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.

Addressing the global burden of paediatric critical COVID-19 and mortality

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Over two years into the coronavirus disease 2019 (COVID-19) pandemic, data demonstrate a profound impact of COVID-19 upon children. In the U.S., children comprise more than 15% of all diagnosed SARS-CoV-2 infections, and about one-quarter of those requiring hospitalization with COVID-19 also require ICU care.[1] To date, over 1000 U.S. children have died with COVID-19, which far exceeds annual seasonal influenza-related deaths (≤200/season).[2,3] Global data are more limited, but an estimated 90% of paediatric mortality due to COVID-19 is observed in low- and middle-income countries (LMICs) with much of this risk concentrated among children <1 year of age.[4] Important questions remain, including what are the clinical characteristics and outcomes of critical paediatric COVID-19 globally? What are risk factors for death among children with critical COVID-19, and can they be modified?

Gonzalez-Dambrauskas et al. in the *Lancet Regional Health − Americas* provide important data to begin to answer these questions.[5] The team should be commended for establishing this unfunded, multinational group of investigators representing paediatric intensive care units from geographically diverse high-income countries (HICs) and LMICs. Strengths of the study include the prospective study design, detailed statistical analyses, and utilization of standardized disease severity classifications. They enrolled over 550 patients with severe or critical COVID-19 or Multisystem Inflammatory Syndrome in Children (MIS-C). Vasopressors (56%) and invasive mechanical ventilation (41%) were the most common ICU-level support modalities. Importantly, about half of the enrolled children had no underlying comorbidities. Given that the majority of enrollments occurred in LMICs, some of which are reported to have high COVID-19-associated paediatric mortality rates,[4] the observed 10% mortality[5] is not unexpected and provided an opportunity to begin to assess risk factors for death, which has not be possible in most other studies. Outcomes were better among the children who had MIS-C and who received usual therapies for MIS-C (e.g., intravenous immunoglobulin, antiplatelet therapy, methylprednisolone). Older children are more likely to have MIS-C, complicating the analysis of the age-associated outcomes. In the subset of children without MIS-C, multivariable analysis found that underlying comorbidities (particularly pulmonary, liver, or malignancy), lower respiratory tract symptoms, hypoxemia on admission, and complications, such as acute respiratory distress syndrome or bacteraemia, were independently associated with mortality.

Data about the impact of interventions intended to decrease death in children have been limited. Although no definitive benefit was observed with dexamethasone in this study when focusing on the subset of children without MIS-C (adjusted Odds Ratio 0.97, 95% Confidence Interval 0.49, 1.91), the RECOVERY Trial in adults had much greater enrollment numbers and power to detect a difference in mortality (>6400 enrolled, 22.9% versus 25.7%, $p < 0.001$).[6] The inability to find a difference in this paediatric study may have been due to a lack of statistical power, unmeasured confounders in the non-randomized design, missing treatment data for some medications, or the percentage of patients receiving mechanical ventilation who derive the most benefit from dexamethasone. Clinical trials are sorely needed to provide more data about the safety, pharmacokinetics and pharmacodynamics, and efficacy of treatment strategies (e.g., remdesivir, baricitinib) in children.

Ultimately, the best approach to mitigating COVID-19-related morbidity and mortality in children will be the prevention of COVID-19 through vaccination. mRNA vaccines are currently available in the U.S. and many HICs down to age 5 years. Post-licensure data suggest that these vaccines, when administered to children, are effective in preventing COVID-19 hospitalizations, critical COVID-19 (even in the Omicron era), and MIS-C.[7-9] Children <5 years of age currently remain ineligible for vaccination, although press releases

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suggest that data may support mRNA vaccine authorization in the near future in children 6 months of age and older. Unfortunately, these life-saving interventions have limited availability in LMICs. Other types of vaccines, such as inactivated SARS-CoV-2 vaccines, have been administered to children down to age 3 years, although publicly available clinical trial data remain limited.[10] In areas with limited resources, prioritizing vaccinating children at highest risk of mortality, as identified by Gonzalez-Dambrauskas et al.,[5] and their close contacts may be an approach to minimizing paediatric deaths until widespread vaccine availability.

Large, multinational studies such as this one are important for identifying modifiable risk factors for severe COVID-19 and guiding targeted interventions to improve paediatric outcomes, especially as novel variants emerge and new therapeutics become available. Future studies are needed to determine the differences in outcomes between HICs and LMICs and to elucidate the driving factors for disparities in resource-limited settings. Such data could inform the prioritization of health policy interventions to mitigate paediatric disease severity and reduce mortality on global and local scales. Addressing the issues of social and health inequities, access to vaccines, and vaccine delivery and hesitancy will be critical to preventing the COVID-19 threat to the health of all children.

Contributors

E.J.A., C.A.R. and S.K. were involved with drafting and editing this linked commentary. They have reviewed and agreed upon the manuscript content.

Declaration of interests

S.K.'s institution has received funding from NIH to conduct clinical trials of Moderna and Janssen COVID-19 vaccines, and funding from Pfizer to conduct clinical trials of Pfizer-BioNTech COVID-19 vaccines. C.A.R.'s institution has received funding to conduct clinical research unrelated to this manuscript from BioFire Inc., GSK, MedImmune, Micron, Merck, Novavax, PaxVax, Regeneron, Pfizer, and Sanofi-Pasteur. She is co-inventor of patented RSV vaccine technology, which has been licensed to Meissa Vaccines, Inc. Her institution has received funding from NIH to conduct clinical trials of Moderna and Janssen COVID-19 vaccines. E.J.A. has consulted for Pfizer, Sanofi Pasteur, Janssen, GSK, and Medscape, and his institution receives funds to conduct clinical research unrelated to this manuscript from MedImmune, Regeneron, PaxVax, Pfizer, GSK, Merck, Sanonfi-Pasteur, Janssen, and Micron. He also serves on data and safety monitoring boards for Kentucky BioProcessing, Inc., and Sanofi-Pasteur. He serves on a data adjudication board for WCG and ACI Clinical. His institution has also received funding from NIH to conduct clinical trials of Moderna and Janssen COVID-19 vaccines.

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