Review article

Coronavirus disease 2019 (COVID-19) in children: Evolving epidemiology, immunology, symptoms, diagnostics, treatment, post–COVID-19 conditions, prevention strategies, and future directions

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The epidemiology of coronavirus disease 2019 (COVID-19) in children has evolved throughout the pandemic, with initially low infection rates rising significantly as a result of the emergence of the more transmissible Omicron variant. Adolescents, children from ethnic minorities and lower-income households, and those with obesity are at increased risk of contracting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The immune response in children leads to milder symptoms compared to adults, with fever and cough being most frequent; tough symptoms vary by SARS-CoV-2 variant and age. Diagnostic methods to confirm current or past infection include reverse transcription PCR, rapid antigen tests, and serology. Treatment is mainly supportive, with antivirals and glucocorticoids reserved for severe cases. While serious conditions like multisystem inflammatory syndrome in children and other post–COVID-19 conditions are rare, they require careful management. Vaccination has proven effective in reducing severe disease and protecting against post–COVID-19 conditions. Continued surveillance, including wastewater monitoring and universal or pooled testing, remains crucial for controlling community spread. Key questions remain regarding the duration and quality of immunity after reinfection or vaccination, the impact of coinfections, and optimal treatment protocols for different pediatric populations. (J Allergy Clin Immunol 2024;■■■:■■■-■■■.)

Key words: *SARS-CoV-2, MIS-C, long COVID, vaccination, pediatrics*

The coronavirus disease 2019 (COVID-19) pandemic has raised important questions about the impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on children's health. While early data indicated that children typically experience milder symptoms, the emergence of variants such as Omicron and the recognition of postacute sequelae, including multisystem inflammatory syndrome in children (MIS-C) and long COVID, emphasize the need for a comprehensive examination of SARS-CoV-2 effects on children. This review provides a synthesis of the evolving epidemiology, immunology, symptoms, diagnostics, treatment, post–COVID-19 conditions, and prevention strategies associated with COVID-19 in children up to 18 years of age.

EPIDEMIOLOGY

The COVID-19 pandemic was officially declared on March 11, 2020, by the World Health Organization.[1] The epidemiology of COVID-19 in children has varied throughout the pandemic. Generally, the proportion of children among those infected was lower compared to adults starting with approximately 5% at the beginning of the pandemic, increasing to 10% to 23% with the emergence of the more transmissible Omicron variant.[2]

Risk factors

Adolescents, children who are overweight, and those from ethnic minorities and/or lower-income households are at a higher risk for SARS-CoV-2 infection (Fig 1).[3-7] Possible reasons include increased SARS-CoV-2 exposure, limited access to health care, language and cultural barriers, and reporting and detection bias.[4,5]

Several risk factors for severe outcomes in pediatric COVID-19 have been identified (Fig 1). In low- and middle-income countries, case-fatality rates are higher compared to high-income countries, while pediatric intensive care unit (PICU) admission rates are lower, the result of fewer cases being identified and limited PICU access for severe cases.[8] The impact of SARS-CoV-2 variants on PICU admission rates remains controversial, with some studies reporting a decrease over the course of the

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Abbreviations used
ACE2: Angiotensin-converting enzyme 2
COVID-19: Coronavirus disease 2019
IVIG: Intravenous immunoglobulin
MIS-C: Multisystem inflammatory syndrome in children
PICU: Pediatric intensive care unit
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2
TMPRSS2: Transmembrane serine protease 2

pandemic[9-11] and others indicating stable rates.[12,13] Limited data on viral coinfections indicate they are associated with longer hospital stays, higher rates of need for oxygen support, and increased PICU admission rates.[14,15] Children under 12 years of age typically have shorter hospital and PICU stays compared to those aged 12 to 17.[11] Children with preexisting conditions (eg, obesity, chronic lung diseases, cardiovascular disease, prematurity, airway abnormality) and those who are immunocompromised (eg, primary or acquired immunodeficiency, immunosuppressive therapy, oncologic disease, transplant recipient) are at greater risk for severe COVID-19, hospital, and PICU admission.[16-19]

Risk factors for MIS-C include age (average of 8 years), with African Black and Hispanic children being most affected (Fig 1). Approximately 20% of children with MIS-C have preexisting conditions, and nearly 20% are obese.[20] Key predictors for PICU admission are age 5 to 11 years, Black ethnicity, and comorbidities.[9] Lymphopenia and elevated troponin T levels at admission are associated with increased needs of inotropic support or mechanical ventilation.[21]

Risk factors for post–COVID-19 syndrome include being over 10 years old, female sex, hospitalization during the acute phase, and preexisting comorbidities.[22,23] Affected children are more likely to have conditions such as attention-deficit/hyperactivity disorder, schizophrenia, chronic urticaria, and allergic rhinitis.[24]

Transmission

Transmission of SARS-CoV-2 among children is influenced by factors such as viral load, virus shedding, mode of contact, and symptoms. Viral loads in infected children are comparable to those in adults.[25-27] Children can shed virus through respiratory secretions as well as feces,[28,29] with gastrointestinal shedding often lasting longer.[29] However, the potential for fecal–oral transmission remains uncertain.[30] Children transmit the virus less frequently than adults, with lower rates of child-to-child transmission compared to child-to-adult transmission.[31] However, transmission rates vary by setting; the highest rates occur in households, followed by social events, day care facilities, and schools.[31,32] Schools tend to follow, rather than lead, community transmission. Importantly, mass mitigation measures—such as school closures—have had significant negative impacts on children.[33]

IMMUNOLOGY

The immune response to SARS-CoV-2 infection in children explains the milder clinical spectrum in children compared to adults.[34,35]

Innate immune response

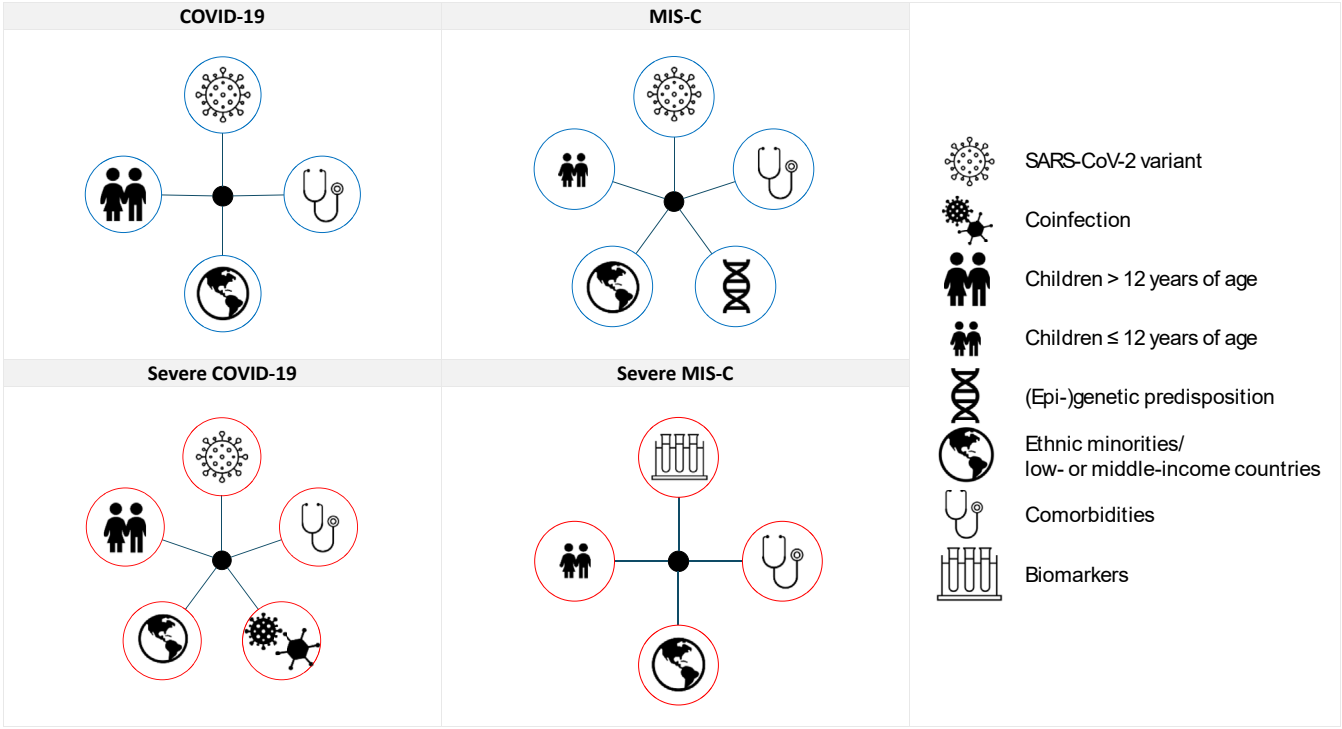
SARS-CoV-2 enters the body through the respiratory tract, binding to angiotensin-converting enzyme 2 (ACE2) receptors on the surface of host cells. For the virus to enter the host cell, the spike protein needs to be primed by proteases such as transmembrane serine protease 2 (TMPRSS2).[36,37] The coexpression of ACE2 receptor and TMPRSS2 shapes SARS-CoV-2's tropism, with the highest prevalence in the ileum, followed by the liver, lungs, nasal mucosa, bladder, testis, prostate, and kidney. Furthermore, ACE2 receptor and TMPRSS2 are also found in pancreatic, brain, and heart cells and fibroblasts.[37] In the placenta, ACE2 receptor is expressed in a small proportion of cells and TMPRSS2 to an even lesser extent.[37] Some studies have found that children have lower levels of ACE2 receptor and *TMPRSS2* gene expression in their nasal and bronchial epithelium compared to adults,[38,39] possibly making children less susceptible to SARS-CoV-2, although others have found no differences.[40]

Host cells detect the virus through several pattern recognition receptors, such as Toll-like receptors, retinoic acid–inducible gene I–like receptors, and nucleotide-binding oligomerization domain-like receptors. Once these pattern recognition receptors on macrophages, dendritic cells, and natural killer cells detect SARS-CoV-2, signaling pathways are activated resulting in production of tumor necrosis factor, interleukins such as IL-1, IL-6 and IL-8, and interferons.[41] Unlike adults, children infected with SARS-CoV-2 may benefit from a preactivated antiviral defense in the upper respiratory tract, expressing higher levels of relevant pattern recognition receptors in their upper respiratory epithelial cells, macrophages, and dendritic cells.[42] Additionally, higher levels of IFN-α2, IFN-γ, IL-1β, and IL-8 are detected in nasal fluid of children of all ages, suggesting a stronger early mucosal immune response compared to adults.[40] In infants, the levels of IFN-γ and IL-6 in the nasal mucosa are associated with SARS-CoV-2 viral load.[43] In plasma, older children and adults both show an early response with interferon production, which resolves more rapidly in children compared to adults, potentially protecting them from COVID-19–associated symptoms and shortening disease duration.[25] Infants show weaker cytokine levels in plasma compared to older children, with most cytokine alterations in nasal fluid not reflected in plasma.[43] The reasons for the differences in mucosal immunity among infants, older children, and adults are not fully understood, but they are thought to be influenced by factors such as the microbiome and the presence of mucosal pathobionts.[43]

Adaptive immune response

Children infected with SARS-CoV-2 show higher absolute lymphocyte counts than adults.[25,40,44] However, they show a weaker T-cell response, marked by lower $CD4^+$ and $CD8^+$ T-cell responses to SARS-CoV-2 structural and ORF1ab proteins, along with reduced T effector memory $CD4^+$ cells.[45,46] This may not only contribute to milder COVID-19 but also lead to a weaker long-term memory response resulting from fewer T effector memory cells.[45] Additionally, children have higher levels of certain B-cell subpopulations (IgD^+CD27^- naive B cells, IgD^+IgM^+ and $IgM^+CD27^-CD38^{dim}$ B cells), suggesting a role in the mildness of their disease.[44]

Seroconversion rates in children after infection with the wild-type virus range from 38% to 100%.[47,48] After infection with the Delta and Omicron variants, higher rates of 81% to 100% were



MIS-C: multisystem inflammatory syndrome in children

FIG 1. Risk factors for COVID-19, severe COVID-19, MIS-C, and severe MIS-C in children.

observed.[48] Studies comparing seroconversion rates between children and adults report conflicting results, with some finding lower rates in children[48] and others reporting higher rates.[47,49] It has been reported that the neutralizing activity of antibodies, which indicates functional capacity, is lower in children.[50] Antibodies persists for 9 to 17 months after infection.[51,52] Children with mild COVID-19 show spike-specific IgA, IgM, and IgG levels comparable to those seen in adults. Interestingly, IgG levels are lower than those observed in adults with severe disease.[53] The initial hypothesis that children are protected by cross-immunity from other coronaviruses has been challenged, as preexisting antibodies to the spike protein are rare in children[54] and no age-related differences in preexisting antibodies to other human coronaviruses have been found.[40]

Immunology of emerging variants and reinfections

As the COVID-19 pandemic evolved, emerging variants became a concern. Variants such as Alpha, Delta, and Omicron have exhibited distinct mutations in the spike glycoprotein, enhancing their transmissibility and their ability to cause severe disease and/or immune evasion compared to the wild type of the virus.[55] The Omicron variant, first identified in late 2021, showed a shift in its entry mechanism by still binding to ACE2 receptors but utilizing endocytosis rather than relying on TMPRSS2.[56] This adaption contributed to the surge in cases among children after the emergence of the Omicron variant.[57] The Omicron variant increased the frequency of reinfections and shortened intervals between infections, with adolescents having the highest risk.[58,59] Reinfections are mostly less severe than first infections.[58-60]

SYMPTOMS AND OUTCOMES

Symptoms

Children generally experience milder illness compared to adults.[61] Early reports indicated that 15-42% of infected children are asymptomatic, with fever and cough being the most frequent symptoms, occurring in 46-67% and 32-56% of cases, respectively.[12,62,63] Less frequent symptoms include other respiratory symptoms, neurologic symptoms, gastrointestinal symptoms, and mucocutaneous symptoms.[12,62] Anosmia and ageusia, common in adults, are rare in children,[64] but they might be underreported in young children. Despite being rare, anosmia and ageusia are strongly associated with a positive PCR test result in children. Other symptoms associated with a positive PCR test result include nausea/vomiting, headache, and fever, particularly when these occur together.[64] Children with COVID-19 typically experience symptoms for an average of 8 days, similar to other respiratory viruses,[65] with anosmia persisting the longest, followed by fatigue and cough. Fatigue lasts longer in SARS-CoV-2–infected children compared to those infected with other respiratory viruses.[65]

Symptoms vary with SARS-CoV-2 variants, viral load, and age. While musculoskeletal symptoms were associated with the wild-type virus, anosmia, ageusia and rash were less common with the Alpha and Omicron variants, and Delta was associated with upper respiratory tract symptoms.[12,13] Children infected with the Omicron variant more frequently presented with fever, neurologic symptoms, and lower respiratory tract symptoms.[12,13] New symptoms like conjunctivitis, croup, and seizures emerged with the Omicron variant.[12,66] Viral loads are higher in children with fever and/or respiratory symptoms compared to asymptomatic children.[67] Fever is more common

in neonates and infants, gastrointestinal symptoms in toddlers, and neurologic symptoms in both toddlers and school-aged children.[12,13] Neonates often present with fever without a source.[68]

Most COVID-19 courses in children are mild, but a small proportion can develop severe illness with respiratory failure.[69] Rare severe extrapulmonary manifestations include cardiologic manifestations (eg, myocardial ischemia, arrhythmia, heart failure, myocarditis[70]), neurologic manifestations (eg, encephalopathy, stroke, central nervous system infection or demyelination, Guillain-Barré syndrome, acute fulminant cerebral edema[71]), hematologic manifestations (eg, thrombotic events, major bleedings[72]), and severe hepatitis,[73] though these have been reported only in small case series.

Outcomes

Less than 20% of children with SARS-CoV-2 infection who visit emergency rooms require hospital admission, compared to 52% in adults.[16,74] The median hospital stay for children with COVID-19 is less than 1 week,[11] with PICU admission rates below 10%[9,10,12] and a median PICU stay of less than 3 days.[11] Rates of mechanical ventilation or inotropic treatment are below 2%,[12] and extracorporeal membrane oxygenation is reported in very few children.[69] The mortality rates among children with SARS-CoV-2 infection are very low, at 0.02% for those infected and 1.1% for those hospitalized.[75]

DIAGNOSTICS

The primary diagnostic method for COVID-19 is the detection of viral RNA via reverse transcription PCR testing, typically performed on nasopharyngeal swabs. While PCR testing from saliva is less invasive, it has lower sensitivity compared to nasopharyngeal swabs.[76] Rapid SARS-CoV-2 antigen tests offer quicker results than PCR testing, but they have low sensitivity, especially in asymptomatic children.[77]

Laboratory parameters can show either leukocytosis or leukopenia, with leukopenia being more common; or lymphocytosis or lymphopenia, with lymphocytosis being more common; they can also show neutropenia, thrombocytopenia, and elevated aspartate aminotransferase, alanine aminotransferase, D-dimers, creatine kinase-MB, and C-reactive protein levels.[63,78]

Serologic tests are of limited relevance for diagnosing acute COVID-19 but are useful in diagnosing MIS-C and monitoring seroconversion and attack rates at the population level.[79] Samples can be collected from serum or saliva, or as dried blood spots.[47,80]

Radiologic imaging, including chest X-rays or computed tomographic scans, can support diagnosis. Compared to adults, children show milder and more localized findings, such as ground-glass opacities, consolidations, and peribranchial thickening, which are mostly observed unilaterally.[81]

TREATMENT AND MANAGEMENT

Supportive care is central to treating COVID-19 in children, including symptomatic relief, oxygen support, rehydration, and monitoring for complications. For children at high risk for severe disease, antiviral and anti-inflammatory medications can be considered (Fig 2).

Antivirals

Remdesivir. The viral RNA polymerase inhibitor remdesivir disrupts viral RNA production, stopping SARS-CoV-2 from multiplying. In hospitalized adults, remdesivir reduces recovery time and mortality compared to placebo.[82] In a phase 2/3 open-label trial involving 53 children, remdesivir raised no new safety concerns and resulted in recovery for 62% of the children by day 10.[83] Two retrospective case–control studies including 68 children who were treated with remdesivir and 52 controls found no significant differences in duration of hospital stay, PICU stay, and need for oxygen treatment and defervescence on day 4.[84,85] However, both studies are limited by small sample sizes and lack of randomization. Remdesivir needs to be administered intravenously.

Nirmatrelvir/ritonavir. Nirmatrelvir inhibits the SARS-CoV-2 main protease, while ritonavir acts as a protease inhibitor for human immunodeficiency virus type 1 and also inhibits cytochrome P450 3A.[86] The combination has recently been shown to reduce hospitalization among outpatient children aged 12 to 17 years in a target trial emulation including 49,378 children.[87]

Monoclonal antibodies

Treatment with monoclonal antibodies has reduced hospitalization and mortality from COVID-19 in adults.[88] Two retrospective case series studies, including a total of 126 children with preexisting conditions, showed that monoclonal antibody treatment (sotrovimab, casirivimab/imdevimab, bamlanivimab/etesevimab) was well tolerated.[89,90] However, no clinical trials have validated the efficacy of such treatment in children.

Glucocorticoids

Dexamethasone. The glucocorticoid dexamethasone has shown efficacy in reducing mortality and rates of mechanical ventilation in adults with severe COVID-19.[91] It is inexpensive and widely available, and its short course of treatment is safe and well tolerated in children. Although high-quality clinical trials on glucocorticoid efficacy in children are lacking, low-dose, short-course dexamethasone may still offer benefits for children with severe COVID-19.[92]

LONG-TERM EFFECTS OF COVID-19 IN CHILDREN

MIS-C

MIS-C, also known as pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (also referred to as PIMS-TS), may develop in children and adolescents 4 to 6 weeks after a SARS-CoV-2 infection. The prevalence of MIS-C was 13 cases per 10,000 SARS-CoV-2 infections before the emergence of the Delta variant, and decreased, especially with the Omicron variant, to 0.8 cases per 10,000 infections.[21,93] The exact pathophysiology of MIS-C is not fully understood, but it is thought to involve a dysregulated immune response.[94]

Clinical symptoms include persistent fever, abdominal pain, vomiting, diarrhea, rash, conjunctivitis, mucocutaneous inflammation, and cardiovascular manifestations such as left ventricular systolic dysfunction, coronary artery abnormality, pericardial effusion, mitral valve regurgitation, and shock.[20,21,95,96] Almost two thirds of MIS-C patients are admitted to the PICU, 17% require mechanical ventilation, and 2% need extracorporeal membrane oxygenation.[20]

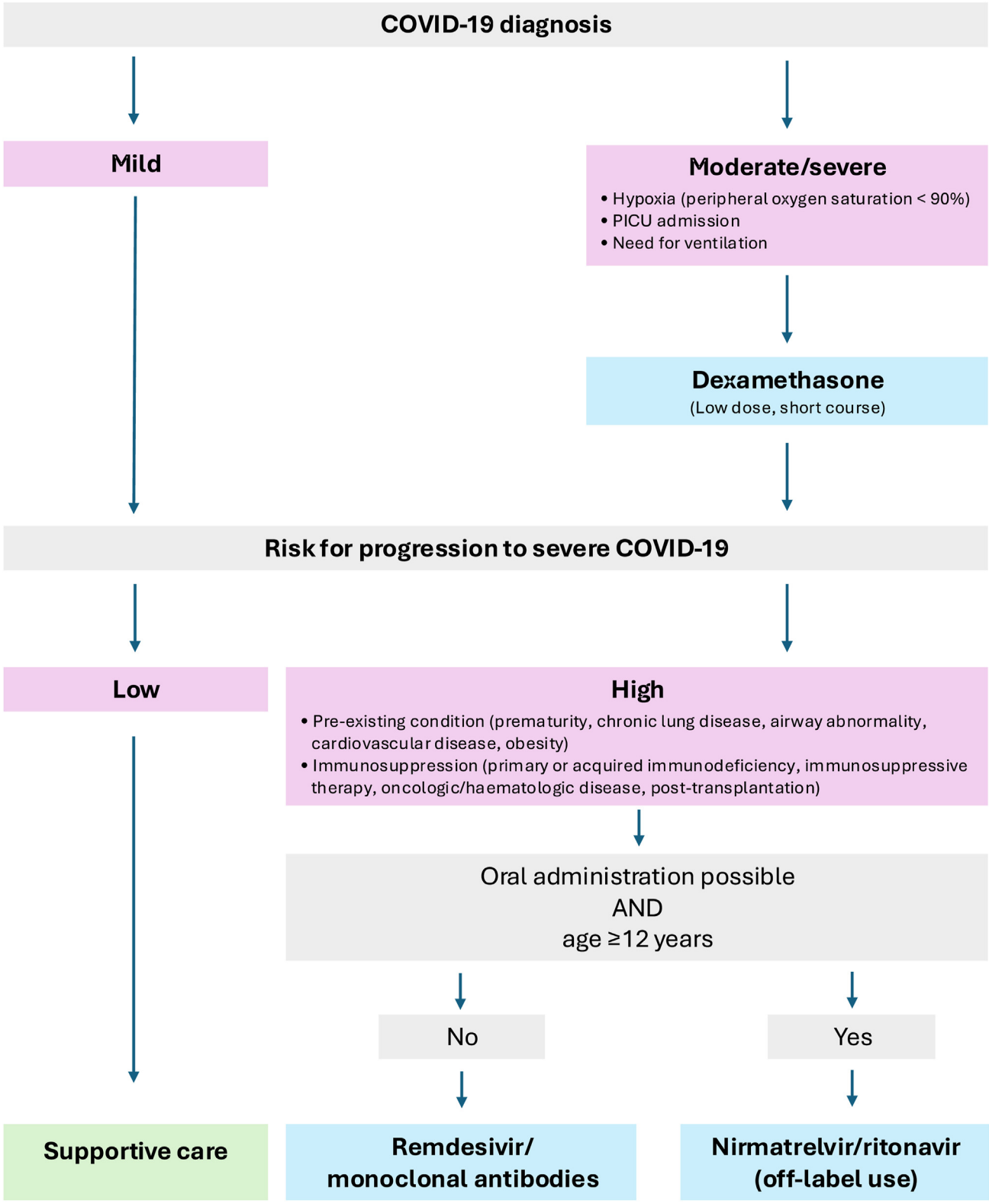


FIG 2. Treatment options for COVID-19 in children.

Diagnosis involves a history of SARS-CoV-2 infection or exposure, fever lasting more than 3 days, laboratory signs of inflammation, multiorgan dysfunction (eg, gastrointestinal, cardiovascular, dermatologic, or neurologic symptoms), and exclusion of other diagnoses.[97-99] While there is an overlap with Kawasaki disease, children with MIS-C are less likely to

present with conjunctivitis, cervical adenopathy, and rash, but more likely to present with gastrointestinal symptoms, mitral valve regurgitation, and pericardial effusion.[20]

MIS-C shares similarities with other hyperinflammatory conditions, such as toxic shock syndrome and Kawasaki disease, but differs in several key aspects. Kawasaki disease predominantly affects younger children and has a higher incidence rate in Asian countries.[100] Clinically, it presents with more oral mucous membrane changes and conjunctival injection, with a lower incidence of shock, cardiac involvement, and gastrointestinal and neurologic symptoms than MIS-C. In contrast, MIS-C is characterized by lower platelet and absolute lymphocyte counts, elevated C-reactive protein, N-terminal pro–B-type natriuretic peptide, troponin, and ferritin levels, along with a higher rate of PICU admissions.[101,102] Toxic shock syndrome typically presents with fewer gastrointestinal symptoms and less cardiac involvement than MIS-C, and laboratory findings include higher fibrinogen, ferritin, and *N*-terminal pro-hormone B-type natriuretic peptide levels in MIS-C. Notably, children with toxic shock syndrome tend to have shorter hospital stays compared to those with MIS-C.[102]

Treatment for MIS-C generally involves supportive care, intravenous immunoglobulins (IVIGs), and/or corticosteroids. Observational studies have suggested that combining IVIGs with corticosteroids may offer advantages over IVIGs alone, including a lower risk of cardiovascular dysfunction[103] and ongoing fever,[104] the need for second-line therapy or hemodynamic support,[104] and shorter PICU stays.[104,105] However, another observational study comparing IVIG alone, corticosteroids alone, the combination of IVIG and corticosteroids, and no immunomodulation found no significant differences in the need for vasoactive or inotropic support from day 2 onward, need for mechanical ventilation, or mortality during hospitalization.[106] Last, a more recent open-label multicenter randomized controlled trial reported no difference in hospital stay duration between children with MIS-C treated with methylprednisolone versus IVIG.[107] The authors suggest intravenous methylprednisolone as an acceptable first-line treatment in children with MIS-C.

While the use of IVIGs and corticosteroids is well established in managing MIS-C, uncertainties persist regarding the optimal treatment regimens. Clinical practice varies, with some clinicians supporting the combination of IVIGs and corticosteroids to reduce cardiovascular complications and others questioning the necessity of such combinations as a result of the conflicting evidence from observational studies.

Despite the severity of cases, mortality remains low, and recovery is generally good.[95,108]

Post–COVID-19 condition, aka long COVID

The World Health Organization defines post–COVID-19 condition in children as symptoms persisting for at least 2 months and beginning within 3 months of a confirmed or probable SARS-CoV-2 infection. Symptoms may be new or may persist from the acute phase and can fluctuate over time, affecting children's daily activities and developmental milestones.[109] However, definitions and names for this post–COVID-19 condition vary, particularly concerning the duration of symptoms,[110,111] leading to a highly variable prevalence estimates ranging from 2% to 70%.[22,112,113] More recent studies indicate a lower risk of post–COVID-19 after Omicron infection compared to earlier variants,[114,115] with a prevalence of 24% observed 3 months after infection.[114]

The pathophysiology of post–COVID-19 condition is not yet fully understood but may involve immune dysregulation, microbiota dysbiosis, autoimmunity, blood clotting, endothelial abnormalities, dysfunctional neurologic signaling, virus persistence, and reactivation of other viruses.[116] Common symptoms include fatigue, headache, arthralgia/myalgia, chest tightness or pain, and dyspnea.[22] To date, no biomarkers for persistent symptoms have been identified. Therefore, initial testing in children with persistent symptoms should focus on excluding alternative conditions. Recommended evaluations include routine blood tests, electrocardiogram, lung ultrasound, and screening for known treatable diseases that may present similarly, such as hypothyroidism, autoimmune disorders, and celiac disease.[23] Treatment in children varies as a result of the limited evidence and a lack of standardized protocols, but it generally involves managing symptoms and providing physical therapy and psychological support.[117] In adults, treatment focuses on managing specific symptoms. For example, postexertional malaise is addressed through pacing, balancing activity with rest to prevent fatigue flare-ups.[116] Postural orthostatic tachycardia syndrome can be treated with β-blockers, increased salt and fluid intake, or compression stockings.[116] Immune dysfunction may be treated with IVIG, cognitive dysfunction with coenzyme Q10 or D-ribose, and abnormal clotting with anticoagulants.[116] Gastrointestinal symptoms can be alleviated with probiotics.[116] Many of these treatments are based on research from studies on myalgic encephalomyelitis/chronic fatigue syndrome.[116]

PREVENTION STRATEGIES

Vaccination

COVID-19 vaccines received emergency authorization in late 2020.[118-120] Although they were initially controversial because of the mild disease in children and concerns about long-term risks,[121] many countries began recommending vaccination for children older than 5 years beginning in summer 2021.[122-125] For children aged 5 to 11 years, a meta-analysis of 17 studies found moderate vaccine effectiveness against Omicron infections (42%) and symptomatic COVID-19 (36%), but high effectiveness against COVID-19–related hospitalizations (71%), shortly after vaccination. For children younger than 5 years, the effectiveness against symptomatic COVID-19 is high (73%) shortly after vaccination.[126] Limited studies on vaccination efficacy against MIS-C indicate rates of up to 78% in children aged 5 to 11 years and 90% in those aged 12 to 18 years, with protective effects persisting beyond 120 days after vaccination.[127,128] Effectiveness against post–COVID-19 conditions in children aged 5 to 17 years is moderate (42%) within 12 months of vaccination.[129] For all age groups and outcomes, vaccination's long-term effectiveness remains uncertain, as most studies assessed outcomes shortly after vaccination.[130] Safety data show no increased risk of serious adverse events, with approximately 0.23 to 1.2 events per 100,000 administered vaccines.[130] The risk of myocarditis is low.[130] Notably, high COVID-19 vaccination coverage is associated with lower prevalence of symptomatic asthma in children, possibly as a result of reduced SARS-CoV-2 infections and cross-protection against other human coronaviruses.[131]

Many countries do not incorporate COVID-19 vaccination in standard immunization schedules for children. However, primary

TABLE I. Knowledge gaps

Topic	Open questions	Relevance
Epidemiology	How do specific risk factors, such as ethnicity, obesity, and socioeconomic status, contribute to the higher susceptibility of certain groups of children to SARS-CoV-2 infection?	Moderate
Immunology	What is the duration and quality of immunity after reinfection?	High
	What are the long-term health implications of multiple reinfections?	Moderate
Outcomes	Which factors contribute to the higher case-fatality rates and lower PICU admission rates in low- and middle-income countries compared to high-income countries?	High
	How do coinfections affect outcomes?	Moderate
	How does obesity increase the risk of severe COVID-19 or PICU admission?	Moderate
Treatment/Management	What is the efficacy of remdesivir in children with COVID-19?	Moderate
	What is the efficacy of monoclonal antibody therapy in children with COVID-19?	Moderate
	What are the potential benefits and risks of combining different treatments, such as antivirals, monoclonal antibodies, and/or glucocorticoids, in children with COVID-19?	Moderate
	How can treatment protocols be optimized for different pediatric age groups and risk profiles?	High
	How does prior vaccination status affect the effectiveness of these treatments in children?	Low
MIS-C	How can the diagnostic criteria for MIS-C be standardized internationally to ensure consistency in identification and treatment?	Moderate
	Why has MIS-C almost disappeared?	Low
Post–COVID-19 condition	How can the diagnostic criteria for post–COVID-19 condition be standardized internationally to ensure consistency in identification and treatment?	Moderate
	What are the underlying pathophysiologic mechanisms of post–COVID-19 condition in children, and how do factors like immune dysregulation, microbiota dysbiosis, and virus persistence contribute to its development?	Moderate
	How do preexisting conditions like attention-deficit/hyperactivity disorder, schizophrenia, chronic urticaria, and allergic rhinitis influence the development and severity of post–COVID-19 condition in children?	Moderate
	What are the most promising therapeutic approaches for post–COVID-19 condition in children, and how can treatment protocols be standardized to improve outcomes?	High
	What are the long-term health outcomes for children with post–COVID-19 condition?	High
Public health	Is fecal–oral transmission of SARS-CoV-2 in children possible?	Low
	Which factors contribute to the heterogeneity of transmission rates in different settings?	Low
	What is the long-term effectiveness of COVID-19 vaccines in children (beyond 6 months)?	High
	What are the optimal vaccination strategies for children of different age groups?	Moderate
	How does high vaccination coverage in the general population affect the incidence of asthma in children?	Moderate

immunization is recommended for unvaccinated high-risk children and annual boosters for those already vaccinated.[132,133] In Australia and France, vaccination is recommended for high-risk children aged 6 months and older.[133,134] In Germany and Japan, it is recommended for high-risk children aged 5 years and older,[132,135] while Switzerland only recommends it for high-risk individuals aged 16 and older.[136] The United States is an exception, recommending vaccination for children older than 6 months.[122]

Children aged 5 to 12 years show higher antibody responses compared to adults, despite receiving lower vaccine doses, while responses in children aged 6 months to 5 years are similar to those in adults.[137,138] The strongest immune responses are observed with hybrid immunity (after infection and vaccination).[138]

Surveillance

With the end of the pandemic and high population immunity, many countries have reduced or ceased surveillance efforts. However, several methods remain effective for monitoring SARS-CoV-2 spread among children. At the community level, wastewater monitoring is an effective tool.[139,140] It provides noninvasive early warning of rising infection rates.[141,142] In schools, day care centers, and pediatric hospitals, various testing strategies are used. Individual, symptom-based testing is commonly used, but because symptoms do not always correlate with SARS-CoV-2 positivity,[143] universal testing may be advisable during high infection periods. In settings with low infection rates and/or for low-resource settings, pooled testing, which combines samples from multiple individuals, offers an efficient screening method.[144,145]

SUMMARY

Initially, COVID-19 epidemiology in children indicated low infection rates, which rose with the emergence of the more transmissible Omicron variant. High-risk groups include adolescents, children from ethnic minorities, those in lower-income households, and those with obesity. Because of their immune response, children generally experience milder symptoms, such as fever and cough, although these can vary by variant and age. Diagnostic methods include reverse transcription PCR, rapid antigen tests, and serology. Supportive treatment is the mainstay, with antivirals and glucocorticoids reserved for severe cases. Serious conditions like MIS-C and other post–COVID-19 conditions are rare but require careful management. Vaccination has proven effective in reducing severe disease and protecting against post–COVID-19 conditions, although its long-term effectiveness remains uncertain. Continued surveillance, including wastewater monitoring and universal or pooled testing, is crucial for controlling community spread. Key questions persist regarding the duration and quality of immunity after reinfection or vaccination, the impact of coinfections, and optimal treatment protocols for different pediatric populations (Table I).

DISCLOSURE STATEMENT

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

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