

## **A Pediatric Infectious Disease Perspective on COVID-19**

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**Article Summary:** SARS-CoV-2 is the newest coronavirus to capture worldwide attention. Clinical and epidemiologic features of infection in children are compared to other common viruses. A theme of less severe disease in individuals with modulated immune systems (youth and some malignancies) is emerging.

## **Abstract**

This review highlights the clinical and epidemiologic characteristics of COVID-19 in children and neonates and contrasts these features with other common respiratory viruses. Although the majority of infections in children are mild, there are many important, as yet, unanswered questions (specifically, the attack rate in children and the role of children as vectors of infection), that will have a major impact on disease in adults. There are no distinctive clinical characteristics that will allow the infectious disease consultant to make the diagnosis without laboratory testing. SARS-CoV-2 appears to be less common with lower morbidity and mortality than RSV or influenza and causes less severe disease in children with cancer than these more common viruses. The range of severity of infection during pregnancy is comparable to infection in non-pregnant cohorts. Intrauterine infection has been documented but is uncommon. A theme of less severe disease in individuals with modulated immune systems is emerging.

**Key Words:** COVID-19; children; infection; epidemiology; pregnancy

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Not since 1918-1919 has the world encountered as catastrophic a pandemic as has occurred with COVID-19 with its far-reaching consequences for our personal, public, population and economic health. COVID-19 is the disease caused by Severe Acute Respiratory Distress Coronavirus 2 (SARS-CoV-2), which first appeared in Wuhan, China in December 2019 and now has spread around the world. The goal of this review is to highlight what is known about the clinical and epidemiologic characteristics of this infection in children and neonates and contrast its characteristics to that of other common community-acquired respiratory viruses. In addition, we review data on maternal-fetal transmission and compare COVID-19 to other infections which present with mild illness in children and severe illness in adults.

### **Clinical and Epidemiologic Characteristics**

We have learned about the clinical features of COVID-19 infection in children through (1) large reports of hospitalized patients in China [1,2], Italy [3], Spain [4] and the United States [5,6], (2) large series of children only [7,8], and (3) numerous small series, family clusters and case reports [9,10]. A synthesis of these publications show that children represent a minority (usually < 2%) of the patients who present with clinically recognized symptoms of SARS-CoV-2 [1,4,5]. In addition, the infection in most children is mild with a substantial proportion (5-21%) being completely asymptomatic and another large group having symptoms of a common viral upper respiratory infection [3,7,8]. The proportion of children with severe illness is in the range of 1-6%, even with the recent recognition of the pediatric multisystem inflammatory syndrome [11]. Although reports of differences in severity according to age have been inconsistent, some have noted increased risk in the first year of life and others during adolescence [5,12]. Fortunately, fatalities have been infrequent

and most, but not all, children who have died have had serious comorbidities including medical complexity, obesity and diabetes [12,13].

Fever and non-productive cough are the most common symptoms in children (nearly 50%), but rhinorrhea, fever alone or mild gastrointestinal symptoms such as abdominal pain, diarrhea and vomiting are also observed [3,7]. Detection of SARS-CoV-2 in asymptomatic children may represent pre-symptomatic detection or truly asymptomatic infection. Asymptomatic infection is not a distinguishing characteristic as virtually all common community-acquired viruses are shed asymptotically in children with substantial frequency [14]. What may be a distinguishing feature is the length of time during which shedding occurs pre-symptomatically (as long as 48 hours) and the intensity of shedding [15]. Jones et al analyzed viral load by real-time RT-PCR threshold cycle values from 3,712 COVID-19 patients to examine the relationship between patient age and SARS-CoV-2 viral load [16]. The author's conclusion that viral loads are the same in children as adults is controversial. It is important to highlight that there are no clinical characteristics that distinguish infections caused by SARS-CoV-2 from any other community-acquired respiratory virus such as RSV, influenza, or parainfluenza. This will present a major challenge in future respiratory seasons as it will be essential to identify cases and trace contacts, requiring systematic laboratory diagnosis in all children with even minor respiratory symptoms. Furthermore, co-infections with other common respiratory viruses occurs as often as 50% of the time; accordingly, documentation of infection with RSV does not assure that the patient is not also infected with SARS-CoV-2 [17].

Most children infected with SARS-CoV-2 acquired their infection within their household from an infected adult. However, schools/daycares were closed very early as a reflexive response to the pandemic in most locations. Therefore, an important question when schools re-open is whether school children will be a source of infection for other children,

their own parents and teachers/daycare workers (thereby exerting a multiplier effect on the proportions of the pandemic) similar to influenza.

*Multisystem Inflammatory Syndrome.* Beginning in April 2020, there have been national and international alerts concerning the multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19 [11,18]. This syndrome presents uniformly with fever and an ill-looking child. In nearly half the children, the clinical signs and symptoms are compatible with either complete [fever plus (4 of 5 clinical features) rash, conjunctival suffusion, swelling of hands/feet, oral mucosal changes and lymphadenopathy] or incomplete Kawasaki syndrome. In the remainder, the clinical presentation is more akin to toxic-shock syndrome, with prominent gastrointestinal symptoms and impressive cardiac dysfunction which often requires inotropic support [18]. About two-thirds of children have definite laboratory evidence of an association with SARS-CoV-2 established with either positive nucleic acid detection or serology; the remainder have an epidemiologic link to a person with COVID-19. Most affected children display laboratory evidence of intense inflammation. Approximately 80% require intensive care including the need for mechanical ventilation in 20%; 15% of children show coronary artery abnormalities [19,20]. While there is great interest in MIS-C, it is uncommon, accounting for less than 1% of all cases.

*COVID-19 in Children with Cancer.* In contrast to MIS-C comes the observation that some children with underlying malignancies on immunosuppressive treatments tolerate infection with SARS-CoV-2 surprisingly well. A report from Memorial Sloan Kettering, a systematic review and a flash survey of European cancer centers show that the overall morbidity of COVID-19 in children with cancer is low with few patients requiring hospitalization [21-23]. This is in sharp contrast to what would be expected with RSV or influenza and contrary to expectations in patients who are immunosuppressed.

COVID-19 in Children in other High Risk Groups. Although there is relatively little written about COVID-19 in children who have undergone solid organ transplantation, the data that are available suggest that children on stable immunosuppression more than 6 months following transplantation, experience infection with SARS-CoV-2 similarly to otherwise healthy children [24,25]. The same is true for children living with human immunodeficiency infection who are well-controlled on their antiretroviral therapy [26].

Limited data from patients with cystic fibrosis (mostly adults) shows infection with SARS-CoV-2 without apparent effect on the severity of the underlying disease [27]. In addition, it appears as though children and adults with allergic asthma are not at increased risk for acquisition of SARS-CoV-2 or experiencing extreme severity as they have diminished receptors for angiotensin-converting enzyme-2 [28].

### **Why are Clinical Infections Uncommon in Children with COVID-19?**

One of the important and intriguing questions has been why the proportion of clinical infections accounted for by children is so low [1,4,5]. Does this simply reflect the fact that most infected children have subclinical or extremely mild infections or that somehow children are truly resistant to the acquisition of infection? The issue is complicated by study methods and the particular population being investigated. When only symptomatic children are evaluated, it appears as though children are resistant to infection. However, in a publication by Bi and colleagues [29] of more than 1286 contacts, the reported attack rate in children was similar to that in older patients. In contrast, a population study in Iceland showed a lower attack rate in children under 10 years of age, compared to those over 10 [30]. An interesting observation in children with cancer and their families also suggests that the attack rate in children is lower than adults. One hundred twenty asymptomatic children with cancer and their asymptomatic caregivers had nasopharyngeal swabs for COVID-19

performed [21]. The colonization rate in children was 2.5% (95% CI, 0.5%-7.2%) vs. 14.7% (95% CI, 7.35-25.4% P= .002) in their caregivers. Several proposed hypotheses for a lower attack rate and less severe disease in children compared to adults include decreased expression of angiotensin converting enzyme 2 (the receptor for the virus), less intense immune responsivity and potential viral interference by co-infecting viruses [31,32]. Determining the attack rate of COVID-19 in children with certainty will await broad scale testing of large numbers of symptomatic and asymptomatic children.

### **Diagnosis and Duration of Infectivity**

The diagnosis of COVID-19 has in most series depended on the results of real-time polymerase chain reaction (rt-PCR) assays for the virus on samples obtained from the nose, throat or nasopharynx [33]. Saliva may also be a suitable specimen [34]. Secretions from the lower respiratory tract, including bronchoalveolar lavage or expectorated sputum, are even more likely to be positive but are less available. Early on, the sensitivity of these tests was variable, but more recent nucleic acid assays are very sensitive [35]. The timing and quality of the acquisition of the sample is critical. Virus is present in high density just before and just after the onset of respiratory symptoms and remains high for several days. However, it is important to recognize that a positive test does not necessarily reflect the presence of viable virus. Wölfel and colleagues [36] demonstrated that virus could not be grown in any sample obtained from a small group of patients beyond the eighth day of illness. This is of particular importance because respiratory secretions can remain PCR positive for long periods of time (25 days after the beginning of the illness) – and fecal detection is even more protracted [37] despite the fact that virus has never been cultured from stool specimens.

Serology is not useful in making a diagnosis of acute disease since, in general, at least 7 to 10 days is required for 50% of infected individuals to have an IgG or IgM response [38].

Nearly universal seroconversion occurs by 3 to 4 weeks [39]. While antibodies are a marker that infection has occurred, interpretation of their presence raises several questions: (1) Are the antibodies specific for SARS-CoV-2 or are they cross-reactive with community coronaviruses? (2) Do they provide protection, and if so, (3) What is the duration of the immunity?

### **Maternal-Fetal Transmission**

*Maternal Infection.* Inevitably, in the context of the COVID-19 pandemic, pregnant women contract the infection, which raises three important questions: the impact of infection on the mother, the impact of infection on the neonate and whether intrauterine transmission occurs.

A June, 2020 study from the Centers for Disease Control and Prevention which described laboratory-confirmed cases of SARS-CoV-2 infection by pregnancy status reported increases in rates of admission to the intensive care unit (1.5% vs 0.7%) and the requirement for mechanical ventilation (0.5% vs. 0.3%) for pregnant vs. non-pregnant patients [40]. As pregnancy alone, without infection, has an impact on morbidity and mortality this would not be surprising. However, the significant differences in the two populations, vis-à-vis co-morbidities and race/ethnicity, plus a tremendous amount of missing data requiring numerous adjustments and assumptions reduces the magnitude and strength of the conclusions. A large prospective experience from New York City, reporting differences in outcomes between pregnant patients with and without infection with SARS-CoV-2 is mostly reassuring despite substantial differences in co-morbidities and race/ethnicity [41]. Among pregnant patients with SARS-CoV-2 infection, 78.6% were asymptomatic; there were no admissions to intensive care and no mortality although there was an increase in post-partum complications.



The overall range and distribution of severity of COVID-19 infection in pregnant patients is similar to that in non-pregnant patients.

*Congenital Infections.* Many congenital infections appear to be transmitted to the fetus *in utero* when the mother is viremic. Alternatively, perinatal infections occur at or around the time of delivery, via contact with maternal vaginal flora. Detection of viremia in SARS-CoV-2 infections has varied from zero to 40% [36,42]. Accordingly, intrauterine transmission is probable if the mother is viremic during pregnancy.

Numerous studies have examined the effect of COVID-19 on the neonate (see Appendix, Table 1). Main effects are similar to other viral infections in pregnancy, including premature labor/birth and small for gestational age. Two neonatal deaths have been reported between January 1, 2020 and May 5, 2020; one was likely due to overwhelming maternal sepsis and multi-organ failure before delivery and the other was likely influenced by the infant's prematurity.

Table 1 shows all studies that detected either IgM or a positive PCR for COVID-19 in a neonate born to a mother with COVID-19 infection. Four infants were diagnosed by a positive nasopharyngeal or oral swab within 48 hours of delivery. Three of the 4 infants had mild but definite clinical symptoms. In each case the child was delivered by Caesarian section and the neonate was isolated from the mother immediately after birth. Two reports described a likely intrauterine transmission on the basis of a positive IgM antibody for SARS-CoV-2 documented at or shortly after birth. The infants in both reports remained asymptomatic and had negative PCRs. Depending on the timing of the maternal infection, the virus may already have been cleared, explaining the negative PCR; this was probably the case in the third study. The presence of IgM reflects neonatal infection rather than passive transfer of maternal antibodies as IgM does not cross the placenta. However, IgM is a relatively nonspecific marker and is prone to false positives. Because of the relative novelty

of this pandemic, there are no data on the outcome of infections that might have been experienced in the first or second trimester.

Postnatal infection caused by COVID-19 may result from contact of a newborn with any person who is shedding the virus, likely the mother or another household contact. Separation of mother and baby when the delivering mother is known to be infected is prudent and recommended [43].

### **Comparison to Other Common Viruses**

Acute respiratory tract infections in children less than 5 years of age are a leading cause of morbidity and mortality worldwide. RSV, influenza and human coronavirus (HCoV) are common viruses identified in children with clinical manifestations ranging from mild upper respiratory infections (URI) to severe lower respiratory tract infections (LRTI) that can result in respiratory failure.

Respiratory Syncytial Virus. RSV is the most common cause of acute LRTI and subsequent hospitalizations in children less than 1 year of age. The majority of infants with RSV infection will have symptoms isolated to the upper respiratory tract, although 20-40% will develop LRTI. Overall, 1-3% of all infants less than 1 year of age will require hospitalization due to RSV-related LRTI, the majority during the first 6 months of life. Almost all children will have experienced at least one episode of RSV by 2 years of age. In the U.S., it is estimated that RSV-related infections result in 58,000 hospitalizations and 2.1 million outpatient visits per year [44].

Previous infection does not appear to provide protection against reinfection with RSV even in those with high titers of specific antibody. A person remains susceptible to reinfection with RSV throughout their lifetime, though reinfections are typically less severe.

Influenza. Fever, cough and rhinorrhea are the most common symptoms in children with influenza. Approximately 9% of children develop symptomatic influenza each year [45]. Hospitalization rates are highest among children younger than 2 years of age and adults older than 65 years of age. In addition, individuals with certain high-risk conditions such as asthma, diabetes, hemoglobinopathies, hemodynamically significant cardiac disease, immunosuppression, and neurodevelopmental disorders have an increased risk of influenza-associated hospitalization, morbidity and mortality.

Coronavirus. The seasonal coronaviruses HCoV-OC43, -NL63, -HKU1 and -229E circulate worldwide and are a very common cause of viral URI. While mild URI symptoms are typical of HCoV infections, LRTI such as bronchiolitis or pneumonia occur in younger children, the elderly and immunocompromised individuals. Overall, HCoV is detected in up to 10% of children in ambulatory settings with respiratory tract infections and in 9% of hospitalized children less than 5 years with LRTI [46]. Reinfection is common and is likely due to waning immunity over time and minimal cross-protection between the different groups.

### **Comparison of RSV, Influenza and Coronavirus to SARS-CoV-2**

Characteristics of RSV, influenza and coronavirus occurring in children are shown in Table 2. RSV has the highest symptomatic incidence, hospitalization rate, and mortality rate [47] for children less than 5 years of age, especially for those less than 2 years, compared to the available data for influenza [45] and coronavirus [46].

In comparison to these three common respiratory viruses, SARS-CoV-2 has a longer incubation period (usually 4 to 6 days, which may extend to 14 days), and a lower likelihood of (1) clinical infection, (2) severe disease in children with cancer [21], (3) hospitalization and (4) mortality. The transmissibility of viruses is estimated using secondary attack rates, which are typically calculated within households. RSV and influenza have a wide range of secondary attack rates due to seasonal variability, strain virulence and population immunity. From a study performed by Bi et al [29], it appears that SARS-CoV-2 has a similar attack rate as seasonal coronaviruses [33], which is probably lower than both influenza and RSV.

### **Severity of Disease in Childhood Compared to Adulthood**

For the common community-acquired respiratory infections in children, both the attack rate and severity of attack is highest in the first year of life. The exceptions are the elderly or immunocompromised individuals. It is during the first exposure to RSV, for example, that infection of the lower respiratory tract, including bronchiolitis or pneumonia, may occur. With each subsequent exposure to RSV, clinical manifestations become milder. The same is true for parainfluenza or influenza – perhaps influenced by partial immunity and also by the local anatomy of the respiratory tract which makes inflammation of the larynx and trachea less symptomatic when the structures affected are larger (size increases with age) and clearance of secretions more effective in the older child.

However, there are several examples of infectious agents for which the opposite is true, *i.e.*, infection in the young child is very often asymptomatic or accompanied by mild and non-specific signs and symptoms that are not recognizable as typical of the infecting agent. Three examples of this phenomenon are Hepatitis A, Epstein-Barr Virus and Poliovirus. In each of these cases, the attack rate is high in the first year of life, but clinical symptoms are mild or completely absent.

*Hepatitis A.* Seventy to 90% of infections caused by hepatitis A in children less than 5 years of age are completely asymptomatic or manifest as a mild gastroenteritis or anorexia for a few days [48]. Jaundice is uncommon. In contrast, in the older child or adult, hepatitis A is an illness marked by jaundice and substantial morbidity that may persist for several months. Liver injury during hepatitis A is not caused directly by the virus but rather is caused by immune-mediated mechanisms [49]. Baba et al [50] showed *in vitro* that non-specific immune mechanisms involving natural killer (NK) cells and lymphokine-activated killer cells probably play a central role in hepatocellular damage. More recently, Lemon et al [51] concluded that hepatocellular damage need not rest on the activity of NK or activated T cells but may be attributable to innate immune activation of mitochondrial antiviral systems and interferon responses.

EBV infections in children less than 5 years of age are most often asymptomatic or characterized by brief periods of fever, poor appetite and mild respiratory symptoms. In adolescents and older individuals with EBV infection, the characteristics of infectious mononucleosis become apparent, including the typical exudative pharyngitis, fever, lymphadenopathy and prolonged fatigue. Infectious mononucleosis in adults is associated with high viral loads and an exaggerated viral-induced immune response involving both CD8+ T cells and NK cells [52]. Although viral loads are just as high in younger children and asymptomatic adults with EBV infection, there is no lymphocytosis and cell-mediated responses (CD8+ T cells) are not as exaggerated either qualitatively or quantitatively as in symptomatic adults [53].

Most children with polio infections were completely asymptomatic when polio was endemic in the U.S. When involvement of the central nervous system occurred, it was observed in 1 out of 1000 children. In adults with polio, involvement of the CNS was observed in 1 out of 100. Between 2 and 5% of children affected with paralytic polio died

compared to 15-30% of adults. In an attempt to understand the spectrum of disease, Andersen [54] and colleagues showed that genetic variants in the innate immune defenses and cell death pathways are probable contributors to the expression of clinical disease in adults.

All of these phenomena point to the pivotal role of immune mechanisms in shaping the clinical face of disease rather than specific effects of the virus. A down-regulated immune response in each instance seems to be responsible for the milder clinical manifestations of disease. Or to turn that around, an up-regulated immune response is probably responsible for severe manifestations of disease rather than the virus itself.

## **Summary**

SARS-CoV-2 is the newest of the coronaviruses to capture worldwide attention. Although in general, disease in children is infrequent and mild, there are many important questions concerning epidemiology and transmission that will have a major impact on disease in adults. There are no distinctive clinical characteristics of infection in children that will allow diagnosis without laboratory testing. It is less common with lower morbidity and mortality in children than RSV and influenza and causes less severe disease in children with cancer than these more common community viruses. The range of severity of infection during pregnancy is similar to infection in non-pregnant cohorts. Intrauterine infection has been documented but appears to be uncommon. A theme of less severe disease in individuals with modulated immune systems is emerging.

## **Notes**

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**Table 1. Studies Including Neonates Positive for SARS-CoV-2\***

Study	Location	Study Type	# of (+) Pregnant Women	# of (+) Neonates*	# Symptomatic**	Diagnosis <48h	Isolated from Mother Immediately	Diagnosis Method	Mortality Rate
A	Wuhan, China	case series		4	3/4	1/4	3/4	NP or anal swab, RT-PCR	0/4
B	Wuhan, China	case series	7	1/3	1	1	3	OP swab, RT-PCR	0/7
C	Wuhan, China	case report	1	1	0	1	1	SARS-CoV-2 IgM (IgG, IL10, IL6 also elevated, PCR negative)	0/1
D	Wuhan, China	case series	33	3/33	3	3	33	NP and anal swabs, RT-PCR	0/3
E	Wuhan, China	case report	1	1	0	1	1	(+) OP PCR, negative cord blood, placenta, breastmilk	0/1
F	Wuhan, China	case series	6	2	0	2	6	SARS-CoV-2 IgM (all 6 had elevated IgG and IL-6 and negative PCRs)	0/6

\*Literature review up to May 5, 2020.

\*Denotes number of infants to undergo testing, not all studies tested all neonates

\*\*Symptoms Include: fever, cough, SOB

Study

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**Table 2. Characteristics of RSV, Influenza and Coronavirus Infections in Children**

Virus	Reservoir of infection	Incubation period (days)	Secondary attack rate (%)	Symptomatic incidence (% per year)	Hospitalization rate (annually per 100,000)	Mortality rate (annually per 100,000)	Viral co-infection rate (%)
RSV	Humans	2-8	6-56	21*	2300* 450-670†	90* 130†	35
Influenza	Humans, animals	1-4	4-30	13.2† 9.3§	77-128† 20-39‡	0.15§	9-27§
Coronavirus (OC43, NL63, HKU1, 229E)	Humans, animals	2-5¶	7-13	--	57* 50-320†# 10‡	--	28-43§
SARS-CoV-2	Humans, animals	2-14	7-15	--	--	--	--

\* children < 2 years of age.

† children < 5 years of age.

‡ children 5-17 years of age.

§ children < 18 years of age.

¶ Represents incubation period of HCoV-229E as other strains have not been studied.

# 26/100,000 in children < 5 years of age if include HCoV-OC43 and HCoV-NL63 single infections without co-infections.