ORIGINAL ARTICLE

COVID-19 in Children: Where do we Stand?

Georgia B. Nikolopoulou,[a] and Helena C. Maltezou[b]

[a] *Department of Hepatitis, National Public Health Organization, Athens, Greece*
[b] *Directorate of Research, Studies and Documentation, National Public Health Organization, Athens, Greece*

From the beginning of the coronavirus disease 2019 (COVID-19) pandemic it became evident that children infected with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) remain mostly asymptomatic or mildly symptomatic. We reviewed the epidemiologic and clinical features of children with SARS-CoV-2 infection. The true prevalence of asymptomatic SARS-CoV-2 infection is most likely underestimated, as asymptomatic children are less frequently tested. Serologic surveys indicate that half of children tested positive for SARS-CoV-2 report no symptoms. Anosmia/ageusia is not frequent in children but it is the strongest predictor of a positive SARS-CoV-2 test. In general, children with COVID-19 are at lower risk of hospitalization and life-threatening complications. Nevertheless, cases of severe disease or a post-infectious multisystem hyperinflammatory syndrome named multisystem inflammatory syndrome in children (MIS-C) have been described. Rarely children with severe COVID-19 develop neurologic complications. In addition, studies indicate that school closures have a limited impact on SARS-CoV-2 transmission, much less than other social distancing measures. The past months new SARS-CoV-2 variants emerged with higher transmissibility and an increased impact on morbidity and deaths. The role of children in the transmission dynamics of these variants must be elucidated. Lastly, preliminary results from COVID-19 vaccine trials indicate very good efficacy and tolerability in children. Very recently the United States Centers for Disease Control and Prevention and other public health authorities recommend vaccination of children 12 years or older to protect them but mostly to contribute to the achievement of herd immunity. © 2021 Instituto Mexicano del Seguro Social (IMSS). Published by Elsevier Inc. All rights reserved.

Introduction

At the end of 2019, a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as the cause of a cluster of pneumonia cases in Wuhan, a city in the Hubei province of China. The virus spread quickly around the world causing a global pandemic of a disease named coronavirus disease 2019 (COVID-19) by World Health Organization (WHO) (1). In the early stages of the COVID-19 pandemic the proportion of confirmed cases among children was relatively small and it was thought that children were rarely affected by SARS-CoV-2 (2–4). Subsequent studies have consistently shown that children and adolescents are susceptible to SARS-CoV-2 infection, yet a large percentage of children are either asymptomatic or pre-symptomatic, therefore the true incidence of infection is underestimated due to the low rate of testing in children (5).

In general, children with COVID-19 present with milder symptoms and are at lower risk of hospitalization and life-threatening complications (6). Nevertheless, cases of severe disease or children developing a post-infectious multisystem hyperinflammatory syndrome named multisystem inflammatory syndrome in children (MIS-C) have been described (7,8). The risk of transmission from an asymptomatic individual with SARS-CoV-2 infection is less

Address reprint requests to: Helena C. Maltezou, Dr. Directorate of Research, Studies and Documentation, National Public Health Organization, 3-5 Agrafon Street, Marousi, 15123 Athens, Greece; Phone: 0030-210-5212175; E-mail: helen-maltezou@ath.forthnet.gr

than the risk from a symptomatic individual (9). Hence, early studies suggested that children, due to their milder symptoms, do not contribute much to the spread of SARS-CoV-2. However, more recent studies raise concerns that children could be capable of spreading the infection (10).

In this article we review the epidemiologic and clinical features of children infected with SARS-CoV-2. To understand the role of children in the spread of SARS-CoV-2, we investigate the ways through which children have been infected and the transmission chain of SARS-CoV-2. The role of schools in virus transmission and the epidemiological consequences of school closure are also reviewed.

Methods

The PubMed was searched for articles published through March 25, 2021, using combinations of the following words: COVID-19, SARS-CoV-2, children, pediatric, adolescents, infants, and school. We read the abstracts of a total of 101 articles and selected 78 articles based on their relevance to the topics discussed. In addition, information from 8 official public health websites was used. We also added 3 articles on children's vaccination against COVID-19. Overall, 89 articles were included in the review. Children were defined as persons ≤18 years old.

Rate of Children Infected by SARS-CoV-2

In surveillance studies from various countries, children typically accounted for up to 2% of laboratory-confirmed SARS-CoV-2-infected cases, at least in the early stages of the COVID-19 pandemic (2–4). In a report of 72,314 laboratory-confirmed or suspected (based on history of exposure), symptomatic or asymptomatic SARS-CoV-2-infected cases by the Chinese Center for Disease Control and Prevention, children <19 years of age accounted for 2% of the total number of cases; in this study there was no difference in the rate of infection among children of different ages (4). In England, between January 16 and May 3, 2020, children represented 1.1% of 129,704 SARS-CoV-2-infected cases (2). In Italy, by March 2020 children <18 years of age with SARS-CoV-2 infection composed only 1% of the total number of patients (3). However, in Ontario, from January 15, 2020–December 29, 2020, 5.1% of the total confirmed COVID-19 cases were reported in children; in particular, the rate of infection among children was dramatically lower (60.4 per 100,000 population) than adults (298.8 per 100,000 population) (11). In this latter study, rates of illness were highest among children 15–19 year of age (109.6 per 100,000 population) compared to younger pediatric age groups (11).

Since these initial stages of the COVID-19 pandemic, the number of infected children has increased significantly. This is possibly since the criteria for testing for SARS-CoV-2 have changed as exposure risks, COVID-19 associated symptoms, laboratory testing capacity and priority populations have evolved over the course of the pandemic. In the United States, children <18 years of age account for approximately 13.3% of laboratory-confirmed SARS-CoV-2 cases (12). Time trends in reported incidence for children and adolescents aged 0–17 years tracked consistently with trends observed among adults. WHO data suggests that children <18 years represent approximately 8.5% of reported cases, usually with mild disease (13).

In terms of age groups, among >1.2 million children <18 years of age with SARS-CoV-2 infection in the United States between March and December 2020, children were distributed as follows (14):

– Preschool (age 0 through 4 years)–7.4%
– Elementary school (age 5 through 10 years)–10.9%
– Middle school (age 11 through 13 years)–7.9%
– High school (age 14 through 17 years)–16.3%

Based on serology studies, the reported number of laboratory-confirmed cases of SARS-CoV-2 infection in children is likely underestimated given the high proportion of mild and asymptomatic cases in which testing may not be performed (15,16). Most but not all studies show slightly more boys than girls being affected in the COVID-19 pandemic (6,17,18); however no significant sex difference has been observed.

Clinical Manifestations

Most children who become infected with the SARS-CoV-2 virus have either no, or mild symptoms. Depending on the study design, studies report the rate of asymptomatic children ranging from 16–35% (17,19,20). It is important to note that this is likely an underestimation of the true prevalence of asymptomatic SARS-CoV-2 infection, as children without symptoms seek testing much less frequently than symptomatic children (10). Indeed, serological studies demonstrate that half of children tested positive for SARS-CoV-2 reported no symptoms (15,16). Children and adolescents with COVID-19 may develop a wide spectrum of clinical manifestations which makes the empiric diagnosis of COVID-19 in children challenging (21).

In the case series we reviewed, fever was the most common sign at presentation, followed by cough, rhinorrhea, and sore throat (17–19,22,23) (Supplementary Table 1). Other common symptoms were headache (16,17,22,24), diarrhea (3,17,20,24), vomiting (3,17,20), fatigue (20,22,24,25), myalgia (16,24,25), tachypnea (18,20), tachycardia (20), and rash (25).

Anosmia/ageusia is not frequent in children (24,26) but it is the strongest predictor of a positive SARS-CoV-2 test in both children and adults (19). Among symptomatic children, altered smell or taste, nausea or vomiting, and headache were more strongly associated with SARS-

CoV-2 than other symptoms (19). However, cough, nasal congestion, sore throat, and fever are non-specific symptoms, since they are frequently encountered in children with COVID-19 as well as with other infectious diseases (2,19) In terms of clinical syndromes, children present as acute respiratory infection, influenza-like illness, isolated fever, gastroenteritis or vomiting and asthma exacerbation (24,27).

The proportion of severe and critical cases is lower in children than in adults. Dong et al found that the proportion of severe and critical cases was 10.6, 7.3, 4.2, 4.1, and 3% for the age groups <1 years, 1–5 years, 6–10 years, 11–15 years, and >15 years, respectively (6). Many studies suggest that children with certain underlying medical conditions such as chronic respiratory illness including moderate-to-severe asthma, obesity, diabetes, sickle cell disease or cancer and infants (age <1 year) might be at increased risk for severe illness from SARS-CoV-2 infection (28). Other studies found that infants were not at increased risk of severe disease (23) and had a good outcome without specific treatments (29). Of the children who have developed severe illness from COVID-19, most have had underlying medical conditions (30,31).

Children with severe COVID-19 may develop neurologic manifestations (up to 22% among 1695 hospitalized children and adolescents) (32), and occasionally acute disseminated encephalomyelitis (33), acute transverse myelitis (8), respiratory failure (31), myocarditis (34), shock (31), ocular symptoms (35,36) acute renal failure (37), and multi-organ system failure (31). In the large series of 1695 hospitalized children and adolescents with COVID-19, neurologic involvement was significantly more frequent among patients with underlying neurologic disorders (32). Some children with COVID-19 have developed other serious problems like intussusception or diabetic ketoacidosis (38,39). Children infected with SARS-CoV-2 are also at risk for developing Multisystem Inflammatory Syndrome in Children (MIS-C) a rare but serious condition associated with COVID-19 that has been reported in children (40,41). Among 440 cases, main findings include gastrointestinal symptoms, dermatologic/mucocutaneous symptoms, cardiac dysfunction, shock, and elevated markers (C-reactive protein, inteleukin-6, and fibrinogen levels) (42). MIS-C may begin weeks after a child is infected with SARS-CoV-2. The child may have been infected from an asymptomatic contact and, in some cases, the child and their caregivers may not even know they have been infected (40). A study of 186 cases from the United States, found that a minority of children had been symptomatic prior to the onset of MIS-C, and the median interval from COVID-19 symptoms onset to MIS-C was 25 d (41).

The United States Centers for Disease Control and Prevention (CDC) issued a Health Advisory (43) that outlines the following case definition for MIS-C:

- An individual aged <21 years presenting with fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological); and
- no alternative plausible diagnoses; and
- positive for current or recent SARS-CoV-2 (COVID-19) infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms.

Most children with MIS-C with severe cardiac manifestations experienced clinical recovery within 30 d. The case fatality rate (CFR) in large cohorts was 0 (44), 1.9 (45), and 2% (46). Obesity is a risk factor for MIS-C, present in a quarter of the 570 patients in the CDC report (46). Beyond MIS-C, we found no published evidence of cases of post-COVID syndrome in children (47).

The rate of hospitalization among children varies depending on the criteria of hospital admission in different countries. In the United States the rate of hospitalization of children is low compared to that of adults (6), but it is increasing. The cumulative COVID-19–associated hospitalization rate among children aged <18 years was highest among children aged <2 years (32.7%); rates were substantially lower in children aged 2–4 years (8.7%) and 5–11 years (16.8%) but higher in ages 12–17 years (41.8%) (30). In Italy 57.7% of children with COVID-19 diagnosed by 28 centers in Italy (mostly hospitals) were hospitalized (18). In Greece 26.1% of the children diagnosed during the first epidemic wave were hospitalized; in this series being <5 years old predicted hospitalization (24).

In the cases series we reviewed few children required intensive care unit (ICU) admission. In particular, we found the following rates of ICU admission: 0 (25,48), 8 (17), 0.5 (24), 12 (18), 9.7 (27), and 18% (23). Risk factors for ICU admission include age <1 month, male sex, pre-existing medical condition, presence of lower respiratory tract infection, and signs and symptoms in presentation. Obesity and high mean peak inflammatory markers (ferritin, C-reactive protein, procalcitonin, D-dimer and IL-6) were significantly associated factors associated with mechanical ventilation (23). In the United States about 1 in 3 children hospitalized with COVID-19 were admitted to the ICU, similar to the rate among adults (30).

In terms of outcome, most children recover and there is no evidence of excess childhood mortality. In the studies we reviewed, CFR in children with COVID-19 was 0 (18,24,27,48), <0.3 (2), 0.69 (17), 0.58% and only one study found a CFR 2% (23) but in this latter study only symptomatic hospitalized children were included.

We should note however, that the full spectrum of consequences of the COVID-19 pandemic remains largely

unknown. A model-based study has shown that the 1918 pandemic influenza virus produced different age-related immune responses against influenza A/(H1N1) pdm09 virus of 2009, with highest titers in the birth cohort born in 1911–1926, followed by the youngest born in 1987–1992 (49). The role of the ongoing COVID-19 pandemic on immune responses of different future birth cohorts remains to be elucidated (49). Similarly, to long-term sequelae of the 1918 influenza pandemic, it is possible that the COVID-19 pandemic will also have long-term consequences on the cohort that was in utero during the pandemic, either because of maternal infection or because of the stress of the pandemic per se (50). Finally, previous influenza pandemics showed that socioeconomic factors may determine both disease detection rates and overall outcomes (51). As we understand more about the immune response to SARS-CoV-2 there is the hypothesis that the early-life adversity-induced pro-inflammatory phenotype may play a role in determining the severity of COVID-19, rendering people vulnerable to COVID-19 many years later (51). Further research is needed to understand the underlying mechanisms.

Why Children have Milder SARS-CoV-2 Infection?

There are multiple explanations as to why children are infected less frequently and severely than adults. This may be related to the fact that children have a lower prevalence of co-morbidities such us hypertension, diabetes and chronic lung disease that have been associated with severe disease (52,53). Another explanation is the fact that children often experience coronaviruses in winter and have higher levels of antibodies against coronaviruses than adults. Antibodies directed against seasonal coronaviruses in children and young people might confer some protection, whereas waning of partly cross-reactive seasonal coronavirus antibodies in older people might place them at higher risk for antibody-dependent enhancement (54).

Some studies have raised controversial speculations regarding angiotensin-converting enzyme-2 (ACE2) receptors that have been proven to bind to SARS-CoV-2 spike protein and promote entry of the virus into human cells (55). It is speculated that children were less sensitive to COVID-19 because the maturity and function (eg, binding ability) of ACE2 in children may be lower than in adults (56). Bunyavanich et al identified a lower ACE2 expression in the nasal epithelium and suggested that it could be related to lower acquisition of SARS-CoV-2 infection in children (57). However, in the lower respiratory tract, it appears that decreased ACE2 expression could signify a higher risk of developing severe acute respiratory distress syndrome and lung injury. ACE2 catalyzes angiotensin II conversion to angiotensin 1–7, which can suppress inflammation, counteracts vasoconstriction and fibrosis by binding to the MAS receptor (58, 59). In animal studies it has been found that ACE2 plays a protective role from severe lung injury (60). Chen et al suggested an inverse relationship between ACE-2 expression and COVID-19 severity (59). In particular, they found a significantly higher ACE2 expression level in Asian females and young people. ACE2 expression decreases with age and is lowest in people with diabetes (59). Further studies are needed to understand the distribution of ACE2 in cells in different tissues across human individuals.

Another explanation for the less severe symptoms in children is that children are mainly infected by the adult members of their families. So children are infected with a second or a third generation of the virus, which may have decreased pathogenicity (61). Furthermore, children have a stronger innate immune system and may respond to pathogens differently from adults. In healthy children, lymphocytes, especially NK cells, are constitutionally in greater amount than healthy adults (62). Lymphocyte count is very high in the first months of life and decreases in later childhood and in adolescence. Both frequent viral infections and live vaccines in children could induce an innate immune system enhanced state of activation, which would result in more effective defense against different pathogens (63,64). Finally, simultaneous presence of other viruses in the respiratory mucosa of children, may compete with SARS-CoV-2 (65).

However, children generally have a lower risk of cumulative exposures to SARS-CoV-2 and a lower likelihood of being tested compared with adults (40). For these reasons, it is difficult to determine how much of an observed difference in detected SARS-CoV-2 infection rates between children and adults may be attributed too biological or to epidemiological differences.

Transmission of SARS-CoV-2

Studies indicate that children are not the major vector of SARS-CoV-2 transmission in the community with most pediatric cases described in family clusters. The prevalent direction of virus transmission is adult-to-child rather than child-to-adult (24,66). In particular, only in 8% of households did a child develop symptoms before any other household member (25). In family clusters, the most common source of infection was a parent, considered the index case in 56% of cases, while in only 4% of cases the most probable index case was a sibling (17). Lastly, new SARS-CoV-2 variants emerged the past months, with higher (up to 90%) reproduction number and an increased impact on morbidity and deaths, based on model projections, compared with preexisting variants (67). The role of children in the transmission dynamics of these variants must be elucidated (67).

The Role of Schools

Transmission of SARS-CoV-2 has been reported to occur within educational settings. To reduce virus transmission,

many countries implemented school closure at the national level. However, epidemiological investigation has revealed that SARS-CoV-2 transmission in schools concerns only a minority of COVID-19 cases in most countries, especially when infection control measures are employed. In Sweden, schools and preschools remained open, and a low incidence of severe COVID-19 among children was reported during the pandemic (68). A prospective cohort study in Australia employing case-contact testing showed that children and teachers did not contribute significantly to COVID-19 transmission when attending educational settings (69). Similarly, in Ireland, studies on pediatric cases of COVID-19 attending school identified no cases of onward transmission to other children or adults within the school, neither in primary nor in secondary school settings (70). In England, when schools re-opened after the first national lockdown, systematic national surveillance detected a low general risk of SARS-CoV-2 infection among staff and students in educational settings (71). In Germany after implementation of infection control measures for the prevention of SARS-CoV-2 transmission in schools and childcare facilities, child-to-child transmission was rare (72). In northern Italy, within-school transmission occurred in high schools, but no secondary cases were found in pre-school children, apart from one case in a primary school, and no secondary cases were detected among teachers (73). Another cross-sectional and prospective cohort study in Italy does not support the notion that school opening was a driving force of the second wave of SARS-CoV-2 epidemic in Italy (74). In Israel, schools fully reopened on May 17, 2020. Ten days later, there was a major outbreak of COVID-19 in a high school (75). The first case was registered on May 26, 2020, and the second on May 27, 2020, but there was no epidemiological link between the two. Testing of the complete school community revealed an attack rate of 13.2% among students and 16.6% among staff (75). A systemic review of 16 articles, including a modeling study, on school closures and other school social distancing practices during coronavirus outbreaks including COVID-19, revealed that school closures would prevent very few deaths, much less than other social distancing interventions (76). Moreover, transmission spread within schools can be drastically reduced with strict implementation of mitigating measures (71). These include frequent cleaning of contact surfaces, regular and interim ventilation of rooms, hand hygiene and use of a face mask inside and outside the classroom. Keeping physical distance among children is also recommended, as well as temporary exclusion of sick children (71). Indeed, a study of upper respiratory viral loads in children with SARS-CoV-2 infection found that asymptomatic children had significantly higher cycle threshold values than symptomatic children, while viral loads were 3–4 logs lower in the former compared to the latter (*p*-value <0.001); these findings were consistent across all institutions and by gender, ethnicity, and race

(77). Moreover, a recent study justifies testing of quarantined contact traced students for SARS-CoV-2 infection on or after 9 d from exposure (78).

Closure of schools has a severely negative impact on children's and adolescents' physical condition (79), their social interactions and well-being (80), and is associated with psychological problems (81), risk of obesity (82), and screen addiction (83). Open schools offer protection from situations of domestic abuse (84) and are important for maintaining and improving learning performance, especially in low-income settings. These data support the well-established belief that perils of school closures are not outweighed by potential benefits. In general, evidence from various studies and the fact that incidence among young children is significantly lower suggest that the risk of SARS-CoV-2 transmission among children associated with reopening childcare centers and elementary schools might be lower than that for high schools and universities (14,73). CDC therefore recommends that K-12 schools be the last to close after all other mitigation measures have been employed and the first to open when that can be done safely (85).

Vaccination

The past months COVID-19 vaccines trials are ongoing in children. Preliminary results show very good efficacy and tolerability (86). The US CDC and other public health authorities recommend persons 12 years and older should get vaccinated with the Pfizer-BioNTech COVID-19 vaccine (87). An age-structured disease transmission model found that in a base-case scenario with an effective reproduction number $R_e = 1.2$ and in the absence of vaccine availability for children, rapid identification of silent infections in this age group is required to mitigate disease burden (88). Vaccination of adults is unlikely to contain COVID-19 outbreaks soon without measures to interrupt transmission chains from silent infections (88). Vaccination of children and adolescents is recommended to protect them against COVID-19, but mostly to contribute to the achievement of herd immunity across all age groups (89).

Competing Interest

Theackre is no conflict of interest to declare.

Funding

References

1. Team EE. Note from the editors: World Health Organization declares novel coronavirus (2019-nCoV) sixth public health emergency of international concern. Euro Surveill 2020;25:200131e.

2. Ladhani SN, Amin-Chowdhury Z, Davies HG, et al. COVID-19 in children: analysis of the first pandemic peak in England. Arch Dis Child 2020;105:1180–1185.

3. Parri N, Lenge M, Buonsenso D. Children with COVID-19 in pediatric emergency departments in Italy. New Engl J Med 2020;383:187–190.

4. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020;323:1239–1242.

5. Bi Q, Wu Y, Mei S, et al. Epidemiology and transmission of COVID-19 in 391 cases and 1286 of their close contacts in Shenzhen, China: a retrospective cohort study. Lancet Infect Dis 2020;20:911–919.

6. Dong Y, Mo X, Hu Y, et al. Epidemiology of COVID-19 among children in China. Pediatr 2020;145:e20200702.

7. Suratannon N, WA Dik, Chatchatee P, van Hagen PM. COVID-19 in children: heterogeneity within the disease and hypothetical pathogenesis. Asian Pac J Allergy Immunol 2020;38:170–177.

8. Biglari HN, Sinaei R, Pezeshki S, Hasani FK. Acute transverse myelitis of childhood due to novel coronavirus disease 2019: the first pediatric case report and review of literature. Iran J Child Neurol 2021;15:107–112.

9. Li F, Li Y-Y, Liu M-J, et al. Household transmission of SARS–CoV-2 and risk factors for susceptibility and infectivity in Wuhan: a retrospective observational study. Lancet Infect Dis 2021;21:617–628.

10. DeBiasi RL, Delaney M. Symptomatic and asymptomatic viral shedding in pediatric patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): under the surface. JAMA Pediatr 2021;175:16–18.

11. Public Health Ontario. COVID-19 infection in children; January 15, 2020. to March 11, 2020. Available at https://www.publichealthontario.ca/-/media/documents/ncov/epi/2020/05/covid-19-epi-infection-children.pdf?la=en Accessed May 18, 2021.

12. American Academy of Pediatrics. Children and COVID-19: State-Level Data Report. Available at: services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/children-and-covid-19-state-level-data-report/2021 (Accessed May 18, 2021).

13. World Health Organization. Coronavirus disease (COVID-19): Schools 2020. Available at: https://www.who.int/news-room/q-a-detail/coronavirus-disease-covid-19-schools (Accessed May 18, 2021).

14. Leidman E, Duca LM, Omura JD, Proia K, Stephens JW, Sauber-Schatz EK. COVID-19 trends among persons aged 0–24 years—United States, March 1–December 12, 2020. Morb Mortal Wkly Rep 2021;70:88–94.

15. Hobbs CV, Drobeniuc J, Kittle T, et al. Estimated SARS–CoV-2 seroprevalence among persons aged <18 years—Mississippi, May–September 2020. Morb Mortal Wkly Rep 2021;70:312–315.

16. Waterfield T, Watson C, Moore R, et al. Seroprevalence of SARS–CoV-2 antibodies in children: a prospective multicentre cohort study. Arch Dis Child 2020 archdischild-2020-320558.

17. Götzinger F, Santiago-García B, Noguera-Julián A, et al. COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. Lancet Child Adolesc Health 2020;4:653–661.

18. Parri N, Magistà AM, Marchetti F, et al. Characteristic of COVID-19 infection in pediatric patients: early findings from two Italian Pediatric Research Networks. Eur J Pediatr 2020;179:1315–1323.

19. King JA, Whitten TA, Bakal JA, McAlister FA. Symptoms associated with a positive result for a swab for SARS-CoV-2 infection among children in Alberta. CMAJ 2021;193:E1–E9.

20. Lu X, Zhang L, Du H, et al. SARS-CoV-2 infection in children. New Engl J Med 2020;382:1663–1665.

21. Poline J, Gaschignard J, Leblanc C, Madhi F, Foucaud E, Nattes E. Systematic severe acute respiratory syndrome coronavirus 2 screening at hospital admission in children: a French prospective multicenter study. Clin Infect Dis 2020 ciaa1044. doi:10.1093/cid/ciaa1044.

22. Du W, Yu J, Wang H, et al. Clinical characteristics of COVID-19 in children compared with adults in Shandong Province. China. Infect 2020;48:445–452.

23. Zachariah P, Johnson CL, Halabi KC, et al. Epidemiology, clinical features, and disease severity in patients with coronavirus disease 2019 (COVID-19) in a children's hospital in New York City, New York. JAMA Pediatr 2020;174:e202430 -e.

24. Maltezou HC, Magaziotou I, Dedoukou X, et al. Children and adolescents with SARS-CoV-2 infection: epidemiology, clinical course and viral loads. Pediatr Infect Dis J 2020;39:e388–e392.

25. Posfay-Barbe KM, Wagner N, Gauthey M, et al. COVID-19 in children and the dynamics of infection in families. Pediatr 2020;146:e20201576.

26. Mak PQ, Chung K-S, Wong JS-C, Shek C-C, Kwan MY-W. Anosmia and ageusia: not an uncommon presentation of COVID-19 infection in children and adolescents. Pediatr Infect Dis J 2020;39:e199–e200.

27. Tagarro A, Epalza C, Santos M, et al. Screening and severity of coronavirus disease 2019 (COVID-19) in children in Madrid, Spain. JAMA Pediatr 2021;175:316–317.

28. Verma S, Lumba R, Dapul HM, et al. Characteristics of hospitalized children with SARS-CoV-2 in the New York City metropolitan area. Hosp Pediatr 2021;11:71–78.

29. Spoulou V, Noni M, Koukou D, Kossyvakis A, Michos A. Clinical characteristics of COVID-19 in neonates and young infants. Eur J Pediatr 2021:1–5. doi:10.1007/s00431-021-04042-x.

30. 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. Morb Mortal Wkly Rep 2020;69:1081–1088.

31. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: a review. Clin Immunol 2020;215:108427.

32. LaRovere KL, Riggs BJ, Poussaint TY, et al. Neurologic involvement in children and adolescents hospitalized in the United States for COVID-19 or Multisystem Inflammatory Syndrome. JAMA Neurol 2021;78:536–547.

33. McLendon LA, Rao CK, Da Hora CC, Islamovic F, Galan FN. Post–COVID-19 acute disseminated encephalomyelitis in a 17-month-old. Pediatr 2021;147:e2020049678.

34. Lara D, Young T, Del Toro K, et al. Acute fulminant myocarditis in a pediatric patient with COVID-19 infection. Pediatr 2020;146:e20201509.

35. Alcalde CF, Fernández MG, Moreno MN, Rey CC, Romero IF, Martín SN. COVID-19 ocular findings in children: a case series. World J Pediatr 2021:1–6. doi:10.1007/s12519-021-00418-z.

36. Ma N, Li P, Wang X, et al. Ocular manifestations and clinical characteristics of children with laboratory-confirmed COVID-19 in Wuhan, China. JAMA Ophthalmol 2020;138:1079–1086.

37. Samies NL, Pinninti S, James SH. Rhabdomyolysis and acute renal failure in an adolescent with coronavirus disease 2019. J Pediatr Infect Dis Soc 2020;9:507–509.

38. Abdulamir A, Hafidh R. The possible immunological pathways for the variable immunopathogenesis of COVID-19 infections among healthy adults, elderly and children. Electron J Gen Med 2020;17 em202.2020.

39. Shekerdemian LS, Mahmood NR, Wolfe KK, et al. Characteristics and outcomes of children with coronavirus disease 2019 (COVID-19) infection admitted to US and Canadian pediatric intensive care units. JAMA Pediatr 2020;174:868–873.

40. Centers for Disease Control and Prevention. Science Brief: transmission of SARS-CoV-2 in K-12 schools. Available at: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/ transmission_k_12_schools.html (Accessed May 18, 2021).

41. Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem inflammatory syndrome in US children and adolescents. New Engl J Med 2020;383:334–346.

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

43. Centers for Disease Control and Prevention. Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19). Available at: https://emergency.cdc.gov/ han/2020/han00432.asp (Accessed May 18, 2021).

44. Toubiana J, Poirault C, Corsia A. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic. Paris, France: prospective observational study. BMJ 2020;369:2094 .m.

45. Feldstein LR, Tenforde MW, Friedman KG, et al. Characteristics and outcomes of US children and adolescents with Multisystem Inflammatory Syndrome in Children (MIS-C) compared with severe acute COVID-19. JAMA 2021;325:1074–1087.

46. Godfred-Cato S, Bryant B, Leung J, et al. COVID-19-associated multisystem inflammatory syndrome in children-United States, March–July 2020. Morb Mortal Wkly Rep 2020;69:1074–1080.

47. Pavli A, Theodoridou M, Maltezou HC. Post-COVID syndrome: incidence, spectrum, and challenges for primary healthcare professionals. Arch Med Res 2021 May 4:S0188-4409(21)00081-3. doi:10.1016/j. arcmed.2021.03.010.

48. Qiu H, Wu J, Hong L, Luo Y, Song Q, Chen D. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. Lancet Infect Dis 2020;2:689–696.

49. Chuah CXP, Lim RL, Chen MIC. Investigating the legacy of the 1918 influenza pandemic in age-related seroepidemiology and immune responses to subsequent influenza A(H1N1) viruses through a structural equation model. Am J Epidemiol 2018;187: 2530–2540.

50. Crimmins Easterlin M, Crimmins EM, Finch CE. Will prenatal exposure to SARS-CoV-2 define a birth cohort with accelerated aging in the century ahead? J Dev Orig Health Dis 2020:1–5 Online ahead of print. doi:10.1017/S204017442000104X.

51. Holuka C, Merz MP, Fernandes SB, et al. The COVID-19 pandemic: does our early life environment, life trajectory and socioeconomic status determine disease susceptibility and severity? Int J Mol Sci 2020;21:5094.

52. Dorjee K, Kim H, Bonomo E, Dolma R. Prevalence and predictors of death and severe disease in patients hospitalized due to COVID-19: A comprehensive systematic review and meta-analysis of 77 studies and 38,000 patients. PloS One 2020;15:e0243191.

53. World Health Organization. COVID-19: vulnerable and high risk groups Available at: https://www.who.int/westernpacific/emergencies/ covid-19/information/high-risk-groups#:~:text=COVID%2D19% 20is%20often,their%20immune%20system.%E2%80%8B (Accessed May 18, 2021).

54. Felsenstein S, Hedrich CM. COVID-19 in children and young people. Lancet Rheumatol 2020;2:e514–e516.

55. Jiatong S, Wenjun L. Epidemiological characteristics and prevention and control measures of Corona Virus Disease 2019 in children. J Trop Med 2020;20:153–156.

56. Fang F, Luo X. Facing the pandemic of 2019 novel coronavirus infections: the pediatric perspectives. Zhonghua Er Ke Za Zhi 2020;58:81–85.

57. Bunyavanich S, Do A, Vicencio A. Nasal gene expression of angiotensin-converting enzyme 2 in children and adults. JAMA 2020;32:2427–2429.

58. Patel AB, Verma A. Nasal ACE2 levels and COVID-19 in children. JAMA 2020;323:2386–2387.

59. Chen J, Jiang Q, Xia X, et al. Individual variation of the SARS–CoV-2 receptor ACE2 gene expression and regulation. Aging Cell 2020;19:e13168.

60. Imai Y, Kuba K, Rao S, et al. Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature 2005; 436:112–116.

61. World Health Organization. Coronavirus disease (COVID-19) weekly epidemiological update and weekly operational update 2021. Available at: https://www.who.int/emergencies/diseases/ novel-coronavirus-2019/situation-reports (Accessed May 18, 2021).

62. Cristiani L, Mancino E, Matera L, et al. Will children reveal their secret? the coronavirus dilemma. Eur Respir J 2020;55:2001617.

63. de Bree LCJ, Koeken VA, Joosten LA, et al. Non-specific effects of vaccines: current evidence and potential implications. Semin Immunol 2018;39:35–43.

64. Benn CS, Netea MG, Selin LK, Aaby P. A small jab–a big effect: nonspecific immunomodulation by vaccines. Trends Immunol 2013;34:431–439.

65. Nickbakhsh S, Mair C, Matthews L, et al. Virus-virus interactions impact the population dynamics of influenza and the common cold. Proc Natl Acad Sci USA 2019;116:27142–27150. doi:10.1073/pnas. 1911083116.

66. Maltezou HC, Vorou R, Papadima K, et al. Transmission dynamics of SARS-CoV-2 within families with children in Greece: A study of 23 clusters. J Med Virol 2021;93:1414–1420.

67. Davies NG, Abbott S, Barnard RC, et al. Estimated transmissibility, and impact of SARS-CoV-2 lineage B.1.1.7 in England. Science 2021;372:eabg3055.

68. Ludvigsson JF, Engerström L, Nordenhäll C, Larsson E. Open schools, COVID-19, and child and teacher morbidity in Sweden. New Engl J Med 2021;384:e66.

69. Macartney K, Quinn HE, Pillsbury AJ, et al. Transmission of SARS–CoV-2 in Australian educational settings: a prospective cohort study. Lancet Child Adolesc Health 2020;4:807–816.

70. Heavey L, Casey G, Kelly C, Kelly D, McDarby G. No evidence of secondary transmission of COVID-19 from children attending school in Ireland, 2020. Euro Surveill 2020;25:2000903.

71. Ismail SA, Saliba V, Bernal JL, Ramsay ME, Ladhani SN. SARS–CoV-2 infection and transmission in educational settings: a prospective, cross-sectional analysis of infection clusters and outbreaks in England. Lancet Infect Dis 2021;21:344–353.

72. Ehrhardt J, Ekinci A, Krehl H, et al. Transmission of SARS-CoV-2 in children aged 0 to 19 years in childcare facilities and schools after their reopening in May 2020. Baden-Württemberg, Germany. Euro Surveill 2020;25:2001587.

73. Larosa E, Djuric O, Cassinadri M, et al. Secondary transmission of COVID-19 in preschool and school settings in northern Italy after their reopening in September 2020: a population-based study. Euro Surveill 2020;25:2001911.

74. Gandini S, Rainisio M, Iannuzzo ML, Bellerba F, Cecconi F, Scorrano L. No evidence of association between schools and SARS-CoV-2 second wave in Italy. medRxiv. Available at: https://www.medrxiv.org/ content/10.1101/2020.12.16.20248134v2 (Accessed May 18, 2021).

75. Stein-Zamir C, Abramson N, Shoob H, et al. A large COVID-19 outbreak in a high school 10 days after schools' reopening, Israel, May 2020. Euro Surveill 2020;25:2001352.

76. Viner RM, Russell SJ, Croker H, et al. School closure and management practices durin gcoronavirus outbreaks including COVID-19: a rapid systemic review. Lancet Child Adolesc Health 2020;4:397–404.

77. Kociolek LK, Muller WJ, Yee R, et al. Comparison of upper respiratory viral load distributions in asymptomatic and symptomatic

children diagnosed with SARS-CoV-2 infection in pediatric hospital testing programs. J Clin Microbiol 2020;59:e02593 -20.

78. Nelson EJ, McKune SL, Ryan KA, et al. SARS-CoV-2 positivity on or after 9 days among quarantined student contacts of confirmed cases. JAMA 2021;325:1561–1562.

79. Dunton GF, Do B, Wang SD. Early effects of the COVID-19 pandemic on physical activity and sedentary behavior in children living in the US. BMC Public Health 2020;20:1–13.

80. Xie X, Xue Q, Zhou Y, et al. Mental health status among children in home confinement during the coronavirus disease 2019 outbreak in Hubei Province, China. JAMA Pediatr 2020;174:898–900.

81. Zhang J, Shuai L, Yu H, et al. Acute stress, behavioural symptoms and mood states among school-age children with attention-deficit/hyperactive disorder during the COVID-19 outbreak. Asian J Psychiatr 2020;51:102077.

82. Ruiz-Roso MB, de Carvalho Padilha P, Mantilla-Escalante DC, et al. COVID-19 confinement and changes of adolescent's dietary trends in Italy. Spain, Chile, Colombia and Brazil. Nutrients 2020;12:1807.

83. Dong H, Yang F, Lu X, Hao W. Internet addiction and related psychological factors among children and adolescents in China during the coronavirus disease 2019 (COVID-19) epidemic. Front Psychiatry 2020;11:00751.

84. Thomas EY, Anurudran A, Robb K, Burke TF. Spotlight on child abuse and neglect response in the time of COVID-19. Lancet Public Health 2020;5:e371.

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

86. Moghadas SM, Fitzpatrick MC, Shoukat A, Zhang K, Galvani AP. COVID-19 vaccines for kids. New Sci 2021;250:8–9.

87. Centers for Disease Control and Prevention. COVID-19 vaccines for children and teens. Available at: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/adolescents.html (Accessed May 18, 2021).

88. Moghadas SM, Fitzpatrick MC, Shoukat A, Zhang K, Galvani AP. Simulated identification of silent COVID-19 infections among children and estimated future infection rates with vaccination. JAMA Netw Open 2021;4:e217097.

89. Callaway E. COVID vaccines and kids: five questions as trials begin. Nature 2021;592:670–671.