

Episode #33 – Pediatric Population & COVID-19: Part 1

March 26, 2021

Prevalence of COVID-19 in children

Global statistics

Children, including very young children, can develop COVID-19. According to the World Health Oganization (WHO), global data to date suggests that children under the age of 18 years represent approximately 8.5% of reported cases, usually experiencing mild disease and relatively few deaths compared to other age groups. [1]

Canadian statistics

As of March 12, 2021, for the 0-19 years age group:

- 17.1% (152,915) of the total COVID-19 cases (n = 896,608)
- 1.6% (767) required hospitalization (n = 49,063)
- 1.3% (113) were admitted to ICU (n = 8,657)
- 0.03% (6) died from COVID-19 (n = 22,290) [2]

Ontario statistics

January 15, 2020 to March 12, 2021 [3] [4]

Age group	Cases	Hospitalizations	Deaths
0-9 years	14,520 (4.6%)	106 (0.7%)	1 (0.01%)
10-19 years	28,406 (8.3%)	101 (0.6%)	1 (0.01%)
Total all ages	314,891	15,812	7,127

Prevalence of COVID-19 by sex

In many systematic reviews related to clinical and epidemiological aspects of COVID-19 in the pediatric population (0-19 years old), the percent of male children ranged from 50% to 59%. Several reviews noted no significant difference in the proportion of male and female children. For example, a systematic review and meta-analysis by Zheng et al. (2020) reported that males did not tend to be more susceptible to infection than females. [5] [6]

Dong et al. (2020) conducted a retrospective study in China of 2,135 children (aged < 18 years) with confirmed or suspected COVID-19. The authors found that slightly more cases occurred in boys (56.6%) than in girls (43.4%), but the difference was not statistically significant. [7]

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Bialek et al. (2020) from the Centers for Disease Control and Prevention (CDC) Response Team also noted a slight male predominance in US pediatric COVID-19 data from February 12 to April 2, 2020. The team reported that among 2,490 pediatric COVID-19 cases (aged <18 years), for which sex was known, 1,408 (57%) were male. [8]

Similarly, differences in sex were not statistically significant in Canadian data. According to the Government of Canada, as of March 12, 2021, approximately 48% of all pediatric COVID-19 cases (≤ 19 years) were female and 52% were male. [9]

Incubation period

The incubation period for children is the same as in adults. The time between exposure to COVID-19 and when symptoms develop is commonly around 5 to 6 days, and ranges from 1 to 14 days. [1]

Clinical manifestations of COVID-19 in children

The reported signs and symptoms in children have been similar to those observed in adults, though often less severe, especially those below 10 years of age. Nonetheless, cases of critical illness have been reported. As with adults, pre-existing medical conditions have been suggested as a risk factor for severe disease and intensive care admission in children. [1] [10] [11]

The most common clinical signs and symptoms in children 0-19 years old were fever (50%–59%) and cough (40%–49%), followed by sore throat/pharyngeal erythema (10%–19%), dyspnea/shortness of breath (10%–19%), and rhinorrhea/nasal congestion (10%–19%). Symptoms reported in less than 10% of children included myalgia, fatigue, diarrhea, vomiting, nausea, headache, and dizziness. However, gastrointestinal manifestations sometimes were the initial and even the only symptoms of COVID-19 infection in children, including abdominal pain, diarrhea, nausea, and vomiting. Olfactory and gustatory anomalies characteristic of adult COVID-19 cases were rare in pediatric populations. [5] [10] [12] [13]

Lu et al. (2020), in a study conducted in Wuhan, China, found the main symptoms in 171 children with COVID-19 to be cough (48.5%), pharyngitis (46.2%), fever (41.5%), diarrhea (8.8%), fatigue (7.6%), rhinorrhea (7.6%), and vomiting (6.4%); and only 2.3% of cases experienced oxygen desaturation upon hospitalization, while 15.8% of cases were asymptomatic. [14]

Moreover, studies have found fever (children 56% vs. adults 71%), cough (children 46% vs. adults 80%), and shortness of breath (children 13% vs. adults 43%) at a lower frequency in children as compared to adults. [13]

The signs and symptoms of COVID-19 in children are similar to those of other infections and non-infectious processes, including influenza, streptococcal pharyngitis, and allergic rhinitis. The lack of specificity of signs or symptoms and the significant proportion of asymptomatic infections make symptom-based screening for identification of COVID-19 in children particularly challenging. [15]

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Clinical manifestations in infants less than 1 year

Clinical manifestations in infants were similar to those reported for older children, with fever and cough being the most common findings. The most common clinical signs and symptoms reported in infants less than 1 year were fever (16%–73%), cough (8%–38%), rhinorrhea/congestion (6%–50%), gastrointestinal symptoms (9%–33%), and other respiratory symptoms (3%–41%). [5]

Differential diagnosis for COVID-19

The following conditions are included in the differential diagnosis of COVID-19:

- Adenovirus infection – adenoviruses are non-enveloped, double-stranded DNA viruses. The site of entry generally determines the site of infection; respiratory tract infections result from droplet inhalation, while gastrointestinal tract involvement results from fecal-oral transmission. Severe morbidity and mortality associated with adenovirus infections are rare in immunocompetent hosts. However, mortality rates may be as high as 70% in immunocompromised individuals. Adenovirus infection typically affects children from infancy to school age, but children of any age may be affected, including neonates. Young adults in any setting of close quarters and stress may be affected, as in the case of military trainees.
- Bacterial pneumonia – is caused by a pathogenic infection of the lungs. The most consistent presenting symptom of bacterial pneumonia is cough productive of sputum.
- Chlamydia pneumoniae – *Chlamydophila pneumoniae*, *Chlamydophila psittaci*, and *Chlamydia trachomatis* can cause pneumonia in humans. *C. pneumoniae* causes mild pneumonia or bronchitis in adolescents and young adults and can be transmitted from person-to-person via respiratory secretions. Infected birds (e.g., cockatiels, parrots, parakeets, macaws, chickens, ducks, turkeys, pigeons, and sparrows) can transmit *C. psittaci* to humans via a respiratory route through direct contact or aerosolization. *C. trachomatis* infection can be transmitted to a neonate during birth via the birth canal of an infected woman. *C. trachomatis* infection may cause neonatal conjunctivitis, nasopharyngitis, otitis media, and pneumonitis.
- Human metapneumovirus infection – is a respiratory viral pathogen that causes a spectrum of illnesses that range from asymptomatic infection, mild upper respiratory tract symptoms to severe bronchiolitis[1] and pneumonia. Human metapneumovirus infection is prevalent during infancy and early childhood. By age 5 years, seroprevalence data suggest infection in all (or nearly all) individuals.
- Influenza – is the one of the most significant causes of acute upper respiratory tract infections globally. Influenza viruses cause a broad array of respiratory illnesses responsible for significant morbidity and mortality in children.
- *Mycoplasma pneumoniae* infection – *M. pneumoniae* bacteria spread from person-to-person contact by respiratory droplets and is exclusively a human pathogen. *M. pneumoniae* infections can occur in the upper or lower respiratory tract. Children

[1] Bronchiolitis is an acute inflammatory injury of the bronchioles that is usually caused by a viral infection. The condition may occur in persons of any age, but severe symptoms are usually evident only in young infants.

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younger than 3 years primarily develop upper respiratory infection. *M. pneumoniae* infection is uncommon in the first year of life; however, in neonates, it may cause severe respiratory disease and extrapulmonary illness. *M. pneumoniae* infection is common in school-aged children and adolescents, with the highest rate of infection in individuals aged 5-9 years, in whom the tendency is to develop bronchitis and pneumonia.

- Human parainfluenza virus infection – human parainfluenza viruses primarily affect young children, in whom the pathogenic spectrum includes upper and lower respiratory tract infections. These viruses are responsible for 30%–40% of all acute respiratory tract infections in infants and children, including common cold with fever, laryngotracheobronchitis (croup), bronchiolitis, and pneumonia.
- Respiratory syncytial virus infection – is the leading cause of lower respiratory tract infections in infants and young children, primarily manifesting as bronchiolitis or viral pneumonia. The peak incidence of severe respiratory syncytial virus (RSV) disease is at age 2-8 months.
- Rhinovirus infection – rhinoviruses are the most common cause of the common cold. They chiefly cause upper respiratory tract infections but may also infect the lower respiratory tract. Potential complications of infection include otitis media, sinusitis, chronic bronchitis, and exacerbations of reactive airway disease (e.g., asthma). Although rhinovirus infections occur year-round, the incidence is highest in the fall and spring.
- Severe acute respiratory syndrome (SARS) – is a serious, potentially life-threatening viral infection caused by the SARS-associated coronavirus (SARS-CoV). Since the 2002-2003 outbreak of SARS, global efforts have virtually eradicated SARS as a threat and since then no further cases have been reported. [16] [17] [18] [19] [20] [21] [22] [23] [24] [25] [26] [27]

Disease severity

Reported disease severity of infected children range from asymptomatic to mild, moderate, severe, and critically ill, based on clinical features, laboratory testing, and radiographic chest imaging. The table below depicts the clinical features of cases classified by disease severity.

Clinical features in pediatric COVID-19 cases according to disease severity

Severity	Clinical Features
Asymptomatic	Positive PCR test without clinical manifestations or radiologic findings (e.g., normal chest imaging results)
Mild	Symptoms of acute upper respiratory tract infection, including, low- or high-grade fever, fatigue, myalgia, sore throat, headache, sneezing, dry cough, runny nose, and nasal congestion. Some may have no fever or have only gastrointestinal symptoms, such as nausea, vomiting, abdominal pain, and diarrhea. Non-severe pneumonia on chest imaging.
Moderate	Lower respiratory tract infection symptoms, fever, dry or productive cough, wheezing, and positive findings on chest imaging.

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Severe	Rapid progression of the disease with dyspnea, central cyanosis, increased respiratory rate above 70/min for infants and above 50/min for children above the age of 1 year, coma, convulsions, somnolence, severe dehydration, and oxygen saturation below 92%.
Critical	Rapidly progressing to acute respiratory symptoms, respiratory failure, and end organ damage, such as heart failure, shock, acute kidney injury, liver injury, encephalopathy, coagulopathy, or myocardial damage.

[7] [12] [28]

Disease severity of COVID-19 in children

Public Health Ontario (PHO) (2020) conducted a systematic, umbrella review (i.e., a review of systematic reviews and meta-analyses) of literature published from January 1 to September 21, 2020. According to their review, most children (80%–89%) experienced mild to moderate disease severity and approximately 10% to 19% of children were asymptomatic. Severe COVID-19 infection in children was rare, with less than 0.1% to 7.0% of all cases considered severe (e.g., requiring hospitalization, breathing support). Similar to severe infections, PHO's review found that critical COVID-19 illness in children was rare, with less than 0.1% to 14.9% of all cases considered critical (e.g., requiring ICU admission), with most studies reporting critical infections in less than 10% of children. [5]

A systematic review by Hoang et al. (2020), comprising 7,780 pediatric patients, reported 3.3% had critical infections. Mortality rates in children were exceedingly rare and were less than 0.4%. [29]

In a study by Dong et al. (2020), among 2,135 children in China, disease severity was lower. For example, 94% had asymptomatic, mild, or moderate disease, 5% had severe disease, and <1% had critical disease. Their data found that severe or critical illness was more common in infants and young children than in older children. More than 10% of infants had severe or critical illness compared with 7% of children aged 1-5 years, 4% of those aged 6-10 years, 4% of those aged 11-15 years, and 3% of those aged 16 years or older. [7]

Current evidence suggests that infants (age <1 year) and children with certain underlying medical conditions might be at increased risk for severe illness from SARS-CoV-2 infection. Of the children who have developed severe illness from COVID-19, most have had underlying medical conditions, such as:

- Asthma and other chronic lung diseases
- Diabetes
- Genetic, neurologic, or metabolic conditions
- Sickle cell disease
- Congenital heart disease
- Immunosuppression
- Medical complexity (e.g., multiple chronic conditions)
- Obesity
- Chronic kidney disease [15]

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Complications experienced by children with COVID-19
Similar to adults, children with serious COVID-19 may develop respiratory failure, myocarditis, shock, acute renal failure, coagulopathy, and multi-organ system failure. Some children with COVID-19 have developed other severe problems, such as intussusception[2] or diabetic ketoacidosis. Children infected with SARS-CoV-2 are also at risk for developing multisystem inflammatory syndrome in children (MIS-C). Guillain-Barré syndrome (GBS) has also been reported in children, although uncommon. The long-term sequelae in children are not well-understood; however, as research accrues, additional long-term impacts will be elucidated. [5] [15]

Multisystem inflammatory syndrome in children (MIS-C)
Multisystem inflammatory syndrome in children (MIS-C), also known as paediatric inflammatory multisystem syndrome (PIMS), is a rare syndrome seen in children approximately 3 to 6 weeks after they have been exposed to SARS-CoV-2. MIS-C has been reported to share features of typical or atypical Kawasaki disease or toxic shock syndrome. [30]

The WHO preliminary case definition for MIS-C states that cases should be suspected in children and adolescents 0-19 years of age with fever for ≥ 3 days and two of the following signs or symptoms:

a. Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet)
b. Hypotension or shock
c. Features of myocardial dysfunction, or pericarditis, or valvulitis, or coronary abnormalities (ECHO findings or elevated Troponin/NT-proBNP)
d. evidence of coagulopathy (abnormal PT, PTT, elevated D-Dimers)
e. acute gastrointestinal problems (diarrhea, vomiting or abdominal pain)

and

- elevated markers of inflammation, such as ESR, C-reactive protein or procalcitonin

and

- no other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes

and

- evidence of COVID-19 (RT-PCR, antigen test or serology positive) or likely contact with patients with COVID-19 [31]

Common signs and symptoms of MIS-C
Signs and symptoms include persistent fever, inflammation (based on laboratory test results), and evidence of organ dysfunction or shock.
Other common symptoms include:

- Kawasaki disease-like features: conjunctivitis, red eyes; red or swollen hands and feet; rash; red cracked lips; and swollen glands. In some children, coronary artery

[2] Intussusception is a serious condition in which part of the intestine slides into an adjacent part of the intestine. This telescoping action creates a blockage or obstruction and also prevents blood supply to the affected part of the intestine, which can lead to perforation, infection, and death of the bowel tissue.

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enlargement and/or aneurysms have been described. Some children presenting with Kawasaki disease-like syndrome have been noted to have a broader age range and presentation with more gastrointestinal (abdominal pain or diarrhea) and neurologic (headaches/meningitis) manifestations.

- Gastrointestinal symptoms, such as abdominal pain, diarrhea, nausea/vomiting; patients have presented with colitis, hepatitis, and questionable appendicitis.
- Toxic shock syndrome-like features with hemodynamic instability and poor heart function. Cytokine storm/macrophage activation or hyperinflammatory features.
- Thrombosis or acute kidney injury.
- Shortness of breath suggestive of congestive heart failure or pulmonary embolism.
- Respiratory symptoms typically reported in adults with COVID-19 may not be present in pediatric patients with MIS-C. [32]

Note that not all children will have the same signs and symptoms, and some children may have symptoms not listed above. 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 had been infected. [33]

Causes of MIS-C

The exact cause of MIS-C is unknown, but it has been linked to SARS-CoV-2. However, many children with MIS-C may test negative for a SARS-CoV2 infection and they may not have a history of symptoms consistent with the virus. It is not known if some children are more likely to develop MIS-C considering that most affected children do not have underlying health conditions. Further, this syndrome can affect children of all age groups and ethnic backgrounds. However, older children and children of Afro-Caribbean, Hispanic, and South Asian descent seem to be at greater risk of developing MIS-C. [30]

Incidence of MIS-C

MIS-C is a very rare syndrome. For example, as of March 1, 2021, the CDC reported 2,617 MIS-C cases that met the case definition and 33 deaths attributed to MIS-C in the US. During the same time period, there were over 3,284,000 COVID-19 pediatric cases and 266 child deaths from COVID-19 in the US. [34] [35]

MIS-C treatment

Treatments have consisted primarily of supportive care and directed care against the underlying inflammatory process. Supportive measures have included:

- Fluid resuscitation
- Inotropic support[3]
- Respiratory support; and

[3] Inotropic agents are medications that change the force of muscle contractions, particularly those of the cardiac muscle. There are two kinds of inotropes: positive inotropes that strengthen the force of the contraction and negative inotropes that weaken the force of the contraction. Intensive care patients often require inotropic support to stabilize circulation and to optimize oxygen supply.

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- In rare cases, extracorporeal membranous oxygenation (ECMO)[4]

Anti-inflammatory measures have included the use of intravenous immunoglobulin (IVIG)[5] and/or corticosteroids. The use of other anti-inflammatory medications and the use of anti-coagulation treatments have been variable. Aspirin has commonly been used due to concerns for coronary artery involvement, and antibiotics are routinely used to treat potential sepsis while awaiting bacterial cultures. Thrombotic prophylaxis is often used given the hypercoagulable state typically associated with MIS-C. Most children with MIS-C recover completely with timely medical care. [13] [33] [30]

Oral manifestations of MIS-C

Several oral manifestations related to MIS-C have been noted in the literature. For example, Verdoni et al. (2020) evaluated the first cluster of MIS-C cases reported in Italy. Out of 10 pediatric patients that presented with MIS-C symptoms, 6 (60%) patients had associated changes of the lips and/or oral cavity. [36]

Pouletty et al. (2020), in a study conducted in France, reported that 87% (14 of 16) of pediatric patients with MIS-C had dry cracked lips. [37]

Cheung et al. (2020) described oral mucocutaneous findings of lip redness and swelling in 53% (9 of 17) children with MIS-C in their study conducted in New York City. [38]

In a study by Whittaker et al. (2020), 29% (17 of 58) of children hospitalized in England with MIS-C presented with red cracked lips. [39]

Young et al. (2020) conducted a retrospective case series of 35 children (median age, 2 years [range, 0.2-17 years]) admitted to two hospitals in New York City between April 1 to July 14, 2020. The object of the study was to describe the mucocutaneous findings observed in children with MIS-C. Among the 35 patients, mucocutaneous changes included lip hyperemia (48% [17 of 35]), lip cracking (37% [13 of 35]), and prominent papillae noted on the dorsal surface of the tongue, consistent with "strawberry tongue"[6] (23% [8 of 35]). Other mucocutaneous findings included conjunctival injection[7] (60% [21 of 35]), palmoplantar erythema[8] (51% [18 of 35]), and malar erythema[9] (17% [6 of 35]). Recognition of mucocutaneous findings occurred a mean of 2.7 days (range, 1-7 days) after the onset of fever. The duration of mucocutaneous findings varied from hours to

[4] ECMO is an advanced form of temporary life support, to aid respiratory and/or cardiac function. It is based on cardiopulmonary bypass technology and diverts venous blood through an extracorporeal circuit and returns it to the body after gas exchange through a semi-permeable membrane. ECMO can be used for oxygenation, carbon dioxide removal, and haemodynamic support.
[5] IVIG is a therapy treatment for patients with antibody deficiencies, prepared from a pool of immunoglobulins (antibodies) from the plasma of thousands of healthy donors.
[6] Strawberry tongue describes a hyperplastic appearance of the fungiform papilla set against either a white (white strawberry tongue) or erythematous (red strawberry tongue) background. The condition usually reflects a systemic issue rather than an oral disorder.
[7] Conjunctival injection or hyperemia is red eye caused by dilation of blood vessels in the conjunctiva.
[8] Palmoplantar erythema is an inflammatory redness of the palms of the hands and soles of the feet.
[9] Malar erythema is defined as redness symmetrically involving the bilateral cheeks as well as the skin on the bridge of the nose.

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days (median duration, 5 days [range, 0-11 days]). Neither the presence nor absence of mucocutaneous findings was significantly associated with overall disease severity. There was no statistically significant difference between patients younger than 3 years (n = 17) and those aged 3 years or older (n = 18) with regard to the development of certain mucocutaneous symptoms. The authors concluded that a wide spectrum of mucocutaneous findings were identified in this case series. Despite their protean and transient nature, these mucocutaneous features serve as important clues in the recognition of MIS-C. [40]

Halepas et al. (2021) conducted a retrospective, cross-sectional study of 47 patients with COVID-19 and MIS-C hospitalized at a children's hospital in New York, New York, from March 15 to June 1, 2020. The purpose of the study was to report the rates of documented oral and oropharyngeal manifestations among these patients and to determine the association of these findings with other MIS-C symptoms.

The mean age of patients with MIS-C was 9.0 years (range, 1.3-20.0 years), and there was no obvious sex difference (51.1% male, 48.9% female). With respect to oral findings, 23 (48.9%) patients had red, cracked, or swollen lips, whereas only 5 (10.6%) had a strawberry tongue. Other oral manifestations were reported in 7 (14.9%) patients, which included oral sores (4 patients), mouth pain (1 patient), posterior oropharyngeal erythema (1 patient), and smile asymmetry and tongue deviation (1 patient). Oral or oropharyngeal findings were associated significantly with the presence of systemic rash and conjunctivitis.

The authors concluded that the presence of oral or oropharyngeal changes may be an early indicator of MIS-C and should be considered suggestive of MIS-C in the setting of COVID-19 infection. Oral healthcare providers may play an integral role both in the early detection of oral manifestations of MIS-C and in the identification of oral lesions in hospitalized patients with confirmed MIS-C. [41]

Multisystem inflammatory syndrome in adults (MIS-A)
There have also been several reports of a similar multisystem inflammatory syndrome in adults (MIS-A). Like children, adults who have had COVID-19 can develop symptoms of MIS-A days to weeks after becoming infected. It is a rare but serious condition. Adults with MIS-A may have various signs and symptoms, including fever, hypotension, gastrointestinal symptoms (e.g., abdominal pain, vomiting, diarrhea), neck pain, skin rash, extreme fatigue, and chest tightness and pain.

A working case definition of MIS-A includes the following five criteria: 1) a severe illness requiring hospitalization in a person aged ≥21 years; 2) a positive test result for current or previous SARS-CoV-2 infection (nucleic acid, antigen, or antibody) during admission or in the previous 12 weeks; 3) severe dysfunction of one or more extrapulmonary organ systems (e.g., hypotension or shock, cardiac dysfunction, arterial or venous thrombosis or thromboembolism, or acute liver injury); 4) laboratory evidence of severe inflammation (e.g., elevated CRP, ferritin, D-dimer, or interleukin-6); and 5) absence of severe respiratory illness (to exclude patients in which inflammation and organ dysfunction might be attributable simply to tissue hypoxia). [42] [43]

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Co-infections associated with COVID-19 in children

From the systematic review and meta-analysis conducted by Zheng et al. (2020) the proportion of coinfection ranged from 4.88% to 24%, with a pooled estimate of 10%, of which *Mycoplasma pneumoniae* (50%) and influenza virus or parainfluenza virus (22%) were the most common pathogens. The researchers also found other coinfecting viruses, such as adenovirus, syncytial virus, and Epstein-Barr virus. However, the authors were unable to determine whether children with coinfection were more likely to be immunologically susceptible to SARS-CoV-2 infection. Additionally, it is unknown whether the coinfected virus would cause increased coronavirus virus virulence or facilitate mutation or severe unidentified complications. The authors highlighted the importance of recognizing the possibility of coinfection in children and testing accordingly. [6]

Treatment for COVID-19

In general, treatment for the pediatric population is symptomatic and supportive. Treatment aims to provide rest, sufficient caloric intake, and maintain water and electrolyte balance. Treatment may include antipyretics for fever; sedatives in case of seizure; oxygen therapy, including mask, nasal catheter, high flow nasal cannula or invasive ventilation; and antibiotics for bacterial superinfection. In some cases, antiviral therapies are used as well. [12]

Prognosis and recovery

Most children with COVID-19 have mild clinical manifestations, if any, and generally require only supportive care. Children typically have a good prognosis and recover within 1–2 weeks after disease onset. [12] [44] [45] [46]

Take home messages

Children form a small proportion of reported cases to date. Most of the infected pediatric patients are asymptomatic, or exhibit mild disease, usually recovering in 2 weeks from the onset of symptoms. Infants have the highest risk of developing severe and critical disease. In addition, children with underlying medical conditions are more likely to experience complications requiring hospital admission.

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