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REVIEW

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Coronavirus global pandemic: An overview of current findings among pediatric patients

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Abstract

Background: The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) epidemic has been emerged as a cardinal public health problem. Children have their own specific clinical features; notably, they seem to be escaping the severe respiratory adverse effects. The international scientific community is rapidly carrying out studies, driving to the need to reassess knowledge of the disease and therapeutic strategies.

Aim: To assess the characteristics of COVID-19 infected children worldwide of all ages, from neonates to children and adolescents, and how they differ from their adult counterparts.

Search Strategy: An electronic search in PubMed was conducted, using combinations of the following keywords: coronavirus, SARS-CoV-2, COVID-19, children. The search included all types of articles written in English between January 1, 2019 until August 15, 2020.

Results: The search identified 266 relevant articles. Children were mainly within family clusters of cases and have relatively milder clinical presentation compared with adults; children were reported to have better outcomes with a significantly lower mortality rate. Cough and fever were the most common symptoms while pneumonia was the cardinal respiratory manifestation of infected children. Laboratory results and thoracic imaging give varying results.

Conclusions: Children were mainly family cluster cases and usually presented with a mild infection, although cases presented with the multisystem inflammatory syndrome are becoming more apparent. Studies determining why the manifestations of SARS-CoV-2 infection are so variable may help to gain a better understanding of the disease and accelerate the development of vaccines and therapies.

KEYWORDS
children, coronavirus, COVID-19, SARS-CoV-2

Abbreviations: ACE-2, angiotensin converting enzyme II; COVID-19, 2019 novel coronavirus disease; CRP, C-reactive protein; EAACI, European Academy of Allergy and Clinical Immunology; GFR, glomerular filtration rate; ILAE, International League Against Epilepsy; ISPAD, International Society of Pediatric and Adolescent Diabetes; MERS-CoV, Middle East respiratory distress syndrome coronavirus; PCT, Procalcitonin; PIMS-TS, pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 infection; RSV, respiratory syncytial virus; SARS-CoV, severe acute respiratory syndrome coronavirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

1 | BACKGROUND

In early December 2019, a cluster of cases of atypical pneumonia of unknown origin appeared in Wuhan city, in the Hubei province of China.[1,2] The majority of patients had been exposed to the Huanan seafood and animal wet market.[1,2] These cases were the first signs of what was to become a pandemic which is currently causing a huge number of deaths and stressing health care systems globally to an unprecedented degree. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the underlying pathogen, belongs to the β-coronavirus genus[3,4]; and its genome sequence has considerable similarity to divers β-coronaviruses discovered in bats.[3,5] Remarkably, the genome is more than 85% homologous to that of bat SARS like virus ZC45 (bat-SL-CoVZC45, MG772933.1).[6] Previously, four common community-acquired human coronaviruses, namely 229E, NL63, OC43, HKU1 had been described. Two other coronaviruses led to previous epidemics infecting more than 10,000 patients, namely severe acute respiratory syndrome coronavirus (SARS-CoV), and Middle east respiratory distress syndrome coronavirus (MERS-CoV).[7,8]

Symptomatic patients infected with SARS-CoV-2 are the main sources of transmission, but asymptomatic carriers can also transmit the disease. Respiratory droplets and person-to-person contact are thought to be the principal routes of transmission,[9] but fecal transmission may also play a role.[6,10–17] A risk of indirect transmission through fomites is also plausible. SARS-CoV-2 has a half-life of 3.5 hours on cardboard, 5.6 h on stainless steel, and 6.8 h on plastic.[18] No age is exempt, but data on children are scarce compared with adults. Nonetheless, the fact that children often only have trivial symptoms which may mimic common childhood illnesses such as mild bronchiolitis or diarrhea means they may become an important source of infection transmission.

The aim of this study was to review the characteristics of SARS-CoV-2 infected children and discuss the differences between adult and pediatric patients with confirmed infection.

2 | METHODS

2.1 | Search strategy

We performed an electronic search in PubMed, using combinations of the following keywords: coronavirus, SARS-CoV-2, COVID-19, children. Articles were screened by title, abstract, and full text to locate all manuscripts pertinent to children. The search included all types of articles written in English, between January 1, 2019 and August 15, 2020.

3 | RESULTS

A total of 1995 articles were found, and 266 relevant scientific articles and letters were eventually included. Exclusion criteria were the following: not written in English (n = 81, 46 Chinese, 4 German, 14 French, 12 Spanish, and Russian, Hebrew, Swedish, Italian, Hungarian n = 1 each), not original research (n = 775), including letters to the editor (n = 335), reviews (n = 293), protocols/guidelines (n = 62) perspectives/expert consensus (n = 85), and data not relevant (n = 873), for example, other coronaviruses and other respiratory viruses, extraneous issues during the outbreak, such as psychological impacts, domestic violence, molecular aspects and pathophysiology of SARS-CoV-2 infection, pediatric surgery during the outbreak. The strategy and results are displayed in Figure 1. Table S1 summarizes the current literature on the characteristics of children infected with SARS-CoV-2. Table 1 summarizes the clinical presentation and outcome of infection from the literature review. In Table 2, we enumerate current knowledge of the differences between adults and children infected with SARS-CoV-2. Infected children are principally in family clusters, or have a history of close contact with an infected patient.[19,20] Furthermore, children with COVID-19 had milder symptoms than adults.[19,20]

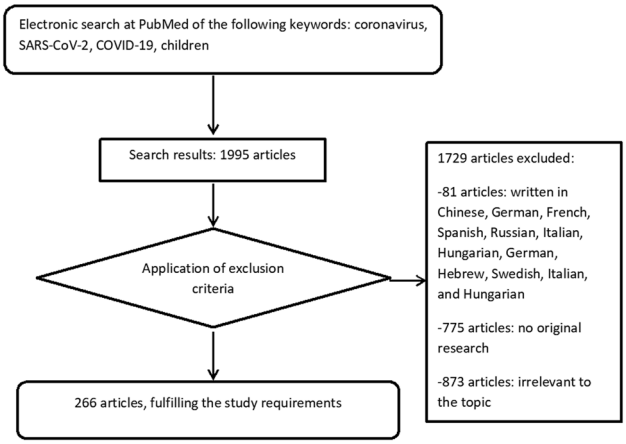

FIGURE 1 Flow chart of the search strategy. COVID-19, 2019 novel coronavirus disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2

Characteristics of pediatric SARS-CoV-2 infected populations included:

Cough: Initial symptoms were fever and cough; even among neonates.[30] Cough was experienced by the majority of patients,[10–12,14,15,19,21–93] it was mainly dry, but was sometimes followed by productive cough in moderately severe cases.[19] There may be upper airway symptoms, such as nasal congestion, rhinitis, and sore throat.[19] Wheezing may be a feature but is generally not prominent.

Fever: One of the commonest early symptoms is fever,[11,14,15,19–22,25–36,38–58,61–65,67,68,70–106] occasionally low grade. In Zhejiang province, fever clinics that exclusively accept for admission patients suspected of being positive for SARS-CoV-2 were set up.[27]

Pneumonia/CT findings: Many pediatric patients had COVID-19 pneumonia[10,11,16,19–24,26,28–31,34,38,40,42–44,47–54,56,57,60,61,64,66,68,70–72,74–76,78–87,90–92,94,95,99,100,103,155] and thoracic computerized tomography (CT) scan showed multifocal or nodular consolidation with ground glass

TABLE 1 Main clinical presentations of pediatric SARS-CoV-2 cases from the reviewed literature

Clinical presentation	Studies	Number of participants (*n*)	Range (%)
Cough	[10–12,14,15,19,21–93]	4845	32–75
Fever	[11,14,15,19,20,22,25–36,38–58,61–65,67,68,70–115]	5077	35–82
Gastrointestinal symptoms	[11,14,15,19,20,22,26,28,31,40,41,52,53,57,59,62,65,67,70–73,77,81,83,84,86–93,100,104,106–108,114,116]	4227	Vomiting: 0–23 Diarrhea: 5–37.5
Disease severity	[19,38,39,55,57,81,83,103,117]	2527	Asymptomatic: 4.4–54.5 Mild: 18–58% Moderate: 19–56 Severe: 0–3.8 Critically ill: 0–1.9

Abbreviation: SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

opacities.[11,15,16,19,22,23,26–30,33,34,39,42–44,47–50,52–54,60,61,64,66,72,74,78–81,83–86,91,95,100,103,107,164,165] More adult patients had all five lobes affected[33,166]; the manifestations of the COVID-19 pneumonia are diverse and our understanding of the spectrum of disease is changing rapidly. Radiologists must therefore have a high index of suspicion. The role of follow up CT scans in children is currently unclear. Chest CT is a particularly sensitive diagnostic instrument to detect pneumonia; the sensitivity relevant to COVID-19 is estimated to be 97.5%.[149]

Gastrointestinal symptoms: It is currently reported that SARS-CoV-2, despite being predominantly a respiratory virus, causes gastrointestinal symptoms in approximately 10% of infected children,[134,167] including abdominal pain, diarrhea, and vomiting.[11,14,15,19,20,22,26,28,31,40,41,52,53,57,59,62,65,67,70–73,77,81,83,84,86–93,100,104,106–108,114,116]

Laboratory results: Complete blood counts may be normal,[11,14–16,19,22,26,29,32,39,40,44,48–50,54,61,79,93,102,165,168] or show either decreased[14,16,19,25,26,29,31,39,40,44,49,55,61,70,93,100,108] or elevated white blood cell counts.[11,14,20,22,26,44,47,50,54,60,61,93,99] Lymphocyte counts may be increased,[15,19,24,26,29,44,60,78,79,82,84,93,96,103,169] or decreased.[14,19,22,23,25–28,31,34,39,44,49,55,70,79,82,84,88,99,100,103,113,116] Increased C-reactive protein (CRP),[15,19,22,25,26,28,29,31,40,41,44,47,49,50,56,73,74,77,83,84,88,93,101,103,104] procalcitonin (PCT)[15,22,26,31,44,49,50,56,73,77,84,88,93,99] and lactate dehydrogenase[14,15,22,25,47,81,83,84,93] have been reported. CRP is estimated to rise in 10%–20% of cases, in one study, the maximum value was 35 mg/L.[10] One group reported that leukocytopenia and CRP levels above 10 mg/L, were pointers to underlying pneumonia.[34] Serum ferritin was markedly higher in severe adult cases compared with moderately affected patients.[170] High serum levels of liver enzymes, muscle enzymes and myoglobin, and raised D-dimers are found in severely affected patients.[157]

In addition, in critically ill cases; a cytokine storm is a feature, characterized by increased serum proinflammatory and anti-inflammatory cytokines.[14,22,56,73,77,84,88,93,156,171,172] In a study of 157 children, moderate cases had higher interleukin 10 levels compared with mild cases.[81] Another original article reporting eight severe or critically ill children, ranged from 2 months to 15 years, reported elevated IL-6 (2/8), IL-10 (5/8), and IFN-γ (2/8).[22] IL-6 and IL-10 levels were significantly elevated in two critically ill children, of whom one was suffering from acute lymphocytic leukemia. These patients had a prolonged course of the disease duration (more than 20 days). A paper written in Chinese described a case of a severely ill infant with increased IL-6 levels.[171] Abnormal blood examinations may prompt pediatricians to screen for SARS-CoV-2.[26]

Co-infections: Children not only vulnerable to SARS-CoV-2 infection, but can also be coinfected with numerous respiratory viral and bacterial pathogens. In a single-center study of 50 children with COVID-19 from Wuhan, there was documented co-infection in 14% of children, $n = 6$ (12%) *Mycoplasma* infection and one (2%) with respiratory syncytial virus (RSV).[103] In a multicenter Italian study of 168 children with laboratory-confirmed SARS-CoV-2, a viral co-infection was demonstrated in 5.9% ($n = 3$ with RSV, $n = 3$ rhinovirus, $n = 2$ Epstein–Barr virus, $n = 1$ influenza A virus, $n = 1$ non-SARS coronavirus, and a bacterial co-infection with *Streptococcus*

TABLE 2 Summary of discrepancy aspects between adults and children COVID-19 patients

Feature	Adults	Children	Comment
Infection rate[118–122]	– The age group of 30–69 years old consists the 77.8% of the total case load	– From a total of 72,314 cases by the Chinese Center for Disease Control and Prevention less than 1% were younger than 10 years old	– Milder symptoms or even asymptomatic carriers among pediatric patients, may be a causation of misdiagnosis or missed diagnosis
Incubation period[6,119]	– 5.4 days reported in adults	– The average incubation period is approximately 6.5 days	– The average incubation period in children may be longer than in adults
Hospitalization status[123]	– 10%–33% were hospitalized, including those admitted to an intensive care unit	– 5.7%–20% were hospitalized, and 0.58%–2% were admitted to intensive care unit	– Children had lower hospitalization rates – Infants had the highest percentage of hospitalization among pediatric population
Fatal outcome[19,71,88–91,106,124–131]	– 4% global mortality rate – In a depictive Chinese study of 85 fatal cases, most were males, over 50 years old, with chronic diseases; the etiology of death of the majority of cases was multiple organ failure	– Deaths are extremely rare, 24 deaths were published; an infant 10-month-old with intussusception, a 14 years old boy with no detail description, 5 cases from a Paris study conducted in a pediatric intensive and high-dependency care unit, and a case with features of hyperinflammatory shock, 2 cases in a U.S. and Canadian Pediatric Intensive Care Units study both had comorbidities and presented multisystem organ failure, and 1 had gram-negative sepsis, a case of 17-year-old boy previously healthy, who died and autopsy demonstrated eosinophilic myocarditis, a 5-month-old infant, from Madrid, with dilated cardiomyopathy and Hurler's disease died, a 7-year-old girl with known cardiomyopathy and chronic lung disease, one died from cardiac arrest followed a prolonged period of severe hypoxia, 3 cases from a study in the Suburbs of Paris, 4 cases from a multicenter study involved 82 institutions across 25 European countries, a	– We are expecting for formal reports regard to children from various countries, especially from Europe – Pediatric life-threatening and fatal cases are seen mostly in patients with underlying diseases; in a study of 48 children, among them 83% had comorbidities, all were admitted to intensive care units and the case fatality rate was 4,2% – Alert in children presenting with features similar to typical or atypical Kawasaki disease, and toxic shock syndrome – There is a serious, emerging suspicion of myocardial disease complicating COVID-19 even among children leading in fatal events

(Continues)

TABLE 2 (Continued)

Feature	Adults	Children	Comment
		case with intussusception and sepsis and 2 cases from New York City one with end-stage osteosarcoma and the second with hemoglobinopathy who suffered from a hypoxic bradycardic arrest	
Common symptoms[121,132–135]	– Fever, dry cough, and fatigue; severe cases have been associated with dyspnea and bilateral ground-glass opacities on CT – Rare development of gastrointestinal symptoms	– Fever, dry cough, pneumonia – Findings have been similar to adults, but fewer children seem to have manifested severe pneumonia – A non-negligible proportion of children had gastrointestinal symptoms	– At present only 3 cases with anosmia/hyposmia and ageusia/dysgeusia has been reported in children – The higher rate of gastrointestinal symptoms in children may be related with elevated expression or different functions of ACE-2 in their gastrointestinal tract
Symptoms on admission[136]	– High fever on admission was linked with ARDS and death	– No symptoms on admission prognosticate outcome	– Fever in children with SARS-CoV-2 tends to ease within three days and is not a predictive marker of the final outcome
Disease severity[34,126,137–146]	– Particular findings are associated with severe illness, such as high ferritin levels and bilateral lesions on chest CT – Most of those who died had co-existing health conditions	– Most pediatric patients had mild or asymptomatic disease, and had faster recovery, and better prognosis compared with adults – A minority of pediatric patients required intensive care support and invasive mechanical ventilation; were suffering from co-existing conditions	– The majority of children will have much milder illness than is developed in adults and, as well, the asymptomatic infections are not unusual – Children have powerful innate immune response and rarely have risk factors, like underlying conditions and obesity
Laboratory findings[85–87,121,138]	– Increased liver enzymes, anemia, abnormal coagulation function, hypoalbuminemia, hypouricemia, increased inflammatory markers, and sometimes hyperglycemia	– Increased inflammatory markers were less common in children and lymphocytopenia seemed in a lesser degree – White blood cells were oftentimes raised contrary to adults – Raised creatine kinase MB isoenzyme (CK-MB) appears more common in children	– Adults have exhibited very high rates of lymphocytopenia – Further studies on the severity of COVID-19 must use lymphocytes and their interaction with the virus as a focal point – CK-MB heightened levels in children, especially in infants, suggests that heart injury would be more probable to take place
Imaging pattern[2,11,22–24,26,28–30,33,94,95,122,138,146–154]	– The pattern of multifocal peripheral patchy ground glass opacities or mixed consolidation is very suspicious for the disease; and when	– Compared with adults, lesions in children are atypical, with more localized ground glass opacities and interlobular	– Whereas most of the infected children appear with a mild clinical course, plain chest radiography frequently miss out the lesions or the detailed

TABLE 2 (Continued)

Feature	Adults	Children	Comment
	improved will be absorbed leaving fibrotic stripes – Initial imaging may be normal, abnormalities are likely to be observed on CT following 6 days after symptom onset	septal thickening is scarce – The most common finding is unilateral or bilateral sub-pleural bilateral ground glass opacity – Also, asymptomatic children have been reported to demonstrate abnormal CT findings	features, indicating that timely thoracic CT imaging is needful – Lung changes in infected adults would gradually be absorbed in 2 weeks; on the contrary, most lesions in infected children would probably fully resolve in a week
Treatment options[9,134,136,155–163]	– Many drug categories have been recommended in adults' articles, such as bronchodilators, steroids, antibiotics, antivirals, and diuretics. Usage of teicoplanin, monoclonal and polyclonal antibodies is under examination	– Management is predominantly symptomatic supportive treatment as no specific therapy is currently available – In severe cases, intravenous immunoglobulin can be administered	– In a retrospective study of 201 adult patients treatment with methylprednisolone was shown to reduce case-fatality risk – None of the studied antiviral medicines is recommended for treatment of children with COVID-19 – Children with immunocompromised diseases should be isolated

Abbreviations: ACE-2, angiotensin converting enzyme II; ARDS, acute respiratory distress syndrome; CK-MB, creatine kinase MB isoenzyme; COVID-19, 2019 novel coronavirus disease; CT, computed tomography; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

pneumoniae was also reported.[41] In another study from Wuhan, 74 children with COVID-19 were included and 19 of the 34 were also coinfected with other common respiratory pathogens, comprising *mycoplasma* pneumoniae ($n = 11$), *mycoplasma* pneumoniae and RSV ($n = 2$), *mycoplasma* pneumoniae and Epstein–Barr virus ($n = 2$), cytomegalovirus ($n = 2$), cytomegalovirus and Ebstein–Barr virus ($n = 1$), and *mycoplasma* pneumoniae and influenza A ($n = 1$).[44] In another Chinese study 37.3% of children were coinfected with *mycoplasma* pneumoniae, however, the infection was diagnosed using an antibody test.[53] In a study of 36 infants with SARS-CoV-2 infection 62.86% had at least one other pathogen detected.[84] In a French study of 192 children, among them 157 confirmed and 35 suspected SARS-CoV-2 cases, co-infection was documented in 8.3%, including 10 children with febrile urinary tract infection and 1 child with parvovirus B-19, 5 children had bacterial co-infection, *Bordetella pertussis* ($n = 1$), methicillin-susceptible *Staphylococcus aureus* ($n = 1$), methicillin-resistant *Staphylococcus aureus* ($n = 1$), *Proteus mirabilis* ($n = 1$), and *Fusobacterium necrophorum* ($n = 1$).[89] In a multinational European study of 582 confirmed SARS-CoV-2 children, additional viruses were detected in 5%, comprising enterovirus or rhinovirus ($n = 18$), influenza virus ($n = 5$), parainfluenza virus ($n = 3$), adenovirus ($n = 3$), RSV ($n = 2$), bocavirus (n = 2), human metapneumovirus ($n = 1$), and other coronaviruses (NL63, HKU1, and OC43, $n = 1$ each).[90]

Perinatal/neonatal transmission: A neonate could become positive for SARS-CoV-2 as a result of close contact with the infected mother postnatally or antenatally via vertical transmission. The evidence on intrauterine transmission and early positive neonatal testing is scarce. This is an important issue in perinatology, as SARS-CoV-2 may have adverse outcomes for the fetus and the newborn.[173,174] The risk of vertical transmission remains unknown as currently published reports are inconsistent.[30,37,59,68,94,99,102–106,173,175–187] There is potential for nosocomial transmission of SARS-CoV-2 because many neonatal infections are asymptomatic, or of insidious onset or present with mild and nonspecific clinical features. There is insufficient data to determine if cesarean section could prevent transmission from a pregnant SARS-CoV-2 positive patient compared with vaginal delivery.[162]

Comorbidities: One study demonstrated a higher risk of hospitalization in children with a history of arrhythmia in a series of 20 children with COVID-19. Seven had an underlying condition; specifically one had sinus tachycardia, two had a history of atrial septal defect surgery, one had an atrial arrhythmia, one had first-degree atrioventricular block, one had an incomplete right bundle-branch block, and one had a previous history of epilepsy as a consequence of previous viral encephalitis.[26] The International League Against Epilepsy (ILAE) and Epilepsy Foundation recommend that children with Dravet syndrome, those taking steroids, everolimus, and other immunosuppressants should be regarded as a group at high risk for complications if they have been infected with SARS-CoV-2.[188] In another study two out of eight children with COVID-19 required invasive mechanical ventilation, of whom one was suffering from acute lymphocytic leukemia.[22] In a study of 171 children with

COVID-19, only three children required intensive care support and invasive mechanical ventilation. All three children had an underlying medical condition; one had hydronephrosis, one had leukemia and was receiving maintenance chemotherapy, and one had intussusception.[34] This last baby died 4 weeks after admission from multiorgan failure.[34] In an Italian pediatric study from a hepatology and liver transplantation center, three of ten children became positive for SARS-CoV-2, did not develop pneumonia and survived.[189] In the CONFIDENCE study, 100 Italian children positive for SARS-CoV-2 were enrolled between March 3 and March 27 from 17 pediatric emergency departments, nine needed respiratory support of whom six had an underlying condition.[38] In a Spanish study, 16 children with chronic renal disease, including renal dysplasia, nephrotic syndrome, uropathy, IgA nephropathy, scarring nephropathy, vasculitis, and cortical necrosis, were positive for SARS-CoV-2 and none of the patients required oxygen therapy or Intensive Care Unit admission, indicating a similar clinical course as healthy peers.[116] In a French study of 27 children hospitalized in a pediatric intensive and high-dependency care unit in Paris, 5 children had a fatal outcome, among them 3 previously well children, one was on chemotherapy for refractory relapse of acute lymphoblastic leukemia, and one had a history of epilepsy and major neonatal encephalopathy.[128] In the U.S. and Canadian study of 48 children admitted to intensive care units, more than 80% had underlying conditions, the most frequent was characterized as medically complex and defined as a long-term dependence on technological support related to either developmental delay or genetic disease.[125] The International Society of Pediatric and Adolescent Diabetes (ISPAD) stresses the importance of adherence to standard diabetes care,[190] although no cases of COVID-19 in children or young adults with diabetes have been published. The European Academy of Allergy and Clinical Immunology (EAACI) published a statement dealing with the issue of managing childhood allergies and immunodeficiencies in the ongoing pandemic.[191] There were six recommendations; ensure optimal control of allergy symptoms and asthma; avoid over-diagnosis COVID-19 as seasonal allergies may present with flu-like symptoms; continue treating atopic children according to guidelines; be flexible in revising any pre-existing recommendations according to new evidence; and have a high index of suspicion in patients with immunodeficiency.[191] In a review of how SARS-CoV-2 affects immunocompromised adults and children, cancer was most frequently linked with a more severe clinical course, but overall patients prescribed immunosuppression appeared to have a favorable outcome, as compared with a general population and a better outcome compared with those with other comorbidities. This may be by preventing an over-exuberant inflammatory response (https://www.rcpch.ac.uk/resources/guidance-paediatric-multisystem-inflammatory-syndrome-temporally-associated-covid-19).[192,193] Of 18 children with renal disease prescribed immunosuppressive medication in 16 pediatric nephrology centers in 11 countries who developed SARS-CoV2 infection, none needed admission in intensive care and generally all were only mildly affected.[194] A study of all children with malignancy, included hematological malignancies and solid tumors, who were infected with SARS-CoV-2 showed similar disease severity as the general pediatric population, with a mild-moderate clinical course. Only 2 out of 15 received oxygen therapy, and all had favorable outcomes.[195] A web-based study of 404 children with autoinflammatory diseases, among whom 375 were on colchicine and 48 were receiving biologic drugs found only 7 confirmed and mild cases of COVID-19, all having a favorable outcome. No infected child was on biologic treatment.[196] In a retrospective study of 182 children, 43 were suffering from allergies, including allergic rhinitis (n = 28), drug allergy (n = 3), atopic dermatitis (n = 3), allergic rhinitis and drug allergy (n = 5), allergic rhinitis and atopic dermatitis (n = 1), allergic rhinitis and food allergy (n = 1), allergic rhinitis and food allergy and drug allergy (n = 1), asthma and urticaria and drug allergy (n = 1); there were no differences in COVID-19 clinical features and disease course between atopic and non-atopic children.[91] Data in cystic fibrosis are scarce and few patients, mainly adults, had confirmed COVID-19, without obvious impact on cystic fibrosis disease severity.[197–199] Interestingly, despite the frequency of these conditions, there are very few reports of SARS-CoV-2 in children with asthma, bronchopulmonary dysplasia, or chronic suppurative lung disease such as cystic fibrosis.

Risk factors for disease severity: Very little is known about this important subject. Radiologic involvement of more than three lung segments carried a higher risk of development of a severe form of the disease.[47] In addition, the elevation of IL-6, total bilirubin and D-dimer are associated with worse disease.[47] In a review of the Chinese experience, risk factors for severity were increased respiratory rate, clouding of consciousness, elevated levels of lactic acid, bilateral or multilobular lesions on imaging, pleural effusion, or rapid progression.[200] Other risk groups were patients below 3 months of age or those with co-existing conditions, such as congenital heart disease, bronchopulmonary dysplasia, severe malnutrition, and immunodeficiency.[200] The majority of infected children were within family clusters; so infection risk will probably be higher for those living in low-income families, in crowded housing, and with blue-collar parents.[201] Sadly, physical distancing is harder to implement in those with adverse social determinants and might further impact the risk of COVID-19.[202] In a study of 48 children admitted to the intensive care unit 83% had underlying conditions including obesity (n = 7).[125] Three adolescents with Covid-19 and septic shock were also all obese.[203] Among 50 children, 9 children with severe disease had significantly higher CRP and PCT on admission, elevated peak IL-6, ferritin, and D-dimer levels and obesity was again significantly related to the need for mechanical ventilation in patients 2 years or older.[88] Obesity is a known significant risk factor for severe disease in adults.[204] The Centers for Disease Control and Prevention COVID-19 Response Team suggests a high index of suspicion and follow up for disease course, especially among infants and children with pre-existing comorbidities.[123] In a study from New York City of 67 hospitalized and critically ill children, admission to intensive care unit was significantly associated with higher CRP, PCT, pro-B type natriuretic peptide, and blood urea and with lower platelet counts; the only clinical symptom significantly related with intensive care admission was shortness of breath.[58] Notably, 23.1% of

patients required intensive care had a history of epilepsy ($n = 3$).[58] In a multicenter study involving 82 institutions across 25 European countries, using univariable analysis, significant factors for requiring intensive care were being younger than 1 month, male sex, pre-existing medical conditions, pyrexia, lower respiratory tract infection, imaging findings suggestive of pneumonia or acute respiratory distress syndrome, and viral co-infection.[90] Moreover, in a study from nine New York City teaching hospitals, 70 critically ill children admitted to the intensive care unit and 90% of patients who developed acute respiratory distress syndrome initially presented with dyspnea, but also had significantly lower platelet counts compared with those without acute respiratory distress syndrome.[131] In the morbidity and mortality weekly report during the period March 1 to July 25 hospitalization rates were higher among Hispanic and black children, eight times and five times, respectively, who also had a higher prevalence of underlying conditions, 45.7% and 29.8%, respectively, compared with their white peers, 14,9%.[205] Gastrointestinal symptoms were reported in 42% of hospitalized children.[205]

Epidemiology: The epidemiology data on pediatric SARS-CoV-2 is incomplete, but some themes are emerging. In particular, there are lower rates of infection in children compared with adults, similar to those reported with other coronaviruses, such as SARS and MERS.[206] Children with COVID-19 are mostly part of a family cluster or have a history of a close contact with a confirmed case.

4 | DISCUSSION

Most studies have shown children infected with COVID-19 have a mild clinical course, analogous with SARS, characterized by relatively nonspecific symptoms such as dry cough, sore throat, rhinorrhea, nasal congestion, fatigue, myalgia, and sneezing, although emerging data about less frequent symptoms are discussed below. This is a much milder disease than that seen in COVID-19 adults[19,21,24,127] and understanding the reasons for this may open up potential new avenues for treatment. Understanding the pathogenesis of the novel coronavirus SARS-CoV-2 will hopefully enable future vaccine development and targeted therapeutics.

SARS-CoV-2 can be transmitted by a patient or an asymptomatic carrier and is an extremely infectious disease. There are probably large numbers of asymptomatic or nonspecifically mildly unwell individuals in the community[25]; asymptomatic carriers can lead to human-to-human transmission and are a covert source of infection keeping the virus is circulating within local communities. Children of all ages are susceptible to SARS-CoV-2, however, symptoms mimic nonspecific childhood infections, and missing the diagnosis means they may transmit the infection. However, anecdotally, a child with COVID-19 did not transmit the virus despite interacting with peers in three schools while symptomatic.[35] Young children were prone to have silent infections with normal CT scans even at the time of hospitalization,[25,155] which suggests widespread testing of even relatively well children will be needed to contain outbreaks. However, preliminary findings from population-based and school studies suggest that children may be less commonly infected or transmit the disease to others, although the current evidence is not definitive.[207]

The issue of testing children for acute infection and antibodies postinfection is complex. Testing kits in at least some settings may be in short supply, the technical requirements are high, and there may be false positive and negative tests. Serological tests, detect the presence of antibodies against SARS-CoV-2. A positive test result is evidence of only a recent exposure and there may also be false positives and negatives. Given these complexities current community preventive strategies, such as physical distancing, use of personal protection measures such as wearing a mask, hand and surface hygiene must be encouraged. The evidence base for much of this in children is not definitive, but there would seem to be no negative consequences of adopting them.

Although most children have mainly respiratory symptoms, there are some who present with gastrointestinal symptoms. Surprisingly, studies reported SARS-CoV-2 detection in stools samples in mild patients and prolonged virus RNA shedding in stools at 10 days[11,67,72] and even longer.[10,12–16,42,44,55,56,67,72,108] These studies mandate careful infection control procedures for gastrointestinal as well as respiratory samples. The fecal-oral route may constitute more risk of transmission in infected children compared with adults.[207] Whether it is valuable to test stool samples for viral clearance as a routine merits further study, but feces should certainly be considered a potential source of infection and handled with appropriate precautions.

The role of investigations other than swabs to confirm the diagnosis and limit the spread of infection are controversial, especially given the paucity of data in children. Most are mildly affected and require no other testing. The value of blood tests in the management of more severe cases is uncertain, given the results are highly variable between cases, and it is not known if any can be used reliably prognostically or to predict complications such as secondary bacterial pneumonia. The role of imaging is unclear; as adults, mild cases do not need imaging.[208] Chest radiography may be normal or show only nonspecific changes.[30] Chest CT may show more characteristic abnormalities, such as ground-glass opacities and multi-focal consolidation.[25] However, the role of CT scanning in pediatric CoVID-19 requires further study.

Levels of many cytokines have been found to be increased in severe, critically ill and fatal cases.[14,22,156,166,171] Of note, there are emerging reports of a rare systemic inflammatory condition in children, resembling typical or atypical Kawasaki disease, presently named Pediatric Inflammatory Multisystem Syndrome temporally associated with SARS-CoV-2 infection (PIMS-TS), toxic shock syndromes, bacterial sepsis and macrophage activation syndromes (https://www.rcpch.ac.uk/resources/guidance-paediatric-multisystem-inflammatory-syndrome-temporally-associated-covid-19)[77,106,107,111,114,203,209–229] of whom some but not all test positive for COVID-19. The clinical characteristics of PIMS-TS include cardiac disease sometimes including coronary artery aneurysms, the need for intensive care and inotrope, and additional treatments. There is insufficient data on more specific treatments such as intravenous immunoglobulin.[209–211] The identification of PIMS-TS

during the with SARS-CoV-2 pandemic is poorly understood and underscores the need for vigilance to detect new manifestations of the disease.

There are no trials of antiviral therapies in children. Management is supportive, including supplemental oxygen, nutritional support, and maintenance fluid and electrolyte balance.[137,157] Systemic steroids are not indicated.

There is a compelling need to understand why the natural history of SARS-CoV-2 is milder in children. This may be related to alterations in the pediatric immune system leading to a qualitatively distinct response to the virus.[137] Developmental differences in the location, quantity, and activation status of the viral receptors are regularly revealed as potent causes of the age-associated variations in incidence.[230,231] One hypothesis about the frequency of mild cases among children is linked to changes in the expression of angiotensin-converting enzyme II (ACE-2) receptor to which SARS-CoV-2 binds[137]; there is lower nasal epithelial ACE-2 expression in children compared with adults.[231]

Most patients described were adults who usually have pneumonia and abnormal CT chest imaging.[2,149,150] Elderly males with comorbidities do worse.[134,136] Those adults doing badly had a high prevalence of diabetes, obesity, hypertension, cardiovascular, and chronic airway disease.[9] Children suffering from other medical conditions, such as congenital heart, and chronic respiratory diseases may be vulnerable to COVID-19.[6] One pediatric study indicates an increased risk of hospitalization in children with a history of arrhythmia.[26] However it is noteworthy that children with pre-existing diseases do not seem to figure prominently in pediatric series.

A major limitation of the current study methodology is that for resource reasons we could not include any foreign language papers and unsurprisingly, many studies are published solely in Chinese, the pandemic having originated in China.

4.1 | Future work

We need more data on how COVID-19 affects children with underlying medical conditions. As with so many diseases, there is a need for randomized controlled trials of treatment in children. The development of a safe and effective vaccine is of paramount importance. We need to be alert to novel manifestations of the disease in children, and understand the pathophysiology and how best to treat the emerging multi-system inflammatory complications discussed above.

5 | CONCLUSION

SARS-CoV-2 infection affects all ages. In contrast to adults, children mostly have a mild form of the disease, as was the case in SARS, but nonetheless, they may transmit the disease. Identification of effective treatment strategies, and above all, a vaccine, is imperative. This literature review has highlighted the paucity of information about the interaction of the disease with underlying medical conditions in children and the lack of evidence with regard to investigation and treatment.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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