Three Hypotheses About Children COVID19

***To the Editors*:**

We have read with interest the recent paper about coronavirus infections in children including new coronavirus disease (COVID-19).[1] One of the central questions in this new coronavirus (SARSCOV2) pandemic is why children are less affected than adults.[2] We think that three main hypotheses should be considered or studied.

(1) Angiotensin-converting enzyme 2 (ACE2) receptor: this receptor is expressed by the alveolar type 2 cells. Maybe a lower presence of ACE2 in children's lungs influences the clinical expression of COVID19.[3] This hypothesis should cautiously be considered. As it has been published, children with less than 1 year are the group at higher risk of complications. This population, empirically, should have lower ACE2 expression. In these cases, the presence of viral or bacterial coinfections must be considered and promptly treated. Maybe they are acting as confounders.

(2) Endothelial damage: it has been described that age, cardiovascular diseases and diabetes mellitus are risk factors for severe COVID19. In these cases, previous endothelial damage may facilitate and increase the inflammatory response to SARSCOV2.[4,5] In healthy children, the endothelial damage is practically absent. This could help to avoid the spread of the inflammatory process. It will be of great interest to add knowledge about children with similar risk factors like the described in adults.

(3) Innate immunity: the first line of defense to SARSCOV2 is the innate immunity. To avoid this, coronavirus blocks the type I interferon route to multiply and increase their copies. The innate immunity in children is well trained not only by community-acquired viral infections[5] but also by the use of vaccines also trains it.[3] The viral vaccines are mainly administered from 1-year-old in advance. The influence of this about the response to SARSCOV2 infection should be studied. Also, the impact over the evolution of previously administered attenuated RNA vaccines should be analyzed. In that way, the influenza vaccine, which also uses the interferon 1 route, may have an impact on the immune response. This hypothesis about the influenza vaccine should also be considered in the adult population.

In summary, as far as we know, children appear to be least affected by COVID19. This must be an expression of multifactorial causes that nowadays are not well defined. Added to the clinical management, the uses of immunologic and basic science approaches will be of great interest. With these three hypotheses, we try to offer a possible explanation for the differences observed with adults. The study and description of this hypothesis or others may help to develop new therapeutic or prognostic tools.

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REFERENCES

1. 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.
2. Dong Y, Mo X, Hu Y, et al. Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in China. *Pediatrics*. 2020. pii: e20200702. doi: 10.1542/peds.2020-0702. [Epub ahead of print].
3. Prompetchara E, Ketloy C, Palaga T. Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. *Asian Pac J Allergy Immunol*. 2020;38:1–9.
4. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395:1054–1062.
5. Qin C, Zhou L, Hu Z, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*. 2020. pii: ciaa248. doi: 10.1093/cid/ciaa248. [Epub ahead of print].

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Comparison of the Clinical Features of SARS-CoV-2, Other Coronavirus and Influenza Infections in Infants Less Than 1-Year-Old

To the Editors:

We read with attention the review of Zimmerman and Curtis[1] on Coronavirus Disease 2019 (COVID-19) among children and take the opportunity of this letter to share additional information. Infection with severe acute respiratory syndrome coronavirus 2 has mostly been reported in adults, though a recent publication described 9 infants <1-year-old with COVID-19.[2] Among infant data are very few, though comparisons with infections due to other coronavirus strains will be helpful. The Pneumo-Study[3] on the etiologic agents of pneumonia in children <5-year-old conducted by the Merieux Foundation Global Approach to Biological Research, Infectious diseases and Epidemics in Low-income countries (GABRIEL) network provides opportunities for comparisons.

We compared the published clinical features of hospitalized infants with COVID-19[2] and hospitalized infants infected with other coronavirus strains or influenza from the GABRIEL project. The incident case-control Pneumo-study was done in children less than 5 in low-/middle-income countries between 2010 and 2014. The protocol and initial results are detailed elsewhere.[3,4] The population was restricted to infants <1-year-old with features of pneumonia (ie, cases).[3] Nasopharyngeal swabs were collected at admission to identify bacteria and viruses by reverse-transcription polymerase chain reaction (RT-PCR). Statistics were restricted to the same variables used by Wei et al[2] and to cases with positive swabs for a coronavirus or influenza virus.

Of the 333 infants with pneumonia, 17 had CoV-positive nasopharyngeal swabs [7 (41.2%) with HKU1, 5 (29.4%) with CoV OC43, 3 (17.7%) with CoV NL63, 2 (11.8%) with CoV 229E] and 31 had an

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TABLE 1. Comparison of the Characteristics of Coronavirus Disease 2019, Other Coronavirus and Influenza Infections Among Infants < 1-yr-old

Characteristics	Patients* With CoV Pneumonia From GABRIEL Pneumo-study (n = 17)† (A)	Patients* With Influenza Pneumonia From GABRIEL Pneumo-study (n = 31)‡ (B)	Patients* Infected with COVID-19 from Wei et al[2] (n = 9) (C)	Comparison (A) vs. (C) *P*§	Comparison (B) vs. (C) *P*§
Male gender, n (%)	9 (52.9)	17 (54.8)	2 (22.2)	0.22	0.13
Median age, mo (min–max)	9 (3–11)	8 (2–11)	7 (1.9–11)	0.25	0.45
Median time between admission and diagnosis, d (min–max)	0 (0–2)	0 (0–2)	1 (1–3)	0.04	<0.001
Fever > 38°C, n (%)	12 (70.6)	20 (64.5)	4 (44.4)	0.65	0.99
Cough, n (%)	17 (100.0)	31 (100.0)	2 (22.2)	<0.001	<0.001
Rhinopharyngitis or runny nose, n (%)	7 (46.7)¶	6 (23.1)‖	1 (11.1)	0.19	0.99
Death, n (%)	3** (17.7)	1 (3.3)	0 (0.0)	0.53	0.99

*Detected by RT-PCR in nasopharyngeal swab.
†CoV OC43, n = 5 (29.4%). CoV NL63, n = 3 (17.7%). CoV 229E, n = 2 (11.8%). CoV HKU1, n = 7 (41.2%).
‡Influenza A virus, n = 22 (71.0%). Influenza B virus, n = 9 (29.0%).
§Qualitative variables were compared with Fisher exact tests; quantitative variables, Wilcoxon tests.
¶n = 15.
‖n = 26.
**One with NL63, 1 with HKU1, 1 with OC43.
CoV indicates coronavirus; COVID-19, Coronavirus Disease 2019; GABRIEL, Global Approach to Biologic Research, Infectious diseases and Epidemics in Low-income countries; RT-PCR, reverse-transcription polymerase chain reaction.

influenza-positive swab [22 (71%) with Influenza A, 9 (29%) with Influenza B]. Cough seems less prevalent in COVID-19 compared with other infected infants (Table 1). While no deaths occurred in infants with COVID-19,[2] 3 infants infected with CoV in Pneumo-study died, 2 of whom were co-infected with *Streptococcus pneumoniae*.

This report underscores the lack of major differences in the clinical features of severe acute respiratory syndrome coronavirus 2 and other types of CoV or influenza infections among infants despite limited clinical features reported. COVID-19 infection does not seem more severe than other CoV or influenza infections in this population, possibly as all infect Angiotensin-Converting Enzyme 2 receptors in the upper airways. As influenza,[5] the contribution of infants to the spread COVID-19 should be investigated. S. pneumoniae was co-detected in the CoV-infected infants who died in Pneumo-study while bacterial co-detection was not reported by Wei et al.[2] Infants in both studies[2,3] were hospitalized limiting selection bias but small sample sizes weakened statistical power. The incidence of COVID-19 in infants less than 1-year-old is currently low, but studies are needed to describe the clinical features, prognosis and impact of infected infants on the COVID-19 spread.

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REFERENCES

1. Zimmermann P, Curtis N. Coronavirus infections in children including COVID-19. *Pediatr Infect Dis J*. 2020.
2. Wei M, Yuan J, Liu Y, et al. Novel Coronavirus Infection in Hospitalized Infants Under 1 Year of Age in China. *JAMA*. 2020. doi:10.1001/jama.2020.2131.
3. Picot VS, Bénet T, Messaoudi M, et al; pneumonia GABRIEL network. Multicenter case-control study protocol of pneumonia etiology in children: Global Approach to Biological Research, Infectious diseases and Epidemics in Low-income countries (GABRIEL network). *BMC Infect Dis*. 2014;14:635.
4. Bénet T, Sánchez Picot V, Messaoudi M, et al; Global Approach to Biological Research, Infectious diseases and Epidemics in Low-income countries (GABRIEL) Network; Global Approach to Biological Research, Infectious diseases and Epidemics in Low-income countries (GABRIEL) Network. Microorganisms associated with pneumonia in children <5 years of age in developing and emerging countries: the GABRIEL pneumonia multicenter, prospective, case-control study. *Clin Infect Dis*. 2017;65:604–612.
5. Heikkinen T. Influenza in children. *Acta Paediatr*. 2006;95:778–784.

Challenges for the Pediatricians During the Coronavirus Disease 2019 Pandemic Start From the Neonatal Period

To the Editors,

We read with interest the recent article published by Chidini et al[1] referring to the challenges encountered in the management of severe acute respiratory syndrome coronavirus 2 infection in children in Milan. This is actually the current situation in various pediatric departments throughout Europe. We fully agree with the suggested management and approach, although the latter still poses major further logistical issues such as the availability of negative pressure rooms for all inpatients with suspected COVID-19 infection pending virologic confirmation. Moreover, 2 negative respiratory samples are required to rule out severe acute respiratory syndrome coronavirus 2 infection which means further inpatient stay and more resources needed. More data in the field are urgently required to guide the pediatricians further.

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