Does the light at the end of the tunnel shine for everyone? The need for early paediatric participation in vaccine trials during infectious pandemics

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Abstract
While most of the mortality associated with severe acute respiratory syndrome coronavirus 2 has been in elderly populations and adults with significant medical comorbidities, there has been death and morbidity in paediatric populations. As vaccine trial data is released to the public, many people look to the future with hope; with good vaccine uptake there is the opportunity to reduce the spread of infectious pandemics. Initial vaccine trials were completed with adults and were expanded to include paediatric populations delaying paediatric COVID-19 vaccine initiatives. The exclusion of children from initial vaccine trials during a pandemic is not morally justifiable and fosters distrust with the pharmaceutical and medical industries and inevitably postpones vaccinating children when there is a surplus of available vaccines. The delayed vaccination of children under twelve may have significant public health and economic consequences as there may be ongoing viral transmission in the context of reopening strategies. The safety and efficacy of these candidate vaccines in children should be assessed expeditiously so that distribution to vulnerable paediatric populations is not impacted. Vaccine uptake compliance in the general population is important in establishing herd immunity and ensuring that there is thorough scientific evidence to support vaccination for children is important in establishing community trust.

Keywords
Bioethics and medical ethics, clinical ethics, care for specific groups, clinical ethics, minors, human experimentation, informed consent

Introduction
The coronavirus disease 2019 (COVID-19) pandemic has dominated the news cycle since its emergence and finally a potential end to months of restrictions, cancellations, hospitalizations and deaths seems to be in sight with the adoption of aggressive vaccination strategies. Vaccine trials have shown that multiple candidate vaccines are safe and effective and prioritized vaccine distribution plans have been implemented.1,2 There are many important ethical considerations with the accelerated development of a vaccine in the context of a global pandemic, and this paper will consider the ethics of the early inclusion of paediatric populations in pandemic vaccine trials. Given low paediatric COVID-related mortality, the vast majority of children have not been considered for prioritized immunizations – appropriately so. The most vulnerable populations should be vaccinated first, however, as vaccine availability has increased and where safety data exists, children have been included in vaccination efforts.

Given their established safety and efficacy in adult testing, children, including those under 12 years old, should be included in early pandemic vaccine trials. Delayed paediatric vaccine study data precipitates obstructions in universal vaccination strategies and the establishment of herd immunity. Where there is no interference with large scale vaccine production, it is vital to proceed with vaccine testing in children to establish safety, efficacy and appropriate dosing in children, including those children under 12 years old, prior to the implementation of widespread vaccination programs. In

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future pandemics this should be an early consideration to minimize the effect of pandemic illnesses.

**Children and COVID-19**

The American Academy of Paediatrics (AAP) advocated strongly for the inclusion of children in COVID-19 vaccine trials.\(^3,4\) Though paediatric participation in these trials was inevitable, ultimately the delay in paediatric trials led to delays in vaccinating children where vaccine availability exceeded the number of individuals who were vaccine eligible and willing. Children have suffered biological, psychological and social consequences as a result of the COVID-19 pandemic – the full effects of which may not be known for a long time.\(^5,6\) School closures, in particular, have been very disruptive to paediatric populations and their social networks, nutrition, childcare and learning – there is a significant benefit to reducing these disruptions through effective vaccination strategies.\(^7\)

The SARS-CoV-2 virus is generally thought of as causing relatively low morbidity and mortality in paediatric populations, however, as of 13 June 2021 the COVKID Project reported over 4.8 million paediatric COVID infections and 582 deaths in children and adolescents in the United States of America – mortality is higher in Hispanic and Black children.\(^8\) These numbers have increased dramatically since those reported early following the declaration of the pandemic.\(^9\) In the context of all clinically significant COVID infections, the burden of disease on children is relatively minor but certainly not insignificant. Where vaccines can prevent severe COVID disease in children, even if the burden of disease is relatively small in the population, the use of vaccines to prevent severe infections should be pursued as has been historically seen with influenza.

We should additionally consider that children may have difficulty respecting distancing guidelines and may transmit viral illnesses to those who live with, and care for children, who may themselves be at increased risk for severe disease resulting from viral infections. The psychosocial consequences of physical distancing guidelines have caused significant disruptions to the lives of many children,\(^5,6\) and there is hope that through vaccination effort they would be able to return to school and recreational activities as they had previously done outside of a pandemic. There are significant benefits in allowing children to return to school and recreational activities without the worry of infecting educators, coaches, other children and extended family members. Children who live in multi-generational homes may have the mild-COVID disease or be asymptomatic but could potentially spread the virus to high-risk senior individuals,\(^8,10\) though transmission from symptomatic children is more likely.\(^11\) The primary vaccination of high-risk individuals should be appropriately prioritized, but it is important to protect children who are around those individuals in order to reduce their risk of contracting the virus and developing clinically significant disease – the establishment of a micro-herd immunity within a household containing high-risk individuals.

In excluding children under 12 from early COVID-19 vaccine trials, there is the potential for harm to this population. As vaccine availability increased there was a delay in vaccine distribution as a result of lack of safety and efficacy studies in paediatric populations. It must be recognized that there are populations of children who are at an increased risk of significant morbidity and mortality resulting from COVID infection given underlying medical conditions or other determinants of health including economic and racial factors.\(^12\) The paediatric medical system could easily become overwhelmed in the context of increased clinically significant paediatric SARS-CoV-2 infections and more severe disease secondary to viral variants.\(^9\) Participation in vaccine trials has few potential harms, including injection discomfort, though adverse reactions to vaccination should be considered – a previous study assessing perceived discomfort in children less than 2 years old noted that vaccinations were perceived to cause significantly less discomfort when compared to venipuncture and nasopharyngeal swabbing.\(^13\) Some of the potential harms associated with participation in a vaccine trial are outweighed by the potential benefits.

There is a common idiom in paediatrics that ‘children are not little adults’ and we cannot say with certainty that candidate vaccines will be absolutely effective and safe based on extrapolations from the results of adult studies – adult data should not be used as sufficient evidence to extrapolate safety and efficacy in children. Multisystem Inflammatory Syndrome (MIS-C), for example, is a condition rarely seen in adults, and antibody responses to SARS-CoV-2, both IgG and IgM, are heightened in children with this complication suggesting that immune dysregulation may contribute to the clinical phenotype.\(^14\) Children have different immunologic responses to the SARS-CoV-2 virus compared to adults,\(^15\) and could ultimately have distinct responses to a vaccine. Given the prevalence of allergies in children and concerns over potential allergic reactions to the COVID candidate vaccines,\(^16\) we must be able to adequately provide children and their decision-making delegates with an accurate assessment of risk in getting vaccinated. Once large-scale distribution can take place, it is important that the vaccine trials have reflected the diverse populations that we intend to vaccinate.\(^9\)

**Community impacts**

Given the composition of the approved candidate vaccines, in that they are not live attenuated vaccines, there will be few absolute contraindications to the COVID-19 vaccines once inclusive trials have been completed. If we fail to include children in our community immunization plans, however, we are unlikely to achieve herd immunity which would otherwise protect vulnerable populations that are
unable to be vaccinated themselves or those populations that do not adequately respond to the vaccine. There is the potential for direct harm to these populations—both from the SARS-CoV-2 virus and additionally from the continued isolation and distancing that will be needed to provide adequate protection from severe disease in the event that herd immunity cannot be achieved. Providing widespread vaccination to children protects susceptible populations who would otherwise be ineligible to receive a vaccine.\textsuperscript{17}

There are groups of children who have been identified as being at higher risk based on biological, psychological and social risk factors. The intersectionality of multiple vulnerabilities contributes to an increased risk of severe COVID-19 infection and death. It is important that the needs of these populations are addressed and that children who have multiple risk factors are managed in a just way. Neglecting to appreciate that risk-factors for severe infections, COVID-19 or otherwise, extend beyond chronological age disproportionately disadvantages these populations. Denying or delaying paediatric vaccine efforts for pandemic illnesses due to lack of safety and efficacy data, contributes to injustice for a group that has contributed so much to vaccine science, herd immunity and infectious disease eradication.

Some argue that children can be adequately protected with limited school and recreational activity cohorts and do not require vaccinations. This argument may be reasonable when children are considered in comparison to healthcare and essential workers who cannot limit the number of people they come in contact with, but most children have large contact ‘bubbles’. Limited educational funding may not allow for universally smaller class sizes and children attending public schools would be at a disadvantage in this regard. Many children are in multiple large cohorts (i.e. sporting leagues) where the potential for viral exposures is significant. Additionally, this argument fails to consider the risk to supervisory adults and the multiple exposures they encounter in the context of these cohorts. While children have been found not to be ‘super spreaders’ in the case of SARS-CoV-2 transmission,\textsuperscript{18} they do have the potential do so and may be very efficient agents of transmission in future pandemics.

### The decision to vaccinate children

Many children, in particular those under 12 years, may not qualify to make health care decisions as mature minors it is imperative to consider the bioethical principle of autonomy. The majority of children will have delegate decision makers (i.e. parents or guardians) making the decision to proceed with vaccinations against pandemic pathogens when they are made available to paediatric populations. That being said, the exclusion of children from vaccine research trials denies mature minors the opportunity to make such decisions with relevant information regarding the safety and efficacy of such vaccines. We can anticipate there will be a population of children who have vaccine-hesitant parents that may advocate to be vaccinated against their parents wishes as mature minors given the potential social and health benefits associated with inoculation. These children will require the support and counsel of public health officials and paediatricians and should be provided with scientific evidence resulting from inclusive trials in order to make an informed decision regarding vaccination.

Where children do not have autonomy and are unable to act as mature minors and make decisions for themselves, it is important to provide delegate decision members with sufficient scientific evidence to make decisions on their behalf. In providing emergency use authorisation for the Pfizer-BioNTech COVID-19 Vaccine,\textsuperscript{4} the Food and Drug Administration does not prohibit those who are pregnant or breastfeeding from making the decision to proceed with vaccination.\textsuperscript{16} This decision respects the autonomy of individuals to make a medical choice for themselves despite the lack of trials in pregnant and breastfeeding populations. As many healthcare workers and long-term care workers may be in their childbearing years, one must consider their risks as individuals in the context of a given pandemic. Such respect for autonomy may be appropriate for adults making decisions for themselves during an initial phase of vaccine distribution, however, it is important that vaccine safety and efficacy be explored further before the vaccines are available to those who are pregnant or breastfeeding and not at high-risk of contracting a pandemic virus or developing severe infection sequelae. For low-risk populations to decide to proceed with the vaccine, there should be evidence of the vaccine safety and efficacy in the specific populations to which they are being administered. Many parents and guardians, for example, are more likely to get the COVID-19 vaccine themselves rather than choose to proceed with vaccination for their children.\textsuperscript{19} It is imperative to appreciate, that the enrolment of children in vaccine trials be voluntary to ensure that trust with the public is established and maintained. While not all parents may be willing to enrol their children in vaccine trials, one study showed that approximately one-fifth of families were willing to consider doing so.\textsuperscript{20}

### Research prioritization

Where there is established low paediatric mortality and morbidity from COVID-19 and other potential pandemic-causing infectious pathogens, many would argue that given the low risks to children, the collection of vaccine safety and efficacy data in paediatrics should not be a research priority. The argument could be made that the research focus should be on high-risk adult populations. This view neglects to recognize that some children do have significant COVID-19 disease and may require hospitalization which may include intensive care. While MIS-C is a rare complication of COVID-19 infection, it can cause debilitating disease...
The risks to all should be minimized where possible. While ongoing monitoring of effects and duration of immunity are being investigated, it is reasonable to proceed with paediatric studies and divert research efforts to diverse populations that have not previously been part of pandemic vaccine trials so that once the vaccines can be safely administered universally.

Lack of inclusion of children in the initial safety research is not novel – medications and therapeutics are tested in adults prior to children. Once safety in adults has been established, however, there are legal mandates to proceed with moving into paediatric trials where there is evidence of paediatric disease. That a disease does not manifest as severely in children does not negate this important legislation. Is it appropriate to proceed with early age de-escalation trials as the risks and benefits to each age group are considered? The Paediatric Research Equity Act requires that therapeutics that will be used for conditions diagnosed in childhood should be studied in paediatric populations. There is legal precedent to support the initiation of paediatric vaccine trials even where paediatric disease is relatively mild given that some children will need to be vaccinated in order to achieve herd immunity and to control the community spread of respiratory pandemic illnesses. Effective paediatric vaccines often take longer to develop than those for adults – enrolment can be limited by difficulties associated with enrolment and dose-dependent immune responses across age groups. Where it is ethically safe and appropriate to do so, children should also be included in studies of therapeutics for pandemic infections.

Promoting the inclusion of children in pandemic vaccine trials may contribute to global injustice as vaccine availability will be remarkably high in some countries and there will be an extreme paucity of vaccines available to other countries based on distance from manufacturing resources, the logistics of vaccine storage and transportation, and economic factors. The obvious question arising from these vaccine inequities is should children who live in countries that have purchased an excess of the vaccine get vaccinated prior to high-risk individuals in other parts of the world? If the question is purely one of resource allocation global justice is relevant, but as it relates to the inclusion of children in vaccine research studies, there is the potential for global benefit. More information benefits all when vaccines are ultimately widely available. If smaller doses of a candidate vaccine can elicit sufficient immune responses in children for example, there is the potential for the inclusion of children in vaccine research trials to increase the amount of vaccine that is available for wide distribution and global disease eradication.

Vaccine education and herd immunity

As many scheduled vaccinations take place in childhood, paediatricians have an obligation to educate themselves and provide information to their patients and communities regarding the safety and efficacy of vaccines. People who provide health care to children are routinely engaged in discussions regarding vaccinations and have a responsibility to continue to provide such information. While many people get information regarding vaccines from a variety of sources, health care practitioners should be a trusted source of relevant and accurate vaccine information. In specific populations, there is mistrust of the medical community. In some cases, for example in the Black community, which is at increased risk for severe COVID disease and COVID-related mortality, this mistrust is justified based on historical events. While it may be easy to question how trust can be established, it is more important to work towards earning the trust of these populations and engaging leaders at the community level in order to be able to ensure that as many people as possible have access to accurate vaccine information and ultimately receive safe and effective vaccines. Paediatricians, who have borne relatively less clinical burden in caring for COVID-19 patients, should assume the responsibilities of education and advocacy with regards to vaccine hesitancy. This reluctance will contribute to difficulties establishing vaccine mandates in the context of pandemic-specific vaccines.

An important consideration is the likelihood of achieving herd immunity in the absence of vaccinating children, including those under 12 years old. There are large populations of people that were under-vaccinated with regards to traditional vaccination schedules prior to the pandemic, and it may be difficult to achieve good vaccine uptake in these previously vaccine-hesitant populations. Given public uncertainty regarding a vaccine that is perceived to be ‘rushed’ and novel in the context of an infectious pandemic, having broad indications and approvals for the vaccines is needed to ensure the greatest percentage of the population is willing to be vaccinated – it is estimated that over seventy percent of a population will need to be vaccinated to achieve herd immunity. It is likely that we will not be able to establish this level of immunity, and further restrictions would continue, if we allow for continued spread within paediatric populations. It is scientifically necessary to vaccinate children in order to protect public health and therefore should be pursued aggressively and early in the development pandemic plans. Any given pandemic is unlikely to end unless we vaccinate all of those who are eligible and willing, including children under 12 years old.

Summary

Many of us are looking towards the post-pandemic world with a feeling of optimism. The hope is that we will be able to return to a time where we were able to leave our homes without heightened concerns for contracting a virus that has caused immeasurable harms around the
world. While the reduced morbidity and mortality of COVID-19 in paediatric populations have been exceptionally fortunate, there is a risk of severe COVID-related sequelae and the effects of restrictions have had significant impacts on children. We must also consider that future infectious pandemics may not spare children to the degree that we have seen with COVID-19, and high paediatric morbidity and mortality may drive the early inclusion of children in vaccine trials. It is important to ensure that we have scientific data regarding the efficacy, safety, and dosing requirements in paediatric populations so that when vaccine supply is robust, they can be used in children with confidence and the support of scientific evidence and without delay. In particular given the increasing vaccine-reluctance that was present prior to the COVID-19 pandemic, it is important to develop and maintain trust with parents and guardians. We can hope that through vaccination programs that include widespread vaccination of all who can safely be vaccinated, the social, economic and health effects of pandemic illnesses can be minimized in the future.

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