Risk Assessment of therapeutic agents under consideration to treat COVID-19 in Pediatric Patients and Pregnant Women

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Abstract

Aim. Repurposing strategies to address the COVID-19 pandemic have been accelerated. As both pregnant and pediatric patients are likely to be excluded from most planned investigations, the list of repurposed options and the available data on these drugs and vaccines provides a baseline risk assessment and identifies gaps for targeted investigation. Methods. Clinical trials have been searched and reviewed; twenty-three repurposed drugs and drug combinations and 9 candidate vaccines have been assessed regarding the availability of relevant data in pediatrics and pregnant women and to evaluate expected or unanticipated risk. Results. Thirteen of the repurposed drugs or drug combinations are indicated for use in pediatrics in some age category albeit for indications other than COVID-19; 10 of these are indicated for use in pregnant women. Even in cases where these drugs are indicated in the populations, source data from which safety and or dosing could be extrapolated for use in COVID-19 is sparse. Vaccine trials are ongoing and generally exclude pregnant women; only in a few instances have pediatric subgroups been planned for enrollment. Data from individual case studies and RWD may suggest that subpopulations of both pediatric patients and pregnant women may be more at risk, particularly those in an increased inflammatory state. Conclusion. In conjunction with more prospective collaboration, plans are evolving to ensure that we will be better prepared to address similar situations especially in pediatrics and pregnant women where experience is limited and actual practice relies heavily on leveraging data from other populations and indications.

Risk Assessment of therapeutic agents under consideration to treat COVID-19 in Pediatric Patients and Pregnant Women

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What is already known about this subject:

- Coronavirus disease (COVID-19) is caused by the SARS-Cov-2 virus that can spread from person to person. While people of any age who have serious underlying medical conditions may be at higher risk for more severe illness, both pregnant women and children are still at risk for both catching and transmitting the virus.
- Various treatment modalities (single agents, drug combinations and vaccines) are currently being researched and clinically evaluated. Given the time-dependent changes in physiologic parameters and

dynamics of both populations, evaluating the risk of treatment for various treatment options is a critical step in evaluating their suitability for pregnant women and children.
- Many (but not all) of the current modalities under investigation represent repurposed drugs and vaccines that have been studied previously for either related or unrelated indications. Given that these agents have been studied previously, it is possible to evaluate risk and preliminary dosing guidance in pediatric and pregnant populations.

What this study adds:

- A risk assessment of the repurposed drugs and vaccines currently under consideration for treating COVID-19 specifically focusing on pregnant women and children.
- Considerations for choosing certain agents, dosing and/or adjustments that may be warranted in pregnant women and children in general and specific to the repurposed drugs currently under consideration for treating COVID-19.
- A recommendation for more prospective integration of real-world data (RWD) from pregnant women and children with repurposed drug risk assessment and M&S tools to highlight readiness in the wake of future pandemics.

ABSTRACT – 250-word limit (299)

Aim. Repurposing strategies to address the COVID-19 pandemic have been accelerated in the hope that one or more of these options can be available quickly. As both pregnant and pediatric patients are likely to be excluded from the majority of planned investigations, the list of repurposed options in light of the COVID-19 disease progression and the available data on these drugs and vaccines provides a baseline risk assessment and identifies gaps for targeted investigation in these populations should mainstream clinical trials look promising.

Methods. Clinical trials have been searched and reviewed; twenty-three repurposed drugs and drug combinations and 9 candidate vaccines have been assessed regarding the availability of relevant data in pediatrics and pregnant women and to make a preliminary evaluation of any expected or unanticipated risk.

Results. Thirteen of the repurposed drugs or drug combinations are indicated for use in pediatrics in some age category (2 exclusively in Japan, 1 exclusively in the EU) albeit for indications other than COVID-19; 10 of these are indicated for use in pregnant women (1 exclusively in Japan). Even in cases where these drugs are indicated in the populations, source data from which safety and or dosing could be extrapolated for use in COVID-19 in sparse. Vaccine trials are ongoing and generally exclude pregnant women; only in a few instances have pediatric subgroups been planned for enrollment. Data from individual case studies and RWD may suggest that subpopulations of both pediatric patients and pregnant women may be more at risk, particularly those in an increased inflammatory state.

Conclusion. In conjunction with more prospective collaboration and data sharing, plans are evolving to ensure that we will be better prepared to address similar situations especially in pediatrics and pregnant women where experience is often limited and actual practice relies heavily on leveraging data from other populations and indications.

INTRODUCTION

The COVID-19 pandemic has been a global phenomenon since the later part of 2019 and will likely continue to represent a serious health crisis well into 2021. Early experience with the disease, particularly in China created perceptions about the disease regarding its infectivity, transmission, lethality and disease progression in general which created an initial benchmark for the development of treatment strategies that include an array of modalities dominated by repurposed drugs and vaccines. The availability of these agents was created to a large extent by previous efforts to combat the Ebola virus and other infectious diseases. While clinical trials are ongoing, the virus continues to spread and likely mutates as it touches every corner of the world challenging our initial perception of its progression, infectivity and transmission as well as long term effects, relevant co-morbidities and other risk factors. Both pregnant women and children represent

typical vulnerable populations for drug and vaccine therapy and are likewise commonly excluded from early clinical trials. Nonetheless, they are not immune to the disease and reflect an important subpopulation that clinical pharmacologists and the entire medical community are called upon to advise regarding the treatment strategy, choice of medication and dosing of potentially life-saving agents.

Data are sparse on the effects of medication use during pregnancy. Despite the fact that half of the world's population is female with the majority of women becoming pregnant at some point and many of those women taking some kind of medication during their pregnancy, women are still typically prescribed formulaic therapy, using doses extrapolated from nonpregnant women, men, or pregnant animals. Children (newborns through adolescents) do not fare much better with extrapolation strategies anchoring limited investigation.[1]

Existing COVID-19 treatment options for both pediatric patients and infected pregnant women are mostly supportive in nature and focus on sufficient fluid and calorie intake and additional oxygen supplementation. The intention in these situations is typically focused on preventing ARDS, organ failure and secondary nosocomial infections. The only treatment recommendation for children, published by the Zhejiang University School of Medicine, suggests the use of nebulized interferon alpha-2b and oral lopinavir/ritonavir together with corticosteroids for complications (ARDS, encephalitis, hemophagocytic syndrome or septic shock) and intravenous immunoglobulin for severe cases.[2] In a broader context, repurposing strategies and new drug development in general target the three key stages of infection: preventing the virus entering our cells in the first place, stopping it replicating if it gets inside the cells, and reducing the damage that occurs in tissues; in the case of COVID-19, the lungs and heart.

The objective of this work was to assess the vulnerabilities of pediatric patients and pregnant women to potential therapeutic strategies under consideration to treat the COVID-19 pandemic and the SARS-CoV-2 virus; both drug and vaccine candidates were considered and the effort was focused primarily on repurposed drug candidates and vaccines previously screened for other pathogens (e.g. Ebola). A systematic review of the current COVID-19 disease etiology in these populations along with a review of available clinical experience with potential drug and vaccine candidates in these populations was undertaken with the intention to summarize the available information and assess potential risk factors which may pose an additional safety concern or suggest dose modification in these populations.

METHODS:

The conduct of COVID-19 clinical vaccine and drug trials was determined through systematic searching of the Clinical Trials.gov website. Similarly, each trial was reviewed for the targeting or inclusion of pediatric patients or pregnant women as well as any criteria describing risk to these populations or special precautions (e.g., breast feeding, contraception, etc). The search for current, 2019-2020, peer-reviewed articles via the National Library of Medicine's PubMed site and included Academic OneFile, JSTOR, Sage Journals, and related databases. Google Scholar was also utilized to locate open access articles. Some of the key search terms used to locate articles specific to this review included: "*pediatrics*" , "*pregnancy*" , "*vaccine*", and "*drug trials*" . All terms in each database combined with Boolean operators (AND, OR and/or NOT). Guidance documents were accessed from FDA and EMA websites and pregnancy categories and drug labels of repurposed drugs were accessed directly from the sponsor's website or other publicly available sites. Identified clinical trials for drug, drug combinations and vaccine investigations were reviewed for their inclusion (or not) of pediatric patients and pregnant women.

DISEASE MANIFESTATION

The SARS-CoV-2 virus enters the host cell via the angiotensin-converting enzyme 2 (ACE2) receptor, to which it attaches via the spike (S) protein on the virus envelope. Another host protein called transmembrane protein serine protease TMPRSS2 also plays a vital role in processing the S protein and receptor. This is necessary for further interaction of the S protein and ACE2 receptor leading to infection.[3,4]Enhanced entry correlated with TMPRSS2-mediated proteolysis of both S and ACE2. These findings indicate that a cell surface complex comprising a primary receptor and a separate endoprotease operates as a portal for activation of virus cell entry. This mechanism is relevant for enveloped coronaviruses (CoVs) in general as

they mediate cell entry by connecting viruses to plasma membrane receptors and by catalyzing subsequent virus-cell membrane fusions.

The incubation period for COVID-19 is thought to extend to 14 days, with a median time of 4-5 days from exposure to symptoms onset.[5] One study reported that 97.5% of persons with COVID-19 who develop symptoms do so within 11.5 days of SARS-CoV-2 infection.[6] The signs and symptoms of COVID-19 present at illness onset vary, but over the course of the disease, most persons with COVID-19 will experience the following: fever (83–99%), cough (59–82%), fatigue (44–70%), anorexia (40–84%), shortness of breath (31–40%), sputum production (28–33%), myalgias (11–35%). Atypical presentations have been described, and older adults and persons with medical comorbidities may have delayed presentation of fever and respiratory symptoms.[7-11] Some persons with COVID-19 have experienced gastrointestinal symptoms such as diarrhea and nausea prior to developing fever and lower respiratory tract signs and symptoms.[11,12] Anosmia or ageusia preceding the onset of respiratory symptoms has been anecdotally reported, but more information is needed to understand its role in identifying COVID-19. Several studies have reported that the signs and symptoms of COVID-19 in children are similar to adults though the disease course is usually milder compared to adults[13,14] but this of course is a generalization based on limited data. Table 1 provides a comparison of COVID-19 disease manifestation between children and adults.

Fu et. al.[15] retrospectively analyzed epidemiological characteristics of 2143 children affected by SARS-CoV-2 infection in China, supporting the evidence that children are as susceptible as adults to infection. They found an elevated vulnerability to SARS-CoV-2 among infants, with a proportion of severe and critical cases of 10.6% in this age group.[15] However, most severe and critical cases in the study were not SARS-CoV-2 confirmed, questioning whether other untested pathogens could have been responsible for these clinical events.[16] Figure 1 shows the COVID-19 disease trajectory indexed with time-based events during pregnancy and childhood development that present concerns for pharmacotherapy intervention.[17,18]

PHYSIOLOGIC DYNAMICS WHICH CONVEY DOSING CHALLENGES

During pregnancy, the pregnant mother undergoes significant anatomical and physiological changes to nurture and accommodate the developing fetus. These changes begin after conception and affect every organ system in the body. For most women experiencing an uncomplicated pregnancy, these changes resolve after pregnancy with minimal residual effects[19]. Pregnancy is a complex state where changes in maternal physiology have evolved to favor the development and growth of the placenta and the fetus. Likewise, pregnancy represents a moving target with respect to optimal pharmacotherapy. Variations in physiology have been shown to alter the pharmacokinetics or pharmacodynamics that determines drug dosing and effect. It follows that detailed pharmacologic information is required to adjust therapeutic treatment strategies during pregnancy. The impact of pregnancy on the various underlying pharmacokinetic processes and physiologic conditions that change during pregnancy (e.g., pregnancy-induced enzyme-specific changes, transporter differences, etc) has been previously reviewed[20] but much of the actual risk towards prescribing drugs to pregnant women revolves around the fact that much of the dosing information available is based on men and nonpregnant women and is hence extrapolated.

Pregnancy-induced maternal physiological changes may affect gastrointestinal function and hence drug absorption rates. Ventilatory changes may influence the pulmonary absorption of inhaled drugs. As the glomerular filtration rate usually increases during pregnancy, renal drug elimination is generally enhanced, whereas hepatic drug metabolism may increase, decrease, or remain unchanged. A mean increase of 8 L in total body water alters drug distribution and results in decreased peak serum concentrations of many drugs. Decreased steady-state concentrations have been documented for many agents because of their increased clearance. Pregnancy-related hypoalbuminemia, leading to decreased protein binding, results in increased free drug fraction. However, as more free drug is available for either hepatic biotransformation or renal excretion, the overall effect is an unaltered free drug concentration. Since the free drug concentration is responsible for drug effects, the above-mentioned changes especially in light of the compensation observed are probably of no clinical relevance. The placental and fetal capacity to metabolize drugs together with physiological factors, such as differences acid-base equilibrium of the mother versus the fetus, determine the

fetal exposure to the drugs taken by the mother. As most drugs are excreted into the milk by passive diffusion, the drug concentration in milk is directly proportional to the corresponding concentration in maternal plasma. The milk to plasma (M:P) ratio, which compares milk with maternal plasma drug concentrations, serves as an index of the extent of drug excretion in the milk. For most drugs, the amount ingested by the infant rarely attains therapeutic levels. Many of these factors are routinely determined during early phase drug development as part of a sponsor's IND submission and this information is likely available for repurposed drug candidates under consideration to treat SARS-CoV-2.[21]

While the relationship between developing pediatric physiology and pharmacokinetic attributes is generally at least qualitatively appreciated, far less emphasis has been placed on the relationships between developmental considerations and pharmacologic pathways. As these represent the target mechanisms of action and/or the off-target effects that govern toxicity, they are often critical in the assessment of the pediatric therapeutic window. These relationships likewise have been absent in the discussion of pediatric development plans and decision trees used to define regulatory expectations for such plans.[22]

Factors such as changes in body composition, total body water, protein binding, cytochrome P450 ontogeny, gastro-intestinal motility and pH, and organ (e.g., renal and hepatic) function all of which can produce significant changes in absorption, distribution, metabolism, and elimination throughout childhood. Human milk is a suspension of protein and fat globules in a carbohydrate-based suspension. The mechanisms by which medications are transferred into breastmilk are no different than those governing passage into any other maternal body fluid or organ system. Most drugs are transferred across membranes by passive diffusion, reaching a concentration equilibrium with the concentration in the blood. Other factors affecting the degree of transfer into a given fluid or tissue include the lipophilicity of the compound, the degree of ionization, and the extent of protein binding. Medications with a low molecular weight that are nonionized and lipophilic are the most likely to be transferred into breastmilk. In addition to passive diffusion, medications also may be transferred into breastmilk incorporated within fat globules or bound to proteins, primarily case in and lactalbumin. Highly protein-bound drugs, though, are unlikely to cross extensively into breastmilk since these drugs bind preferentially to serum albumin. By overlaying the PK and PD attributes of target drug molecules, we can get a sense of the susceptibility for the underlying PK (absorption, distribution, metabolism and elimination) and PD (receptor affinities, dissociation, enzyme kinetics, signal transduction, cascade events, etc) processes to be affected by changes in the aforementioned physiologic factors. Likewise, knowledge of pediatric clinical pharmacology is essential to the design and conduct of informative pediatric trials. More than ever, pharmaceutical sponsors are encouraged to plan for the pediatric investigation as an essential part of their clinical development plans. For older drugs on the market, NIH and FDA collectively administrate the appropriation of funds that support pediatric research for off-patent drugs through the Best Pharmaceuticals for Children Act (BPCA).[23]

Tables 2 and 3 summarize the physiological and pharmacokinetic factors respectively which contribute to the dynamic changes that occur in both pregnancy and pediatric subpopulations that make both groups vulnerable to pharmacotherapy especially in the absence of targeted investigation (i.e., extrapolations form mainstream patient trials from which they are typically excluded).

VACCINES

With respect to the vaccines under development to treat COVID-19, efforts ramped up quickly while still early in pandemic onset. As of April 2020, there were 115 vaccine candidates in some stage of development.[24] There was a broad array of strategies employed; some of these represented next-generation technology platforms and others had been repurposed from efforts to develop an Ebola vaccine.[25] In any case, multiple stakeholders including the vaccine development industry, the Coalition for Epidemic Preparedness Innovations (CEPI) and the World Health Organization (WHO) have joined forces to quickly advance efforts into clinical stage testing all while informing the global regulatory community and securing their "buy-in" to the accelerated pace of evaluation and testing. As with drug development, there is some hesitation to expose children and pregnant women in early phase testing particularly when the viability of these candidates is unknown. The most advanced of these candidates have been assessed herein for their intentions and any unusual risk factors that

these candidates may possess. In addition to the adenovirus type-5 (Ad5) vectored COVID-19 vaccine, seven candidate COVID-19 vaccines are in ongoing clinical trials, including Moderna's mRNA COVID-19 vaccine, Inovio Pharmaceuticals' DNA vaccine, Sinovac, Wuhan and Beijing Institute of Biological Products' inactive COVID-19 vaccines, University of Oxford's chimpanzee adenovirus-vectored vaccine, and BioNTech's mRNA COVID-19 vaccine. A more current and accurate view of the landscape of COVID 19 candidate vaccines can be found at the World Health Organization's website.[26]

MECHANISTIC ASSESSMENT OF RISK IN SPECIAL POPULATIONS

Historically, the interests of pregnant women have not adequately featured in global responses to outbreaks and epidemics. Funders have not asked if the vaccine candidates they are investing in are suitable for pregnant women, and pregnant women have not been included in vaccine trials. The absence of data about the effects of vaccines during pregnancy has in turn resulted in delays or outright denials of access to lifesaving vaccines, as evident in recent responses to Ebola outbreaks.[27] Vaccine risk in pregnant women is generally considered low, especially if the vaccine is not a live or attenuated virus. Most risk-assessment models are for preterm birth, perinatal morbidity and mortality, Cesarean delivery, or vaginal birth after Cesarean or uterine rupture. No risk-assessment models, or tools, specifically address the risk of maternal morbidity and mortality however and there is no consensus on how to judge pharmacotherapy risk either. The U. S. Food and Drug Administration (FDA)'s list of Pharmaceutical Pregnancy Categories help doctors (and their patients) know the prenatal safety of approved medications. The categories are A, B, C, D, and X. Drugs within Category A have been found to be safe for use in pregnant women, whereas drugs within Category X have been found to be harmful to fetuses and should not be used by pregnant women.[28] When available, these have been listed in Table 4 (discussed below).

Regarding the risk of pharmacotherapy to children, most medications are formulated and packaged for adults, which requires manipulation of the dosage form to administer the precise dose to the child. This creates uncertainty around the diagnosis and the assignment of pharmacotherapy. Additionally, pediatric patients often cannot communicate effectively to providers and/or caregivers any adverse effects caused by medications making risk difficult to assess. Likewise, in the fetus and newborn caregivers are also concerned with maternal-fetal transfer. In most cases, placental transfer is only estimated based on preclinical toxicity experiments by the sponsor with guidance provided in package insert. Despite the dramatic increase in the percentage of women choosing to breastfeed, knowledge of the safety of most medications remains limited. Research into the quantity of drug transferred into milk is complex and provides only a limited degree of certainty on the safety of medication use.

When we consider the risks associated with vaccine administration it should be broadly appreciated that under most situations the risk of harm is greater from not vaccinating a child or pregnant women. In August 2011, the Institute of Medicine (IOM) released a report that examined eight childhood vaccines and potential side effects.[29] It found that vaccines are largely safe and that side effects are usually very rare and minor. Nonetheless, there are considerations for both populations that need to be addressed. The overwhelming medical evidence finds that most vaccine side effects among newborns and young children are mild—swelling, redness and a small, hard lump at the site of the injection—and typically pass within a couple of days. A far less common but serious vaccine side effect, occurring in fewer than one in a million cases, is an immediate allergic reaction that can be treated with common medications to ease itching or swelling or, in more serious cases, by administering epinephrine. Rarely, with certain vaccinations there can be other problems. After receiving the first shot of the measles-mumps-rubella (MMR) vaccination, for example, a child has a roughly one in 3,000 chance of developing a fever that leads to a seizure.[29] Such seizures do not lead to any permanent neurological damage. Moreover, they also occur more generally when kids develop high fevers—afflicting up to 5 percent of young children. Safety consideration for pregnant women varies based on the nature of the disease (or pathogen) and vaccine type. Generally, vaccines that contain killed (inactivated) viruses can be given during pregnancy. Vaccines that contain live viruses are not recommended for pregnant women. For many vaccines (e.g, influenza, tetanus, diphtheria, whooping cough (pertussis)), vaccination is absolutely recommended for the mother's protection and for the protection of the baby. For

others, even though the vaccine may not be recommended for pregnant women (e.g., human papillomavirus, measles, mumps, rubella, varicella, and zoster) there is no cause for concern from a safety perspective.[30] In the final category, the vaccine may be recommended for pregnant women if there is an obvious risk factor (e.g., hepatitis A, hepatitis B, Hib and meningococcal ACWY).[31] Figure 2 provides a high-level evaluation of the primary risk factors for both pregnant women and children for both drug and vaccine therapy with consideration for the COVID-19 impact to both populations.

RESULTS

The comparison of COVID1-19 disease progression between adults and children as summarized in Table 1 is clearly dominated by the early experience with the virus and mostly influenced by the early experience in China. As such, it is currently unknown how generalizable this evaluation will be to later stages of the pandemic experience (i.e., second wave of transmission) or even other parts of the world as the virus is transmitted more extensively to low and middle income countries and potentially mutates. Another interesting factor to re-examine over time is the extent to which other comorbidities and conditions play a role in the most serious disease trajectories for both pediatric and adult populations. The inflammatory component of the disease progression and patient susceptibility seems intimately correlated to severe cases in adults (e.g., cardiovascular events including stroke) and children (e.g. Kawasaki's disease and PIMS). Emerging data from case studies is also changing how the medical community revisits early assumptions regarding viral transmission. Recent evidence from a single case study thus far[32] suggests that SARS-CoV-2 also causes maternal viremia, placental infection demonstrated by immunohistochemistry and very high viral load; placental inflammation, as shown by histological examination and immunohistochemistry, and neonatal viremia following placental infection which is in contrast to early views on maternal – neonatal transmission. This would also seemingly be corroborated by the multisystem inflammatory syndrome observed in children in New York State.[33]

Drug candidates for early consideration of treatment of COVID-19 have been predominantly comprised of repurposed drugs. As these typically represent drugs either approved for other indications or drugs where a significant amount of experience has been obtained, there is typically a fair amount of data to be evaluated some of which may be relevant for extrapolation for pediatric patients or pregnant women. Table 4 summarizes the list of common repurposed drugs for consideration of use to treat COVID-19. Thirteen of the repurposed drugs or drug combinations are indicated for use in pediatrics in some age category (2 more exclusively in Japan, 1 exclusively in the EU) albeit for indications other than COVID-19; 10 of these are indicated for use in pregnant women (1 exclusively in Japan). Remdesivir has been granted investigational use only for pediatrics and pregnancy and has not been formally approved for either. Even in cases where these drugs are indicated in the populations, source data from which safety and or dosing could be extrapolated for use in COVID-19 in sparse. While many of the drugs listed are in fact listed as suitable for use in pregnant women under certain conditions (Categories A, B and C) most of these also reflect risk assessment based on preclinical toxicology studies and not actual clinical use in pregnant women.

Regarding vaccines, Table 5 lists the most promising vaccine candidates entering clinical stage testing for prevention against COVID-19. As the table indicates, vaccine candidates come from varied origins around thew world (EU, US, Japan, and China) and reflect government, private sector, and academic stakeholders either separately or in partnership. The list of candidates also reflects varied approaches including novel technologies and traditional vaccine strategies including recombinant-protein based vaccines, replicating or non-replicating viral vector-based vaccines, DNA vaccines, and mRNA vaccines (mostly focused on the spike glycoprotein or receptor binding domain), live attenuated vaccines, and inactivated virus vaccines. While all candidates are being evaluated in ongoing trials which can be identified in the National Library of Medicine's ClinicalTrials.gov website, the underlying preclinical data is kept with the study sponsors for now as none of these are approved yet. Most of these trials exclude both children and pregnant women but there are at least plans to include younger patients in future trials as viable vaccine candidates become more well defined. Protocols also require contraception from both men and women planning to conceive around the trial and breast-feeding women are commonly excluded from trials as well.

Early results from vaccine trials are focused on safety and proof of immune response to vaccination. Thus far, the usual safety related findings for vaccines have been generated with injection site reaction being the most common event. The most common injection site adverse reaction has been pain; the most-commonly reported systematic adverse reactions have been fever, fatigue, headache, and muscle pain.[34] Most adverse reactions that reported have been mild or moderate in severity.

Finally, Table 6 shows the current list of ongoing drug combination trials from industrial and academic collaboration and investigator-initiated trials respectively which again are mostly reflective of repurposed drug candidates listed in Table 4. The primary driver for such trials is of course the attempt to combat the virus at multiple points in its life cycle while hopefully minimizing drug interaction potential. Some, but not all of these trials, include pharmacokinetic sampling to assess whether presumed target exposures are achieved but again the vast majority of them are not conducted in pediatric patients or pregnant women leaving an extrapolation approach to bridge this gap should outcomes look favorable. While searching for these trials through the end of July 2020 is difficult given the number of global stakeholders it is also immediately clear that the list immediately becomes outdated given the pace of R&D during the pandemic. In review, it is somewhat disappointing that the majority of current study designs for these trials are not novel and few adaptive trials have been proposed or conducted.

DISCUSSION

Epidemiological evidences show that SARS-CoV-2 infection in children is less frequent and severe than adults. Age-related ACE2 receptor expression and maturation, lymphocyte count and trained immunity might all be contributing factors to explain pediatric superiority[35] with respect to early infectivity and disease severity. We can speculate that high ACE2 receptor concentrations, trained immunity and a constitutional high lymphocyte count in children may partially explain the mild disease observed in this group of patients but this is not yet established by definitive research. Real reasons will probably remain a mystery fortunately because the number of infected children is too low to allow good-sized immunological studies. This may be related to both exposure and host factors as has been previously speculated.[14] Likewise, the age at which children appear similar to adults with respect to disease progression is not firmly established. One study suggesting that this may be true as early as 10 years of age will need to be challenged by additional studies that include patients other than overly infected and symptomatic pediatric patients.[36] Children are usually well cared for at home and might have relatively fewer opportunities to expose themselves to pathogens and/or patients who are sick. This observation is heavily skewed by the experience thus far and will likely need to be re-evaluated as the virus moves to other geographic areas particularly LMICs where care, proximity and infection opportunities are likely very different.

Current risk assessment for pediatrics and pregnancy to COVID-19 treatment options suggests that the usual concerns for both these populations are relevant for many of the repurposed agents currently being evaluated. The disease itself does pose additional risks mostly due to its extensive distribution and effect on the inflammatory system particularly in later stages of duration. Unfortunately, the majority of single agent and combination drug trials excludes pediatric patients and pregnant women at present, though hopefully there will be an opportunity for prospective testing in both populations as one or more therapeutic options become viable. The same is true for vaccines of course. As has been the case for other antiviral drug therapies, successful treatment of SARS-CoV-2 likely involves drug combination, multimodal therapy. Similar to the experience with HIV, effective treatment likely lies with multiple mechanisms to kill the virus, stop the virus from entering cells and stop the virus from replicating. Also like HIV hopefully, choices of agents that represent the standard of care will be tailored to limit side effects and drug interaction potential and will also be tailored to the target population of interest which may present different benefit:risk profiles different from mainstream patients (i.e., pediatrics and pregnant women). Experience with HIV in the populations may also shed light on timing of therapy considerations[37] or combination choices that may be given to women during pregnancy, to reduce the risk of vertical transmission to the child.[38]

Recent trends to share real world data (RWD) from COVID-19 patients is very encouraging in addition to the collaborative events in general. It provides a forum from which the available basic and clinical

pharmacology can be linked to more rapidly pressure-test repurposed drugs and vaccines while providing a benchmark for new drugs and drug combinations for the purpose of future readiness. The PEDIATRIC COVID-19 Registry (https://www.pids.org/news/764-usa-pediatric-covid-19-registry.html) similarly creates a repository of surveyed pediatric patients treated for COVID-19. Under the umbrella of the Pediatric Infectious Diseases Transplant Network (PIDTRAN) and through its Coordinating Center at St. Jude Children's Research Hospital, in collaboration with Children's Hospital of Philadelphia, Seattle Children's and Chicago Children's Hospital survey data captures epidemiologic and clinical information about all cases of pediatric COVID-19 infections in the United States. Other efforts to accumulate COVID-19 RWD for evaluating real-time clinical performance of therapies representing the current standard of care and potentially guiding us on future pandemic readiness include the ISPY-2 for COVID accelerator, the CURE-ID and the COVID-19 Diagnostics Evidence Accelerator. CURE ID is an internet-based repository that lets the clinical community report novel uses of existing drugs for difficult-to-treat infectious diseases through a website, a smartphone or other mobile device. The platform enables the crowdsourcing of medical information from health care providers to facilitate the development of new treatments for neglected diseases. CURE ID is a collaboration between the FDA and the National Center for Advancing Translational Sciences (NCATS), part of the National Institutes of Health (NIH). FDA and NIH are also collaborating with the World Health Organization and the Infectious Disease Society of America to assess the global utility of the CURE ID. The Diagnostics Evidence Accelerator is organized by the Reagan-Udall Foundation for the FDA in collaboration with Friends of Cancer Research. The Diagnostics Evidence Accelerator is the companion project to the previously announced Therapeutic Evidence Accelerator, which brings together leading experts in health data aggregation and analytics in a unified, collaborative effort to share insights, compare results and answer key questions to inform the collective COVID-19 response. In addition, less traditional RWD sources such as patient-centric data[39,40] and large-scale twitter feed data are coming to bear on quantifying COVID-19 prevalence and treatment response.[5]

On the vaccine front, as of July 2020, 205 vaccine candidates were in development, with 17 in human testing: two in Phase II efficacy and dose-testing studies in human subjects, five in Phase I–II safety and efficacy trials, and ten in Phase I trials.[34] Early results are promising but still too preliminary to assess a viable clinical candidate. The National Institute of Allergy and Infectious Diseases (NIAID) has established a new clinical trials network that aims to enroll thousands of volunteers in large-scale clinical trials testing a variety of investigational vaccines and monoclonal antibodies intended to protect people from COVID-19. The COVID-19 Prevention Trials Network (COVPN)[41] was established by merging four existing NIAID-funded clinical trials networks: the HIV Vaccine Trials Network (HVTN)[42], based in Seattle; the HIV Prevention Trials Network (HPTN)[43], based in Durham, N.C.; the Infectious Diseases Clinical Research Consortium (IDCRC)[44], based in Atlanta; and the AIDS Clinical Trials Group, based in Los Angeles. The presumption that using real-world data can provide actionable information about the prevalence of SARS-CoV-2 in specific populations and highlight individual risk factors for patients, helping to improve our understanding of the disease, tailor public health interventions and strategies to mitigate risks for individuals and communities, and help stop the spread of SARS-CoV-2 is an important milestone for these efforts and may indeed provide a roadmap to handle future crisis situations. The evidence generated through the various RWD platforms is intended to be complementary to actual clinical studies that have been conducted or are underway as well as a mechanism to address questions not yet answered. One can only hope that the spirit of collaboration continues despite a devolving political landscape that makes collaboration and open science policies more difficult, especially in the face of a global pandemic.

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