



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Commentary

Children and SARS-CoV-2 infection: innocent bystanders...until proven otherwise

M. Lanari ¹, A. Chiereghin ^{2,*}, G.B. Biserni ¹, A. Rocca ¹, M.C. Re ², T. Lazzarotto ²¹) Department of Medical and Surgical Sciences, Paediatric Emergency Unit, St Orsola Polyclinic, University of Bologna, Bologna, Italy²) Department of Specialised, Experimental and Diagnostic Medicine, Operative Unit of Clinical Microbiology, St Orsola Polyclinic, University of Bologna, Bologna, Italy

ARTICLE INFO

Article history:

Received 13 April 2020

Received in revised form

12 June 2020

Accepted 16 June 2020

Available online 25 June 2020

Editor: M. Paul

Introduction

Children, along with other members of vulnerable populations, such as the elderly and individuals with preexisting comorbidities, typically pay a high price in terms of incidence and severity of respiratory tract illnesses. However, the current available data on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) show that from the beginning of the outbreak until now, there is a low attack rate in children worldwide. In particular, in the region of Madrid (Spain), individuals <18 years old accounted for 0.8% of the laboratory-confirmed cases during the first 2 weeks of the epidemic [1]. In the same age group in the United States, from 12 February to 2 April, 1.7% was reported [2], and in Italy, according to the national integrated surveillance of coronavirus disease 2019 (COVID-19), on 10 June 2020, only 2.2% of all confirmed cases were among persons 0 to 18 years old. Preliminary data from Dutch and Spanish national seroprevalence studies (Pienter Corona and ENE-COVID-19) showed a lower prevalence of SARS-CoV-2 infection among children (aged

0–19 years) than adults: 1.1–3.9% versus 5.5% and 1% versus 4.2% respectively.

These epidemiologic data raise the question whether children are less susceptible to the infection, or whether the incidence of infection in this population is undercounted as a result of clinical manifestations that are not brought to the attention of a physician. According to data in the literature, children seem to develop COVID-19 with milder symptoms than adults. Some authors describing SARS-CoV-2 infection in children reported a percentage of asymptomatic cases of up to 28% [3].

We considered some hypotheses regarding the mild symptomatology related to SARS-CoV-2 infection and the apparent low attack rate observed so far in this population.

Why do children seem to develop less severe COVID-19?

SARS-CoV-2 binds the angiotensin-converting enzyme 2 (ACE2) for host cell entry and the serine protease TMPRSS2 for the viral spike protein priming. ACE2 is represented in several human tissues and is scantily expressed on cell membranes of the lung and gut. Animal models have shown that ACE2 drives lung development; its density is maximal in early life, whereas ageing is associated with decreased expression [4]. Moreover, ACE2 plays a lung-protective role against the development of acute respiratory distress syndrome; in fact, a higher risk of lung injury appears to be associated with decreased ACE2 expression in the lower respiratory tract [5]. Assuming a similar role of ACE2 and a similar age-dependent expression in human cells, these observations may suggest that children may be prone to SARS-CoV-2 infection with no or mild symptoms.

Specifically, in murine model, some authors have demonstrated that SARS-CoV infections and the spike protein of SARS-CoV reduce ACE2 expression, causing an imbalance in the renin–angiotensin system supporting proinflammatory angiotensin II production [5]. Therefore, a similar mechanism would explain the milder lung disease due to SARS-CoV-2 in children, where potential higher ACE2 density on pneumocytes could attenuate the ACE2 down-regulation. Moreover, the adaptive response is weaker but more tolerogenic in children, thus making them more prone to develop a

* Corresponding author. A. Chiereghin, Department of Specialised, Experimental and Diagnostic Medicine, OU of Clinical Microbiology, St Orsola Polyclinic, University of Bologna, Via Giuseppe Massarenti, 9, 40138 Bologna, Italy.

E-mail address: angela.chiereghin2@unibo.it (A. Chiereghin).

milder course of the illness [6]. In children, the induced innate immune response to viral infections leads to the secretion of type I interferons (IFN- α/β), which play a fundamental antiviral activity. Conversely, ageing leads to the increase of circulating pro-inflammatory cytokines (interleukin (IL) 1b, IL-6, IL-18 and tumor necrosis factor α), compromises apoptotic cellular function and decreases phagocyte respiratory burst [6]. Therefore, in this scenario, the respiratory tract infections of adults can potentially progress to disease.

Finally, given that the four human coronaviruses (HCoVs) (OC43, NL63, HKU1 and 229E) are continuously circulating in young children (HCoVs are found as coinfections with other respiratory viruses in up to almost half of paediatric acute respiratory tract infections), the immunity to one HCoV may protect against infection by one of the other HCoVs. At this point, we speculate that the immunity induced by these four common and diffuse viruses could confer partial protection against SARS-CoV-2 infection in children. This immunity wanes within 1 or 2 years and could not be reinforced in older individuals. Ren et al. [7], in considering a 4-year period, found that HCoVs were responsible for 1% of all cases of acute respiratory tract infections in Chinese adult outpatients with symptoms of respiratory tract infections. Nevertheless, this hypothesis should be studied and confirmed with *in vitro* neutralization investigations using human sera known to contain HCoV-specific antibodies and sera from SARS-CoV-2-recovered patients.

Of note, recently a new paediatric inflammatory multisystem syndrome resembling a mix of signs and symptoms of Kawasaki disease and toxic shock syndrome (PIMS-TS) is being temporally associated with SARS-CoV-2 infection [3]. As of 15 May 2020, more than 300 suspected classical Kawasaki disease and PIMS-TS cases are under investigation in Europe and North America [3]. Studies are needed to understand the causality and to define the clinical characteristics of this syndrome, its risk factors and its treatment interventions.

Why do children seem to have a COVID-19 low attack rate?

Case identification for SARS-CoV-2 infection in children is challenging. Distinguishing COVID-19 from other viral respiratory tract diseases may be complicated in children, specifically during epidemic season, when common HCoVs, respiratory syncytial virus, human metapneumovirus, parainfluenza and influenza viruses are typically in circulation. This complexity is due to the nonspecificity of the main symptoms (fever and dry cough). In very young children, there is also difficulty in identifying signs of fatigue, myalgias, headache, anosmia and ageusia, which frequently occur in adults with COVID-19.

Tian et al. [8] speculated that children might be more prone to gastrointestinal symptoms than respiratory symptoms compared to adults. The authors analysed two studies in which, at disease onset, 10% of children showed only gastrointestinal symptoms instead of respiratory symptoms, compared to 3% of adults [8]. This symptomatology may also not lead to suspecting COVID-19 in children, if the fact is taken into account that children <5 years old are commonly affected by gastroenteritis.

Finally, the lockdown imposed until recently by some governments, along with the growing fear of going to hospitals, has led to a significant reduction in the circulation of the other respiratory pathogens and in the number of paediatric visits to the emergency department. This all could have led to a lack of laboratory confirmation of SARS-CoV-2 infection in children showing mild COVID-19 symptoms.

What role can children play in the SARS-CoV-2 public health emergency?

Unlike other respiratory viruses (e.g. influenza viruses), the transmission of which tends to be driven by children, a systematic literature review by Ludvigsson [9] on transmission of SARS-CoV-2 infection by children suggested a marginal role of children in the spread of outbreaks. The author reported that the low virus transmission risk could be attributed to the milder or absent disease as well as the lower virus loads detected in children than adults. However, as Ludvigsson recognizes, data on the magnitude of virus load in asymptomatic children are currently scarce, and further studies are needed [10].

To date, child-to-adult transmission seems to be uncommon [3], and large evidence on child-to-child transmission is unavailable because many countries have instituted school closures since March 2020 [10], with gradual reopening just starting. However, the few available data show a limited spread of SARS-CoV-2 infection in schools [9]. According to a Center for Global Development online report (<https://www.cgdev.org/>), most countries that have already reopened their schools have not observed a rise in infection cases.

Closing remarks

Currently it would be prudent to consider children as potentially infected, implementing appropriate hygienic care and avoiding unprotected contact with fragile populations, such as the elderly, who are frequently involved in child care.

On the basis of modelling studies of pandemic and available evidence [9,10], the gradual reopening of kindergartens and schools is considered appropriate, even for counteracting the profound social and economic burden imposed by the pandemic. However, because children lack the capacity to follow basic behavioural prevention measures for reducing the risk of acquiring or transmitting the virus, hygiene and physical distancing in schools should be promoted. It should also be taken into account that a longer incubation period for COVID-19 in children than in adults as well as prolonged respiratory and faecal virus shedding have been reported [11]. Furthermore, though it remains to be defined whether faecal–oral transmission of SARS-CoV-2 is possible, this could represent a peculiar infection transmission route among infants.

In order to control school outbreaks, reopening will require close epidemiologic and virologic surveillance to promptly isolate suspected cases of SARS-CoV-2.

Only in the absence of lockdown conditions and with schools reopened worldwide will it be possible to draw definitive conclusions on the role children play in the pandemic and to establish whether or not they are indeed innocent bystanders.

Transparency declaration

All authors report no conflicts of interest relevant to this article.

Acknowledgement

The authors would like to thank their linguistic consultant, L. Scioscia, for editing the English-language text.

References

- [1] Tagarro A, Epalza C, Santos M, Sanz-Santaefemia FJ, Otheo E, Moraleda C, et al. Screening and severity of coronavirus disease 2019 (COVID-19) in children in Madrid, Spain. *JAMA Pediatr* 2020:e201346. <https://doi.org/10.1001/jamapediatrics.2020.1346>.

- [2] Coronavirus disease 2019 in children—United States, February 12–April 2, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:422–6.
- [3] European Centre for Disease Prevention and Control (ECDC). Paediatric inflammatory multisystem syndrome and SARS-CoV-2 infection in children—15 May 2020. Stockholm: ECDC; 2020.
- [4] Wallace KB, Bailie MD, Hook JB. Angiotensin-converting enzyme in developing lung and kidney. *Am J Physiol* 1978;234:R141–5.
- [5] Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus–induced lung injury. *Nat Med* 2005;11:875–9.
- [6] Simon AK, Hollander GA, McMichael A. Evolution of the immune system in humans from infancy to old age. *Proc Biol Sci* 2015;282:20143085.
- [7] Ren L, Gonzalez R, Xu J, Xiao Y, Li Y, Zhou H, et al. Prevalence of human coronaviruses in adults with acute respiratory tract infections in Beijing, China. *J Med Virol* 2011;83:291–7.
- [8] Tian Y, Rong L, Nian W, He Y. Gastrointestinal features in COVID-19 and the possibility of faecal transmission. *Aliment Pharmacol Ther* 2020;51:843–51 [review].
- [9] Ludvigsson JF. Children are unlikely to be the main drivers of the COVID-19 pandemic—a systematic review. *Acta Paediatr* 2020. <https://doi.org/10.1111/apa.15371>.
- [10] Viner RM, Russell SJ, Croker H, Packer J, Ward J, Stansfield C, et al. School closure and management practices during coronavirus outbreaks including COVID-19: a rapid systematic review. *Lancet Child Adolesc Health* 2020;4:397–404.
- [11] Cai J, Xu J, Lin D, Yang Z, Xu L, Qu Z, et al. A case series of children with 2019 novel coronavirus infection: clinical and epidemiological features. *Clin Infect Dis* 2020. <https://doi.org/10.1093/cid/ciaa198>.