COVID-19 in Children

Clinical Manifestations and Pharmacologic Interventions Including Vaccine Trials

Ramon Galindo, MD[1], Heather Chow, DO[1],
Chokechai Rongkavilit, MD*

KEYWORDS

• COVID-19 • SARS-CoV-2 • Coronavirus • Children • Infant • Treatment • Vaccine

KEY POINTS

- COVID-19 in children usually presents with milder symptoms as compared with adults.
- Supportive care alone is appropriate for most children with COVID-19.
- There has been a rapid development of vaccines globally to prevent COVID-19.
- As of June 2021, only Pfizer–BioNTech BNT162b2 mRNA vaccine is approved for emergency authorization use in the pediatric population age 12 years and older.
- A serious hyperinflammatory process after COVID-19 in children known as multisystemic inflammatory syndrome in children has been described. Its clinical features can overlap with Kawasaki disease.

INTRODUCTION

There have been reports of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infecting children in all age groups; however, children still comprise a small percentage of the total number of cases of coronavirus disease 2019 (COVID-19). As low as 2% of 80,900 COVID-19 cases during the case surge in China were pediatric cases.[1] Similarly, a systematic review showed that children accounted for 1% to 5% of reported COVID-19 cases.[2] Interestingly, the proportion of children with COVID-19 seems to be higher in the United States. By the end of 2020, 2,128,587 COVID-19 cases in US children have been reported, and children represented 12% of all reported cases in the United States. The overall rate was 2828 cases per 100,000 US children.[3] The difference in prevalence among different geographic locations could be due to multiple factors, including the case definition used, access to testing, varied sensitivity

Department of Pediatrics, University of California San Francisco-Fresno Branch Campus, 155 North Fresno Street, Suite 219, Fresno, CA 93701-2302, USA
[1] The first author and the second author contributed equally to this article.
* Corresponding author.
E-mail address: chokechai.rongkavilit@ucsf.edu

Pediatr Clin N Am 68 (2021) 961–976
https://doi.org/10.1016/j.pcl.2021.05.004 **pediatric.theclinics.com**

of the tests used, differences in anatomic respiratory sampling sites, variability in sample collection by personnel, levels of case surge within communities, and other as yet unknown host and pathogen factors.

CLINICAL MANIFESTATIONS IN CHILDREN

COVID-19 Symptoms in Children Are Milder Compared with Those in Adults

It has been observed since early in the pandemic that children seem to experience milder symptoms when compared with adults. Correspondingly, in a large case series of 2135 pediatric patients with COVID-19 in China, 55% of cases were asymptomatic or had only mild symptoms.[4] Only 6% of pediatric cases were classified as severe and critical cases. This number is fewer compared with the number of severe and critical cases in the adult population, which was found to be about 18.5%. In a report from the US Centers for Disease Control and Prevention (CDC), 73% of pediatric COVID-19 cases had symptoms of fever, cough, or shortness of breath compared with 93% of adults aged 18 to 64 years during the same reporting period, and only 6% of all pediatric cases required hospitalization.[5] Thus, the majority of pediatric COVID-19 cases are either asymptomatic or mild in disease severity.

Theories for the milder symptoms and lower prevalence in children

Multiple theories have been suggested to explain why children may contribute to such a small percentage of reported COVID-19 cases and why children may have a milder clinical presentation than adults. In a systematic review and meta-analysis including 32 studies, children and adolescents younger than 20 years had a 44% lower odds of infection with SARS-CoV-2 compared with adults 20 years and older, and the finding was most marked in those younger than 10 to 14 years.[6]

Davies and colleagues[7] generated a modeling study to determine the manifestation of clinical symptoms based on susceptibility of infection in children versus adults. Their data suggested an "age gradient," in which the risk for severe disease increases with advancing age. More specifically, they found that 79% of pediatric patients in the 10- to 19-year-old group are asymptomatic, and that individuals 20 years and older are 2 times more susceptible to COVID-19 than those younger than 20 years of age.

Several potential causes have been implicated in creating this distribution across the different age groups. Having more mild symptoms or being asymptomatic may contribute to reporting bias and account for the low number of reported cases of COVID-19 in children. Those with less noticeable symptoms are less likely to seek medical care, and in turn the cases are less likely to be confirmed and reported.

Second, because children get frequent viral upper respiratory tract infections including coronaviruses that cause common cold, it has also been proposed that infections from other coronaviruses offer some immunity to children, rendering children less susceptible to infection by SARS-CoV-2. This phenomenon may be due to either cross-protection from other types of previous coronavirus infections or nonspecific protection from other respiratory viruses. Coinfection with another virus could also compete with SARS-CoV-2 and decrease its replication, and thus result in a milder illness.[8]

Third, SARS-CoV-2 uses its spike protein to bind with human angiotensin-converting enzyme 2 (ACE-2) receptor for host cell entry.[9] In a cohort study of 305 individuals aged 4 to 60 years, ACE-2 gene expression in the nasal epithelium was lowest in children less than 10 years of age and it increased with advancing age.[10] Low ACE-2 expression could limit SARS-CoV-2 entry into host cells. This factor could lead to a lower risk of infection and a milder clinical presentation in children. Moreover, the lower prevalence of comorbidities such as diabetes, chronic lung disease, and

cardiovascular disease in children may contribute to a milder clinical course as compared with adults.[11]

Many pediatric COVID-19 cases have been found to be linked to a family member. In a study with 34 confirmed pediatric cases, 13 (38%) patients were found to have an exposure to COVID-19 from a family member.[12] It has been suggested that if an adult transmits SARS-CoV-2 to a child, the infection would be caused by a second or third generation of virus, and the infection may be milder owing to decreased pathogenicity. A retrospective review analyzed the data collected from 9 children and their 14 adult family members.[13] It was found that 3 children had symptoms of fever or cough, and 6 were asymptomatic. Four children (44%) had abnormal chest radiograph findings, whereas 71% of the adults had abnormal radiograph studies. Thus, this concept of family clusters may also explain why pediatric patients have a milder presentation.[8,11]

Clinical Manifestations

The most common symptoms in children include fever, upper respiratory symptoms, and gastrointestinal symptoms. Because SARS-CoV-2 attaches to human cells via ACE-2 receptors, the expression of ACE-2 receptors on epithelial cells in the lung and the intestines may account for the manifestations of respiratory and gastrointestinal symptoms, respectively.[8]

In a review of 333 pediatric patients, the most common symptoms included cough with a prevalence of 48%, fever (42%), and sore throat (42%). Moreover, 35% of cases were reported to be asymptomatic.[11] Similarly, in a study in Wuhan, China, that examined 171 children with confirmed COVID-19, 49% of children had cough, 42% had fever, and 46% had pharyngitis.[2] Other symptoms that have been reported include rhinorrhea, nasal congestion, myalgia, fatigue, shortness of breath, dyspnea, abdominal pain, diarrhea, vomiting, nausea, headache, dizziness, decreased oral intake, and rash. **Fig. 1** provides a compilation of clinical symptom data from 3 review articles that altogether include 26 studies for a total of 1793 children with COVID-19.[1,11,14] Fever

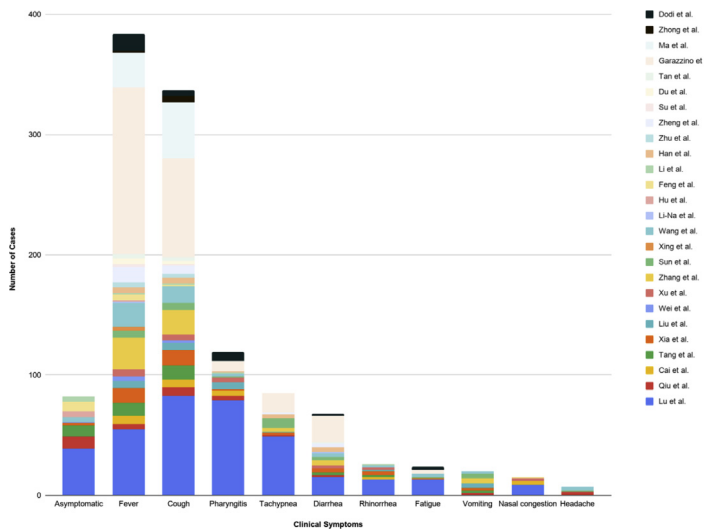

Fig. 1. Summary of clinical manifestations in reported pediatric patients with COVID-19.

and cough were by far the most prevalent symptoms (see Fig. 1). Recovery occurred within 1 to 2 weeks after the onset of symptoms.[8]

In adults, anosmia and ageusia have been reported in COVID-19 cases. These symptoms have been reported less frequently in children. Coronaviruses as a family of viruses invade the olfactory bulb, leading to loss of smell. Parisi and colleagues[15] emphasizes the importance of further evaluation in pediatric patients with COVID-19 complaining of loss of smell. Nasal endoscopy and smell tests, such as the Pediatric Smell Wheel, can be used to help identify the degree of olfactory loss.[15]

Severe and Critical Disease in Children

Although most children with COVID-19 are mildly symptomatic or asymptomatic, there have been reported cases of severe infection and even death, albeit few. Reported symptoms of severe and critical disease include hypoxia defined as an oxygen saturation of less than 92%, acute respiratory distress syndrome, shock, and various organ failure such as encephalopathy, heart failure, abnormal coagulation, and acute kidney injury.[4] According to a review by Zimmerman and colleagues, 9 (3%) of 333 children required admission to pediatric intensive care units, and two of these children had preexisting conditions, namely, leukemia and hydronephrosis.[11]

The adult and elderly population have experienced more COVID-19–related deaths than the pediatric population.[1] The presence of comorbidities such as cancer, diabetes, cardiovascular disease, chronic lung disease, and a weaker immune system has been implicated in the greater prevalence of deaths in adults. One study of 44,672 COVID-19 cases found that 26% had comorbidities.[2] Additionally, there were 965 deaths, and only one of these deaths was a pediatric patient. No information was provided on the 14-year-old boy in this study. By March 2020, this case was 1 of the 2 deaths reported in children with COVID-19. The other child was a 10-month-old girl with intussusception, encephalopathy, septic shock, and multiorgan failure.[2,11]

In a review of 29 studies with 4300 children included, 19% were asymptomatic and 37% had no radiographic abnormalities.[16] A small proportion of 0.1% required admission to intensive care units and 4 deaths were reported. Among 208 hospitalized children with complete medical chart reviews by the US COVID-19-Associated Hospitalization Surveillance Network, 33% were admitted to an intensive care unit, 6% required invasive mechanical ventilation, and 1 child (0.5%) died.[17] The comorbid conditions included obesity (38%), chronic lung disease (18%), and prematurity (15%). Overall, children with COVID-19 have a good prognosis. However, a serious postinfectious hyperinflammatory process known as multisystemic inflammatory syndrome in children has been described. See details in Chapter 5 in this issue.

COVID-19 Symptoms in Newborns and Infants

COVID-19 in neonates has also been reported. In China, between early December 2019 and February 2020, 9 infants (1–11 months of age) were hospitalized. Four had fever, 2 had mild upper respiratory tract infections, 1 was asymptomatic, and there was no information on 2 infants.[18] Another review reported 3 neonatal cases.[2] One had fever and cough, one had rhinorrhea and vomiting, and the third had respiratory distress. Neonatal complications from COVID-19–infected mothers have been reported as well. In 67 neonates born to 65 mothers who had COVID-19 during pregnancy, 12 had respiratory distress or pneumonia (18%), 9 were born with low birth weight (13%), 2 developed a rash (3%), 2 developed disseminated intravascular coagulation (3%), 1 had asphyxia (2%), and 2 died (3%).[11]

Inverse Relationship between Severity and Age in Pediatrics

Even though severity of COVID-19 seems to increase with advancing age in the general population overall, severity in the pediatric population seems inversely related to age, as depicted by the study performed by Dong and colleagues.[4] Infants were the most susceptible to severe illness, with 10.6% of infants less than 1 year of age presenting with severe or critical disease. A decreasing frequency of severity with advancing age was demonstrated, with severe illness being reported in 7.3% in the 1- to 5-year-old group, 4.2% in the 6- to 10-year-old group, 4.1% in the 11- to 15-year-old group, and 3.0% in the 16 or older group. In the United States, infants less than 1 year old accounted for the highest percentage (estimated range, 15%–62%) of hospitalizations among pediatric patients with COVID-19.[5]

PHARMACOLOGIC INTERVENTIONS, INCLUDING VACCINE TRIALS

Pharmacologic Interventions

Antivirals

Remdesivir. The antiviral that has perhaps received the most attention is remdesivir. Remdesivir has a broad spectrum antiviral activity that was first developed to treat hepatitis C and respiratory syncytial virus and subsequently repurposed to treat the Ebola virus.[19] SARS-CoV-2 is part of the Coronaviridae family characterized by positive sense single-stranded RNA that requires the function of an RNA-dependent RNA polymerase for replication. Remdesivir is a nucleoside analog capable of inhibiting the RNA polymerase via chain termination and has demonstrated in vitro activity against SARS-CoV-1 and Middle Eastern respiratory syndrome coronavirus.[20–22] The efficacy of remdesivir in treating adults with lower respiratory tract infection with COVID-19 was assessed in a double-blinded placebo-controlled trial with the primary outcome being time to recovery. The results demonstrated that a 10-day course of remdesivir resulted in a shorter time to recovery with a median of 10 days versus 15 days with placebo. Despite the shorter recovery, the study did not demonstrate a reduction in mortality.[23] At present, a phase II/III study evaluating safety, tolerability, pharmacokinetics, and efficacy of remdesivir in the pediatric population is ongoing. Despite the lack of clinical trial data, there have been reported cases of its use in children.[24,25] The most recent guidelines regarding antiviral therapy in children has been set forth by a panel of pediatric infectious disease physicians and pharmacists in the United States. Their suggestion is that supportive care alone is appropriate for most cases given the mild course of COVID-19 in children in general. For children with severe or critical illness, as defined by the need for supplemental oxygen, noninvasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation, remdesivir should be considered. A treatment duration of 5 days is appropriate for most children.[26] Although approved for use in children with COVID-19 by the US Food and Drug Administration (FDA) through an Emergency Use Authorization (EUA), the safety and efficacy of remdesivir have not been evaluated fully in pediatric patients aged less than 12 years or weighing less than 40 kg. Other medications including chloroquine, hydroxychloroquine, azithromycin, or lopinavir/ritonavir are not recommended for the treatment of COVID-19.[27]

Corticosteroids

The use of corticosteroids for COVID-19 is based primarily on the results of the multicenter, randomized, open-label RECOVERY trial.[28] Mortality at 28 days was lower among adult patients on invasive mechanical ventilation who received up to 10 days of dexamethasone 6 mg once daily (29.3%) than among those who received the standard of care (41.4%). This benefit was also observed in patients who required

supplemental oxygen. No mortality benefit was seen in those who required no supplemental oxygen. According to the National Institutes of Health guidelines, if dexamethasone is not available, alternatives such as prednisone, methylprednisolone, or hydrocortisone can be used.[27] The safety and effectiveness of dexamethasone or other corticosteroids for COVID-19 treatment have not been sufficiently evaluated in children. However, dexamethasone may be beneficial in children who require mechanical ventilation. The use of dexamethasone for those who require supplemental oxygen support should be considered on a case-by-case basis.

Monoclonal antibodies

Bamlanivimab (LY-CoV555). Bamlanivimab is an antispike neutralizing monoclonal antibody that was discovered from the convalescent plasma of a patient with COVID-19. This antibody was shown to bind the receptor-binding domain of the trimeric spike protein in both its up (active) or down (resting) state. This finding generated interest because the up state has been shown to be required for ACE-2 binding and viral fusion for cell entry. In a study in nonhuman primates, the administration of this antibody in rhesus monkeys decreased SARS-CoV-2 replication in both the upper and lower respiratory tracts.[29] In the outpatient setting, the administration of bamlanivimab to adults with mild to moderate COVID-19 was shown to decrease the viral load from baseline compared with placebo and to decrease hospitalizations or emergency department visits.[30] Unfortunately, the administration of bamlanivimab among hospitalized adults did not result in a decrease in the clinical severity or in the time to recovery compared with placebo.[31] At this time, there are no published data on the efficacy of bamlanivimab in children; however, the BLAZE-1 trial (NCT04427501) is currently planned to assess the efficacy of bamlanivimab in children greater than 12 years of age with high-risk medical conditions. Despite the lack of published data in persons less than 18 years of age, the FDA issued an EUA in November 2020 granting the use of bamlanivimab for both adults and high-risk children older than 12 years of age who have mild to moderate COVID-19 and who are at high risk of progression to severe COVID-19 and/or hospitalization.

REGN-COV2 (casirivimab and imdevimab). The REGN-COV2 cocktail is composed of 2 fully humanized antibodies that were generated from genetically humanized immune systems of mice. The pair of monoclonal antibodies known as casirivimab and imdevimab bind noncompetitively to the receptor-binding domain of the SARS-CoV-2 spike protein.[32] The idea behind using pairs rather than a single antibody is to help decrease the emergence of escape mutations and in fact REGN-COV2 cocktail was shown to prevent the emergence of spike protein mutants in vitro.[33] In rhesus macaques, the use of the REG-COV2 cocktail was shown to successfully prevent and treat SARS-CoV2 infection.[34] The results of the phase III randomized double-blinded placebo-controlled trial demonstrated that the use of the antibody cocktail in nonhospitalized persons greater than 18 years of age with COVID-19 produced a modest decrease in SARS-CoV-2 viral load levels from baseline as compared with placebo at day 7 of infection.[35] This effect was observed among those who had a high baseline viral load. Secondary end points such as hospitalization or emergency room visits were similar between the placebo group and the antibody treated groups. On November 21, 2020, the FDA issued an EUA for casiravimab and imdevimab to be used together in the treatment of mild to moderate COVID-19 in both ambulatory adults and pediatric patients older than 12 years of age who are at high risk for a poor outcome.[27]

Currently, there is no evidence for the safety and efficacy of monoclonal antibody therapy for treatment of COVID-19 in children or adolescents. Moreover, there is

evidence for potential harm associated with monoclonal antibody infusion reactions or anaphylaxis. As of December 2020, the pediatric expert panel suggested against the routine administration of monoclonal antibody therapy (bamlanivimab, or casirivimab and imdevimab) for the treatment of COVID-19 in children or adolescents, including those designated by the FDA as being at high risk of progression to hospitalization or severe disease.[36]

Convalescent plasma

Convalescent plasma has been used for centuries to treat infectious diseases; however, to date the use of convalescent plasma has only been shown to be of clear value in the treatment of Argentine hemorrhagic fever.[37] There are reported cases (n = 4) of improvement after convalescent plasma use in children with severe COVID-19.[38] However, to date no clinical studies have systematically evaluated the efficacy of convalescent plasma in pediatrics. In a placebo-controlled trial in adults with severe COVID-19 with evidence of radiologically confirmed pneumonia and signs of respiratory distress, the use of convalescent plasma did not improve the clinical outcome at 7, 14, or 30 days when compared with placebo, nor did it decrease mortality (11.0% in convalescent plasma group vs 11.4% in placebo).[39] Of note, there was no statistically significant difference in transfusion-related adverse events between the convalescent plasma and the placebo group.

SARS-CoV-2 vaccines

The emergence of SARS-CoV-2 has prompted international efforts to develop effective vaccines at an unprecedented rate. As of January 2021, just 11 months after the announcement of the COVID-19 pandemic by the World Health Organization, 64 vaccines are under clinical evaluation and 173 in preclinical evaluation.[40] The United States has directed more than $10 billion to help streamline the production and distribution of promising antivirals and vaccines in a strategy known as Operation Warp Speed. This operation is a large-scale collaboration between the Department of Health and Human Services, the CDC, the US National Institutes of Health, and the Biomedical Advanced Research and Development Authority along with the Department of Defense.[41] **Table 1** lists the 6 vaccines whose data have shown promise against COVID-19 as of January 2021.

To better appreciate the latest development of COVID-19 vaccines, a brief discussion on messenger RNA (mRNA)-based vaccines is merited, especially because 2 of the 6 vaccines to be discussed elsewhere in this article use this new mRNA-based vaccine technology. Although the technology has been around since the 1990s,[42] its use in the development of vaccines has largely been hindered by its poor stability, unpredictable immune response, and inefficient delivery methods when used in vivo. As a result, vaccine approaches have largely relied on traditional methods using subunits, live attenuated, or inactivated pathogens. In the past decade, however, major advancements through the use of modified nucleosides, synthetic cap analogues, the incorporation of regulatory genetic elements, and purification techniques have resulted in an increased stability of mRNA and improved control over its immunogenicity. Furthermore, the use of lipid nanoparticle technology has greatly enhanced the delivery of mRNA into target cells. In 2017, the first successful use of an mRNA-based vaccine was shown to protect mice against Zika virus.[43] Since then, multiple clinical trials have been initiated to test the efficacy of mRNA-based vaccines against rabies and influenza in humans.[44,45] A review on the latest advancements of mRNA-based vaccine technology is well beyond the scope of this article, but has been excellently reviewed elsewhere.[46] In summary, mRNA-based vaccines have been touted to

Table 1
Current SARS-CoV-2 vaccines (as of January 11, 2021)

Company	Vaccine	Key Component	Series	Efficacy	Storage
Pfizer–BioNTech	*BNT162b2*	mRNA lipid particle encoding SARS-CoV-2 S-P2 spike protein	2 doses 21 d apart	95%	Storage between −80 °C to −60 °C
Moderna	*mRNA-1273*	mRNA lipid particle encoding SARS-CoV-2 S-P2 spike protein	2 doses 28 d apart	94.1%	Short-term storage: 2 °C–8 °C. Long-term storage: −20 °C
Oxford–AstraZeneca	*ChAdOx1 nCov-19*	Replication-deficient chimpanzee adenovirus vector expressing SARS-CoV2 Spike gene	2 doses 28 d apart	70.4%	Storage between 2 °C and 8 °C
Janssen	*Ad26.COV2.S*	Replication-deficient adenovirus vector serotype 26 encoding full length stabilized SARS-CoV2 spike protein	Single dose vs double dose being studied	Pending	Short-term storage: 2 °C–8 °C. Long-term storage: −20 °C
Novavax	*NVX-CoV2373*	Purified recombinant SARS-CoV-2 spike glycoprotein and Matrix-M1 adjuvant.	2 doses, 21 d apart	Pending	Storage between 2 °C and 8 °C

have superiority over traditional vaccines via their improved safety profile, efficacy at delivery, and relatively rapid and low-cost production. However, the need for costly laboratory-grade freezers for storage could hinder the widespread use of mRNA-based vaccines in real-world settings.

Pfizer–BioNTech BNT162b2 mRNA vaccine. The Pfizer–BioNTech vaccine consists of a nucleoside-modified mRNA molecule enveloped within a lipoprotein nanoparticle that encodes the SARS-CoV-2 spike protein in a prefusion state. The phase I/II trials were conducted in Germany and the United States and initially involved testing 2 vaccine candidates (BNT162b1 and BNT162b2) for safety and immunogenicity. The molecular difference between these vaccine candidates is that the BNT162b1 mRNA encodes a soluble trimerized SARS-CoV-2 receptor-binding domain protein, whereas the BNT162b2 mRNA encodes a full-length membrane-anchored SARS-CoV-2 spike protein in a prefusion conformation. The phase I/II trial in the United States involved healthy adults 18 to 55 and 65 to 85 years of age. The administration of a primer dose and a booster dose spaced apart by 21 days demonstrated equally robust IgG responses against the S1-binding domain of the spike protein in both vaccine candidates and in all age groups.[47] Furthermore, the immunogenicity was greatly enhanced after the booster dose. One notable difference between BNT162b1 and BNT162b2 was that the latter was associated with a lower incidence of severe systemic reactions such as fever, fatigue, and chills in adults older than 65 years of age. It is worth mentioning that no participants reported a fever of greater than 40 °C or systemic events requiring emergency department visit or hospitalization. Meanwhile the phase I/II trial in Germany demonstrated that the vaccine elicited a strong humoral and cell-mediated immune response as demonstrated by the activation of $CD4^+$ and $CD8^+$ T cells and release of immune-modulatory cytokines such as interferon-gamma, suggesting that the vaccine not only elicited an antibody response, but also an appropriate T-helper type-1 T-cell mediated response.[48] Owing to the preferred safety profile of BNT162b2, it went on to phase III clinical trials. This is a double-blinded randomized trial of 43,448 persons ages 16 years or older who either received a 2-dose placebo or a 2-dose 30 μg BNT162b2 vaccine spaced apart by 21 days.[49] The results demonstrated a 95% efficacy at preventing symptomatic COVID-19. The adverse effects included short-term, mild-to-moderate pain at the injection site along with systemic signs of fatigue, fever, and headache. The incidence of serious adverse events was low and was similar to placebo. The vaccine received FDA EUA for persons ages 16 years and older on December 11, 2020 and subsequently on May 10, 2021 for persons ages 12 years and older. Since the rollout of Pfizer–BioNTech vaccine, there have been 21 reported cases of anaphylaxis among the 1,893,360 first doses (ie, 11.1 cases per million doses given).[50] At the time of this writing according to the CDC, a history of immediate or severe allergic reactions after either mRNA-based COVID-19 vaccine or its components is a contraindication to vaccination with either Pfizer–BioNTech or Moderna COVID-19 vaccine.[51] A history of any immediate allergic reaction to any other vaccine or injectable therapy not related to a component of mRNA COVID-19 vaccines or polysorbate is a precaution but not a contraindication to vaccination.

Moderna mRNA-1273 vaccine. Moderna mRNA-based vaccine also known as mRNA-1273 is composed of a nucleoside-modified mRNA molecule encapsulated within a lipoprotein nanoparticle. The mRNA encodes an anchored transmembrane SARS-CoV-2 S-2P spike protein. The mRNA has been modified such that 2 consecutive prolines are inserted at positions 986 and 987 during translation of the S-2P mRNA. This

change maintains the trimeric spike protein in a prefusion state also known as the down or inactive state. To place this in context, viral cell entry via fusion requires that the spike protein to be in the up or active state to facilitate binding to human ACE-2 receptor.[52] This phase I trial involved healthy participants more than 18 years of age being randomized to receive 2 doses of either placebo, 25 μg mRNA-1723 vaccine, or 100 μg mRNA-1723 vaccine given 28 days apart. Both doses of the vaccines elicited robust antispike antibody response in a dose-dependent manner. The level of binding and neutralizing antibody titers generated were greater than antibody titers observed from convalescent serum of patients recovered from COVID-19 and the titers remained elevated at 119 days after the first dose of the vaccine.[53] In addition to eliciting a strong humoral response, the 100 μg dose was shown to preferentially stimulate T-helper type-1 $CD4^+$ cells over T-helper type-2 $CD4^+$ cells, suggesting that the vaccine not only induced a humoral immune response, but also stimulated cell-mediated immunity. Last, the results from the phase I study demonstrated that the most common adverse events consisted of headache, fatigue, myalgia, chills, and pain at the injection site, all of which were reported to be mild to moderate with the majority resolving within 1 day.[54,55] The Moderna mRNA-1273 vaccine entered phase III trials in July 2020. This is a double-blinded study with more than 30,000 participants 18 years of age or older being randomized to receive 2 doses of either placebo or 100 μg mRNA-1273 vaccine given 28 days apart.[56] The vaccine showed 94.1% efficacy at preventing COVID-19 illness including severe COVID-19 disease. Aside from transient local and systemic reactions, no safety concerns were identified.[57] The vaccine received FDA EUA for persons ages 18 years and older on December 18, 2020.

Oxford–AstraZeneca ChAdOx1 nCov-19 vaccine. Unlike Pfizer's and Moderna's mRNA-based vaccines, the University of Oxford–AstraZeneca vaccine known as ChAdOx1 nCov-19 (AZD1222) uses a replication-deficient adenovirus vector to express the SARS-CoV-2 trimeric spike protein. The adenovirus, which causes the common cold in chimpanzees, is modified so as to not replicate in humans. An interim analysis of the randomized controlled trials in the United Kingdom and Brazil demonstrated a vaccine efficacy of 62.1% among participants who received 2 standard doses and 90.0% among participants who received a half dose followed by a standard dose. The overall vaccine efficacy across both groups was 70.4%.[58] Although the overall efficacy was not as high as the mRNA-based vaccines, this vaccine has some advantages, namely, the low cost per dose and no requirement for ultralow temperature storage.[59] These factors makes it attractive for resource-limited settings. It is important to keep in mind that the US FDA and World Health Organization require a vaccine to be at least 50% efficacy for licensure. This vaccine has been authorized for emergency use for persons 18 years and older in the United Kingdom on December 30, 2020.

Janssen Ad26.COV2.S (JNJ-78436725). Similar to the Oxford–AstraZeneca vaccine, the Janssen Ad26.COV2.S vaccine is built on a replication-deficient adenovirus serotype 26 vector that has been modified so as to not replicate in humans. The adenovirus vector was used by Janssen during the design of Ebola virus vaccine. Like the previous vaccines discussed, the adenovirus vector encodes a prefusion stabilized spike protein that is membrane bound and contains a mutation at the furin cleavage site along with 2 protein stabilizing mutations at positions 986 and 987. The basis behind the prefusion conformation is 2-fold. First, the prefusion state facilitated the initial crystallography of this highly glycosylated spike protein,[60] Second, the prefusion conformation

has been shown to illicit the highest binding and neutralizing antibody titers when compared with other spike protein variants.[61] The preclinical findings demonstrated that the Ad26.COV2.S vaccine is capable of inducing a humoral immune response in rhesus macaques and that the immunogenicity provided protection when animals were challenged with SARS-CoV-2.[62] One potential benefit of this vaccine is that it could induce immunogenicity (ie, neutralizing antibodies) after a single dose up to day 71 after vaccination as observed in the phase I/IIa trials.[63] This feature would be a benefit over the 2-dose vaccine regimen, particularly in the real-world setting. At the time of this writing, it has entered a phase III (ENSEMBLE) study.

Novavax NVX-CoV2373. Unlike the previous vaccines discussed thus far, the Novavax NVX-CoV2373 vaccine contains purified recombinant full-length trimeric SARS-CoV-2 spike proteins. The recombinant spike protein is modified such that it is resistant to proteolytic cleavage and stabilized to maintain the prefusion conformation. In addition, the vaccine also contains a patented saponin-based Matrix-M adjuvant that enhances immune response and thereby produces high levels of neutralizing antibodies. In a phase I/II study in healthy persons 18 to 59 years of age, the 2-dose 5-μg adjuvanted regimen induced geometric mean antispike IgG antibody and neutralization responses that were greater than those observed in convalescent serum of COVID-19 patients.[64] Reactogenicity was absent or mild. At the time of this writing, it is undergoing phase III trials in the United Kingdom, Mexico, and the United States.

Sanofi–GlaxoSmithKline COVID-19 vaccine. This is an adjuvanted recombinant protein-based vaccine. The phase I/II study involved adults ages 18 to 49 years of age. The vaccine demonstrated immune responses comparable to those who had recovered from COVID-19.[65] Unfortunately, there was a lower immune response observed among those older than 50 years of age. A phase IIb study using an amended formulation is planned for early 2021.

VACCINE CONSIDERATIONS

At the time of this writing, there are currently 64 COVID-19 vaccines in clinical trials and 173 in preclinical development[40]; thus, it is important we do not overlook the usefulness of other upcoming vaccines. This process is ever more important because scientists have discovered the presence of SARS-CoV-2 mutated variants in the United Kingdom, Brazil, and South Africa that have a potential to spread rapidly.[66–68] Published data are lacking on whether immunogenicity from current vaccines can prevent infections by these variants. Our armamentarium against variant strains may rely on the swift identification of new mutations and the rapid development of diverse vaccine candidates.

It is also critical to point out that the clinical trials have not focused specifically on children thus far. It is imperative that we do not delay the development of vaccines for this population. Although children are less likely to suffer from severe COVID-19, children particularly those 10 years of age and older could readily spread COVID-19 as effectively as adults. Furthermore, approximately 12% of all COVID-19 cases are seen in children and some have succumbed to a severe disease.[3] In addition, children have been greatly affected by the pandemic, with large disruptions to in-person school, limited peer interactions, and decreased access to activities that helps to develop their physical and emotional well-being. Thus, the development of COVID-19 vaccines must not only target the adult population, but also the pediatric population. It is encouraging that at the time of this writing, Pfizer has enrolled children to the age of 6 months and its EUA for vaccine indications down to the age of 12 years

was approved. Moderna is initiating a similar study, as is Janssen. AstraZeneca vaccine has an approval to enroll children ages 5 to 12 years in the United Kingdom.

SUMMARY

The COVID-19 pandemic has significantly impacted a large number of children worldwide. Although most children present with no or mild symptoms from COVID-19, more data are needed regarding its long-term effects in children. Antivirals and immune-based therapies may play a role in management of those with severe diseases; however, such interventions have not been evaluated fully in pediatric patients to date. The development of vaccines is rapidly evolving, and several vaccine candidates are being assessed in the pediatric population.

CLINICS CARE POINTS

- COVID-19 in children is usually mild, and COVID-19–related deaths in the pediatric population are extremely rare.
- Cases in children have been linked to having a family member with COVID-19.
- Severity in the pediatric population seems to be related inversely with age, with infants being most susceptible to severe COVID-19.
- Supportive care alone is sufficient for most children and antiviral remdesivir may be appropriate for those with severe or critical illness.
- Several vaccine candidates are being evaluated in pediatrics. At this time, only the Pfizer–BioNTech mRNA vaccine is approved for emergency authorization use in the pediatric population ages 12 years and older.

DISCLOSURE

All contributing authors declare no conflicts of interest.

REFERENCES

1. Lok Tung Ho C, Oligbu P, Ojubolamo O, et al. Clinical characteristics of children with COVID-19. AIMS Public Health 2020;7(2):258–73.
2. Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. Acta Paediatr 2020;109(6):1088–95.
3. American Academy of Pediatrics and the Children's Hospital Association. Children and COVID-19: state-level data report. Available at: https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/children-and-covid-19-state-level-data-report/. Accessed January 6, 2021.
4. Dong Y, Mo X, Hu Y, et al. Epidemiology of COVID-19 among children in China. Pediatrics 2020;145(6):e20200702.
5. CDC COVID-19 Response Team, CDC COVID-19 Response Team, Bialek S, et al. Coronavirus disease 2019 in children — United States, February 12–April 2, 2020. MMWR Morb Mortal Wkly Rep 2020;69(14):422–6.
6. Viner RM, Mytton OT, Bonell C, et al. Susceptibility to SARS-CoV-2 infection among children and adolescents compared with adults: a systematic review and meta-analysis. JAMA Pediatr 2020;25. https://doi.org/10.1001/jamapediatrics.2020.4573.

7. CMMID COVID-19 Working Group, Davies NG, Klepac P, et al. Age-dependent effects in the transmission and control of COVID-19 epidemics. Nat Med 2020; 26(8):1205–11.
8. Balasubramanian S, Rao NM, Goenka A, et al. Coronavirus disease 2019 (COVID-19) in children - what we know so far and what we do not. Indian Pediatr 2020;57(5):435–42.
9. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020;181(2):271–80.e8.
10. Bunyavanich S, Do A, Vicencio A. Nasal gene expression of angiotensin-converting enzyme 2 in children and adults. JAMA 2020;323(23):2427–9.
11. Zimmermann P, Curtis N. Coronavirus infections in children including COVID-19: an overview of the epidemiology, clinical features, diagnosis, treatment and prevention options in children. Pediatr Infect Dis J 2020;39(5):355–68.
12. Zhang C, Gu J, Chen Q, et al. Clinical and epidemiological characteristics of pediatric SARS-CoV-2 infections in China: a multicenter case series. Persson LÅ. PLoS Med 2020;17(6):e1003130.
13. 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.
14. Martins MM, Prata-Barbosa A, Magalhães-Barbosa MC de, et al. Clinical and laboratory characteristics of SARS-COV-2 infection in children and adolescents. Rev Paul Pediatr 2021;39:e2020231.
15. Parisi GF, Brindisi G, Indolfi C, et al. Upper airway involvement in pediatric COVID-19. Eigenmann P. Pediatr Allergy Immunol 2020;31(S26):85–8.
16. Liu C, He Y, Liu L, et al. Children with COVID-19 behaving milder may challenge the public policies: a systematic review and meta-analysis. BMC Pediatr 2020; 20(1):410.
17. 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.
18. Hong H, Wang Y, Chung H-T, et al. Clinical characteristics of novel coronavirus disease 2019 (COVID-19) in newborns, infants and children. Pediatr Neonatol 2020;61(2):131–2.
19. Warren TK, Jordan R, Lo MK, et al. Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. Nature 2016;531(7594):381–5.
20. Sheahan TP, Sims AC, Leist SR, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun 2020;11(1):222.
21. Sheahan TP, Sims AC, Graham RL, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci Transl Med 2017;9(396). https://doi.org/10.1126/scitranslmed.aal3653.
22. Gordon CJ, Tchesnokov EP, Feng JY, et al. The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus. J Biol Chem 2020;24. https://doi.org/10.1074/jbc.AC120.013056. jbc.AC120.013056.
23. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med 2020. https://doi.org/10.1056/NEJMoa2007764.

24. Frauenfelder C, Brierley J, Whittaker E, et al. Infant With SARS-CoV-2 Infection Causing Severe Lung Disease Treated With Remdesivir. Pediatrics 2020;146(3). https://doi.org/10.1542/peds.2020-1701.
25. Patel PA, Chandrakasan S, Mickells GE, et al. Severe Pediatric COVID-19 Presenting With Respiratory Failure and Severe Thrombocytopenia. Pediatrics 2020;146(1):e20201437. https://doi.org/10.1542/peds.2020-1437.
26. Chiotos K, Hayes M, Kimberlin DW, et al. Multicenter interim guidance on use of antivirals for children with COVID-19/SARS-CoV-2. J Pediatr Infect Dis Soc 2020; 12. https://doi.org/10.1093/jpids/piaa115.
27. The US National Institutes of Health. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at: https://www.covid19treatmentguidelines.nih.gov/. Accessed January 22, 2021.
28. Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report. N Engl J Med 2020. https://doi.org/10.1056/NEJMoa2021436.
29. Jones BE, Brown-Augsburger PL, Corbett KS, et al. LY-CoV555, a rapidly isolated potent neutralizing antibody, provides protection in a non-human primate model of SARS-CoV-2 infection. bioRxiv 2020. https://doi.org/10.1101/2020.09.30.318972.
30. Chen P, Nirula A, Heller B, et al. SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19. N Engl J Med 2020. https://doi.org/10.1056/NEJMoa2029849.
31. ACTIV-3/TICO LY-CoV555 Study Group, Lundgren JD, Grund B, et al. A Neutralizing Monoclonal Antibody for Hospitalized Patients with Covid-19. N Engl J Med 2020. https://doi.org/10.1056/NEJMoa2033130.
32. Hansen J, Baum A, Pascal KE, et al. Studies in humanized mice and convalescent humans yield a SARS-CoV-2 antibody cocktail. Science 2020;369(6506):1010–4.
33. Baum A, Fulton BO, Wloga E, et al. Antibody cocktail to SARS-CoV-2 spike protein prevents rapid mutational escape seen with individual antibodies. Science 2020;369(6506):1014–8.
34. Baum A, Ajithdoss D, Copin R, et al. REGN-COV2 antibodies prevent and treat SARS-CoV-2 infection in rhesus macaques and hamsters. Science 2020; 370(6520):1110–5.
35. Weinreich DM, Sivapalasingam S, Norton T, et al. REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19. N Engl J Med 2020. https://doi.org/10.1056/NEJMoa2035002.
36. Wolf J, Abzug MJ, Wattier RL, et al. Initial Guidance on Use of Monoclonal Antibody Therapy for Treatment of COVID-19 in Children and Adolescents. J Pediatr Infect Dis Soc 2021. https://doi.org/10.1093/jpids/piaa175.
37. Maiztegui J, Fernandez N, Damilano AD. Efficacy of immune plasma in treatment of Argentine hæmorrhagic fever and association between treatment and a late neurological syndrome. Lancet 1979;314(8154):1216–7.
38. Diorio C, Anderson EM, McNerney KO, et al. Convalescent plasma for pediatric patients with SARS-CoV-2-associated acute respiratory distress syndrome. Pediatr Blood Cancer 2020;67(11):e28693.
39. Simonovich VA, Burgos Pratx LD, Scibona P, et al. A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia. N Engl J Med 2020. https://doi.org/10.1056/NEJMoa2031304.
40. Draft landscape of COVID-19 candidate vaccines. Available at: https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines. Accessed January 21, 2021.

41. Explaining operation Warp Speed. :7.
42. Wolff JA, Malone RW, Williams P, et al. Direct gene transfer into mouse muscle in vivo. Science 1990;247(4949 Pt 1):1465–8.
43. Richner JM, Himansu S, Dowd KA, et al. Modified mRNA Vaccines Protect against Zika Virus Infection. Cell 2017;168(6):1114–25.e10.
44. Alberer M, Gnad-Vogt U, Hong HS, et al. Safety and immunogenicity of a mRNA rabies vaccine in healthy adults: an open-label, non-randomised, prospective, first-in-human phase 1 clinical trial. Lancet Lond Engl 2017;390(10101):1511–20.
45. Bahl K, Senn JJ, Yuzhakov O, et al. Preclinical and Clinical Demonstration of Immunogenicity by mRNA Vaccines against H10N8 and H7N9 Influenza Viruses. Mol Ther 2017;25(6):1316–27.
46. Pardi N, Hogan MJ, Porter FW, et al. mRNA vaccines — a new era in vaccinology. Nat Rev Drug Discov 2018;17(4):261–79.
47. Walsh EE, Frenck RW, Falsey AR, et al. Safety and immunogenicity of two RNA-based Covid-19 vaccine candidates. N Engl J Med 2020. https://doi.org/10.1056/NEJMoa2027906.
48. Sahin U, Muik A, Derhovanessian E, et al. COVID-19 vaccine BNT162b1 elicits human antibody and T H 1 T cell responses. Nature 2020;586(7830):594–9.
49. 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.
50. CDCMMWR. Allergic reactions including anaphylaxis after receipt of the first dose of Pfizer-BioNTech COVID-19 vaccine — United States, December 14–23, 2020. MMWR Morb Mortal Wkly Rep 2021;70. https://doi.org/10.15585/mmwr.mm7002e1.
51. Interim clinical Considerations of Use of MRNA COVID-19 vaccines currently authorized in the United States. Available at: https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html. January 21, 2021.
52. Wrapp D, Wang N, Corbett KS, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science 2020;367(6483):1260–3.
53. Widge AT, Rouphael NG, Jackson LA, et al. Durability of Responses after SARS-CoV-2 mRNA-1273 Vaccination. N Engl J Med 2020. https://doi.org/10.1056/NEJMc2032195.
54. Jackson LA, Anderson EJ, Rouphael NG, et al. An mRNA Vaccine against SARS-CoV-2 — Preliminary Report. N Engl J Med 2020;383(20):1920–31.
55. Anderson EJ, Rouphael NG, Widge AT, et al. Safety and Immunogenicity of SARS-CoV-2 mRNA-1273 Vaccine in Older Adults. N Engl J Med 2020. https://doi.org/10.1056/NEJMoa2028436.
56. ModernaTX, Inc. A Phase 3, Randomized, Stratified, Observer-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of MRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older. clinicaltrials.gov. 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT04470427. Accessed December 28, 2020.
57. Baden LR, El Sahly HM, Essink B, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med 2020. https://doi.org/10.1056/NEJMoa2035389.
58. Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet 2020. https://doi.org/10.1016/S0140-6736(20)32661-1.
59. Knoll MD, Wonodi C. Oxford–AstraZeneca COVID-19 vaccine efficacy. Lancet 2020. https://doi.org/10.1016/S0140-6736(20)32623-4.

60. Kirchdoerfer RN, Cottrell CA, Wang N, et al. Pre-fusion structure of a human coronavirus spike protein. Nature 2016;531(7592):118–21.
61. Bos R, Rutten L, van der Lubbe JEM, et al. Ad26 vector-based COVID-19 vaccine encoding a prefusion-stabilized SARS-CoV-2 Spike immunogen induces potent humoral and cellular immune responses. NPJ Vaccin 2020;5(1):1–11.
62. Mercado NB, Zahn R, Wegmann F, et al. Single-shot Ad26 vaccine protects against SARS-CoV-2 in rhesus macaques. Nature 2020;586(7830):583–8.
63. Sadoff J, Le Gars M, Shukarev G, et al. Interim Results of a Phase 1-2a Trial of Ad26.COV2.S Covid-19 Vaccine. N Engl J Med 2021;13. https://doi.org/10.1056/NEJMoa2034201.
64. Keech C, Albert G, Cho I, et al. Phase 1–2 Trial of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine. N Engl J Med 2020;383(24):2320–32.
65. Sanofi's two vaccine candidates against COVID-19. Available at: https://www.sanofi.com/en/about-us/our-stories/sanofi-s-response-in-the-fight-against-covid-19. Accessed January 21, 2021.
66. Korber B, Fischer WM, Gnanakaran S, et al. Tracking changes in SARS-CoV-2 spike: evidence that D614G increases infectivity of the COVID-19 virus. Cell 2020;182(4):812–27.e19.
67. Tegally H. Emergence and rapid spread of a new severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) lineage with multiple spike mutations in South Africa. Available at: https://www.medrxiv.org/content/10.1101/2020.12.21.20248640v1. Accessed January 21, 2021.
68. Leung K, Shum MH, Leung GM, et al. Early transmissibility assessment of the N501Y mutant strains of SARS-CoV-2 in the United Kingdom, October to November 2020. Euro Surveill Bull Eur Sur Mal Transm Eur Commun Dis Bull 2021;26(1). https://doi.org/10.2807/1560-7917.ES.2020.26.1.2002106.