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VIEWPOINTS

Coronavirus Disease 2019 (COVID-19) Pharmacologic Treatments for Children: Research Priorities and Approach to Pediatric Studies

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Clinical trials of pharmacologic treatments of coronavirus disease 2019 (COVID-19) are being rapidly designed and implemented in adults. Children are often not considered during development of novel treatments for infectious diseases until very late. Although children appear to have a lower risk compared with adults of severe COVID-19 disease, a substantial number of children globally will benefit from pharmacologic treatments. It will be reasonable to extrapolate efficacy of most treatments from adult trials to children. Pediatric trials should focus on characterizing a treatment's pharmacokinetics, optimal dose, and safety across the age spectrum. These trials should use an adaptive design to efficiently add or remove arms in what will be a rapidly evolving treatment landscape, and should involve a large number of sites across the globe in a collaborative effort to facilitate efficient implementation. All stakeholders must commit to equitable access to any effective, safe treatment for children everywhere.

Keywords. COVID-19; children; trials; pharmacokinetics; research.

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (COVID-19), continues to spread rapidly globally. Most individuals infected have mild-to-moderate disease manifestations. However, a substantial subset of infected adults, and some children, have more severe disease needing hospitalization, with some who are critically ill, requiring mechanical ventilation, circulatory support and, in some instances, extracorporeal membrane oxygenation [1]. The reported case-fatality rates in adults are variable, with the true value estimated to be 0.2–3% [2, 3], with increased mortality risk associated with older age and chronic underlying medical conditions [1]. There is a clear need for treatment options for adults with COVID-19 and both pre- and postexposure prophylaxis in exposed adult contacts. Clinical trials for adults have been rapidly designed, are being implemented across the globe, and will provide high-quality evidence to inform treatment and prevention approaches [4].

Contrary to adults, children and adolescents (hereafter the term "children" is inclusive of adolescents) are often not considered during initial development of novel therapies for infectious diseases until late, limiting their access to efficacious treatments or resulting in off-label use of medications without pediatric safety data or evidence-based dosing recommendations [5, 6]. Although their risk of poor outcomes appears to be lower than in adults, children still stand to benefit substantially from potential COVID-19 treatments. In addition to direct impact by infections, children may serve as an important intermediary for transmission in communities, as is seen with influenza [7]. Thoughtful and timely inclusion of children in COVID-19 therapeutic research should be initiated now to avoid unnecessary delays and preventable morbidity and mortality in children.

We review the rationale for studying pharmacologic treatment in children with COVID-19, highlight the key research priorities for children from a study design perspective, and propose potential approaches to move this field of research forward. Studies of COVID-19 vaccines and convalescent plasma for children are critical but require different considerations and are not discussed here.

COVID-19 DISEASE IN CHILDREN AND RATIONALE FOR PEDIATRIC PHARMACOLOGIC TREATMENT STUDIES

Emerging data suggest that children have less severe manifestations of COVID-19 than adults, although infants appear to be at higher risk for severe or critical disease than older children. In a large cohort of laboratory-confirmed and probable

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pediatric cases reported by the Chinese Centers for Disease Control, 125 of 2143 cases were classified as severe (112 [5%], defined as dyspnea, cyanosis, or oxygen saturation <92%) or critical (13 [0.6%], defined as respiratory failure or other organ dysfunction) [8]. Children less than 1 year of age had a higher risk of severe or critical disease (10.6%) compared with children of older ages (ranging from 3.0% to 7.3%). Only 1 child, a 14-year-old boy, died. In another cohort of 171 children with confirmed SARS CoV-2 from China, 4 (2.3%) children had oxygen saturations less than 92% and 3 (1.8%) required intensive care and invasive mechanical ventilation, one of whom died [9]. A preliminary report from the US Centers for Disease Control and Prevention describes comparable disease characteristics in 2572 confirmed cases of COVID-19 in children younger than 18 years of age [10]. Of all pediatric cases reported, 5.7% were hospitalized, although, for many, the hospitalization status was not reported. Of 745 pediatric cases with known hospitalization status, 145 (20%) were hospitalized, including 15 admitted to the intensive care unit (ICU). Many, but not all, had some underlying comorbidity, including chronic lung disease, immunosuppression, or cardiovascular disease. Of the 95 children younger than 1 year of age with known hospitalization status, 59 (62%) were hospitalized including 5 admitted to the ICU. Three deaths were reported; whether the underlying cause of death in these cases was COVID-19 was not confirmed.

These data demonstrate that, although the risk of severe disease and mortality is significantly lower for COVID-19 in children than in adults, children may still develop severe illness and require supportive care, with some progressing to critical illness and death. A consensus statement of pediatric experts notes that, even though many children with severe or even critical COVID-19 may be treated with supportive care alone, pharmacologic treatment should be considered on a case-by-case basis for those with severe disease, and with a lower threshold in critical cases [11].

As the magnitude of this pandemic grows, the number of children expected to benefit from COVID-19 treatment will increase. Using data on pediatric disease burden and severity from China and early data from US pediatric ICUs (PICUs), model-based estimates suggest that, in the United States alone, if 5% of children nationally become COVID-19 infected, 9907 children would require hospitalization with 1086 requiring PICU admission [12]. If 50% of children nationally become infected, then as many as 99 073 and 10 865 children would require hospitalization and PICU admission, respectively. These factors alone justify the need for safe, effective pharmacologic treatment for children.

However, in populations in whom conditions such as malnutrition, human immunodeficiency virus (HIV), and tuberculosis (TB) are prevalent, the risk of poor outcomes from COVID-19 in children may be even higher. Undernutrition in children, which increases the risk of poor outcomes from many infectious diseases, is highly prevalent globally and likely to rise during the pandemic [13, 14]. Child undernutrition may become a more widespread problem during the pandemic even in well-resourced settings where there has been a very low prevalence traditionally. Only approximately half of the 2.8 million children living with HIV globally are currently on antiretroviral therapy, with those not on treatment likely to be immunosuppressed and potentially at higher risk of severe COVID-19 should they become infected [15]. An estimated 1 million children develop incident TB disease each year, and many of those children develop post-TB lung disease; these are also likely higher-risk pediatric groups for complicated disease [16]. Additionally, these comorbidities are most prevalent in resource-limited settings with strained health systems that have limited capacity to deliver supportive care, such as oxygen therapy, intensive care, and mechanical ventilation [17–19]. The potential benefit of safe, effective medications for COVID-19 will be even greater in such settings.

Other than children with severe disease, there may also be a role for agents that act directly on the virus for treatment of children with mild or even asymptomatic disease to interrupt the transmission of the virus or as pre- or postexposure prophylactic treatment for children at a high risk of poor outcomes. There is currently insufficient evidence to justify either approach, and any treatments studied in children for these indications would need to have an excellent safety profile, as the direct benefit for uninfected or infected but minimally symptomatic children would be lower.

KEY CONSIDERATIONS FOR RESEARCH OF COVID-19 TREATMENTS IN CHILDREN

Efficacy studies of pharmacologic treatments for COVID-19 in children, such as from randomized controlled trials, would be difficult to implement given the large sample size typically required for such trials and the lower numbers of children who develop clinically severe disease. However, efficacy data from adult clinical trials can often be extrapolated to children if children are expected to have a similar risk of disease progression and response to treatment as adults, assuming similar drug exposures in children and a similar exposure–response relationship as adults [20]. There is still much that is unknown about the pathophysiology of COVID-19, the risk of disease progression, and potential response to treatment, in both adults and children. However, if a medication is shown to be efficacious in adults with COVID-19, it is reasonable to assume that it would be similarly effective in children for a comparable indication. This would likely be true for antivirals that target the virus itself. Whether this will be true across all ages for agents with different mechanisms, such as modulation of the immune reaction, would need to be carefully considered, especially among young children in whom immune systems are immature. It may not be possible to extrapolate efficacy from adult studies for

treatment of disease types that are clearly different or specific to children. The Kawasaki disease–like multisystem inflammatory syndrome in children (MIS-C) now being described in children is an example [21]. The efficacy of pharmacologic treatments for MIS-C will need to be evaluated specifically in children.

Additional information in adults and children about biomarkers of treatment response, such as longitudinal changes in viral shedding, variability in baseline or cytokine measurements, and characterizing pharmacokinetic-pharmacodynamic (PK-PD) relationships of treatments to clinical outcomes and any biomarkers, would be critical for understanding how to extrapolate efficacy to children. Despite these knowledge gaps, the efficacy of pharmacologic treatments for COVID-19 will be challenging to definitively establish or confirm in children through large phase III trials. Attempting to do so may ultimately result in unnecessary delays in access to critical treatments for children when, alternatively, efficacy can likely be extrapolated from adults for most pharmacologic treatments.

The pediatric research priorities for pharmacologic treatments of COVID-19 are to characterize each agent's pharmacokinetics and optimal dose, and safety at that dose, across the age and disease spectrum. Weight-based dosing cannot simply be extrapolated from adults to children, although this is frequently done in clinical practice. Due to well-described changes in biological processes with body size, the linear extrapolation of milligram/kilogram doses from adults to children results in lower drug exposures in children, with the worst underexposure in the smallest children [22]. Additionally, age-related changes due to maturation of gastrointestinal function and gastric pH, renal function, alterations in body composition, such as percentage of body fat and body water, and the capacity of enzymes responsible for drug metabolism have important effects on pharmacokinetics in young children [23]. Critical illness can also affect pharmacokinetics of drugs in adults and children and is an important consideration for COVID-19 treatments [24]. Pharmacokinetic studies that include children across the age and disease spectrum are therefore needed to identify optimal pediatric doses [22]. As the need is urgent, pharmacokinetic modeling methods, including use of physiologically based population models or the application of allometric scaling to adult pharmacokinetic parameters to account for size, should be used to define rational pediatric dosing in the interim.

For most medications, children tend to have similar or even reduced risks of adverse effects. However, this cannot be assumed, as there are idiosyncratic cases where children have unexpected or more severe adverse effects [25, 26]. Evaluating safety in children is therefore critical. While children have better outcomes than adults with COVID-19, the risk–benefit ratio of therapy may be different. Where possible, characterizing the relationships between drug exposure and adverse effects, such as QT-interval prolongation, in children is very useful.

The approach described here is consistent with the current regulatory framework for pediatric drug development, which is described in detail elsewhere [20, 27]. Application of this framework to the development of COVID-19 pharmacologic treatments should consider the urgency of the current situation. We urge acceleration of this process, as pediatric trials and approvals are frequently very delayed, with often more than 10 years between adult and pediatric approvals of TB and HIV medications as examples [28, 29]. We propose the following approach and key considerations for research on COVID-19 pharmacologic treatments for children.

1. Begin planning for pediatric trials immediately. General preparation for pediatric trials can and should begin immediately. This would include identifying potential sites, starting to develop a protocol template, liasing with relevant laboratory, regulatory, statistical, and other trial support. These activities would not be contingent on the details of any specific agents and would allow for rapid protocol development and opening of pediatric trials with minimal delay once adult efficacy data are available.
2. Open pediatric trials promptly when appropriate. Trials in children should begin when there is reasonable evidence from adults of efficacy and safety of an agent. This would ideally be from large phase III randomized controlled trials in adults, and many such studies are ongoing with results expected to be rapidly disseminated. However, given the lack of available agents and the urgent need, it may be preferred to start pediatric trials ahead of such definitive results. The timing of trials would depend on the balance of potential risks and benefits to participants of individual pharmacologic treatments. This would necessarily include a careful consideration of (1) the expected outcome in the absence of any pharmacologic treatment, which may be dependent on the indication of the tested treatment (treatment of severe COVID-19 vs prophylaxis) and may be context specific, with greater risks of nontreatment in low-resource settings with limited capacity to provide supportive care such as oxygen, mechanical ventilation, intensive care; (2) the expected efficacy of the treatment being evaluated, with a lower threshold for testing of agents with evidence of substantial efficacy; (3) the safety of the treatment, with a lower threshold for testing of agents with evidence of an excellent safety profile.
3. Phase I/II pediatric trials are the priority. The primary focus of pediatric trials for most treatments should be characterizing the pharmacokinetics and optimal dose, and establishing safety and documenting any short- and long-term toxicity at that dose, across the age and disease spectrum. Although not primarily efficacy trials, these studies should carefully document outcomes and treatment response, including with any biomarkers, in relation to drug exposures. Pediatric trials should follow emerging

best practices, including enrolling children of all ages in parallel rather than utilizing an age de-escalation design as has been frequently used historically, and dosing medications in weight bands [30]. Child-friendly formulations of orally administered medications that are acceptable, palatable, and able to be taken by young children are important pediatric considerations and will ultimately be needed. However, given the urgency, adult formulations may need to be evaluated initially in pediatric studies [31], and absence of a child-friendly formulation should not unnecessarily delay access for children to treatments they could benefit from.

4. Utilize a platform- or adaptive-trial approach. The treatment landscape will rapidly evolve, especially early during the pandemic. Preclinical work has identified many potentially effective agents that may be evaluated once more information is available. A platform- or adaptive-type trial that would allow addition of arms to an ongoing trial as efficacy data for other agents emerge in adults would be a highly efficient and cost-effective approach. Developing individual trials for single agents will be costly and result in substantial avoidable delays. The complexity and the potential for many diverse stakeholders including multiple industry partners will require an organizing partner such as the World Health Organization (WHO) and/or the US National Institutes of Health (NIH). The WHO and Unitaid, along with multiple international partners, have convened the Access to COVID-19 Tools (ACT) Accelerator to coordinate development of COVID-19 treatments and other products [32]. The NIH has established a public–private partnership called Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) to coordinate and speed development of promising COVID treatments and vaccines [33]. However, it is not clear if and how these groups are considering the needs of children. These collaborations should take an active role in developing pediatric trials, and should include pediatricians, pediatric trialists, and trial Network representatives.
5. Utilize existing experienced trial networks with multiple international sites in diverse settings. Multicenter studies will be required in order to rapidly enroll sufficient children across the age and disease spectrum, as the overall number of children requiring treatment will likely be inadequate in any one or small number of sites. The intensity of the pandemic will vary in different places at different times and may be difficult to predict. To account for this, sites should ideally be established in diverse, international settings, including US domestic and other well-resourced settings, and resource-limited settings where feasible and appropriate. Existing pediatric therapeutics research networks, such as pediatric HIV and TB trial networks, are strategically placed and well established to rapidly develop and implement such trials. These networks have core functions for trial support, a history of working with regulatory agencies and industry, and maintain diverse international sites with expertise in implementing phase I/II trials. Collaboration of multiple existing networks may further improve efficiency.
6. Obtain opportunistic pharmacokinetic data where appropriate ahead of formal trials. Prior to the availability of high-quality evidence, it may be that severely ill children with COVID-19 are treated with one or more agents at the discretion of their treatment teams, either off-label or through compassionate use. Registries should be developed, as has been done in the United States [34], and used for all pediatric patients being treated with COVID-19, and serum collected and banked for further analysis. This provides an opportunity to generate important preliminary data on pharmacokinetics and safety prior to a formal trial. The risk of doing such pharmacokinetics studies in children already receiving these treatments is minimal, but the potential benefit is substantial. An observational pharmacokinetic study of these treatments with data pooled from multiple sites and analyzed using optimal statistical methods would inform both plans for definitive future pediatric trials and dosing recommendations for routine treatment.
7. Utilize pharmacometrics, data integration, and population pharmacokinetic modeling methods. Pharmacokinetic modeling methods should be used to optimally inform trial design and analyze data. The population approach can leverage sparse data and suboptimal sampling designs and characterize inter-child variability, which are essential given the high variability in pharmacokinetics in children and consideration of the demanding and critical environment of treating this disease. Population pharmacokinetic models with clinical trial simulations can then be used to propose practical doses for use in the field or to inform additional trials. Even in the absence of pediatric data, population pharmacokinetic models based on adult data can be scaled using allometry to better inform pediatric dosing.
8. Disseminate results rapidly. Results should be disseminated rapidly and publicly to inform ongoing clinical care and the evolving research agenda.
9. Ensure equitable access to safe, effective pharmacologic treatments for all children. Governments, international agencies, and industry partners must ensure widespread, equitable, low-cost access to effective treatments for children, including in resource-limited settings.

PEDIATRIC CONSIDERATIONS FOR SELECTED POTENTIAL COVID-19 TREATMENTS

The evidence on high-priority potential candidates that are being evaluated in ongoing or planned trials in adults, or are being used off-label or for compassionate use, has been recently reviewed in detail [4, 11, 35]. Table 1 describes pediatric considerations

Table 1. Summary of Pediatric Considerations and Research Priorities for Select Key COVID-19 Pharmacologic Treatment

Pharmacologic Treatment	Overview, Data in Adults	Pediatric Considerations	Pediatric Research Priorities
Remdesivir or GS-5347 (Gilead Pharmaceuticals)	• An adenine nucleoside analogue with in vitro antiviral activity against multiple RNA viruses, including SARS-CoV, MERS-CoV, and now SARS-CoV-2 [36]. • Dose in trials in adults with COVID-19: 200 mg IV on day 1 followed by 100 mg IV daily up to day 10 [4, 37], but minimal PK, safety data in adults or children is in the public domain. • Preliminary reports are conflicting, but results from at least 1 trial in adults show a shortened time to recovery with remdesivir [38].	• 41 children received remdesivir in the PALM trial (2018–19) for Ebola. Pediatric safety data were not separately reported; it is unclear whether PK was done [39]. • It is available for compassionate use for children <18 years, with confirmed COVID-19 and severe disease [40]. • Currently recommended dose for children <40 kg: 5 mg/kg IV loading dose on day 1, followed by 2.5 mg/kg IV q24h for 5–10 days [11]. • Milligram/kilogram dosing across all ages may result in low exposures in smaller children.	• As 1 adult controlled trial supports the use of remdesivir for COVID-19, its dosing and safety should be evaluated in children across the age spectrum in a pediatric trial. • Sparse PK sampling in children in the compassionate-use program could be easily accomplished, and Gilead should support or allow this until a trial is open. • Adult PK data should be adapted using allometric scaling to inform more optimal dosing for children now, which could be further informed by any pediatric PK data from the PALM trial if available.
Hydroxychloroquine	• A chloroquine derivative, used for malaria and rheumatologic conditions [41] that, compared with chloroquine, may have an improved safety profile and potency against SARS-CoV-2 in vitro [4, 42]. • Causes QT prolongation, and ventricular arrhythmia and torsades de pointes have been reported [41]; initial reports of its use in adults with COVID-19 describe a substantial risk of QT prolongation [43, 44]. • It has complex pharmacology with a long half-life and adult COVID-19 trials are evaluating multiple different dosing strategies [4, 45]; PK data in adult COVID-19 patients [45] and modeled optimal doses for adults with COVID-19 have been published [42, 46]. • A trial showed no benefit of hydroxychloroquine for postexposure prophylaxis in high-risk adults [47].	• There is limited high-quality published pediatric data to date. • We did not identify pediatric PK data in the public domain. • Children may be particularly susceptible to QT-interval prolongation with 4-aminoquinoline compounds, such as chloroquine and hydroxychloroquine, with serious adverse effects possible after small overdoses of chloroquine [48]. • Consensus statement recommends multiple possible dosing strategies, although there is minimal supporting PK data [11].	• Pediatric PK, dosing, safety data are needed if it continues to be used, especially as drug-related QT-interval prolongation is usually concentration-dependent and children may have increased susceptibility. • For children with COVID-19 receiving hydroxychloroquine for treatment, opportunistic PK data would inform dosing guidance and future studies. • Should adult clinical trials demonstrate that hydrochloroquine is safe, effective for COVID-19 treatment, a pediatric trial should characterize PK and dosing in children across the age spectrum that achieves exposures approximating those in adults receiving the recommended dosing strategy, and characterize safety at that dose.
Lopinavir/ritonavir	• A protease inhibitor widely used for HIV treatment in adults and children. • Initial report of lopinavir/ritonavir for COVID-19 was disappointing; it is still being studied in international trials in adults [4], but none in the United States. • Adult studies are evaluating the same dose as for HIV treatment (400/100 mg/dose BID).	• The pediatric dose that approximates these exposures in adults is well established from children with HIV [49]. • It should be used with caution in preterm neonates in the postnatal period due to potentially serious adverse effects [49]. • Consensus among US experts is that currently it has a limited role, if any, for children with COVID-19 [11].	• Should adult trials demonstrate efficacy against COVID-19, given the existing robust knowledge base in children, lopinavir/ritonavir PK and safety studies in children are a much lower priority.
Tocilizumab	• Some adults with COVID-19 develop hyperinflammation with a viral-induced cytokine release syndrome dominated by IL-6, where elevated levels are associated with an increased risk of mortality [50–52]. • Tocilizumab, an anti–IL-6 receptor monoclonal antibody, is FDA approved to treat cytokine-release syndrome in children 2 years of age and older and adults [53], and being studied in trials in adults with COVID-19 [4]. • Tocilizumab may be effective in treating a subgroup of COVID-19 patients who develop cytokine release syndrome [54].	• Although not yet described in pediatric COVID-19, children are known to develop cytokine release syndrome [55]. • Prior PK studies of tocilizumab in 28 children for cytokine release syndrome following CAR-T cells for B-cell ALL showed doses of 6.9 to 12 mg/kg were pharmacologically active and resulted in appropriate concentrations [56]. • Optimal dosing of tocilizumab for infection-related cytokine release syndrome remains unknown. • The increased risk of developing TB with tocilizumab is a serious concern for its use in high-TB-burden settings [53].	• Better characterization of cytokine release syndrome in critically ill pediatric patients with COVID-19 is needed. • PK and safety data in children <2 years of age are needed. • Opportunistic PK and safety data in young children (<2 years) with COVID-19 treated off-label could rapidly inform current care and future research.

Abbreviations: ALL, acute lymphoblastic leukemia; BID, twice daily; CAR, chimeric antigen receptor; COVID-19, coronavirus disease 2019; FDA, Food and Drug Administration; HIV, human immunodeficiency virus; IL-6, interleukin 6; IV, intravenous; MERS-CoV, Middle East respiratory syndrome coronavirus; PALM, Pamoja Tulinde Maisha; PK, pharmacokinetics; q24h, every 24 hours; SARS-CoV, severe acute respiratory syndrome virus; TB, tuberculosis.

related to 4 select agents being evaluated as priorities in adult trials and used currently in some scenarios in routine clinical care: remdesivir, hydroxychloroquine, lopinavir/ritonavir, and tocilizumab [4, 11].

This is not an exhaustive list of potential COVID-19 treatment candidates, as a broad range of agents are currently being considered [4]. Other potential pharmacologic treatments include, but are not limited to, ribavirin, umifenovir, interferon-β,

nitazoxanide, and favipiravir [4]. Innovative preclinical studies have identified a large number of potential candidates that may have effects on COVID-19, including existing and novel compounds [57]. This treatment landscape is likely to evolve rapidly. Pediatric trials will need to be responsive to the emerging data from adult observational studies and trials in order to ensure that knowledge gaps for potentially efficacious therapies can be rapidly addressed in children.

Other important research areas for children include the role of passive antibody transfer via breast milk and the benefit of maternal treatment (including during pregnancy and breastfeeding). Although vertical transmission appears rare, early-life exposure to maternal or other caregiver disease likely increases the risk of neonatal infection, highlighting the need for more data regarding safety of treatments in pregnant and breastfeeding women, and the role of passive immunity and protection via breast milk.

CONCLUSIONS

Despite their apparent lower risk of severe disease, there are a substantial number of children who will benefit from safe, effective COVID-19 treatments and this number will continue to increase globally. In addition, postexposure chemoprophylaxis may prove to be a potent tool in controlling disease transmission, especially in the absence of effective vaccines. Children should not be overlooked in therapeutic research for this global pandemic threat. Priority pediatric research questions should target the knowledge gaps for each specific agent and should focus on the pharmacokinetics, optimal dosing, and safety across the entire age spectrum, including young children and those with comorbidities. Such studies will require coordinated efforts across multiple sites. The global community should commit to ensuring equitable access to any evidence-based treatments for children, including in resource-limited settings.

Notes

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