



Early View

Correspondence

Children coronavirus dilemma

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Children coronavirus dilemma.

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Dear Editors,

We thank Dr. Ebmeier and Dr. Cunningham for their commentary on our editorial [1], providing another point of view on such a controversial topic.

In their letter, the authors assume that the greater burden of coronavirus disease 19 (COVID-19) in adults may be related to the absence in the population of prior immunity to Sars-CoV-2, as occurred in fully susceptible population during previous viral epidemics. In particular, Shanks et al. report that measles mortality rate in a fully susceptible population during the 1846 measles epidemic was higher in adults and in children under 2 years of age [2]. However, nowadays children younger than 5 years of age and adults older than 20 years of age are still more likely to suffer from measles complications, despite not being fully susceptible [3]. Moreover, Plotkin et al. reported that case–fatality ratio is still high in children under one year of age, lower in children aged one to nine years, whereas it rises again in teenagers and adults [4]. Reported data suggest that greater morbidity and mortality in adults is not a unique feature of first-contact measles epidemics.

As regards West Nile virus infection [5], Severe Fever with Thrombocytopenia Syndrome [6] and Plasmodium falciparum malaria [7], several factors such as pathogen features, transmission dynamics and population characteristics could be potential confounders; therefore, we think that those diseases could be not comparable to COVID-19. Moreover, Rutledge et al. [5] and Li H et al. [6] described a higher mortality rate in adults, but data were collected over several years and we are not sure that the population can be considered fully susceptible over time.

Furthermore, Sars-CoV-2 viral genome is 75 to 80% identical to the SARS-CoV [8] that caused global pandemic in 2002-2003. Human coronaviruses' infections are very common worldwide [9, 10,11]. Recently, Grifoni et al. analysed adaptive immunity to Sars-CoV-2 and detected SARS-CoV-2-reactive CD4+ T cells in ~40-60% of unexposed individuals, suggesting a cross-reactive T cell recognition between circulating 'common cold' coronaviruses and SARS-CoV-2 [12]. In view of these overall considerations, we can speculate that Sars-CoV-2 infection may not have spread in a fully susceptible population. This hypothesis may be also confirmed by a previous study by Fedson which reported that the different age-related mortality during 1918

influenza pandemic could be related to previously exposures to the H1N1-like viruses, suggesting a fundamental role of “antigenic imprinting” on individual response [13].

In conclusion, we are more likely to consider that other reasons rather than absence of prior immunity could play a crucial role in the children coronavirus dilemma.

References

- [1] Cristiani L, Mancino E, Matera L, Nenna R, Pierangeli A, Scagnolari C, Midulla F. Will children reveal their secret? The coronavirus dilemma. *Eur Respir J* 2020; <https://doi.org/10.1183/13993003.00749-2020>.
- [2] Shanks GD, Waller M, Briem H, Gottfredsson M. Age-specific measles mortality during the late 19th-early 20th centuries. *Epidemiol Infect* 2015; 143(16); 3434–3441. <https://doi.org/10.1017/S0950268815000631>.
- [3] Centers for Disease Control and Prevention. National Center for Immunization and Respiratory Diseases, Division of Viral Diseases. Complications of Measles. Page last reviewed: June 13, 2019 <http://www.cdc.gov/measles/about/complications.html>
- [4] Plotkin SA, Orenstein WA, Offit PA et al. *Vaccines*, 7th edition. Philadelphia, PA: Elsevier. 2018; chapter 37.
- [5] Rutledge TF. Morbidity and Mortality Weekly Report Surveillance for Human West Nile Virus Disease — United States, 1999 – 2008. *MMWR Weekly Report* 2010; 59(31), 1999–2008.
- [6] Li H, Qing-Bin L, Xing B, Zhang SF, Liu K, Du J, Li X, Cui N, Yang Z, Wang L, Jian-Hu G, Cao W, Liu W. Epidemiological and clinical features of laboratory-diagnosed severe fever with thrombocytopenia syndrome in China, 2011–17: a prospective observational study. *Lancet Infect Dis* 2018; 18(10); 1127–1137. [https://doi.org/10.1016/S1473-3099\(18\)30293-7](https://doi.org/10.1016/S1473-3099(18)30293-7).
- [7] Checkley AM, Smith A, Smith V, Blaze M, Bradley D, Chiodini PL, Whitty CJM. (2012). Risk factors for mortality from imported falciparum malaria in the United Kingdom over 20 years: An observational study. *BMJ (Online)* 2012; 344(7854); 1–11. <https://doi.org/10.1136/bmj.e2116>.
- [8] Zhou P, Yang X-L, Wang X-G et al. Discovery of a novel coronavirus associated with the recent pneumonia outbreak in 2 humans and its potential bat origin, *bioRxiv*, 2020.
- [9] Litty Varghese, Philip Zachariah, Celibell Vargas, Philip LaRussa, Ryan T Demmer, Yoko E Furuya, Susan Whittier, Carrie Reed, Melissa S Stockwell, Lisa Saiman, *Epidemiology and Clinical Features of Human Coronaviruses in the Pediatric Population*, *Journal of the Pediatric Infectious Diseases Society*, Volume 7, Issue 2, June 2018, Pages 151–158, <https://doi.org/10.1093/jpids/pix027>.
- [10] Gorse, G.J., Patel, G.B., Vitale, J.N., and Connor, T.Z. Prevalence of Antibodies to Four Human Coronaviruses Is Lower in Nasal Secretions than in Serum. *Clinical and Vaccine Immunology*. 2010; 17, 1875.
- [11] Mancino E, Cristiani L, Pierangeli A, et al. A single centre study of viral community-acquired pneumonia in children: No evidence of SARS-CoV-2 from October 2019 to March

2020 [published online ahead of print, 2020 Apr 29]. *J Clin Virol.* 2020;128:104385. doi:10.1016/j.jcv.2020.104385

[12] Grifoni, A., Weiskopf, D., Ramirez, S.I., et al. Targets of T cell responses to SARS-CoV-2 coronavirus in humans with COVID-19 disease and unexposed individuals. 2020. *Cell.* doi: <https://doi.org/10.1016/j.cell.2020.05.015>.

[13] Fedson David S. Influenza, evolution, and the next pandemic. *Evolution, Medicine, and Public Health*, pp. 260–269, 2018 doi:10.1093/emph/eoy027.

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