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# Severe Acute Respiratory Syndrome Coronavirus 2 Infections in Children



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## KEYWORDS

- SARS-CoV-2 • COVID-19 • Pediatrics • Adolescents • MIS-C • Vaccinations
- Children

## KEY POINTS

- Children are at risk for Coronavirus disease 2019 (COVID-19) although the proportion of severe disease is lower than in adults; optimal treatment for pediatric COVID-19 has not been fully vetted through clinical trials.
- Pediatric COVID-19 vaccines that are authorized by the Food and Drug Administration and approved by the Advisory Committee on Immunization Practices or World Health Organization are available in the United States and in other countries, with varying indications for booster doses. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccinations are safe and effective in preventing severe COVID-19, and as of early 2022, vaccinations have been authorized for use in children aged  $\geq 5$  years.
- The identification of SARS-CoV-2 variants may impact the severity of pediatric COVID-19 and community transmissibility, as well as modify the effectiveness of approved vaccine and COVID-19 therapeutics; studies of new biologics to address COVID-19 caused by viral mutations are ongoing.
- The multisystem inflammatory syndrome in children (MIS-C) is a hyperinflammatory condition resulting in significant morbidity but low mortality.
- The pandemic has affected child health, contributing to delays in health care, decreases in routine childhood vaccination rates, disruption to education, and impact on mental health.

## INTRODUCTION

Since the start of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic in 2020, acute coronavirus disease 2019 (COVID-19) has affected children of all ages.<sup>1,2</sup> Overall, the number and incidence of reported infections and cases of

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severe disease in children are fewer than those reported in adults.<sup>3</sup> Treatment of pediatric COVID-19 has largely been extrapolated from adult trials, but management has been focused on prevention and mitigation of transmission. Among the many complications associated with COVID-19, the multisystem inflammatory syndrome in children (MIS-C) has drawn much attention due to the hyperinflammatory findings and acuity at hospital presentation. SARS-CoV-2 vaccinations will likely play an important role in infection prevention in children as more are vaccinated. By the beginning of 2022, the safety and efficacy of vaccinations in the <5-year-old age group remain under evaluation. New studies will expand our knowledge of SARS-CoV-2 epidemiology, change our understanding of disease processes, and improve clinical management recommendations. Here, we summarize the current epidemiology, clinical features, and management of SARS-CoV-2 infection in children.

## EPIDEMIOLOGY

Children of all ages are at risk for SARS-CoV-2 infection and severe COVID-19<sup>4,5</sup>; however, the number of infections and disease severity vary by age, with a higher number of infections and cases of severe disease in older age groups. There have been fewer reported cases of COVID-19 in children than in adults, and assessments of the true SARS-CoV-2 incidence in the pediatric population have been challenging, as early data relied on observational studies and convenience sampling. Children more frequently experience asymptomatic and mild disease, and early SARS-CoV-2 testing was prioritized to cases of severe disease,<sup>6–8</sup> leading to underreporting of pediatric cases at the start of the pandemic.<sup>9</sup> Lock-down procedures may have disproportionately mitigated transmission in children. As schools and childcare centers closed, children remained at home, reducing their exposure to SARS-CoV-2, thus likely reducing the role children played in community transmission early in the pandemic. By the fall of 2021, children returned to in-person school attendance in many locales, although the effect on community SARS-CoV-2 burden remains unclear. Stark differences in pediatric cases between communities of high and low vaccination rates illustrate the importance of vaccination campaigns in pediatric disease mitigation. The spread of SARS-CoV-2 variants is also likely to alter the epidemiology of COVID-19, including its impact on pediatric infections. As further steps are taken to reopen communities by governments around the world, additional impact of SARS-CoV-2 in pediatric populations is anticipated.

There are limited data on the global pediatric COVID-19 burden due to highly variable SARS-CoV-2 testing and changes in community mitigation efforts throughout the course of the pandemic. As of December 2021, UNICEF estimated that 0.4% of global deaths due to COVID-19 occurred in individuals younger than 20 years with 58% of those deaths occurring in adolescents aged 10 to 19 years and 42% in children aged 0 to 9 years.<sup>10</sup> These data likely underestimate the total COVID-19 mortality, given the disparities of resources, testing capability, differential reporting between regions, and the lack of inclusion of new variant viruses. Among Sub-Saharan African countries, pediatric COVID-19 is estimated to be 9% of confirmed cases and 2.4% of reported deaths, with variations in testing protocols by country.<sup>11</sup> Seroprevalence studies involving the detection of antibodies in response to infection have been undertaken to expand our understanding of the true burden of COVID-19. These studies show that SARS-CoV-2 infections in children have been frequently underdiagnosed.<sup>12–14</sup> Many of these studies conducted in different countries before<sup>15–18</sup> and after vaccine availability<sup>19</sup> showed a lower number of infection-derived SARS-CoV-2 antibody detection in children compared with adults. However, country and regional

study differences conducted at varying timepoints during the pandemic have reported mixed results.<sup>20</sup> In the United States, individuals younger than 18 years comprise 22% of the population,<sup>21</sup> yet only 13% of COVID-19 cases have been reported in children.<sup>3</sup> Although the true incidence of pediatric SARS-CoV-2 infections is unknown, the US Centers for Disease Control and Prevention (CDC) estimates the cumulative incidence in the United States to be 25,844,005 total infections among those aged 0 to 17 years, with an infection rate of 35,490 per 100,000 individuals between February 2020 and September 2021 (Table 1).<sup>22</sup> In a summary of reported SARS-CoV-2 infections from March 1 to December 12, 2020, 17.4% of infections occurred in individuals aged 0 to 4 years, 25.7% among those aged 5 to 10 years, 18.6% in those aged 11 to 13 years, and 39.3% among those aged 14 to 17 years.<sup>2</sup>

Early in the pandemic from March 1 to July 25, 2020, age groups comprising the greatest proportion of hospitalized children in the United States were 12 to 17 years (42%), 0 to 2 months (19%) and 5 to 11 years (17%) with a hospitalization rate of 8 per 100,000 individuals.<sup>5</sup> The appearance and spread of SARS-CoV-2 variants had led to subsequent waves of infection across all age groups. By mid-June 2021, US pediatric hospitalizations were at their lowest with a rate of 0.3 per 100,000 children before the spread of the Delta (B.1.617.2 lineage)<sup>23</sup> SARS-CoV-2 variant.<sup>24</sup> Thereafter, the predominance of the Delta variant led to higher numbers of US pediatric emergency room visits and hospital admissions, particularly in regions where community-wide vaccinations were low.<sup>25</sup> In August 2021, the cumulative hospitalization rate for pediatric COVID-19 rose to 49.7 per 100,000 individuals.<sup>24</sup> Similarly, SARS-CoV-2 seropositivity had increased in children in England, coinciding with the spread of the Delta variant, reduction of lock-down procedures, and the start of the academic school year.<sup>26</sup> On November 26, 2021, the Omicron (B.1.1.529) SARS-CoV-2 variant was designated by the World Health Organization (WHO) as a variant of concern due to early evidence of increased transmissibility<sup>27</sup> and viral mutations allowing the evasion of prior immunity leading to rapid global spread and a spike in infection numbers.<sup>28</sup> In the United States, the spread of the Omicron variant<sup>29</sup> was associated with a rapid increase in COVID-19-associated pediatric hospitalizations.<sup>30</sup> With communities pursuing varying stages of re-opening, the identification of new variants and the increased availability of vaccinations for younger age groups, fluctuations in SARS-CoV-2 cases are likely to continue.

**Table 1**  
SARS-CoV-2 point estimates of cumulative incidence and rates of COVID-19 outcomes by age group: United States, February 2020 to September 2021

Age-Group	Infections		Hospitalizations		Deaths	
	Estimated Cumulative Incidence	Estimated Rates per 100,000	Estimated Cumulative Incidence	Estimated Rates per 100,000	Estimated Cumulative Incidence	Estimated Rates per 100,000
0–17 y	25,844,005	35,490	266,597	366	645	0.9
18–49 y	75,179,070	54,860	1,996,830	1457	60,355	43.7
50–64 y	27,407,088	43,656	2,009,141	3200	159,489	253.5
≥65 y	18,012,882	32,363	3,232,213	5807	700,882	1296.5
Overall	146,585,169	44,650	7,506,029	2286	921,371	280.7

From Centers for Disease Control and Prevention. Estimated COVID-19 Burden. Accessed January 12, 2022. <https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/burden.html>

The pandemic has accentuated racial and ethnic disparities among people in the United States.<sup>31–36</sup> A disproportionate number of children with COVID-19 who experience severe outcomes including hospitalizations and death come from communities of underrepresented racial and ethnic groups.<sup>5,36,37</sup> Among American Indian and Alaskan Natives, incidence of COVID-19 among those younger than 18 years was 3 times that of white, non-Hispanic individuals.<sup>38</sup> Hispanic and Latinx adults and children have experienced some of the highest rates of SARS-CoV-2 test positivity,<sup>39,40</sup> particularly during community-wide shelter-in-place directives.<sup>35</sup> Among individuals younger than 18 years with SARS-CoV-2 infection, rates of hospitalization were highest among Hispanic and Latinx children.<sup>5,39</sup> The cause of these disparities is likely multifactorial, including disproportionate burden of chronic conditions,<sup>33</sup> decreased access to health care and testing,<sup>41</sup> difficulty with social distancing in multigenerational households,<sup>35</sup> and greater representation in essential and in-person occupations with exposure risk to COVID-19<sup>42</sup> within the Hispanic and Latinx communities.<sup>39</sup> Survey studies also suggest that Black and Hispanic parents had a lower willingness to immediately vaccinate their children against COVID-19, highlighting the need for outreach, education, and messaging of the benefits of vaccination to these specific communities.<sup>43</sup> See Hernandez Acosta and colleagues' article, "Awakening: The unveiling of historically unaddressed social inequities during the COVID-19 pandemic in the United States", in this issue.

## **PEDIATRIC SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 TRANSMISSION**

Lock-down procedures, including closure of schools,<sup>44</sup> were first implemented in 2020 to reduce community transmission.<sup>45,46</sup> As communities have reopened and schools resumed in-person learning, questions remain about how best to limit the ongoing spread of SARS-CoV-2 and establish the role children play in community transmission.<sup>47–49</sup> Past experiences with other viruses demonstrate that children carry the community burden of influenza and respiratory syncytial viral infections,<sup>48</sup> and public health interventions,<sup>50</sup> such as vaccination of children, can reduce community-wide infections.<sup>51–53</sup> Thus far, data show fewer and milder pediatric SARS-CoV-2 infections compared with adult cases.

The primary mode of person-to-person transmission of SARS-CoV-2 is by respiratory spread,<sup>54</sup> and the use of face coverings, social distancing, and school closures contributed to community mitigation of infection early in the pandemic.<sup>44,55–57</sup> Children are both at risk for acquiring infection and spreading SARS-CoV-2.<sup>49,58,59</sup> Factors influencing individual transmissibility include symptomology, viral load, and behavioral patterns.<sup>60</sup> Both biological and social-behavioral factors vary by age, as a child younger than 5 years has different risks than adolescents. Vaccination status likely modifies an individual's risk of transmission, and vaccine availability to younger age groups will further influence SARS-CoV-2 epidemiology. The impact vaccines play in transmission by children will become evident as uptake and availability in younger age groups continues.

The first reports of pediatric COVID-19 were identified within household transmission investigations,<sup>61–64</sup> in which pediatric index cases of household SARS-CoV-2 infections were less common.<sup>58,59,64–66</sup> One study of household transmissions in which the index case was a child, showed fewer index cases in those aged 0 to 3 years, but a higher risk of household transmission in that age group than in index cases aged 14 to 17 years.<sup>58</sup> These findings suggest an individual's risk of transmission may have nuanced age-related associations. Younger age groups may be less likely to socially distance, cover their mouths when sneezing or coughing, or consistently wear masks,

behaviors expected of older children and adults.<sup>49</sup> Furthermore, families are likely to physically interact more with younger ill children, leading to an increased risk for viral transmission.<sup>49,67</sup> Secondary attack rates (SAR) are calculated as the rate of infection among susceptible individuals from an index case and can be a helpful measure of person-to-person transmission. A systematic review of factors associated with SAR demonstrated higher rates for adult contacts than for children; pooled SAR was not associated with the index case's age.<sup>68</sup> These studies were limited to smaller sample sizes<sup>69</sup> and more finely defined age data were not available.

The risk of SARS-CoV-2 transmission has also been shown to be higher in exposed contacts of cases with higher viral loads.<sup>70–72</sup> In one community-based surveillance study, SARS-CoV-2 viral loads were similar regardless of symptoms and age.<sup>73</sup> Children experienced fewer symptoms for shorter duration when ill with COVID-19 and the presence of symptoms was correlated with a higher viral load than asymptomatic cases. Given that more children experience asymptomatic SARS-CoV-2, and viral load is lower in asymptomatic cases, children may play a smaller role in transmission than adults. The possibility of fecal-oral transmission has been raised, as infectious SARS-CoV-2 virus has been cultured from fecal samples of infected individuals<sup>74</sup> with prolonged shedding and higher levels of viral particles in pediatric fecal samples.<sup>75,76</sup> Thus far, significant fecal-oral transmission in close contacts of children with persistent fecal detection of SARS-CoV-2 has not been reported.<sup>75</sup> SARS-CoV-2 reinfection has been documented in children, although the degree at which it occurs is unknown.<sup>77</sup> With the appearance of novel variants, immune evasion may become more common.

The understanding of school and daycare-based transmission dynamics of SARS-CoV-2 is evolving. One systematic review of SAR found lower pediatric rates in school than household settings.<sup>78</sup> One early investigation in Ireland, where reported SARS-CoV-2 cases were screened for recent school attendance, reported no confirmed cases among school contacts.<sup>79</sup> An analysis of childcare centers in Washington, DC, found a limited number of outbreaks associated with each facility, with most cases acquired outside the facility.<sup>80</sup> A Delta variant outbreak investigation at a California elementary school involving an unvaccinated teacher as the index case found higher risks of infection with seating proximity to the teacher.<sup>81</sup> All students were unvaccinated at the time and had a reported high adherence to social distancing and mask wearing. A study in Los Angeles schools found that school-associated SARS-CoV-2 case rates among those aged 5 to 17 years were lower than community case rates but fluctuated with changes in the general community incidence.<sup>82</sup> In a series of school-based studies, the risk of a SARS-CoV-2 outbreak was 3.7 times higher in schools without mask requirements,<sup>83</sup> and larger increases of county case rates were seen when school mask mandates were optional.<sup>84</sup> These findings suggest that school-based transmission and community-wide case counts can be mitigated by implementing public health interventions as children return to school.

To minimize disruptions to attendance of in-person learning, some grade schools implemented the "Test to Stay" (TTS) strategy in which unvaccinated individuals who experienced a school-related SARS-CoV-2 exposure were allowed to stay in school if certain criteria were met. TTS required that both the index case and the close contact had to have been masked when exposed, and during the quarantine period, the close contact may remain in school provided they remained asymptomatic while wearing a mask and practiced social distancing and submitted to regular testing after the exposure. Schools adopting TTS between August and October 2021 in Illinois and California found a low SAR and low tertiary transmission after TTS implementation while minimizing loss of in-person school days.<sup>85,86</sup>

## SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 VACCINATIONS IN CHILDREN

The most significant public health breakthrough during the pandemic has been the development of SARS-CoV-2 vaccines (Table 2). As of December 17, 2021, the WHO has approved 9 vaccines against COVID-19 under their Emergency Use Listing process<sup>87</sup> including the Pfizer-BioNTech (BNT162b2) vaccine for those aged  $\geq 12$  years<sup>88</sup> (see William O. Hahn and Zanthia Wiley's article, "COVID-19 Vaccines," in this issue). More recently, individual countries have granted emergency use authorization (EUA) to vaccinations for younger children (vaccines produced by Pfizer-BioNTech, Cadila, Bharat, Sinopharm, and Sinovac). Given limited vaccine availability in many countries, WHO has prioritized vaccine use for those most at risk for severe disease, including adults and children aged 12 to 17 years who have high-risk underlying conditions. The CDC Advisory Committee on Immunization Practices (ACIP) recommends the SARS-CoV-2 vaccine for all individuals aged  $\geq 5$  years.<sup>89–91</sup> Since December 11, 2020, the mRNA-based SARS-CoV-2 vaccine produced by Pfizer-BioNTech at a 30- $\mu$ g dose has been approved for individuals  $\geq 16$  years,<sup>92</sup> receiving full FDA approval on August 23, 2021.<sup>93</sup> On May 10, 2021, this vaccine was granted EUA in those aged 12 to 15 years,<sup>94</sup> with a 10 micro gram dose receiving EUA on October 29, 2021, for those ages 5 to 11 years.<sup>95</sup> Booster doses of vaccine were first authorized by the FDA on November 19, 2021, to adults, followed by approval for those aged 16 and 17 years on December 9, 2021,<sup>96</sup> and for those aged 12 to 15 years on January 3, 2022.<sup>97</sup> Booster doses administered  $\geq 5$  months after completion of the primary series are increasingly important with the spread of the Omicron variant.<sup>98</sup> A third primary dose of Pfizer-BioNTech has been authorized by the FDA for moderately or severely immunocompromised children aged  $\geq 5$  years.<sup>97</sup> On December 8, 2021, the FDA granted EUA to tixagevimab/cilgavimab (Evusheld), a combination monoclonal antibody, for those aged  $\geq 12$  years and weighing  $\geq 40$  kg who are not currently infected with SARS-CoV-2, have moderately to severely compromised immune systems, or a history of severe adverse reactions to the approved SARS-CoV-2 vaccines, as preexposure prophylaxis.<sup>99</sup> As of January 2022, pediatric data with this new long-acting monoclonal antibody have not been published, but approval offers an alternative to vaccinations in those who are unable to mount sufficient immunity to approved vaccines or those for whom current vaccines are not clinically recommended.

Vaccine trials and real-world effectiveness studies have shown that SARS-CoV-2 mRNA vaccines are highly effective against COVID-19. Before the predominance of SARS-CoV-2 variants, the Pfizer-BioNTech vaccine reported vaccine efficacy of 95% against confirmed COVID-19 in those aged  $\geq 16$  years.<sup>100</sup> In a subsequent analysis on the safety and efficacy of the same vaccine in participants aged 12 to 15 years, vaccine efficacy was 100% against confirmed COVID-19 after completion of the 2-dose series.<sup>101</sup> The Phase 2 to 3 vaccine trial (conducted between June 7, 2021 and October 8, 2021) evaluating the Pfizer-BioNTech mRNA vaccine in the 5-year-old to 11-year-old age group found a vaccine efficacy of 91% with no observation of myocarditis or pericarditis up to 2 months after the second dose of the vaccine.<sup>102</sup> Similarly, clinical trials with the Moderna (mRNA-1273) vaccine conducted between December 9, 2020, and February 28, 2021, showed no cases of acute COVID-19 in adolescents aged 12 to 17 years 2 weeks after the second injection, whereas 4 cases were reported in the placebo group.<sup>103</sup> Although early booster studies only included children aged 16 to 17 years, a reduction in confirmed SARS-CoV-2 infections and severe illness was seen in those who received a booster dose of the Pfizer-BioNTech vaccine than those who did not.<sup>104</sup>

**Table 2**  
**SARS-CoV-2 vaccines available in the United States**

Vaccine Name	Manufacturer	Vaccine Type	Reported Vaccine Efficacy in Children	Schedule	Approval for Children	Approval Dates
BNT162b2 (Comirnaty)	Pfizer- BioNTech	mRNA (Intramuscular)	<ol style="list-style-type: none"> <li>100% vaccine efficacy against confirmed COVID-19 in individuals aged 12–15 y<sup>101</sup></li> <li>90.7% vaccine efficacy against confirmed COVID-19 in individuals aged 5–11 y<sup>102</sup></li> </ol>	<ol style="list-style-type: none"> <li>2-dose primary series separated by 21 d</li> <li>1 additional primary dose in immunocompromised persons<sup>a</sup> (≥28 d since 2nd dose)</li> <li>Booster dose ≥5 mo after last dose in primary series</li> </ol>	<ol style="list-style-type: none"> <li>FDA approved for individuals ≥16 y</li> <li>FDA EUA for individuals 5–15 y</li> <li>Booster dose approval for individuals aged ≥12 y</li> <li>Third primary series dose for certain immunocompromised children ≥5 y</li> </ol>	<ol style="list-style-type: none"> <li>December 11, 2020: FDA EUA for individuals ≥16 y<sup>92</sup></li> <li>May 10, 2021: FDA EUA for individuals 12–15 y<sup>94</sup></li> <li>August 12, 2021: FDA EUA for third primary dose for certain immunocompromised individuals<sup>a, 257</sup></li> <li>August 23, 2021: FDA approved for individuals ≥16 y<sup>93</sup></li> <li>September 22, 2021: FDA updated EUA to allow for single booster dose for high-risk populations<sup>b</sup> aged ≥18 y administered at least 6 mo after completion of primary series<sup>258</sup></li> <li>October 20, 2021: FDA updated EUA to allow for heterologous booster dose in eligible individuals</li> </ol>

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**Table 2**  
(continued)

Vaccine Name	Manufacturer	Vaccine Type	Reported Vaccine Efficacy in Children	Schedule	Approval for Children	Approval Dates
						7. October 29, 2021: FDA EUA for individuals 5–11 y <sup>95</sup> 8. November 19, 2021: FDA updated EUA to allow for single booster dose for all individuals aged $\geq 18$ y <sup>259</sup> 9. December 9, 2021: FDA updated EUA to allow for single booster dose in individuals aged 16–17 y <sup>96</sup> 10. January 3, 2022: FDA updated EUA to expand use of booster dose in individuals aged 12–15 y; shorten time interval for booster dose to $\geq 5$ mo and allow for third primary series dose for certain immunocompromised children aged 5–11 y <sup>97</sup>
mRNA-1273	Moderna	mRNA (Intramuscular)	Vaccine efficacy against COVID-19 in adolescents aged 12–17 y showed 100%	1. 2-dose primary series separated by 28 d 2. 1 additional	Not approved by FDA for children	1. December 18, 2020: FDA EUA for individuals $\geq 18$ y <sup>260</sup>

			<p>efficacy 14 d after second primary dose, although not statistically significant given low incidence of infection (4 cases in placebo group and none in vaccine arm)<sup>103</sup></p>	<p>primary dose in immunocompromised persons<sup>a</sup> (<math>\geq 28</math> d since 2nd dose)</p> <p>3. Booster dose <math>\geq 5</math> mo after last dose in primary series</p>		<p>2. August 12, 2021: FDA EUA for third primary dose for certain immunocompromised individuals<sup>a,260</sup></p> <p>3. October 20, 2021: FDA updated EUA to allow for booster dose for high-risk populations<sup>b</sup> aged <math>\geq 18</math> y administered at least 6 mo after completion of primary series, including the use of a heterologous booster dose in eligible individuals<sup>260</sup></p> <p>4. November 19, 2021: FDA updated EUA to allow for single booster dose for all individuals aged <math>\geq 18</math> y<sup>260</sup></p> <p>5. January 7, 2022: FDA updated EUA to shorten interval between completion of primary vaccine series to booster to <math>\geq 5</math> mo for all individuals <math>\geq 18</math> y<sup>261</sup></p>
Ad26.COV2.S	Janssen/ Johnson & Johnson	Viral vector (Intramuscular)	Data not available	<p>1. Single primary dose</p> <p>2. Booster dose <math>\geq 2</math> mo after primary dose</p>	Not approved by FDA for children	<p>1. February 27, 2021: FDA EUA for individuals <math>\geq 18</math> y<sup>262</sup></p> <p>2. October 20, 2021: FDA updated EUA to allow for a single booster dose</p> <p><i>(continued on next page)</i></p>

**Table 2**  
(continued)

Vaccine Name	Manufacturer	Vaccine Type	Reported Vaccine Efficacy in Children	Schedule	Approval for Children	Approval Dates
						at least 2 mo after completion of the single-dose primary series for all individuals aged $\geq 18$ y and allows for the use of a heterologous booster dose in eligible individuals <sup>262</sup>
						3. December 16, 2021: CDC ACIP recommendations updated, preferring approved mRNA vaccines over Janssen vaccine for primary and booster vaccinations <sup>263</sup>

*Abbreviations:* ACIP, Advisory Committee on Immunization Practices; CDC, Centers for Disease Control and Prevention; COVID-19, coronavirus disease 2019; EUA, emergency use authorization; FDA, Food and Drug Administration; mRNA, messenger RNA.

<sup>a</sup> Moderately to severely immunocompromised persons may include (not limited to) individuals undergoing active treatment for solid tumor and hematologic malignancies, receiving a solid organ transplant and taking immunosuppressive therapy, receiving chimeric antigen receptor T-cell or hematopoietic cell transplant; individuals who have moderate or severe primary immunodeficiency, advanced or untreated human immunodeficiency virus infection, receiving active treatment with high-dose corticosteroids, alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutics agents classified as severely immunosuppressive, tumor necrosis factor blockers, and other immunosuppressive or immunomodulatory biologic agents.

<sup>b</sup> High-risk populations include individuals 65 y and older; individuals 18 to 64 y with an underlying medical condition putting them at high risk for severe COVID-19, and individuals 18 to 64 y with frequent institutional or occupational exposure to SARS-CoV-2 putting them at risk for serious complications of COVID-19, including severe COVID-19. Interim updated CDC list of high-risk underlying conditions include but are not limited to asthma, cancer, cerebrovascular disease, chronic kidney disease, certain types of chronic lung diseases, certain types of chronic liver disease, cystic fibrosis, diabetes mellitus (type 1 and type 2), Down syndrome, heart conditions, human immunodeficiency virus, hypertension, immune deficiencies, certain mental health disorders (ie, mood disorders, schizophrenia spectrum disorders), obesity (body mass index [BMI]  $\geq 30$  kg/m<sup>2</sup>) and overweight (BMI  $\geq 25$  kg/m<sup>2</sup> but  $< 30$  kg/m<sup>2</sup>), pregnancy and recent pregnancy, sickle cell disease, smoking (current and former), solid organ or blood stem cell transplantation, substance use disorders, thalassemia, tuberculosis, and use of corticosteroids or other immunosuppressive medications (an ongoing updated list of high-risk underlying conditions can be found on the CDC Web site)<sup>141</sup>.

Vaccine effectiveness (VE) studies have been integral in understanding the effectiveness of vaccines in real-world settings at various stages of the pandemic. In one VE study in adolescents aged 12 to 18 years from June to September 2021 when the Delta variant was the predominant virus, the Pfizer-BioNTech vaccine was found to have a VE of 93% against COVID-19 hospitalizations.<sup>105</sup> Another VE study of the Pfizer-BioNTech vaccine in adolescents aged 12 to 17 years from July to December 2021 (when the Delta variant was widespread but before the predominance of the Omicron variant), VE against SARS-CoV-2 infection was 92%.<sup>106</sup> In a population-based study of SARS-CoV-2 infection, incidence rates also occurring during the Delta variant wave, the incidence rate ratio of laboratory-confirmed SARS-CoV-2 infections was 8.9 comparing unvaccinated with vaccinated adolescents aged 12 to 17 years.<sup>107</sup> Furthermore, early data show the protective effects of SARS-CoV-2 vaccination against MIS-C with a lower incidence with vaccination<sup>108</sup> and an estimated VE of 91% in adolescents 12 to 18 years who had completed a primary vaccine series with the Pfizer-BioNTech vaccine.<sup>109</sup> Despite vaccine availability and effectiveness, the percentage of vaccinated eligible children was less than 65% as of December 30, 2021, with fewer than 15% of children aged 5 to 11 years full vaccinated.<sup>110</sup> In some situations, there may be discordance in vaccine hesitancy between parents and guardians and their children. There remains regional variability of minor consent laws in which minors are allowed to consent to medical interventions that include vaccines.<sup>111</sup>

Overall, SARS-CoV-2 vaccines have had a favorable safety profile among children aged 5 to 17 years.<sup>100,101,112</sup> Most vaccine reactions to the Pfizer-BioNTech vaccine reported were local or mild systemic reactions,<sup>112,113</sup> with the exception of a small group of individuals, overwhelmingly male adolescents and younger adults, who reported self-limited cases of myocarditis and pericarditis.<sup>114</sup> In a nationwide study, the Pfizer-BioNTech vaccine was associated with an excess risk of 1 to 5 events per 100,000 vaccinated persons of all ages compared with the excess risk of 11.0 events per 100,000 persons after SARS-CoV-2 infection.<sup>115</sup> Myocarditis after SARS-CoV-2 vaccination was more common in younger age groups, whereas pericarditis was more common in older individuals, with onset generally within 3 days of vaccination.<sup>116,117</sup> Among individuals younger than 30 years with data reported to the Vaccine Adverse Event Reporting System, cases of myocarditis, pericarditis, and myopericarditis after SARS-CoV-2 vaccines occurred in individuals with a median age of 19 years (range: 12–29 years) with 96% hospitalized and no deaths.<sup>118</sup> Given the severe outcomes of SARS-CoV-2 infection including myocarditis,<sup>119</sup> the ACIP concluded that the benefits of vaccination outweighed the risk posed by these rare adverse events.

## CLINICAL COURSE AND MANIFESTATIONS OF ACUTE CORONAVIRUS DISEASE 2019 IN CHILDREN

The clinical picture and severity of SARS-CoV-2 infection in children of all ages can vary from no symptoms to critical illness. When symptoms develop, most children will experience respiratory tract symptoms or an exacerbation of underlying conditions. Children with COVID-19 not requiring hospitalization have more subclinical, asymptomatic infection, and upper respiratory tract symptoms than adults.<sup>8,120</sup> One systematic review of early studies on pediatric COVID-19 found that 2% of SARS-CoV-2 infections in children were categorized as severe, whereas 0.6% had critical COVID-19,<sup>121</sup> although the spread of variants and increased exposure to SARS-CoV-2 may lead to increased numbers of infection and severe presentations of disease.

As in adults, the incubation period likely ranges from 2 to 14 days (mean, 6 days).<sup>122,123</sup> Illness duration is estimated to be a median of 6 days, but prolonged illness greater than 28 days can occur.<sup>124</sup> Overall, symptom duration is shorter in younger children.<sup>124</sup> Symptoms vary by age group (Table 3) and study type. In an early surveillance report of pediatric COVID-19, fever and cough were the most commonly reported symptoms, with headache a common symptom in older children.<sup>9</sup> In a longitudinal cohort study of infected school-aged children, headache and fatigue were the most common symptoms identified, with sore throat, altered taste or smell, and fever also frequently reported.<sup>124</sup> Neonates and infants may experience nonspecific symptoms, such as feeding difficulty with fever, so COVID-19 should be considered in the workup for infectious etiologies.<sup>125</sup> The presence of gastrointestinal (GI) symptoms, such as abdominal pain, nausea, vomiting, and diarrhea, are also common in pediatric acute COVID-19. Altered taste or smell is more commonly reported in older age groups.<sup>9,124</sup>

The National Institutes of Health (NIH) developed COVID-19 severity categories to unify treatment recommendations: asymptomatic or presymptomatic, mild, moderate, severe, and critical acute COVID-19 (Table 4).<sup>126</sup> Given these definitions are

**Table 3**  
Symptom frequency in pediatric patients with acute COVID-19

Symptoms	CDC Surveillance Report - United States <sup>9</sup>			Longitudinal Cohort of School-Aged Children - UK <sup>124</sup>		
	Overall	Age Group		Overall	Age Group	
		0– 9 y	10– 19 y		5– 11 y	12– 17 y
	%	%	%	%	%	%
Cough	40	37	41	26	25	26
Fever	38	46	35	38	44	35
Headache	34	15	42	62	55	66
Sore throat	24	13	29	46	36	51
Myalgias	24	10	30	16	9	20
Diarrhea	14	14	14	7	8	7
Shortness of breath	13	7	16	10	4	12
Nausea	10	10	10	17	16	17
Runny nose	8	7	8	—	—	—
Change in sense of taste or smell	7	1	10	40	22	48
Abdominal pain	7	7	8	21	28	17
Fatigue	—	—	—	55	44	61
Dizziness	—	—	—	22	14	26
Anorexia	—	—	—	22	20	22
Eye soreness	—	—	—	19	15	22
Voice change	—	—	—	13	11	14
Chest pain	—	—	—	10	6	12
Confusion	—	—	—	6	3	7
Red welts	—	—	—	3	3	3
Blisters	—	—	—	2	1	2

Abbreviations: CDC, Centers for Disease Control and Prevention; COVID-19, coronavirus disease 2019.

**Table 4**  
**Definitions of acute COVID-19 severity and available treatment**

Severity of COVID-19	General Definition	Pediatric Considerations	Treatment Recommendations
Asymptomatic infection	An individual who tests positive for SARS-CoV-2 but does not exhibit any symptoms over the course of the infection.	Diagnosis of asymptomatic or presymptomatic SARS-CoV-2 infections in infants and toddlers are reliant on clinical history gathering and specific questions to the child's caregiver. Symptoms may be subtle and difficult to ascertain in the nonverbal child.	Supportive care and ensuring caregivers and close contacts take appropriate precautions including encouraging SARS-CoV-2 vaccine uptake, if eligible. SARS-CoV-2-directed therapies should be used only in the context of a clinical trial.
Presymptomatic infection	An individual who tests positive for SARS-CoV-2 and does not exhibit symptoms at the time, but then develops symptoms later in the illness course.		Supportive care and ensuring caregivers and close contacts take appropriate precautions including encouraging SARS-CoV-2 vaccine uptake, if eligible. SARS-CoV-2-directed therapies should be used only in the context of a clinical trial; when symptoms develop, treatment provided based on level of severity.
Mild	An individual who tests positive for SARS-CoV-2 and has signs or symptoms consistent with COVID-19, which may include fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, or change in sense of taste or smell. These individuals have no evidence of lower respiratory tract disease, including no shortness of breath, dyspnea, or abnormal chest imaging.	Children, particularly younger age groups, may also have nonspecific symptoms of feeding refusal, fussiness, runny nose, or nasal congestion.	Supportive care and ensuring caregivers and close contacts take appropriate precautions, including encouraging SARS-CoV-2 vaccine uptake, if eligible. Remdesivir and other therapies, including nirmatrelvir/ritonavir, should be used only in the context of a clinical trial; if remdesivir is used in an outpatient setting, this would be an off-label indication; molnupiravir is not approved for use in children, given concerns for interference with normal bone and cartilage development.
Moderate	An individual who tests positive for SARS-CoV-2 and has signs or symptoms consistent with	In young children, a weak cry, grunting, tracheal tugging, nasal flaring, head bobbing,	Supportive care and ensuring caregivers and close contacts take appropriate precautions,

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**Table 4**  
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Severity of COVID-19	General Definition	Pediatric Considerations	Treatment Recommendations
	lower respiratory tract disease, including shortness of breath or dyspnea or abnormal chest imaging. These individuals have normal baseline oxygen saturation typically $\geq 94\%$ on room air.	and sternal or intercostal retractions are additional indicators of respiratory distress, and may also suggest a lower respiratory tract infection.	including encouraging SARS-CoV-2 vaccine uptake, if eligible. Remdesivir and other therapies including nirmatrelvir/ritonavir should be used only in the context of a clinical trial; if remdesivir is used in an outpatient setting, this would be an off-label indication; molnupiravir is not approved for use in children given concerns for interference with normal bone and cartilage development.
Severe	An individual who tests positive for SARS-CoV-2 and has oxygen saturation $< 94\%$ or below baseline, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen ( $P_{aO_2}/F_{iO_2}$ ) $< 300$ mm Hg, respiratory rate $> 30$ breaths/min, or lung infiltrates $> 50\%$ .	Radiographic abnormalities may be common in children and findings should be considered in the context of other symptoms, including hypoxemia.  Normal respiratory rate by age group <sup>264</sup> : Newborn 40–60 breaths/min $< 1$ y 24–38 breaths/min 1–3 y 22–30 breaths/min 4–6 y 20–24 breaths/min 7–9 y 18–24 breaths/min 10–14 y 16–22 breaths/min 14–18 y 14–20 breaths/min	<ol style="list-style-type: none"> <li>Caregivers and close contacts take appropriate precautions including encouraging SARS-CoV-2 vaccine uptake, if eligible.</li> <li>Remdesivir can be used as an antiviral in those with severe or critical acute COVID-19 weighing at least 3.5 kg. A multicenter pediatric COVID-19 guideline committee suggests using respiratory support requirement as the indicator for its use.<sup>177</sup></li> </ol>
Critical	An individual who tests positive for SARS-CoV-2 and develops respiratory failure, septic shock or organ dysfunction.	Careful consideration should be made to distinguish cases of critical COVID-19 and multisystem inflammatory syndrome in children (MIS-C). See <a href="#">Table 5</a> .	<ol style="list-style-type: none"> <li>Dexamethasone<sup>b</sup> can be considered in critical disease, particularly in older age groups.</li> <li>Interleukin-6 (eg, tocilizumab) or interleukin-1 (eg, anakinra) inhibitors can be considered in critical disease, preferably in the setting of a clinical trial.</li> </ol>

Abbreviations: COVID-19, coronavirus disease 2019; EUA, emergency use authorization; SARS-CoV-2, severe acute respiratory distress syndrome coronavirus 2.

<sup>a</sup> Risk factors based on the consensus by a multicenter panel of pediatric providers include children with medical complexity, young age less than 1 y, older age greater than 12 y, immunocompromised state, underlying severe cardiac or pulmonary disease, obesity, and diabetes.<sup>177</sup>

<sup>b</sup> If there is a concurrent condition for which steroids are indicated, steroids should be used as part of the treatment course (eg, asthma exacerbation).

extrapolated to pediatric infections, normal vital signs and symptoms will differ by age. The diagnosis of asymptomatic or presymptomatic infection in younger children will rely on clinical history provided by the caregiver and findings on physical examination. Minimally symptomatic children will require careful assessment of vital signs and physical examination to ensure appropriate counseling is given. Weak cry, grunting, retractions, nasal flaring, and head bobbing may also be indicators of respiratory distress, and acute COVID-19 should be suspected in younger children, especially in the absence of alternative explanation. Rapid clinical deterioration with abrupt changes in respiratory status may occur a week into the illness course.<sup>127</sup> In children with critical illness, careful consideration should be given in distinguishing cases of acute COVID-19, MIS-C, and other diseases as evaluation and management may differ.

There remains a paucity of data on risk factors associated with severe outcomes of pediatric acute COVID-19. Data extrapolated from adult reports and observational studies highlight several chronic diseases in children that increase risk for infection, hospitalization, admission to the intensive care unit (ICU) and death.<sup>128–132</sup> In a study of hospitalized children younger than 18 years with COVID-19 when the Delta variant was widespread, 67.5% had one or more underlying medical conditions.<sup>133</sup> In another study of individuals younger than 21 years, at least one underlying medical condition was associated with 75% of SARS-CoV-2.<sup>129</sup> There does not appear to be a significant risk of severe disease associated with male gender, as there is in adults.<sup>134</sup> Some studies suggest that younger children (infants aged <1 year) did not have increased risk for severe disease<sup>131</sup> although early reports showed higher proportions of severe and critical illness in the younger age groups.<sup>1,132</sup> In a cross-sectional study of children with acute COVID-19, risk of hospitalization or severe COVID-19 was highest in those with obesity, sleeping disorders, diabetes (type 1 or type 2), congenital heart disease, neurodevelopmental disorders, psychiatric illness, hypertension and seizure disorders.<sup>135</sup> Among children aged 12 to 18 years, those with asthma were at increased risk for severe illness.<sup>135</sup> Other possible conditions at risk for severe outcomes in children include complex medical conditions,<sup>135</sup> genetic disorders such as trisomy 21,<sup>136</sup> sickle cell disease,<sup>137</sup> congenital heart disease<sup>138</sup> and immunosuppression.<sup>139,140</sup> However, few published reports of pediatric patients with these conditions are available, making statistical inferences challenging. Experience with other viral infections suggest that individuals with these chronic conditions should be treated as having a higher risk of severe disease. The CDC maintains a list of underlying medical conditions with higher risk of severe COVID-19 reported in the literature, although this list is not specific to pediatric patients.<sup>141</sup> Although uncommon, newborns are also at risk for SARS-CoV-2 infection with the highest risk when the mother or other caregiver has COVID-19 onset around delivery. With proper precautions, mothers and newborns may room safely together.<sup>142,143</sup> In addition, there has been little evidence to suggest transmission via breast milk, and breastfeeding is encouraged for those who are interested.<sup>143</sup>

SARS-CoV-2 infection commonly results in respiratory tract illness with extrapulmonary manifestations documented in case reports or case series in children. A variety of neurologic complications associated with pediatric acute COVID-19 has been described, including encephalopathy, seizures, encephalitis, Guillain-Barre Syndrome, acute demyelinating syndromes, movement disorders, and psychiatric disorders.<sup>144</sup> Acute COVID-19 in children can also be complicated by cardiovascular events, including myocarditis,<sup>145,146</sup> pericarditis,<sup>147,148</sup> pulmonary embolic events,<sup>149</sup> arrhythmias,<sup>150</sup> and acute myocardial infarction.<sup>151</sup> So-called “COVID toes,” or pseudo-chilblains, caused by inflammation of small blood vessels leading to painful



sores can also be seen in pediatric acute COVID-19.<sup>152,153</sup> GI<sup>154–156</sup> and renal<sup>157</sup> complications have also been described. Invasive mold infections (eg, pulmonary aspergillosis and mucormycosis) are increasingly recognized complications of severe COVID-19 in adults,<sup>158</sup> although rarely reported in children.<sup>159</sup> There remains little information on COVID-19–associated fungal infections in children, possibly owing to fewer cases of severe COVID-19.

## LABORATORY AND IMAGING FINDINGS

Diagnosis of SARS-CoV-2 infection requires laboratory confirmation. Suspected cases may be identified based on characteristic symptoms and exposure to an individual with laboratory-confirmed SARS-CoV-2 infection. Adult acute COVID-19 has been associated with characteristic laboratory abnormalities, including lymphopenia in early disease, elevated inflammatory markers, and findings of a hypercoagulable state<sup>160</sup> that have been used to predict severe disease. In pediatric acute COVID-19, laboratory findings have been more variable, differ by age, and are less predictive of severe disease.<sup>140,161</sup> In addition to lymphopenia and hypercoagulability, markers of inflammation in children may be abnormal, including D-dimer, lactate dehydrogenase, fibrinogen, ferritin, procalcitonin, interleukin (IL)-6, C-reactive protein (CRP), aspartate aminotransferase, alanine aminotransferase, and erythrocyte sedimentation rate.<sup>160,162,163</sup> Elevations of creatine kinase, pro B-type natriuretic peptide, and troponin can be seen in those with end-organ disease.<sup>162</sup> Significantly elevated inflammatory markers with cardiovascular involvement should also prompt clinical consideration of an MIS-C diagnosis. Chest radiographic findings including characteristic multifocal ground glass opacities and pulmonary consolidations may be the most common imaging abnormalities in pediatric acute COVID-19.<sup>164,165</sup> Children may have abnormalities of chest imaging even with asymptomatic and presymptomatic infection.<sup>165</sup> Except in cases of severe disease or workup of alternative conditions, computed tomography is unlikely to provide additional clinical information when a diagnosis of acute COVID-19 is already known.

## CLINICAL MANAGEMENT CONSIDERATIONS AND CORONAVIRUS DISEASE 2019 THERAPEUTICS

Management of symptomatic acute COVID-19 depends on the severity of the illness (see [Table 4](#)), and special consideration should be given to the evolution of SARS-CoV-2 variants, including the appearance of the Omicron variant, as they alter the landscape of effective monoclonal antibodies and available therapeutics.<sup>166</sup> Most children will not require specific therapy, especially with milder disease. Children with underlying medical conditions may be at greater risk for severe outcomes, thus close follow-up and baseline control of chronic illnesses may help mitigate the effects of infections. The mainstay of management in children with mild to moderate acute COVID-19 is supportive care, although cases of poor feeding or dehydration may prompt admission to the hospital for nutritional resuscitation. Children whose symptoms worsen may require higher levels of care because of progression of disease, end-organ complications, and coinfections. If new or worsening symptoms evolve, workup should be pursued to identify the etiology of the clinical change. During the pandemic, the use of antibiotics has exceeded the estimated prevalence of bacterial coinfections, leading to overuse in cases of COVID-19.<sup>167</sup> Continuation of antibiotics should be guided by culture results and risk factors, and generally reserved for severe or critical COVID-19 with presumed or confirmed bacterial coinfection. Acute COVID-

19 can lead to a hypercoagulable state; the use of thromboprophylaxis should be considered based on individual risk factors for coagulopathy.

Monoclonal antibodies have been used for risk reduction of severe disease in adults, in those with predisposing factors, but some approved therapies have diminished effectiveness against novel variants, including the Omicron variant. Currently, bamlanivimab-etesevimab, casirivimab-imdevimab, and sotrovimab are the only therapies available through EUA for individuals aged  $\geq 12$  years and  $\geq 40$  kg who have mild to moderate acute COVID-19 at risk of severe COVID-19 and are not hospitalized for COVID-19 (see Jakharia and colleagues' article, "COVID-19 in the Immunocompromised Host, including People with HIV," in this issue). Bamlanivimab-etesevimab and casirivimab-imdevimab were authorized as postexposure prophylaxis for those exposed and at high risk of severe COVID-19. The EUA for bamlanivimab-etesevimab has also been extended to younger children (from birth and older), including those who are hospitalized between birth and 2 years of age for treatment of mild to moderate acute COVID-19, but circulating variants have limited their use.<sup>168</sup> Hospital admission thresholds may be lower for neonates and young children who develop mild to moderate COVID-19, hence the EUA extension of its use during hospitalization for this younger age group. There remain limited data regarding the use of monoclonal antibodies in children,<sup>169</sup> with pediatric experts recommending against its routine use in children, including those with risk factors for severe disease.<sup>170</sup>

Antiviral therapy has formed the basis for COVID-19 therapy early in the illness course. Remdesivir, a nucleoside analog and viral RNA polymerase inhibitor, has been available through EUA since May 1, 2020. On October 22, 2020, remdesivir became the first FDA-approved antiviral treatment for use in hospitalized individuals aged  $\geq 12$  years and weighing  $\geq 40$  kg with COVID-19.<sup>171</sup> It remains available under EUA to children weighing 3.5 kg to less than 40 kg or those younger than 12 years and weighing  $\geq 3.5$  kg.<sup>171</sup> The data to support the use of remdesivir in COVID-19 has been derived from clinical trials of adult COVID-19. A 5-day course of remdesivir was associated with a reduction in median time to recovery, but not mortality in severe COVID-19.<sup>172-174</sup> The NIH recommends remdesivir for children  $\geq 12$  years and weighing  $\geq 40$  kg with new or increasing oxygen requirement with risk factors for severe disease,<sup>169</sup> and allows for the off-label treatment of nonhospitalized children with mild to moderate COVID-19 at risk for severe disease within 7 days of symptom onset.<sup>175</sup> They also recommend remdesivir for children aged  $\geq 16$  years with acute COVID-19 and new or increasing oxygen requirement regardless of the presence of severe disease risk factors.<sup>169</sup> Although there are data to support early remdesivir to mitigate severe acute COVID-19 in outpatients with symptomatic SARS-CoV-2 infection,<sup>176</sup> a panel of pediatric experts recommends the use of remdesivir for mild to moderate acute COVID-19 only in the context of a clinical trial, and 5 days of remdesivir therapy in children with severe and critical acute COVID-19. Up to 10 days of remdesivir could be considered in critical acute COVID-19.<sup>177</sup> WHO has recommended against the use of remdesivir for children, citing a lack of important clinical differences in mortality and severe outcomes.<sup>178</sup> In general, remdesivir is well tolerated. Reports of sinus bradycardia associated with its use have been documented in pediatric cases of COVID-19,<sup>179</sup> which appears to self-resolve after drug discontinuation.

In December 2021, the FDA granted EUA to 2 additional antiviral agents for the treatment of mild to moderate acute COVID-19, which include molnupiravir,<sup>180</sup> a ribonucleoside analog, and nirmatrelvir/ritonavir (Paxlovid),<sup>181</sup> a novel combination protease inhibitor. Molnupiravir may be associated with abnormalities in bone and cartilage development in children and as such, only nirmatrelvir/ritonavir has been granted approval for use in pediatric patients aged  $\geq 12$  years of age and weight of  $\geq 40$  kg

with SARS-CoV-2 infection and high risk for progression to severe disease within 5 days of symptom onset. Careful consideration should be given to its use, given the potential for drug-drug interactions.

Immune dysregulation likely contributes to the progression of severe disease, and various immunomodulators have been proposed as treatment to mitigate inflammatory effects. Trials show that glucocorticoids in adults, specifically dexamethasone, can reduce days of mechanical ventilation and mortality in those with severe or critical disease<sup>182–184</sup>; however, data in children are lacking.<sup>185</sup> The NIH recommends dexamethasone in patients requiring high-flow oxygenation, mechanical ventilation, or extracorporeal membrane oxygenation.<sup>169</sup> A panel of pediatric experts maintains that glucocorticoids be considered for critical disease preferentially in the context of a clinical trial, and should still be used in other non-COVID-19 conditions in which steroids are indicated (eg, asthma exacerbation).<sup>186</sup> Dexamethasone use, typically up to 10 days or until discharge,<sup>185</sup> may be of more importance in older children and adolescents who have immune system physiology similar to adults. Among other immunomodulators, including IL-6 inhibitors (eg, tocilizumab), IL-1 (eg, anakinra), and Janus kinase (JAK) inhibitors (eg, baricitinib) have shown some clinical benefit in adult COVID-19, but in children, these study data are also lacking. Guidance from a panel of pediatric experts encourage the use of IL-1 or IL-6 inhibitors in the setting of a clinical trial for the treatment of critical acute COVID-19, whereas they recommend against the use of JAK inhibitors except for in cases of a clinical trial,<sup>186</sup> despite their authorization for use in these younger age groups. Consultation with pediatric rheumatologists and infectious disease specialists may be helpful in stratifying patients benefiting most from these therapies when clinical trials are not available. Convalescent plasma has been used as an adjunctive therapy for many different viral infections, and the data supporting its use in COVID-19 is sparse. As such, NIH has recommended against its use generally in pediatric acute COVID-19 except in the setting of a clinical trial.<sup>169</sup>

Other antivirals and anti-inflammatory agents had been considered for COVID-19 treatment early in the pandemic, including hydroxychloroquine, lopinavir-ritonavir, and ivermectin. No data support the use of these medications for pediatric (or adult) acute COVID-19 of any severity. Treatment guidelines have routinely recommended against their use given the lack of efficacy in reducing severe outcomes.<sup>169,177,178</sup>

### **MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN ASSOCIATED WITH SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 INFECTION**

MIS-C is a systemic hyperinflammatory condition seen after SARS-CoV-2 infection. It is one of the most dramatic manifestations associated with COVID-19 in which multiple organ systems are affected; shock can sometimes occur, prompting ICU admission.<sup>187</sup> In April 2020, European clinicians reported unusual clusters of pediatric patients admitted to the hospital with hyperinflammation<sup>188</sup> and clinical features resembling Kawasaki disease (KD),<sup>189</sup> toxic shock syndrome,<sup>190</sup> and myocarditis.<sup>191</sup> Many patients were previously healthy, with symptoms appearing 2 to 6 weeks after the first wave of COVID-19 in Europe. Although few patients tested positive by SARS-CoV-2 polymerase chain reaction (PCR), most cases had antibody evidence of prior infection.<sup>187,192,193</sup> US cases were soon reported in New York after the first surge of SARS-CoV-2 infections.<sup>192</sup> Initially called the pediatric inflammatory multi-system syndrome temporally associated with SARS-CoV-2 (PIMS-TS),<sup>194,195</sup> a new case definition and new name, MIS-C, was published by the CDC.<sup>196</sup> The name change was made to allow for cases in adults that have now been described.<sup>197–200</sup>

Several epidemiologic case definitions are published for MIS-C (**Table 5**) each requiring clinical, virologic, and inflammatory marker data.<sup>194,196,201</sup> Of note, the CDC case definition specifically requires severe illness and hospitalization highlighting an important distinction between the definitions. Although a clinically significant condition, MIS-C is thought to be rare. Early estimates in New York State showed that although laboratory-confirmed SARS-CoV-2 infection in people younger than 21 years old was 322 per 100,000 individuals, the number of MIS-C cases over the same time-frame was 2 per 100,000 individuals.<sup>192</sup> Using surveillance data from US jurisdictions reporting MIS-C cases, the incidence between April and June 2020 was estimated to be 5.1 persons per 1,000,000 person-months, with 316 MIS-C cases per 1,000,000 SARS-CoV-2 infections.<sup>202</sup> Few MIS-C cases were reported in China and other countries in eastern Asia early in the pandemic with possible explanations including differences in SARS-CoV-2 burden, changes in the virus, or the implementation of different public health interventions.<sup>203</sup> Cases of MIS-C have now been reported in these regions.

Despite efforts to uncover the underlying mechanism of disease, the pathophysiologic cause of the syndrome is not fully understood.<sup>203</sup> Hypotheses based on associations with KD, a form of childhood vasculitis that shares clinical features with MIS-C, and the clinical course after acute COVID-19, suggests an immune-mediated process possibly driven by auto-antibody activity.<sup>204</sup> Immune profiling in those with KD, acute COVID-19, and MIS-C show differences in cellular subtypes and inflammatory protein composition that distinguish the 3 different diagnoses.<sup>204</sup> Antibody profiling also showed evidence of possible cardiac-specific auto-recognition, suggesting a mechanism for the cardiovascular and coronary damage characteristic of both MIS-C and KD.<sup>204</sup> Additional research will be needed to further stratify the immune differences between these 2 conditions and to identify the mechanisms that may provide clues to future therapies.

Children with MIS-C tend to be older and more racially and ethnically diverse than those with KD.<sup>205,206</sup> One US population-based study of MIS-C found the median age of children with MIS-C to be 9 years,<sup>207</sup> with children as young as less than 1 month old reported in the literature.<sup>192,205</sup> Whether race is an important risk factor in developing MIS-C after acute COVID-19 is still being investigated. Early studies showed a disproportionate risk of MIS-C in communities of color,<sup>190,207</sup> initially considered a reflection of disparities seen in acute SARS-CoV-2 infection.<sup>208,209</sup> However, more recent studies comparing MIS-C and COVID-19 showed an unexplained independent risk of MIS-C that continues to exist for those of Hispanic ethnicity or Black race.<sup>210,211</sup> Children affected by MIS-C tend to have fewer underlying medical conditions, with obesity a common diagnosis if chronic conditions were present.<sup>192,207</sup> Although MIS-C case definitions allow for the use of SARS-CoV-2 PCR, antibodies, antigen, or exposure as virologic confirmation, most children will have evidence of prior infection via SARS-CoV-2 antibodies.<sup>207</sup> As more children are vaccinated, use of anti-SARS-CoV-2 antibody tests other than spike protein antibodies will be required to differentiate between immunity from prior infection and vaccination. In the absence of SARS-CoV-2 testing, exposure to an individual with diagnosed COVID-19 or COVID-19-compatible symptoms also satisfy case definition requirements.

Clinical features of MIS-C vary by case and by age group.<sup>192</sup> All current MIS-C case definitions require fever during the illness as part of the diagnosis. Fever may be subjective or measured ( $\geq 38^{\circ}\text{C}$ ), and is commonly persistent, lasting approximately 6 days in most children.<sup>193</sup> Many children will present to the hospital still febrile.<sup>192</sup> Other common symptoms at hospital presentation include GI symptoms (eg, abdominal pain, diarrhea, nausea, and vomiting), headache and neck pain,

lymphadenopathy, myalgias, fatigue, sore throat, and mucocutaneous findings (eg, rash, red tongue, cracked lips and conjunctivitis).<sup>192,212–214</sup> Severe GI complications (eg, adenomesenteritis, appendicitis, abdominal fluid collections, pancreatitis, and intussusception) were frequently diagnosed in children with acute COVID-19 and MIS-C.<sup>213</sup> Chest pain and symptoms of myocarditis are more common in older children and adolescents.<sup>192</sup> Patients with MIS-C may have respiratory symptoms such as cough and shortness of breath, but these are more common in patients with acute COVID-19.<sup>207</sup> At hospital admission, vital signs seen in patients with MIS-C include fever, tachycardia, and tachypnea, typically without hypoxemia.<sup>192</sup> Symptoms of shock, including hypotension, were seen in approximately one-third of the cases described in New York State.<sup>192</sup> Subsets of patients may fulfill criteria for the diagnosis of KD, particularly those in the younger age groups.<sup>192</sup>

Laboratory findings show evidence of severe systemic inflammation. Complete blood count results can include neutrophilia, lymphopenia, anemia, and thrombocytopenia.<sup>192,193,212</sup> Inflammatory markers are broadly elevated, which generally include CRP, erythrocyte sedimentation rate, fibrinogen, ferritin, D-dimer, lactate dehydrogenase, procalcitonin, alanine aminotransferase, and IL-6 levels.<sup>192,193</sup> Other laboratory abnormalities, such as hypoalbuminemia, hyponatremia, and prolonged international normalized ratio, may be present.<sup>192,193</sup> Evidence of cardiovascular injury with elevated troponin, brain natriuretic peptide (BNP), or N-terminal proBNP is also common.<sup>192</sup> Specific level cutoffs and the predictive ability of individual tests for MIS-C diagnosis have not been established, although one observational study found that patients with MIS-C may have lower absolute counts of lymphocytes and platelets as well as greater CRP concentrations than children without MIS-C who are evaluated for outpatient febrile illness.<sup>215</sup> MIS-C is frequently associated with echocardiographic findings, including evidence of ventricular dysfunction with depressed ejection fraction, pericardial effusion, valvular dysfunction, and coronary artery dilatation or aneurysms.<sup>192,216</sup> Given the prominent GI symptoms at presentation, children with MIS-C may also undergo abdominal imaging to rule out other etiologies, including appendicitis. Common abnormal findings seen on abdominal ultrasonography or CT include liver and spleen enlargement, mesenteric adenopathy, trace ascitic or pelvic fluid, and inflammation of the intestines and appendix with bowel-wall thickening and fluid-filled bowel loops.<sup>192</sup> In children who receive chest radiography, evidence of pulmonary opacities or infiltrates may be present.<sup>217</sup> The hospital course for children with MIS-C may include admission to the ICU for close clinical monitoring, vasopressor support, and less frequently mechanical ventilation.<sup>192,193</sup> Extracorporeal membrane oxygenation may be required in a small number of patients.<sup>192,193</sup> Despite the morbidity associated at hospital presentation, children with MIS-C are often discharged within a week of admission,<sup>192</sup> mortality remains low,<sup>207</sup> and long-term outcomes, including functional outcomes, have been minimal<sup>218</sup> with resolution of most cardiac findings at subsequent follow-up visits.<sup>219</sup> Among those with persistent cardiovascular abnormalities, aneurysmal changes were seen in one group of children followed longitudinally.<sup>219</sup> Whether MIS-C can reoccur in children who experience reinfection is unknown; however, one published case study showed no reoccurrence of MIS-C with subsequent SARS-CoV-2 infection.<sup>77</sup>

The American College of Rheumatology, American Academy of Pediatrics, and the PIMS-TS National Consensus Management Study Group have provided a tiered guidance approach for the workup and management of MIS-C (**Table 6**).<sup>220–222</sup> Cases of MIS-C likely constitute a spectrum of disease with mild cases less frequently represented in the literature. Children with evidence of critical illness require workup for alternative diagnoses including, but not limited to, acute COVID-19, acute non-

**Table 5**  
Case definitions of MIS-C

Institution	US Centers for Disease Control and Prevention <sup>196</sup>	World Health Organization <sup>201</sup>	Royal College of Pediatrics and Child Health <sup>194</sup>
Age group	An individual aged <21 y presenting with the following:	Children and adolescents 0–19 y of age with the following:	A child presenting with the following:
Fever	fever $\geq 38.0^{\circ}\text{C}$ for $\geq 24$ h, or report of subjective fever lasting $\geq 24$ h AND	fever $\geq 3$ d AND	persistent fever $>38.5^{\circ}\text{C}$ AND
Inflammation	Laboratory evidence of inflammation including, but not limited to, 1 or more of the following: elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin AND	Elevated markers of inflammation such as ESR, CRP, or procalcitonin AND	Inflammation (neutrophilia, elevated CRP, and lymphopenia) AND
Severity of illness	Evidence of clinically severe illness requiring hospitalization AND		
Organ system involvement	With multisystem ( $\geq 2$ ) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurologic)	2 of the following: (1) Rash or bilateral nonpurulent conjunctivitis or mucocutaneous inflammation signs (oral, hands or feet). (2) Hypotension or shock. (3) Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiogram findings or elevated troponin/NT-proBNP. (4) Evidence of	Evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal gastrointestinal or neurologic disorder)

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<b>Table 5 (continued)</b>			
<b>Institution</b>	<b>US Centers for Disease Control and Prevention<sup>196</sup></b>	<b>World Health Organization<sup>201</sup></b>	<b>Royal College of Pediatrics and Child Health<sup>194</sup></b>
		coagulopathy (by PT, PTT, elevated d-Dimers). (5) Acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain).	
	AND	AND	AND with additional features <sup>a</sup> AND
Alternative explanations	No alternative for plausible diagnoses	No other obvious microbial cause of inflammation, including the following: Bacterial sepsis Staphylococcal or streptococcal shock syndromes	Exclusion of any other microbial cause including the following: Bacterial sepsis Staphylococcal or streptococcal shock syndromes Infections associated with myocarditis (such as enterovirus)
	AND	AND	AND
Virologic testing	Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 wk before the onset of symptoms	Evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19	SARS-CoV-2 PCR testing may be positive or negative
Additional comments	Some individuals may fulfill full or partial criteria for Kawasaki disease but should be reported if they meet the case definition for MIS-C Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection		This may include children fulfilling full or partial criteria for Kawasaki disease

**Abbreviations:** COVID-19, coronavirus disease 2019; MIS-C, multisystem inflammatory syndrome in children; NT-proBNP, N-terminal pro brain natriuretic peptide; PT, prothrombin time; PTT, partial thromboplastin time; RT-PCR, reverse-transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory distress syndrome coronavirus 2.

<sup>a</sup> Additional features: abnormal fibrinogen, high D-dimer, high ferritin, hypoalbuminemia, acute kidney injury, anemia, coagulopathy, high interleukin (IL)-10, high IL-6, proteinuria, raised creatine kinase, raised lactate dehydrogenase, raised triglycerides, raised troponin, thrombocytopenia, transaminitis.

SARS-CoV-2 infection, and KD. For children in whom MIS-C is considered, basic laboratory workup should be pursued. If there is evidence of inflammation, a broader scope of inflammatory markers should be obtained to help differentiate between MIS-C and other etiologies of inflammation. Chest and abdominal radiography can be considered, especially in the workup of other disease processes, but a diagnosis of MIS-C cannot be made based on these results alone. Given the prominence of cardiovascular findings, guidance extrapolated from the workup of KD has been recommended, which includes obtaining laboratory markers of cardiac injury (BNP and troponin), echocardiography, and electrocardiography. Treatment is also extrapolated from the management of KD; expert panelists note that not all patients will require immunomodulatory therapy. When therapy is considered, immunomodulators include intravenous immunoglobulin (IVIG) with or without glucocorticoids, as well as biologics are options. Biologics such as anakinra or infliximab are used if the patient's disease is refractory to the first-line therapies of IVIG and glucocorticoids. To date, there have been no clinical trial data available to guide the treatment of MIS-C. Observational data comparing IVIG with glucocorticoid and IVIG alone suggested that combined therapy was associated with fewer days of fever and may be associated with lower risk of new or persistent MIS-C–associated cardiovascular dysfunction.<sup>223,224</sup>

### POST-ACUTE SEQUELAE OF CORONAVIRUS DISEASE 2019 IN CHILDREN

A picture of long-term symptoms experienced by children after SARS-CoV-2 infection is emerging. First recognized in adults, post-acute sequelae of COVID-19 (PASC) or “long COVID-19,” is a constellation of persistent symptoms affecting different organ systems reported by patients recovering from all spectrums of acute COVID-19, including those with asymptomatic infection.<sup>225,226</sup> Currently, no formal definition or diagnostic criteria describes PASC, and individuals experiencing longer term symptoms likely represent a heterogeneous cohort. The prevalence of PASC is unknown, although a review of published reports show variability by study from 4% to 66%.<sup>227</sup> Among the few studies describing persistent symptoms in children, fatigue, persistent cough, difficulties with concentration, chest pain, heart palpitations, dyspnea, headache, dizziness, sore throat, and sleep disturbances were experienced up to 8 months after acute infection.<sup>228–232</sup> Short-term cognitive and psychiatric complications have also been observed in the aftermath of acute COVID-19, and whether these will persist in the long-term is not known.<sup>233</sup> Similar to adults, these symptoms may relapse and remit over the illness course. Information on the cause and optimal management of these patients is unknown and may require interdisciplinary rehabilitation<sup>234</sup> directed toward specific symptoms experienced by the individual. Long-term follow-up studies of children recovering from SARS-CoV-2 infection, including the UK CLoCK<sup>235</sup> and NIH RECOVER<sup>236</sup> studies, will be helpful to further characterize PASC in children.

### OTHER HEALTH IMPACTS ON CHILDREN DURING THE CORONAVIRUS DISEASE 2019 PANDEMIC

In addition to the direct health effects of COVID-19, the pandemic has had adverse collateral health impacts on children due to the impacts of COVID-19 in adults, community-wide mitigation efforts, and school closures. Early in the pandemic, the number of primary care preventive and acute care visits decreased.<sup>237</sup> Changes in health-care-seeking behavior have led to decreased routine screening tests, such as blood lead level testing<sup>238</sup> and a decrease in childhood vaccination rates.<sup>239</sup> Delays in care have exacerbated health-related outcomes, including appendicitis,<sup>240</sup> asthma



**Table 6**  
**MIS-C workup and treatment**

Pediatric Organization	American College of Rheumatology <sup>220</sup>	American Academy of Pediatrics <sup>222</sup>	PIMS-TS National Consensus Management Study Group <sup>221</sup>
	Children presenting with unremitting high fever, an epidemiologic link to SARS-CoV-2 and suggestive clinical symptoms of MIS-C	Persistent fever ( $\geq 3$ d) without a clear clinical source accompanied by symptoms concerning in their severity or coincident with recent exposure to a person with COVID-19	Children presenting to the hospital with fever, abdominal pain, gastrointestinal, respiratory or neurologic symptoms who are stable
Laboratory studies	<p>Tier 1: Complete blood cell count with differential, complete metabolic panel, ESR, CRP, and testing for SARS-CoV-2 (by PCR or serology); If ESR or CRP are elevated and at least 1 other laboratory feature: lymphopenia, neutrophilia, thrombocytopenia, hyponatremia, or hypoalbuminemia, then proceed to tier 2;</p> <p>Tier 2: includes cardiac assessment and markers of systemic inflammation, which may include D-dimer, ferritin, procalcitonin, LDH, cytokine panels (including IL-6, tumor necrosis factor, or IL-10), and Cardiac laboratory values: troponin, B-type natriuretic peptide; a peripheral blood smear for assessment of microangiopathic changes can be considered</p>	<p>Initial: Complete blood cell count with differential, urine analysis, ESR, and CRP</p> <p>Subsequent studies based on initial clinical suspicion or evidence of inflammation: Ferritin, LDH, comprehensive metabolic panel, proBNP, troponin, and fibrinogen</p> <p>In addition to the above, hospitalized children should also obtain triglycerides, creatinine kinase, amylase, blood and urine culture, D-dimer, prothrombin time/partial thromboplastin time, INR, SARS-CoV-2 PCR and SARS-CoV-2 serology (before the administration of IVIG)</p> <p>In severely ill-appearing or hemodynamically fragile patients, laboratory testing should be obtained regardless of duration of fever</p>	<p>Initial: Full blood count, CRP, urea, creatinine, electrolytes, and liver function</p> <p>Second line (done within 12 h of admission): blood gas and lactate, fibrinogen, ferritin, D-dimer, troponin, NT-proBNP, LDH, SARS-CoV-2 RT-PCR test, and SARS-CoV-2 serology, septic and viral screen (lumbar puncture only if specifically indicated)</p>
Imaging	Echocardiogram; cardiac computed tomography should be considered in patients with suspected distal	Chest radiograph, consider echocardiogram and/or cardiac MRI	Done within 12 h of admission: chest radiograph; echocardiogram (daily in those who are physiologically

	coronary artery aneurysms not well visualized on echocardiogram	under consultation with pediatric cardiology	unstable) Abdominal ultrasound to rule out alternative diagnoses
Other studies	ECG every 48 h; telemetry in those with conduction abnormalities	ECG	ECG
Treatment	<p>Depending on the severity of symptoms, in addition to supportive care, the following therapies are recommended:</p> <p>First tier: IVIG (2 g/kg) should be given to patients with MIS-C who are hospitalized and/or fulfill KD criteria;</p> <p>Adjunctive: low to moderate dose steroids can be considered in children with milder forms of MIS-C who are persistently febrile and symptomatic despite IVIG; low to moderate dose glucocorticoids should be used with IVIG in those with severe or refractory disease; high and pulse dose glucocorticoids can be considered in those who do not respond to IVIG and low to moderate dose glucocorticoids</p> <p>Refractory disease: Anakinra (&gt;4 mg/kg per d) can be considered in those refractory to IVIG and glucocorticoids.</p> <p>Low-dose aspirin (3–5 mg/kg per d) should be used until normalization of platelet count and normal coronary arteries at <math>\geq 4</math> wk after</p>	<p>IVIG (2 g/kg with max of 100 g)</p> <p>In patients who do not improve either clinically or by laboratory values, additional treatment can include steroid therapy (2–30 mg/kg per d of methylprednisolone depending on illness severity) and biologics (anakinra, 2–10 mg/kg per d, subcutaneously or intravenously, divided every 6–12 h)</p> <p>All patients with MIS-C should be started on low-dose aspirin (except for those with platelets &lt; 100,000 or active bleeding)</p>	<p>Continue treatment for presumed sepsis until microbiological cultures are available and preferred enrollment in a clinical trial for additional therapies; in the absence of a clinical trial, then the following was recommended:</p> <p>Children with KD-like phenotype (fulfills complete or incomplete KD criteria):</p> <p>First line: IVIG (2 g/kg single or divided dose) is recommended and a second dose can be considered for children who partially responded or have not responded at all to the first dose;</p> <p>Second line: methylprednisolone is recommended (10–30 mg/kg per d for 3 d) 24 h after IVIG if child remains unwell; given at the same time as IVIG in high-risk children (eg, age &lt;12 mo and those with coronary artery changes)</p> <p>Third line: biological therapy is recommended with infliximab as biological therapy of choice for KD-like phenotype</p> <p>Children with nonspecific</p>

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**Table 6**  
(continued)

Pediatric Organization	American College of Rheumatology <sup>220</sup>	American Academy of Pediatrics <sup>222</sup>	PIMS-TS National Consensus Management Study Group <sup>221</sup>
	<p>diagnosis (except in those with active bleeding, risk of bleeding, or platelet count <math>\leq 80,000/\mu\text{L}</math>)</p> <p>Patients with MIS-C with coronary artery aneurysm with z-score <math>\geq 10</math> should be treated with low-dose aspirin and therapeutic anticoagulation with enoxaparin or warfarin</p>		<p>presentation and evidence of coronary artery abnormality, meeting criteria for toxic shock syndrome, evidence of progressive disease or extended duration of fever <math>&gt;5</math> d:</p> <p>First line: IVIG (2 g/kg single or divided dose) is recommended and a second dose can be considered for children who partially responded or have not responded at all to the first dose;</p> <p>Second line: methylprednisolone is recommended (10–30 mg/kg per d for 3 d)</p> <p>Third line: biological therapy is recommended (may include anakinra, infliximab, and tocilizumab)</p> <p>All children <math>&lt;12</math> y should wear compression stockings</p> <p>Follow local KD guidelines for aspirin dosing and continued for a minimum of 6 wk</p> <p>Follow local protocols for children with a thrombotic event</p> <p>Discuss with hematologist regarding long-term antiplatelet and anticoagulation therapy in children with abnormal coronary arteries</p>

Follow-up	<p>Echocardiogram: 7–14 d then 4–6 wk after presentation; consider 1 y echocardiogram in those with cardiac abnormalities</p> <p>Cardiac MRI at 2–6 mo in those with moderate to severe left ventricular dysfunction</p> <p>ECG: at each follow-up; consider a Holter monitor in those with conduction abnormalities</p>	Close follow-up 1–2 wk after discharge with pediatric cardiology and, if steroids or biologics were used, pediatric rheumatology	Recommended follow-up at 1–2 wk and 6 wk after discharge with echocardiography; multidisciplinary follow-up with pediatric infectious disease, immunology, and cardiology in those with coronary artery abnormalities or who have required organ support
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*Abbreviations:* CRP, C-reactive protein; ECG, electrocardiogram; ESR, erythrocyte sedimentation rate; IL, interleukin; INR, international normalized ratio; IVIG, intravenous immunoglobulin; KD, Kawasaki disease; LDH, lactate dehydrogenase; MIS-C, multisystem inflammatory syndrome in children; NT-proBNP, N-terminal pro brain natriuretic peptide; PCR, polymerase chain reaction; PIMS-TS, pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2; RT-PCR, reverse-transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory distress syndrome coronavirus 2.

exacerbation,<sup>241</sup> and cancer treatment.<sup>242</sup> The global prevalence of depression and anxiety in children highlight the persistent exacerbation of mental health illnesses.<sup>243</sup> In addition to these acute medical issues, the pandemic has altered the daily habits of families, resulting in decreases in physical activity<sup>244</sup> and increase in hours of screen time in children.<sup>245</sup> These and other social disruptions have had substantial adverse effects on mental health<sup>246,247</sup> and behavior.<sup>248</sup> Family units have also been disrupted because of the deaths of parents and caregivers as a result of COVID-19,<sup>249</sup> exacerbating income inequalities<sup>250</sup> and food insecurity.<sup>251,252</sup> Early studies during the pandemic suggested increases in cases of child abuse and neglect<sup>253,254</sup>; however, there is some evidence to suggest that the increase in family time and strengthening of family support systems helped mitigate instances of physical abuse of children.<sup>255</sup> With school closures, learning was adapted to minimize face-to-face contact.<sup>256</sup> Although schools have resumed in-person learning for the most part, the full impact of changes in childhood education during the pandemic has yet to be fully quantified.

## SUMMARY

The SARS-CoV-2 pandemic has led to unprecedented worldwide morbidity and mortality impacting children of all ages. Pediatric acute COVID-19 has likely been underestimated given the milder presentation of disease and testing paradigms, although severe outcomes have been experienced by all age groups. The post-acute sequelae of acute COVID-19, including MIS-C and chronic persistent symptoms, experienced by children who recovered from acute COVID-19 emphasize the importance of infection mitigation. Safe and effective SARS-CoV-2 vaccines are available to most pediatric age groups and are becoming more available worldwide, with booster doses available in some settings. There is a dearth of clinical trial data to determine the ideal treatment in children; future studies must include children to help guide therapy. In addition to direct impacts of infection, children have suffered disproportionately given the closure of schools, loss of adult caregivers, and disruption to household stability. Further changes in the pandemic are likely as SARS-CoV-2 variants arise and public health measures are loosened, but community-wide public health interventions aimed at curbing the pandemic will have important consequences for children's health.

## CLINICS CARE POINTS

- SARS-CoV-2 infections are more commonly asymptomatic, with milder disease presentations of COVID-19 in children, although children of all ages are at risk for severe outcomes; SARS-CoV-2 vaccines remain a mainstay of COVID-19 prevention in children.
- MIS-C and persistent symptoms after SARS-CoV-2 infection are important post-acute COVID-19 sequelae in children and emphasize the need for preventing pediatric infections.
- The management of acute COVID-19 and MIS-C requires clinical and laboratory investigations to rule out alternative etiologies for which treatment is available, and follow-up may be required.
- Optimal therapy for acute COVID-19 and MIS-C is unknown and is guided by expert panels; consultation with subspecialists is advised when therapy is considered in children.
- Maintaining regular preventive care and ensuring high rates of childhood vaccine uptake are vital to prevent long-term consequences of non-COVID-19 disease and other infectious disease outbreaks.

- Indirect impacts of the SARS-CoV-2 pandemic threaten the health and well-being of children worldwide.

## DISCLOSURE

E.J. Chow has no conflicts of interest to disclose. J.A. Englund reports research support from AstraZeneca, Merck, and Pfizer, and has been a consultant for Sanofi Pasteur, Meissa Vaccines, Teva Pharmaceuticals, AstraZeneca.

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