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# An Insight of COVID-19 and Wheezes among Children

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## Abstract

Wheezing is a relatively high-pitched whistling noise produced by the movement of air through narrowed or compressed small airways. It is common in the first few years of life and is typically caused by viral respiratory tract infection or asthma, but other possible causes include inhaled irritants or allergens, esophageal reflux, and heart failure. Pediatric coronavirus disease 2019 (COVID-19) has now been documented to be a milder illness worldwide. Viral respiratory tract infections are the most common triggers of wheezing illnesses in children. With the ongoing pandemic, a rapid increase in wheezing-related illnesses may be theoretically anticipated. However, COVID-19 induced wheezing is currently thought to be rare. On a related note, a recently published online survey of members of the Pediatric Asthma in Real Life thinks tank and the World Allergy Organization Pediatric Asthma Committee also suggested that COVID-19 is not associated with acute onset wheezing in children with underlying asthma.

**Keywords**: Wheezes, COVID-19

## Background

Wheezing is a relatively high-pitched whistling noise produced by the movement of air through narrowed or compressed small airways. It is common in the first few years of life and is typically caused by viral respiratory tract

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infection or asthma, but other possible causes include inhaled irritants or allergens, esophageal reflux, and heart failure. Wheezing in early life is a common disorder, with approximately 50% of children having an episode of wheezing in the first year of life **(1).**

Data have confirmed that wheezing is clinically heterogeneous in early life in terms of its temporal pattern (i.e., age of onset and duration until symptoms disappear) and its risk factors, which include atopy and genetic or environmental factors, and the outcomes are different for such phenotypes **(2).**

A recurrent wheeze is estimated to occur in one-third of children of preschool age and can cause significant morbidity, decrease quality of life, and increase the frequency of the use of health care services and economic costs **(3).**

**Epidemiology**

Wheeze in young children is very common. Approximately 30%-50% of children under the age of five years will have wheeze at some point. It is usually caused by a virus and is usually called a viral-induced wheeze. The virus causes the breathing tubes in the lung to become swollen and narrow, causing a wheeze. Children who have other conditions affecting their lungs or have eczema/food allergies/family history of asthma may be more likely to get wheezing with a virus **(4).**

Virus-induced wheeze is not only a burden in early childhood, but also may be one of the causes or signs of childhood asthma. Therefore, clarifying the risk factors for virus-induced wheezing in epidemiological studies can and have provided clues about the pathogenesis of asthma **(5).**

Epidemiologic studies have shown a correlation between the seasonality of viral upper respiratory tract infections—particularly respiratory syncytial virus (RSV) and human rhinovirus (HRV)—and asthma exacerbations. In the northern hemisphere, RSV infections are most common during the midwinter months. These are months when infants are more likely to be seen in clinics, emergency rooms, and the hospital for acute attacks of wheezing **(3).**

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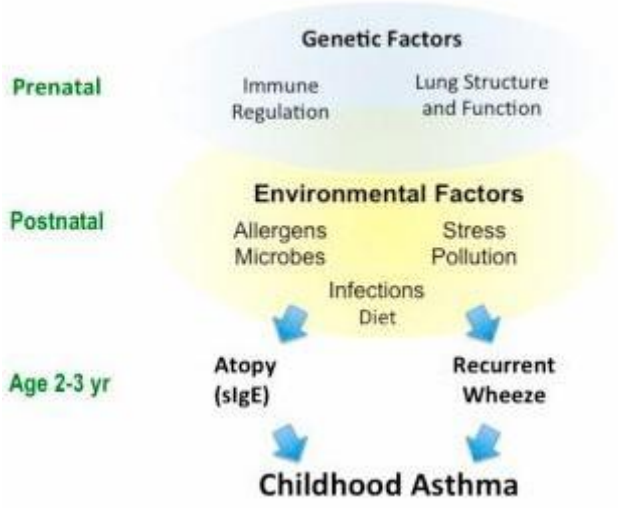
In a time/trend analysis, the seasonal patterns of respiratory tract infections and hospital admissions were evaluated for older children and adults. A particularly strong correlation was found between the seasonal pattern of upper respiratory tract infections, particularly HRV, and hospital admissions for asthma among children. Upper respiratory tract infections and admissions for asthma also are more frequent during periods of school attendance and less frequent during school holidays **(6).**




**FigureI:**Riskfactorsforvirus-inducedwheezingandchildhoodasthma**(7).**

Although wheezing is very common in children, its pathophysiology is complex and not well understood. Multiple factors play a role in wheezy conditions and include anatomical, genetic, environmental, and immunological factors that can interact with each other and affect airway patency **(2).**

Airflow obstruction is affected by the caliber of the airway and compliance of the child's lung. Resistance to airflow through the airway is inversely related to the radius of the tube to the power of 4. A small amount ofadditional narrowing of the airway can cause further flow limitation and a subsequent wheeze, especially in infancy **(8).**

During infancy, the very compliant chest wall and inward pressure produced during expiration lead to the collapse of the intrathoracic airway and a

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consequentially wheezy chest, and this is why most children outgrow this type of wheeze as they get older, and their airway becomes larger **(8).**

## COVID-19

SARS-CoV-2 (or 2019-nCoV) is the causative agent for COVID-19. This virus belongs to lineage B of the β-coronavirus genus. Coronaviruses are relatively large enveloped, positive-sense, single-stranded RNA (~30 kb) viruses. The SARS-CoV-2 genome encodes four structural proteins and other accessory or non-structural proteins (including the viral pp1a- pp1ab replicate, the 3C-like protease (3CLpro), the papain-like protease (PLpro), and the RNA-dependent RNA-polymerase (RdRp)) **(9).**

Functional studies have also demonstrated that SARS-CoV-2 S proteins utilize transmembrane serine protease 2 in addition to ACE2 for entry into the host cell. The following binding through the receptor-binding domain (RBD) of the *S* glycoprotein, the *S* protein undergoes large-scale conformational changes that allow the virus to endocytose into the cell cytoplasm where it undergoes replication **(10).**

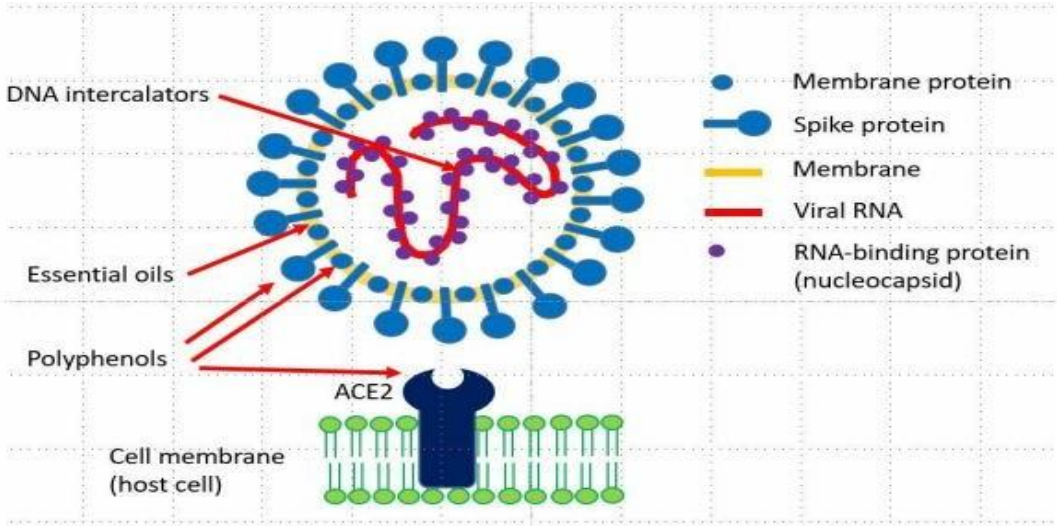


Figure 2: A simplified and schematic structure of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which can bind to a cellular receptor

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ACE2 of a host cell with its spike proteins. Targets for antiviral drugs (essential oils, polyphenols, and DNA intercalators) are indicated by red arrows **(11).**

Like other coronaviruses, SARS-CoV-2 replicates using a mechanism of continuous RNA synthesis but conducts transcription through a discontinuous process unique in the RNA virus world and is a characterizing feature of the *Nidovirales*order **(12).**

Coughing and sneezing generate large respiratory droplets (>5 μm) whereas exhaling and regular talking generate small aerosols (≤5 μm). In a study of facemask efficacy in reducing spread in respiratory viruses, coronavirus was found to only be detectable in samples of respiratory droplets and aerosols collected from patients not wearing facemask coverings. Because the previous SARS-CoV-1 virus could be detected in patient tears, and the current SARS-CoV-2 is transmitted through fomites and droplets that could contact the eyes, eyewear protection is necessary for spread prevention **(13).**

The pandemic's rapid global spread is partially attributed to asymptomatic transmitters of disease that would go on to develop symptoms after creating clusters of outbreaks. Early symptomatic presentation trendslead research to suggest a median incubation period of approximately five days **(14).** A previous study asserts that the incubation period is longer, lasting nearly eight days with 10% of patients demonstrating the first onset of symptoms after 14 days **(15).** This is a public health concern as the current quarantine guidelines suggest only a 14-day quarantine in those with suspected exposure**(12).**

Although asymptomatic transmission of COVID-19 occurs at a high rate, andthe entirely asymptomatic course is unlikely, totaling up to as few as 1% of cases **(16).** The asymptomatic incubation period is better thought of as a pre-symptomatic period. Because the WHO classification of disease starts with clinical presentation, and symptomology can take more than 14 days to present, prompt recognition of signs and symptoms is paramount to halt the spread of the

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disease. The most reported and reliable presenting features of COVID-19 infection are fever and cough **(17).** Other frequent presenting symptoms include fatigue, myalgia, and dyspnea. Atypical symptoms of infection include chills, gastrointestinal (GI) upset, and neurological changes **(18)**

Fever and dyspnea

A meta-analysis compared clinical features and outcomes of COVID-19 patients between those classified as severe ICU and non-severe ICU. Fever and dyspnea were significantly associated with severe disease, though increased fever >39 °C was not statistically significant between groups. Other symptoms such as cough, nausea, headache, sore throat, diarrhea, myalgia, and fatigue were not statistically favored by either group **(19).**Consistent with these findings, Xiang et al. found dyspnea to be the most valuable prognostic

indicator of severe pathology, regardless of independent patient risk factors, high fever, headache, and diarrhea as statistically insignificant concerning prognosis.

Chills are not a highly prevalent manifestation of COVID-19 infection, but when stratified against other clinical features and lab findings, they show strong positive correlations with diagnostic markers of infection. Chills demonstrate a strong negative correlation to age and lymphopenia, which are associated with worse clinical outcomes **(20).**

Limited data have been collected regarding chills as a feature of the disease. Still, these data suggest chills to be helpful in diagnosis and as an excellent prognostic indicator of disease course.

**Gastrointestinal Manifestations**

Gastrointestinal (GI) symptoms were overlooked in early studies due to low prevalence, but recent data show prevalence can range from 5% to 61% **(21)**.

The ACE2 receptor is a known receptor for entry into host cells in both SARS-CoV-1 and SARS-CoV-2. High expression of this receptor has been

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detected in cells of the lungs and intestinal mucosa. Viral shedding has been detected in fecal samples and on objects such as toilets and sinks that encounter fecal matter, lending credence to the plausibility of fecal-oral transmission **(22).**

Though most studies have found diarrhea and other GI symptomatology to be insignificant concerning disease severity, one meta-analysis demonstrated the presence of GI symptoms in 17.6% of patients with a higher prevalence among severe COVID-19 patients, and a study of pediatric patients found GI symptom prevalence in 43% of severe cases **(18)**

**Neurological Manifestations**

Data on neurological pathology in COVID-19 patients is not extensive because it was not initially considered a manifestation of the disease. A study of hospitalized patients showed 36.4% of patients had nervous system manifestations, including central nervous system (CNS), peripheral nervous system (PNS), and skeletal muscle injury. Patients with severe infection (41%) were more likely to develop neurological manifestations, and some of these patients presented without typical symptoms of fever, cough, anorexia, and diarrhea **(23).**

The presentation of COVID-19 in children is variable, though the disease course is generally considered mild. Available data could be influenced by cluster testing that occurs when asymptomatic parent tests positive for COVID-19. It is possible that when children are tested, they are still within the pre-symptomatic period of the disease course**(24).**

A meta-analysis (n = 774) showed nearly all children who tested positive for COVID-19 only developed mild disease manifestation. An entirely asymptomatic course was reported in 19% of cases as compared to the 1% demonstrated in the adult population **(18)**

The WHO recommends that the decision for COVID-19 testing is based on clinical and epidemiological factors and should be linked to assessing the

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likelihood of infection **(25).** Epidemiological factors include anyone who has had close contact with a patient with laboratory-confirmed COVID-19 within 14 days of symptom onset or a history of travel from affected geographic areas within 14 days of symptom onset **(12).**

Criteria for testing symptomatic patients include the presentation of clinical manifestations, recent visits to COVID-prone countries, exposure to COVID-19 patients, and detecting the resolution of the disease. Criteria for testing asymptomatic patients include a known recent exposure to COVID-19 patients, unknown exposure to COVID-19 patients, olfactory dysfunction, the loss of smell and/or taste, transplant donors, and recipients **(12).**

Viral testing detects the SARS-CoV-2 nucleic acid or antigen. Presently, suspected patients with COVID-19 are confirmed with viral RNA detection by nucleic acid amplification tests (NAAT) **(25).**

Polymerase chain reaction assay (PCR) is the gold standard test for the molecular diagnosis of viral or bacterial infections due to its high specificity and sensitivity. NAAT methods, including reverse-transcription polymerase chain reaction (RT-PCR), real-time RT-PCR (rRT-PCR), and reverse transcription loop-mediated isothermal amplification **(26).**

Computed tomography (CT) imaging has been routinely performed on COVID-19 patients. Chest CT is strongly recommended in suspected COVID-19 cases for initial evaluation and follow-up due to the respiratory system being primarily affected **(27)**

As with mild cases, febrile moderate COVID-19 cases should be tested and treated for other endemic infections that cause fever (i.e., malaria, dengue, etc.) per routine protocol if necessary, irrespective of the presence of respiratory signs and symptoms due to the possibility of coinfection. Patients with suspected or confirmed moderate COVID-19 should not be administered antibiotics unless under the clinical suspicion of bacterial infection. However, a recent systematic

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review reported only 8% of patients were hospitalized with COVID-19-experienced secondary bacterial infection/fungal coinfection during hospital admission. For older patients, particularly those in long-term care facilities, and children less than five years of age, providing empiric antibiotic treatment for possible pneumonia should be considered **(12).**Given these patients arenot hospitalized, access to antibiotic treatment (e.g., co-amoxicillin) is sufficient, and the preferential treatment is broad-spectrum antibiotics.Hospitalized patients should be regularly monitored for vital signs using pulse oximetry while utilizing medical early warning scores (i.e., National Early Warning Score-2 [NEWS2] and Pediatric Early Warning Scores [PEWS]) that facilitate the early recognition and escalation of treatment for deteriorating patients. At-home patients and caregivers should receive counseling on signs and symptoms of complications (i.e., difficulty breathing, chest pain, etc.), informed to seek urgent care immediately if such complications arise **(25;12).**

According to the U.S. CDC, a limited number of individuals with severe illnesses may produce a replication-competent virus beyond 10 days of onset (typical isolation protocol), which may warrant the extension of the duration of isolation and precautionary measures for up to 20 days after symptom onset. With this in mind, consultation with infection control experts would be beneficial **(12).**

The FDA approved 2020; the antiviral drug, remdesivir, to treat COVID-19. Remdesivir is for use in adult and pediatric patients 12 years of age and older and weighing at least 40 kg (88 pounds) for the treatment of COVID- 19 that requires hospitalization. Remdesivir can be administered in a hospital or treatment facility capable of delivering acute care equivalent to inpatient hospital care. Remdesivir is the first medication for COVID-19 to be approved by the FDA **(25).**

Although complications of both diseases can be similar, the onset of influenza complications and the severe disease usually occur within a week of

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illness onset, as opposed to severe COVID-19 that occurs in the second week of illness. This overlap in signs and symptoms requires diagnostic testing for both viruses while they are cocirculating to distinguish between the two or to identify coinfection that has been reported with both influenza A and B viruses with SARS-CoV-2. At this time, there is no information on the frequency, severity, and risk factors for coinfection with these viruses versus either alone **(12).**

Children and adolescents usually demonstrate fewer and milder symptoms of SARS-CoV-2 infection compared to adults and are less likely than adults to experience severe COVID-19**(28).**

Wheeze is often clinically diagnosed as requiring no further tests, but patients who continue to have recurrent or persistent wheeze should be investigated by, for example, chest X-rays, which are mainly used to identify structural anomalies or other underlying conditions, such as foreign body aspirations **(29).**

Chest radiography is indicated in children who present with unexplained wheezing that is unresponsive to bronchodilators or with recurrent wheezing. Plain-film radiography can identify congenital anomalies of the lung, parenchymal lung disease, and some foreign bodies and cardiac abnormalities **(30).**

If radiography is normal and the child continues to wheeze, bronchoscopy should be the next step to rule out a congenital anomaly **(29).**

Short-acting and rapidly acting $\beta_2$-agonists are the most popular and most commonly used first-line bronchodilators used to treat acute symptoms including wheeze, cough, and shortness of breath. Furthermore, these drugs are more effective than placebos in controlling acute wheezing in children younger than 2 years but may not achieve clinically significant improvements. However, the presence of wheeze alone with no other condition may be best treated with observation alone or investigation of the potential underlying cause. Therapies

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can be initiated if wheeze is associated with increased difficulty in breathing **(31).**

If the patient is young (less than 6 months old), the best option is a referral to a tertiary center for a detailed evaluation. If the baby is more than 6 months old, two main factors should be considered: whether the patient is atopic and the severity of the wheeze episode **(32).**

Inhaled steroids can be used in recurrent wheeze in the presence of positive indicators with careful monitoring of efficacy. This treatment is effective in persistent and late-onset wheezing, but it is not as effective in transient wheezing, in which its effects are similar to those observed in viral-induced wheeze **(33).**

## Spectrum of Respiratory Clinical Presentation of COVID-19 in Children Wheezing:

The systemic review study of **de Souza et al. (34)**examined 1124 pediatric cases and stratified COVID-19 symptoms based on their severity and frequency. According to the study, once infected with SARS-CoV-2, a child might follow one of the following clinical patterns:

1. **Asymptomatic infection** (14.2% of cases). These children have no clinical symptoms, and the infection is confirmed by a positive nucleic acid test.

2. **Mild disease** (36.3% of cases). A child develops the symptoms of an illness of the upper respiratory tract, and the most common is fever. Other symptoms include cough, myalgia, sore throat, nasal catarrh, and sneezing. Fewer children might present with gastrointestinal symptoms, such as abdominal pain, nausea, emesis, and diarrhea. The results of chest auscultation are unremarkable.

3. **Moderate disease** (46% of cases). This group of children presents with pneumonia.

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4. **Severe disease** (2.1% of cases). The initial manifestations might be a combination of symptoms of the respiratory and digestive tracts, followed by dyspnea and central cyanosis within a week. Oxygen desaturation below 92% is a striking feature.

5. **Critical cases** (1.2% of cases). A minority of infected children progress to acute respiratory distress syndrome with or without multiple organ dysfunction.

Egypt is one of the lower-middle-income countries with limited resources which require a simple and practical clinical guideline to diagnose and treat COVID-19 cases, as well as to protect health care workers from catching infection**(25)**.

The study of **Abdel Baki et al.(1)**aimed to study the clinical and epidemiological characteristics of COVID-19 in Egyptian children. This is an observational retrospective cohort study performed at two specialized COVID-19 isolation hospitals in Egypt. This study include 40 COVID-19 confirmed pediatric patients (mean age, 9.4 years), 67.5% were male, 85% wereasymptomatic, and 15% had mild symptoms. There were no confirmed severe or criticallyillcasesamongthepatients.TheauthorconcludedthatCOVID-19 runsin abenign coursein Egyptian childrenwithnomortalityand no significant morbidity.

Due to the lack of a standardized score for COVID-19 patients, some cliniciansdependonotherpreviouslyvalidatedscores,suchasthelungultrasound aeration score. **Eltahlawi et al.(35)**designed a new scoring model including four items and tested its validity in predicting COVID-19 using bedsidelungultrasound(LUS)intheemergencydepartment(ED).Theyfound that all four items of a score were significant independent predictors forCOVID-19 infection by linear regression analysis. This score has high sensitivity (93.8%) in detecting COVID-19 infection, making it a good negative test. In patients with suspected COVID-19 or those presented to ED, applyingthis new score help

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physicians exclude those non-infected patients as a first screeningstepbeforedealingwiththem.Theapplicationofthisscoremayhave a good impact on the safety of medical personnel.

Regarding other investigations, CT chest shows more consolidation and ground glass appearance in COVID-19 infected patients. This is consistent with other reports showing prominent radiologic abnormalities were bilateral ground-glass opacity and subsegmental consolidation areas**(35)**.

The timely transfer of patients to ICU or a designated unit (isolation or quarantine) with sufficient rescue equipment should be considered even if their RT-PCR test results for pharyngeal swab specimens are negative to limit the spread of infection. According to laboratory findings **Eltahlawi et al. (35)**showed that COVID-19 infected patients had less blood $O_2$ saturation and less lymphocytic count than other causes of pneumonia. However, in our study, lymphopenia has not reached a significant degree of correlation with mortality.

A review systemic study of **Yasuhara et al.(36)**emphasizes that the majority of children with COVID-19 either remain asymptomatic or develop a less severe phenotype. Notwithstanding, some infants might be seriously ill, and some older children might develop a multi-system inflammatory syndrome necessitating admission to intensive care. They also reported that, three deaths, and they mentioned that "although most pediatric COVID-19 patients were not severe, a serious COVID-19 illness could result in severe outcomes including an ICU admission and even death in children".

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