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.

2. Centers for Disease Control and Prevention. Criteria for Return to Work for Healthcare Personnel with SARS-CoV-2 Infection (Interim Guidance). Updated August 10, 2020. https://www.cdc.gov/coronavirus/2019-ncov/hcp/return-to-work.html. Accessed August 25, 2020.
3. Singanayagam A, Patel M, Charlett A, Lopez Bernal J, Saliba V, Ellis J, et al. Duration of infectiousness and correlation with RT-PCR cycle threshold values in cases of COVID-19, England, January to May 2020. Euro Surveill 2020;25:2001483.
4. Walsh KA, Jordan K, Clyne B, Rohde D, Drummond L, Byrne P, et al. SARS-CoV-2 detection, viral load and infectivity over the course of an infection. J Infect 2020;81:357-71.
5. Han MS, Seong M-W, Kim N, Shin S, Cho SI, Park H, et al. Viral RNA load in mildly symptomatic and asymptomatic children with COVID-19, Seoul. Emerg Infect Dis 2020;26:2497-9.
6. Jones TC, Mühlemann B, Veith T, Biele G, Zuchowski M, Hoffmann J, et al. An analysis of SARS-CoV-2 viral load by patient age. medRxiv 2020. In press.
7. Baggio S, L'Huillier AG, Yerly S, Bellon M, Wagner N, Rohr M, et al. SARS-CoV-2 viral load in the upper respiratory tract of children and adults with early acute COVID-19. Clin Infect Dis 2020. In press.
8. Wölfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Müller MA, et al. Virological assessment of hospitalized patients with COVID-2019. Nature 2020;581:465-9.

Reply

To the Editor:

Coronavirus disease 2019 (COVID-19) carries significant morbidity and mortality for adults whereas children have been felt to be "spared." The justification for the apparent difference in clinical response remains to be understood. We provide data pertinent to viral load, angiotensin-converting enzyme 2 expression, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibody responses for children infected with SARS-CoV-2. Comparisons with adults probed for factors driving the apparent dichotomous response between children and adults following infection with SARS-CoV-2. Our data show that children can, in fact, carry high viral loads despite mild symptoms, in contrast to adults, who become quite ill even as viral load wanes. We do not infer that children carry a greater viral load than adults at paralleled days of symptoms, although the sample size in our adult cohort was limited for individuals with less than 7 days of symptoms. Heald-Sargent et al, however, suggested that children <5 years of age had significantly lower cycle threshold values on SARS-CoV-2 reverse-transcription polymerase chain reaction (and therefore higher viral load) than adults >18 years of age.[1] Comparing children with adults is justified to ascertain factors driving disease. Our data, combined with the study by Heald-Sargent, suggest that viral load is unlikely the sole factor driving severe disease in adults, as children also can carry high viral loads.

We did not culture live virus in our study. However, live virus has been shown to be readily isolated from respiratory secretions during the first week of symptoms.[2] To assume that only <5% of individuals with a viral load >5.4 log10 RNA copies/mL are infectious without taking symptom duration into consideration may underestimate the number of children carrying live virus, as Wolfel et al obtained this threshold using samples collected across all time points of symptom duration.[2] Further, Wolfel et al state that there was genetic evidence of active viral replication in the first 5 days of throat swabs and 9 days of sputum.[2] Further, an outbreak of COVID-19 in a childcare facility highlights the potential for transmission from infected children to adults and other children.[3] Therefore, inferring the possibility of infectivity in children with high viral loads early in the infectious course is prudent until research can directly prove this is not the case.

Our study was conducted from April to June 2020, when schools were shut down and in-person children's extracurricular activities were cancelled. Therefore, contact tracing of infected children at that time would have been of limited value. Despite the constraints in social interactions during the time of this study, 18% of acute pediatric SAR-CoV-2 infections and 56% of children with multisystem inflammatory syndrome in children did not have a known household contact. This suggests that they could have contracted the virus from an asymptomatic family member or an interaction with a presymptomatic individual outside of the home. Asymptomatic individuals are recognized as carrying virus and contribute to SAR-CoV-2 transmission.[4,5] A case series in Korea found that of 91 children exposed to adults with COVID-19, only 8.5% of these children had symptoms before testing positive for SARS-CoV-2, and 22% never developed symptoms.[6] Contact tracing, which relies on symptom report, could miss detection of asymptomatic individuals.

More research is needed to further define how children are affected by SARS-CoV-2 infection as compared with adults, and what role children will play in the COVID-19 pandemic as schools open. Based on our data, we feel safety precautions for children of all ages are justified. Mask-wearing, hand washing, physical distancing, and viral testing are logical strategies for minimizing the spread of this pandemic as children return to schools and daycares.

Lael M. Yonker, MD
Mucosal Immunology and Biology Research Center
Department of Pediatrics

Anne M. Neilan, MD
Department of Pediatrics and Department of Internal Medicine, Massachusetts General Hospital; Harvard Medical School, Boston, Massachusetts

Yannic Bartsch, PhD
Ragon Institute of Massachusetts General Hospital Massachusetts Institute of Technology and Harvard, Harvard Medical School, Cambridge; Harvard Medical School Boston, Massachusetts

Ankit B. Patel, MD, PhD
Department of Medicine, Renal Division, Brigham and Women's Hospital; Harvard Medical School Boston, Massachusetts

James Regan, BS
Department of Infectious Diseases, Brigham and Women's Hospital, Boston, Massachusetts

Puneeta Arya, MD
Department of Pediatrics, Massachusetts General Hospital Harvard Medical School, Boston, Massachusetts

Elizabeth Gootkind, BA
Grace Park, BS
Margot Hardcastle, BA
Anita St John, RN
Lori Appleman, RN
Department of Pediatrics, Massachusetts General Hospital Boston, Massachusetts

Michelle L. Chiu, MD
Department of Pediatrics, Massachusetts General Hospital Harvard Medical School, Boston, Massachusetts

Allison Fialkowski, BS
Harvard Medical School, Boston, Massachusetts

Denis De La Flor, BS
Rosiane Lima, BS
Mucosal Immunology and Biology Research Center Department of Pediatrics, Massachusetts General Hospital Boston, Massachusetts

Evan A. Bordt, PhD
Department of Pediatrics, Massachusetts General Hospital Harvard Medical School, Boston, Massachusetts

Laura J. Yockey, MD, PhD
Department of Internal Medicine, Vincent Center for Reproductive Biology

Paolo D'Avino, BS
Mucosal Immunology and Biology Research Center Massachusetts General Hospital, Boston, Massachusetts

Stephanie Fischinger, MSc
Ragon Institute of Massachusetts General Hospital Massachusetts Institute of Technology, and Harvard Harvard Medical School, Cambridge, Massachusetts

Jessica E. Shui, MD
Paul H. Lerou, MD
Department of Pediatrics, Massachusetts General Hospital

Joseph V. Bonventre, MD, PhD
Department of Medicine, Renal Division, Brigham and Women's Hospital; Harvard Medical School Boston, Massachusetts

Xu G. Yu, MD
Ragon Institute of Massachusetts General Hospital Massachusetts Institute of Technology, and Harvard Harvard Medical School, Cambridge, Massachusetts

Department of Infectious Diseases, Brigham and Women's Hospital; Harvard Medical School, Boston, Massachusetts

Edward T. Ryan, MD
Department of Pediatrics and Department of Internal Medicine, Massachusetts General Hospital; Harvard Medical School; Harvard T. H. Chan School of Public Health Boston, Massachusetts

Ingrid V. Bassett, MD, MPH
Department of Internal Medicine

Daniel Irimia, MD, PhD
Center for Engineering in Medicine, Department of Surgery Massachusetts General Hospital; Harvard Medical School Boston, Massachusetts

Andrea G. Edlow, MD
Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, Vincent Center for Reproductive Biology

Galit Alter, PhD
Vincent Center for Reproductive Biology

Jonathan Z. Li, MD, MMSc
Department of Infectious Diseases, Brigham and Women's Hospital

Alessio Fasano, MD
Mucosal Immunology and Biology Research Center Department of Pediatrics, Massachusetts General Hospital Harvard Medical School, Boston, Massachusetts

https://doi.org/10.1016/j.jpeds.2020.09.049

Supported by the National Heart, Lung, and Blood Institute (5K08HL143183 [to L.Y.]), the Cystic Fibrosis Foundation (YONKER18Q0 [to L.Y.]), the National Institute of Child Health and Human Development (K08 HD094638 [to A.N.] and R01HD100022 [to A.E.]), Mark and Lisa Schwartz (to J.L.), the National Institute of Diabetes and Digestive and Kidney Diseases (DK039773, DK072381 [to J.B.] and DK104344 [to A.F.]), the National Institute of Allergy and Infectious Disease (K24AI141036 [to I.B.]), the Centers for Disease Control and Prevention (U01CK000490 [to E.R.]), and the Department of Pediatrics and the Department of Obstetrics/Gynecology at Massachusetts General Hospital (to L.Y. and A.E.). The authors declare no conflicts of interest.

References

1. Heald-Sargent T, Muller WJ, Zheng X, Rippe J, Patel AB, Kociolek LK. Age-related differences in nasopharyngeal severe acute respiratory syndrome

coronavirus 2 (SARS-CoV-2) levels in patients with mild to moderate coronavirus disease 2019 (COVID-19). JAMA Pediatr 2020;174:902-3.
2. Wolfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Muller MA, et al. Virological assessment of hospitalized patients with COVID-2019. Nature 2020;581:465-9.
3. Lopez AS, Hill M, Antezano J, Vilven D, Rutner T, Bogdanow L, et al. Transmission dynamics of COVID-19 outbreaks associated with child care facilities—Salt Lake City, Utah, April–July 2020. MMWR Morb Mortal Wkly Rep 2020;69:1319-23.
4. Gandhi M, Yokoe DS, Havlir DV. Asymptomatic transmission, the Achilles' heel of current strategies to control Covid-19. N Engl J Med 2020;382:2158-60.
5. Lee S, Kim T, Lee E, Lee C, Kim H, Rhee H, et al. Clinical course and molecular viral shedding among asymptomatic and symptomatic patients with SARS-CoV-2 infection in a community treatment center in the Republic of Korea. JAMA Intern Med 2020;180:1-6.
6. Han MS, Choi EH, Chang SH, Jin BL, Lee EJ, Kim BN, et al. Clinical characteristics and viral RNA detection in children with coronavirus disease 2019 in the Republic of Korea. JAMA Pediatr 2020.

Comment regarding pediatric severe acute respiratory syndrome coronavirus 2: clinical presentation, infectivity, and immune responses

To the Editor:

In the report by Yonker et al, despite having tested 11 asymptomatic children with 3 positives, there are no details about this group selection and there is no information about the viral load in this group.[1] It would be important to compare this group with the group study, instead of comparing asymptomatic/early infection with adults at a later stage of the disease. One study found a higher viral load in adults during the first week of symptoms with a progressive decrease over time, as observed in the present study in children, reinforcing that comparing viral load at different stages of the disease may be inadequate.[2] Also, they correlated multisystem inflammatory syndrome in children with low viremia, and posed it as an obstacle to control strategies as reopening schools. However, studies show that multisystem inflammatory syndrome in children is a later complication, with a low incidence and mortality.[3,4]

Data suggest that the majority of pediatric cases are mild or asymptomatic.[5,6] Therefore, we should ponder the impact of quarantine on childhood. There are psychological and physical burdens imposed on children with home confinement and school closure: lack of children-children interaction and inadequate eating patterns generate distress, obesity/malnutrition, depression, and many other behavioral and neurodevelopmental disorders. Additionally, vulnerable children like those exposed to domestic violence and abuse have no place to shelter.[7,8] Furthermore, in low-income countries, socioeducational disparity may be enhanced, because there is no universal access to audiovisual system or Internet access; in addition, some children receive vital nutritional assistance in schools that has been halted since the pandemic began.[7]

Mitigating the psychosocial impact may require risk stratification of children, teachers, and their household contacts and contact tracing all symptomatic individuals making isolation possible.[9] The central question after their findings is if there is direct correlation between viral load and transmissibility.[10]

Juliana Ferreira Ferranti, MD
Pediatric Intensive Care
Children's Institute
Faculty of Medicine
University of Sao Paulo

Pediatric Intensive Care
Brazilian Israeli Beneficent Society Albert Einstein (SBIBAE)
Sao Paulo, Brazil

Natalia Viu Degaspare, MD
Pediatric Intensive Care
Children's Institute
Faculty of Medicine
University of Sao Paulo
Sao Paulo, Brazil

Luciana Becker Mau, MD
Emilio Ribas Institute of Infectology
Sao Paulo, Brazil

Artur Figueiredo Delgado, MD, PhD
Werther Brunow de Carvalho, MD, PhD
Pediatric Intensive Care
Children's Institute
Faculty of Medicine
University of Sao Paulo
Sao Paulo, Brazil

https://doi.org/10.1016/j.jpeds.2020.09.034

The authors declare no conflicts of interest.

References

1. Yonker LM, Neilan AM, Bartsch Y, Patel AB, Regan J, Arya P, et al. Pediatric Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): clinical presentation, infectivity, and immune responses. J Pediatr 2020;227:45-52.e5.
2. To KK-W, Tsang OT-Y, Leung W-S, Tam AR, Wu TC, Lung DC, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. Lancet Infect Dis 2020;20:565-74.
3. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. N Engl J Med 2020;383:334-46.
4. Dufort EM, Koumans EH, Chow EJ, Rosenthal EM, Muse A, Rowlands J, et al. Multisystem inflammatory syndrome in children in New York State. N Engl J Med 2020;383:347-58.
5. 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.
6. Lee B, Raszka WV Jr. COVID-19 Transmission and Children: the Child Is Not to Blame. Pediatrics 2020;146:e2020004879.
7. Ghosh R, Dubey MJ, Chatterjee S, Dubey S. Impact of COVID -19 on children: special focus on the psychosocial aspect. Minerva Pediatr 2020;72:226-35.
8. Wong CA, Ming D, Maslow G, Gifford EJ. Mitigating the impacts of the COVID-19 pandemic response on at-risk children. Pediatrics 2020;146:e20200973.