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Severe Acute Respiratory Syndrome Coronavirus 2 Infections in Children

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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.\textsuperscript{1,2} Overall, the number and incidence of reported infections and cases of...
severe disease in children are fewer than those reported in adults. 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; 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, leading to underreporting of pediatric cases at the start of the pandemic. 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. 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. 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. Many of these studies conducted in different countries before and after vaccine availability 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. In the United States, individuals younger than 18 years comprise 22% of the population, yet only 13% of COVID-19 cases have been reported in children. 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). 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.

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. 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) SARS-CoV-2 variant. 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. In August 2021, the cumulative hospitalization rate for pediatric COVID-19 rose to 49.7 per 100,000 individuals. 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. 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 and viral mutations allowing the evasion of prior immunity leading to rapid global spread and a spike in infection numbers. In the United States, the spread of the Omicron variant was associated with a rapid increase in COVID-19–associated pediatric hospitalizations. 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.

| 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 |

*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*

*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. 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. 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. Hispanic and Latinx adults and children have experienced some of the highest rates of SARS-CoV-2 test positivity, particularly during community-wide shelter-in-place directives. Among individuals younger than 18 years with SARS-CoV-2 infection, rates of hospitalization were highest among Hispanic and Latinx children. The cause of these disparities is likely multifactorial, including disproportionate burden of chronic conditions, decreased access to health care and testing, difficulty with social distancing in multigenerational households, and greater representation in essential and in-person occupations with exposure risk to COVID-19 within the Hispanic and Latinx communities. 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. 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, were first implemented in 2020 to reduce community transmission. 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. Past experiences with other viruses demonstrate that children carry the community burden of influenza and respiratory syncytial viral infections, and public health interventions, such as vaccination of children, can reduce community-wide infections. 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, and the use of face coverings, social distancing, and school closures contributed to community mitigation of infection early in the pandemic. Children are both at risk for acquiring infection and spreading SARS-CoV-2. Factors influencing individual transmissibility include symptomology, viral load, and behavioral patterns. 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, in which pediatric index cases of household SARS-CoV-2 infections were less common. 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. 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. Furthermore, families are likely to physically interact more with younger ill children, leading to an increased risk for viral transmission. 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. These studies were limited to smaller sample sizes 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. In one community-based surveillance study, SARS-CoV-2 viral loads were similar regardless of symptoms and age. 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 with prolonged shedding and higher levels of viral particles in pediatric fecal samples. Thus far, significant fecal-oral transmission in close contacts of children with persistent fecal detection of SARS-CoV-2 has not been reported. SARS-CoV-2 reinfection has been documented in children, although the degree at which it occurs is unknown. 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. One early investigation in Ireland, where reported SARS-CoV-2 cases were screened for recent school attendance, reported no confirmed cases among school contacts. 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. 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. 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. 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, and larger increases of county case rates were seen when school mask mandates were optional. 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.
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\(^8\) including the Pfizer-BioNTech (BNT162b2) vaccine for those aged \(\geq 12\) years\(^8\) (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.\(^8\) 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,\(^9\) receiving full FDA approval on August 23, 2021.\(^9\) On May 10, 2021, this vaccine was granted EUA in those aged 12 to 15 years\(^9\) with a 10 micro gram dose receiving EUA on October 29, 2021, for those ages 5 to 11 years.\(^9\) 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,\(^9\) and for those aged 12 to 15 years on January 3, 2022.\(^9\) Booster doses administered \(\geq 5\) months after completion of the primary series are increasingly important with the spread of the Omicron variant.\(^8\) A third primary dose of Pfizer-BioNTech has been authorized by the FDA for moderately or severely immunocompromised children aged \(\geq 5\) years.\(^9\) 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.\(^9\) 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.\(^1\) 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.\(^2\) 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.\(^3\) 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.\(^4\) 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.\(^5\)
# 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) | 1. 100% vaccine efficacy against confirmed COVID-19 in individuals aged 12–15 y | 1. 2-dose primary series separated by 21 d 2. 1 additional primary dose in immunocompromised persons (≥28 d since 2nd dose) 3. Booster dose ≥5 mo after last dose in primary series | 1. FDA approved for individuals ≥16 y 2. FDA EUA for individuals 5–15 y 3. Booster dose approval for individuals aged ≥12 y 4. Third primary series dose for certain immunocompromised children ≥5 y | 1. December 11, 2020: FDA EUA for individuals ≥16 y 2. May 10, 2021: FDA EUA for individuals 12–15 y 3. August 12, 2021: FDA EUA for third primary dose for certain immunocompromised individuals 4. August 23, 2021: FDA approved for individuals ≥16 y 5. September 22, 2021: FDA updated EUA to allow for single booster dose for high-risk populations aged ≥18 y administered at least 6 mo after completion of primary series 6. October 20, 2021: FDA updated EUA to allow for heterologous booster dose in eligible individuals |
| Vaccine Name | Manufacturer | Vaccine Type | Reported Vaccine Efficacy in Children | Schedule | Approval for Children | Approval Dates |
|--------------|--------------|--------------|---------------------------------------|----------|-----------------------|----------------|
| mRNA-1273    | Moderna (Intramuscular) | mRNA | 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$^{260}$ |
|              |              |              |                                       |          |                       | 7. October 29, 2021: FDA EUA for individuals 5–11 y$^{259}$ |
|              |              |              |                                       |          |                       | 8. November 19, 2021: FDA updated EUA to allow for single booster dose for all individuals aged $\geq 18$ y$^{259}$ |
|              |              |              |                                       |          |                       | 9. December 9, 2021: FDA updated EUA to allow for single booster dose in individuals aged 16–17 y$^{96}$ |
|              |              |              |                                       |          |                       | 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$^{97}$ |
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)\(^{103}\) primary dose in immunocompromised persons\(^a\) (\(\geq 28\) d since 2nd dose) 3. Booster dose \(\geq 5\) mo after last dose in primary series 2. August 12, 2021: FDA EUA for third primary dose for certain immunocompromised individuals\(^a,260\) 3. October 20, 2021: FDA updated EUA to allow for booster dose for high-risk populations\(^b\) aged \(\geq 18\) y administered at least 6 mo after completion of primary series, including the use of a heterologous booster dose in eligible individuals\(^{260}\) 4. November 19, 2021: FDA updated EUA to allow for single booster dose for all individuals aged \(\geq 18\) y\(^{260}\) 5. January 7, 2022: FDA updated EUA to shorten interval between completion of primary vaccine series to booster to \(\geq 5\) mo for all individuals \(\geq 18\) y\(^{261}\) Ad26.COV2.S Janssen/Johnson & Johnson Viral vector (Intramuscular) Data not available 1. Single primary dose 2. Booster dose \(\geq 2\) mo after primary dose Not approved by FDA for children 1. February 27, 2021: FDA EUA for individuals \(\geq 18\) y\(^{262}\) 2. October 20, 2021: FDA updated EUA to allow for a single booster dose (continued on next page)
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 ≥18 y and allows for the use of a heterologous booster dose in eligible individuals |          |                      |               |
|              |              |              | December 16, 2021: CDC ACIP recommendations updated, preferring approved mRNA vaccines over Janssen vaccine for primary and booster vaccinations |          |                      |               |

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.

a 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.

b 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] ≥30 kg/m²) and overweight (BMI ≥25 kg/m² but < 30 kg/m²), 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).
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. In 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%. 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. Furthermore, early data show the protective effects of SARS-CoV-2 vaccination against MIS-C with a lower incidence with vaccination and an estimated VE of 91% in adolescents 12 to 18 years who had completed a primary vaccine series with the Pfizer-BioNTech vaccine. 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 fully vaccinated. 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.

Overall, SARS-CoV-2 vaccines have had a favorable safety profile among children aged 5 to 17 years. Most vaccine reactions to the Pfizer-BioNTech vaccine reported were local or mild systemic reactions, with the exception of a small group of individuals, overwhelmingly male adolescents and younger adults, who reported self-limited cases of myocarditis and pericarditis. 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. 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. 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. Given the severe outcomes of SARS-CoV-2 infection including myocarditis, 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. 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, 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).\textsuperscript{122,123} Illness duration is estimated to be a median of 6 days, but prolonged illness greater than 28 days can occur.\textsuperscript{124} Overall, symptom duration is shorter in younger children.\textsuperscript{124} 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.\textsuperscript{9} 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.\textsuperscript{124} 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.\textsuperscript{125} 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.\textsuperscript{9,124}

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).\textsuperscript{126} Given these definitions are

| **Table 3** | Symptom frequency in pediatric patients with acute COVID-19 |
|-------------|----------------------------------------------------------|
|             | CDC Surveillance Report - United States\textsuperscript{9} | Longitudinal Cohort of School-Aged Children - UK\textsuperscript{124} |
|             | Age Group | Overall | 0–9 y | 10–19 y | Age Group | Overall | 5–11 y | 12–17 y |
| Symptoms    | %         | %       | %       | %       | %         | %       | %       | %       |
| 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.
| 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. Monoclonal antibodies are available by EUA to individuals ≥12 y and >40 kg who are at risk for severe disease, but preferably be used in the context of a clinical trial. The EUA for bamlanivimab–etesevimab has been extended to children of all ages including hospitalized children from birth to 2 y of age; with the Omicron variant, sotrovimab is the only approved monoclonal antibody with maintained efficacy against the new virus and should be administered within 10 d of symptom onset. |
| 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. | | |
| 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, |

(continued on next page)
### Table 4 (continued)

| Severity of COVID-19 | General Definition | Pediatric Considerations | Treatment Recommendations |
|----------------------|--------------------|--------------------------|---------------------------|
| **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 (Pao<sub>2</sub>/FiO<sub>2</sub>) <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. | 1. Caregivers and close contacts take appropriate precautions including encouraging SARS-CoV-2 vaccine uptake, if eligible.  
2. 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.  
3. Dexamethasone<sup>a</sup> can be considered in critical disease, particularly in older age groups.  
4. Interleukin-6 (eg, tocilizumab) or interleukin-1 (eg, anakinra) inhibitors can be considered in critical disease, preferably in the setting of a clinical trial. |
| **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 Table 5. | |

**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. 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. 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. In another study of individuals younger than 21 years, at least one underlying medical condition was associated with 75% of SARS-CoV-2. There does not appear to be a significant risk of severe disease associated with male gender, as there is in adults. Some studies suggest that younger children (infants aged <1 year) did not have increased risk for severe disease although early reports showed higher proportions of severe and critical illness in the younger age groups. 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. Among children aged 12 to 18 years, those with asthma were at increased risk for severe illness. Other possible conditions at risk for severe outcomes in children include complex medical conditions, genetic disorders such as trisomy 21, sickle cell disease, congenital heart disease and immunosuppression. 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. 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. In addition, there has been little evidence to suggest transmission via breast milk, and breastfeeding is encouraged for those who are interested.

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. Acute COVID-19 in children can also be complicated by cardiovascular events, including myocarditis, pericarditis, pulmonary embolic events, arrhythmias, and acute myocardial infarction. 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. GI and renal complications have also been described. Invasive mold infections (eg, pulmonary aspergillosis and mucormycosis) are increasingly recognized complications of severe COVID-19 in adults, although rarely reported in children. 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 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. 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. Elevations of creatine kinase, pro B-type natriuretic peptide, and troponin can be seen in those with end-organ disease. 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. Children may have abnormalities of chest imaging even with asymptomatic and presymptomatic infection. 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. 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. 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 ≥12 years and ≥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.168 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,169 with pediatric experts recommending against its routine use in children, including those with risk factors for severe disease.170

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 ≥12 years and weighing ≥40 kg with COVID-19.171 It remains available under EUA to children weighing 3.5 kg to less than 40 kg or those younger than 12 years and weighing ≥3.5 kg.171 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-19.172–174 The NIH recommends remdesivir for children ≥12 years and weighing ≥40 kg with new or increasing oxygen requirement with risk factors for severe disease,169 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.175 They also recommend remdesivir for children aged ≥16 years with acute COVID-19 and new or increasing oxygen requirement regardless of the presence of severe disease risk factors.169 Although there are data to support early remdesivir to mitigate severe acute COVID-19 in outpatients with symptomatic SARS-CoV-2 infection,176 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-19.177 WHO has recommended against the use of remdesivir for children, citing a lack of important clinical differences in mortality and severe outcomes.178 In general, remdesivir is well tolerated. Reports of sinus bradycardia associated with its use have been documented in pediatric cases of COVID-19,179 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,180 a ribonucleoside analog, and nirmatrelvir/ritonavir (Paxlovid),181 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 ≥12 years of age and weight of ≥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 \(^{182-184}\); however, data in children are lacking. \(^{185}\) The NIH recommends dexamethasone in patients requiring high-flow oxygenation, mechanical ventilation, or extracorporeal membrane oxygenation. \(^{169}\) 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). \(^{186}\) Dexamethasone use, typically up to 10 days or until discharge, \(^{185}\) 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, \(^{186}\) 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. \(^{169}\)

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. \(^{169,177,178}\)

**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. \(^{187}\) In April 2020, European clinicians reported unusual clusters of pediatric patients admitted to the hospital with hyperinflammation \(^{188}\) and clinical features resembling Kawasaki disease (KD), \(^{189}\) toxic shock syndrome, \(^{190}\) and myocarditis. \(^{191}\) 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. \(^{187,192,193}\) US cases were soon reported in New York after the first surge of SARS-CoV-2 infections. \(^{192}\) Initially called the pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS), \(^{194,195}\) a new case definition and new name, MIS-C, was published by the CDC. \(^{196}\) The name change was made to allow for cases in adults that have now been described. \(^{197-200}\)
Several epidemiologic case definitions are published for MIS-C (Table 5) each requiring clinical, virologic, and inflammatory marker data. 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 timeframe was 2 per 100,000 individuals. 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. 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. 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. 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. 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. 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. 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. One US population-based study of MIS-C found the median age of children with MIS-C to be 9 years, with children as young as less than 1 month old reported in the literature. 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, initially considered a reflection of disparities seen in acute SARS-CoV-2 infection. 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. Children affected by MIS-C tend to have fewer underlying medical conditions, with obesity a common diagnosis if chronic conditions were present. 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. 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. All current MIS-C case definitions require fever during the illness as part of the diagnosis. Fever may be subjective or measured (≥38°C), and is commonly persistent, lasting approximately 6 days in most children. Many children will present to the hospital still febrile. 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). 192,212–214 Severe GI complications (eg, adenomesenteritis, appendicitis, abdominal fluid collections, pancreatitis, and intussusception) were frequently diagnosed in children with acute COVID-19 and MIS-C.213 Chest pain and symptoms of myocarditis are more common in older children and adolescents.192 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-19.203 At hospital admission, vital signs seen in patients with MIS-C include fever, tachycardia, and tachypnea, typically without hypoxemia.192 Symptoms of shock, including hypotension, were seen in approximately one-third of the cases described in New York State.192 Subsets of patients may fulfill criteria for the diagnosis of KD, particularly those in the younger age groups.192

Laboratory findings show evidence of severe systemic inflammation. Complete blood count results can include neutrophilia, lymphopenia, anemia, and thrombocytopenia.192,193,212 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.192,193 Other laboratory abnormalities, such as hypoalbuminemia, hyponatremia, and prolonged international normalized ratio, may be present.192,193 Evidence of cardiovascular injury with elevated troponin, brain natriuretic peptide (BNP), or N-terminal proBNP is also common.192 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.215 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.192,216 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.192 In children who receive chest radiography, evidence of pulmonary opacities or infiltrates may be present.217 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.192,193 Extracorporeal membrane oxygenation may be required in a small number of patients.192,193 Despite the morbidity associated at hospital presentation, children with MIS-C are often discharged within a week of admission.192 mortality remains low,207 and long-term outcomes, including functional outcomes, have been minimal218 with resolution of most cardiac findings at subsequent follow-up visits.219 Among those with persistent cardiovascular abnormalities, aneurysmal changes were seen in one group of children followed longitudinally.219 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.77

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).220–222 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-
| Institution | US Centers for Disease Control and Prevention\(^\text{196}\) | World Health Organization\(^\text{201}\) | Royal College of Pediatrics and Child Health\(^\text{194}\) |
|-------------|--------------------------------------------------|----------------------------------|--------------------------------------------------|
| 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 | fever \(\geq 3\) d | persistent fever \(>38.5^\circ\text{C}\) |
| 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 | Elevated markers of inflammation such as ESR, CRP, or procalcitonin | Inflammation (neutrophilia, elevated CRP, and lymphopenia) |
| Severity of illness | Evidence of clinically severe illness requiring hospitalization | Evidence of clinically severe illness requiring hospitalization | Evidence of clinically severe illness requiring hospitalization |
| 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) |

(continued on next page)
### Table 5 (continued)

| Institution | US Centers for Disease Control and Prevention\(^{196}\) | World Health Organization\(^{201}\) | Royal College of Pediatrics and Child Health\(^{194}\) |
|-------------|------------------------------------------------|---------------------------------|--------------------------------------------------|
|             | coagulopathy (by PT, PTT, elevated d-Dimers). (5) Acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain). | AND | AND |
| AND         | AND                                               | with additional features\(^a\) | 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 | 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.

\(^a\) 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.223,224

**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.225,226 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%. 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.228–232 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.233 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 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 and NIH RECOVER 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.237 Changes in health-care–seeking behavior have led to decreased routine screening tests, such as blood lead level testing and a decrease in childhood vaccination rates.239 Delays in care have exacerbated health-related outcomes, including appendicitis,240 asthma
### Table 6
MIS-C workup and treatment

| Pediatric Organization | American College of Rheumatology | American Academy of Pediatrics | PIMS-TS National Consensus Management Study Group |
|-----------------------|----------------------------------|--------------------------------|--------------------------------------------------|
| | Children presenting with unremitting high fever, an epidemiologic link to SARS-CoV-2 and suggestive clinical symptoms of MIS-C | Persistent fever (≥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 | 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; 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 | Initial: Complete blood cell count with differential, urine analysis, ESR, and CRP Subsequent studies based on initial clinical suspicion or evidence of inflammation: Ferritin, LDH, comprehensive metabolic panel, proBNP, troponin, and fibrinogen 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) In severely ill-appearing or hemodynamically fragile patients, laboratory testing should be obtained regardless of duration of fever | Initial: Full blood count, CRP, urea, creatinine, electrolytes, and liver function 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 (lumbar puncture only if specifically indicated) |
| 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**

- Depending on the severity of symptoms, in addition to supportive care, the following therapies are recommended:
  - **First tier:** IVIG (2 g/kg) should be given to patients with MIS-C who are hospitalized and/or fulfill KD criteria;
  - **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
  - **Refractory disease:** Anakinra (>4 mg/kg per d) can be considered in those refractory to IVIG and low to moderate dose glucocorticoids.
  - **Low-dose aspirin (3–5 mg/kg per d)** should be used until normalization of platelet count and normal coronary arteries at ≥4 wk after IVIG (2 g/kg with max of 100 g)
  - 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)
  - All patients with MIS-C should be started on low-dose aspirin (except for those with platelets < 100,000 or active bleeding)
  - 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:
    - Children with KD-like phenotype (fulfills complete or incomplete KD criteria):
      - **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;
      - **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 <12 mo and those with coronary artery changes)
      - **Third line:** biological therapy is recommended with infliximab as biological therapy of choice for KD-like phenotype

Children with nonspecific

(continued on next page)
| Table 6 (continued) |
|---------------------|
| **Pediatric Management Study Group** |

**American College of Rheumatology**
- Patients with MIS-C with coronary artery aneurysm should be treated with low-dose aspirin and therapeutic anticoagulation with enoxaparin or warfarin.

**American Academy of Pediatrics**
- Patients with MIS-C with high-risk criteria (including active bleeding, risk of bleeding, or platelet count ≤ 80,000/mL) should be treated with low-dose aspirin and therapeutic anticoagulation with enoxaparin or warfarin.

**Diagnosis** (except in those with active bleeding, risk of bleeding, or platelet count ≤ 80,000/mL):

- Patients with MIS-C with coronary artery aneurysm should be treated with low-dose aspirin and therapeutic anticoagulation with enoxaparin or warfarin.

**Presentation and evidence of coronary artery abnormality, meeting criteria for toxic shock syndrome, evidence of progressive disease or extended duration of fever > 5 d:**

- **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.
- **Second line:** Methylprednisolone is recommended (10-30 mg/kg per day for 3 d).
- **Third line:** Biological therapy is recommended (may include anakinra, infliximab, and tocilizumab).

- All children < 12 y should wear compression stockings.
- Follow local KD guidelines for aspirin dosing and continued for a minimum of 6 wk.
- Follow local KD guidelines for aspirin long-term antiplatelet and anticoagulation therapy in children with abnormal coronary arteries.
- Discuss with hematologist regarding long-term antiplatelet and anticoagulation therapy in children with abnormal coronary arteries.
Follow-up

- Echocardiogram: 7–14 d then 4–6 wk after presentation; consider 1 y echocardiogram in those with cardiac abnormalities
- Cardiac MRI at 2–6 mo in those with moderate to severe left ventricular dysfunction
- ECG: at each follow-up; consider a Holter monitor in those with conduction abnormalities

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

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 and cancer treatment. The global prevalence of depression and anxiety in children highlight the persistent exacerbation of mental health illnesses. In addition to these acute medical issues, the pandemic has altered the daily habits of families, resulting in decreases in physical activity and increase in hours of screen time in children. These and other social disruptions have had substantial adverse effects on mental health and behavior. Family units have also been disrupted because of the deaths of parents and caregivers as a result of COVID-19, exacerbating income inequalities and food insecurity. Early studies during the pandemic suggested increases in cases of child abuse and neglect; 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. With school closures, learning was adapted to minimize face-to-face contact. 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.

REFERENCES

1. Dong Y, Mo X, Hu Y, et al. Epidemiology of COVID-19 among children in China. Pediatrics 2020;145(6). https://doi.org/10.1542/peds.2020-0702.
2. Leidman E, Duca LM, Omura JD, et al. COVID-19 trends among persons aged 0-24 years - United States, March 1-December 12, 2020. MMWR Morb Mortal Wkly Rep 2021;70(3):88–94.
3. Centers for Disease Control and Prevention. COVID Data Tracker: Demographic Trends of COVID-19 Cases and Deaths in the US Reported to CDC. Available at: https://covid.cdc.gov/covid-data-tracker/#demographics. Accessed January 12, 2022.
4. Team CC-R. Coronavirus disease 2019 in children - United States, February 12-April 2, 2020. MMWR Morb Mortal Wkly Rep 2020;69(14):422–6.
5. Kim L, Whitaker M, O’Halloran A, et al. Hospitalization rates and characteristics of children aged <18 years hospitalized with laboratory-confirmed COVID-19 - COVID-NET, 14 States, March 1-July 25, 2020. MMWR Morb Mortal Wkly Rep 2020;69(32):1081–8.
6. Lu X, Zhang L, Du H, et al. SARS-CoV-2 infection in children. N Engl J Med 2020;382(17):1663–5.
7. Davies NG, Klepac P, Liu Y, et al. Age-dependent effects in the transmission and control of COVID-19 epidemics. Nat Med 2020;26(8):1205–11.
8. Yousaf AR, Duca LM, Chu V, et al. A prospective cohort study in nonhospitalized household contacts with severe acute respiratory syndrome coronavirus 2 infection: symptom profiles and symptom change over time. Clin Infect Dis 2021;73(7):e1841–9.
9. Stokes EK, Zambrano LD, Anderson KN, et al. Coronavirus disease 2019 case surveillance - United States, January 22-May 30, 2020. MMWR Morb Mortal Wkly Rep 2020;69(24):759–65.
10. UNICEF: Child Mortality and COVID-19. Available at: https://data.unicef.org/topic/child-survival/covid-19/. Accessed January 12, 2022.
11. Rodriguez Velasquez S, Jacques L, Dalal J, et al. The toll of COVID-19 on African children: a descriptive analysis on COVID-19-related morbidity and mortality among the pediatric population in Sub-Saharan Africa. Int J Infect Dis 2021;110:457–65.
12. Indenbaum V, Lustig Y, Mendelson E, et al. Under-diagnosis of SARS-CoV-2 infections among children aged 0-15 years, a nationwide seroprevalence study, Israel, January 2020 to March 2021. Euro Surveill 2021;26(48). https://doi.org/10.2807/1560-7917.ES.2021.26.48.2101040.
13. Jeewandara C, Guruge D, Abyrathna IS, et al. Seroprevalence of SARS-CoV-2 infection in the Colombo Municipality Region, Sri Lanka. Front Public Health 2021;9. https://doi.org/10.3389/fpubh.2021.724398. 724398.
14. Zinszer K, McKinnon B, Bourque N, et al. Seroprevalence of SARS-CoV-2 antibodies among children in school and day care in Montreal, Canada. JAMA Netw Open 2021;4(11):e2135975.

15. Pollan M, Perez-Gomez B, Pastor-Barriuso R, et al. Prevalence of SARS-CoV-2 in Spain (ENE-COVID): a nationwide, population-based seroepidemiological study. Lancet 2020;396(10250):535–44.

16. Stringhini S, Wisniak A, Piumatti G, et al. Seroprevalence of anti-SARS-CoV-2 IgG antibodies in Geneva, Switzerland (SEROCoV-POP): a population-based study. Lancet 2020;396(10247):313–9.

17. Tonshoff B, Muller B, Elling R, et al. Prevalence of SARS-CoV-2 infection in children and their parents in Southwest Germany. JAMA Pediatr 2021;175(6):586–93.

18. Rostami A, Sepidarkish M, Leeflang MMG, et al. SARS-CoV-2 seroprevalence worldwide: a systematic review and meta-analysis. Clin Microbiol Infect 2021;27(3):331–40.

19. Stringhini S, Zaballa ME, Pullen N, et al. Seroprevalence of anti-SARS-CoV-2 antibodies 6 months into the vaccination campaign in Geneva, Switzerland, 1 June to 7 July 2021. Euro Surveill 2021;26(43). https://doi.org/10.2807/1560-7917.ES.2021.26.43.2100830.

20. Maltezou HC, Krumbholz B, Mavrouli M, et al. A study of the evolution of the third COVID-19 pandemic wave in the Athens metropolitan area, Greece, through two cross-sectional seroepidemiological surveys: March, June 2021. J Med Virol 2021. https://doi.org/10.1002/jmv.27465.

21. United States Census Bureau Quick Facts. Available at: https://www.census.gov/quickfacts/fact/table/US/AGE295219#AGE295219. Accessed January 12, 2022.

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

23. Dhar MS, Marwal R, Vs R, et al. Genomic characterization and epidemiology of an emerging SARS-CoV-2 variant in Delhi, India. Science 2021;374(6570):995–9.

24. Delahoy MJ, Ujamaa D, Whitaker M, et al. Hospitalizations associated with COVID-19 among children and adolescents - COVID-NET, 14 States, March 1, 2020-August 14, 2021. MMWR Morb Mortal Wkly Rep 2021;70(36):1255–60.

25. Siegel DA, Reses HE, Cool AJ, et al. Trends in COVID-19 cases, emergency department visits, and hospital admissions among children and adolescents aged 0-17 years - United States, August 2020-August 2021. MMWR Morb Mortal Wkly Rep 2021;70(36):1249–54.

26. Oeser C, Whitaker H, Linley E, et al. Large increases in SARS-CoV-2 seropositivity in children in England: effects of the delta wave and vaccination. J Infect 2021. https://doi.org/10.1016/j.jinf.2021.11.019.

27. Ito K, Piantham C, Nishiura H. Relative instantaneous reproduction number of Omicron SARS-CoV-2 variant with respect to the Delta variant in Denmark. J Med Virol 2021. https://doi.org/10.1002/jmv.27560.

28. World Health Organization. Classification of Omicron (B.1.1.529): SARS-CoV-2 Variant of Concern. Available at: https://www.who.int/news/item/26-11-2021-classification-of-omicron-(b.1.1.529)-sars-cov-2-variant-of-concern. Accessed January 12, 2022.

29. Team CC-R. SARS-CoV-2 B.1.1.529 (Omicron) Variant - United States, December 1-8, 2021. MMWR Morb Mortal Wkly Rep 2021;70(50):1731–4.
30. Centers for Disease Control and Prevention. New admissions of patients with confirmed COVID-19 per 100,000 population by age group, United States. Available at: https://covid.cdc.gov/covid-data-tracker/#new-hospital-admissions. Accessed January 12, 2022.

31. Chowkwanyun M, Reed AL Jr. Racial health disparities and Covid-19 - caution and context. N Engl J Med 2020;383(3):201–3.

32. Gold JAW, Wong KK, Szablewski CM, et al. Characteristics and clinical outcomes of adult patients hospitalized with COVID-19 - Georgia, March 2020. MMWR Morb Mortal Wkly Rep 2020;69(18):545–50.

33. Webb Hooper M, Napoles AM, Perez-Stable EJ. COVID-19 and racial/ethnic disparities. JAMA 2020;323(24):2466–7.

34. Bhala N, Curry G, Martineau AR, et al. Sharpening the global focus on ethnicity and race in the time of COVID-19. Lancet 2020;395(10238):1673–6.

35. Chamie G, Marquez C, Crawford E, et al. Community transmission of severe acute respiratory syndrome Coronavirus 2 disproportionately affects the Latinx population during shelter-in-place in San Francisco. Clin Infect Dis 2021; 73(Suppl 2):S127–35.

36. Bandi S, Nevid MZ, Mahdavinia M. African American children are at higher risk of COVID-19 infection. Pediatr Allergy Immunol 2020;31(7):861–4.

37. McCormick DW, Richardson LC, Young PR, et al. Deaths in children and adolescents associated with COVID-19 and MIS-C in the United States. Pediatrics 2021;148(5). https://doi.org/10.1542/peds.2021-052273.

38. Hatcher SM, Agnew-Brune C, Anderson M, et al. COVID-19 among American Indian and Alaska Native persons - 23 states, January 31-July 3, 2020. MMWR Morb Mortal Wkly Rep 2020;69(34):1166–9.

39. Martinez DA, Hinson JS, Klein EY, et al. SARS-CoV-2 positivity rate for Latinos in the Baltimore-Washington, DC Region. JAMA 2020;324(4):392–5.

40. Goyal MK, Simpson JN, Boyle MD, et al. Racial and/or ethnic and socioeconomic disparities of SARS-CoV-2 infection among children. Pediatrics 2020; 146(4). https://doi.org/10.1542/peds.2020-009951.

41. Tan TQ, Kullar R, Swartz TH, et al. Location matters: geographic disparities and impact of coronavirus disease 2019. J Infect Dis 2020;222(12):1951–4.

42. Kong STJ, Lee RY, Rodriguez F, et al. Racial and ethnic disparities in household contact with individuals at higher risk of exposure to COVID-19. J Gen Intern Med 2021;36(5):1470–2.

43. Rane MS, Robertson MM, Westmoreland DA, et al. Intention to vaccinate children against COVID-19 among vaccinated and unvaccinated US parents. JAMA Pediatr 2021. https://doi.org/10.1001/jamapediatrics.2021.5153.

44. Honein MA, Christie A, Rose DA, et al. Summary of guidance for public health strategies to address high levels of community transmission of SARS-CoV-2 and related deaths, December 2020. MMWR Morb Mortal Wkly Rep 2020; 69(49):1860–7.

45. Haston JC, Pickering LK. Non-household transmission of SARS-CoV-2 underscores importance of stay-at-home orders. Available at: https://www.aappublications.org/news/2020/05/21/mmwr052120?utm_source=TrendMD&utm_medium=TrendMD&utm_campaign=AAPNews_TrendMD_1. Accessed January 12, 2022.

46. Ghinai I, Woods S, Ritger KA, et al. Community transmission of SARS-CoV-2 at two family gatherings - Chicago, Illinois, February-March 2020. MMWR Morb Mortal Wkly Rep 2020;69(15):446–50.
47. Rajmil L. Role of children in the transmission of the COVID-19 pandemic: a rapid scoping review. BMJ Paediatr Open 2020;4(1):e000722.
48. Kelvin AA, Halperin S. COVID-19 in children: the link in the transmission chain. Lancet Infect Dis 2020;20(6):633–4.
49. Coffin SE, Rubin D. Yes, children can transmit COVID, but we need not fear. JAMA Pediatr 2021;175(11):1110–2.
50. Wu JT, Cowling BJ, Lau EH, et al. School closure and mitigation of pandemic (H1N1) 2009, Hong Kong. Emerg Infect Dis 2010;16(3):538–41.
51. Weycker D, Edelsberg J, Halloran ME, et al. Population-wide benefits of routine vaccination of children against influenza. Vaccine 2005;23(10):1284–93.
52. Anderson EJ, Daugherty MA, Pickering LK, et al. Protecting the community through child vaccination. Clin Infect Dis 2018;67(3):464–71.
53. Cohen SA, Chui KK, Naumova EN. Influenza vaccination in young children reduces influenza-associated hospitalizations in older adults, 2002-2006. J Am Geriatr Soc 2011;59(2):327–32.
54. Centers for Disease Control and Prevention. Scientific brief: SARS-CoV-2 transmission. Available at: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/sars-cov-2-transmission.html. Accessed January 12, 2022.
55. Yehya N, Venkataramani A, Harhay MO. Statewide interventions and coronavirus disease 2019 mortality in the United States: An Observational Study. Clin Infect Dis 2021;73(7):e1863–9.
56. Courtemanche C, Garuccio J, Le A, et al. Strong social distancing measures in the United States reduced the COVID-19 growth rate. Health Aff (Millwood) 2020;39(7):1237–46.
57. Zhou L, Ayeh SK, Chidambaram V, et al. Modes of transmission of SARS-CoV-2 and evidence for preventive behavioral interventions. BMC Infect Dis 2021;21(1):496.
58. Paul LA, Daneman N, Schwartz KL, et al. Association of age and pediatric household transmission of SARS-CoV-2 infection. JAMA Pediatr 2021;175(11):1151–8.
59. Park YJ, Choe YJ, Park O, et al. Contact tracing during coronavirus disease outbreak, South Korea, 2020. Emerg Infect Dis 2020;26(10):2465–8.
60. Rostad CA, Kamidani S, Anderson EJ. Implications of SARS-CoV-2 viral load in children: getting back to school and normal. JAMA Pediatr 2021;175(10):e212022.
61. Su L, Ma X, Yu H, et al. The different clinical characteristics of coronavirus disease cases between children and their families in China - the character of children with COVID-19. Emerg Microbes Infect 2020;9(1):707–13.
62. Kam KQ, Yung CF, Cui L, et al. A well infant with coronavirus disease 2019 with high viral load. Clin Infect Dis 2020;71(15):847–9.
63. Chan JF, Yuan S, Kok KH, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet 2020;395(10223):514–23.
64. Posfay-Barbe KM, Wagner N, Gauthey M, et al. COVID-19 in children and the dynamics of infection in families. Pediatrics 2020;146(2). https://doi.org/10.1542/peds.2020-1576.
65. Maltezou HC, Vorou R, Papadima K, et al. Transmission dynamics of SARS-CoV-2 within families with children in Greece: A study of 23 clusters. J Med Virol 2021;93(3):1414–20.
66. Li F, Li YY, Liu MJ, et al. Household transmission of SARS-CoV-2 and risk factors for susceptibility and infectivity in Wuhan: a retrospective observational study. Lancet Infect Dis 2021;21(5):617–28.

67. Hall CB, Douglas RG Jr. Modes of transmission of respiratory syncytial virus. J Pediatr 1981;99(1):100–3.

68. Madewell ZJ, Yang Y, Longini IM Jr, et al. Factors associated with household transmission of SARS-CoV-2: an updated systematic review and meta-analysis. JAMA Netw Open 2021;4(8):e2122240.

69. Grijalva CG, Rolles MA, Zhu Y, et al. Transmission of SARS-COV-2 infections in households - Tennessee and Wisconsin, April-September 2020. MMWR Morb Mortal Wkly Rep 2020;69(44):1631–4.

70. Kawasuji H, Takegoshi Y, Kaneda M, et al. Transmissibility of COVID-19 depends on the viral load around onset in adult and symptomatic patients. PLoS One 2020;15(12):e0243597.

71. Goyal A, Reeves DB, Cardozo-Ojeda EF, et al. Viral load and contact heterogeneity predict SARS-CoV-2 transmission and super-spreading events. Elife 2021;10. https://doi.org/10.7554/eLife.63537.

72. Marks M, Millat-Martinez P, Ouchi D, et al. Transmission of COVID-19 in 282 clusters in Catalonia, Spain: a cohort study. Lancet Infect Dis 2021;21(5):629–36.

73. Chung E, Chow EJ, Wilcox NC, et al. Comparison of symptoms and RNA levels in children and adults with SARS-CoV-2 infection in the community setting. JAMA Pediatr 2021;175(10):e212025.

74. Xiao F, Sun J, Xu Y, et al. Infectious SARS-CoV-2 in feces of patient with severe COVID-19. Emerg Infect Dis 2020;26(8):1920–2.

75. Hua CZ, Miao ZP, Zheng JS, et al. Epidemiological features and viral shedding in children with SARS-CoV-2 infection. J Med Virol 2020;92(11):2804–12.

76. Han MS, Seong MW, Kim N, et al. Viral RNA load in mildly symptomatic and asymptomatic children with COVID-19, Seoul, South Korea. Emerg Infect Dis 2020;26(10):2497–9.

77. Buddingh EP, Vossen A, Lamb HJ, et al. Reinfection with severe acute respiratory syndrome coronavirus 2 without recurrence of multisystem inflammatory syndrome in children. Pediatr Infect Dis J 2021;40(12):e491–2.

78. Viner R, Waddington C, Mytton O, et al. Transmission of SARS-CoV-2 by children and young people in households and schools: a meta-analysis of population-based and contact-tracing studies. J Infect 2021. https://doi.org/10.1016/j.jinf.2021.12.026.

79. Heavey L, Casey G, Kelly C, et al. No evidence of secondary transmission of COVID-19 from children attending school in Ireland, 2020. Euro Surveill 2020(21):25. https://doi.org/10.2807/1560-7917.ES.2020.25.21.2000903.

80. Kim C, McGee S, Khuntia S, et al. Characteristics of COVID-19 cases and outbreaks at child care facilities - District of Columbia, July–December 2020. MMWR Morb Mortal Wkly Rep 2021;70(20):744–8.

81. Lam-Hine T, McCurdy SA, Santora L, et al. Outbreak associated with SARS-CoV-2 B.1.617.2 (Delta) variant in an elementary school - Marin County, California, May–June 2021. MMWR Morb Mortal Wkly Rep 2021;70(35):1214–9.

82. Yin S, Barnes K, Fisher R, et al. COVID-19 case rates in transitional kindergarten through grade 12 schools and in the community - Los Angeles County, California, September 2020–March 2021. MMWR Morb Mortal Wkly Rep 2021;70(35):1220–2.
83. Jehn M, McCullough JM, Dale AP, et al. Association between K-12 school mask policies and school-associated COVID-19 outbreaks - Maricopa and Pima Counties, Arizona, July-August 2021. MMWR Morb Mortal Wkly Rep 2021; 70(39):1372–3.

84. Budzyn SE, Panaggio MJ, Parks SE, et al. Pediatric COVID-19 cases in counties with and without school mask requirements - United States, July 1-September 4, 2021. MMWR Morb Mortal Wkly Rep 2021; 70(39):1377–8.

85. Nemoto N, Dhillon S, Fink S, et al. Evaluation of test to stay strategy on secondary and tertiary transmission of SARS-CoV-2 in K-12 schools - Lake County, Illinois, August 9-October 29, 2021. MMWR Morb Mortal Wkly Rep 2021; 70(5152): 1778–81.

86. Harris-McCoy K, Lee VC, Munna C, et al. Evaluation of a test to stay strategy in transitional kindergarten through grade 12 schools - Los Angeles County, California, August 16-October 31, 2021. MMWR Morb Mortal Wkly Rep 2021; 70(5152): 1773–7.

87. World Health Organization. COVID-19 vaccines WHO EUL issued. Available at: https://extranet.who.int/pqweb/vaccines/vaccinescovid-19-vaccine-eul-issued. Accessed January 12, 2022.

88. World Health Organization. COVID-19 advice for the public: getting vaccinated. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines/advice. Accessed January 12, 2022.

89. Oliver SE, Gargano JW, Marin M, et al. The Advisory Committee on Immunization Practices’ Interim Recommendation for Use of Pfizer-BioNTech COVID-19 Vaccine - United States, December 2020. MMWR Morb Mortal Wkly Rep 2020; 69(50):1922–4.

90. Wallace M, Woodworth KR, Gargano JW, et al. The Advisory Committee on Immunization Practices’ Interim Recommendation for Use of Pfizer-BioNTech COVID-19 Vaccine in Adolescents Aged 12-15 Years - United States, May 2021. MMWR Morb Mortal Wkly Rep 2021; 70(20):749–52.

91. Woodworth KR, Moula D, Collins JP, et al. The Advisory Committee on Immunization Practices’ Interim Recommendation for Use of Pfizer-BioNTech COVID-19 Vaccine in Children Aged 5-11 Years - United States, November 2021. MMWR Morb Mortal Wkly Rep 2021; 70(45):1579–83.

92. U.S. Food and Drug Administration: FDA Takes Key Action in Fight Against COVID-19 By Issuing Emergency Use Authorization for First COVID-19 Vaccine. Available at: https://www.fda.gov/news-events/press-announcements/fda-takes-key-action-fight-against-covid-19-issuing-emergency-use-authorization-first-covid-19. Accessed January 12, 2022.

93. U.S. Food and Drug Administration: FDA Approves First COVID-19 Vaccine. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-first-covid-19-vaccine. Accessed January 12, 2022.

94. U.S. Food and Drug Administration: Coronavirus (COVID-19) Update: FDA Authorizes Pfizer-BioNTech COVID-19 Vaccine for Emergency Use in Adolescents in Another Important Action in Fight Against Pandemic. Available at: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-pfizer-biontech-covid-19-vaccine-emergency-use. Accessed January 12, 2022.

95. U.S. Food and Drug Administration. FDA Authorizes Pfizer-BioNTech COVID-19 Vaccine for Emergency Use in Children 5 through 11 Years of Age. Available at: https://www.fda.gov/news-events/press-announcements/fda-authorizes-pfizer-
biontech-covid-19-vaccine-emergency-use-children-5-through-11-years-age. Accessed January 12, 2022.

96. U.S. Food and Drug Administration. Coronavirus (COVID-19) Update: FDA Expands Eligibility to Pfizer-BioNTech COVID-19 Booster Dose to 16- and 17-Year-Olds. Available at: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-expands-eligibility-pfizer-biontech-covid-19-booster-dose-16-and-17. Accessed January 12, 2022.

97. U.S. Food and Drug Administration. Coronavirus (COVID-19) Update: FDA Takes Multiple Actions to Expand Use of Pfizer-BioNTech COVID-19 Vaccine. Available at: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-takes-multiple-actions-expand-use-pfizer-biontech-covid-19-vaccine. Accessed January 12, 2022.

98. Cameroni E, Bowen JE, Rosen LE, et al. Broadly neutralizing antibodies overcome SARS-CoV-2 Omicron antigenic shift. Nature 2021. https://doi.org/10.1038/s41586-021-04386-2.

99. U.S. Food and Drug Administration. Coronavirus (COVID-19) Update: FDA Authorizes New Long-Acting Monoclonal Antibodies for Pre-exposure Prevention of COVID-19 in Certain Individuals. Available at: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-new-long-acting-monoclonal-antibodies-pre-exposure. Accessed January 12, 2022.

100. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med 2020;383(27):2603–15.

101. Frenck RW Jr, Klein NP, Kitchin N, et al. Safety, immunogenicity, and efficacy of the BNT162b2 Covid-19 vaccine in adolescents. N Engl J Med 2021;385(3):239–50.

102. Walter EB, Talaat KR, Sabharwal C, et al. Evaluation of the BNT162b2 Covid-19 vaccine in children 5 to 11 years of age. N Engl J Med 2022;386(1):35–46.

103. Ali K, Berman G, Zhou H, et al. Evaluation of mRNA-1273 SARS-CoV-2 vaccine in adolescents. N Engl J Med 2021;385(24):2241–51.

104. Bar-On YM, Goldberg Y, Mandel M, et al. Protection against Covid-19 by BNT162b2 booster across age groups. N Engl J Med 2021;385(26):2421–30.

105. Olson SM, Newhams MM, Halasa NB, et al. Effectiveness of Pfizer-BioNTech mRNA vaccination against COVID-19 hospitalization among persons aged 12-18 years - United States, June-September 2021. MMWR Morb Mortal Wkly Rep 2021;70(42):1483–5.

106. Lutrick K, Rivers P, Yoo YM, et al. Interim estimate of vaccine effectiveness of BNT162b2 (Pfizer-BioNTech) vaccine in preventing SARS-CoV-2 infection among adolescents aged 12-17 years - Arizona, July-December 2021. MMWR Morb Mortal Wkly Rep 2021;70(5152):1761–5.

107. Naleway AL, Groom HC, Crawford PM, et al. Incidence of SARS-CoV-2 infection, emergency department visits, and hospitalizations because of COVID-19 among persons aged =>12 years, by COVID-19 vaccination status - Oregon and Washington, July 4-September 25, 2021. MMWR Morb Mortal Wkly Rep 2021;70(46):1608–12.

108. Levy M, Recher M, Hubert H, et al. Multisystem inflammatory syndrome in children by COVID-19 vaccination status of adolescents in France. JAMA 2021. https://doi.org/10.1001/jama.2021.23262.

109. Zambrano LD, Newhams MM, Olson SM, et al. Effectiveness of BNT162b2 (Pfizer-BioNTech) mRNA vaccination against multisystem inflammatory
syndrome in children among persons aged 12–18 years — United States, July–December 2021. MMWR Morbidity Mortality Weekly Rep 2022;71(2):52–8.

110. Centers for Disease Control and Prevention. Demographic Trends of People Receiving COVID-19 Vaccinations in the United States. Available at: https://covid.cdc.gov/covid-data-tracker/#vaccination-demographics-trends. Accessed January 12, 2022.

111. Morgan L, Schwartz JL, Sisti DA. COVID-19 vaccination of minors without parental consent: respecting emerging autonomy and advancing public health. JAMA Pediatr 2021;175(10):995–6.

112. Hause AM, Baggs J, Marquez P, et al. COVID-19 vaccine safety in children aged 5-11 years - United States, November 3-December 19, 2021. MMWR Morb Mortal Wkly Rep 2021;70(51):1755–60.

113. Hause AM, Gee J, Baggs J, et al. COVID-19 vaccine safety in adolescents aged 12-17 years - United States, December 14, 2020-July 16, 2021. MMWR Morb Mortal Wkly Rep 2021;70(31):1053–8.

114. Truong DT, Dionne A, Muniz JC, et al. Clinically suspected myocarditis temporally related to COVID-19 vaccination in adolescents and young adults. Circulation 2021. https://doi.org/10.1161/CIRCULATIONAHA.121.056583.

115. Barda N, Dagan N, Ben-Shlomo Y, et al. Safety of the BNT162b2 mRNA Covid-19 vaccine in a nationwide setting. N Engl J Med 2021;385(12):1078–90.

116. Diaz GA, Parsons GT, Gering SK, et al. Myocarditis and Pericarditis After Vaccination for COVID-19. JAMA 2021;326(12):1210–2.

117. Dionne A, Sperotto F, Chamberlain S, et al. Association of myocarditis with BNT162b2 messenger RNA COVID-19 vaccine in a case series of children. JAMA Cardiol 2021;6(12):1446–50.

118. Gargano JW, Wallace M, Hadler SC, et al. Use of mRNA COVID-19 vaccine after reports of myocarditis among vaccine recipients: update from the Advisory Committee on Immunization Practices - United States, June 2021. MMWR Morb Mortal Wkly Rep 2021;70(27):977–82.

119. Boehmer TK, Kompaniyets L, Lavery AM, et al. Association between COVID-19 and myocarditis using hospital-based administrative data - United States, March 2020-January 2021. MMWR Morb Mortal Wkly Rep 2021;70(35):1228–32.

120. Li B, Zhang S, Zhang R, et al. Epidemiological and clinical characteristics of COVID-19 in children: a systematic review and meta-analysis. Front Pediatr 2020;8. https://doi.org/10.3389/fped.2020.591132. 591132.

121. Liguoro I, Pilotto C, Bonanni M, et al. SARS-COV-2 infection in children and newborns: a systematic review. Eur J Pediatr 2020;179(7):1029–46.

122. Centers for Disease Control and Prevention. COVID-19: Information for Pediatric Healthcare Providers. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/pediatric-hcp.html. Accessed January 12, 2022.

123. Lauer SA, Grantz KH, Bi Q, et al. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. Ann Intern Med 2020;172(9):577–82.

124. Molteni E, Sudre CH, Canas LS, et al. Illness duration and symptom profile in symptomatic UK school-aged children tested for SARS-CoV-2. Lancet Child Adolesc Health 2021;5(10):708–18.

125. Ng KF, Bandi S, Bird PW, et al. COVID-19 in neonates and infants: progression and recovery. Pediatr Infect Dis J 2020;39(7):e140–2.

126. National Institutes of Health. COVID-19 Treatment Guidelines: Clinical Spectrum of SARS-CoV-2 infection. Available at: https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/. Accessed January 12, 2022.
127. Gandhi RT, Lynch JB, Del Rio C. Mild or moderate Covid-19. N Engl J Med 2020; 383(18):1757–66.
128. Shekerdemian LS, Mahmood NR, Wolfe KK, et al. Characteristics and outcomes of children with coronavirus disease 2019 (COVID-19) infection admitted to US and Canadian pediatric intensive care units. JAMA Pediatr 2020. https://doi.org/10.1001/jamapediatrics.2020.1948 doi:10.1001/jamapediatrics.2020.1948.
129. Bixler D, Miller AD, Mattison CP, et al. SARS-CoV-2-associated deaths among persons aged <21 years - United States, February 12-July 31, 2020. MMWR Morb Mortal Wkly Rep 2020;69(37):1324–9.
130. Bailey LC, Razzaghi H, Burrows EK, et al. Assessment of 135794 pediatric patients tested for severe acute respiratory syndrome coronavirus 2 across the United States. JAMA Pediatr 2021;175(2):176–84.
131. Ouldali N, Yang DD, Madhi F, et al. Factors associated with severe SARS-CoV-2 infection. Pediatrics 2021;147(3). https://doi.org/10.1542/peds.2020-023432.
132. Gotzinger F, Santiago-Garcia B, Noguera-Julian A, et al. COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. Lancet Child Adolesc Health 2020;4(9):653–61.
133. Wanga V, Gerdes ME, Shi DS, et al. Characteristics and clinical outcomes of children and adolescents aged <18 years hospitalized with COVID-19 - six hospitals, United States, July-August 2021. MMWR Morb Mortal Wkly Rep 2021; 70(5152):1766–72.
134. Tsabouri S, Makis A, Kosmeri C, et al. Risk factors for severity in children with coronavirus disease 2019: a comprehensive literature review. Pediatr Clin North Am 2021;68(1):321–38.
135. Kompaniyets L, Agathis NT, Nelson JM, et al. Underlying medical conditions associated with severe COVID-19 illness among children. JAMA Netw Open 2021;4(6):e2111182.
136. Newman AM, Jhaveri R, Patel AB, et al. Trisomy 21 and coronavirus disease 2019 in pediatric patients. J Pediatr 2021;228:294–6.
137. Arlet JB, de Luna G, Khimoud D, et al. Prognosis of patients with sickle cell disease and COVID-19: a French experience. Lancet Haematol 2020;7(9):e632–4.
138. Sanna G, Serrau G, Bassareo PP, et al. Children's heart and COVID-19: up-to-date evidence in the form of a systematic review. Eur J Pediatr 2020;179(7):1079–87.
139. DeBiasi RL, Song X, Delaney M, et al. Severe coronavirus disease-2019 in children and young adults in the Washington, DC, Metropolitan Region. J Pediatr 2020;223:199–203.e1.
140. Kosmeri C, Koumpis E, Tsabouri S, et al. Hematological manifestations of SARS-CoV-2 in children. Pediatr Blood Cancer 2020;67(12):e28745.
141. Centers for Disease Control and Prevention. Underlying medical conditions associated with higher risk for severe COVID-19: information for healthcare providers. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html. Accessed January 12, 2022.
142. Walker KF, O’Donoghue K, Grace N, et al. Maternal transmission of SARS-COV-2 to the neonate, and possible routes for such transmission: a systematic review and critical analysis. BJOG 2020;127(11):1324–36.
143. American Academy of Pediatrics. FAQs: management of infants born to mothers with suspected or confirmed COVID-19. Available at: https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/faqs-management-of-infants-born-to-covid-19-mothers/. Accessed January 12, 2022.
144. Ray STJ, Abdel-Mannan O, Sa M, et al. Neurological manifestations of SARS-CoV-2 infection in hospitalised children and adolescents in the UK: a prospective national cohort study. Lancet Child Adolesc Health 2021;5(9):631–41.

145. Trogen B, Gonzalez FJ, Shust GF. COVID-19-associated myocarditis in an adolescent. Pediatr Infect Dis J 2020;39(8):e204–5.

146. Lara D, Young T, Del Toro K, et al. Acute fulminant myocarditis in a pediatric patient with COVID-19 infection. Pediatrics 2020;146(2). https://doi.org/10.1542/peds.2020-1509.

147. Raymond TT, Das A, Manzuri S, et al. Pediatric COVID-19 and pericarditis presenting with acute pericardial tamponade. World J Pediatr Congenit Heart Surg 2020;11(6):802–4.

148. Dimopoulou D, Spyridis N, Dasoula F, et al. Pericarditis as the main clinical manifestation of COVID-19 in adolescents. Pediatr Infect Dis J 2021;40(5):e197–9.

149. Panjabi AL, Foster RC, McCarthy AM, et al. Pulmonary embolism as the initial presentation of coronavirus disease 2019 in adolescents. Pediatr Infect Dis J 2021;40(5):e200–2.

150. Samuel S, Friedman RA, Sharma C, et al. Incidence of arrhythmias and electrocardiographic abnormalities in symptomatic pediatric patients with PCR-positive SARS-CoV-2 infection, including drug-induced changes in the corrected QT interval. Heart Rhythm 2020;17(11):1960–6.

151. Persson J, Shorofsky M, Leahy R, et al. ST-elevation myocardial infarction due to acute thrombosis in an adolescent with COVID-19. Pediatrics 2021;148(2). https://doi.org/10.1542/peds.2020-049793.

152. Andina D, Belloni-Fortina A, Bodemer C, et al. Skin manifestations of COVID-19 in children: Part 1. Clin Exp Dermatol 2021;46(3):444–50.

153. Andina D, Belloni-Fortina A, Bodemer C, et al. Skin manifestations of COVID-19 in children: Part 2. Clin Exp Dermatol 2021;46(3):451–61.

154. Paz L, Eslava E, Ribes M, et al. Acute pancreatitis in a teenager with SARS-CoV-2 infection. Pediatr Infect Dis J 2021;40(4):e161–2.

155. Brisca G, Mallamaci M, Tardini G, et al. SARS-CoV-2 infection may present as acute hepatitis in children. Pediatr Infect Dis J 2021;40(5):e214–5.

156. Perez A, Kogan-Liberman D, Sheflin-Findling S, et al. Presentation of severe acute respiratory syndrome-coronavirus 2 infection as cholestatic jaundice in two healthy adolescents. J Pediatr 2020;226:278–80.

157. Stewart DJ, Hartley JC, Johnson M, et al. Renal dysfunction in hospitalised children with COVID-19. Lancet Child Adolesc Health 2020;4(8):e28–9.

158. Marr KA, Platt A, Tornheim JA, et al. Aspergillosis complicating severe coronavirus disease. Emerg Infect Dis 2021;27(1). https://doi.org/10.3201/eid2701.202896.

159. Dulski TM, DeLong M, Garner K, et al. Notes from the field: COVID-19-associated mucormycosis - Arkansas, July-September 2021. MMWR Morb Mortal Wkly Rep 2021;70(50):1750–1.

160. Samprathi M, Jayashree M. Biomarkers in COVID-19: an up-to-date review. Front Pediatr 2020;8. https://doi.org/10.3389/fped.2020.607647.607647.

161. Henry BM, Benoit SW, de Oliveira MHS, et al. Laboratory abnormalities in children with mild and severe coronavirus disease 2019 (COVID-19): A pooled analysis and review. Clin Biochem 2020;81:1–8.

162. Irfan O, Muttalib F, Tang K, et al. Clinical characteristics, treatment and outcomes of paediatric COVID-19: a systematic review and meta-analysis. Arch Dis Child 2021. https://doi.org/10.1136/archdischild-2020-321385.
163. Wang Y, Zhu F, Wang C, et al. Children hospitalized with severe COVID-19 in Wuhan. Pediatr Infect Dis J 2020;39(7):e91–4.
164. Qiu H, Wu J, Hong L, et al. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. Lancet Infect Dis 2020;20(6):689–96.
165. Shelmerdine SC, Lovrenski J, Caro-Dominguez P, et al. Collaborators of the European Society of Paediatric Radiology Cardiothoracic Imaging T. Coronavirus disease 2019 (COVID-19) in children: a systematic review of imaging findings. Pediatr Radiol 2020;50(9):1217–30.
166. Cameroni E, Saliba C, Bowen JE, et al. Broadly neutralizing antibodies overcome SARS-CoV-2 Omicron antigenic shift. bioRxiv 2021. https://doi.org/10.1101/2021.12.12.472269.
167. Langford BJ, So M, Raybardhan S, et al. Antibiotic prescribing in patients with COVID-19: rapid review and meta-analysis. Clin Microbiol Infect 2021;27(4):520–31.
168. U.S. Food and Drug Administration. Fact Sheet for Health Care Providers Emergency Use Authorization (EUA) of Bamlanivimab and Etesevimab. Available at: https://www.fda.gov/media/145802/download. Accessed January 12, 2022.
169. National Institutes of Health. COVID-19 Treatment Guidelines. Available at: https://files.covid19treatmentguidelines.nih.gov/guidelines/covid19treatmentguidelines.pdf. Accessed January 12, 2022.
170. Wolf J, Abzug MJ, Wattier RL, et al. Initial guidance on use of monoclonal antibody therapy for treatment of coronavirus disease 2019 in children and adolescents. J Pediatr Infect Dis Soc 2021;10(5):629–34.
171. U.S. Food and Drug Administration: Veklury (remdesivir) EUA Letter of Approval, reissued 10/22/2020. Available at: https://www.fda.gov/media/137564/download. Accessed January 12, 2022.
172. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 - final report. N Engl J Med 2020;383(19):1813–26.
173. Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 days in patients with severe Covid-19. N Engl J Med 2020;383(19):1827–37.
174. Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. JAMA 2020;324(11):1048–57.
175. National Institutes of Health. The COVID-19 treatment guidelines panel's statement of therapies for high-risk, nonhospitalized patients with mild to moderate COVID-19. Available at: https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-therapies-for-high-risk-nonhospitalized-patients/. Accessed January 12, 2022.
176. Gottlieb RL, Vaca CE, Paredes R, et al. Early remdesivir to prevent progression to severe Covid-19 in outpatients. N Engl J Med 2021. https://doi.org/10.1056/NEJMoa2116846.
177. Chiotos K, Hayes M, Kimberlin DW, et al. Multicenter interim guidance on use of antivirals for children with coronavirus disease 2019/severe acute respiratory syndrome coronavirus 2. J Pediatr Infect Dis Soc 2021;10(1):34–48.
178. World Health Organization: Therapeutics and COVID-19: Living Guidelines. Available at: https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2021.3. Accessed January 12, 2022.
179. Chow EJ, Maust B, Kazmier KM, et al. Sinus bradycardia in a pediatric patient treated with remdesivir for acute coronavirus disease 2019: a case report and a review of the literature. J Pediatr Infect Dis Soc 2021;10(9):926–9.
180. U.S. Food and Drug Administration. Coronavirus (COVID-19) update: FDA authorizes additional oral antiviral treatment of COVID-19 in certain adults. Available at: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-additional-oral-antiviral-treatment-covid-19-certain. Accessed January 12, 2022.

181. U.S. Food and Drug Administration. Coronavirus (COVID-19) update: FDA authorizes first oral antiviral for treatment of COVID-19. Available at: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-oral-antiviral-treatment-covid-19. Accessed January 12, 2022.

182. Villar J, Ferrando C, Martinez D, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. Lancet Respir Med 2020;8(3):267–76.

183. Group RC, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med 2021;384(8):693–704.

184. Tomazini BM, Maia IS, Cavalcanti AB, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. JAMA 2020;324(13):1307–16.

185. World Health Organization: Corticosteroids for COVID-19. Available at: https://www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1. Accessed January 12, 2022.

186. Dulek DE, Fuhlbrigge RC, Tribble AC, et al. Multidisciplinary guidance regarding the use of immunomodulatory therapies for acute coronavirus disease 2019 in pediatric patients. J Pediatr Infect Dis Soc 2020;9(6):716–37.

187. Whittaker E, Bamford A, Kenny J, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. JAMA 2020;324(3):259–69.

188. Paediatric Intensive Care Society Statement: increased number of reported cases of novel presentation of multisystem inflammatory disease. Available at: https://pccsociety.uk/wp-content/uploads/2020/04/PICS-statement-re-novel-KD-C19-presentation-v2-27042020.pdf. Accessed January 12, 2022.

189. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet 2020;395(10239):1771–8.

190. Riphagen S, Gomez X, Gonzalez-Martinez C, et al. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020;395(10237):1607–8.

191. Grimaud M, Starck J, Levy M, et al. Acute myocarditis and multisystem inflammatory emerging disease following SARS-CoV-2 infection in critically ill children. Ann Intensive Care 2020;10(1):69.

192. Dufort EM, Koumans EH, Chow EJ, et al. Multisystem inflammatory syndrome in children in New York State. N Engl J Med 2020;383(4):347–58.

193. Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. N Engl J Med 2020;383(4):334–46.

194. Royal College of Paediatrics and Child Health. Guidance: paediatric multisystem inflammatory syndrome temporally associated with COVID-19. Available at: https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatric-multipystem-%20inflammatory%20syndrome-20200501.pdf. Accessed January 12, 2022.

195. Levin M. Childhood Multisystem Inflammatory Syndrome - A New Challenge in the Pandemic. N Engl J Med 2020;383(4):393–5.
196. Centers for Disease Control and Prevention. Multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease 2019 (COVID-19). Available at: https://emergency.cdc.gov/han/2020/han00432.asp. Accessed October 28, 2021.

197. Morris SB, Schwartz NG, Patel P, et al. Case series of multisystem inflammatory syndrome in adults associated with SARS-CoV-2 infection - United Kingdom and United States, March-August 2020. MMWR Morb Mortal Wkly Rep 2020;69(40):1450–6.

198. Hekimian G, Kerneis M, Zeitouni M, et al. Coronavirus disease 2019 acute myocarditis and multisystem inflammatory syndrome in adult intensive and cardiac care units. Chest 2021;159(2):657–62.

199. Davogustto G, Clark DE, Hardison E, et al. Characteristics associated with multisystem inflammatory syndrome among adults with SARS-CoV-2 infection. JAMA Netw Open 2021;4(5):e2110323.

200. Chow EJ. The multisystem inflammatory syndrome in adults with SARS-CoV-2 infection—another piece of an expanding puzzle. JAMA Netw Open 2021;4(5):e2110344.

201. World Health Organization. Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19. Available at: https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19. Accessed January 12, 2022.

202. Payne AB, Gilani Z, Godfred-Cato S, et al. Incidence of multisystem inflammatory syndrome in children among US persons infected with SARS-CoV-2. JAMA Netw Open 2021;4(6):e2116420.

203. Rowley AH. Understanding SARS-CoV-2-related multisystem inflammatory syndrome in children. Nat Rev Immunol 2020;20(8):453–4.

204. Consiglio CR, Cotugno N, Sardh F, et al. The immunology of multisystem inflammatory syndrome in children with COVID-19. Cell 2020;183(4):968–81.e7.

205. Godfred-Cato S, Bryant B, Leung J, et al. COVID-19-associated multisystem inflammatory syndrome in children - United States, March-July 2020. MMWR Morb Mortal Wkly Rep 2020;69(32):1074–80.

206. Sharma C, Ganigara M, Galeotti C, et al. Multisystem inflammatory syndrome in children and Kawasaki disease: a critical comparison. Nat Rev Rheumatol 2021;17(12):731–48.

207. Feldstein LR, Tenforde MW, Friedman KG, et al. Characteristics and outcomes of US children and adolescents with multisystem inflammatory syndrome in children (MIS-C) compared with severe acute COVID-19. JAMA 2021;325(11):1074–87.

208. Lee EH, Kepler KL, Geevarughese A, et al. Race/ethnicity among children with COVID-19-associated multisystem inflammatory syndrome. JAMA Netw Open 2020;3(11):e2030280.

209. Abrams JY, Godfred-Cato SE, Oster ME, et al. Multisystem inflammatory syndrome in children associated with severe acute respiratory syndrome coronavirus 2: a systematic review. J Pediatr 2020;226:45–54.e1.

210. Stierman B, Abrams JY, Godfred-Cato SE, et al. Racial and ethnic disparities in multisystem inflammatory syndrome in children in the United States, March 2020 to February 2021. Pediatr Infect Dis J 2021;40(11):e400–6.

211. Javalkar K, Robson VK, Gaffney L, et al. Socioeconomic and racial and/or ethnic disparities in multisystem inflammatory syndrome. Pediatrics 2021;147(5). https://doi.org/10.1542/peds.2020-039933.
212. Ahmed M, Advani S, Moreira A, et al. Multisystem inflammatory syndrome in children: a systematic review. EClinicalMedicine 2020;26. https://doi.org/10.1016/j.eclinm.2020.100527. 100527.

213. Lo Vecchio A, Garazzino S, Smarrazzo A, et al. Factors associated with severe gastrointestinal diagnoses in children with SARS-CoV-2 infection or multisystem inflammatory syndrome. JAMA Netw Open 2021;4(12):e2139974.

214. Young TK, Shaw KS, Shah JK, et al. Mucocutaneous manifestations of multisystem inflammatory syndrome in children during the COVID-19 pandemic. JAMA Dermatol 2021;157(2):207–12.

215. Carlin RF, Fischer AM, Pitkowsky Z, et al. Discriminating multisystem inflammatory syndrome in children requiring treatment from common febrile conditions in outpatient settings. J Pediatr 2021;229:26–32.e2.

216. Sperotto F, Friedman KG, Son MBF, et al. Cardiac manifestations in SARS-CoV-2-associated multisystem inflammatory syndrome in children: a comprehensive review and proposed clinical approach. Eur J Pediatr 2021;180(2):307–22.

217. Kaushik A, Gupta S, Sood M, et al. A systematic review of multisystem inflammatory syndrome in children associated with SARS-CoV-2 infection. Pediatr Infect Dis J 2020;39(11):e340–6.

218. Penner J, Abdel-Mannan O, Grant K, et al. 6-month multidisciplinary follow-up and outcomes of patients with paediatric inflammatory multisystem syndrome (PIMS-TS) at a UK tertiary paediatric hospital: a retrospective cohort study. Lancet Child Adolesc Health 2021;5(7):473–82.

219. Davies P, du Pre P, Lillie J, et al. One-year outcomes of critical care patients post-COVID-19 multisystem inflammatory syndrome in children. JAMA Pediatr 2021;175(12):1281–3.

220. Henderson LA, Canna SW, Friedman KG, et al. American College of Rheumatology clinical guidance for multisystem inflammatory syndrome in children associated with SARS-CoV-2 and hyperinflammation in pediatric COVID-19: version 2. Arthritis Rheumatol 2021;73(4):e13–29.

221. Harwood R, Allin B, Jones CE, et al. A national consensus management pathway for paediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS): results of a national Delphi process. Lancet Child Adolesc Health 2021;5(2):133–41.

222. American Academy of Pediatrics: multisystem inflammatory syndrome in children (MIS-C) interim guidance. Available at: https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/multisystem-inflammatory-syndrome-in-children-mis-c-interim-guidance/. Accessed January 12, 2022.

223. Ouldali N, Toubiana J, Antona D, et al. Association of intravenous immunoglobulins plus methylprednisolone vs immunoglobulins alone with course of fever in multisystem inflammatory syndrome in children. JAMA 2021;325(9):855–64.

224. Son MBF, Murray N, Friedman K, et al. Multisystem inflammatory syndrome in children - initial therapy and outcomes. N Engl J Med 2021;385(1):23–34.

225. Nalbandian A, Sehgal K, Gupta A, et al. Post-acute COVID-19 syndrome. Nat Med 2021;27(4):601–15.

226. Ashkenazi-Hoffnung L, Shmueli E, Ehrlich S, et al. Long COVID in children: observations from a designated pediatric clinic. Pediatr Infect Dis J 2021;40(12):e509–11.

227. Zimmermann P, Pittet LF, Curtis N. How common is long COVID in children and adolescents? Pediatr Infect Dis J 2021;40(12):e482–7.
228. Ludvigsson JF. Case report and systematic review suggest that children may experience similar long-term effects to adults after clinical COVID-19. Acta Paediatr 2021;110(3):914–21.

229. Buonsenso D, Munblit D, De Rose C, et al. Preliminary evidence on long COVID in children. Acta Paediatr 2021;110(7):2208–11.

230. Brackel CLH, Lap CR, Buddingh EP, et al. Pediatric long-COVID: an overlooked phenomenon? Pediatr Pulmonol 2021;56(8):2495–502.

231. Radtke T, Ulyte A, Puhan MA, et al. Long-term symptoms after SARS-CoV-2 infection in children and adolescents. JAMA 2021. https://doi.org/10.1001/jama.2021.11880.

232. Say D, Crawford N, McNab S, et al. Post-acute COVID-19 outcomes in children with mild and asymptomatic disease. Lancet Child Adolesc Health 2021;5(6):e22–3.

233. Kumar S, Veldhuis A, Malhotra T. Neuropsychiatric and cognitive sequelae of COVID-19. Front Psychol 2021;12:577529. https://doi.org/10.3389/fpsyg.2021.577529.

234. Morrow AK, Ng R, Vargas G, et al. Postacute/Long COVID in pediatrics: development of a multidisciplinary rehabilitation clinic and preliminary case series. Am J Phys Med Rehabil 2021;100(12):1140–7.

235. Stephenson T, Shafran R, De Stavola B, et al. Long COVID and the mental and physical health of children and young people: national matched cohort study protocol (the CLoCk study). BMJ Open 2021;11(8):e052838.

236. National Institutes of Health. RECOVER: research COVID to enhance recovery. Available at: https://recovercovid.org/. Accessed January 12, 2022.

237. Schweiberger K, Patel SY, Mehrotra A, et al. Trends in pediatric primary care visits during the coronavirus disease of 2019 pandemic. Acad Pediatr 2021;21(8):1426–33.

238. Courtney JG, Chuke SO, Dyke K, et al. Decreases in young children who received blood lead level testing during COVID-19 - 34 jurisdictions, January-May 2020. MMWR Morb Mortal Wkly Rep 2021;70(5):155–61.

239. DeSilva MB, Haapala J, Vazquez-Benitez G, et al. Association of the COVID-19 pandemic with routine childhood vaccination rates and proportion up to date with vaccinations across 8 US health systems in the Vaccine Safety Datalink. JAMA Pediatr 2022;176(1):68–77.

240. Gerall CD, DeFazio JR, Kahan AM, et al. Delayed presentation and sub-optimal outcomes of pediatric patients with acute appendicitis during the COVID-19 pandemic. J Pediatr Surg 2021;56(5):905–10.

241. Levene R, Fein DM, Silver EJ, et al. The ongoing impact of COVID-19 on asthma and pediatric emergency health-seeking behavior in the Bronx, an epicenter. Am J Emerg Med 2021;43:109–14.

242. Graetz D, Agulnik A, Ranadive R, et al. Global effect of the COVID-19 pandemic on paediatric cancer care: a cross-sectional study. Lancet Child Adolesc Health 2021;5(5):332–40.

243. Racine N, McArthur BA, Cooke JE, et al. Global prevalence of depressive and anxiety symptoms in children and adolescents during COVID-19: a meta-analysis. JAMA Pediatr 2021;175(11):1142–50.

244. Chaffee BW, Cheng J, Couch ET, et al. Adolescents’ substance use and physical activity before and during the COVID-19 pandemic. JAMA Pediatr 2021;175(7):715–22.
245. Tandon PS, Zhou C, Johnson AM, et al. Association of children’s physical activity and screen time with mental health during the COVID-19 pandemic. JAMA Netw Open 2021;4(10):e2127892.

246. Gassman-Pines A, Ananat EO, Fitz-Henley J 2nd. COVID-19 and parent-child psychological well-being. Pediatrics 2020;146(4). https://doi.org/10.1542/peds.2020-007294.

247. Raffagnato A, Iannattone S, Tascini B, et al. The COVID-19 pandemic: a longitudinal study on the emotional-behavioral sequelae for children and adolescents with neuropsychiatric disorders and their families. Int J Environ Res Public Health 2021;18(18). https://doi.org/10.3390/ijerph18189880.

248. Hanno EC, Fritz LS, Jones SM, et al. School learning format and children’s behavioral health during the COVID-19 pandemic. JAMA Pediatr 2022. https://doi.org/10.1001/jamapediatrics.2021.5698.

249. Hillis SD, Unwin HJT, Chen Y, et al. Global minimum estimates of children affected by COVID-19-associated orphanhood and deaths of caregivers: a modelling study. Lancet 2021;398(10298):391–402.

250. Dooley DG, Bandealy A, Tschudy MM. Low-income children and coronavirus disease 2019 (COVID-19) in the US. JAMA Pediatr 2020;174(10):922–3.

251. Parekh N, Ali SH, O’Connor J, et al. Food insecurity among households with children during the COVID-19 pandemic: results from a study among social media users across the United States. Nutr J 2021;20(1):73.

252. Adams EL, Caccavale LJ, Smith D, et al. Food insecurity, the home food environment, and parent feeding practices in the era of COVID-19. Obesity (Silver Spring) 2020;28(11):2056–63.

253. Swedo E, Idaikkadar N, Leemis R, et al. Trends in U.S. emergency department visits related to suspected or confirmed child abuse and neglect among children and adolescents aged <18 years before and during the COVID-19 pandemic - United States, January 2019-September 2020. MMWR Morb Mortal Wkly Rep 2020;69(49):1841–7.

254. Ortiz R, Kishton R, Sinko L, et al. Assessing child abuse hotline inquiries in the wake of COVID-19: answering the call. JAMA Pediatr 2021;175(8):859–61.

255. Sege R, Stephens A. Child physical abuse did not increase during the pandemic. JAMA Pediatr 2021. https://doi.org/10.1001/jamapediatrics.2021.5476.

256. Parks SE, Zviedrite N, Budzyn SE, et al. COVID-19-related school closures and learning modality changes - United States, August 1-September 17, 2021. MMWR Morb Mortal Wkly Rep 2021;70(39):1374–6.

257. U.S. Food and Drug Administration. Coronavirus (COVID-19) update: FDA authorizes additional vaccine dose for certain immunocompromised individuals. Available at: https://www.fda.gov/news-events/press-announcements/fda-authorizes-booster-dose-pfizer-biontech-covid-19-vaccine-certain-populations. Accessed January 12, 2022.

258. U.S. Food and Drug Administration. FDA authorizes booster dose of Pfizer-BioNTech COVID-19 vaccine for certain populations. Available at: https://www.fda.gov/news-events/press-announcements/fda-authorizes-booster-dose-pfizer-biontech-covid-19-vaccine-certain-populations. Accessed January 12, 2022.

259. U.S. Food and Drug Administration. Coronavirus (COVID-19) update: FDA expands eligibility for COVID-19 vaccine boosters. Available at: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-expands-eligibility-covid-19-vaccine-boosters. Accessed January 12, 2022.
260. U.S. Food and Drug Administration. Moderna COVID-19 Vaccine. Available at: https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/moderna-covid-19-vaccine. Accessed January 12, 2022.

261. U.S. Food and Drug Administration. Coronavirus (COVID-19) update: FDA shortens interval for booster dose of Moderna COVID-19 vaccine to five months. Available at: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-shortens-interval-booster-dose-moderna-covid-19-vaccine-five-months. Accessed January 12, 2022.

262. U.S. Food and Drug Administration. Janssen. COVID-19 vaccine. Available at: https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/janssen-covid-19-vaccine. Accessed January 12, 2022.

263. Centers for Disease Control and Prevention. CDC endorses ACIP’s updated COVID-19 vaccine recommendations. Available at: https://www.cdc.gov/media/releases/2021/s1216-covid-19-vaccines.html. Accessed January 12, 2022.

264. A manual for pediatric house officers: the Harriet Lane handbook, 21st edition., 2018, Elsevier, https://www.lebpedsoc.org/doc/HIGHLIGHTS%20FROM%20THE%20LITERATURE/Harriet%20Lane%20Handbook%20%20%2021st%20ed%20%20%202018.pdf.