MAEDICA – a Journal of Clinical Medicine
2021; 16(3): 499-506
https://doi.org/10.26574/maedica.2021.16.3.499

MÆDICA - a Journal of Clinical Medicine

REVIEW

# Pathophysiology and Clinical Presentation of COVID-19 in Children: Systematic Review of the Literature

G. VIDYA, M. KALPANA, K. ROJA, John Ashok NITIN, Madhuri TARANIKANTI

Department of Physiology, All India Institute of Medical Sciences (AIIMS), Bibinagar, India

*ABSTRACT*

***Introduction:*** *Coronavirus disease 2019 (COVID-19) is due to severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2) infection, which belongs to beta-coronaviruses of the Coronaviridae family. SARS-coV-2 causes acute respiratory infection with varying severity in different age groups, wherein adults can develop severe disease, while children are relatively spared until now, with COVID-19 in children accounting for only 1-5% of diagnosed cases. Although COVID-19 incidence rate in children is relatively low, their protection from COVID-19 is still a matter of increasing concern as children constitute a large vulnerable population. In order to develop effective therapeutic management and preventive measures against COVID-19 in children, there is an urgent need for a better understanding of its pathophysiology at the molecular level and clinical presentation as well as possible protective mechanisms in the pediatric population.*

***Objectives:*** *There is limited data regarding the incidence and clinical presentation of SARS-CoV-2 infection in children. Our goal was to understand the clinical picture and presentation of pediatric patients with confirmed COVID-19.*

***Methods:*** *A systematic literature search of popular medical databases (PubMed, Cochrane Central Register of Clinical Trials and Scopus), restricted to English language publications only, was conducted by us. We chose published peer-reviewed and cross-sectional articles as well as case series providing clinical signs, imaging findings and laboratory results of pediatric patients, using the following inclusion criteria: children aged up to 18 years who tested positive for COVID-19 and in whom SARS-Co-V-2 was detected in the nasal/throat swab by real time polymerase chain reaction (RT-PCR).*

***Conclusion:*** *Our review revealed that, in children, COVID-19 was milder in terms of disease severity and clinical presentation, and it had a better prognosis and a lower mortality rate than adults.*

**Keywords**: pathophysiology of COVID-19, clinical presentation of COVID-19, low incidence of COVID-19 in children, novel corona virus, mild illness.

*Address for correspondence:*
*Dr. G. VIDYA*
*Assistant Professor, Physiology, AIIMS, Bibinagar, India*
*Tel.: 9959157930, email: docvidyaganji@gmail.com*

*Article received on the 14th of May 2021 and accepted for publication on the 6th of August 2021*

## INTRODUCTION

Coronavirus disease 2019 (COVID-19) is due to the severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2) infection, which belongs to beta-coronaviruses of the Coronaviridae family. In December 2019, the coronavirus disease spread from China to other parts of the world, affecting around 200 countries, and the World Health Organization (WHO) declared it as pandemic on the 11th of March 2020 (1, 2). It is the biggest public health crises of recent times. As per the WHO update from the 28th of February 2021, there have been 111 million confirmed cases and 2.46 million deaths worldwide (3), and 2.59 million new cases, 11.3 million cases and 1,56,418 deaths due to COVID-19 in India (4) at the time of writing this paper.

SARS-coV-2 causes acute respiratory infection with varying severity in different age groups, wherein adults tend to have severe disease, while children are relatively spared until now and account for only 1-5 % of diagnosed cases (5-7). Mortality in children is rarely reported. Evidence suggests that as much as half of children infected with corona virus may be asymptomatic and therefore not diagnosed (6, 7). National and global data indicated that only 2-3% of infected children required hospitalization. Deaths due to COVID-19 in children contributes to <2 % of all deaths (8). There is a knowledge gap related to the low susceptibility of children to COVID-19 and appearance of mild illness in the pediatric population. Several theories to explain the differences in the pathogenesis of COVID-19 between children and adults have been proposed (8, 11). However, there are cases of multisystem inflammatory syndrome in children (MIS-C) that appear to be associated with COVID-19 manifesting with high fever, rash, conjunctivitis and gastrointestinal symptoms with multiorgan failure (9), which is of concern. It has been observed that children with comorbid conditions such as congenital heart disease or lung and airway disease are prone to severe illness with COVID-19 (10). Although the incidence of COVID-19 in children is low, ensuring their protection from COVID-19 remains a matter of increasing concern as the pediatric population constitute a large vulnerable group (11). There is limited data regarding the incidence and clinical presentation of SARS-CoV-2 infection in children.

To develop effective therapeutic management and preventive measures against COVID-19 in children, there is an urgent need for a better understanding of its pathophysiology at the molecular level and clinical presentation as well as possible protective mechanisms in the pediatric population. Hence, these facts gave an impetus to conduct a systematic review focusing on clinical presentation of COVID-19 in children and discussing the proposed hypothesis and factors responsible for the mild nature of COVID-19 in children. ❑

## METHODS

### Search strategy and selection criteria

Adhering to the PRISMA guidelines for 2020, we did a systematic literature search of medical databases (PubMed, Cochrane Central Register of Controlled Trials and Scopus) between the 1st of January 2020 and the 28th of February 2021. Three authors independently searched the databases using the following keywords: "novel coronavirus", "COVID-19", "SARS-CoV-2", "low incidence of covid-19 in children" and "COVID-19 in children OR pediatric COVID-19". The search terms were kept broad to encompass all possibilities for the studies applicable. Some records were also retrieved *via* cross-references from selected published papers.

Searches were limited to English language articles only. All published articles which were in line with national and international guidelines and under recommendations of international committee of medical journal editors were included in the current review.

The following inclusion criteria were used: children aged up to 18 years who tested positive for COVID-19 and in whom SARS-Co-V-2 was detected in the nasal/throat swab by real time polymerase chain reaction (RT-PCR).

Isolated case reports, case series with a sample size <5 and suspected cases of COVID-19 without positive RT-PCR test results were excluded.

The remaining eligible articles were further analyzed. ❑

## RESULTS

Based on our search criteria, 1 350 articles were identified and pre-selected for detailed analysis. Of these, retracted papers, editorials,

reviews or commentaries that did not meet our criteria were removed. A total of 120 articles were selected according to the above-mentioned inclusion criteria, out of which 46 were excluded based on their titles and abstracts as some of them were duplicates, their topics were outside the scope of the present study and some articles were not in English. Figure 1 is a schematic representation of our search, showing the inclusion and exclusion criteria used to select only relevant articles. A final list of 52 published articles was retrieved and analyzed.

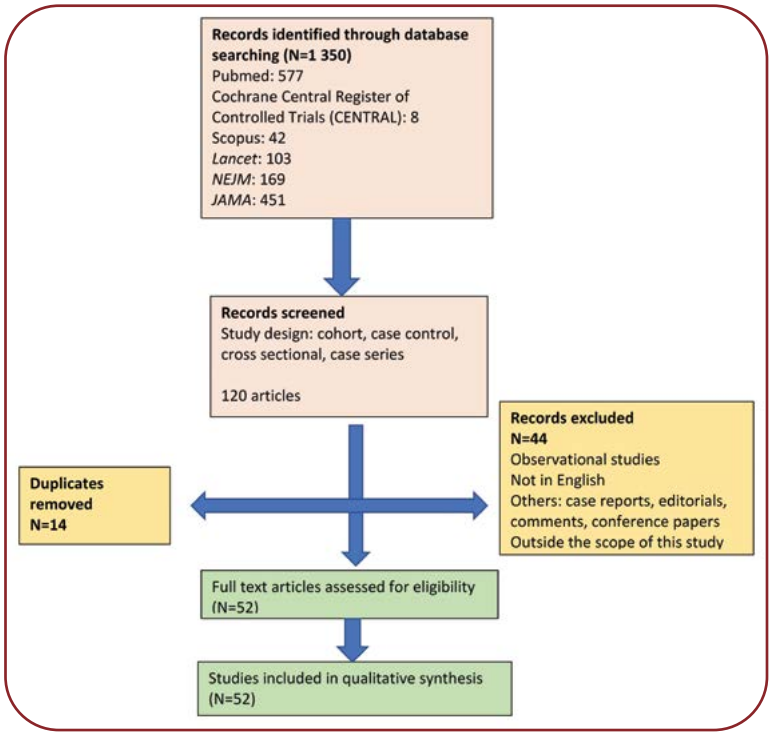


**FIGURE 1.** Prisma flow diagram showing a schematic representation of article search and exclusion and inclusion criteria

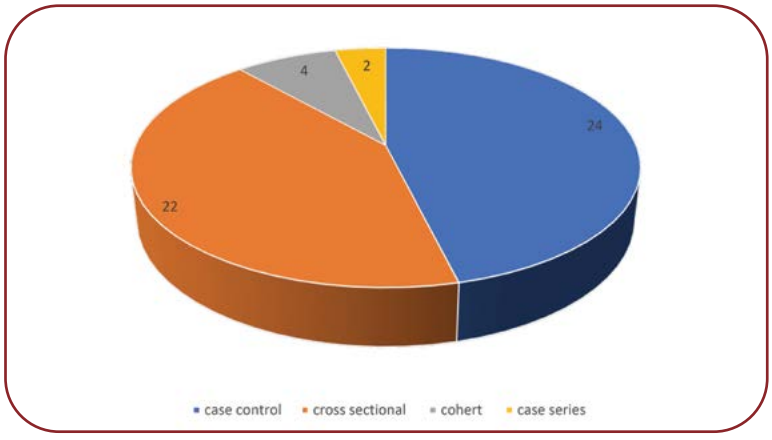


**FIGURE 2.** The proportions of each selected study category included in the present review

The present review included case series, scientific papers, published articles, peer-reviewed articles, altogether describing a total of 3 316 pediatric patients (N=3 316) with COVID-19. Figure 2 shows the proportions of each selected study category.

All children included in our study had positive results with SARS-CoV-2 RT-PCR (reverse transcription-polymerase chain reaction).

## Pathogenesis of COVID-19 in children

SARS-CoV-2 is an enveloped single stranded RNA virus that utilizes angiotensin converting enzyme 2 receptors (ACE2) as its cell surface receptor (12-14). The ACE2 receptors are expressed in epithelial cells in human lungs and also in the intestines, kidney and bladder (15). CD-147 and the 78 kDa glucose regulated protein (GRP78) are other newly described cell surface receptors of SARS-CoV-2 for their cellular entry (16, 17).

It has been found that ACE2 receptors were expressed by the epithelial cells of the gastrointestinal tract, suggesting the virus entry through ACE2 receptors and its replication causing gastrointestinal symptoms. The cardiovascular system is also involved in COVID-19, which may explain the increased level of biomarkers such as troponin-T and natriuretic peptides (17, 18).

## Transmission of COVID-19

SARS-CoV-2 is transmitted from person to person through respiratory droplets and aerosols from an infected person's cough or sneeze and respiratory secretions, which occurs through exposure of the host's mucosal surfaces such as eyes, nose and mouth. Transmission of COVID -19 in children is the result of a child's exposure to a COVID positive adult (19). Transmission to newborns through infected mothers is known, but vertical transmission is not documented yet (20). A large proportion of children are asymptomatic and may act as carriers contributing to transmission (21). A study by Cai *et al* identified the first case of pediatric COVID-19 and suggested that children as a source of adult infection (22). According to the existing data, 56% (n/N= 1 039/1 856) of infected children were clearly shown to have acquired the infection after family gatherings. Airborne transmission of COVID-19 has been a matter of debate. In exceptional cases, it can occur during medical procedures that generate aerosols (18).

In adults, the incubation period is five days, but in some cases it can be as long as 14 days (16), during which the infected individuals can act as carriers and transmit the virus to healthy individuals. Current studies show that the incubation period in children varies from 1 to 14 days (21), with a mean incubation period of 6.5 days, which is longer than in adults.

### Age and sex distribution characteristics of COVID-19 in children

Children of all ages can be infected with COVID-19, with more cases being reported among younger children and infants. Among COVID positive children, where gender distribution in the study sample was available, we found that 58% (n/N= 394/680) of infected children were males and 42% (285/680) females. Studies reported that COVID had a higher incidence in males than females. The youngest of all children diagnosed with COVID was one day old, while the oldest was 17 years old (22). The median age of infection in children was found to be 6-7 years. ❑

## DISCUSSION

Data showed that, in India, less than 12% of all COVID-19 patients were children, who generally developed mild illness (5-7). Until now, children have been relatively spared from serious disease and poor outcomes. They were generally asymptomatic or showed mild symptoms (6, 23), presented with fever, cough and fatigue, sometimes accompanied by few other symptoms of the upper respiratory tract infection such as nasal congestion and rhinorrhea. Some children may experience gastrointestinal symptoms, including abdominal pain, diarrhea, nausea and vomiting (23).

In our review, we found that 41.6% (n/N = 1 379/3 316) of the total pediatric cases who tested positive for COVID-19 were asymptomatic and they were identified by contact tracing from exposure to COVID-19 positive patients. Chang *et al* (45) reported that there were higher rates of asymptomatic and mild cases of COVID-19 in children. Recent evidence suggested there were no differences between asymptomatic and symptomatic patients in terms of viral load, meaning that the asymptomatic ones could be a potential source of COVID-19 (24-26). Therefore, more efforts should be made to screen children for COVID-19 as they can be carriers of SARS-CoV-2.

We found that 26.4% (n/N= 875/3 316) of the total number of cases had mild symptoms. Among children with mild symptoms, 20% patients recovered following mild flu-like illness without progressing to a critical phase. Ludvigsson reported that children had milder symptoms, a better prognosis and lower mortality than adults (2). In a study conducted by Gupta N *et al* on the clinical features and epidemiological characteristics of 21 patients from New Delhi, India, patients had mild illness, except for one subject with lung consolidation, who required inhalation of oxygen (27). A retrospective study by Fang Zeng *et al* (28) showed that the majority of infected children had mild symptoms and upper respiratory tract infection. The authors classified the study participants according to disease severity into asymptomatic infection (no clinical signs and symptoms), mild disease (with typical signs of respiratory tract infection such as cough, fever, rhinorrhea, sneezing, and fatigue), moderate disease (with typical signs and symptoms of pneumonia), severe disease (with signs of respiratory distress), and critical disease (characterized by progression to ARDS or respiratory failure).

Out of all cases, 27.1% (n/N = 898/3 316) had moderate disease and only 4.9% (n/N = 162/3316) severe disease. In a study done by Dong *et al*, the proportion of critical and severe cases was 10.6%, 7.3%, 4.2%, 4.1% and 3% in subjects aged less than one year, between 1-5 years, 6-10 years and 11-15 years, respectively (27). These findings suggested that, in children with COVID-19, clinical manifestations were less severe and had a milder course compared to adults, and the proportion of severe cases decreased with age. The reduced number of symptomatic cases makes it challenging to diagnose and control the infection among children.

Our literature search revealed that fever was the most common symptom in children, with a mean duration of three days, indicating that the illness lasted for a shorter period compared to 10 days in adults. Cough was the second most common symptom in pediatric patients. Other presenting symptoms included sore throat/pharyngitis in 12.5% (n/N = 414/3 316) of children, nasal congestion in 11% (n/N = 364/3 316), dysp-

nea in 17.25% (n/N = 572/3 316), vomiting in 29.7% (n/N=984/3 316), and diarrhoea in 18.5% (n/N = 613/3 316); only 5% (n/N = 166/3 316) of children had fatigue. We found that children under seven years of age presented with vomiting and diarrhea along with fever more than older children (23), which was supported by the findings of Chang *et al*, who reported that diarrhea and vomiting through gastrointestinal involvement were the most common symptoms in children (28). Dermatological lesions have been also registered as clinical manifestations in children. While anosmia and ageusia were described as early symptoms of COVID-19 in adults, they were not found in any of the children in our study. The authors have also observed that children with COVID-19 did not require antibiotic and antiviral treatment with remdesivir or steroids. This analysis indicated that fever and cough were the most frequent clinical manifestations in children with COVID-19.

Co-infections with other respiratory viruses, bacteria and fungi were observed in a smaller proportion of children with COVID-19, *i.e*, 5.6% (n/N = 185/3 316) (29).

Data regarding other laboratory markers of COVID-19 positive children were rare, with leucopenia and leukocytosis being the most prevalent laboratory findings. Lymphopenia and CRP elevation are less common in children than adults with COVID-19s. Thus, CRP levels were found to be raised in 26% (n/N = 862/3 316) of children. Laboratory results indicated lymphopenia in 8% of the infected children. Data on non-specific inflammatory markers, including CRP, D-dimer, creatine kinase, and interleukin-6, were scarce. A single study with a small sample of only 20 children reported elevated procalcitonin levels in 80% of cases (n/N = 16/20) (30). In contrast, few studies (31-34) reported that 69.2% (n/N = 41/59) of children had normal leucocyte counts and 31.8 % (19/59) neutrophilia. Han *et al* found abnormal coagulation functions in infected pediatric patients and a median incubation period of five days (35). In another study, Jain *et al* reported that disease progression was associated with an increase in inflammatory markers such as D-dimer, IL-6 and troponin levels (36). Su *et al* detected elevated CK-MB levels in six children with COVID-19, which suggested that SARS-CoV-2 might have caused heart injury (37). The main mechanisms of SARS-CoV-2 induced myocardial injury may include direct injury by the virus, inflammatory cytokine storm and distribution of ACE2 receptors in heart (36).

Only few chest CT findings are available in children and most of show mild injury (37). Five studies included in the review described the CT findings in which Patchy consolidation and ground glass opacities were present in 29% of children (n/N = 47/162).

Comorbidities were rarely found in only 1.2 % (n/N = 40/3 316). Children with previous history of congenital diseases or acquired diseases may be more susceptible to COVID-19 infection (29, 30, 38). In hospitalized children with COVID-19, the mortality rate was 0.09% (n/N = 29/3 316).

However, atypical presentations such as multisystem inflammatory syndrome (MIS-C) was found in 0.15% of hospital admitted COVID-19 positive children (n/N = 186/2 306) in Europe and USA, which resembled Kawasaki disease. These children with fever, vomiting and abdominal pain at presentation developed cardiovascular manifestations and other atypical manifestations, including hypotension, myocarditis, pericardial effusion, and received treatment for MIS-C (39). Cardiac manifestations were predominant in MIS-C; reduced ejection fraction was the most common cardiac abnormality and it was associated with elevated troponin levels. Multisystem inflammatory syndrome is believed to be associated with post-infectious inflammatory process related to COVID-19 (40). A more concerning finding is that even asymptomatic children could develop MIS-C. The literature supports the fact that typically, MIS-C manifests 3-4 weeks after SARS-CoV-2 (40, 41). The underlying factors for some children's predisposition to MIS-C are unknown and more research is required to understand why some children are more susceptible for developing MIS-C. With early recognition and prompt medical treatment, most children with MIS-C survive, but long-term outcomes of this condition are not known.

## Why children with COVID-19 have only mild illness?

Multiple reports demonstrated that children had a milder form of the disease compared to adults. Asymptomatic, mild and moderate infections comprise over 90% of all cases in children who

tested positive for COVID-19 (32). With an immature immune system, children in general are more severely affected by respiratory viruses such as influenza and respiratory syncytial virus than adults. On the contrary, the relative sparing of children and mild nature of COVID-19 in them have perturbed the epidemiologists, clinicians and scientists throughout the world (42). Currently, there are no clear answers to this; so, only theories and hypotheses have been put forward to explain the mild nature of COVID-19 in children, which are described below.

## Decreased generation of thrombin and fibrin formation

Children may have a low risk of COVID-19 associated acute respiratory distress syndrome (ARDS) due to decreased generation of thrombin and fibrin formation (43).

## Angiotensin-converting enzyme 2 and renin angiotensin system

Angiotensin-converting enzyme 2 (ACE2) is a regulatory enzyme of the renin angiotensin system (RAS), which acts by converting angiotensin-2 to angiotensin 1-7. After entering pneumocytes, SARS-CoV-2 downregulates ACE2 expression, decreasing angiotensin-2 metabolism (44). Angiotensin-2 levels have been found to be increased in COVID-19 patients compared to healthy adults. The proposed hypothesis is that the cellular expression of the ACE2 receptor and the binding between the receptor and the spike protein (S) of the virus may be different in children compared to adults (22), which may be responsible for mild illness in children.

## Effects of lung development

Good regenerative capacity could explain the overall less severity and early recovery of COVID-19 in children compared to adults. Due to a greater upper airway resistance in children, aerosol particles deposit more in tracheobronchial tree than alveoli. This could lead to more bronchiolitis-like infections and less pneumonia with SARS-CoV-2 infection in children (35, 43). From a physiological point of view, a higher frequency of ciliary beating of epithelial cells of lungs in children might hinder the virus entry into lung pneumocytes (45).

## Differences in immune system between adults and children

The immune system varies with age both in terms of constitution and function, particularly during the phenomenon of immunosenescence, which is defined as a gradual deterioration of the immune function associated with the natural ageing process (46). Immunosenescence due to thymic involution is associated with gradual decrease in T cell count and activity. In children, as thymic activity is increased, T cell count and activity is also greater, which is providing protection against viral infection (47). Children have an immature and not fully developed immune system, which may explain why they are not mounting an intense inflammatory response and therefore, the host-mediated damage is limited. There is a decline in the number of T cells with age as a result of thymus atrophy, which may account for the mild form of the disease in children.

## Innate immunity in children

Innate immune responses, which act as first line of defense, seems to play an important role in reducing the viral infection in children. These responses are mediated by the production of type 1 interferons, which play a role in blocking the replication of the virus in early stages of infection (46, 47). In addition, the function of macrophages, neutrophils, natural killer cells and even T lymphocytes becomes impaired with age, which can lead to severe manifestations in adults. Maternal antibodies protecting neonates and young infants are unlikely to act against novel viruses like SARS-CoV-2 (48).

## Trained immunity

Trained immunity is the functional reprogramming of innate immune cells to a more activated state following initial antigen stimulation through metabolic reprogramming and epigenetic changes (acetylation and demethylation leading to enhanced transcription of IL-1beta, IL-6 and TNF-alpha genes). It can affect progenitor cells of myeloid and monocyte cell lines as well as local cells such as lung macrophages and dendritic cells (49). Children receive several doses of different vaccines as part of the universal immunization programme and it has been observed that in developing countries like India, with routine

The BCG vaccine, they have less COVID-19 related morbidity and mortality (50). BCG vaccine might influence the innate and T cell immunity by epigenetic reprogramming of immune cells and by altering cytokine responses (51).

It is proposed that, following BCG vaccination, there is an enhanced pattern recognition of receptors expression in monocytes and elevation of Th1 and Th17 immune response to non-mycobacterial stimulation up to one year of vaccination (52). The BCG vaccine has been associated with a decrease in acute upper respiratory tract infection in elders and decreased mortality in children aged under five years (53). Trained immunity due to routine live vaccines and frequent viral infections could be an important protective mechanism against SARS-CoV-2 infection in children. Cross reactive antibodies targeting the highly conserved domain of SARS-CoV-1 showed a low affinity for SARS-CoV-2 (54). Cross protection by antibodies generated following measles vaccination and cell mediated immune response generated by BCG vaccination needs evaluation.

### Role of co-infections

The lack of co-infections and co-morbidities, such as diabetes, hypertension and chronic lung and heart disease, and less exposure to particulate matter and pollutants provides protection to children's lungs and airways. ❑

## CONCLUSION

Our review showed that children appeared to be largely spared from severe symptoms of the disease, which generally had a milder course, better prognosis and less impact of mortality compared to adults. Although children might not be the face of this pandemic, special attention should be given to them as they risk being among the biggest victims. Additional care may be needed for children with comorbidities. They might be impending carriers of virus and transmit the disease to adults with whom they are in close contact. Therefore, being aware of the clinical presentations in children will be helpful for early clinical diagnosis and treatment approach of COVID-19 in the pediatric population.

It is also useful to discuss the age-specific pattern of coronavirus infection more accurately. Life-saving health services and complete vaccination of children could protect them from serious risk of COVID-19 and may be useful to control the expected third and fourth waves of the pandemic, which are anticipated to have a disproportionately high burden in the pediatric population. ❑

*Conflicts of interest: none declared.*
*Financial support: none declared.*

## References

1. **Zimmermann P, Curtis N.** Coronavirus infections in children including COVID-19. PIDJ 2020;5:355-368.
2. **Ludvigsson JF.** Systematic review of COVID-19 in children show milder cases and better prognosis than adults. *Acta Paediatr* 2020;6:1088-1095.
3. World Health Organization. WHO coronavirus disease (COVID-19) Dashboard, 2020.
4. Ministry of health and family, Government of India. Graphical illustration of data from COVID-19 cases in India. National Centre for Disease Control (NCDC), 2020.
5. Children and COVID-19: state data report, February 2021.
6. **Wolters Kluwer Health.** "COVID-19 appears less severe in children". *Science Daily*, March 13, 2020.
7. Centers for Disease Control and Prevention. Coronavirus Disease 2020: Children
8. Johns Hopkins University of Medicine. COVID-19 dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU). Accessed April 28, 2020.
9. **Wu Z, McGoogan JM.** Characteristics of and important lessons from the coronavirus disease 2019 outbreak in China. *JAMA* 2020;323:1239.
10. **Mubbasheer Ahmed, Shailesh Advani, et al.** Multisystem inflammatory syndrome in children: a systematic review. *EClinical Medicine* 2020;26:100527.
11. India Office of the Registrar General and Consensus commissioner, Ministry of Home Affairs, Government of India, "Age structure and marital status", 2011.
12. Report on the WHO-China joint mission on coronavirus disease 2019 (COVID-19) assessed on March 31, 2020.
13. **Yi J, Xiaoxia L, Runming J, et al.** Novel coronavirus infections: standard/ protocol/guidelines recommendations for diagnosis, prevention and control of the 2019 novel coronavirus in children. *Chin J Appl Clin Pediatr* 2020;2:143-150.
14. **Wenhui Li, Moore MJ, Vasilieva N, et al.** Angiotensin converting enzyme 2 is a functional receptor for SARS coronavirus. *Nature* 2003;6965:450-454.
15. **Hamming I, Timens W, Bulthuis MLC, et al.** Tissue distribution of ACE2 protein, the receptor of SARS coronavirus. A first step in understanding SARS pathogenesis. *J Path* 2004;2:631-637.
16. **Ke Wang, Wei Chen, Y usen Zhou, et al.** SARS-COV-2 invades host cells via a novel route: CD147-spike protein: Oxford

Immunology Network COVID-19: APRIL 2020.
17. **Ibrahim M Ibrahim, Doaa H Abdemalek, et al.** COVID-19 spike-host cell receptor GRP78 binding site prediction. *J Infect* 2020;5:554-562.
18. **Chan J F, Yuan S, et al.** A Familial cluster of pneumonia associated with 2019 novel coronavirus indicating person to person transmission: A study of a family cluster. *Lancet* 2020;395:514-523.
19. **Yan J, Guo J, Fan C, et al.** Coronavirus disease 2019 in pregnant woman. A report based on 116 cases. *Am J Obstet Gynecol* 2020;1:111.e1-111.e14.
20. **He X, Lau, et al.** Temporal dynamics in viral shedding and transmissibility of COVID-19. *Nature Med* 2020;26:672-675.
21. **Cai JH, Wang XS, Ge YI.** First case of 2019 novel coronavirus infection in children in Shanghai. *Zhonghua Er Ke Za Zhi* 2020;58:E002.
22. **Cai J, Xu J, Lin D, et al.** A case series of children with 2019 novel coronavirus infection: clinical and epidemiological features. *Clin Infect Dis* 2020;16:1547-1551.
23. **Anant Parasher.** COVID-19: Current understanding of its Pathophysiology, Clinical presentation and Treatment. *Post Grad Med J* 2021;1147:312-320.
24. **Wu Z, McGoogan JM.** Characteristics of and Important Lessons From the Coronavirus Disease 2019 Outbreak in China. *JAMA* 2020;13:1239-1242.
25. **Wolfel R, Cornman VM, et al.** Virological assessment of hospitalized patients with COVID-2019. *Nature* 2020;581:465-469.
26. **Zou L, Ruan F, et al.** SARS-Co-V-2 viral load in upper respiratory specimens of infected patients. *N Engl J Med* 2020;382:1177-1179.
27. **Gupta N, Agarwal S, et al.** Clinical and epidemiological profile of the initial COVID-19 pateints at a tertiary care centre in India. *Monaldi Arch Chest Disease* 2020;10:90.
28. **Feng F, Xiaoping L.** Facing the pandemic of 2019 novel coronavirus infections: the pediatric perspectives. *Chin J Pediatr* 2020;2:81-85.
29. **Dong Y, Mo X, Hu Y, et al.** Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in China. *Pediatrics* 2020;145:e20200702.
30. **Tu-Hsuan Chang, Jhong-Lin-Wu, Luan Yin Chang.** Clinical characteristics and diagnostic challenges of pediatric COVID-19: A systematic review and meta-analysis. *J Formos Med Assoc* 2020;5:982-989.
31. **Siddiqui H K, Lang J, et al.** COVID-19 for the cardiologist: A current review of the virology, clinical epidemiology, cardiac and other clinical manifestations and potential strategies. *JACC Basic Transl Sci* 2020;5:518-536.
32. **Lu X, Zhang L, Du H, et al.** SARS-CoV-2 infection in children. *N Engl J Med* 2020;382:1663-1665.
33. **Cascella M, Rajnik M, Cuoma A, et al.** Features, evaluation and treatment coronavirus (COVID -19) Stat pearls. Treasure island: Stat Pearls Publishing, Jan 2020.
34. **Xu Z, Shi L, Wang Y, et al.** Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* 2020:8;420-422.
35. **Han X, Xuemei Li, Yinan Xiao, et al.** Distinct characteristics of COVID-19 infection in children. *Front Pediatr* 2021;9:619738.
36. **Jain N, Animesh Choudhury, Jayesh Sharma, et al.** A review of novel coronavirus infection (Coronavirus Disease-19) *GJTM* 2020;1:22-26.
37. **Su Liang, Xiang Ma, et al.** The different clinical characteristics of corona virus disease cases between children and their families in China – the character of children with COVID-19. *Emerging Microbes and Infections* 2020;9:707-713.
38. **Bansal M.** Cardiovascular disease and COVID-19. *Diabetes Metab Syndr* 2020;3:247-250.
39. **Xia W, Shao J, Peng X, et al.** Clinical and CT features in pediatric patients with COVID-19 infection: Different points from adults. *Pediatr Pulmonol* 2020:55:1169-1174.
40. **Cheung KS, Hung IF, Chan PP, et al.** Gastrointestinal manifestations of SARS-Co-V2 infection and virus load in fecal samples from the HongKong cohert and systematic review and metanalysis. *Gastroeneterology* 2020;1:81-95.
41. **Diorio C, Henrickson SE, Vella LA, et al.** Multisystem inflammatory syndrome in children and COVID-19 are distinct presentations of SARS-Co-V-2. *J clin Invest* 2020;11:5967-5975.
42. **Weisberg SP, Conners, et al.** Antibody responses to SARS-Co-V2 are distinct in children with MIS-C compared to adults with COVID-19. *Med R* 2020. doi: 10.1101/2020.07.12.20151068.
43. **Lee P-I, Hu Y-L, Chen P-Y, et al.** Are children less susceptible to COVID-19? *J Microbiol Immunol Infect* 2020;3:371-372.
44. **Nitin Dhochak, Tanu Singhal, et al.** Pathophysiology of COVID-19: Why children fare better than adults? *Indian J Pediatr.*2020;7:537-546.
45. **Glowacka, et al.** Differential downregulation of ACE2 by spike proteins of severe acute respiratory syndrome coronavirus and human coronavirus NL63. *J Virol* 2010;84:1198-1205.
46. **Chilvers MA, Rutman A, O'Callagham C.** Functional analysis of cilia and ciliated epithelial ultrastructure in healthy children and young adults. *Thorax* 2003;58:333-338.
47. **Sadik Yurttutan, Hatice Guines, et al.** What chances do children have against COVID-19? Is the answer hidden within the thymus? *European Journal of Pediatrics* 2021;180:983-986.
48. **Pou C, Nkulikiyimfura D, et al.** The repertoire of maternal anti-viral antibodies in human newborns. *Nat Med.*2019;25:591-596.
49. **Kleinnijenhuis J, Van Crevel R, Netea MG.** Trained immunity: Consequenses for the heterologous effects of BCG vaccination. *Trans R Soc Trop med Hyg* 2015;109:29-35.
50. **Gasparyan AY, MIsra DP, et al.** Perspectives of immune therapy in coronavirus disease 2019. *J Korean Med Sc*i 2020;18:e176.
51. **Miller A, Reandelar MJ, et al.** Correlation between universal BCG vaccination policy and reduced morbidity and mortality for COVID-19: An epidemiological study. medRxiv 2020. doi: https://doi.org/10.1101/2020.03.24.20042937.
52. **Kleinnijenhuis J, Quintin J, et al.** Long-lasting effects of BCG vaccination on both heterologous Th1/Th17 responses and innate trained immunity. *J Innate Immun* 2014;6:152-158.
53. **Han MS, Choi EH, Chang, et al.** Clinical characteristics and viral RNA detection in children with coronavirus disease 2019 in the Republic of Korea. *JAMA Pediatr* 2021;175:73-80.
54. **Huibin LV, Nicholas C Wu, et al.** Cross-reactive antibody response between SARS-Co-V-2 and SARS-Co-V infections. *Cell Rep* 2020;9:107725.