Pediatric Off-Label Use of Covid-19 Vaccines: *Ethical and Legal Considerations*

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Can Covid-19 vaccines be used off-label? Should they be? These were questions on the minds of parents, pediatricians, and the media when the U.S. Food and Drug Administration fully approved the Pfizer-BioNTech Covid-19 vaccine (Pfizer vaccine) for people aged sixteen and up. That same day, the American Academy of Pediatrics (AAP) cautioned against pediatric off-label use of the vaccine,[1] citing dosing differences between pediatric and adult vaccine recipients. They encouraged expedited review and authorization of pediatric Covid-19 vaccines rather than off-label use.

There are three Covid-19 vaccines now available for use in the United States: the fully approved Pfizer vaccine and two vaccines that are available only under an emergency-use authorization (EUA) in adults: the Moderna Covid-19 vaccine and the Johnson & Johnson/Janssen Covid-19 vaccine. The Pfizer vaccine was also initially available under an EUA in adults, prior to full FDA approval of Pfizer's biologics license application (BLA) for people aged sixteen and up, and it remains (at the time of writing) under an EUA only for children ages twelve to fifteen. We are focused on questions pertaining to pediatric off-label use of the Pfizer vaccine in children under twelve in light of the approved BLA for the Pfizer vaccine for individuals sixteen and older.[2]

Popular and social media reflected additional concerns, including legal and ethical permissibility, legal and clinical precedent, and perceived or presumed risks to patients, providers, and society of off-label vaccination. Certain questions about legality and malpractice revealed that both medical professionals and the public misunderstood established legal precedents that allow providers to engage in clinically and ethically appropriate off-label use. If legal liability is avoided by ensuring that clinical decisions are ethically appropriate, then the question becomes how to assess ethical permissibility. Theoretically, the same legal and ethical norms apply to pediatric off-label Covid-19 vaccination as to other instances of off-label use. Based on our analysis, there is no singular answer to the ethical permissibility of off-label pediatric Covid-19 vaccine use; the ethics depend on the benefits, risks, and alternatives for each patient.

Yet in practice, the U.S. Covid-19 vaccination program departs from policy and practice norms for off-label vaccination. The Centers for Disease Control and Prevention's (CDC's) vaccine provider agreement (VPA) sets the terms and conditions for the use of federally purchased Covid-19 vaccines and therefore of all Covid-19 vaccines administered in the United States outside of clinical trials, since all Covid-19 vaccines for U.S. residents have been purchased and supplied by the U.S. government. According to the VPA, administering vaccines to individuals younger than the ages for whom the FDA has approved or authorized use is prohibited and risks repercussions to providers, including legal liability, loss of payment, and removal from the Covid-19 vaccine program. The VPA effectively prevents providers from even considering recommending or administering pediatric Covid-19 vaccines off-label. The prohibition reveals a tension between health policy and individual health care choices and options, as well as the distinct ethical considerations that contribute to each.

After briefly contextualizing ethical and legal precedents regarding off-label use, we offer an analysis of the ethical permissibility of and considerations for pediatric off-label Covid-19 vaccination based on individual benefits, risks, and available alternatives. Our analysis challenges the ethics of the blanket prohibition against off-label pediatric Covid-19 vaccination in the VPA, as it blocks clinicians from providing the care they may determine to be clinically and ethically appropriate for their patient. At the same time, our analysis acknowledges that

Elizabeth Lanphier and Shannon Fyfe, "Pediatric Off-Label Use of Covid-19 Vaccines: Ethical and Legal Considerations," *Hastings Center Report* 51, no. 6 (2021): 27-32. DOI: 10.1002/hast.1296

Covid-19 creates population-level ethical considerations that are at times in tension with individual health interests.

Off-Label Use

Once a pharmaceutical meets the safety and efficacy standards required to receive FDA approval (that is, an approved BLA), it can be used for new indications or in populations outside those for which it was approved. Either use, whether for a new indication or in a different population, is considered off-label. Such off-label use can minimize the costs of additional clinical trials and increase efficiency of prescribing options. Medical providers do not face additional liability by prescribing or recommending FDA-approved medications or vaccines off-label, as long as they are following appropriate clinical and ethical practice. Courts have consistently sided with providers in such cases.[3]

Studies suggest that 10 percent to 20 percent of prescriptions are off-label,[4] although this figure is higher in certain populations, such as children. Federal regulations on research in populations identified as vulnerable, which according to the U.S. Code of Federal Regulations include children; "pregnant women, human fetuses, and neonates"; and "prisoners,"[5] create obstacles to conducting clinical trials in these populations. Additionally, members of these vulnerable populations, as well as others not explicitly named by the regulations, may be less inclined to participate in clinical trials (although, as we discuss below, this has not proven to be true for parental willingness to enroll in pediatric Covid-19 vaccine trials). For these reasons, people in these groups are disproportionately reliant upon off-label use for access. For example, one systematic literature review found that more than half of pregnant people use at least one prescription medicine during pregnancy.[6] Since few drugs are approved for use during pregnancy, taking medicines during pregnancy largely means using them off-label, although the FDA maintains registries for individuals to self-report their experiences taking medications while pregnant.[7] The permissibility of off-label use may be a further disincentive for research in vulnerable populations.[8]

Studies in pediatric settings suggest that over half[9] and possibly as many as 70 percent of in-patient stays[10] in children's hospitals involve at least one off-label medication. A sample of outpatient pediatric visits conducted from 2001 to 2004 found off-label prescribing in 62 percent of visits.[11] The AAP Committee on Drugs statement on off-label use, which was reaffirmed in November 2020, states, "The purpose of off-label use is to benefit the individual patient. Practitioners use their professional judgment to determine these uses. As such, the term 'off-label' does not imply an improper, illegal, contraindicated, or investigational use. Therapeutic decision-making must always rely on the best available evidence and the importance of the benefit for the individual patient."[12]

To treat Covid-19, medical providers trialed various approved drugs off-label early in the pandemic.[13] Some of these have since received FDA authorization for use in fighting Covid-19, but others have not, and some of these off-label uses remain controversial and explicitly discouraged by the FDA.

Though off-label vaccine administration is less common than off-label medication prescribing (as we discuss below), it is not without precedent. Off-label vaccine use should follow the same ethical and legal norms as off-label prescribing, grounded in legal permissibility and ethical analysis of clinical risks, benefits, and alternatives. The anticipated risks and benefits to a potential off-label vaccine recipient may be different from the risks and benefits to a patient receiving an off-label prescription for disease treatment. The novelty of the SARS-COV-2 virus and Covid-19 vaccines further complicates this assessment, given the ongoing collection of new scientific information about risks and benefits.

Some evidence suggests that third doses of Pfizer vaccines, or "booster" shots more generally, have been sought and administered "off-label" in adults. Initially, the FDA authorized third doses of only the Pfizer vaccine, and the FDA and CDC guidance indicated that this was for use in immunocompromised individuals, people aged sixty-five and over, and adults (people eighteen and over) at high risk of severe Covid-19 or experiencing increased workplace exposure to Covid-19.[14] Yet individuals falling outside these groups pursued, and many obtained, third doses of vaccines.[15] The FDA has now authorized third doses of the Moderna vaccine for the same categories as for the Pfizer third doses, and second doses of the Johnson & Johnson vaccine in any adults, as well as mix-and-match additional doses (meaning that people can receive an additional dose from a different manufacturer than that of their original vaccine). However, prior to these authorizations, some individuals sought a dose of an mRNA vaccine on top of a single dose of the Johnson & Johnson vaccine, having determined their own risks and benefits, despite there being no mRNA vaccine authorized by the FDA for this purpose at the time.[16] Without an FDA-approved BLA for any indication or population, the Moderna and Johnson & Johnson vaccines cannot and should not be administered off-label at all. Until Moderna or Johnson & Johnson apply for and receive an approved BLA, only the Pfizer vaccine could be ethically and legally administered as an off-label "booster" dose to individuals who fall outside the authorized ages or indications for an additional dose.

Benefits

The primary benefit of off-label Covid-19 vaccination in children for whom no vaccine has yet received an EUA, let alone full approval, is the possibility of faster and more effective protection against the SARS-COV-2 virus. Early in the pandemic, Covid-19 cases were relatively low among children, and those children who became infected tended to have fewer symptoms and less severe cases. However, the advent of the Delta variant has resulted in higher rates of

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infection in young people, as well as more severe symptoms, increased hospitalizations, and deaths.[17]

As the risks of infection and severe disease from Covid-19 increase, so do the benefits of having some immune protection through vaccination. The risks of remaining unvaccinated and the potential benefits of vaccination are most heightened for children with underlying health conditions that increase their likelihood of developing severe disease.[18] There remains uncertainty about which health conditions these are, and clinicians who opted to provide the vaccine off-label would be faced with making their own determinations, resulting in possible inconsistencies. The risk of long Covid in children who develop even mild cases also remains uncertain,[19] and the ability to weigh this potential risk alongside known short-term risks of Covid-19 infection, and against the known and unknown short- and long-term risks of vaccination, could be a benefit for some patients. These uncertainties indicate a potential role for advisory boards to generate relevant guidance.

In addition to the direct health benefits, vaccination may be a tool to increase some children's consistent participation in in-person learning. Vaccination could add an additional layer of protection for children, which could be especially helpful for those who are medically vulnerable or in classrooms where evidence-based mitigation strategies are not adopted. In these situations, having children remain unvaccinated could risk impeding their social, emotional, and educational opportunities.

Risks

As noted, the AAP recommendation against pediatric off-label use of the vaccine was based on uncertainty about dosing. The adult dose cannot be assumed to be appropriate, nor should pediatricians be making ad hoc dosing decisions. Existing data from phase 2/3 clinical trials can guide dosing, however, and the closer trials get to completion with satisfactory results, the more reliable the data are as guideposts for off-label use. (This risk analysis may also change as a vaccine receives authorization for a new age group. Risks for off-label use in children under five may be mitigated following FDA authorization of a vaccine for children ages five to eleven, for example, despite additional dosing differences between these two age groups.)

Assessing the risks of off-label pediatric vaccination includes identifying who is administering the vaccine and with what resources. Pediatricians are experienced at off-label use, given the frequency of the practice with their patient population. This familiarity could mitigate risks that might occur if pharmacists administer doses or if physicians who primarily care for adult patients administer doses to children. Off-label Covid-19 vaccination for children under twelve may therefore be ethically justifiable only when done by a pediatrician who is an expert in children's health and physiology, has experience with off-label pediatric use, is comfortable ordering doses corresponding to the physiology of their pediatric patients, and has the available resources to draw and prepare appropriate doses for this patient population. (Pfizer vaccines come in multidose vials and need to be prepared for administration, so the logistics of drawing doses of different amounts should not be a barrier to off-label use but could require specific planning and training.)

One might argue that it is ethically necessary to await clear and convincing evidence that Covid-19 vaccines are safe and efficacious in children. That pediatric clinical trials are ongoing raises concerns about safety risks because the very data being collected are the data that would inform an assessment of vaccine safety. Pediatricians or parents may worry that children could experience dangerous side effects not seen in adults. Yet the state of trials needs to be weighed against already-known information about safety and efficacy in other age groups. Given the relatively small numbers of participants in pediatric trials (even following their expansion at the request of the FDA), there is a reasonable worry that exceptionally rare side effects could emerge that trials will not uncover—a concern already flagged by the FDA.

Some assume that off-label-use guidelines are for the treatment of sick people, not prevention in healthy people. One might imagine, for instance, prescribing a critically ill patient an off-label therapy in a last-ditch effort at saving the patient's life. But there is precedent for other kinds of off-label use, including vaccines for healthy people during outbreaks. For example, the measles-mumps-rubella (MMR) vaccine has been administered in children younger than the FDA-approved ages during measles outbreaks.[20] Off-label vaccination during an outbreak or pandemic is not intended as a public health tool, but it is a medical strategy to confer protection to individual patients after weighing the risks and benefits.

For pediatricians themselves, legal liability is a serious concern about off-label vaccine use, especially if a child should present with an unanticipated side effect. Individuals or practice groups may also weigh reputational risks and concerns about public criticism and public trust if a pedia-

trician's off-label administration of Covid-19 vaccines becomes widely known. Some medical providers may be part of a practice group that collectively decides not to permit their individual providers to expose the rest of the practice group to these risks.

These concerns are reasonable. However, the FDA does not regulate the practice of medicine, and physicians are legally allowed to use drugs approved by the FDA off-label as long as such use does not qualify as "research."[21] Generally, off-label use intended to provide treatment or prevention of a disease is ethically permissible.[22] As long as a physician puts the patient's interests first and can point to sound scientific and clinical data that support the particular off-label use, there is no malpractice liability.[23] As with any medical intervention, providers must obtain informed consent from the patient or surrogate, which includes sharing the risks, benefits, and alternatives of a proposed treatment. Notifying patients that a proposed pharmaceutical is off-label has not historically been a legal requirement for off-label use, but in the case of vaccination, which providers recommend and administer rather than prescribe, an explanation of why a provider is recommending vaccination off-label would be clinically and ethically relevant.

The risks of off-label administration of Covid-19 vaccines to children are modified by the terms of the VPA issued by the CDC. Our goal, however, is to consider the ethical and legal norms that ought to guide medical decision-making regarding off-label Covid-19 vaccination, establishing its theoretical ethical and legal permissibility and how the CDC's VPA departs from these norms.

Finally, there are concerns about the impact of administering Covid-19 vaccines off-label for public health, and these may contribute to the CDC's prohibition of age-based off-label use of Covid-19 vaccines in their VPA. One worry could be that vaccines remain a scarce resource and that allocating them off-label could limit access for those for whom vaccines are authorized or approved.[24] At a global scale, this risk could be considerable, and some have argued that children in developed countries should not receive vaccines prior to higher-risk populations in developing countries. Yet the benefits of individual off-label use would be relative to the individual risks, suggesting that instances of Covid-19 pediatric off-label vaccination would be most ethically defensible for high-risk children who are part of vulnerable risk groups themselves.

Alternatives

One potential alternative to age-based off-label use of Covid-19 vaccines would be to further expand enrollment of children under twelve in clinical trials. The benefits of increased trial enrollment could include access to more study data (by expanding the sample size) and close oversight of dosing, timing, and side effects related to vaccination. Access to vaccines via clinical trials would also guarantee consistent dosing, as well as systems of tracking, monitoring, and reporting adverse events.

Yet there are feasibility constraints for expanding trial enrollment, which requires additional funding and personnel to manage a potential surge of enrollees. Media reports suggest the demand for enrolling in pediatric Covid-19 vaccine trials greatly outpaces the number of trial slots available, even after the FDA asked the Pfizer and Moderna pediatric Covid-19 trials to increase enrollment.[25] Additionally, participating in a vaccine trial does not ensure vaccination. The Pfizer Covid-19 trials in children under twelve administer placebos in one-third of their participant cohorts.[26] Enrolling in the trial creates an opportunity for early vaccination, however; study details indicate participants are unblinded after six months and that those who received placebos are offered vaccine doses.

Moreover, expanded trial enrollment would not address the needs of populations who may be the best candidates for receiving a vaccine off-label: children with underlying health conditions that put them at risk of severe Covid-19 complications. Trials recruit only healthy children with no known underlying serious health conditions. For these individuals, the remaining alternative may be for vaccine manufacturers to grant access directly, such as through an expanded access program (also colloquially known as a "compassionate-use agreement"), though there is no evidence that this has been done to date during the Covid-19 pandemic.

Population-Level Challenges

That individual decisions about Covid-19 vaccination are made in the context of a global pandemic and public health crisis cannot be overstated. While we have focused on individual patient and provider decision-making, we recognize that the decisions are made within obligations to—and policies supporting—public health. These obligations create additional considerations and challenges.

Off-label vaccination could benefit public health by increasing the overall share of the population vaccinated. This is not a reason to make any individual patient decision, which should be the locus of evaluation for off-label use. But given that many concerns with off-label vaccination reveal a conflict between individual and public health priorities, this is one instance in which individual and population-level needs could be compatible. Misinformation about legal and ethical considerations relevant to off-label use, which we have tried to clarify here, adds an additional layer of complication in the relationship between public health goals and individual health options.

Misinformation can also contribute to equity concerns regarding off-label vaccination. Some parents might be better positioned to obtain off-label vaccines for their children because they have access to good information about the possibility of off-label vaccinations, preexisting relationships with health care providers willing to facilitate off-label use,

or the time and resources to seek out a provider willing to consider off-label vaccination.

Inequitable vaccine access, whether within the United States or globally, has been a stumbling block for equity and public health at every step of Covid-19 vaccine rollout. Some may worry that off-label vaccination of children further diverts vaccine doses from vulnerable populations for whom vaccines are already authorized or approved. Similar concerns have been raised about "booster" shots for adults. In both cases, limiting vaccination to those whom it would likely significantly benefit is compatible with equity concerns.

Another potential public health challenge for off-label use relates to vaccine messaging and the potential to undermine vaccine confidence or add fuel to anti-vaccine fires. Off-label use is not experimental, but it could be mistakenly interpreted as such. There is also a distinction between *offering* vaccines off-label as a health tool for high-risk patients (which should be ethically and legally permissible) and *mandating* them off-label as a population health tool (which is neither ethically nor legally permissible). It is also unclear whether using vaccines off-label would make any difference in curbing or reducing vaccine hesitancy. These concerns should not be a reason to make any individual patient decision, but they may contribute to public health concerns surrounding off-label use.

The legal structure created by the CDC's VPA is the biggest challenge for pediatric off-label Covid-19 vaccination. The CDC has even issued guidance that providers who administer vaccines off-label risk being kicked entirely out of the vaccine program and may not receive payment for those vaccines. The CDC has also warned providers that administering the Covid-19 vaccine off-label may curtail their liability protection under the Public Readiness and Emergency Preparedness Act. Finally, the CDC has warned that patients receiving off-label vaccines may not be eligible "for federal compensation after an adverse event."

The VPA applies to "[f]ederally purchased Covid-19 vaccines,"[27] suggesting that if vaccines could be obtained apart from the federal government, then restrictions on age-related off-label use would not apply. Theoretically, providers willing to consider off-label administration for some pediatric patients would need to independently source Covid-19 vaccines directly from pharmaceutical companies. The cost of these doses would likely be borne by patients, creating additional access and equity concerns (though the negotiated per-dose costs of Covid-19 vaccines might keep this barrier low). The result of the Covid-19 VPA, then, is to place significant barriers in the way of providing vaccines off-label.

The CDC should provide sufficient and transparent reasons for overriding standard ethical norms and legal precedent in its provider agreement. Currently, we do not know what their reasons are, though we worry that they are due to the kinds of unspecified or even incorrect inferences many hold about off-label use: erroneous beliefs that it is illegal, that it heightens provider liability, or that it is experimental. The CDC's mission to support population health and concerns related to vaccine messaging, confidence, and anything that may undermine perceptions of vaccine safety or fuel vaccine hesitancy may be contributing factors, but these are public health concerns that generally fall outside the scope of the permissibility of off-label use. Without soundly explaining why Covid-19 vaccination is different from other cases in which off-label use is permitted, the CDC is not ethically justified in enforcing a VPA that removes this option for individual patients.

One way that the VPA does mirror existing practices relates to the government's role as payor for vaccines. A barrier to off-label treatment is often cost. Insurance companies may be unwilling to approve payment for off-label drugs or vaccines (raising additional equity concerns that only those who can afford to pay out of pocket may have access to off-label pharmaceuticals). In this case, the CDC's prohibition is consistent with the policies of many payors. But while financial gatekeeping is a practical constraint to accessing pharmaceuticals, it does not render their use less clinically indicated or ethically permissible.

Acknowledgments

We would like to thank Kelly W. Harris, Vanessa Carbonell, members of the Institute for Philosophy and Public Policy, as well as a reviewer for the *Hastings Center Report*, for valuable feedback on various stages of this project.

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