COVID-19: A Pediatric Update in Epidemiology, Management, Prevention, and Long-term Effects

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EDUCATION GAP

Coronavirus disease 2019 (COVID-19) has become an integral part of clinical care in both primary care and hospital-based care settings. Information related to COVID-19 has accumulated rapidly in the first 2 years of the pandemic (2020–2022), and pediatric providers should keep up with recent updates on the condition. In particular, pediatric providers should be familiar with the epidemiology and transmission of severe acute respiratory syndrome coronavirus 2, the virus that causes COVID-19, as well as the clinical manifestations of COVID-19, including acute COVID-19, multisystem inflammatory syndrome in children, and post-acute COVID-19 syndrome; management, including antiviral and anti-inflammatory therapies; and preventive measures, including immunization and transmission reduction measures.

OBJECTIVES *After completing this article, readers should be able to:*

1. Describe clinical manifestations of pediatric coronavirus disease 2019 (COVID-19), including acute COVID-19, multisystem inflammatory syndrome in children, and post-acute COVID-19 syndrome.
2. Discuss management of COVID-19, including antiviral and anti-inflammatory therapeutics in children.
3. Discuss preventive strategies against COVID-19 in children, including transmission reduction measures and vaccination.
4. Describe the epidemiology of COVID-19 in children.

ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic has significantly affected the lives of children in many ways, both directly and indirectly. Although severe acute respiratory syndrome coronavirus 2 infection and the resultant COVID-19 tend to be mild in children, they can be associated with severe manifestations, such as severe acute COVID-19 requiring hospitalization, especially in specific

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ABBREVIATIONS

CDC	Centers for Disease Control and Prevention
COVID-19	coronavirus disease 2019
EUA	emergency use authorization
FDA	Food and Drug Administration
IVIg	intravenous immunoglobulin
MIS-C	multisystem inflammatory syndrome in children
NIH	National Institutes of Health
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
WHO	World Health Organization

high-risk populations, or with the rare but serious complication of multisystem inflammatory syndrome in children. Therapeutic approaches were developed based on clinical trials and observational data, although evidence remains relatively scarce in children and the data are largely extrapolated from adult studies. In addition, studies have reported that post-acute COVID-19 conditions may be uncommon in children, although manifestations of long-term effects may be difficult to detect in children and are a subject of active study. The virus continues to evolve as the pandemic progresses, and a degree of protection against infection with previously developed immunity has been reported, but vaccines remain highly effective against severe outcomes such as hospitalization. In this article, we review pediatric aspects of COVID-19.

BACKGROUND

The coronavirus disease 2019 (COVID-19) pandemic has impacted the lives of children in many ways, both directly and indirectly. Two years into the pandemic in 2022, we have gained substantial knowledge about COVID-19 and its causative virus, known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). However, given the overwhelming amount of information, it has been challenging for clinicians to keep up with the literature. Although the breadth and depth of the long-term effects of COVID-19 on children are yet to be seen, from both biological and psychological perspectives, herein we review the current knowledge on pediatric aspects of COVID-19. We provide an update on the direct and indirect effects that the COVID-19 pandemic has had on children for the pediatric practitioner based on the available information as of 2022.

EPIDEMIOLOGY

After initial cases of pneumonia of unknown etiology were reported in Wuhan, China, in late 2019, a rapid investigation into the causative organism led to the identification of a betacoronavirus, later named SARS-CoV-2, as the cause of the pneumonia. (1) The epidemic of this virus soon spread to other continents, and the World Health Organization (WHO) declared a pandemic in March 2020. Initial reports of COVID-19 suggested disproportionate effects of the pandemic on adult populations, particularly older adults, and many lives were lost worldwide. Despite the early evidence of the frequent manifestations as a severe disease in adults, (2) children tended to have a milder disease, and children accounted for a small proportion of the total case counts reported. (3)(4) However, studies on household infection revealed that the incidence rate of SARS-CoV-2 infection in children was similar to that of adults, although a large proportion of infected children were asymptomatic. (5) Indeed, it has become clear that the case count of children was vastly underestimated, particularly in the early phase of the pandemic; some studies found that the actual number of infections may have been more than 10 times higher than the reported case counts, resulting from the lack of adequate virus detection testing. (6) Although asymptomatic cases predominated in children, most initial studies suggested that severe pediatric SARS-CoV-2 infection manifested in a bimodal distribution; infants (7) or adolescents were the populations more likely to experience severe acute COVID-19, (8) although there were some variations between studies. (9) Children with underlying conditions across age groups, however, also seemed to be more vulnerable to severe disease. (10)(11) In addition, there may be genetic host susceptibility factors that predispose individuals to severe COVID-19. (12)(13) In contrast, multicenter studies have shown that children with multisystem inflammatory syndrome (MIS-C, the severe hyperinflammatory syndrome occurring in children 2–6 weeks after infection with SARS-CoV-2) are less likely to have chronic medical conditions. (14)(15)

Viruses evolve while they circulate among hosts, and SARS-CoV-2 is no exception. Genetic sequence variants conferring amino acid changes that may result in increased infectivity started being reported by mid-2020. (16) By the end of 2020 to early 2021, the WHO designated viruses from certain phylogenetic lineages with specific amino acid changes as variants of concern. Some of the first ones included the Alpha (lineage B.1.1.7), Beta (lineage B.1.351), and Gamma (lineage P.1) variants. (17)(18)(19) New variants became dominant as they emerged, replacing previously circulating variants, (20) most likely related to the new variants' abilities to evade immune responses. (21) The Delta (lineage B.1.617.2) variant was first detected in late 2020, and then spread worldwide. (22) It was reported that the Delta variant was associated with increased severity of illness and transmissibility compared with the previous variants, (23)(24) but the studies were limited by their observational nature. Vaccine effectiveness against the Delta variant seemed to be maintained at the time, (25) with the real-world pediatric data demonstrating significant protection against severe acute COVID-19 in adolescents. (26) However, the Omicron (lineage B.1.1.529) variant emerged in late 2021, and its ability to escape from a broad range of neutralizing antibody responses raised concerns about control measures such as vaccines and monoclonal antibodies. (27) Indeed, vaccine effectiveness against infection was

reported to be noticeably decreased during the Omicron wave, (28) although, as discussed later in the Transmission Reduction and Prevention section, vaccines remain highly effective against severe outcomes such as hospitalization and death significantly in children. (29) Reinfection may be more common with the Omicron variant than with previous variants. (30) It has been reported that the Omicron variant infection may be associated with less severe disease than the Delta variant in children, (31)(32)(33) but the number of hospitalizations increased substantially due to the high overall number of infected children. (34) The SARS-CoV-2 virus is expected to evolve as it circulates in humans, and clinicians should be aware of the characteristics of the variants circulating in the community.

Soon after the pandemic onset, health disparities, which have existed for a long time, (35) became apparent in association with COVID-19, resulting in increased hospitalizations and mortality among adults categorized as belonging to racial and ethnic minorities. (36)(37) Similar disparities have been observed in children in various jurisdictions. (38)(39)(40) Questions as to whether certain groups of specific racial and ethnic minorities were more likely to test positive for SARS-CoV-2 and, therefore, be more likely to develop severe disease due to differences in the testing availability/likelihood or even prevalence of underlying conditions remain outstanding. Interestingly, in a study performed in Mississippi using seroprevalence as a denominator, cumulative incidence of MIS-C was 5 times higher and severe acute COVID-19 (requiring hospitalization) was 2 times higher among Black children compared with white children. (41) As discussed in the Transmission Reduction and Prevention section, understanding the epidemiology of these health disparities allows for targeted interventions. (42)

Diagnosis and Clinical Aspects

The diagnosis of SARS-CoV-2 infection can be made by tests that detect viral nucleic acid (nucleic acid amplification tests) or protein antigen, and either test may be negative earlier in the illness; moreover, testing for SARS-CoV-2 antibodies is not appropriate for the diagnosis of acute infection. (43) Up to half of children infected with SARS-CoV-2 may remain asymptomatic. (5) When present, signs and symptoms can be nonspecific, consisting of fever, cough, myalgia, sore throat, headache, malaise, and others. (44) Gastrointestinal signs and symptoms, such as diarrhea, vomiting, and abdominal pain, can also be seen, (45) occasionally without respiratory symptoms. (46) Olfactory dysfunction manifesting as the loss or alteration of smell and taste is a common complication among adults (47) and may be seen with different variants. (33) In children, the incidence of olfactory dysfunction was thought to be low at the beginning of the pandemic, (44) but a subsequent study with evaluation by otolaryngologists revealed that this complication was quite common among children, occurring in 86% by odor identification test and 68% by survey. (48) However, most of these children recovered from olfactory dysfunction by the end of the first month. (48) The apparently low prevalence of olfactory dysfunction observed at the beginning of the pandemic was likely because of the limited ability of children to recognize and report their symptoms. Pediatric providers should keep in mind that olfactory dysfunction can manifest as solid food aversion or refusal in infants and young children. (49) In infants, COVID-19 can be severe (50) and can manifest as bronchiolitis, (51) apnea, (52) croup, (53) and fever without a source. (54)

Overall, severe acute COVID-19 is relatively uncommon, especially in younger children. It has been estimated that the overall incidence of severe disease, defined in a study as the presence of ICU hospitalization, invasive mechanical ventilation, or death, was 12 per 100,000 children in the United States. (11) As referenced previously herein, children with underlying disorders, such as chronic lung disease, neurologic disorders, cardiovascular diseases, and prematurity in those younger than 2 years and tube feeding dependence, diabetes, and obesity in those 2 years and older, are at higher risk for severe disease. (11) Life-threatening complications of COVID-19 in children are comparable with those of another vaccine-preventable disease, influenza. (55) Although uncommon, death can occur in the setting of COVID-19 in children. A study conducted in Brazil between March 2020 and October 2021 reported 2,424 deaths among 33,991 children and adolescents aged 0 to 19 years with COVID-19. (56) Another multinational study reported that mortality was associated with cardiac and pulmonary comorbidities, admission hypoxemia, and lower respiratory tract symptoms. (57) As of mid-2022, it has been estimated that up to 0.03% of children with COVID-19 may have died in the United States, (58) and a study from the United Kingdom suggested that excess mortality from COVID-19 may not be substantial in children. (59) Cardiovascular manifestations such as myocarditis, (60) ST-segment elevation myocardial infarction, (61) and pericarditis (62) have been reported but with low incidence. Neurologic manifestations have been reported to be common, and a case series that included a large number of children reported that 22% had neurologic involvement, with fatigue/weakness, altered awareness or confusion, and headache being the most

common signs and symptoms. (63) Although most neurologic complications are transient, life-threatening conditions can occur in a small number of children, including stroke, severe encephalopathy, demyelination, Guillain-Barré syndrome, and cerebral edema. (63)

MIS-C is an important complication associated with COVID-19. The Centers for Disease Control and Prevention (CDC) defines MIS-C as a febrile (temperature, ≥100.4°F [≥38°C]) and clinically severe illness requiring hospitalization (or resulting in death) with evidence of systemic inflammation (C-reactive protein level, ≥3.0 mg/dL [≥30 mg/L]) and multisystem (≥2) organ involvement (cardiac, mucocutaneous, hematologic, or gastrointestinal involvement or shock) with no alternative plausible diagnosis. A suspected MIS-C case would be categorized as confirmed when evidence of current or recent SARS-CoV-2 infection is present and as probable when epidemiologic linkage is present. (64) Age younger than 21 years is a criterion for MIS-C, although similar illness has been reported in adults. (65) Although laboratory testing can aid the diagnosis by documenting multiorgan involvement, no specific marker for this condition has been identified. Acute-phase reactants such as C-reactive protein and ferritin, blood cell count abnormalities such as lymphopenia, and other factors, including B-type natriuretic peptide and D-dimers, can be helpful in approaching the diagnosis. (66) At the beginning of the pandemic, MIS-C was described as a Kawasaki disease–like condition. (67)(68)(69) In a large case series that included children with current or past evidence of SARS-CoV-2 infection presenting with multiorgan involvement in the United States, 40% of patients included in the analysis had features of Kawasaki disease, and coronary artery aneurysms were observed in 8% of patients. (70) However, gastrointestinal, cardiovascular, and respiratory manifestations were common, (70) which are generally not prominent in Kawasaki disease. MIS-C can be associated with mortality in up to 1% to 2% of patients. (71)(72) Thus, early signs of severe COVID-19 or MIS-C should not be overlooked, although it remains a diagnosis of exclusion. Clear risk factors for the development of this rare syndrome remain elusive. (73) In the beginning of the pandemic, the incidence of MIS-C was estimated to be 2 per 100,000 persons younger than 21 years of age, (74) but the incidence has varied over time and by variant. (75)(76) Indeed, CDC data suggest that in the United States there has been a decrease in MIS-C incidence after the onset of the Omicron variant surge. (77) It remains unclear what factors predispose children to this rare condition: whether the contribution of immunity developed at this point in the pandemic or whether variants, or other environmental or genetic factors, (73)(78) are at play for MIS-C incidence remains an area requiring further investigation.

Management

Once a child is suspected of or diagnosed as having COVID-19, supportive care should be provided. If the child has underlying at-risk conditions, such as those that result in immunosuppression, or if the child has severe COVID-19, then treatment could be considered. However, most of the clinical trials on COVID-19 therapeutics to date have focused on adult patients, and the therapeutic approaches for children have largely been extrapolated from the adult data.

Although most children without underlying conditions recover from COVID-19 with supportive care only, patients with high-risk conditions can benefit from antiviral therapy even when the illness is mild to moderate without requirement for hospitalization for COVID-19 (Table 1). Early in the course of COVID-19 illness, the virus is supposedly actively replicating, and antiviral agents that can inhibit the replication can alter the disease course. As of mid-2022, ritonavir-boosted nirmatrelvir is considered a first-line oral antiviral therapy in this setting. (79) In a phase 2/3 double-blind randomized controlled trial enrolling unvaccinated and nonhospitalized high-risk patients, the risk of progression to severe COVID-19 leading to hospitalization or death was 89% lower in the treatment group compared with the placebo group. (80) However, the trial enrolled individuals 18 years and older, and whether similar efficacy is promised in children is unknown. Emergency use authorization (EUA) was granted for treating individuals as young as 12 years old weighing 88 lb (40 kg) or more, (81) although future pediatric trials may result in the availability of this agent to more children. Because ritonavir is a strong CYP3A4 inhibitor (classically used as a booster agent for protease inhibitors in anti–human immunodeficiency virus therapeutic regimens), the potential for serious drug interactions should be carefully evaluated (https://www.covid19-druginteractions.org/checker). Particular caution is necessary when the patient takes anticonvulsants such as carbamazepine, antiarrhythmic agents such as amiodarone, or lipid-lowering agents such as lovastatin. In addition, dosing adjustment is necessary in the setting of renal impairment. Note that nirmatrelvir-ritonavir has not been extensively tested in pregnant women, although its use is being endorsed by the National Institutes of Health (NIH) guideline given the substantial risk of severe disease in this population and the theoretical safety of the medicine. (79)(82) Caution and shared decision making regarding the use of ritonavir-

Table 1. Pharmacologic Treatment for Acute Coronavirus Disease 2019

INDICATION AND AGENT	COMMENTS
Mild to moderate (no oxygen requirement)	
Nirmatrelvir-ritonavir	High-risk patients[a] aged ≥12 y Drug interaction needs to be checked Start within 5 d of symptom onset Dose adjustment necessary for kidney impairment Treatment duration is 5 d
Remdesivir	High-risk patients[a] aged ≥28 d Intravenous formulation only Start within 7 d of symptom onset Treatment duration is 3 d
Molnupiravir	High-risk patients[a] aged ≥18 y Contraindicated in pregnant or breastfeeding women Start within 5 d of symptom onset Treatment duration is 5 d Less preferred compared with nirmatrelvir-ritonavir and remdesivir
Severe (requiring hospitalization and oxygen)	
Dexamethasone	Consider whether respiratory support is needed, including: Supplemental oxygen High-flow oxygen Noninvasive ventilation Mechanical ventilation Extracorporeal membrane oxygenation No randomized trials showing benefit in children; consider consultation with experts Treatment duration is up to 10 d or until discharge
Remdesivir	May consider if respiratory support is needed, including: Supplemental oxygen High-flow oxygen Noninvasive ventilation No randomized trials showing benefit in children; consider consultation with experts Treatment duration is up to 5 d or until discharge
Tocilizumab or baricitinib	May consider if condition worsens rapidly while taking dexamethasone for severe infection as above (age ≥2 y) No randomized trials showing benefit in children; consider consultation with experts

For the most up-to-date information, visit https://www.covid19treatmentguidelines.nih.gov/.
[a]High-risk conditions may include moderately or severely immunocompromised status; obesity (BMI ≥95th percentile for age); dependence on respiratory technology; severe neurologic, genetic, metabolic, or other disabilities resulting in impairing airway clearance or limitations in activities of daily living; severe asthma or other severe chronic lung disease requiring 2 or more inhaled or 1 or more systemic medications daily; severe congenital or acquired heart disease; or multiple moderate to severe chronic diseases.

boosted nirmatrelvir during pregnancy should be noted, and benefits and risks should also be discussed in breastfeeding women due to the relative lack of data on the use of ritonavir-boosted nirmatrelvir in this patient population. (83) Remdesivir was used primarily for the treatment of severe COVID-19 in the hospital earlier in the pandemic, but a randomized study involving nonhospitalized patients with mild to moderate COVID-19 showed that a 3-day course of intravenous remdesivir was efficacious against progression of the disease with 87% risk reduction. (84) Although this is promising because remdesivir is the only therapeutic agent with Food and Drug Administration (FDA) approval and it can be used in children as young as 28 days old, the need for administration via an intravenous route for 3 consecutive days limits its use for this purpose substantially. In addition, the same considerations for pregnant and breastfeeding women apply for remdesivir in terms of shared treatment decisions due to relative lack of data on use of remdesivir in this population, which must be weighed against potential clinical benefit. (83) To date, several monoclonal antibodies have been used clinically, although the emergence of variants of SARS-CoV-2 with alterations in the antigenic sites has resulted in these monoclonal antibodies losing their effectiveness. Overall, the anticipated effect of monoclonal antibody therapy is particularly vulnerable to alterations of the antigenic site associated with viral evolution. A combination of bamlanivimab and etesevimab, monoclonal neutralizing antibodies that bind to the SARS-CoV-2 S protein, was associated with better clinical outcomes when given to patients with mild to moderate COVID-19 early in the course of infection, according to a randomized controlled study conducted in mid-2020. (85) However, as the virus acquired sequence variants resulting in altered antigenic sites, in vitro activity decreased substantially, (86) and the EUA for bamlanivimab and etesevimab was revoked in early 2021.

Similarly, casirivimab-imdevimab, sotrovimab, and bebtelovimab lost their EUAs as new variants emerged; as a result, there is no therapeutic monoclonal antibody that is in clinical use at the time of writing this article. Molnupiravir is another oral antiviral agent with activity against SARS-CoV-2. In a phase 3 clinical trial with 1,433 adult participants with mild to moderate COVID-19, administration of molnupiravir reduced the rate of hospitalization or death by 30%. (87) Note that pregnancy is a contraindication to this agent due to animal studies showing teratogenicity, and a pregnancy test needs to be performed before treatment in women of childbearing age. It is also recommended that women should not breastfeed during treatment and for 4 days after the last dose is taken. In addition, this agent is available only for patients 18 years and older at this time. (88) All of the previously mentioned antiviral agents are expected to work best at the phase of active viral replication and should be given as early in the course as possible. In particular, the EUAs for ritonavir-boosted nirmatrelvir and molnupiravir specify that these agents are to be taken within 5 days of symptom onset. (81)(88) Remdesivir should be given within 7 days of symptom onset for the purpose of preventing progression to severe disease. On the other hand, corticosteroids, azithromycin, ivermectin, hydroxychloroquine, and selective serotonin reuptake inhibitors should not be routinely used to treat COVID-19 in outpatient settings. (79)

In severely ill patients requiring hospitalization with supplemental oxygen, dexamethasone is generally included in the treatment regimen based on a randomized controlled trial of adults with severe COVID-19 requiring respiratory support. (89) Although its efficacy has not been shown in children, corticosteroids are often used in children by extrapolating the adult data (Table 1). No benefit was seen among adults not receiving respiratory support in the study, and the routine use of corticosteroids is not recommended for hospitalized patients who do not need respiratory support. The use of interleukin-6 receptor antagonists (tocilizumab and sarilumab) in addition to dexamethasone can further improve outcomes in critically ill patients requiring respiratory or cardiovascular organ support. (90) Baricitinib, a Janus kinase inhibitor, has been associated with shorter time to recovery when used with remdesivir. (89) When a patient shows clinical worsening despite the use of dexamethasone, these agents can be considered. Remdesivir has been associated with shorter time to recovery in adults hospitalized with COVID-19 and evidence of lower respiratory tract infection. (89) However, the WHO Solidarity trial did not show benefit of remdesivir. (91) Based on this trial, the WHO has made a conditional recommendation against the use of remdesivir in clinical settings, although the NIH (https://www.covid19treatmentguidelines.nih.gov/) and the Infectious Diseases Society of America (https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/) guidelines list remdesivir as an option in hospitalized patients with COVID-19 requiring respiratory support without the need for mechanical ventilation or extracorporeal membrane oxygenation. (79) Although the risk of thrombosis associated with COVID-19 is well established in adults, (92) and anticoagulation can be recommended depending on clinical information, (93) prophylactic approaches for venous thrombosis in the setting of COVID-19 have not been standardized in children, and close monitoring and a case-by-case approach are necessary.

In contrast to the amount of evidence available for the management of acute COVID-19 (although mostly extrapolated from adult data), the treatment of children with MIS-C, a serious condition associated with COVID-19, continues to rely on low-quality data. Because of the apparent similarity between MIS-C and Kawasaki disease, intravenous immunoglobulin (IVIg) has been commonly used for the treatment of MIS-C since early in the pandemic despite the lack of clinical evidence. (94) A retrospective cohort study from France reported less frequent treatment failure in children treated with a combination of IVIg and corticosteroids compared with IVIg alone, (95) and a study from the United States reported that a combination of IVIg and corticosteroids was associated with a lower risk of new or persistent cardiovascular dysfunction than IVIg monotherapy. (96) A systematic review and meta-analysis of this clinical question supported the findings. (97) In addition, another retrospective cohort study from the United States with propensity score adjustment reported similar rates of treatment failure in patients treated with corticosteroids alone compared with a combination therapy of IVIg and corticosteroids, suggesting that corticosteroid monotherapy may be reasonable at least in a subset of patients. (98) On the other hand, an international retrospective cohort study found no significant differences in these therapies in MIS-C outcome. (99) Based on the total evidence, the NIH guidelines recommend against IVIg monotherapy for the initial treatment of MIS-C, and corticosteroid therapy is to be included in the initial regimen unless there is a contraindication. Providers should keep in mind that no randomized controlled study has been conducted on this topic, and evidence remains inconclusive overall. Evidence regarding options for children who do not improve with initial treatment is even more scarce. Possible treatments may include other immunomodulatory treatments, for both severe acute

COVID-19 and MIS-C (79)(100); however, there are limited data on the use of these treatments, and NIH guidelines highlight this point in their recommendations. Longer-term follow-up for children treated with these modalities also should be considered.

Long-term Effects of COVID-19

Although the acute illness and mortality associated with COVID-19 were the initial focus of public interest and scientific investigations, it soon became apparent that COVID-19 was not always a short-lived, self-limited disease such as common respiratory virus infections. A cohort study conducted in April and May 2020 in Italy enrolling 179 adult participants requiring hospitalization reported that 87.4% of patients complained of persistence of at least 1 symptom, including fatigue, dyspnea, joint pain, chest pain, cough, and anosmia. (101) Although it is now well-accepted that a certain number of patients who survived COVID-19 have persistent symptoms, there has been no clear consensus on the definition of the condition. A panel of scientific experts has defined *post-acute COVID-19 syndrome* as persistent symptoms and/or delayed or long-term complications of SARS-CoV-2 infection beyond 4 weeks from the onset of symptoms. (102) The CDC uses *post-COVID conditions* as an umbrella term for a wide range of health consequences affecting neurologic, cardiopulmonary, digestive, and other systems that are present 4 or more weeks after infection with SARS-CoV-2. (103) The WHO also calls this condition *post–COVID-19 condition*, and the definition is similar but at least 2 months of symptoms are required. (104) This disease entity has also been called *long-COVID, long-haul COVID,* and *chronic COVID,* among other terms, and these terms are generally used interchangeably. The estimate of the prevalence varies by study approaches, settings, and the case definition used in the study, but more than 50% of adult patients hospitalized for COVID-19 are estimated to meet the previously mentioned criteria for persistent symptoms. (105)(106)(107) Persistent symptoms are common even in patients with COVID-19 not requiring hospitalization, with approximately one-third of the adult patients reporting to have not returned to their usual state of health 2 to 3 weeks after having a positive test result. (108) Risk factors for post-COVID conditions have not been well-defined, but an increased number of symptoms during the first week of illness has been associated with persistent symptoms. (109) Another study reported that type 2 diabetes, SARS-CoV-2 virus viremia, Epstein-Barr virus viremia, and specific autoantibodies were associated with post-acute sequelae of COVID-19. (110) However, the mechanism of the disease remains unknown.

As in adults, a certain number of children have persistent symptoms. Less is known about the condition in children compared with adults, but evidence is accumulating. A study from the United Kingdom enrolling children aged 11 to 17 years in early 2021 reported that children testing positive for SARS-CoV-2 with or without symptoms were more likely to have symptoms 3 months after infection compared with the control group with negative test results. (111) On the other hand, a retrospective study from Germany of children younger than 18 years who had COVID-19 between late 2020 and mid-2021 reported a low prevalence (1.7%) of post–COVID-19 conditions. (112) Similarly, 4% and 2% of SARS-CoV-2 seropositive and seronegative children, respectively, were reported to have at least 1 symptom lasting beyond 12 weeks, suggesting low prevalence compared with baseline. (113) Another study from the United States reported higher overall prevalence of symptoms after COVID-19 testing, but the rates were similar between test-positive and -negative children. (114) A study using a large medical claims database reported that children with a history of COVID-19 were more likely to have diagnoses of pulmonary embolism, myocarditis, venous thrombosis, renal failure, and type 1 diabetes, although these conditions were rare. (115) A systematic review found that many published studies reported a relatively short duration of symptoms (in most cases shorter than 8–12 weeks) but acknowledged that most studies had substantial limitations. (116) Similar observations had been made early in the pandemic in patients who had MIS-C that few organ-specific sequelae were observed at 6 months. (117) These findings on MIS-C seemed to be corroborated by subsequent publications, (118)(119) unless there were aneurysms present, which dictated the need for more intensive monitoring and follow-up. (120) Also, a large cohort study of children in the United States reported that at least a quarter of children hospitalized with acute COVID-19 or MIS-C experienced persistent symptoms or activity impairment for at least 2 months. (121) The American Academy of Pediatrics outlines specific guidelines for return to activity and sports for children who have had varying degrees of COVID-19 and MIS-C. (122) Although there are variable reports on the prevalence of post–COVID-19 conditions in children, (123) clinicians should keep in mind that children may not be able to express what they are experiencing, unlike adults, and there will most likely be

variations in persistent symptom presentation among individuals. A single-center case series reported on 9 pediatric patients (age range, 11–17 years) who presented with persistent and debilitating dizziness after COVID-19. (124) Some of these patients met the criteria for postural orthostatic tachycardia syndrome, but the etiology of their dysautonomia was unclear besides the history of COVID-19. A child's ability to cope with such prolonged symptoms is likely to be quite different from that of an adult, and persistent symptoms may have profound implications for a child's development and academic success. Thus, post–COVID-19 conditions in children should continue to be a focus of research considering the potentially debilitating illness that can ensue.

There are other aspects of long-term effects of COVID-19 specific to children. Children require support of the adult caregivers for their survival and well-being, and the large number of deaths in adults translates into the loss of supportive adults for the children. It has been estimated that 5.2 million children may have lost a parent or a caregiver in the first 20 months of the pandemic, (125) and this number will predictably increase as the pandemic continues, rising to more than 10 million of such children by mid-2022. (57) The potential long-term psychological effects of the loss of their loved ones are enormous given that many children are already experiencing psychological effects of the pandemic. (126)(127) Pediatricians should carefully evaluate children for signs of psychological distress. The psychosocial effects of the deaths of surrounding adults on children require long-term follow-up. The nonpharmacologic interventions against the COVID-19 outbreaks, including the closure of schools and businesses, were essential preventive measures in the beginning of the pandemic, but they were accompanied by decreased physical activities, (128) and an increase in the BMI of children has been reported, which can take a long time to recover. (129) Infants born to mothers with SARS-CoV-2 infections during pregnancy had a greater rate of neurodevelopmental diagnoses, with third-trimester infections being associated with a higher magnitude of risks (odds ratio, 2.34; 95% CI, 1.23–4.44 in third-trimester infection) in a retrospective cohort study that included 7,772 live births from 7,466 pregnancies. (130) Whether this is a direct effect of maternal SARS-CoV-2 infection or an indirect/secondary effect due to unmeasured confounding factors is unknown, but pediatricians should be aware of this association, and information on maternal SARS-CoV-2 infection during pregnancy may be an important additional history to obtain when evaluating new pediatric patients.

Transmission Reduction and Prevention

The standard prevention measures, including mask wearing and physical distancing, have clearly been shown to reduce the transmission of SARS-CoV-2 infection: for children, it is essential to note that when mitigation measures are in place in school, (131) even in areas of intense transmission, (132) children are less likely to test positive. Vaccines against COVID-19 have played a pivotal role in curbing the pandemic. (133) Since publication of the In Brief "Coronavirus Disease 2019 Vaccine in Children" in the October 2021 issue of the journal, the FDA has authorized the use of Pfizer-BioNTech COVID-19 vaccine for children aged 5 through 11 years in late October 2021 (134) and a booster in May 2022. (135) In addition, Moderna and Pfizer-BioNTech COVID-19 vaccines for children aged 6 months through 4 years became available in June 2022 under an EUA. (136) A protein subunit vaccine (Novavax Inc, Gaithersburg, MD) has been issued an EUA for use in individuals 12 years or older in August 2022. (137) Vaccines available for use in children are summarized in Table 2.

As the virus continues to evolve, there have been concerns about vaccine effectiveness against SARS-CoV-2 infection, as discussed briefly in the Epidemiology section. (28)(138) However, vaccines still maintain their high effectiveness against severe disease requiring hospitalization particularly after a booster, even with emergence of the Omicron variant. (139) Studies in children have also reported that vaccines are highly protective against severe illnesses requiring hospitalization. (29)(140) Protection against infection is also supported by the current evidence, (141) but prevention against severe disease remains a primary goal in managing COVID-19. The FDA issued an EUA for updated booster vaccines that contain mRNA encoding for the Omicron spike protein, in addition to the ancestral virus spike protein endorsed by the CDC in September 2022 given the ongoing pandemic with continued virus evolution. (142) Studies have reported a reduced risk of post–COVID-19 conditions after vaccinations, (143)(144) although the effect has been perceived as modest by the public as reported by the mass media. On the other hand, the effectiveness of COVID-19 vaccines against MIS-C is quite high (approximately 90%). (145)(146) Vaccines have been found to be safe, although mRNA vaccines have been associated with myocarditis, (147) and adenovirus vector vaccines have been associated with vaccine-induced immune thrombocytopenia and thrombosis, (148)(149) respectively. However, the risk of myocarditis is higher with SARS-CoV-2 infection than with vaccination (2–6 times the risk after vaccination in teen boys aged 12–17 years),

Table 2. Coronavirus Disease 2019 Vaccines Available for Children as of Late 2022

VACCINE PRODUCT AND PATIENT AGE	PRIMARY SERIES			BOOSTER[a] (INTERVAL FROM LAST DOSE)
	FIRST DOSE	SECOND DOSE (INTERVAL FROM FIRST DOSE)	THIRD DOSE (INTERVAL FROM SECOND DOSE)	
Immunocompetent				
Pfizer-BioNTech				
6 mo–4 y	✓	✓ (3–8 wk)	✓[a] (≥8 wk)	
5 y	✓	✓ (3–8 wk)		✓ (≥2 mo, with Pfizer-BioNTech)
≥6 y	✓	✓ (3–8 wk)		✓ (≥2 mo, with Pfizer-BioNTech or Moderna)
Moderna				
6 mo–4 y	✓	✓ (4–8 wk)		✓ (≥ 2 mo, with Moderna)
≥5 y	✓	✓ (4–8 wk)		✓ (≥2 mo, with Pfizer-BioNTech or Moderna)
Novavax				
≥12 y	✓	✓ (3–8 wk)		✓ (≥2 mo, with Pfizer-BioNTech or Moderna)
Immunocompromised[b]				
Pfizer-BioNTech				
6 mo–4 y	✓	✓ (3 wk)	✓[a] (≥8 wk)	
5 y	✓	✓ (3 wk)	✓ (≥4 wk)	✓ (≥2 mo, with Pfizer-BioNTech)
≥6 y	✓	✓ (3 wk)	✓ (≥4 wk)	✓ (≥2 mo, with Pfizer-BioNTech or Moderna)
Moderna				
6 mo–4 y	✓	✓ (4 wk)	✓ (≥4 wk)	✓ (≥2 mo, with Moderna)
≥5 y	✓	✓ (4 wk)	✓ (≥4 wk)	✓ (≥2 mo, with Pfizer-BioNTech or Moderna)
Novavax				
≥12 y	✓	✓ (3 wk)		✓ (≥2 mo, with Pfizer-BioNTech or Moderna)

For the most up-to-date information, visit https://www.cdc.gov/coronavirus/2019-ncov/vaccines/index.html.
[a]Use a bivalent booster vaccine.
[b]Immunocompromised conditions may include, but are not limited to, individuals receiving active cancer treatment, organ or bone marrow transplant recipients, recipients of chimeric antigen receptor T-cell therapy, moderate or severe primary immunodeficiency, advanced or untreated human immunodeficiency virus infection, and active treatment with high-dose corticosteroids or other drugs that may suppress the immune response.

(150) and the risk of thrombosis associated with COVID-19 is well established. (92) Also, vaccination of pregnant women can reduce the risk of hospitalization and critical illness in infants younger than 6 months, (151)(152) which is important to highlight as infants can experience severe disease. (50) Vaccine hesitancy has been a major obstacle to the public health and children's health. (153)(154) In addition, racial and ethnic disparities have been reported not only in clinical outcomes but also in vaccine coverage, although the gap seems to have narrowed as the distribution of vaccines became widespread. (155) Disparities in vaccine coverage have also been described by sexual orientation and gender identity, (156) and between the rural and urban communities. (157) Pediatric providers have a role of being an advocate for protecting children regardless of their background and of appropriately informing parents to assist with their decision of immunizing their children and the entire household.

In addition to vaccines, monoclonal antibodies have also become available for preexposure prophylaxis. Tixagevimab-cilgavimab is a combination of 2 neutralizing monoclonal antibodies against SARS-CoV-2 that have an extended the half-life associated with modifications in the Fc region of the immunoglobulin. (158)(159) In the phase 3 trial enrolling adults who had an increased risk of an inadequate response to vaccination, the intramuscular administration of this monoclonal antibody cocktail resulted in approximately 80% reduction in symptomatic COVID-19. (160) This preventive agent has become available for use in individuals 12 years and older with moderate to severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments and may not be able to mount an adequate immune response to COVID-19 vaccination. However, this combination monoclonal antibody is also expected to become less and less effective as variants emerge with altered spike proteins that result in resistance. (On January 26, 2023, the FDA announced that tixagevimab-cilgavimab is no longer authorized for emergency use in the United States.)

Summary

- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative virus of coronavirus disease 2019 (COVID-19), continues to evolve as the pandemic progresses, and immunologic and clinical characteristics can change. (According to moderate evidence)
- Pediatric providers should be vigilant for health disparities in the setting of COVID-19 and any

other health conditions. (According to moderate evidence)

- Children tend to have asymptomatic or mild disease with SARS-CoV-2 infection, but severe disease does occur, particularly in children with comorbidities. (According to moderate evidence)
- Multisystem inflammatory syndrome in children is an important complication associated with COVID-19, characterized by multisystem (≥2) organ dysfunction with no alternative plausible diagnosis. (According to moderate evidence)
- Treatment of COVID-19 in children is largely extrapolated from adult studies, and oral antivirals, monoclonal antibodies, and intravenous antiviral medication can be indicated for at-risk patients with mild to moderate COVID-19 depending on age and weight. (According to moderate evidence)
- In severely ill children, anti-inflammatory therapy and antiviral therapy are combined depending on the severity of illness, although this approach is largely derived from adult data. (According to weak to moderate evidence)
- Multisystem inflammatory syndrome in children is treated primarily with anti-inflammatory or immunomodulatory therapies, although evidence is evolving. (According to weak to moderate evidence)
- Post-acute COVID-19 condition is uncommon in children, but providers should keep in mind that this condition can manifest atypically in children. (According to weak evidence)
- Many children are estimated to have lost a parent or caregiver due to COVID-19, which may have psychological implications. (According to moderate evidence)
- With the emergence of variants of SARS-CoV-2, there have been concerns about vaccine effectiveness against infection, but vaccines still maintain high effectiveness against severe disease requiring hospitalization. (According to moderate evidence)

SUGGESTION FOR QI PROJECTS:

- Immunization rate of children eligible for COVID-19 vaccines.
- Screening for residual symptoms in children with a history of COVID-19.

References and teaching slides for this article can be found at https://doi.org/10.1542/pir.2022-005686.

PIR QUIZ

1. Which of the following is the most accurate statement concerning the epidemiology and clinical characteristics of coronavirus disease 2019 (COVID-19) infection and response to COVID-19 vaccine in children compared with adults?

   A. Fifty percent higher risk of long-COVID.
   B. Greater risk of thromboembolism.
   C. Greater risk of chronic loss of smell.
   D. Higher proportion of asymptomatic infection.
   E. Significantly reduced immunologic response to COVID-19 vaccine in children 6 months or older.

2. A 10-month-old girl is brought by her parents to the office due to a concern of refusing to eat in the past 2 days, although she will still breastfeed. Five days ago she developed low-grade fever (100.5°F–101.2°F [38.1°C–38.4°C]) with nasal congestion and cough. She was tested at an urgent care center for COVID-19 and was positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by polymerase chain reaction. Her brother and father recently had COVID-19. Her fever subsided by day 3 of illness, and her congestion and cough are much improved. She has not had vomiting or diarrhea. In the office she is afebrile with a normal heart rate and respiratory rate. Her oxygen saturation is 96% on room air. Her physical examination findings are normal. This patient's refusal to eat is most likely secondary to which of the following?

   A. Esophageal ulcer.
   B. Esophagitis.
   C. Gastroesophageal reflux.
   D. Olfactory dysfunction.
   E. Swallowing disorder.

3. A 14-year-old boy is admitted to the hospital after presenting to the emergency department with a 3-day history of fever (101°F–104°F [38.3°C–40.0°C]), abdominal pain, vomiting, diarrhea, and progressive fatigue. He was diagnosed as having COVID-19 five weeks ago with a positive SARS-CoV-2 polymerase chain reaction, and his symptoms resolved after 4 days. He appears ill. His temperature is 103.2°F (39.6°C), heart rate is 110 beats/min, respiratory rate is 24 breaths/min, and blood pressure is 96/62 mm Hg. He has mild conjunctival injection without drainage but no other abnormal findings on physical examination. His C-reactive protein level is 16.7 mg/dL (167 mg/L), and his platelet count is $103 \times 10^3/\mu L$ ($103 \times 10^9/L$). His hemoglobin level and white blood cell count are normal, and his absolute lymphocyte count is $890/\mu L$ ($0.89 \times 10^9/L$). An echocardiogram shows moderately reduced left ventricular ejection fraction with normal coronary arteries. Which of the following is the most likely diagnosis?

   A. Classic Kawasaki disease.
   B. Incomplete Kawasaki disease.
   C. Multisystem inflammatory syndrome in children.
   D. Staphylococcal toxic shock syndrome.
   E. Streptococcal toxic shock syndrome.

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4. A 15-year-old boy with moderate persistent asthma and obesity (BMI = 35) presents to the office with a 2-day history of sore throat, congestion, and mild cough. He had a temperature of 100.8°F (38.2°C) at home. His medications are inhaled fluticasone and inhaled salmeterol. His mother was diagnosed as having COVID-19 with a home antigen test 4 days ago. His immunizations are up to date except he has not received a COVID-19 vaccine. He has been hospitalized twice in the past 14 months for asthma exacerbation. On physical examination he is afebrile and his vital signs are normal, with oxygen saturation of 97% on room air. He does not have increased work of breathing or wheezing. Which of the following is the most appropriate current management to prevent progression to severe acute COVID-19 disease for this patient?

   A. Intravenous casirivimab-imdevimab as a single infusion today.
   B. Intravenous sotrovimab as a single infusion today.
   C. Intravenous remdesivir as a single infusion today.
   D. Oral molnupiravir for 1 day.
   E. Oral ritonavir-boosted nirmatrelvir for 5 days.

5. A 6-year-old girl is brought to the office by her parents for a well-child examination. She was diagnosed as having type 1 diabetes mellitus 15 months ago and is doing well on her current insulin regimen. She has regular follow-up with a pediatric endocrinologist. Her immunizations are up-to-date to include a primary series of mRNA COVID-19 vaccine, which she completed 4 months ago. She has never been diagnosed as having COVID-19. Her parents state that a friend has advised them to not have her get a booster COVID-19 vaccine due to it not being safe and that it is no longer effective. The parents would like your opinion on the safety and efficacy of the mRNA COVID-19 vaccine to help them determine whether she should get a booster. Which of the following statements is most accurate concerning mRNA COVID-19 vaccine effects?

   A. Fourfold increased risk of myocarditis from vaccine compared with COVID-19 infection.
   B. High effectiveness in preventing hospitalization from severe COVID-19 infection.
   C. Increased risk of infertility in women.
   D. Not effective in preventing multisystem inflammatory syndrome in children.
   E. Sixfold increased risk of deep venous thromboembolism from vaccine compared with COVID-19 infection.