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Review article

COVID-19 in children: current data and future perspectives

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Coronaviruses (CoVs) are a large family of enveloped, single-stranded, zoonotic RNA viruses that represent one of the major pathogens that primarily targets the respiratory system. CoVs are divided into 4 genera: alpha, beta, delta, and gamma; alpha and beta CoVs are known to infect humans (human coronaviruses - HCoVs).[1] They resulted previously in the severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV).[2] Since December 2019, a novel CoV (SARS-CoV-2) started to cause infections in humans, first reported in Wuhan, Hubei province, China, with a cluster of patients presenting with pneumonia. Afterwards, the novel CoV has quickly spread throughout the world.[3,4]

Genomic analyses suggest that the 2019-nCoV sequencing is closely related to the bat SARS-related CoV, but the pathogen was probably transmitted to humans by other animals which may have served as intermediate hosts facilitating the virus recombination and mutation, further adding to its genetic diversity.[5,6]Two different types of 2019-nCoV were identified, designated type L (accounting for 70 % of the strains) and type S (accounting for 30 %) but the difference between the two strains and clinical implications remain to be determined. The L type predominated during the early days of the epidemic in China but accounted for a lower proportion of strains outside of Wuhan.[7]

Infectivity and clinical presentation

Droplet transmission with the virus released in the respiratory secretions is the main mode of transmission, with increasing evidence towards aerosol transmission as well, while feco-oral transmission has not been documented yet.[8,9] Based on the published reports, the incubation period ranges between 1-24 days (median three days) and the median duration of viral RNA shedding from oropharyngeal specimens is 20 days (range of 8 to 37 days).[6,8]

The initial clinical sign of novel coronavirus disease 2019 (COVID-19) which allowed case detection was pneumonia. However, similar to other HCOVs, 2019-nCoV causes a wide spectrum of clinical manifestations in humans, ranging from a common cold like symptoms to more severe disease as pneumonia, severe acute respiratory distress syndrome, multiorgan failure and even death. The most common symptoms at onset are fever, cough, and fatigue, while other symptoms include sputum production, headache, hemoptysis and dyspnea. Gastrointestinal symptoms have also been reported.[9,10]

Preliminary evidence suggests that children are as likely as adults to become infected with 2019-nCoV but are less likely to be symptomatic or develop severe symptoms, which mean that children might not be tested for 2019-nCoV as frequently as adults. However, the importance of children remains in their ability to transmit infections even in asymptomatic cases.[11,12] On the other hand, older people and people of all ages with severe chronic medical conditions like heart disease, lung disease and diabetes, seem to be at higher risk of developing serious COVID-19 illness and have higher risk of COVID-19 related death.[13]

Data from China and USA reports suggest that a majority of COVID-19 related deaths have occurred among adults aged ≥60 years, particularly those aged above 85 years and those with underlying serious health conditions.[14,15] The period from the onset of COVID-19 symptoms to death ranged from 6 to 41 days with a median duration of 14 days.[16] ARDS is the main cause of death in COVID-19. One of the main mechanisms for ARDS is the cytokine storm with uncontrolled systemic inflammatory response resulting from the release of large amounts of pro-inflammatory cytokines (IFN-α, IFNγ-, IL-1b, IL-6, TNF- α, etc.) and chemokines leading to ARDS and multiple organ failure (figure 1). This feature might represent under-recognized secondary hemophagocytic lymphohistiocytosis (sHLH).[17] Although the virus stimulates both humoral and cellular immune mechanisms, however data showed that both CD4+ and CD8+ T cells, although activated, are significantly reduced in the peripheral blood of 2019-nCoV-infected patients.[18]

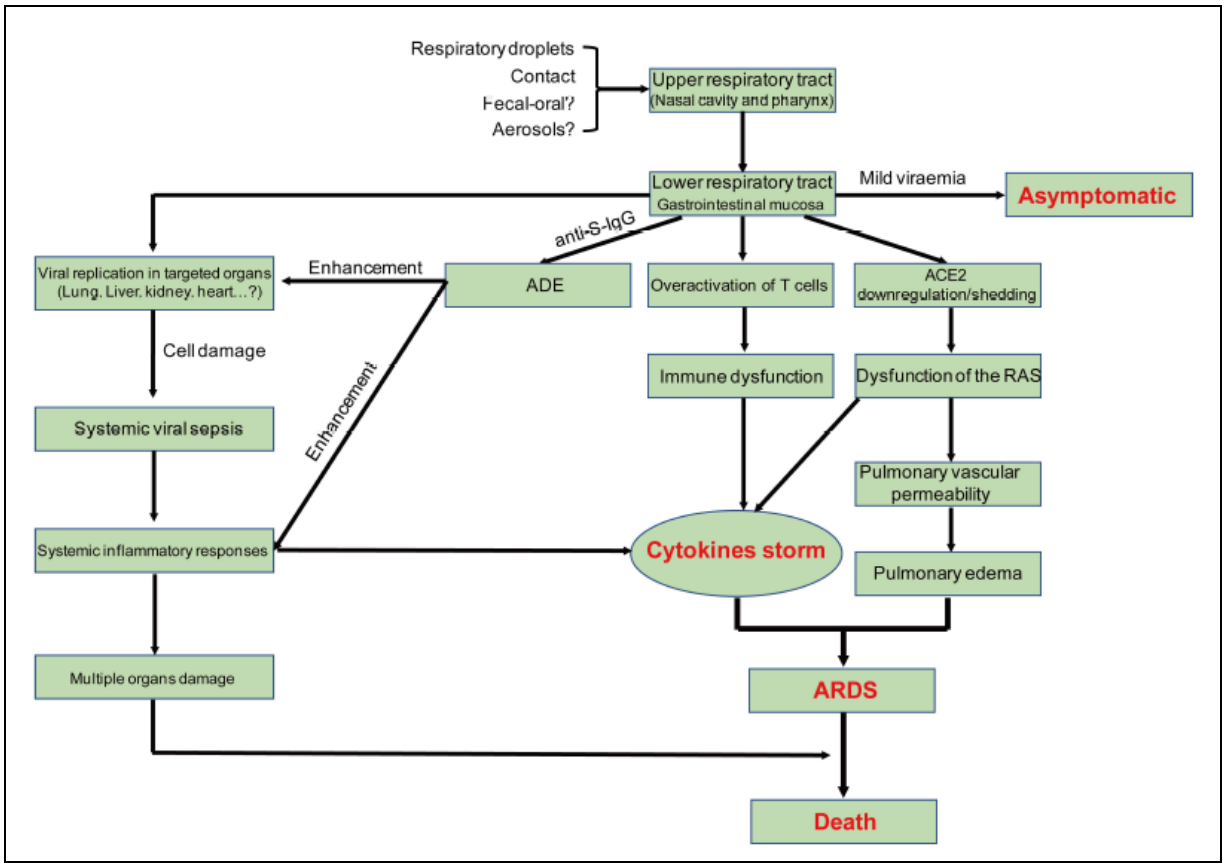

Figure 1. Postulated pathogenesis of SARS-CoV-2 infection (Quoted from Jin et al, 2020)[19]
ACE2: angiotensin-converting enzyme 2; ADE: Antibody-dependent enhancement; ARDS: acute respiratory distress syndrome. RAS: renin-angiotensin system. Red words represent the important turning points in SARS-CoV-2 infection.

Clinical presentation of COVID-19 in children

Liu et al analyzed the data of 6 COVID-19 confirmed cases out of 366 children, who were hospital admitted for respiratory infections. They noticed that these 6 children whose median age was 3 years (range 1-7 years) had moderate to severe respiratory distress, four had pneumonia and one was admitted to the intensive care unit. However, none of them died.[20]

The clinical and epidemiological findings of 25 COVID-19 confirmed children admitted in 100 hospitals across Hubei province were published. Forty percent of the cases were below the age of 3 years. Eight patients had upper respiratory tract infections, 15 had mild pneumonia while 2 patients aged 8-12 months old, boys, with underlying congenital heart disease, were admitted to the intensive care unit and received invasive mechanical ventilation, steroids and immunoglobulins.[21] Wei et al., described nine hospitalized infants diagnosed with COVID-19 in China, with age range of 1-11 months. Four had fever, two mild upper respiratory symptoms and one has been asymptomatic with the duration of hospital admission ranging between 1 to 3 days. None of them required mechanical ventilation. All of them were infected following an infected family member.[22] COVID-19 has also been reported in several neonates although there is no evidence for vertical transmission.[23] Recently, several infants were suspected to die from the disease with no confirmed causal relationship. US state of Illinois announced the death of an infant under one year of age who was positive for 2019-nCoV.[24]

By February 10, a total of 398 confirmed pediatric versus 10,924 adult cases were reported nationwide in China.[25] The data on 44,672 COVID-19 confirmed cases in China revealed that only 0.9% were less than 10 years of age and 1.2% between 10 and 20 years of age.[14] Qiu et al., analyzed the hospital medical records of 36 children (aged 1–16 years; mean age 8.3 [3.5] years) out of 661 COVID-19 confirmed cases from Ningbo and Wenzhou in China. Seventeen (47%) had mild (n=7) or no (n=10) symptoms, while 19 (53%) had mild pneumonia and no severe or critical cases were reported, while pulmonary ground-glass opacities were evident in 13 patients (64%). In comparison to adults, pediatric patients had a significantly lower prevalence of fever (36% for children versus 86%

for adults), cough (19% versus 62%), pneumonia (53% versus 95%), elevated C-reactive protein (3% versus 49%), and severe disease type (0% versus 23%). However, pediatric and adult groups were comparable in terms of leukopenia, lymphopenia and elevated myocardial enzymes. Worth to note is that COVID-19 pediatric patients had higher incidence of pneumonia, but less frequent upper respiratory tract symptoms as compared to those with H1N1.[25]

A larger cohort that included 2143 pediatric patients with COVID-19 from China, of whom 731 were laboratory-confirmed and 1412 were just suspected was analyzed. The median age of all patients was 7 years (range: 1 month-18 years). Cases were classified into asymptomatic infection (4.4%), mild (50.9%), and moderate (38.8%) while the severe and critical categories accounted for only 5.9% of cases and one death was encountered in a 14-year-old boy. Clinical manifestations of pediatric patients were generally less severe than those of adult patients.[27] Another report by Lu et al who analyzed the data of 171 children with confirmed SARS-CoV-2 of whom 27 were clinically and radiologically free, 12 had only radiological features of pneumonia and 3 required intensive care and mechanical ventilation. The three critical patients had underlying health conditions, namely leukemia, hydronephrosis and intussusception. The 10 months old boy with intussusception died 4 weeks after admission with multiorgan failure.[28]

Among the Italian population, children represented 1.2% of 22,512 COVID-19 confirmed cases, with no reports of death among children in one report.[29] In the US, children represented 5% of 4,226 COVID-19 cases and accounted for less than 1% of COVID-19 related hospitalizations until March 16, 2020 with no ICU admissions or deaths among persons aged ≤19 years.[30] The death of a 12 years old Belgian girl, 13 years old boy from UK and 16 years old girl from Paris who were all confirmed COVID-19 cases were recently reported; yet, there are no published details about their clinical background.[31]

The available data might not reflect the exact numbers of 2019-nCoV infected children, but it is obvious that children are more common to be asymptomatic or have milder symptoms in comparison to adults and have significantly lower hospitalization and mortality rates.[32] (figure 2)

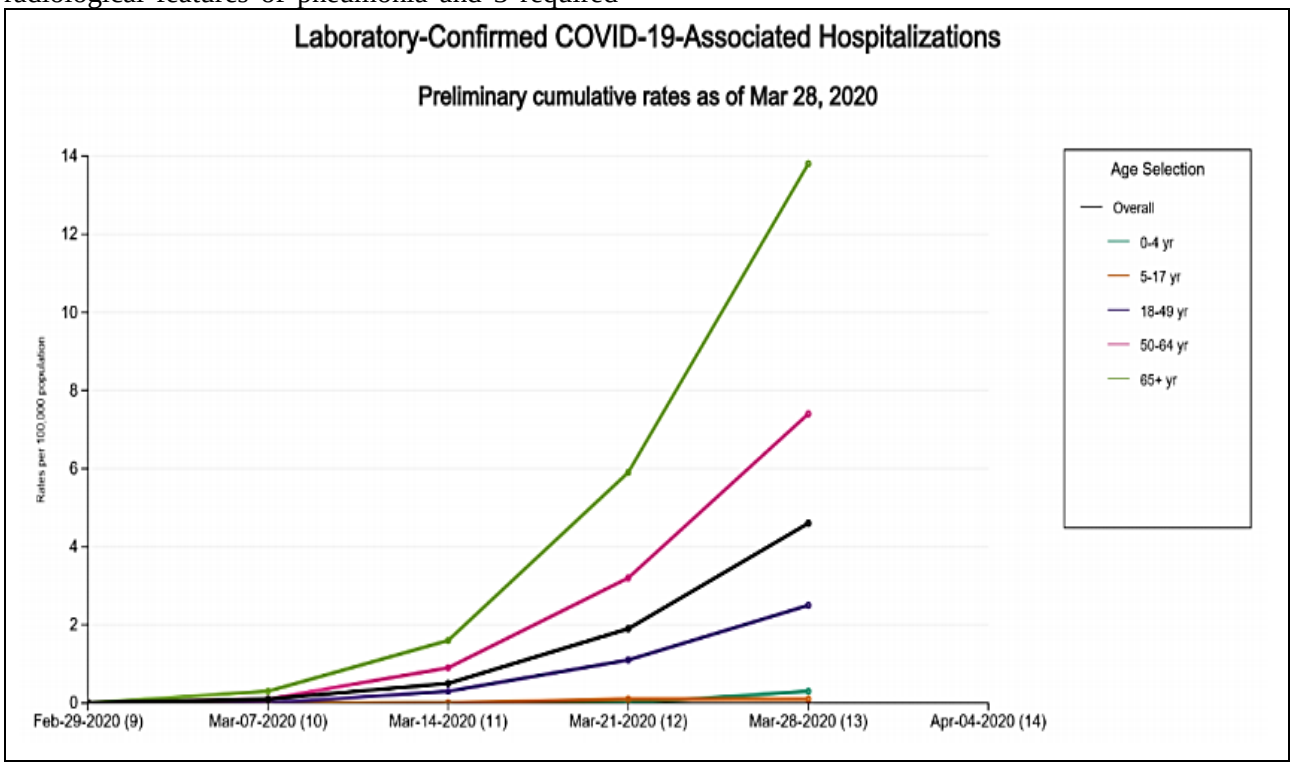

Figure 2. United States cumulative rates of laboratory-confirmed COVID-19-associated hospitalizations according to age group till March 28, 2020.
https://gis.cdc.gov/grasp/COVIDNet/COVID19_3.html [32]

What makes children less vulnerable to severe and/or fatal COVID-19?

None of the aforementioned reports convincingly explain why children are relatively tolerant to COVID-19 but not to other viral infections such as Ebola, influenza or measles. However, several speculations have emerged. One hypothesis relates this difference to a lower degree of maturation and function (e.g., binding ability) of the angiotensin converting enzyme II (ACE2) which is considered to be a cell receptor for the 2019-nCoV, leading to a relative resistance to the 2019-nCOV in children.[6] However, this speculation needs further investigations to validate. Another speculation relates it to the more active innate immune response and healthier respiratory tracts in the young children because they have not been exposed to as much cigarette smoke and air pollution as adults, in addition to fewer underlying chronic health disorders.[11] The presence of associated viral co-infection and/or respiratory tract bacterial colonization might have an impact but this assumption is not yet extensively investigated.

The phenomenon of immunosenescence may be involved in the explanation of COVID-19 age variability. It refers to the accelerated aging of the immune system, with the inability to mount an appropriate and effective immune response to challenge in the elderly.[33,34] With age, there is gradual decrease of naïve T cell numbers related to thymic involution. The thymus itself undergoes structural changes with a progressive decrease in the mass of functional tissues, and replacement by fat. Aging is also associated with shrinking of the TCR repertoire that determines antigenic diversity broadness with concomitant increased proportion of terminally differentiated oligoclonal effector memory T-cell populations. In addition, there is loss of the costimulatory receptor CD28, which is critical for complete T-cell activation. With aging, T cells gradually switch to a pro-inflammatory cytokine profile with increased production of IL-6, TNF-α and IFN-γ.[35-39] All these factors are expected to impair the immunological response of the elderly against newly encountered pathogens and might explain the enhanced COVID-19 cytokine storm among this age group.

Shortened telomere length in blood leukocytes might have a role as well. Telomeres are DNA-protein complexes at the end regions of chromosomes, decrease in length with every cell division and their shortening is associated with impaired immune response to new antigens together with increased synthesis of proinflammatory cytokines. CD8+ T cells were shown to have a higher rate of telomere shortening in comparison to other lymphocyte subsets. Advanced aging is associated with more prevalence of very short telomeres and hence poor immune response.[40-45] Eisenberg et al., investigated leukocyte telomere length among young men from 11 European countries and observed that Italian men showed the shortest while the Belgian had the longest telomere length among the studied countries.[46] Leukocyte telomere length was also found to be significantly longer among sub-Saharan Africans than in both Europeans and African Americans.[47] Furthermore, Zhu et al., who investigated 667 adolescents, noticed longer telomeres among black adolescents in comparison to white controls and girls had longer telomeres than boys.[48] Noteworthy, males were found to have higher rates of COVID-19 related morbidity and mortality than females.[49]

One may speculate that childhood obligatory vaccination may have a role in the mysterious under-expression of the disease in the pediatric age group. For instance, BCG (bacillus Calmette-Guérin) vaccine against tuberculosis was assumed by investigators from several countries to offer some protection. Australian researchers at the Murdoch Children's Research Institute in Melbourne are fast-tracking to see if a vaccine used for decades to prevent tuberculosis can protect from COVID-19. The trial of the BCG vaccine will be conducted with 4,000 health workers in hospitals around Australia to determine if it can mitigate COVID-19 symptoms. BCG is known to boost human 'frontline' innate immunity for prolonged periods following vaccination. Similar trials are being conducted in several countries including the Netherlands, Germany and the United Kingdom.[50] For instance, a randomized placebo-controlled study published in 2018 proved that BCG can protect against experimental infection with a weakened form of the yellow fever virus.[51]

What argues against this assumption is that BCG vaccination is compulsory in many countries that are bombarded with high rates of mortality from COVID-19 including China and Iran. Also, children from countries that do not include BCG in their vaccination program, including the US and most European nations, still have lower rates of morbidity and mortality from COVID-19. The results of the above-mentioned trials are awaited as are trials of specific vaccines against this dreadful virus.

In conclusion, COVID-19 is a highly contagious disease and its real burden in children including infection and/ or carrier state still needs to be identified by screening at a wider scale. The

forthcoming years may offer more comprehensive explanation to the mysterious lower morbidity and mortality of COVID-19 in infants and children who should theoretically be vulnerable to emerging micro-organisms such as SARS-CoV-2. Multinational, epidemiologic and molecular genetic studies are needed to identify possible racial differences in the Corona viruses' susceptibility and disease outcome. Integrated international efforts are needed to defy its global threat to humankind.

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