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EDITORIAL

The intriguing features of COVID-19 in children and its impact on the pandemic☆

As características intrigantes da COVID-19 em crianças e seu impacto na pandemia

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In December, 2019 the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus, emerged in China, associated with reported clusters of patients with pneumonia who were epidemiologically linked to a seafood and wet live animal market in the city of Wuhan, Hubei Province.[1] COVID-19, the term used for the clinical disease caused by SARS-CoV-2, was declared a pandemic by the World Health Organization (WHO) on March 11 — the first ever caused by a coronavirus.[2] As of April 2nd, the number of confirmed cases worldwide has almost reached one million, with 50,000 deaths, and with confirmed cases in almost all countries from all continents.[3] The number of reported COVID-19 cases is certainly underestimating the true burden of disease, given the widespread unavailability of tests, and also the significant proportion of persons that, despite being infected, develop asymptomatic or mild unidentified forms of the disease.[4] Therefore, we should be careful when calculating the case fatality rates (CFR) of COVID-19 (currently at global rates as high as 5%), acknowledging that these rates will likely be lower once the denominator is adjusted to reflect the true number of individuals who acquired the infection. Seroprevalence studies, once available, will provide information on the proportion of the population that was infected, making possible a more accurate estimation of the CFR associated with COVID-19 in the different age groups and populations.

Given the rapid spread (determined by its basic reproduction number – R_0, estimated at the beginning of the epidemic as a value of 2.38 [95% CI: 2.04–2.77])[4] and the profound global impact of COVID-19, with increasing rates of hospitalizations and mortality among a population fully naïve to the virus, as well as the lack of available vaccines or specific efficacious antivirals against SARS-CoV-2, the COVID-19 pandemic represents the most serious public health threat associated with a respiratory viral infection since the 1918 influenza A H1N1 pandemic.[5]

Preliminary data from China, confirmed in the most recent experience from Europe and US, shows that the elderly, particularly those with determined underlying health conditions, are disproportionally at higher risk for severe COVID-19-associated illness and death when compared with younger adults, adolescents, and children.[6–10] In the first large report from the Chinese Center for Disease Control and Prevention, including 44,672 confirmed cases of COVID-19, only one death occurred in a person aged ≤19 years and approximately 80% of deaths occurred among adults aged ≥ 60 years.[8] The first report from the US of outcomes among patients with COVID-19 has indicated that 80% of deaths occurred among adults aged ≥65 years, with the highest percentage of severe outcomes among persons aged ≥85 years, and no fatalities among persons aged ≤19 years.[9] In Italy, only 1.1% of the initial deaths reported occurred among persons <50 years, and none of them were children.[10]

One of the most striking and consistent findings from COVID-19 reports globally is that, in contrast with infected

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adults, children rarely experience severe forms of the disease. The spectrum of manifestations described in 171 children (1 day–15 years) infected with SARS-CoV-2 and treated at the Wuhan Children's Hospital showed that the most common signs and symptoms included cough (present in 48.5% of the cases), pharyngeal erythema (46.2%), and fever (41.5%). Other less common signs and symptoms found in less than 10% of the children were diarrhea, fatigue, rhinorrhea, and nasal congestion. Tachypnea on admission was found in 28.7% of the children and hypoxemia (oxygen saturation <92% during the period of hospitalization) in only 2.3% of the children. The most common radiologic finding was bilateral ground glass opacity, observed in 1/3 of the cases.[11] Strikingly, and similar to what has been observed in adults with COVID-19 pneumonia,[12] imaging abnormalities were found in chest computed tomography (CT) from asymptomatic children, highlighting the concept that evaluation of imaging features with clinical and laboratory findings may facilitate early diagnosis of COVID-19 pneumonia.

In the largest case series of pediatric patients reported to date, 2143 children with suspected or confirmed COVID-19 were included. Among the 731 children with virologically-confirmed disease, 94 (12.9%), 315 (43.1%), and 300 (41%) were classified as asymptomatic, mild, or moderate cases, respectively, together accounting for 97% of the confirmed cases. The proportions of children classified as severe and critical cases, respectively 2.5% and 0.6%, were substantially lower than those observed in adults with COVID-19. Interestingly, infants and pre-school children were more likely to have severe clinical manifestations than older children, which is in line with previous data of children with non-SARS-CoV-2 coronavirus infections.[13] In another study that investigated the clinical features of a cohort of 36 children with COVID-19 in China, the authors found that approximately half of the cases were either asymptomatic or had only mild acute upper respiratory symptoms, and the other half had moderate disease with pneumonia. Clinical manifestations of COVID-19 in children are much milder than in adults.[14] Compared with pediatric patients with influenza infection, children with COVID-19 had a larger proportion of asymptomatic cases, although pneumonia was more prevalent. Based on the experience from the first cases treated in our hospital in Sao Paulo (unpublished data), pediatricians should be alert for the possibility of co-infections with other respiratory viruses when treating infants and young children with COVID-19.

Available data on COVID-19 severity in children with comorbidities are scarce, limiting the possibility to identify conditions at increased risk of complications and mortality. Clinical and laboratorial markers of disease severity and poorer outcomes are being investigated. Preliminary results, most of them from adult patients, showed that respiratory distress on admission and lymphopenia, increased cytokine levels (particularly IL-6, IL-10, and TNFα) and a rise in D-dimer over time, and decreased IFNγ expression in CD4+ T cells are associated with severe COVID-19.[11,15]

The reasons for the overwhelmingly lower risk of severe forms of COVID-19 in children (consistent with what was also previously observed for SARS and Middle East respiratory syndrome [MERS] coronavirus outbreaks), when compared to older age groups, remain elusive and several hypotheses have been raised to explain this phenomenon,[16,17] including different patterns of immunological responses across ages, with adults being more likely, once infected with SARS-CoV-2, to develop unbalanced immune responses, leading to a cytokine storm often associated with lung damage and poorer prognosis for patients, as opposed to infants and children, in whom differences in the innate immunity and a more efficient T cell response to clear the virus would be expected.[17,18] Cross protection acquired from prior exposure to human coronaviruses (HuCoV), frequently associated with mild infections in children, has also been raised as a theoretical explanation for the lower severity in children, which does not appear to be a reasonable hypothesis given the lack of severe cases reported in very young infants, an age group unlikely to have been previously exposed to these HuCoV infections. In my understanding, the most attractive hypothesis for the lower severity of COVID-19 may be related to the expression of angiotensin-converting enzyme 2 (ACE2) on type I and II alveolar epithelial cells. ACE2 was found to be the receptor for SARS-CoV-2, necessary for host cell entry and subsequent viral replication.[19] Therefore, a limited expression of ACE2 in childhood, a period where lungs are still in development, could protect children from severe forms of disease. Interestingly, men have higher levels of ACE2 in their alveolar cells comparing to women, which could also explain the higher rates of worse outcomes in the male sex,[7–10] a trend also observed in studies in children, when comparing rates of hospitalization between boys and girls.[11,13]

Data from China looking at the risk of *in utero* transmission did not show any evidence of congenital infection with SARS-CoV-2 from mothers with COVID-19 pneumonia.[20,21] However, two recent studies reported intriguing results: the first one[22] demonstrated the presence of IgM and IgG antibodies in blood sera collected at birth from two infants born to mothers with COVID-19 pneumonia, and the second one[23] described three infants with early-onset SARS-CoV-2 infection. Although provocative, it is important to note that none of the infants described in these two studies had virological evidence of SARS-CoV-2 infection, emphasizing the need for more data before establishing that SARS-CoV-2 infection can be acquired *in utero*.

Although at this time we do not know whether mothers with COVID-19 can transmit the SARS-CoV-2 *via* breast milk, the WHO, as well as the Brazilian Society of Pediatrics, made clear recommendations supporting mothers to breastfeed their infants.[24,25] Therefore, precautions to avoid transmission of the virus to the infant should be followed, including hand washing before holding the infant and wearing a face mask when in close contact.

A crucial point for investigation – yet to be determined – is the role of children in transmission. Several studies conducted in different populations and age groups demonstrated that a significant proportion of COVID-19 cases were diagnosed without presenting symptoms or with very mild presentations,[11,14,26–28] likely to be missed with the current case-definition ascertainment criteria. Despite being asymptomatic or oligosymptomatic, infected infants and children may have high viral loads in their nasopharynx, as well as fecal shedding of SARS-CoV-2 for longer periods.[29–31] Moreover, a study performed in Shenzen compared cases identified through symptomatic surveillance and contact tracing, showing that children were at similar risk of being

infected as adults.[32] Together, all this evidence shows that children are susceptible to SARS-CoV-2 infection, frequently presenting asymptomatic or mild forms of disease, representing a substantial source of infection in the community, which anticipates that they may play an important role in viral transmission. Robust epidemiologic studies, able to shed light on the uncertainties behind the exact role that children play on the transmission of SARS-CoV-2, are urgently needed.

This information will be of paramount importance to help guide and modulate non-pharmaceutical interventions, implemented to reduce the magnitude of the epidemic peak of COVID-19 and lead to a smaller number of overall cases, hospitalizations, and deaths from this devastating disease. These interventions, which include not only home isolation of suspected cases and quarantine of household contacts, but also population-wide social distancing, as well as school and university closures, face several challenges to being implemented in a timely manner and effectively sustained for longer periods.[5] In places like Brazil we must acknowledge that these challenges are even greater, considering the proportion of the population that lives in extreme poverty, in large, densely populated cities.

Understanding how SARS-CoV-2 emerged and jumped animal species, from a bat reservoir, and probably with Malayan pangolins acting as intermediate hosts before zoonotic transfer,[33] is also crucial. Among the important lessons learned from this coronavirus pandemic one is that urgent measures should be taken to extinguish these wet markets of live wild animals in Asia. These markets are a potential source for the periodic emergence of zoonotic respiratory viruses that can adapt to humans, representing a continued threat to the world, unless serious measures are taken to change this scenario.

At the time of writing, no specific anti-viral is currently available to treat COVID-19. Treatment in children includes fluid and nutritional intake, together with oxygen supplementation and ventilatory support.[34] Due to the rare number of severe cases in children, there is no data on the safety and efficacy of the different therapeutic interventions that are being tested in adults.[35] If we mirror what was found in other respiratory infections, like influenza, one key finding was that the earlier it is possible to start the antivirals, after onset of symptoms, the better the outcomes will be. Assuming that most of these studies were performed in critical patients, usually during the late stage of the disease, we should be cautious when interpreting the results and try to design trials that have the power to answer these uncertainties on the efficacy as well as the potential side effects in the different age groups and clinical presentations of COVID-19.

The development of a vaccine against SARS-CoV-2 is a clear priority. Several platforms are being investigated, including RNA- and DNA-based vaccines, subunit-recombinant vaccines, live-attenuated vaccines, and viral vector vaccines, among others. Previous experience with candidate vaccines against SARS-CoV and MERS-CoV paved the way and will facilitate the development of vaccines for SARS-CoV-2. There is concern regarding several aspects, including the possibility of inducing antibody-dependent enhancement (ADE), increasing the risk of severe disease among vaccinated subjects, the lack of specific correlates of protection for SARS-CoV-2, the capacity for large scale production, and the need for adjuvants (to optimize immune responses as well as for dose sparing).[36]

Until a vaccine becomes available, which is not expected for another 12–18 months from now if everything works well, we should implement timely and effective non-pharmaceutical interventions to reduce the burden of disease and to protect the most vulnerable population, minimizing the tremendous societal cost we are already facing, expand the health-care capacity, provide sufficient protective equipment for health-care workers, stimulate frequent hand washing – and when feasible, the use of masks – and increase, as much as possible, the capacity for testing suspected cases. The time has come to, at last, learn lessons from pandemics that can be transmitted to future generations.

Conflicts of interest

The author declares no conflicts of interest.

References

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382:727–33.
2. World Health Organization (WHO). WHO Director-General's opening remarks at the media briefing on COVID-19-11 March 2020; 2020. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19—11-march-2020 [cited 02.04.20].
3. World Health Organization (WHO). Coronavirus disease 2019 (COVID-19) situation report – 72; 2020. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200401-sitrep-72-covid-19.pdf?sfvrsn=3dd8971b_2 [cited 02.04.20].
4. Li R, Pei S, Chen B, Song Y, Zhang T, Yang W, et al. Substantial undocumented infection facilitates the rapid dissemination of novel coronavirus (SARS-CoV2). Science. 2020;368:489–93.
5. Ferguson NM, Laydon D, Nedjadi-Gilani G, Imai N, Ainslie K, Baguelin M, et al. Report 9: impact of non-pharmaceutical interventions (NPIs) to reduce COVID19 mortality and healthcare demand. Imperial College COVID-19 Response Team; 2020. Available from: https://doi.org/10.25561/77482 [cited 02.04.20].
6. Centers for Disease Control Prevention (CDC). The novel coronavirus pneumonia emergency response epidemiology team. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. Zhonghua Liu Xing Bing Xue Za Zhi. 2020;41:145–51. China, 2020. China CDC Weekly. 2020;2:113–22.
7. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323:1061–9.
8. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020;323:1239–42.
9. CDC COVID-19 Response Team. Severe outcomes among patients with coronavirus disease 2019 (COVID-19) — United States, February 12–March 16, 2020. MWR Morb Mortal Wkly Rep. 2020;69:343–6.

10. Epicentro – Istituto Superiore di Sanità. Characteristics of COVID-19 patients dying in Italy; 2020. Available from: https://www.epicentro.iss.it/en/coronavirus/sars-cov-2-analysis-of-deaths [cited 02.04.20].
11. Lu X, Zhang L, Du H, Zhang J, Li YY, Qu J, et al. SARS-CoV-2 infection in children. N Engl J Med. 2020;382:1663–5.
12. Ai T, Yang Z, Hou H, Zhan C, Chen C, Lv W, et al. Correlation of chest CT and RT-PCR testing in coronavirus disease 2019 (COVID-19) in China: a report of 1014 cases. Radiology. 2020, http://dx.doi.org/10.1148/radiol.2020200642 [epub ahead of print].
13. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z. Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in China. Pediatrics. 2020:e20200702.
14. Qiu H, Wu J, Hong L, Luo Y, Song Q, Chen D. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. Lancet Infect Dis. 2020 Mar 25, http://dx.doi.org/10.1016/S1473-3099(20)30198-5. pii:S1473-3099(20)30198-5 [epub ahead of print].
15. Pedersen SF, Ho YC. SARS-CoV-2: a storm is raging. J Clin Invest. 2020, http://dx.doi.org/10.1172/JCI137647, pii:137647 [epub ahead of print].
16. Brodin P. Why is COVID-19 so mild in children? Acta Paediatr. 2020;109:1082–3.
17. Sun P, Lu X, Xu C, Sun W, Pan B. Understanding of COVID-19 based on current evidence. J Med Virol. 2020;92:548–51.
18. Rudolph M, McArthur MA, Barnes RS, Magder LS, Chen WH, Sztein MB. Differences between pediatric and adult T cell responses to *in vitro* staphylococcal enterotoxin B stimulation. Front Immunol. 2018;9:498.
19. Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensive Care Med. 2020;46:586–90.
20. Zhu H, Wang L, Fang C, Peng S, Zhang L, Chang G, et al. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. Transl Pediatr. 2020;9:51–60.
21. Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet. 2020;395:809–15.
22. Zeng H, Xu C, Fan J, Tang Y, Deng Q, Zhang W, et al. Antibodies in infants born to mothers with COVID-19 pneumonia. JAMA. 2020, http://dx.doi.org/10.1001/jama.2020.4861 [epub ahead of print].
23. Dong L, Tian J, He S, Zhu C, Wang J, Liu C, et al. Possible vertical transmission of SARS-CoV-2 from an infected mother to her newborn. JAMA. 2020, http://dx.doi.org/10.1001/jama.2020.4621 [epub ahead of print].
24. Brazilian Society of Pediatrics (SBP). O aleitamento materno nos tempos de COVID-19!; 2020. Available from: https://www.sbp.com.br/fileadmin/user_upload/22393c-Nota_de_Alerta_sobe_Aleitam_Materno_nos_Tempos_COVID-19.pdf [cited 31.03.20].
25. World Health Organization (WHO). Breast feeding advice during COVID-19 pandemic; 2020. Available from: http://www.emro.who.int/nutrition/nutrition-infocus/breastfeeding-advice-during-covid-19-outbreak.html [cited 31.03.20].
26. Zou L, Ruan F, Huang M, Liang L, Huang H, Hong Z, et al. SARS-CoV-2 viral load in upper respiratory specimens of infected patients. N Engl J Med. 2020;382:1177–9.
27. Wölfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Müleer MA, et al. Clinical presentation and virological assessment of hospitalized cases of coronavirus disease 2019 in a travel-associated transmission cluster. MedRxiv. 2020, http://dx.doi.org/10.1101/2020.03.05.20030502.
28. Liu Y, Yan L-M, Wan L, Xiang T-X, Le A, Liu J-M, et al. Viral dynamics in mild and severe cases of COVID-19. Lancet Infect Dis. 2020, http://dx.doi.org/10.1016/S1473-3099(20). pii:S1473-3099(20)30232-2 [epub ahead of print].
29. Kam K, Yung CF, Cui L, Pin RL, Mak TM, Maiwald M, et al. A well infant with coronavirus disease 2019 (COVID-19) with high viral load. Clin Infect Dis. 2020, http://dx.doi.org/10.1093/cid/ciaa201, pii:ciaa201 [epub ahead of print].
30. Tang A, Tong ZD, Wang HL, Dai YX, Li KF, Liu JN, et al. Detection of novel coronavirus by RT-PCR in stool specimen from asymptomatic child, China. Emerg Infect Dis. 2020;26, http://dx.doi.org/10.3201/eid2606.200301 [epub ahead of print].
31. Zhang T, Cui X, Zhao X, Wang J, Zheng J, Zheng G, et al. Detectable SARS-CoV-2 viral RNA in feces of three children during recovery period of COVID-19 Pneumonia, March 2020. J Med Virol. 2020, http://dx.doi.org/10.1002/jmv.25795 [epub ahead of print].
32. Bi Q, Wu Y, Mei S, Ye C, Zou X, Zhang Z, et al. Epidemiology and transmission of COVID-19 in Shenzhen China: analysis of 391 cases and 1286 of their close contacts. MedRxiv. 2020, http://dx.doi.org/10.1101/2020.03.03.20028423.
33. Andersen KG, Rambaut A, Lipkin WI, Holmes EC, Garry RF. The proximal origin of SARS-CoV-2. Nat Med. 2020;26:450–2.
34. Zimmermann P, Curtis N. Coronavirus infections in children including COVID-19: an overview of the epidemiology, clinical features, diagnosis, treatment and prevention options in children. Pediatr Infect Dis J. 2020;39:355–68.
35. Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). Drug Discov Ther. 2020;14:58–60.
36. Lurie N, Saville M, Hatchett R, Halton J. Developing Covid-19 vaccines at pandemic speed. N Engl J Med. 2020, http://dx.doi.org/10.1056/NEJMp2005630 [epub ahead of print].