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COVID Commentary

Exploration and Ethical Analysis of Open-label Pediatric Vaccine Trials in a Pandemic

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ABSTRACT

Young children will ultimately need to be vaccinated to stop the spread of coronavirus disease 2019 (COVID-19). Initial studies of vaccine were performed in adults. Randomized controlled trials are the gold standard. In the COVID-19 pandemic, many questions need to be answered about the ethics and feasibility of these trials. Given the harms of the COVID-19 pandemic and the now-known efficacy of the vaccines in adults and teens, the question of whether clinical equipoise exists for a placebo-controlled trial of vaccines in younger children remains. Parents may be reluctant to enroll children in these trials because they want their child to receive the vaccine or because they are worried about vaccines or clinical trials in general. One option for gathering data on tolerability and efficacy in children would be to use a nonrandomized trial to enroll parents willing to vaccinate their children and those who are hesitant. We discuss the advantages and disadvantages of such an open-label trial that could provide guidance for future pandemics. (*Clin Ther.* (*Clin Ther.* 2021;43:e163–e172.) © 2021 Elsevier Inc.

Keywords: clinical trials, Ethics, safety, COVID-19, children, Vaccines.

INTRODUCTION

Several coronavirus disease 2019 (COVID-19) vaccines have been authorized for emergency use in adults. Studies in older children are under way. The harms children faced during this pandemic were underappreciated, which may have influenced the lack of urgency at which vaccines have been tested on children. With these harms, benefits, and tolerability of vaccines come important questions that must be asked around the ethics and feasibility of traditional ways of testing vaccines in the context of a pandemic. In this article, we consider the ethical and feasibility issues surrounding pediatric vaccine clinical trials in the context of the COVID-19 pandemic.

Vaccines can take varied paths in clinical development before their widespread use. Those vaccines designed for routine childhood administration (eg, rotavirus) are only studied in children,[1] whereas those designed for both adults and children have been studied in both populations. For example, with the emergence of the H1N1 influenza pandemic in 2009, the established infrastructure for preparing seasonal influenza vaccine was mobilized to generate a candidate vaccine for testing. The first study was performed from August 7 to August 21 in 814 adults, and the pediatric study was performed immediately after from August 19 to September 9 in 583 children.[2,3]

There are clear precedents and cautionary tales associated with using drugs for children who have not been well studied in pediatric populations.[4–6] Infants died of "gray baby syndrome" when chloramphenicol was used to treat neonatal infections.[7] Premature infants developed retrolental fibroplasia and blindness because of a lack of research about the tolerability of oxygen in this population.[8] The lack of pediatric tolerability testing of propofol led to fatal developments of metabolic acidosis in critically ill children.[9,10] In an ideal world, all medications for use in children should be rigorously studied in children, but this has not been the case. The Best Pharmaceuticals Act was passed

Accepted for publication April 16, 2021
https://doi.org/10.1016/j.clinthera.2021.04.010
0149-2918/$ - see front matter

in 2002 and reauthorized in 2017 to encourage the pharmaceutical industry to perform pediatric studies to ensure that drugs used in children have been studied in this population.[11]

Many thousands of people are still dying of COVID-19 around the world every day. Delayed immunization of children may lead to more COVID-19–related deaths in both adults and children. Our desire is to protect children from the potential harms of undertested therapies and to protect them and the public health community at large from the imminent harms of the pandemic. The global nature of and social response to the pandemic offer some unique challenges to our traditional methods of testing vaccine tolerability and efficacy in children.

Studies are under way in children aged 12 to 15 years, and we anticipate that vaccines will soon become available for children in this age group.[12] A key question, however, is whether the results of studies in older children can be generalized to younger children or whether it is necessary to perform a randomized controlled trial (RCT) in younger children. In this article, we discuss a compromise based on ethical principles and feasibility considerations.

FEASIBILITY AND ETHICALITY OF AN RCT

RCTs are considered the gold standard for scientific rigor. They are also thought to appropriately balance concerns about risk, tolerability, and efficacy in situations where we want to find out the comparative harms and benefits of 2 treatments (or a treatment compared with placebo). Placebo-controlled trials are only ethically supportable if there is no alternative standard treatment and the risks and benefits of treatment versus nontreatment are sufficiently uncertain.

For adults, COVID-19 is associated with high rates of serious illness and death. Thus, a potentially effective vaccine is likely much more tolerable than contracting the disease. However, the calculus in children is different. Children are not as susceptible as adults to severe complications from COVID-19. Still, many children have gotten seriously ill and died.[13] Between May 2020 and April 2021, a total of 3185 US children have become ill with multisystem inflammatory syndrome and continue to have long-term effects, and 36 have died.[14] As of April 11, 2021, there were >3 million cases of COVID-19 and 331 COVID-19–related deaths in children in the United States.[15] Children can also transmit the disease. Infection and transmission rates by older children and teens are equal to those for adults.[16]

In addition to the medical risks, children face psychosocial harms from COVID-19. School closures have negatively impacted social, emotional, and behavioral aspects of childhood development and academics, particularly in young, already disadvantaged children.[17,18] Reports of increased mental health emergency department visits, suicide attempts, and child abuse also suggest significant psychological and physical harms being felt by children as a result of social mitigation strategies.[17–29] These effects will compound with the already existing effects of racism and poverty that are significantly affecting the health and well-being of many children of color in the United States. There is a significant need to consider issues of justice in vaccinating children.

Schools and social activities may not return to normal until COVID-19 prevalence is substantially reduced, which will likely not happen until herd immunity is achieved. The sooner we achieve herd immunity, the more we can minimize both the medical and psychosocial harms of disease. Thus, we have a strong incentive to make vaccines available to children. To do that, we need to study the tolerability and efficacy of vaccines in children in an efficient and scientifically rigorous manner.

As noted above, there are important reasons to study vaccines in children even when those vaccines have been well studied in adults. Sometimes vaccines generate different responses in young children compared with adults. For example, polysaccharide vaccines are poorly immunogenic in those >2 years of age, and responses to live vaccines in children >12 months of age can be diminished by transplacentally transferred maternal antibodies.[30] These phenomena would not be expected to occur with older children or with currently available messenger RNA (mRNA) vaccines whose response is to a protein antigen produced from vaccine-derived mRNA.[31]

The question we want to suggest is not whether we should study COVID-19 vaccines in children. We must. Instead, the question is how we should study them. There are reasons to think that a traditional RCT may not be feasible. Children could only be enrolled in such a study with parental permission. Parents who are vaccine hesitant may not want their children exposed to the vaccine; they will likely not enroll their children in clinical trials.[32] Parents who are eager to immunize

their children will want the vaccine. They may think that randomization into a placebo group is too risky given the benefit of the vaccine. Parents may pressure politicians to make the vaccine available to children. If it becomes available, these parents may be unwilling to enroll their children in RCTs and take the risk that their child will receive placebo. This is particularly true for the 2 versions of the COVID-19 mRNA vaccines and their estimated efficacy of 95%.[33,34] In this case, feasibility is linked to ethical considerations. Parents may not think that there is equipoise and thus feel reticent to enroll their children in RCTs.

There is another reason why RCTs might not be feasible. Appropriate powering of RCTs will require a target number of COVID-19 infections to be identified. Pediatric trials may require a larger number of enrollees if they are to have the statistical power to detect a difference between vaccine and placebo. However, large numbers of enrollees will be difficult to achieve, and it may be difficult to find differences if numbers are small and if the number of infections is further reduced by social mitigation strategies established to reduce transmission and the lower rates of disease. These barriers to feasible design and implementation of pediatric COVID-19 trials present a dilemma to policymakers and pediatricians. Although many potential options for clinical trials and vaccine distribution without clinical trials exist, each is associated with unique benefits and drawbacks that must be considered (Table I). Although feasibility is important, there is also a need to address the complicated ethical tensions.

The 4 principles of bioethics, respect for autonomy, beneficence, nonmaleficence, and justice, need to be considered.[35] With the harms from mitigation strategies combined with infection-related harms, the balance of beneficence and nonmaleficence against the potential harms from expediting vaccine trials might require that our tolerance of risk shift. There is also an important justice issue because many children will disproportionately bear higher burdens from mitigations strategies and face disproportionate representation in vaccine studies. Ethical guidance and protection of human participants in research are important elements required in consideration of which type of study would be the most appropriate.

Ethical guidance for protection of human participants in research came out of the Nuremberg War Crime Trials.[36] The Nuremberg code led to many formal documents, such as *The Belmont Report* in the United States. *The Belmont Report* summarizes the basic ethical principles that guide researchers and those reviewing research.[36] These basic principles are respect for persons, beneficence, and justice.[36] The Belmont Report informed US federal policy on the protection of human research participants, which is referred to as the Common Rule.[37] The Common Rule, which has a section for research that involves children, holds all government-funded and nearly all academic research accountable to its guidelines for the protection of human research participants through internal review boards. This document details which types of research are subject to regulation; defines the key terms of *research*, *human subjects*, and *minimal risk*; and details the requirements of informed consent.[37]

The Belmont Report and the Common Rule note the importance of assessing risks and benefits. These risks and benefits need not be only about the conduct within the study but also about the type of study or whether the study should be performed at all. For example, in a randomized, placebo-controlled study, if the treatment is found to have unquestionable benefits, it is considered unethical to proceed with a placebo arm. The determination of minimal risk is important.

For research that involves greater than minimal risk but with direct benefits to the participants if an institutional review board finds that the risk is justified by the anticipated benefits. The research can proceed if the relation of anticipated benefits to risks is at least as favorable to the participants as the alternative approaches, and assent from the child and permission from the parents is provided.[37] For research in which there is greater than minimal risk and no benefit, the research must be likely to discover generalizable knowledge about a disorder or condition affecting the participant.[37]

The risk of not performing an RCT would need to be far greater than minimal and greater than the alternative, which would be continuing social mitigation strategies. Clinical equipoise, a state of uncertainty between the benefit of a new treatment and conventional care, must exist to consider randomization into an experimental and placebo group ethical.[38] A state of equipoise must exist between the benefit of the vaccine compared with no vaccine. Given the known significant harms children are facing from mitigation strategies, the harms directly from COVID-19, and the efficacy of the 2 approved vaccines in adults to date, we suggest that clinical equipoise does not

exist. Thus, an RCT may be ethically challenging to justify.[39]

There is, however, an alternative that may be more feasible, be more ethical, be more acceptable to parents, and may yield valuable information about tolerability and efficacy. Instead of randomization, we could offer an open-label trial in which parents could choose active treatment or a control (ie, nonvaccinated) arm.

Table I. Comparing ethicality and feasibility of various strategies for implementing childhood COVID-19 vaccination programs.

Strategy	Details	Benefits	Drawbacks
Clinical trial: RCT	Perform large Phase III RCT in children before implementing a childhood vaccine program	• Prospectively gain strong understanding of tolerability and efficacy in children before widespread administration to children • Maximize public confidence in vaccine investigation process • Understand vaccine performance in children to guide future trials for similar vaccine technology for other pathogens or reemergence of the same or similar pandemic coronavirus	• Delays widespread initiation of childhood vaccination for several months or longer, potentially prolonging achievement of herd immunity and control of COVID-19 activity • Concomitant community vaccination programs in adults may reduce community activity, challenging ability to timely meet vaccine trial end points that depend on COVID-19 infections in trial participants to reach statistical power
Clinical trial: open label	Perform open-label trial in children before implementing a childhood vaccine program	• Prospectively gains strong understanding of tolerability in children before widespread administration to children • Can be more efficiently completed than a RCT	• Limits understanding of vaccine effectiveness to nonrandomized, observational studies
Universal childhood vaccination (no clinical trial)	Apply vaccine guidance derived from adult trials to children universally without first performing a pediatric-specific clinical trial	• Permits rapid dissemination of vaccine to children • If vaccine is effective, may permit more rapid return to normal in-person educational environments and childhood social programs • If vaccine is effective, may result in more rapid decrease in community COVID-19 activity, which has important medical, social, and economic impact	• Limits understanding of both vaccine tolerability and effectiveness to nonrandomized, observational studies • Failing to identify vaccine harm before widespread use may foster vaccine hesitancy sentiment more broadly, increasing risk of emergence of other vaccine-preventable diseases

(*continued on next page*)

Table I. (*continued*)

Strategy	Details	Benefits	Drawbacks
Vaccination of children with high-risk conditions (no clinical trial)	Apply vaccine guidance derived from adult trials to children who are at high risk for COVID-19–related complications without first performing a pediatric-specific clinical trial	• Permits rapid dissemination of vaccine to children at highest risk of COVID-19–related complications • If vaccine is effective but has tolerability concerns in children, the risk of vaccine events in high-risk children may be more favorable in those who have a greater potential for personal benefit from vaccine	• Failing to achieve herd immunity in schools may prolong ability to return to normal in-person educational environments and childhood social programs • Risk factors for COVID-19–related complications, such as MIS-C, have not yet been clearly determined, leaving many otherwise healthy children at risk for this severe complication
Omit children from vaccination programs	Neither approve for clinical use nor perform clinical trials for COVID-19 vaccines in children	• Potential harm from vaccine is eliminated as a societal risk	• May indefinitely prolong achievement of herd immunity and control of COVID-19 activity • Fail to gain important insight on vaccine performance in future pandemics or reemergence of pandemic coronaviruses

COVID-19 = coronavirus disease 2019; MIS-C = multisystem inflammatory syndrome in children; RCT = randomized controlled trial.

ETHICS AND FEASIBILITY OF AN OPEN-LABEL TRIAL

An open-label study to examine the tolerability and efficacy of each vaccine in pediatric patients offers an appropriate balance between beneficence and nonmaleficence and allows the collection of valuable data. There are clear methodological issues that will be present in any future vaccine studies in children. In an open-label trial, participants will be self-selecting differently from the randomization in an RCT, which may lead to confounding features in the analysis of results. Parents who choose to not have their children vaccinated as part of an open-label trial might be more risk averse rather than vaccine hesitant. These parents may avoid areas that are high risk for viral transmission, which might give the appearance of lower disease rates in the unvaccinated arm and suggest lower vaccine efficacy. On the other hand, parents who do not want the vaccine for their children might believe that the disease is not serious and so not take the precautions associated with mitigation strategies. It is hard to predict which ways biases would tilt.

The ethical and implementation trade-offs between an RCT and open-label study are given in Table II. Of note, self-selection will be present in either method. The lack of equipoise raises questions around the ethics of using a placebo. The open-label trial raises questions about scientific rigor.

Ethically, the high efficacy of the vaccines being rolled out under an Emergency Use Authorization for adults is important because it informs how we conceptualize maximizing benefits and minimizing harms in protecting children from the risks of research but also providing the benefits of vaccination and reducing the harms of the pandemic mitigation strategies.[33] If children were experiencing no harms,

Table II. Comparison of ethics and feasibility of clinical trials in pediatrics.

Strategy	Rigor	Recruitment	Time	Selection bias	Benefits	Harms
Clinical trial: RCT	More	Parental hesitancy to enroll Parental demand to receive nonplacebo	Longer trial period before vaccination approval and use	Investigator bias Group nonparticipation	More complete tolerability data	Longer mitigation strategies required, increased infections
Clinical trial: open label	Less	Parental hesitancy to vaccinate	Immediate and ongoing vaccination and monitoring	All healthy children whose parents choose vaccine	Faster return to societal norms	Incomplete tolerability data

RCT = randomized clinical trial.

then an RCT in children might have less potential harm compared with the benefit, although equipoise may still be an issue.[39] However, children are experiencing significant harms, and given the efficacy of the vaccines in the adult trials, the benefit of earlier immunization before traditional RCTs may outweigh any potential harms from longer placebo-controlled studies.

The risks of being in the study are balanced by the risks of getting the disease. This is, necessarily, a moving target that depends, in part, on the prevalence of disease in the target community. The proportion of risk to benefit will likely change during a pandemic. In previous phases of the pandemic, there was widespread activity throughout the United States; we understand the clear negative direct and indirect impact of the pandemic on children.

The trickiest calculation to make in the COVID-19 pandemic is a result of a feature of COVID-19 that makes the current situation unlike most situations in which vaccines have been tested in the past. The most significant harms to children from COVID-19 were not from the disease itself but instead were the harms that follow continued school closures and pandemic mitigation strategies. In our opinion, those harms tip the scales away from a traditional RCT and make the risk-benefit ratio of an open-label study more ethically acceptable. An open-label study has similar issues regarding the determination of efficacy, but it allows for both earlier community protection and individual child benefits while allowing for continued collection of safety data. Effectiveness can also be estimated by measuring biomarkers of COVID-19 immunity in trial participants, as well as comparing trends in childhood COVID-19 cases and hospitalizations between communities participating and not participating in pediatric open-label trials.

Many of these issues have been weighed for pregnant individuals. Given that pregnant individuals make up a nontrivial proportion of health care professionals, the current guidance for including them in the highest-priority group and following their outcomes using a registry effectively constitutes an open-label study.[40] Studies in pregnant individuals raise a different set of ethical concerns that are beyond the scope of this article.

GUIDANCE ON CONDUCTING A COVID-19 VACCINE OPEN-LABEL TRIAL IN YOUNG CHILDREN

RCTs are designed to balance confounding variables that might reduce the ability to infer efficacy. Given the global nature of the pandemic, these variables may be hard to distinguish because many are not living life in a generalizable way. Self-selecting participants may be even more similar in their belief of science and thus public health measures, making exposure rates low. Alternatively, persons who decline to participate will do so because they do not want the risk of placebo, they need more data and do not feel comfortable enrolling their children in trials, or they have lower concern about the virus. This last group may be less concerned and might have higher risk of exposure, which necessarily requires thought as to how we control for exposure to the virus.

One strategy might be to use survey methods to assess for COVID-19 attitudes, infection prevention behavior, and number of person-to-person contacts per a particular period. Propensity scores then might help analyze these differences and allow for a self-selecting, nonrandomized control group. Of course, given the efficacy in adult studies, our main concern in children is tolerability. Focusing on safety data as the goal would be much simpler.

The primary outcomes of an open-label study for COVID-19 vaccines will be tolerability and efficacy. Such a study could provide essential and high-quality data while increasing that rate of vaccination among children. Parents who are comfortable with the tolerability and efficacy data in adults will be able to vaccinate their children. Those more hesitant will obtain further tolerability data while vaccines are being administered.

Either method requires intentional engagement with communities at highest risk. These communities have generally experienced abuse and exclusion from health care motivated by racism,[41] which has led to understandable vaccine hesitancy.[42] Equitable amounts of time for community educational engagement, intentional consideration of barriers to access, and balancing of equity over efficiency will be required to achieve meaningful inclusion.

The US Food and Drug Administration and professional societies will first need to develop interim guidance, taking into account existing scientific evidence and ethical principles used in other allocation strategies (benefiting children and limiting harm, prioritizing the disadvantaged, and equal concern) and adjust guidance as more evidence becomes available).[43–45] These guidelines must also acknowledge and consider what action is permissible in situations of a public health emergency, such as an outbreak in daycare centers, schools, or community. Second, in lieu of a new registry, the existing systems for tracking vaccines and adverse events could be coopted for specific monitoring of these new COVID-19 vaccines. Children who received a vaccine could be identified by regular queries of state immunization registries, and reports of adverse events would be submitted to the Vaccine Adverse Events Reporting System. These events would receive priority review to examine whether there was need for concern about causality after vaccination. Third, exquisite attention will need to be given to the informed consent process in which risk and benefits are clearly explained to parents, including the recommendation for vaccination.

SUPPORTING PEDIATRIC PRACTITIONERS AND PARENTS

It will, for a time, be unclear whether the vaccine is completely tolerable and effective for children. Parents might feel conflicted. Even if some tolerability data are available or there is a scientifically held presumption of tolerability based on extrapolation of experience in adults, there is significant public mistrust in new vaccines that will need to be allayed.[38,46,47] This will likely be the case in any future pandemics as well.

Pediatric practitioners will remain an important conduit for information sharing with families when discussing COVID-19 vaccination.[48,49] Despite lack of evidence, the arguments for allowing vaccination in the pediatric population include the following. First, to the extent that a clinical trial of the vaccine is ethically justifiable in children, we would have to assume that the risks associated with the vaccine are judged to be at least similar to the risks associated with getting COVID-19 and the risks from mitigation strategies. Otherwise, the clinical trials would not be ethically appropriate.[37,50] If that is so, then the question is not whether it is acceptable to give the vaccine to some children but whether the only way to study vaccine tolerability in children is through a placebo-controlled, prospective RCT. Second, limited data are better than no data, and this will be a moving target (especially for older children for whom extrapolation of data may be more reasonable from the adult studies). Third, some high-risk children may benefit from vaccination (those specific populations that have the highest morbidity). In addition, we know the secondary benefit of school opening is paramount for children and possibly larger than the individual medical benefit to children.

Given the complexity of this current situation, professional organizations and societies will need to clearly delineate recommendations that practitioners can follow and help families navigate through this period. Individual practitioners, then, will need to convey those recommendations to parents and engage in a process of shared decision-making to help parents make informed and sensible choices.

We urge professional societies and organizations to weigh the encouraging tolerability and efficacy data from the adult vaccine trials, the direct harms from COVID-19 infection, the well-described harms

to children from the social mitigation strategies, and the implications of vaccine hesitancy for clinical trial recruitment, along with the potential risks of administering a vaccine to children with limited data. That calculation, we believe, should lead to the conclusion that waiting for data from an adequately powered randomized, placebo-controlled study might not be ethically defensible given the efficacy data and the harms on children from the mitigation strategies. In addition to all the concerns raised above, we also suggest that the availability of vaccine for adults may lower the prevalence of COVID-19 and make it harder to achieve adequately powered studies in children. Studies may not be feasible given the possible low perception of equipoise by some parents combined with hesitancy by others.

CONCLUSION

The COVID-19 pandemic has led to rapid development of vaccines in new ways. To date, vaccine trials and allocation strategies have not prioritized children based on the actual and perceived risks and harms of COVID-19. As described in this article, children remain an important group to vaccinate for both individual and long-term public health benefit. We propose that the optimal approach to accomplish that, while balancing the risks of disease, social mitigation strategies, and the vaccine itself, is to conduct an open-label, nonrandomized trial, with meticulous collection of tolerability and efficacy data. Although this would not be as rigorous as a traditional RCT, it would be more generalizable to real-world situations, would have an appropriate balance of risks and benefits, and would produce valuable data quickly while increasing vaccine participation and reducing overall harm to children.

DISCLOSURES

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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