VIEWPOINT

Inclusion of Children in Clinical Trials of Treatments for Coronavirus Disease 2019 (COVID-19)

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Clinical trials of several novel and repurposed therapies for coronavirus disease 2019 (COVID-19) are being rapidly designed or already enrolling patients. However, few trials are currently open to enrolling children. Between February 1 and April 11, 2020, there were 275 COVID-19 interventional clinical trials registered on ClinicalTrials.gov, of which only 30 were open to any patients younger than 18 years (**Figure**). Global large-scale trials by the National Institutes of Health (NIH) and the World Health Organization that plan to study multiple treatment options simultaneously (ie, the Adaptive COVID-19 Treatment Trial[1] and SOLIDARITY Trial,[2] respectively) plan to enroll only adults according to study protocols as of April 15, 2020.

The exclusion of children from COVID-19 clinical trials is a tremendous lost opportunity to generate timely knowledge to guide treatment of pediatric populations. Without adequate studies, if any COVID-19 therapies successfully obtain regulatory approval, clinicians would need to prescribe them for children off label. Simple extrapolation from adult to pediatric patients may not account for developmental differences in pathophysiology and drug metabolism. In the absence of pediatric data available at the time of regulatory approval, children may be exposed to ineffective dosing or possibly unsafe treatments. Pediatric investigators are currently working collaboratively to collect multicenter observational data as the next best option. It is possible that pediatric trials could be initiated after regulatory approval, but these likely will be more challenging and time consuming to conduct once the peak of the COVID-19 pandemic has passed.

Early reports were that the clinical course of COVID-19 generally appears to be milder in children, but there are emerging epidemiologic data suggesting that the infection can be serious in certain pediatric populations, underscoring the public health need for rigorous study of potential COVID-19 therapies in children. As of April 15, 2020, there have been 132 COVID-19 pediatric intensive care unit admissions for patients younger than 18 years reported among 182 North American pediatric intensive care units submitting data.[3] In the largest case series to date and to our knowledge of pediatric patients with COVID-19, 125 of 2141 patients (5.8%) had severe or critical disease, and the reported proportion of severe or critical cases was highest in the youngest age groups: 10.6% (40 of 379) in those younger than 1 year and 7.3% (36 of 493) in those aged 1 to 5 years.[4] The risks of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and severe COVID-19 also may be heightened in children who are immunocompromised, receiving immunosuppressive medications, or have preexisting lung or respiratory conditions (including e-cigarette use or vaping).

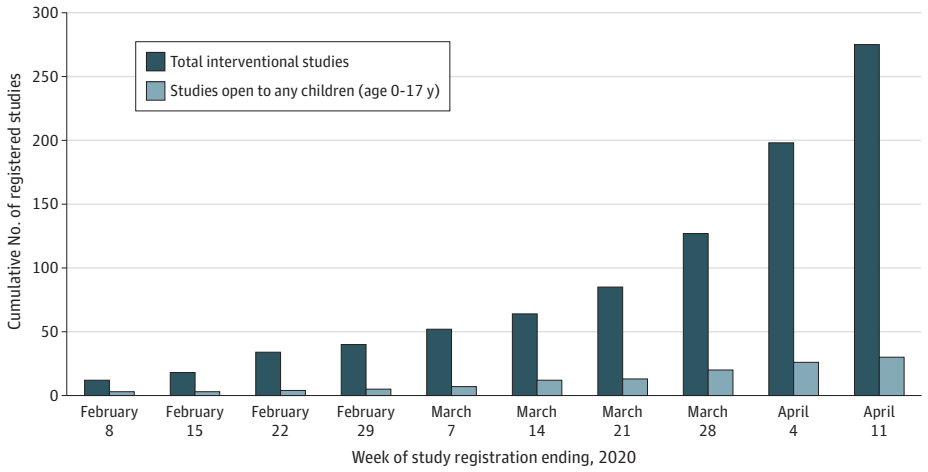
Past experience demonstrates that it is possible to enroll children in clinical trials during epidemics. During the 2014 Ebola epidemic, for example, the NIH and partners conducted a randomized clinical trial of a monoclonal antibody (PREVAIL II) and a larger trial of 4 investigational therapies for Ebola virus disease[5]: both trials were open to patients of any age and ultimately enrolled 23 (32%) and 172 children (26%), respectively. (One of the therapies included in the Ebola trial, remdesivir, is now being studied for COVID-19.)

Legislators in the US and European Union have enacted statutory and regulatory changes over the past decade intended specifically to address the underrepresentation of children in clinical trials. In the US, the Pediatric Research Equity Act authorizes the US Food and Drug Administration (FDA) to require pediatric studies for new drugs or biologics as well as new indications and formulations of already-approved products. In addition, the Best Pharmaceuticals for Children Act grants a financial incentive (additional 6 months of market exclusivity) to sponsors that voluntarily conduct pediatric studies requested by the FDA and directs the NIH to identify key therapeutic needs in children. In the European Union, the Pediatric Regulation similarly requires pediatric studies and grants a 6-month extension of patent protection once all such studies are completed.

These policies have led to substantial changes in the pediatric research enterprise, including the completion of hundreds of pediatric studies. However, there are important limitations to these pediatric requirements and incentives. Pediatric studies required under the Pediatric Research Equity Act[6] or the European Union's Pediatric Regulation[7] are often deferred until after approval and are subject to multiple delays. In the US, 18 of 114 drugs (15.8%) had any pediatric efficacy, safety, or dosing information in their labels at the time of approval, and 47 of 114 (41.2%) had any pediatric information after a median follow-up of 6.8 years.[7]

Regulators, public health agencies, and trial investigators and sponsors should act to ensure the clinical study of COVID-19 in children and the availability of pediatric labeling data on market entry of new products. First, the NIH could use its authority under the Best Pharmaceuticals for Children Act to designate COVID-19 therapies as high priority for pediatric study and sponsor a treatment trial in pediatric populations parallel to its ongoing adaptive study in adults (alternatively, the NIH and World Health Organization could broaden the inclusion criteria for their trials to include all ages). Second, in addition to encouraging sponsors to enroll adolescents in currently adult-only trials, the FDA should specifically require pediatric studies under the Pediatric

Figure. Number of Total Studies and Studies Open to Children for Coronavirus Disease 2019 Interventions Registered on ClinicalTrials.gov



The cumulative number of total studies and studies open to children (age 0-17 years) registered on ClinicalTrials.gov by week of study registration is shown. Excludes observational studies and patient registries.

Research Equity Act to ensure timely initiation of pediatric study through concurrent enrollment of children and adults in ongoing trials. The FDA and European Medicines Agency should also coordinate their pediatric study requirements to reduce inefficiencies and duplication. Third, institutions joining multicenter trials as a research site should work with sponsors to advocate for the enrollment of pediatric patients whenever feasible. Fourth, these considerations also support the importance of including children in other COVID-19 studies, including population screening and serosurveys, transmissibility studies, and vaccine trials. Finally, the pandemic has revealed substantial health disparities, and it is critical that COVID-19 studies enroll participants from underrepresented communities across the lifespan.

Even in the race to develop new therapies for COVID-19, generating high-quality evidence to guide the treatment of children is necessary, feasible, and could be done efficiently, such as through expansion of existing studies and through parallel pediatric adaptive trials. The past decade of policy reforms and improved research infrastructure—aimed at closing the evidence gap for the use of new medications in children—should serve as the foundation for this urgent advocacy to include pediatric patients in COVID-19 clinical trials.

ARTICLE INFORMATION

Published Online: May 7, 2020. doi:10.1001/jamapediatrics.2020.1888

Conflict of Interest Disclosures: Mr Hwang reports prior employment by Blackstone and Bain Capital, which have invested in health care companies. Dr Randolph reports grants from Centers for Disease Control and Prevention during the conduct of the study. Dr Bourgeois' work is supported by a grant from the Burroughs Wellcome Fund and by the Harvard-MIT Center for Regulatory Science.

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