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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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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