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A NARRATIVE REVIEW ON SARS-COV-2 INFECTION IN PEDIATRICS: CONCERNS, CHALLENGES, MANAGEMENT, AND MITIGATION STRATEGIES

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Abstract:
The coronavirus disease (COVID-19) is a viral respiratory disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The COVID-19 infection in pediatric population has not been studied much because of the comparatively less number of cases among children during COVID-19 pandemic. As less number of cases in pediatric population has been documented, less is known about the epidemiology of virus among children. However, the other coronaviruses are comparatively more understood. As the SARS-CoV-2 has progressed, the mutations have been occurred and reported. The current study explores mutants' infection in infants and children, as well as concerns, problems, management, and mitigation measures based on therapeutic targets of the virus. The articles were searched using keywords (COVID-19 among children, SARS-CoV-2 infection among children, pediatric infections, coronavirus therapies for children, therapeutic management of hospitalized pediatric patients) from Google scholar, PubMed, Scopus, MDPI and Web of Science data bases. The most important outcomes and clinical features of viral infections in children and adolescents were studied. The current study also explores the rate of infection, clinical manifestations, clinical findings, and transmission dynamics for SARS-CoV-2 in children. Drug repositioning might be the sole answer to the outbreak of unexpected contagious illnesses because of the delayed mechanism of new drug expansion. The current review systematically compared the proteins expressed by the SARS-CoV-2 genes to those produced by other coronaviruses. This research will also provide novel lead compounds and targets for additional SARS-CoV-2 in both *in-vitro* and *in-vivo* investigations. The new insights for medications already in clinical trials, and possibly new drug repositioning techniques will be known to treat SARS-CoV-2 infections in more better ways.

Keywords: Children; Infants; Health concerns, Coronavirus, therapeutic targets, mutations.

1. Introduction

Before December 2019, there were six types of coronaviruses (CoVs) identified which were affecting humans and producing respiratory illnesses. The human coronavirus (HCoV)-HKU1, HCoV-229E, HCoV-OC43, HCoV-229E and HCoV-NL63 are coronaviruses that generally produce relatively moderate upper respiratory infections in newborns babies, and young children **[1].** Middle East respiratory syndrome (MERS) COVID-19 & SARS-CoV are more harmful, as they may affect the lower respiratory tracts and produce a serious breathing illness in people **[2,3].** Certain coronaviruses infect birds, bats, rodents, giraffes, whales, and a variety of more wild creatures, although they may too affect cattle, resulting in significant economic damage **[4,5].** Domestic animals may also serve as intermediary hosts, allowing viruses to spread from natural, wild animal hosts to human beings **[6,7].** Domestic animals may also be infected with bat-borne or nearly identical coronavirus infections. Bats have been shown to contain genomic series, which are extremely identical to the porcine epidemic diarrhea virus (PEDV). A HKU2-associated Bat-CoV, swine severe diarrhea syndrome CoV, generated a huge-scale pandemic of a viral in piglets in south China in 2016 that killed 24,000 piglets **[8].** This was the first time a Bat-CoV virus has been linked to a serious sickness in animals.
A latest strain of coronavirus was recognized in the lavage of the broncho alveoli samples of a patient with pneumonia of unidentified etiology in early January 2020 **[9].** To distinguish it from the SARS-CoV **[10]** and the Middle East respiratory syndrome coronavirus (MERS-CoV) **[11],** which were

accountable for two past outbreaks in 2002 and 2012, correspondingly **[12],** the new virus was initially named the novel coronavirus ("2019-nCoV") **[13,14].** The International Committee on taxonomy of viruses (ICTV) designated it as SARS-CoV-2, and the sickness connected with it was dubbed "2019 coronavirus disease" or COVID-19. The World Health Organization (WHO) declared the infectivity of epidemic on 11th March after the virus spread globally **[15].**

Since May 1st, 2020, there have been 3,519,901 cases recorded in 187 countries across the world excluding Antarctica, with 247,630 fatalities **[16].** Infants appear to be less impacted than adults; however, proof on the epidemiological characteristics and medical aspects of COVID-19 in infants are sparse and centered on restricted case reports **[17,18].** Approximately 2% of all individuals in a Chinese study of 72,314 cases were under the age of 19, but no medical findings details were provided **[19].** Italy was one of the initial country to be struck by the COVID-19 pandemic, accounting for 1.2% of all cases **[20].** Although the projected total case-mortality rates in Italy were greater than in China **[21],** no deaths in the infant age group were recorded, demonstrating that fatality remained low and that no particular risk factor has been discovered **[22].** Other multicenter study involving pediatric COVID-19 demonstrated the milder disease in children though having preexisting medical conditions were associated with longer hospitalization [14].

SARS-CoV-2 infections in newborns are likewise uncommon, and there has been no indication of intrauterine infections produced by vertical transmission **[23].** Amniotic fluids, cord blood, newborn throat swabs, and colostrum specimens that were taken from affected women were negative for SARS-CoV-2, according to a case report and case studies **[24].** Nevertheless, the issue remains controversial, since IgM antigens were found in neonates of COVID-19-positive women, even if the possibility of a false-positive should be considered. There is also a rising body of data that SARS-CoV-2 disease is linked to newborn pneumonia **[25].** In China, every newborn is isolated from the affected mothers for at least 14 days, whereas the center for disease control and prevention (CDC) recommends considering volatile isolation amidst the affected mother and the newborn on a case-by-case pattern, depending on mutual decision-making among the patients and the medical organization [26]. The current review offers a comprehensive and structured assessment of the existing medical literature on medical, laboratory, and radiological observations in infants and children infected with the virus.

1.1. Structure of SARS-CoV-2

This virus is related to beta coronavirus genus [3]. It comprises a ss, non-segmented RNA genome with positive charges, and the N-proteins of the nucleocapsid, the transmembrane (M) proteins, the envelope (E) proteins, and the spikes (S) proteins are the four key morphological proteins found in the viral genome (Figure 1). Nevertheless, the whole array of structural protein is not required for the formation of a full, contagious viral genome in certain coronaviruses; other proteins with overlapping compensatory roles may be expressed **[27,28].**

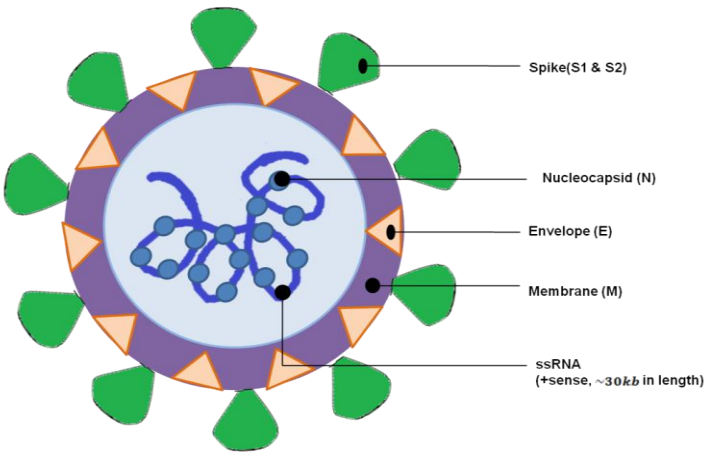

Figure 1. Pattern of SARS-CoV-2.

The N protein is the sole one that makes up the nucleocapsid and is accountable for attaching to the coronavirus RNA genomes [29]. These N proteins are engaged in viral genome-associated functions, but it also takes part in viral RNA replications plus the host's biological reaction to viral infections. The N protein distribution in the endoplasmic reticulum has a role in assembling and splitting [28]. Moreover, N proteins expression is demonstrated to promote the formation of virus-like structures in several coronaviruses. The host diversity of coronaviruses and the diversity of cell tropism are mostly due to changes in the S glycoprotein. The S glycoprotein is a kind 1 membrane glycoprotein containing operational regions at the amino (S1), carboxyl (S2) ends. S2 component is a trans-membrane protein that mediates the union of viral and tissue surfaces, whereas the S1 sub-layer is a surface protein involved in receptor binding **[30].** Generally, the S glycoprotein aids viral attachment to vulnerable tissues, promotes tissue merging, and triggers neutralizing antigens to be produced. S1 monoclonal antibody seems to arise more effectively of the two functional subunits including many antigenic sites, S1 and S2, since it has a greater degree of neutralizing ability **[31].** The coronavirus M protein is important in virus assembly because it converts cell layers into factories wherein viral and host components combine to generate unique virus particles. SARS-CoV-2, MERS-CoV, murine and hepatitis viruses (MHV), FCoV, A Golgi apparatus-targeting M protein is found in the infectious bronchitis virus (IBV), the transmissible gastroenteritis virus, and bovine coronaviruses. Reverse genetic research and virus-like protein (VLP) accumulation research proposes as to the M protein promotes accumulation by communicating among the viral ribonucleo proteins and S glycoprotein at the budding spot and forming a system of M-M relations that neglect a few host membrane proteins from the viral envelopes **[32].**

First supplement of the virus particle to the host tissue is started by communications among the S proteins and its receptors. Receptor binding domain (RBD) positions enclosed the S1 area of a COVID-19 S protein change based on the viruses. Several coronaviruses employ aminopeptidase N as its receptors to penetrate human tissue **[33].** Following receptor engagement, the virus should get entry to the cytoplasm of the host tissue. It is commonly done by a cathepsin, or alternate protease cleaving the S protein in an acid-reliant proteolytic response, succeeded by the union of the viral and tissue layers.

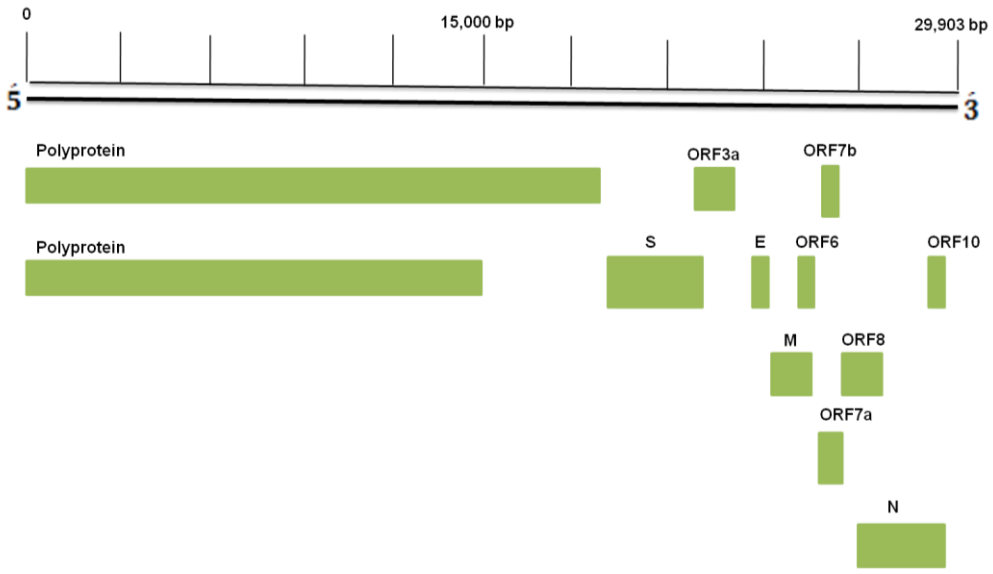

Figure 2. Genomic structure of SARS-CoV-2 [34]; ORF-Open Reading Frame, S-Spikes, E-Envelope, M-Membranes, N-Nucleocapsid.

Chan et al., (2020) **[35]** discovered that the new HCoV genome, taken from a cluster of people who suffered atypical pneumonia, shared nucleotides 89% with the bat SARS-likes CoVZXC21 virus and

bipedel SARS-CoV viruses in 82% of cases. It was given the name SARS-CoV-2 because of its single-strand RNA genome.

2. Diagnosis techniques of SARS-CoV-2

SARS-CoV-2 infections often misdiagnosed as influenza or any other seasonal virus of the upper respiratory tract **[36-38]**. Due to treatment options and containment requirements, a timely diagnosis is necessary. Fever, sore throat, cough, chest and muscular discomfort, dyspnea, disorientation, anosmia, and headache are all symptoms of COVID-19. The heart, kidney, liver, and neurological systems may all be affected, and the condition can worsen to the point of being life-threatening [37].

2.1. Clinical diagnosis

Fever, tiredness, dry cough, dyspnea, and other indications of SARS-CoV-2 infection might occur without or with runny noses, watery nose, or alternate upper respiratory signs **[39].** Flu-like symptoms, such as exhaustion, and trouble breathing, are experienced by the patients. The SARS-CoV-2 infection often results in deadly pneumonia in individuals in more severe instances. Fire fighters with post-traumatic stress disorder are more likely to have respiratory problems when they inhale smoke, according to earlier research **[40].**

2.1.1. Physical analysis

All through the pandemic duration of COVID-19 in China, the general population experienced moderate to severe psychological symptoms. Symptoms can be minor or severe, depending on the degree of COVID-19 symptoms. Few individuals may have any symptoms at all. Spreading the disease is possible even if you don't show any symptoms at all (asymptomatic transmission). Symptoms of a severe condition include difficulty breathing, wet coughing, diminished inhalation sounds, lack of dynamism in the sound, and tactile speech tremors may be enhanced or diminished. Muscle soreness, chills, sore throats, nosebleeds, headaches, chest pains, pink eye (conjunctivitis), nausea, vomiting, diarrhea, and rashes are all possible side effects. Warning sign in children are comparable to those in adults; however, they are usually less severe.

About a week after symptoms begin, some patients may notice worsening warning sign such as worsening shortness of breath and pneumonia. In addition, those with pre-existing therapeutic disorders may be great dangerous of developing a life-threatening disease. Tumor, chronic obstructive pulmonary diseases, diabetics (type 1 or type 2), and some considerable heart disorders, like cardiac failure, coronary artery diseases, cardiomyopathy, sickle thalassemia, chronic renal diseases, asthma, incurable lung disorders like cystic fibrosis, pulmonary hypertensions, liver diseases, Down syndromes, weakened immunity following bone marrow transplantations may raise the threat of grave sickness of COVID-19 **[41].**

2.2. Laboratory diagnosis

As compared to influenza virus, para-influenza virus, respiratory syncytial virus, rhinovirus, and other pneumonia viruses, the diagnosis of COVID-19 infections is quite different and advances. It must also be separated from non-contagious conditions **[42,43].** COVID-19 is identified initially by virus separation and viral nucleic acid testing. Viral separation is the "gold standard" for viral analysis in laboratories, in accordance. Nasal swab, oral swabs, nasopharyngeal swabs, oropharyngeal swabs, saliva, nasopharynx extractions, and lung tissues can be used for the accurate diagnosis of COVID-19 infection **[44,45].**

The greater essential aspect about viral nucleic acids is that they may be utilized for initial detection. As a result, we should look for SARS-CoV-2 nucleic acid. The ability to identify SARS-CoV-2 RNA accurately in timey manners is important **[46].** Also, there are now many kits available for gene sequence for SARS-CoV-2 that may be performed with real time reverse transcription polymerase chain reaction (RT-PCR), trying on persons suspected of having the COVID-19 infection **[47,48].**

Additionally, in the earlier stages of the illness the overall count of leukocytes drops or stays ordinary may also help out in confirming the diagnosis of COVID-19 [49].
Depending on the clinical picture of the suspected patients, local recommendations, and the availability of testing facility, the recommended laboratory tests for COVID-19 diagnosis in children varies [37]. Although, the reference standard test for the diagnosis of acute COVID-19 infection in symptomatic or asymptomatic children exposed to COVID-19 is a PCR test, many other antigen/antibody tests are available which might be less accurate and may need to be followed up, especially if a child has COVID-19-compatible symptoms or negative antigen test findings [37,38].
One of the better options for the early and accurate diagnosis of COVID-19 infection in children are use of antigen or antibody detection assays. But they need a high-quality sample with sufficient viral loads. They might be employed as a complement to qRT-PCR tests if the accuracy of lateral flow immunoassays using monoclonal anti-SARS-CoV-2 antibodies, which target SARS-CoV-2 antigens, is comparable to that of real-time RT-PCR assays. Although the first commercial assay for SARS-CoV-2-specific antigen testing was approved by the regulatory body in the middle of 2020, the market pressure brought on by the pandemic has led to the commercial availability of several more tests [37].

2.3. Radiological imaging examination

Because of the wide availability of diagnostic options, the modalities such as chest CT scan, X-rays and ultrasound are no longer used to assist with proper diagnosis. The patient's age, immune state, illness phase during scanning, critical disorders, and pharmacological treatments influences the imaging modality and results. COVID-19 may be diagnosed via a chest computed tomography (CT) scan. SARS-CoV-2 has been routinely detected using CT scans. In the preliminary screening, CT examination is needed for the auxiliary analysis This pandemic is often subjected to imaging tests as part of their first assessment. For example, a CT scan or a pulmonary ultrasound may be performed in addition to the chest X-ray (CXR). SARS-CoV-2 infection may be set up using any or all of these methods [50].

2.3.1. CXR examination

After being exposed to the illness, individuals with COVID-19 infection developed a lung infection, according to a clinical study of those who were infected. When it comes to identifying lung-related issues, a chest CXR is more helpful. Ground glass opacity (GGO) and patchy reticular opacities are common in non-ICU individuals, but impenetrable lung association are seen in ICU patients **[51].**
Small patchy shadows & interstitial abnormalities may be seen on chest CXR in the early stages of pneumonia episodes **[52],** especially in the lung periphery. In acute situations, pleural effusion is quite infrequent, however bilaterally multiple ground-glass opacity, infiltrate shadow, & lung aggregation may occur in these cases **[42].**

2.3.2. Chest CT scan

Bilateral lung region with GGO and segmental accumulation, especially in peripheral region of the lungs, are seen more strongly on CT than on X-ray scanning. Multiple lobar nodules in both lungs might well be observed in children with a severe illness. Three of twenty-one individuals with SARS-CoV-2 disease had ordinary CT images, 12 had ground-glass opacity alone, and 6 had an opacity of ground-glass with accumulation, according to a research of CT scans **[53,54].** On chest radiographs, 41 individuals with proven SARS-CoV-2 disease were shown to have bilateral lung engagement in another investigation**.** Generally, imaging results for COVID-19 are comparable to those for SARS **[55]** and MERS-CoV **[56],** which is not unexpected given that the viruses causative are coronaviruses.

3. SARS-CoV-2 mutant infection in pediatric population for COVID-19

The SARS-CoV-2-CHZJU sequencing identified from the infant is quite similar to existing strains [57]. On November 24, initially recorded to the “World Health Organization” (WHO). The WHO designated the strain as a variation of concern (VOC) and called it Omicron on November 26, 2021,

according to the advice of scientists from the WHO's technical advisory groups on SARS-CoV-2 Virus Evolution (TAG-VE). In correlation to the quadruple VOCs (Alpha, Beta, Gamma, and Delta), Omicron diversity had the fewest mutations, with 50 mutations dispersed over the genome. The spike protein in the Omicron variation has at least 32 mutations, which is double as often as the Delta variant **[29].**

This isolate differs from the fifty familiar strains by 0.08-0.10 percent in sequencing. Except for the orf1ab area that is extremely diverse in every SARS-CoV-2 strain globally, this isolate does not have many mutations. Alone pentamerous missense variants like S, ORF3a, E, M, and ORF8 were discovered, highly preserved area when contrasted to the reference sequence, and two of such variants namely S and ORF8 happen regularly in several SARS-CoV-2 isolates. The 24435C>A series differs from the one recovered from throat swabs. A missense A958D mutations in the S2 areas of S protein is caused by a mutation found in the feces. Since A958 interacts with R1014 of the adjacent helix, **[57]** anticipate that the A958D mutation would always result in the creation of a salt bridge among D958 and R1014, greatly improving the spike protein's functional properties. Because A958 is found on HR1 of the S2 sublayer, it probably influences tissue-tissue merging after viral connection to the host tissue receptors. They hypothesize that the novel A958D mutation could be an issue in SARS-protracted CoV-2's stay in the child's intestine without causing syndromes. SARS-CoV-2 thermostability is improved by the novel A958D mutation of the S protein, which may impact cell-cell merging following viral attachment to the host tissue receptors. In a genomic assessment of SARS-CoV-2 isolates, **[58]** found that virtually all of them had the D614G mutation in the S protein. When contrasted to other isolates in the GISAID dataset that revealed 10% predominance in Feb, 65 percent in Mar, and not reaching a relative predominance of 96 percent until Jun, the predominance of this mutation in the individuals earlier in the pandemic was especially striking. The D614G mutation has been linked to decreased CT numbers in vitro and in vivo, but not to infection intensity or case mortality proportions in samples from North America and Europe **[59].** The function of the D614G mutation in the virus pathogenicity is still a hot topic of research. While certain researches imply that such mutation shall enhance the risk of transmission, further research is needed **[60].** The mutation does not seem to be a key factor of disease intensity in this juvenile cohort, since it was found in all stages of infection, from asymptomatic to severe illness. Figure 3 shows the schematic representation of the D614G mutation.

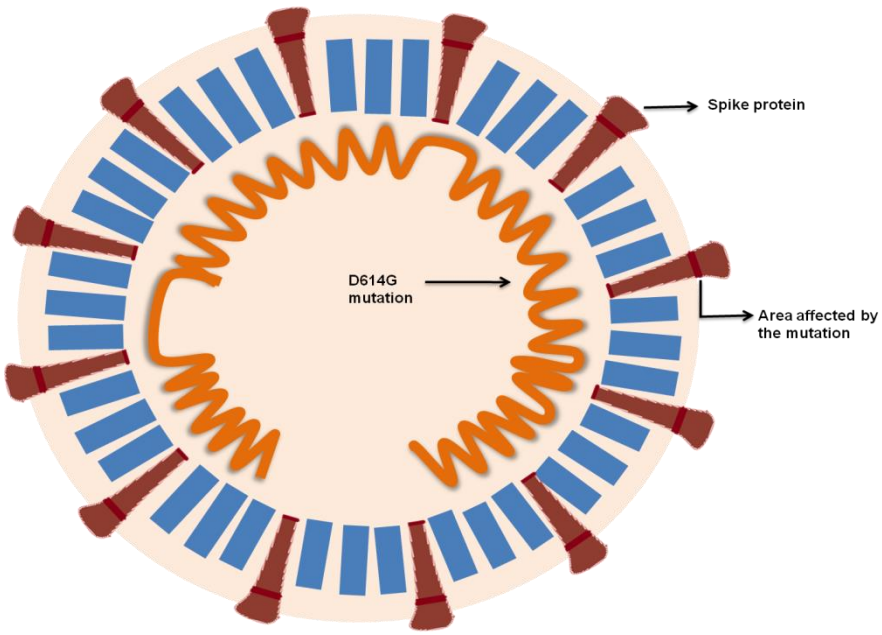

Figure 3. D614G mutation of SARS-CoV-2.

They also discovered two common mutations (F924F and P4715L) among the samples, as well as the D614G mutation **[61].** Nsp12, which is critical for viral replication, contains ORF1ab P4715L. P4715L and D614G mutations were shown to be affiliated with greater fatality rates in a study of approximately 12,400 SARS-CoV-2 genome series from 28 nations **[62].** The functional relevance of these alterations, however, has yet to be completely examined. Sequencing and correlation analyses of a larger number of juvenile COVID-19 instances would be required to verify these identified variants and get a greater comprehension of their potential implications.

4. Clinical Analysis and Epidemiology of SARS-CoV-2 in Infants

Infants are considered children from the time they are born when they become a year old. SARS-CoV-2 strains circulating in the preterm infants, when merged with demographic and clinical evidence, indicate that on average four lineages circulated widely in the pediatric community during the four COVID-19 waves. Children were also susceptible to SARS-CoV-2 in the society [63]. The epidemiology and medical aspects of SARS-CoV-2 illness must be updated regularly. However, most data come from adult patients, and many characteristics of the illness in youngsters are still unknown. According to multiple case studies **[64,65]**

Infants are less prone than adolescents to develop severe CoV-19 symptoms, with 95 percent of every case varying from asymptomatic to mild-moderate medical structures. Furthermore, just 2% of individuals were admitted to the Pediatric ICU or needed mechanical ventilation **[66].** Six fatalities were documented (mortality rate of 0.08%): the majority of patients suffered problems, including a premature infant who died of sepsis **[67].** About 2/3rd of individuals who died of CoV-19 in adulthood had co-morbidity, but around 20 percent of infants with underlying illness were detected, and nobody had a poor medical course of infection than earlier healthier individuals. The reduced death rate in children may be due to more than just epidemiological factors. Some researchers proposed a biological mechanism that might make youngsters less vulnerable to SARS-CoV-19 disease. The connections between the human coronavirus's trans-membrane S protein and particular tissue receptors of angiotensin-transforming enzyme II are critical for the virus's pathogenesis **[68].** Late infancy seems to be the optimal time for the production of this enzyme, according to new research **[48],** which may safeguard youngsters from the infection's most severe type.

Children, on the other hand, may not be tested for the virus as often as adolescents. Only symptomatic individuals are tested and centralized in most countries. We may assume that just a limited number of youngsters have been examined since they are usually asymptomatic and so confined to their homes. Furthermore, RT-polymerase chain reaction on respiratory tract samples is the current gold standard for identifying the virus. The analytical efficiency of the virus test might be limited by false virus-negative owing to lower rates of infection, especially in asymptomatic or minimally symptomatic individuals who potentially spread the illness **[69].** According to new findings from German research, viral loads in infants do not vary considerably from those in adolescents. It implies that, although infants are less likely to show symptoms, they shall be just as contagious as adolescents **[70].** COVID-19 spreads within families, according to much previous research. Initial data revealed that at the beginning and within & within family clusters, the degree of viral shedding varied, with adolescent individuals staying positive for an extended period **[58].** Further research with the viral genome included might be worthwhile.

4.1. Multisystem Inflammatory Syndrome in Children

Typically, COVID-19 in children is not severe. However, in some of the cases the children might sometimes be badly impacted by the infection, and their clinical symptoms could be different as compared to adults [71]. Incomplete Kawasaki disease (KD) or toxic shock syndrome-like presentations in children were were reported from the United Kingdom in April 2020. Since then, there have been reports of children in other countries who have been similarly impacted. This condition in children was called as multisystem inflammatory syndrome in children (MIS-C) which is basically an uncommon post COVID-19 complictaion characterized by systemic inflammation,

persistent fever, and multisystem organ dysfunction (MID). Primarily for shock and for vasopressor and inotropic support, majority of the children with MIS-C requires intensive care unit (ICU) care. The MIS-C may includes cardiac dysfunction (including myocarditis), thromboembolic events, acute kidney injuy and neurological involvments [72].

Children with COVID-19 or MIS-C should typically be treated according to the standard paediatric critical care standards. In reported cohorts of children with MIS-C, intravenous immunoglobulin (IVIG) and glucocorticoids are the two immunomodulatory drugs that are most often used. Initial diagnostic and therapeutic considerations for MIS-C have been defined by the American College of Rheumatology, and for the majority of hospitalised children with MIS-C, first-tier therapy is IVIG combined with glucocorticoids [73]. In comparison to front-line IVIG monotherapy, many nonrandomized trials show that front-line IVIG combined with glucocorticoids is linked with less treatment failure, quicker recovery of cardiac function, shorter stays in the ICU, and less need for treatment escalation. Based on these findings, the recommendations are to give IVIG together with low to moderate-dose glucocorticoids to children who are being treated with MIS-C in a hospital setting [74].

4.2. Clinical features

Fever and cough are frequent indications of acute respiratory infections. According to some writers, up to 1/3rd of symptomatic youngsters shall possess a higher temperature, although it is usually less than 39°C. Extra-respiratory syndromes are more frequent in infants than in adolescents **[75],** with diarrhea and vomiting being the most often identified symptoms. When present, gastrointestinal symptoms have been shown to predict the normal respiratory structure **[76].** Earlier research on SARS-CoV affected individuals found the virus in gut biopsy tissues and recovered individuals' faces, suggesting a potential gastrointestinal tract tropism that might help explain additional-respiratory syndromes and sustained viral shedding via the fecal-oral pathway **[77].** There is mounting proof that such excretion procedure is also common in this virus. The virus was still observed in rectal swabs after nasopharyngeal swabs were negative, according to a case study of 10 affected children **[78].**

An extrapulmonary finding of viral RNA could not always imply the existence of a contagious virus, however, two independent labs in China recently announced that they had profitably identified live 2019-nCoV from the feces of individuals. Furthermore, according to recent research, ACE2 was found in the upper esophageal region and absorptive enterocytes from the lower digestive tract **[79].** According to research, infants' clinical presentation differs somewhat from that of age infants, with a larger percentage of them presenting with an acute structure **[80].** Although the virus's vertical transmission has yet to be verified, Although the mother was infected in 84 percent of neonatal cases. Furthermore, nosocomial infection is a possibility, and careful precautions should be always taken to minimize this risk **[81].** 2019-nCoV infections or morbidities in infants might be connected to hypoxemia of the contaminated mother, which may increase the danger of perinatal adversity outcomes like natality hypoxia, early delivery. This assertion has yet to be backed up by any concrete proof.

4.2.1. Laboratory findings

Generally, no major anomalies were found, which matched the findings of a prior study with a entire sample strength of 66 infants with assured infections. The majority of those tested showed normal levels of whole blood cell count, with just 2 cases showing significant proportions of lymphopenia. This discovery, however, appears to be at odds with adolescent information, since fewer lymphocyte counts have been reported in up to 80 percent of affected crucially sick patients. The non-appearance of considerable lymphopenia in kids may be explained in segment by the small incidence of severe COVID-19 infections. The previous study showed that inflammatory indices might be aberrant in 1/3rd of infants with infections, although Henry et al., (2020) **[82]** reported just 10–13% of individuals with elevated CRP**.** The substantial variation in setting a cut-off of abnormal scores across every enclosed research possibly explains this divisive conclusion. In adolescents, however, a PCT score of

less than 0.5 ng/mL has been linked to a nearly fivefold increment in the probability of severe CoV-19 infection **[83].** Higher CPK levels and liver enzymes were two other notable laboratory investigations revealed 12.3%. During viral infections, these enzymes are often changed **[84].** Higher CPK degrees or aspartate aminotransferase activities were linked to more severe clinical structures in adolescent sufferers [85]. Abnormal transaminase degrees might be a symptom of direct liver injury. SARS-CoV-2 may cause direct injury to intrahepatic bile ducts, according to recently published findings that showed ACE-2 expression in cholangiocytes **[86].**

4.3. Radiology findings

Although, the accurate diagnostics are widely available now and modalities such as chest CT scan, X-rays and ultrasound are no longer used to assist with proper diagnosis, many of the previous studies have reported radiological manifestations after the radiological examination of children. Depending of the severity of infection, non-specific patchy peri-bronchial and peripheral opacity can be seen in the lungs of children even using chest X-rays which are comparatively less accurate than CT images **[87].** Because the pattern of illness among children is generally milder, the chest X-rays might not be able to detect specific nodules. But the chest X-rays can be used to see the radiological manifestations in new born babies. For the children with suspected COVID-19 infection, the commonly used method for radiological diagnosis is CT scan [88].

One of the previous studies have found 15% of asymptomatic infants with aberrant radiological manifestations. However, since the study was conducted on comparatively smaller population and then the radiological examination was done on case-to-case basis, this percentage of individuals may increase in studies with larger population. A ground-glass density nodule (GGN) was the most common identifiable nodules, with unilateral or bilateral propagation **[61].** In another study, more than one-third of asymptomatic children who went under CT scan diagnosis were found normal **[89]**. Data from the recent study suggested that the sensitivity of CT scan diagnostic technique for suspected COVID-19 individuals may be higher than that of RT-PCR in the diagnosis of infection **[90].** However, the use of CT scan routinely has many apparent side effects, particularly in the pediatric population, where the concerns about needless radiation exposure should be highlighted. As a result, different parallel diagnostic imaging or clinical laboratory techniques might be employed for timely diagnosis [37].

Lung ultrasound is favorably used in adolescents with COVID-19 infection **[89].** A recent case series from Italy reported the lung ultrasound observations in eight infants with COVID-19 infections. All of the patients had sub-pleural consolidation and confluent B-line, and the results were counter confirmed by chest X-rays and CT scan [21].

5. Treatment and mitigation strategies

The moderately or severely immunocompromised people (for example; children, old age people, cancer patients etc.) are at high risk of acquiring severe COVID-19 infection which may lead to the death. Additionally, comparing to the healthy people who are not immunocompromised, the COVID-19 vaccination immune response may not be too strong [17]. For an increased protection against COVID-19 variants and to help restoring the protection that has declined since the previous vaccination, the CDC advises individuals with the age of 12 or above to get a COVID-19 booster vaccine shot. The booster doses, (also known as bivalent boosters) target the original SARS-CoV-2 as well as the most current Omicron subvariants (BA.4 and BA.5) [91].

The CDC recommends Pfizer-BioNTech vaccine for 12-17 years old children with preferable 4 doses (second dose after 3 weeks of first dose, third dose after 4 weeks of second dose and fourth dose is after 2 months of third dose). Moderna is also recommended for 12-17 years old children with 4 doses (second dose after 4 weeks of first dose, third dose after 4 weeks of second dose and fourth dose is after 2 months of third dose). Novavax is recommended for 12-17 years old children with preferable 3 doses (second dose after 3 weeks of first dose, third dose after 2 months of second dose) [92].

The recommended vaccine for children of 6 months to 11 years of age are Pfizer-BioNTech and Moderna. For 5-11 years old children, the Pfizer-BioNTech have 4 doses (second dose after 3 weeks of first dose, third dose after 4 weeks of second dose and fourth dose is after 3 months of third dose), while 3 doses for children of age 6 months to 4 years (second dose after 3 weeks of first dose, third dose after 8 weeks of second dose). The Moderna have 3 doses of vaccine for children of age 6 months to 11 years (second dose after 4 weeks of first dose, third dose after 4 weeks of second dose) [92].
Symptomatic therapy is the basis of clinical management, including organ assistance in critical care for very unwell individuals **[93].** Bed rest and supportive treatments, such as anti-viral medication, antibiotic applications, immune-modulating therapies **[94],** organ function assistance, respiratory assistance, lavage of the bronchial tubes, blood purifications, and extracorporeal membrane oxygenation **[95],** are some of the general techniques which may also help out. Controlling the infection source, restricting the transmission pathway, and safeguarding vulnerable groups are all critical infection control measures. The WHO and other worldwide public health organizations have concentrated their unusual flurry of work on avoiding transmissions, infection preventive steps, and traveler screenings **[96].**
The children have been enrolled in a few registered clinical trial studies for COVID-19 experimental therapy **[97].** In the majority of cases, symptomatic therapy was employed alone, particularly in neonates. Only nebulized IFN and oral antiviral medications were recommended for pediatric patients, with CCS for complications and IVIg for acute conditions**.** None of these medicines has revealed a demonstrable advantage in the medication of the virus in children **[98]**. The table 1 has described the comparison of treatment options for COVID-19 positive children.

Table 1. Comparison of treatments for children who have been identified with SARS-CoV-2 infections.

S. no	References	N	Paediatric ICU	Ventilator	Noninvasive Oxygen	Symptomatic alone	Antiviral	Antibiotic	Intravenous immunoglobulin	corticosteroids	Interferon	Others
1	**[99]**	173	4	4	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified
2	**[70]**	31	1	1	1	1	21	1	1	1	1	1
3	**[100]**	1	1	1	3	3	1	1	1	1	1	1
4	**[101]**	3	1	1	1	3	1	1	1	1	1	1
5	**[45]**	5	2	3	2	1	7	1	2	5	1	1
6	**[54]**	6	1	1	1	1	3	3	6	1	3	4
7	**[102]**	22	1	1	1	1	13	14	3	1	13	2
8	**[103]**	2	1	1	1	2	1	1	1	1	1	1
9	**[104]**	0	1	1	1	1	2	1	1	2	1	1
10	**[105]**	9	1	1	1	6	1	6	1	1	1	1
11	**[106]**	32	1	1	1	33	1	1	1	1	1	1
12	**[107]**	3	1	1	1	3	1	1	1	1	1	1
13	**[108]**	8	1	1	1	10	1	1	1	1	1	1
14	**[109]**	2	1	1	1	0	1	1	1	1	3	1

5.1. Therapeutic treatments

RdRp inhibitor Remdesiviris a nucleoside analog. It has not yet been licensed for sale in any country and may block viruses by reducing viral nucleic acid production. Remdesivir showed promise in the therapy of the initial individual infected with a new coronavirus. For SARS-COV2 infections the EC50 of redelver in Vero E6 tissues is 0.77 mol/L, and the election index is larger than 12949.

Remdesivir was being tested in China in stage III clinical trial that was random, double-blind clinical trial.

Lopinavir and ritonavir are mostly utilized to administer HIV-1 infections in adolescents and infants over the age of two years. *In vitro* investigations have revealed that those drugs may limit the reproduction of SARS-CoV and MERS-CoV to provide anti-viral impacts. Darunavir is a protease inhibitor for HIV-1 infection, which avoids the production of mature contagious viral particles by restricting the division of HIV-encoded Gag-Pol polyproteins in virally affected tissues. Darunavir may strongly limit viral multiplication at a dose of 300 mol/L, with a 280-fold inhibition effectiveness compared to the untreated group. Flu is treated with favipiravir, which is a broad-spectrum antiviral medication. The Shenzhen Health Commission has begun clinical trials to see whether favipiravir can be employed to cure a viral infection or not. The docking values for favipiravir with the targets in the virtual screening are less **[19].** Apart from this monoclonal antibody therapy (combination bamlanivimab-etesevimab) for children younger than two years of age hospitalized with mild to moderate COVID-19 who are at risk of progression to severe disease can also be utilized [92].

5. Conclusions

The COVID-19 infection is milder in children as compare to the elderly population with the comparatively lower fatality rate and most of the children with COVID-19 infections are asymptomatic. Although the vertical transmission of COVID-19 in children is very rare, the probable or suspected cases of vertical transmission have been reported. The severity of COVID-19 infection in children may develops multisystem inflammatory syndrome. To further understand the potential consequences of COVID-19 infection in children, larger epidemiological and clinical cohort studies at national or international level are required.

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References

1. Saif, L.J.; Wang, Q.; Vlasova, A.N.; Jung, K.; Xiao, S. Coronaviruses. *Diseases of swine* **2019**, 488-523.
2. Chen, Y.; Liu, Q.; Guo, D. Emerging coronaviruses: genome structure, replication, and pathogenesis. *Journal of medical virology* **2020**, *92*, 418-423.
3. Ahmed, N.; Rizvi, A.; Naeem, A.; Saleem, W.; Ahmed, A.; Parveen, S.; Ilyas, M. COVID-19 and public awareness. *The Professional Medical Journal* **2020**, *27*, 1710-1716.
4. Suzuki, T.; Otake, Y.; Uchimoto, S.; Hasebe, A.; Goto, Y. Genomic characterization and phylogenetic classification of bovine coronaviruses through whole genome sequence analysis. *Viruses* **2020**, *12*, 183.
5. Ali, Z.; Jatoi, M.A.; Al-Wraikat, M.; Ahmed, N.; Li, J. Time to enhance immunity via functional foods and supplements: Hope for SARS-CoV-2 outbreak. *Altern. Ther. Health Med* **2021**, *27*, 30-44.
6. Cui, J.; Li, F.; Shi, Z.-L. Origin and evolution of pathogenic coronaviruses. *Nature reviews microbiology* **2019**, *17*, 181-192.
7. Song, R.; Han, B.; Song, M.; Wang, L.; Conlon, C.P.; Dong, T.; Tian, D.; Zhang, W.; Chen, Z.; Zhang, F. Clinical and epidemiological features of COVID-19 family clusters in Beijing, China. *Journal of Infection* **2020**, *81*, e26-e30.

8. Zhou, P.; Fan, H.; Lan, T.; Yang, X.-L.; Shi, W.-F.; Zhang, W.; Zhu, Y.; Zhang, Y.-W.; Xie, Q.-M.; Mani, S. Fatal swine acute diarrhoea syndrome caused by an HKU2-related coronavirus of bat origin. *Nature* **2018**, *556*, 255-258.
9. Li, Q.; Guan, X.; Wu, P.; Wang, X.; Zhou, L.; Tong, Y.; Ren, R.; Leung, K.S.; Lau, E.H.; Wong, J.Y. Early transmission dynamics in Wuhan, China, of novel coronavirus–infected pneumonia. *New England journal of medicine* **2020**.
10. Ren, L.-L.; Wang, Y.-M.; Wu, Z.-Q.; Xiang, Z.-C.; Guo, L.; Xu, T.; Jiang, Y.-Z.; Xiong, Y.; Li, Y.-J.; Li, X.-W. Identification of a novel coronavirus causing severe pneumonia in human: a descriptive study. *Chinese medical journal* **2020**, *133*, 1015-1024.
11. Al-Rabiaah, A.; Temsah, M.-H.; Al-Eyadhy, A.A.; Hasan, G.M.; Al-Zamil, F.; Al-Subaie, S.; Alsohime, F.; Jamal, A.; Alhaboob, A.; Al-Saadi, B. Middle East Respiratory Syndrome-Corona Virus (MERS-CoV) associated stress among medical students at a university teaching hospital in Saudi Arabia. *Journal of infection and public health* **2020**, *13*, 687-691.
12. Ashour, H.M.; Elkhatib, W.F.; Rahman, M.M.; Elshabrawy, H.A. Insights into the recent 2019 novel coronavirus (SARS-CoV-2) in light of past human coronavirus outbreaks. *Pathogens* **2020**, *9*, 186.
13. Zhu, N.; Zhang, D.; Wang, W.; Li, X.; Yang, B.; Song, J.; Zhao, X.; Huang, B.; Shi, W.; Lu, R. A novel coronavirus from patients with pneumonia in China, 2019. *New England journal of medicine* **2020**.
14. Almuzaini, Y.; Alsohime, F.; Subaie, S.A.; Temsah, M.H.; Alsofayan, Y.; Alamri, F.; Alahmari, A.; Alahdal, H.; Sonbol, H.; Almaghrabi, R.; et al. Clinical profiles associated with SARS-CoV-2 infection and complications from coronavirus disease-2019 in children from a national registry in Saudi Arabia. *Annals of thoracic medicine* **2021**, *16*, 280-286, doi:10.4103/atm.atm_709_20.
15. Liguoro, I.; Pilotto, C.; Bonanni, M.; Ferrari, M.E.; Pusiol, A.; Nocerino, A.; Vidal, E.; Cogo, P. SARS-COV-2 infection in children and newborns: a systematic review. *European journal of pediatrics* **2020**, *179*, 1029-1046.
16. Dong, E.; Du, H.; Gardner, L. An interactive web-based dashboard to track COVID-19 in real time. *The Lancet infectious diseases* **2020**, *20*, 533-534.
17. Alsohime, F.; Temsah, M.H.; Al-Nemri, A.M.; Somily, A.M.; Al-Subaie, S. COVID-19 infection prevalence in pediatric population: Etiology, clinical presentation, and outcome. *Journal of infection and public health* **2020**, *13*, 1791-1796, doi:10.1016/j.jiph.2020.10.008.
18. Senniyappan, M.; Garadi, S.; Deol, R. Impact of COVID-19 on Children: Indian Perspective and Concerns: Are we Sentient? *International Journal of Medicine and Public Health* **2021**, *11*.
19. Wu, Z.; McGoogan, J.M. 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*, 1239-1242.
20. Lambertini, M.; Toss, A.; Passaro, A.; Criscitiello, C.; Cremolini, C.; Cardone, C.; Loupakis, F.; Viscardi, G.; Meattini, I.; Dieci, M.V. Cancer care during the spread of coronavirus disease 2019 (COVID-19) in Italy: young oncologists' perspective. *ESMO open* **2020**, *5*, e000759.
21. Onder, G.; Rezza, G.; Brusaferro, S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. *Jama* **2020**, *323*, 1775-1776.

22. Eastin, C.; Eastin, T. Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in China: Dong Y, Mo X, Hu Y, et al. Pediatrics. 2020. *Journal of Emergency Medicine* **2020**, *58*, 712-713.
23. Schwartz, D.A. An analysis of 38 pregnant women with COVID-19, their newborn infants, and maternal-fetal transmission of SARS-CoV-2: maternal coronavirus infections and pregnancy outcomes. *Archives of pathology & laboratory medicine* **2020**, *144*, 799-805.
24. Peng, Z.; Wang, J.; Mo, Y.; Duan, W.; Xiang, G.; Yi, M.; Bao, L.; Shi, Y. Unlikely SARS-CoV-2 vertical transmission from mother to child: a case report. *Journal of infection and public health* **2020**, *13*, 818-820.
25. Zeng, L.; Xia, S.; Yuan, W.; Yan, K.; Xiao, F.; Shao, J.; Zhou, W. Neonatal early-onset infection with SARS-CoV-2 in 33 neonates born to mothers with COVID-19 in Wuhan, China. *JAMA pediatrics* **2020**, *174*, 722-725.
26. Openshaw, J.J.; Travassos, M.A. COVID-19 outbreaks in US immigrant detention centers: the urgent need to adopt CDC guidelines for prevention and evaluation. *Clinical Infectious Diseases* **2021**, *72*, 153-154.
27. Schoeman, D.; Fielding, B.C. Coronavirus envelope protein: current knowledge. *Virology journal* **2019**, *16*, 1-22.
28. Yusof, W.; Irekeola, A.A.; Wada, Y.; Engku Abd Rahman, E.N.S.; Ahmed, N.; Musa, N.; Khalid, M.F.; Rahman, Z.A.; Hassan, R.; Yusof, N.Y. A global mutational profile of SARS-CoV-2: a systematic review and meta-analysis of 368,316 COVID-19 patients. *Life* **2021**, *11*, 1224.
29. Tian, D.; Sun, Y.; Xu, H.; Ye, Q. The emergence and epidemic characteristics of the highly mutated SARS-CoV-2 Omicron variant. *Journal of Medical Virology* **2022**, *94*, 2376-2383.
30. Sevinc Temizkan, S.; Alkan, F. Bovine coronavirus infections in Turkey: molecular analysis of the full-length spike gene sequences of viruses from digestive and respiratory infections. *Archives of virology* **2021**, *166*, 2461-2468.
31. Huang, Y.; Yang, C.; Xu, X.-f.; Xu, W.; Liu, S.-w. Structural and functional properties of SARS-CoV-2 spike protein: potential antivirus drug development for COVID-19. *Acta Pharmacologica Sinica* **2020**, *41*, 1141-1149.
32. Cao, Y.; Yang, R.; Wang, W.; Jiang, S.; Yang, C.; Liu, N.; Dai, H.; Lee, I.; Meng, X.; Yuan, Z. Probing the formation, structure and free energy relationships of M protein dimers of SARS-CoV-2. *Computational and Structural Biotechnology Journal* **2022**, *20*, 573-582.
33. Wang, X.; Yao, H.; Xu, X.; Zhang, P.; Zhang, M.; Shao, J.; Xiao, Y.; Wang, H. Limits of detection of 6 approved RT–PCR kits for the novel SARS-Coronavirus-2 (SARS-CoV-2). *Clinical chemistry* **2020**, *66*, 977-979.
34. Hasöksüz, M.; Kilic, S.; Saraç, F. Coronaviruses and sars-cov-2. *Turkish journal of medical sciences* **2020**, *50*, 549-556.
35. Chan, J.F.-W.; Kok, K.-H.; Zhu, Z.; Chu, H.; To, K.K.-W.; Yuan, S.; Yuen, K.-Y. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. *Emerging microbes & infections* **2020**, *9*, 221-236.
36. Flerlage, T.; Boyd, D.F.; Meliopoulos, V.; Thomas, P.G.; Schultz-Cherry, S. Influenza virus and SARS-CoV-2: pathogenesis and host responses in the respiratory tract. *Nature Reviews Microbiology* **2021**, *19*, 425-441.

37. Ahmed, N.; Kalil, M.N.A.; Yusof, W.; Bakar, M.A.A.; Sjahid, A.S.; Hassan, R.; Fauzi, M.H.; Yean, C.Y. A Performance Assessment Study of Different Clinical Samples for Rapid COVID-19 Antigen Diagnosis Tests. *Diagnostics* **2022**, *12*, 847.
38. Kalil, M.N.A.; Yusof, W.; Ahmed, N.; Fauzi, M.H.; Bakar, M.A.A.; Sjahid, A.S.; Hassan, R.; Yean Yean, C. Performance Validation of COVID-19 Self-Conduct Buccal and Nasal Swabs RTK-Antigen Diagnostic Kit. *Diagnostics* **2021**, *11*, 2245.
39. Holshue, M.L.; DeBolt, C.; Lindquist, S.; Lofy, K.H.; Wiesman, J.; Bruce, H.; Spitters, C.; Ericson, K.; Wilkerson, S.; Tural, A. First case of 2019 novel coronavirus in the United States. *New England journal of medicine* **2020**.
40. Guan, W.-j.; Ni, Z.-y.; Hu, Y.; Liang, W.-h.; Ou, C.-q.; He, J.-x.; Liu, L.; Shan, H.; Lei, C.-l.; Hui, D.S. Clinical characteristics of 2019 novel coronavirus infection in China. *MedRxiv* **2020**.
41. Dai, M.; Liu, D.; Liu, M.; Zhou, F.; Li, G.; Chen, Z.; Zhang, Z.; You, H.; Wu, M.; Zheng, Q. Patients with Cancer Appear More Vulnerable to SARS-CoV-2: A Multicenter Study during the COVID-19 OutbreakPatients with Cancer in SARS-COV-2 Infection. *Cancer discovery* **2020**, *10*, 783-791.
42. Jin, Y.-H.; Cai, L.; Cheng, Z.-S.; Cheng, H.; Deng, T.; Fan, Y.-P.; Fang, C.; Huang, D.; Huang, L.-Q.; Huang, Q. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). *Military Medical Research* **2020**, *7*, 1-23.
43. Ahmed, N.; Khan, M.; Saleem, W.; Karobari, M.I.; Mohamed, R.N.; Heboyan, A.; Rabaan, A.A.; Mutair, A.A.; Alhumaid, S.; Alsadiq, S.A. Evaluation of bi-lateral co-infections and antibiotic resistance rates among COVID-19 patients. *Antibiotics* **2022**, *11*, 276.
44. Yang, D.; Leibowitz, J.L. The structure and functions of coronavirus genomic 3′ and 5′ ends. *Virus research* **2015**, *206*, 120-133.
45. Liu, W.; Zhang, Q.; Chen, J.; Xiang, R.; Song, H.; Shu, S.; Chen, L.; Liang, L.; Zhou, J.; You, L. Detection of Covid-19 in children in early January 2020 in Wuhan, China. *New England Journal of Medicine* **2020**, *382*, 1370-1371.
46. Yu, F.; Du, L.; Ojcius, D.M.; Pan, C.; Jiang, S. Measures for diagnosing and treating infections by a novel coronavirus responsible for a pneumonia outbreak originating in Wuhan, China. *Microbes and infection* **2020**, *22*, 74-79.
47. Corman, V.M.; Landt, O.; Kaiser, M.; Molenkamp, R.; Meijer, A.; Chu, D.K.; Bleicker, T.; Brünink, S.; Schneider, J.; Schmidt, M.L. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. *Eurosurveillance* **2020**, *25*, 2000045.
48. Mahmood, T.B.; Saha, A.; Hossan, M.I.; Mizan, S.; Arman, S.A.S.; Chowdhury, A.S. A next generation sequencing (NGS) analysis to reveal genomic and proteomic mutation landscapes of SARS-CoV-2 in South Asia. *Current research in microbial sciences* **2021**, *2*, 100065.
49. Anis, S.; Khan, M.M.; Ali, Z.; Khan, A.; Arsalan, H.M.; Naeem, S.; Saleem, I.; Qamar, S.; Khan, M.M.; Ahmad, A. Novel corona virus disease (COVID-19): An updated review on epidemiology, pathogenicity, clinical course, treatments, migrant health concerns and risk factors predictions. *Pak. J. Pharm. Sci* **2021**, *34*, 1807-1822.
50. Bonam, S.R.; Kotla, N.G.; Bohara, R.A.; Rochev, Y.; Webster, T.J.; Bayry, J. Potential immuno-nanomedicine strategies to fight COVID-19 like pulmonary infections. *Nano today* **2021**, *36*, 101051.

51. Chandra, T.B.; Verma, K.; Singh, B.K.; Jain, D.; Netam, S.S. Coronavirus disease (COVID-19) detection in chest X-ray images using majority voting based classifier ensemble. *Expert systems with applications* **2021**, *165*, 113909.
52. Huang, C.; Wang, Y.; Li, X.; Ren, L.; Zhao, J.; Hu, Y.; Zhang, L.; Fan, G.; Xu, J.; Gu, X. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The lancet* **2020**, *395*, 497-506.
53. Chung, M.; Bernheim, A.; Mei, X.; Zhang, N.; Huang, M.; Zeng, X.; Cui, J.; Xu, W.; Yang, Y.; Fayad, Z.A. CT imaging features of 2019 novel coronavirus (2019-nCoV). *Radiology* **2020**.
54. Li, W.; Cui, H.; Li, K.; Fang, Y.; Li, S. Chest computed tomography in children with COVID-19 respiratory infection. *Pediatric radiology* **2020**, *50*, 796-799.
55. Ooi, G.C.; Khong, P.L.; Müller, N.L.; Yiu, W.C.; Zhou, L.J.; Ho, J.C.; Lam, B.; Nicolaou, S.; Tsang, K.W. Severe acute respiratory syndrome: temporal lung changes at thin-section CT in 30 patients. *Radiology* **2004**, *230*, 836-844.
56. Das, K.M.; Lee, E.Y.; Enani, M.A.; AlJawder, S.E.; Singh, R.; Bashir, S.; Al-Nakshbandi, N.; AlDossari, K.; Larsson, S.G. CT correlation with outcomes in 15 patients with acute Middle East respiratory syndrome coronavirus. *American Journal of Roentgenology* **2015**, *204*, 736-742.
57. Yao, H.; Fu, J.; Shu, Q.; Chen, Z.; Wu, N.; Ye, S.; Wang, W.; Ni, Y.; Shang, S.; Li, W. The low contagiousness and new A958D mutation of SARS-CoV-2 in children: An observational cohort study. *International Journal of Infectious Diseases* **2021**, *111*, 347-353.
58. Pandey, U.; Yee, R.; Shen, L.; Judkins, A.R.; Bootwalla, M.; Ryutov, A.; Maglinte, D.T.; Ostrow, D.; Precit, M.; Biegel, J.A. High prevalence of SARS-CoV-2 genetic variation and D614G mutation in pediatric patients with COVID-19. In Proceedings of the Open Forum Infectious Diseases, 2021; p. ofaa551.
59. Plante, J.A.; Liu, Y.; Liu, J.; Xia, H.; Johnson, B.A.; Lokugamage, K.G.; Zhang, X.; Muruato, A.E.; Zou, J.; Fontes-Garfias, C.R. Spike mutation D614G alters SARS-CoV-2 fitness. *Nature* **2021**, *592*, 116-121.
60. Li, Q.; Wu, J.; Nie, J.; Zhang, L.; Hao, H.; Liu, S.; Zhao, C.; Zhang, Q.; Liu, H.; Nie, L. The impact of mutations in SARS-CoV-2 spike on viral infectivity and antigenicity. *Cell* **2020**, *182*, 1284-1294. e1289.
61. Koyama, T.; Platt, D.; Parida, L. Variant analysis of SARS-CoV-2 genomes. *Bulletin of the World Health Organization* **2020**, *98*, 495.
62. Toyoshima, Y.; Nemoto, K.; Matsumoto, S.; Nakamura, Y.; Kiyotani, K. SARS-CoV-2 genomic variations associated with mortality rate of COVID-19. *Journal of human genetics* **2020**, *65*, 1075-1082.
63. Alteri, C.; Scutari, R.; Costabile, V.; Colagrossi, L.; Yu La Rosa, K.; Agolini, E.; Lanari, V.; Chiurchiù, S.; Romani, L.; Markowich, A.H. Epidemiological characterization of SARS-CoV-2 variants in children over the four COVID-19 waves and correlation with clinical presentation. *Scientific reports* **2022**, *12*, 1-12.
64. Du, W.; Yu, J.; Wang, H.; Zhang, X.; Zhang, S.; Li, Q.; Zhang, Z. Clinical characteristics of COVID-19 in children compared with adults in Shandong Province, China. *Infection* **2020**, *48*, 445-452.
65. Coronavirus disease 2019 in children—United States, February 12–April 2, 2020. MMWR Morb Mortal Wkly Rep. Centers for Disease Control Prevention. . **2020**, *69*, 422-426.

66. Sun, D.; Li, H.; Lu, X.-X.; Xiao, H.; Ren, J.; Zhang, F.-R.; Liu, Z.-S. Clinical features of severe pediatric patients with coronavirus disease 2019 in Wuhan: a single center's observational study. *World Journal of Pediatrics* **2020**, *16*, 251-259.
67. Zhu, H.; Wang, L.; Fang, C.; Peng, S.; Zhang, L.; Chang, G.; Xia, S.; Zhou, W. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. *Translational pediatrics* **2020**, *9*, 51.
68. Wang, D.; Ju, X.; Xie, F.; Lu, Y.; Li, F.; Huang, H.; Fang, X.; Li, Y.; Wang, J.; Yi, B. Clinical analysis of 31 cases of 2019 novel coronavirus infection in children from six provinces (autonomous region) of northern China. *Zhonghua er ke za zhi* **2020**, 269-274.
69. Yang, R.; Gui, X.; Xiong, Y. Comparison of clinical characteristics of patients with asymptomatic vs symptomatic coronavirus disease 2019 in Wuhan, China. *JAMA network open* **2020**, *3*, e2010182-e2010182.
70. Jones, T.C.; Mühlemann, B.; Veith, T.; Biele, G.; Zuchowski, M.; Hofmann, J.; Stein, A.; Edelmann, A.; Corman, V.M.; Drosten, C. An analysis of SARS-CoV-2 viral load by patient age. *MedRxiv* **2020**.
71. Kim, M.M.; Murthy, S.; Goldman, R.D. Post–COVID-19 multisystem inflammatory syndrome in children. *Canadian Family Physician* **2021**, *67*, 594-596.
72. Loncharich, M.; Klusewitz, S.; Jones, O. Post-COVID-19 Multisystem Inflammatory Syndrome in Children and Adults: What Happens After Discharge? *Cureus* **2022**, *14*.
73. Merticariu, C.I.; Merticariu, M.; Cobzariu, C.; Mihai, M.M.; Dragomir, M.S. Pediatric inflammatory multisystem syndrome induced Panuveitis associated with SARS-CoV-2 infection: What the Ophthalmologists need to know. *Romanian Journal of Ophthalmology* **2022**, *66*, 198.
74. Brzyska, A.; Bogucka, J.; Bojarska, M.; Domańska, N. Manifestations of the pediatric multisystem inflammatory syndrome temporally related with SARS-CoV-2 (PIMS) in the gastrointestinal, cardiovascular, nervous and respiratory systems. *Journal of Education, Health and Sport* **2022**, *12*, 34-43.
75. Zimmermann, P.; Curtis, N. Coronavirus infections in children including COVID-19: an overview of the epidemiology, clinical features, diagnosis, treatment and prevention options in children. *The Pediatric infectious disease journal* **2020**, *39*, 355.
76. Gu, J.; Han, B.; Wang, J. COVID-19: gastrointestinal manifestations and potential fecal–oral transmission. *Gastroenterology* **2020**, *158*, 1518-1519.
77. Cimolai, N. Features of enteric disease from human coronaviruses: Implications for COVID-19. *Journal of Medical Virology* **2020**, *92*, 1834-1844.
78. Xu, Y.; Li, X.; Zhu, B.; Liang, H.; Fang, C.; Gong, Y.; Guo, Q.; Sun, X.; Zhao, D.; Shen, J. Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding. *Nature medicine* **2020**, *26*, 502-505.
79. Zhang, C.; Gu, J.; Chen, Q.; Deng, N.; Li, J.; Huang, L.; Zhou, X. Clinical characteristics of 34 children with coronavirus disease-2019 in the west of China: a multiple-center case series. *MedRxiv* **2020**.
80. Lu, Q.; Shi, Y. Coronavirus disease (COVID-19) and neonate: What neonatologist need to know. *Journal of medical virology* **2020**, *92*, 564-567.

81. Wang, L.; Shi, Y.; Xiao, T.; Fu, J.; Feng, X.; Mu, D.; Feng, Q.; Hei, M.; Hu, X.; Li, Z. Chinese expert consensus on the perinatal and neonatal management for the prevention and control of the 2019 novel coronavirus infection. *Annals of translational medicine* **2020**, *8*.
82. Henry, B.M.; Lippi, G.; Plebani, M. Laboratory abnormalities in children with novel coronavirus disease 2019. *Clinical Chemistry and Laboratory Medicine (CCLM)* **2020**, *58*, 1135-1138.
83. Sahu, K.K.; Cerny, J. A review on how to do hematology consults during COVID-19 pandemic. *Blood Reviews* **2021**, *47*, 100777.
84. Xiong, T.-Y.; Redwood, S.; Prendergast, B.; Chen, M. Coronaviruses and the cardiovascular system: acute and long-term implications. *European heart journal* **2020**.
85. Kordzadeh-Kermani, E.; Khalili, H.; Karimzadeh, I. Pathogenesis, clinical manifestations and complications of coronavirus disease 2019 (COVID-19). *Future microbiology* **2020**, *15*, 1287-1305.
86. Macias, A.E.; McElhaney, J.E.; Chaves, S.S.; Nealon, J.; Nunes, M.C.; Samson, S.I.; Seet, B.T.; Weinke, T.; Yu, H. The disease burden of influenza beyond respiratory illness. *Vaccine* **2021**, *39*, A6-A14.
87. Silverstein, W.K.; Stroud, L.; Cleghorn, G.E.; Leis, J.A. First imported case of 2019 novel coronavirus in Canada, presenting as mild pneumonia. *The Lancet* **2020**, *395*, 734.
88. Xia, W.; Shao, J.; Guo, Y.; Peng, X.; Li, Z.; Hu, D. Clinical and CT features in pediatric patients with COVID-19 infection: different points from adults. *Pediatric pulmonology* **2020**, *55*, 1169-1174.
89. Buonsenso, D.; Piano, A.; Raffaelli, F.; Bonadia, N.; Donati, K.D.G.; Franceschi, F. Novel coronavirus disease-19 pnemoniae: a case report and potential applications during COVID-19 outbreak. *Eur Rev Med Pharmacol Sci* **2020**, *24*, 2776-2780.
90. Fang, Y.; Zhang, H.; Xie, J.; Lin, M.; Ying, L.; Pang, P.; Ji, W. Sensitivity of chest CT for COVID-19: comparison to RT-PCR. *Radiology* **2020**.
91. Centers for Disease Control Prevention. Stay Up to Date with COVID-19 Vaccines Including Boosters. Accessed on: 15-09-2022. Available at: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/stay-up-to-date.html. **2022**.
92. Centers for Disease Control Prevention. COVID-19 Vaccines for People Who Are Moderately or Severely Immunocompromised. Accessed on: 18-09-2022. Available at: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/immuno.html. **2022**.
93. Raoult, D.; Zumla, A.; Locatelli, F.; Ippolito, G.; Kroemer, G. Coronavirus infections: Epidemiological, clinical and immunological features and hypotheses. *Cell stress* **2020**, *4*, 66.
94. Phua, J.; Weng, L.; Ling, L.; Egi, M.; Lim, C.-M.; Divatia, J.V.; Shrestha, B.R.; Arabi, Y.M.; Ng, J.; Gomersall, C.D. Intensive care management of coronavirus disease 2019 (COVID-19): challenges and recommendations. *The lancet respiratory medicine* **2020**, *8*, 506-517.
95. Chen, Z.-M.; Fu, J.-F.; Shu, Q.; Chen, Y.-H.; Hua, C.-Z.; Li, F.-B.; Lin, R.; Tang, L.-F.; Wang, T.-L.; Wang, W. Diagnosis and treatment recommendations for pediatric respiratory infection caused by the 2019 novel coronavirus. *World journal of pediatrics* **2020**, *16*, 240-246.
96. Zumla, A.; Hui, D.S.; Azhar, E.I.; Memish, Z.A.; Maeurer, M. Reducing mortality from 2019-nCoV: host-directed therapies should be an option. *The Lancet* **2020**, *395*, e35-e36.
97. Chiotos, K.; Hayes, M.; Kimberlin, D.W.; Jones, S.B.; James, S.H.; Pinninti, S.G.; Yarbrough, A.; Abzug, M.J.; MacBrayne, C.E.; Soma, V.L. Multicenter initial guidance on use of antivirals

for children with coronavirus disease 2019/severe acute respiratory syndrome coronavirus 2. *Journal of the Pediatric Infectious Diseases Society* **2020**, *9*, 701-715.

98. *World Health Organization. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: interim guidance. Accessed on 13 March 2020.*; 2020.
99. Lu, X.; Zhang, L.; Du, H.; Zhang, J.; Li, Y.Y.; Qu, J.; Zhang, W.; Wang, Y.; Bao, S.; Li, Y. SARS-CoV-2 infection in children. *New England Journal of Medicine* **2020**, *382*, 1663-1665.
100. Li, Y.; Guo, F.; Cao, Y.; Li, L.; Guo, Y. Insight into COVID-2019 for pediatricians. *Pediatric pulmonology* **2020**, *55*, E1-E4.
101. Salako, A.; Odubela, O.; Musari-Martins, T.; Ezemelue, P.; Gbaja-Biamila, T.; Opaneye, B.; James, A.; Oforomeh, O.; Osuolale, K.; Musa, A. Prevalence and Presentation of Paediatric Coronavirus Disease 2019 in Lagos, Nigeria. *International Journal of Pediatrics* **2021**, *2021*.
102. Zheng, F.; Liao, C.; Fan, Q.-h.; Chen, H.-b.; Zhao, X.-g.; Xie, Z.-g.; Li, X.-l.; Chen, C.-x.; Lu, X.-x.; Liu, Z.-s. Clinical characteristics of children with coronavirus disease 2019 in Hubei, China. *Current medical science* **2020**, *40*, 275-280.
103. Park, J.Y.; Han, M.S.; Park, K.U.; Kim, J.Y.; Choi, E.H. First pediatric case of coronavirus disease 2019 in Korea. *Journal of Korean medical science* **2020**, *35*.
104. Liu, Y.; Yang, Y.; Zhang, C.; Huang, F.; Wang, F.; Yuan, J.; Wang, Z.; Li, J.; Li, J.; Feng, C. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. *Science China Life Sciences* **2020**, *63*, 364-374.
105. Yu, X.; Sun, X.; Cui, P.; Pan, H.; Lin, S.; Han, R.; Jiang, C.; Fang, Q.; Kong, D.; Zhu, Y. Epidemiological and clinical characteristics of 333 confirmed cases with coronavirus disease 2019 in Shanghai, China. *Transboundary and emerging diseases* **2020**, *67*, 1697-1707.
106. Wang, Y.; Wang, Y.; Chen, Y.; Qin, Q. Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia (COVID-19) implicate special control measures. *Journal of medical virology* **2020**, *92*, 568-576.
107. Zhang, G.X.; Zhang, A.M.; Huang, L.; Cheng, L.Y.; Liu, Z.X.; Peng, X.L.; Wang, H.W. Twin girls infected with SARS-CoV-2. *Zhongguo dang dai er ke za zhi= Chinese journal of contemporary pediatrics* **2020**, *22*, 221-225.
108. Wei, M.; Yuan, J.; Liu, Y.; Fu, T.; Yu, X.; Zhang, Z.-J. Novel coronavirus infection in hospitalized infants under 1 year of age in China. *Jama* **2020**, *323*, 1313-1314.
109. Lou, M.X.X.; Shi, C.X.; Zhou, C.C.; Tian, M.Y.S. Three children who recovered from novel coronavirus 2019 pneumonia. *Journal of Paediatrics and Child Health* **2020**.