

# Outbreak of COVID-19 infection in children: fear and serenity

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**Abstract. – OBJECTIVE:** The recent outbreak of SARS-CoV-2 greatly involves the resources of the global healthcare system, as it affects newborns, adults, and elders. This infection runs in three major stages: a mild cold-like illness, a moderate respiratory syndrome and a severe acute interstitial pneumonia. SARS-CoV-2 infection seems to have a more benign evolution in children. As a matter of fact, low susceptibility and minor aggressivity have been highlighted in most cases. There are currently no effective antiviral drugs treatment for the affected children. No sufficient results have been reached by the use of interferon (IFN), lopinavir/ritonavir, orbidol, and oseltamivir in the treatment of the coronaviruses infection. The aim of this short review is to highlight the differences existing between COVID-19 cases in adults and children.

*Key Words:*

COVID-19, SARS-CoV-2, Children.

## Introduction

The recent outbreak of Coronavirus infection greatly involves the resources of the global healthcare system, as it affects in first line older adult and individuals already burdened by a great number of comorbidities. This novel Coronavirus may equally affect newborns, adults, and elders.

Since its first identification, this novel Coronavirus changed its name from “2019 novel coronavirus (2019-nCoV)”, to “severe acute respiratory syndrome coronavirus 2” (SARS-CoV-2), to better reflect the respiratory disorder which is the mainstay clinical sign of the severe disease<sup>1,2</sup>. SARS-CoV-2, the current taxonomical identifica-

tion for this virus, belongs to the beta-coronavirus together with the “Middle East Respiratory Syndrome “(MERS), and the “Severe Acute Respiratory Syndrome” (SARS) which have been responsible of previous severe outbreaks<sup>1</sup>. As suggested by Wilder-Smith et al<sup>3</sup> and Ceccarelli et al<sup>4</sup> several clinical aspects distinguish COVID-19 from SARS-CoV, including different infection period, transmissibility, clinical severity, and extent of community spread. SARS-CoV-2 replicates in the upper respiratory tract, mainly during the prodromal phase of the infection, reaching a high viral load which contributes to a quick spread of the virus. By contrast, the transmission of the infection caused by SARS-CoV occurs less frequently during the prodromal period, but the virus is highly contagious during the acute phase of the disease<sup>5</sup>. Moreover, Kannan et al<sup>6</sup> reported that the chemical and structural differences also exist between the two Coronaviruses with regards to the amino acid sequence in the regions of the non-structural protein (nsP) 1a/b and the surface glycoprotein or S protein.

Why the viral infection causes pulmonary dysfunction and why the clinical course of the infection is milder in children are still a matter of debate<sup>1,7</sup>. The aim of this short review is to highlight the differences existing between COVID-19 cases in adults and children.

## SARS-CoV-2 and COVID-19

SARS-CoV-2 invades human cells binding to the angiotensin converting enzyme II (ACE2) on cell surfaces. This receptor is expressed on type I and II alveolar epithelial cells at different levels. As a matter of fact, it is more expressed

in men than women, and different levels are found also according to age and race. ACE2 is considered to have a protective function against acute lung injury caused by respiratory virus infection<sup>1,7,8</sup>. It has been suggested that the virus, by binding ACE2 may increase its expression with subsequent damage to alveolar cells<sup>1</sup>.

The mean period of incubation of the SARS-CoV-2 is reported to be 6.4 days, ranging from 2.1 to 11.1 days<sup>9</sup>. The mean period might be of 6 days, with a range of up to 14 days, or 5.2 days<sup>10,11</sup>. Respiratory droplets containing the virus represent the main source of infection, through proximity with aerosolized secretions, with a sneeze or cough, or from direct contact with secretions of affected individuals<sup>5</sup>. The infection may be also transmitted by contact with contaminated objects<sup>12</sup>. Clinical manifestations in general recall those of a normal cold, with malaise, fever, cough, fatigue, diffuse pain in association with expectoration, headache, and dyspeptic episodes. Laboratory examinations show in some case leukopenia and mild lymphocytosis. Chest computerized tomography (CT) scan might show, in the symptomatic phase, signs of bilateral opacities.

This infection runs in three major stages: a mild cold-like illness, a moderate respiratory syndrome and a severe acute interstitial pneumonia. Mild illness is characterized by upper respiratory tract as initial symptoms, which more often are the only manifestation of the diseases. Sometimes, it progresses to a moderate respiratory syndrome, with respiratory signs slowly worsening over the course of several days; in some cases, the signs of pneumonia become more severe, with rapid deterioration of the clinical conditions and onset of signs of acute respiratory distress, which requires treatment in intensive care unit<sup>5</sup>.

### ***SARS-CoV-2 in Children***

In contrast, SARS-CoV-2 infection seems to have a more benign evolution in children. As a matter of fact, low susceptibility and minor aggressivity have been highlighted in most cases. Clinical reports show a milder form of infection in children affected by COVID-19. Signs recall a cold-like infection with fever, cough, runny nose, and gastrointestinal manifestations, such as diarrhea and vomiting. Laboratory analysis are not informative, as blood cell count, procalcitonin, C-reactive protein, and other markers of inflammation are usually within the normal

range. Positivity of viral nucleic acid test is often found. Severe complications, such as septic shock and signs of acute respiratory distress syndrome have been rarely observed and only in children affected by other severe comorbidities<sup>13,14</sup>.

As reported by the experience of the outbreak in South Korea, in which general population has a similar composition to that of Italy, the prevalence of the infection in individuals younger than 19 years was 18% (update March 2<sup>nd</sup>, 2020). Since the diagnosis of the first pediatric case on February 19<sup>th</sup>, 2020, the number of pediatric cases gradually increased, and 201 children were diagnosed to be infected with SARS-CoV-2 as of March 2<sup>nd</sup>, 2020. The first pediatric case in Korea was a 10-year old girl who was exposed to positive family members. The proportion of pediatric cases was 4.8% of total confirmed cases. Children younger than 9 years represented 15.9% of the pediatric cases. Of note, one of the cases was a 4-year old boy who attended the daycare center before being tested and found positive. Identifying the transmission pattern in young children requires more data. As of March 2<sup>nd</sup>, the youngest pediatric case with COVID-19 in South Korea was a 45-day old male baby who was infected by his father. Most pediatric patients show only the mild clinical syndrome<sup>15</sup>.

The data drawn from the recent COVID-19 outbreak confirm that the infection in adult patients is clinically different from the infection affecting children. In particular, two points deserve to be highlighted. First of all, epidemiology confirms that the infection seems to be less frequent in children. Secondly, clinical manifestations are milder with less complications.

The minor susceptibility may be due to home confinement, a decreased number of outdoor activities, and a lower chance of exposition of children<sup>14-16</sup>. Moreover, a different distribution, maturation, and functioning of viral receptors ACE2 are reported as a possible cause of the age-related different incidence<sup>14</sup>. Several cases of infection in children may be missed. As a matter of fact, a minor number of tests might be carried out because of a milder form of the infection<sup>13</sup>. In addition, a relative resistance of children to some infectious diseases is well known even if the reason has not been clearly defined. Azhar et al<sup>17</sup> reported that in the SARS-CoV outbreak spread in 2002, only 2% of cases involved children.

Respiratory viruses tend to suppress innate immune response to gain a route for efficient

virus replication and spreading. It is suggested that children may have a more active innate immune response to this aggression<sup>14,18</sup>. Another possible explanation is linked to a cross-protective action carried out by other previous viral respiratory infections. Rhinoviruses, respiratory syncytial virus, and influenza are reported with high frequency in children. These infections may provide protection against to the aggressivity of COVID-19<sup>18,19</sup>. Moreover, the respiratory tract of children is healthier since is less exposed to different noxious agents, such as cigarette smoke, air pollution, and severe lung disorder<sup>20</sup>.

### **COVID-19 Treatment in Children**

There are currently no effective antiviral drugs treatment for the affected children. No sufficient results have been reached by the use of interferon (IFN), lopinavir/ritonavir, orbidol, and oseltamivir in the treatment of the coronavirus infection. Tolicizumab, a monoclonal antibody used for the treatment of rheumatoid arthritis, has been used in adult patients. In Italy the drug is in experimental trials in patients with severe pneumonia. IFN, in particular, has been used in a variety of viral respiratory infections, with not significant results. Antibiotic therapy and corticosteroid treatment should be avoided. The clinical treatment is directed to alleviate symptoms and to correct metabolic unbalance with supportive management of complications<sup>14,21</sup>. Severe cases require the definition of a Pediatric Critical Illness Score (PCIS) at admission.

### **Vertical Transmission**

Mother-to-child transmission of SARS-CoV-2 has not been confirmed, but severe disorders were reported in newborns of mothers affected around the time of delivery<sup>22</sup>. As a matter of fact, Zhu et al<sup>22</sup> report about 9 pregnant women affected by COVID-19 before, on the same day, and after the delivery. The initial symptom consisted in dyspnea in 6 cases, fever in 2 cases, thrombocytopenia with abnormal liver function in 2 cases, and tachycardia, vomiting, pneumothorax in 1 case each. The authors suggest that COVID-19 in pregnant women causes severe neonatal complications, including fetal distress, premature labor, respiratory distress, thrombocytopenia with abnormal liver function, and even death. Therefore, it is necessary to isolate the newborn soon after the delivery.

### **Conclusions**

SARS-CoV-2 infection remains a source of severe complications both in adults and children. However, in children there is a lower incidence of a symptomatic disease and especially of a severe one. Nonetheless, the infection is still dangerous.

Early isolation should be imposed to protect children with underlying diseases.

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### **Conflict of Interest**

The Authors declare that they have no conflict of interests.

### **References**

- 1) SUN P, LU X, XU C, SUN W, PAN B. Understanding of COVID-19 based on current evidence. *J Med Virol* 2020. Doi: 10.1002/jmv.25722. [Epub ahead of print].
- 2) PERRELLA A, CARANNANTE N, BERRETTA M, RINALDI M, MATURO N, RINALDI L. Novel Coronavirus 2019 (Sars-CoV2): a global emergency that needs new approaches? *Eur Rev Med Pharmacol Sci* 2020; 24: 2162-2164.
- 3) WILDER-SMITH A, CHIEW CJ, LEE VJ. Can we contain the COVID-19 outbreak with the same measures as for SARS? *Lancet Infect Dis* 2020. pii: S1473-3099(20)30129-8. doi: 10.1016/S1473-3099(20)30129-8. [Epub ahead of print].
- 4) CECCARELLI M, BERRETTA M, VENANZI RULLO E, NUNNARI G, CACOPARDO B. DIFFERENCES AND SIMILARITIES BETWEEN SEVERE Acute Respiratory Syndrome (SARS)-CoronaVirus (CoV) and SARS-CoV-2. Would a rose by another name smell as sweet? *Eur Rev Med Pharmacol Sci* 2020; 24: 2781-2783.
- 5) HEYMANN DL, SHINDO N; WHO SCIENTIFIC AND TECHNICAL ADVISORY GROUP FOR INFECTIOUS HAZARDS. COVID-19: what is next for public health? *Lancet* 2020; 395: 542-545.
- 6) KANNAN S, SHAIK SYED ALI P, SHEEZA A, HEMALATHA K. COVID-19 (Novel Coronavirus 2019) - recent trends. *Eur Rev Med Pharmacol Sci* 2020; 24: 2006-2011.
- 7) WALLS AC, PARK YJ, TORTORICI MA, WALL A, MCGUIRE AT, VEESLER D. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. *Cell* 2020. pii: S0092-8674(20)30262-2. Doi: 10.1016/j.cell.2020.02.058. [Epub ahead of print].
- 8) ZOU X, CHEN K, ZOU J, HAN P, HAO J, HAN Z. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of dif-

- ferent human organs vulnerable to 2019-nCoV infection. *Front Med* 2020. Doi: 10.1007/s11684-020-0754-0. [Epub ahead of print].
- 9) BACKER JA, KLINCKENBERG D, WALLINGA J. Incubation period of 2019 novel coronavirus (2019-nCoV) infections among travellers from Wuhan, China, 20-28 January 2020. *Euro Surveill* 2020; 25. Doi: 10.2807/1560-7917.ES.2020.25.5.2000062.
  - 10) CHENG AC, WILLIAMSON DA. An outbreak of COVID-19 caused by a new coronavirus: what we know so far. *Med J Aust* 2020. Doi: 10.5694/mja2.50530. [Epub ahead of print].
  - 11) LI Q, GUAN X, WU P, WANG X, ZHOU L, TONG Y, REN R, LEUNG KSM, LAU EHY, WONG JY, XING X, XIANG N, WU Y, LI C, CHEN Q, LI D, LIU T, ZHAO J, LI M, TU W, CHEN C, JIN L, YANG R, WANG Q, ZHOU S, WANG R, LIU H, LUO Y, LIU Y, SHAO G, LI H, TAO Z, YANG Y, DENG Z, LIU B, MA Z, ZHANG Y, SHI G, LAM TTY, WU JTK, GAO GF, COWLING BJ, YANG B, LEUNG GM, FENG Z. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *N Engl J Med* 2020. Doi: 10.1056/NEJMoa2001316. [Epub ahead of print].
  - 12) CAO Q, CHEN YC, CHEN CL, CHIU CH. SARS-CoV-2 infection in children: transmission dynamics and clinical characteristics. *J Formos Med Assoc* 2020; 119: 670-673.
  - 13) YANG P, LIU P, LI D, ZHAO D. Corona Virus disease 2019, a growing threat to children? *J Infect* 2020. pii: S0163-4453(20)30105-5. Doi: 10.1016/j.jinf.2020.02.024. [Epub ahead of print].
  - 14) LEE PI, HU YL, CHEN PY, HUANG YC, HSUEH PR. Are children less susceptible to COVID-19? *J Microbiol Immunol Infect* 2020. pii: S1684-1182(20)30039-6. Doi: 10.1016/j.jmii.2020.02.011. [Epub ahead of print].
  - 15) KOREAN SOCIETY OF INFECTIOUS DISEASES, KOREAN SOCIETY OF PEDIATRIC INFECTIOUS DISEASES, KOREAN SOCIETY OF EPIDEMIOLOGY, KOREAN SOCIETY FOR ANTIMICROBIAL THERAPY, KOREAN SOCIETY FOR HEALTHCARE-ASSOCIATED INFECTION CONTROL AND PREVENTION AND KOREA CENTERS FOR DISEASE CONTROL AND PREVENTION. Report on the epidemiological features of Coronavirus disease 2019 (COVID-19) outbreak in the Republic of Korea from January 19 to March 2, 2020. *J Korean Med Sci* 2020; 35: e112.
  - 16) WANG G, ZHANG Y, ZHAO J, ZHANG J, JIANG F. Mitigate the effects of home confinement on children during the COVID-19 outbreak. *Lancet* 2020. pii: S0140-6736(20)30547-X. doi: 10.1016/S0140-6736(20)30547-X. [Epub ahead of print].
  - 17) AZHAR EI, LANINI S, IPPOLITO G, ZUMLA A. The Middle East Respiratory syndrome Coronavirus - a continuing risk to global health security. *Adv Exp Med Biol* 2017; 972: 49-60.
  - 18) KIKKERT M. innate immune evasion by human respiratory RNA viruses. *J Innate Immun* 2020; 12: 4-20.
  - 19) CASELLI D, ARICÒ M. 2019-nCoV: polite with children! *Pediatr Rep* 2020; 12: 8495.
  - 20) GU H, XIE Z, LI T, ZHANG S, LAI C, ZHU P, WANG K, HAN L, DUAN Y, ZHAO Z, YANG X, XING L, ZHANG P, WANG Z, LI R, YU JJ, WANG X, YANG P. Angiotensin-converting enzyme 2 inhibits lung injury induced by respiratory syncytial virus. *Sci Rep* 2016; 6: 19840.
  - 21) JERNIGAN DB; CDC COVID-19 RESPONSE TEAM. Update: public health response to the Coronavirus disease 2019 outbreak - United States, February 24, 2020. *MMWR Morb Mortal Wkly Rep* 2020; 69: 216-219.
  - 22) ZHU H, WANG L, FANG C, PENG S, ZHANG L, CHANG G, XIA S, ZHOU W. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. *Transl Pediatr* 2020; 9: 51-60.