^{54,55}.

3. Services for support: Children can be impacted by stress in many different ways. Common reactions include difficulty sleeping, enuresis, abdominal or headache pain, and feelings of worry, distance, hostility, touchiness, or boredom when left alone. Reactions from children should be supported, and their parents should be informed that these are common responses to odd events. Pay attention to their concerns, spend time calming and affecting them, ensuring their safety, and never stop praising them. physical separation, and solitude are all difficult situations for anyone. Children miss communication with their peers, and we fear that being separated from them for an extended period will result in drastic behavioral changes⁶⁰. If at all possible, provide youngsters with opportunities to play and unwind. Maintain as many regular habits and activities as possible, especially before bedtime, or help establish new routines in your new environment^{56,57}.

4. Uses of nutrition: For toddlers under the age of two, a nourishing diet is especially important to maintain their immunity and encourage further growth. Parents and other caregivers may not be able to afford or receive the food that they usually give their young children as a result of the COVID-19 issue. This can reflect a change in routine⁵⁷. All of a child's nutritional needs are met by breastmilk, which also shields them from illness until they reach the age of 6 months old. For infants, additional meals or liquids are not needed and may be dangerous. Starting around the age of six months, children must eat a variety of foods, including beans and grains, nuts, fruits, vegetables, dairy, and animal products. They must drink plenty of liquids, such as breastmilk and pure water, to stay hydrated. nutritious foods between meals, along with plenty of purified water to keep

kids hydrated all day. Ideal snacks include soft fruit and vegetables that have been sliced into bite-sized bits. Commercial food for babies and formula feeding should be avoided. Due to the COVID-19 issue, household members are able to remain at home, which presents an opportunity to switch out prepared meals and formula for homemade ones. If the food is wholesome, varied, and safely prepared, children who are young can eat it. While conserving money and encouraging healthy living, it teaches kids to appreciate different Favors^{57,58}.

5. Vaccination treatments: Vaccinations against COVID-19 are now widely available, and the CDC recommends that everyone over the age of 12 acquire one. On August 23, 2021, the US Food and Drug Administration (FDA) granted a license for a 2-dose regimen of an mRNA vaccine (Pfizer-BioNTech) for clinical COVID-19 prevention in individuals 16 years of age and older⁵⁹. The use of this vaccine in youngsters between the ages of 12 and 15 is also permitted under an Emergency Use Authorization (EUA). A second mRNA vaccine (Moderna) and a recombinant, replication-incompetent adenovirus serotype 26 (Ad26) vector vaccine (Janssen vaccine [Johnson & Johnson]) have also received EUA approval for usage⁶⁰.

Conclusion:

The effect of COVID-19 on pediatric patients has typically been less severe than on adults. The majority of kids either exhibited mild, moderate, or severe symptoms or showed no symptoms. Although they were very infrequent, serious instances and consequences did happen. Pediatric COVID-19 patients' management and treatment plans have changed throughout the course of time, with a focus on supportive care, symptom management, and monitoring. As vaccinations became accessible to all age groups who were able, vaccination efforts became increasingly important in limiting transmission and protecting children. Despite the fact that COVID-19 had a variety of effects on pediatric patients, the medical community's response, involving vaccination campaigns and modified treatment modalities, was crucial in reducing the overall effect of the virus on children. We must continue our research and exercise caution as we deal with the persistent problems caused by pandemic.

References:

1. World Health Organization. Coronavirus disease 2019. <https://www.who.int/emergencies/diseases/novel-coronavirus-2019> (2020).
2. Cruz, A. & Zeichner, S. COVID-19 in children: initial characterization of the pediatric disease. *Pediatrics* <https://doi.org/10.1542/peds.2020-0834> (2020).
3. Rothan, H. A. & Byrareddy, S. N. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *J. Autoimmun.* <https://doi.org/10.1016/j.jaut.2020.102433> (2020).
4. Pyrc, K.; Berkhout, B.; Van der Hoek, L. The novel human coronaviruses NL63 and HKU1. *J. Virol.* 2007, 81, 3051–3057. [CrossRef] [PubMed]
5. Sawicki, S.G.; Sawicki, D.L.; Siddell, S.G. A contemporary view of coronavirus transcription. *J. Virol.* 2007, 81, 20–29. [CrossRef]
6. Wang, L.; Byrum, B.; Zhang, Y. Detection and genetic characterization of deltacoronavirus in pigs, Ohio, USA, 2014. *Emerg. Infect. Dis.* 2014, 20, 1227–1230. [CrossRef] [PubMed]
7. Zhu, N.; Zhang, D. A novel coronavirus from patients with pneumonia in China, 2019. *N. Engl. J. Med.* (2019).
8. De Wit, E.; Van Doremalen, N.; Falzarano, D.; Munster, V.J. SARS and MERS: Recent insights into emerging coronaviruses. *Nat. Rev. Microbiol.* 2016, 14, 523–534. [CrossRef] [PubMed]
9. Van der Hoek, L.; Pyrc, K.; Jebbink, M.F.; Vermeulen-Oost, W.; Berkhout, R.J.M.; Wolthers, K.C.; Wertheim-van Dillen, P.; Kaandorp, J.; Spaargaren, J.; Berkhout, B. Identification of a new human coronavirus. *Nat. Med.* 2004, 10, 368–373. [CrossRef]
10. Wei M, Yuan J, Liu Y, et al. Novel Coronavirus Infection in Hospitalized Infants Under 1 Year of Age in China. *JAMA.* 2020;323(13):1313.
11. Adeyinka A, Bailey K, Pierre L, et al. COVID 19 infection: pediatric perspectives. *J Am Coll Emerg Physicians Open.* 2021;2(1): e12375.
12. Wu Z, McGoogan JM. Characteristics of and important lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China. *JAMA.* 2020;323(13):1239.
13. Lee P-I, Hu Y-L, Chen P-Y, et al. Are children less susceptible to COVID-19? *J Microbiol Immunol Infect.* 2020;53(3):371–372.
14. Felsenstein S, Hedrich CM. COVID-19 in children and young people. *Lancet Rheumatol.* 2020;2(9):e514–e516.

15. Ziegler CGK, Allon SJ, Nyquist SK, et al. SARS-CoV-2 receptor ACE2 Is an interferon-stimulated gene in human airway epithelial cells and is detected in specific cell subsets across tissues. *Cell*. 2020;181(5):1016–1035.e19.
16. Carsetti R, Quintarelli C, Quinti I, et al. The immune system of children: the key to understanding SARS-CoV-2 susceptibility? *Lancet Child Adolesc Heal*. 2020;4(6):414–416.
17. Zimmermann P, Curtis N. Why is COVID-19 less severe in children? A review of the proposed mechanisms underlying the age-related difference in severity of SARS-CoV-2 infections. *Arch Dis Child*. 2021;106:429–439.
18. Chang T-H, Wu J-L, Chang L-Y. Clinical characteristics and diagnostic challenges of pediatric COVID-19: a systematic review and meta-analysis. *J Formos Med Assoc*. 2020;119(5):982–989.
19. Tosif S, Neeland MR, Sutton P, et al. Immune responses to SARS-CoV-2 in three children of parents with symptomatic COVID-19. *Nat Commun*. 2020;11(1):5703.
20. Steinman JB, Lum FM, Ho PP-K, et al. Reduced development of COVID-19 in children reveals molecular checkpoints gating pathogenesis illuminating potential therapeutics. *Proc Natl Acad Sci*. 2020;117(40):24620–24626.
21. Henry BM, Lippi G, Plebani M. Laboratory abnormalities in children with novel coronavirus disease 2019. *Clin Chem Lab Med*. 2020;58(7):1135–1138.
22. Brookman S, Cook J, Zucherman M, et al. Effect of the new SARS-CoV-2 variant B.1.1.7 on children and young people. *Lancet Child Adolesc Heal*. 2021;5(4):e9–e10.
23. Mwenda M, Saasa N, Sinyange N, et al. Detection of B.1.351 SARS-CoV-2 variant strain-Zambia, December 2020. 2021. [Cited 2021 Jul 18]. Available from: <https://stacks.cdc.gov/view/cdc/102801>
24. Christy A (2020) COVID-19: a review for the pediatric neurologist. *J Child Neurol* 35(13):934–939
25. Martinkevich P, Larsen LL, Græsholt-Knudsen T, Hesthaven G, Hellfritsch MB, Petersen KK et al (2020) Physical child abuse demands increased awareness during health and socioeconomic crises like COVID-19: a review and education material. *Acta Orthop* 91(5):527–533
26. Higgins DJ, McCabe MP (2001) Multiple forms of child abuse and neglect: adult retrospective reports. *Aggress Violent Behav* 6(6):547–578
27. Saini SM, Hofmann CR, Pantelis C, Everall IP, Bousman CA (2019) Systematic review and critical appraisal of child abuse measurement instruments. *Psychiatry Res* 1(272):106–113
28. Ulfat A (2017) Post-Traumatic Stress Disorder (PTSD) in children of Kashmir and role of nurse. *Indian J Psychiatr Nurs Care* 14(6). <https://doi.org/10.4103/2231-1505.262422>
29. Mamani JI (2018) Child labor and reproduction of family poverty in Puno: a pending social debt. *OALib* 05(04):1–14
30. Sharma M, Aggarwal S, Madaan P, Saini L, Bhutani M (2021) Impact of COVID-19 pandemic on sleep in children and adolescents: a systematic review and meta-analysis. *Sleep Med [Internet]* 84:259 (/pmc/articles/PMC8687656/). Cited 29 Sep 2022.
31. Alimoradi Z, Broström A, Tsang HWH, Griffiths MD, Haghayegh S, Ohayon MM et al (2021) Sleep problems during COVID-19 pandemic and its' association to psychological distress: a systematic review and meta-analysis. *EClinicalMedicine [Internet]* 36:100916. Available from: <http://www.thelancet.com/article/S2589537021001966/fulltext>). Cited 29 Sep 2022
32. Ustuner Top F, Cam HH (2022) Sleep disturbances in school-aged children 6–12 years during the COVID-19 pandemic in Turkey. *J Pediatr Nurs* 1(63):125–130
33. Knowland VCP, van Rijn E, Gaskell MG, Henderson L (2022) UK children's sleep and anxiety during the COVID-19 pandemic. *BMC Psychol* 10(1):76
34. Patrick SW, Henkhaus LE, Zickafoose JS, Lovell K, Halvorson A, Loch S et al (2020) Well-being of parents and children during the COVID-19 pandemic: a national survey. *Pediatrics* 146(4):e2020016824
35. Wilke NG, Howard AH, Pop D (2020) Data-informed recommendations for services providers working with vulnerable children and families during the COVID-19 pandemic. *Child Abus Negl* 1:110
36. Dodge KA, Bates JE, Pettit GS (1990) Mechanisms in the cycle of violence. *Science* (80-) 250(4988):1678–83
37. Pereda N, Díaz-Faes DA (2020) Family violence against children in the wake of COVID-19 pandemic: a review of current perspectives and risk factors. *Child Adolesc Psychiatry Ment Health [Internet]* 14(1):1–7 Available from: <https://capmh.biomedcentral.com/articles/10.1186/s13034-020-00347-1>. Cited 29 Sep 2022
38. M. Hoffmann, H. Kleine-Weber, S. Schroeder, N. Kruger, T. Herrler, S. Erichsen, T. S. Schiergens, G. Herrler, N.H. Wu, A. Nitsche, M.A. Muller, C. Drosten, S. Pohlmann, SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor, *Cell* 181 (2020) 271–280, e278.

39. J. Frontera, S. Mainali, E.L. Fink, C.L. Robertson, M. Schober, W. Ziai, D. Menon, P. M. Kochanek, J.I. Suarez, R. Helbok, M. McNett, S.H. Chou, G.C.-N. Study, Global consortium study of neurological dysfunction in COVID-19 (GCS-NeuroCOVID): study design and rationale, *Neurocrit. Care* 33 (2020) 25–34.
40. R. Chen, K. Wang, J. Yu, D. Howard, L. French, Z. Chen, C. Wen, Z. Xu, The spatial and cell-type distribution of SARS-CoV-2 receptor ACE2 in human and mouse brain, *bioRxiv* (2020), 2020.2004.2007.030650.
41. D.H. Brann, T. Tsukahara, C. Weinreb, M. Lipovsek, K. Van den Berge, B. Gong, R. Chance, I.C. Macaulay, H.-j. Chou, R. Fletcher, D. Das, K. Street, H.R. de Bezieux, Y.-G. Choi, D. Risso, S. Dudoit, E. Purdom, J.S. Mill, R.A. Hachem, H. Matsunami, D.W. Logan, B.J. Goldstein, M.S. Grubb, J. Ngai, S.R. Datta, Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia, *bioRxiv* (2020), 2020.2003.2025.009084.
42. Gupta, M.V. Madhavan, K. Sehgal, N. Nair, S. Mahajan, T.S. Sahrawian, B. Bikdeli, N. Ahluwalia, J.C. Ausiello, E.Y. Wan, D.E. Freedberg, A.J. Kirtane, S.A. Parikh, M. S. Maurer, A.S. Nordvig, D. Accili, J.M. Bathon, S. Mohan, K.A. Bauer, M.B. Leon, H.M. Krumholz, N. Uriel, M.R. Mehra, M.S.V. Elkind, G.W. Stone, A. Schwartz, D. D. Ho, J.P. Bilezikian, D.W. Landry, Extrapulmonary manifestations of COVID-19, *Nat. Med.* 26 (2020) 1017–1032.
43. E. Song, C. Zhang, B. Israelow, A. Lu-Culligan, A.V. Prado, S. Skriabine, P. Lu, O.- E. Weizman, F. Liu, Y. Dai, K. Szigeti-Buck, Y. Yasumoto, G. Wang, C. Castaldi, J. Heltke, E. Ng, J. Wheeler, M.M. Alfajaro, E. Levavasseur, B. Fontes, N. G. Ravindra, D. Van Dijk, S. Mane, M. Gunel, A. Ring, S.A. Jaffar Kazmi, K. Zhang, C.B. Wilen, T.L. Horvath, I. Plu, S. Haik, J.-L. Thomas, A. Louvi, S.F. Farhadian, A. Huttner, D. Seilhean, N. Renier, K. Bilguvar, A. Iwasaki, Neuroinvasion of SARSCoV-2 in human and mouse brain, *bioRxiv* (2020), 2020.2006.2025.169946.
44. E. Gulko, P. Overby, S. Ali, H. Mehta, F. Al-Mufti, W. Gomes, Vessel wall enhancement and focal cerebral arteriopathy in a pediatric patient with acute infarct and COVID-19 infection, *AJNR Am. J. Neuroradiol.* (2020).
45. F.A. Klok, M. Kruip, N.J.M. van der Meer, M.S. Arbous, D. Gummer's, K.M. Kant, F. H.J. Kaptein, J. van Paassen, M.A.M. Stals, M.V. Huisman, H. Endeman, Incidence of thrombotic complications in critically ill ICU patients with COVID-19, *Thromb. Res.* 191 (2020) 145–147.
46. H.R. Niazkar, B. Zibae, A. Nasimi, N. Bahri, The neurological manifestations of COVID-19: a review article, *Neurol. Sci.* 41 (2020) 1667–1671
47. The COVID NMA Initiative 2021. Available from: <https://covidnma.com>.
48. Living Guidelines: National COVID-19 Clinical Evidence Taskforce 2021. Available from: www.covid19evidence.net.au.
49. Australian Government Department of Health. Australian prescription medicine decision summaries: Xevudy. 20 August 2021.
50. Brown SM, Doom JR, Lechuga-Peña S, Watamura SE, Koppels T (2020) Stress and parenting during the global COVID-19 pandemic. *Child Abus Negl* 1:110
51. Gupta S, Jawanda K (2020) resumen de políticas: el impacto de COVID-19 en los niños 15. *Acta Paediatr Int J Paediatr* [Internet] 109(11):2181–3 Available from: https://www.un.org/sites/un2.un.org/files/policy_brief_on_covid_impact_on_children_16_april_2020.pdf
52. Protecting children online | UNICEF. <https://www.unicef.org/protection/violence-against-children-online>. Accessed 26 Oct 2022
53. Hsiao C-M (2022) Effects on second waves of COVID-19 epidemics: social stringency, economic forces and public health. *Theor Econ Lett* 12(01):287–320
54. Jones KD, Thitiri J, Ngari M, Berkley JA (2014) Childhood malnutrition: toward an understanding of infections, inflammation, and antimicrobials. *Food Nutr Bull* 35:S64-70
55. Tezer H, Bedir DT (2020) Novel coronavirus disease (COVID-19) in children. *Turkish J Med Sci* 50(9):592–603
56. Alsohime F, Tamsah MH, Al-Nemri AM, Somily AM, Al-Subaie S (2020) COVID-19 infection prevalence in pediatric population: etiology, clinical presentation, and outcome. *J Infect Public Heal* 13(12):1791–1796
57. Capanna F, Haydar A, McCarey C, Bernini Carri E, Bartha Rasero J, Tsibizova V et al (2022) Preparing an obstetric unit in the heart of the epidemic strike of COVID-19: quick reorganization tips. *J Matern Neonatal Med* 35(7):1412–1418
58. Ding Q, Lu P, Fan Y, Xia Y, Liu M (2020) The clinical characteristics of pneumonia patients coinfecting with 2019 novel coronavirus and influenza virus in Wuhan. *China J Med Virol* 92(9):1549–1555

59. Guedes A, Bott S, Garcia-Moreno C, Colombini M (2016) Bridging the gaps: a global review of intersections of violence against women and violence against children. *Glob Heal Action* 9(1):31516
60. Amin U (2017) Post Traumatic Stress Disorder (PTSD) in children of Kashmir and role of nurse. *Indian J Psychiatr Nurs* 14(1):37