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Off-Label Prescription of COVID-19 Vaccines in Children: Clinical, Ethical, and Legal Issues

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Abbreviation: ACIP-Advisory Committee on Immunization Practices, AAP-American Academy of Pediatrics, BLA-Biologics License Application, CDC-Centers for Disease Control and Prevention, CICP-Countermeasures Injury Compensation Program, EUA-Emergency Use Authorization, FDA-Food and Drug Administration, HHS-Department of Health and Human Services, MIS-C-Multisystem Inflammatory Syndrome in Children, PREP-Public Readiness and Emergency Preparedness

Table of Contents Summary: The commentators analyze the clinical, ethical, and legal issues in off-label prescribing of the COVID-19 vaccine to children.

Contributors' Statement Page

Dr. Antommaria conceptualized, designed, reviewed, and revised the manuscript. He drafted the abstract, introduction, case, and his commentary.

Drs. deSante-Bertkau and Knilans, and Prof. Persad designed, drafted, reviewed, and revised their respective commentaries, and reviewed and revised the abstract, introduction, and case.

Profs. Zettler and Fernandez Lynch designed, reviewed, and revised their commentary, and reviewed and revised the abstract, introduction, and case.

All authors approved the final manuscript as submitted and agree to be accountable for their aspects the work.

ABSTRACT: The United States Food and Drug Administration's (FDA's) approval of the biologics license application (BLA) for the Pfizer-BioNTech COVID-19 vaccine (Comirnaty) on August 23, 2021 opened the door to the off-label vaccination of children younger than the age range currently covered by either the BLA (16 years old and older) or the emergency use authorization (12 to 15 years old). While prescribing medications at doses, for conditions, or in populations other than those approved by the FDA is generally legal and is common in pediatrics, the FDA, the Centers for Disease Control and Prevention, and the American Academy of Pediatrics have recommended against off-label prescription of the COVID-19 vaccine. Several commentaries consider a case in which parents ask their child's pediatrician to prescribe the vaccine for their 11-year-old with special healthcare needs before approval or authorization in her age group. The first commentary considers the potential benefits and risks to the patient, as well as to the family, the provider, and society, emphasizing the unknown risks in younger patients and the need for adequate informed consent. The second commentary describes an algorithm and principles for evaluating off label prescribing and argues that the current benefits of prescribing Comirnaty off label to children under 12 do not outweigh the risks. The third commentary addresses ethical and legal issues, ultimately calling on federal agencies to remove legal barriers to making the vaccine available to children in age groups that currently lack authorization.

Age de-escalation and the United States Food and Drug Administration's (FDA's) approval of the Pfizer-BioNTech COVID-19 vaccine (Comirnaty) have created the context for potential off-label use. Age de-escalation entails initially conducting clinical trials of new pharmaceuticals in adults, then in adolescents, and finally in younger children. Its justification is that it is preferable to conduct research on individuals capable of giving informed consent and then assent before enrolling individuals who are not capable of either. This permits a product's potential benefits and risks to be better understood before exposing individuals with lesser degrees of capacity.[1] Following this approach, the FDA issued Emergency Use Authorizations (EUAs) for Pfizer-BioNTech's COVID-19 vaccine in individuals 16 years old and older on December 11, 2020 and individuals 12 through 15 years of age on May 10, 2021, before granting "full approval" to the biologics license application (BLA) for individuals 16 years old and older on August 23, 2021.[2]

Approval of the BLA makes "off-label" prescription of the vaccine possible. Once the FDA approves a drug, including a vaccine, licensed prescribers generally may prescribe it for other indications, consistent with the view that the FDA regulates medical products rather than the practice of medicine. Off-label prescription may involve a different clinical condition, dose, and/or patient population. The American Academy of Pediatrics (AAP) states that "the term 'off label' does not imply an improper, illegal, contraindicated, or investigational use."[3] Such off-label prescribing is common in pediatrics. Katelyn Yackey and colleagues found that at least 1 in 4 patient encounters at children's hospitals involved prescribing off label.[4] The use of morphine in individuals under 18 years of age, for example, is off label.[5] The FDA, Centers for Disease Control and Prevention (CDC), and AAP have, however, recommended against administering the COVID-19 vaccine to children under 12 until additional information is obtained from ongoing studies.[6-8] The following case and commentaries consider the clinical, ethical, and legal issues in off label use of a COVID-19 vaccine.

Case

Jane is an 11-year-old who was born at 28-weeks estimated gestational age and now has chronic lung disease, cerebral palsy, and developmental delay. Her parents are very concerned about her risk of contracting COVID-19 and experiencing severe complications. While they have limited her social contacts since the start of the pandemic to decrease her risk of infection, they believe that this has had significant negative psychological and developmental effects on Jane and strongly desire that she attends school in person during the current academic year. The school district that Jane attends is encouraging, but not requiring, masking. All eligible family members have been vaccinated against COVID-19 to protect themselves and Jane.

Jane's parents tried to enroll her in a pediatric COVID-19 vaccine trial, recognizing that she could be randomized to the placebo arm or experience side-effects from the vaccine, but she was ineligible. In early September 2021, days after the FDA approved Pfizer-BioNTech's BLA, they contact you, Jane's primary care provider or primary subspecialist, to request that you prescribe the vaccine for her off label. They understand that the vaccine is still undergoing clinical trials in Jane's age group, the vaccine's safety and efficacy may be different in younger children, and the AAP has recommended that members not prescribe the vaccine off label. They nonetheless believe that the potential benefits outweigh the potential risks for Jane and know that off label prescribing is generally legal. What do you do?

Jennifer deSante-Bertkau, pediatric hospitalist and bioethicist, comments

Ethically, the clinician should weigh the potential benefits and risks of off label treatment and decide whether it is reasonable to prescribe it. In this case, the primary potential benefit to the patient is protection from serious illness due to COVID-19. Jane may be at increased risk of severe illness due to her complex chronic condition.[9] Vaccination would also grant Jane additional protection to attend in-person school, which carries significant cognitive, social, and emotional benefits. The COVID-19 vaccine has been shown to be safe and effective in preventing COVID-19 in individuals 16 years and older.[10] Clinical trials have shown that it is also effective in adolescents 12 to 15 years old—they produce similar neutralizing antibody titers to 16-to-25-year olds, and they are protected against COVID-19.[11] While this data has been sufficient to support an EUA for this age group, as of September 24, 2021, Pfizer and BioNTech have not applied for licensure in this age group.

Children under 12 years old may, however, have different immune responses and the vaccine may be ineffective or less effective in this age group. The effect of vaccination on rates of Multisystem Inflammatory Syndrome in Children (MIS-C) is also unknown. There is the additional uncertainty regarding the appropriate dose of the COVID-19 vaccine in the younger age groups. In individuals 12 years of age and older, each dose is 30 micrograms. Based on a Phase 1 study, the current Phase 2/3 trials are administering 3 micrograms per dose in children aged 6 months to 4 years and 10 micrograms in children 5 to 11 years.[12,13] However, the efficacy of these doses is unknown.

The risks to the patient include local and systemic events such as injection-site pain, headache, and fatigue.[2] After the EUA was granted in adolescents and the vaccine was administered to a larger number of individuals, a risk of myocarditis, which appears greater in younger males, was identified.[14] While initial reports suggest that the myocarditis is treatable or self-limited, additional research is needed to monitor the long-term risks and clarify which population(s) are at increased risk. There is also the risk of other previously unidentified side-effects. Finally, the potential benefits and risks also depend on local and personal factors including the risk of transmission in the local community and the patient's risks of severe disease.

In addition to the risks and benefits, the provider and the parents should consider alternatives. The primary alternative is masking, physical distancing, and hand washing. Other "alternatives" include treatment for COVID-19 should Jane become infected. Vaccination might unintentionally provide a sense of security and reduce adherence to these measures. Jane's

pediatrician would be ethically justified in prescribing her the COVID-19 vaccine off label although reasonable pediatricians might weigh the potential benefits and risks differently and decline to prescribe it.

Even though the decision to prescribe a treatment off label should be based on the potential benefits and risks to the patient, there are other factors to consider. The patient's vaccination status could have implications for the patient's family. Vaccination might substantially reduce Jane's parents' anxiety about her well-being. If the vaccine is safe and effective in children under 12, having the child vaccinated might reduce the risk of the child becoming infected and transmitting the infection to other family members. It might also reduce the financial strain of losing income or employment to care for an ill child.

Second, the clinician will need to develop a standard practice and treat all his/her/their patients fairly. At a minimum, if the physician prescribed the vaccine to this patient, the physician should also prescribe the vaccine to similar patients. Given the increasing role of social media, the provider should anticipate the possibility of being contacted by potential new patients seeking vaccination. Given the discretion that providers have in establishing new provider-patient relationships, it would be reasonable for the provider to decline to establish new relationships for this purpose to focus on the care of his/her/their current patients.

The clinician should also take steps to ensure consistency in the response among members of a group practice or clinical division. One clinician's willingness to prescribe the vaccine may

create pressure for his/her/their colleagues to also prescribe it in this manner. Colleagues could benefit from discussing these requests together to develop a consistent framework when evaluating them. They, however, do not need to all agree to prescribe or not prescribe.

The broader societal impacts of prescribing the COVID-19 vaccine to children off label are unclear. It is unlikely that such prescribing would create a domestic vaccine shortage preventing individuals in higher risk groups from being vaccinated. Individuals should however be aware of global inequities and advocate for fair vaccine allocation internationally.[15] Additionally, the shifts in public health recommendations over the past 18 months have contributed to some people's distrust of science and medicine. It is unclear whether or how off label prescriptions for the COVID-19 vaccine would affect the broader vaccine hesitancy and concern that vaccine development was rushed, and the vaccine has not been sufficiently tested.

Based on the current information on the benefits and risks of the COVID-19 vaccine in children under 12, prescribing the COVID-19 vaccine to Jane off label is ethically acceptable but not ethically obligatory. The practice of prescribing treatments off-label is relatively commonplace in pediatrics and this instance does not appear to be categorically different. Therefore, individual provider discretion should not be usurped. Providers should however be attentive to the broader social and political context in which this decision is made. Even if the clinician offers to prescribe and the parents provide informed consent, there are regulatory and logistical issues discussed below that may impede the patient's ability to receive the vaccination off label.

Timothy K. Knilans, a pediatric cardiologist and chair of a pharmacy and therapeutics committee, comments

The physician in the case, if not a COVID-19 vaccine provider, would need to find a vaccine provider, hospital, or pharmacy to administer the vaccine and they would need to consider the parents' request.

As the Chair of the Pharmacy and Therapeutics Committee at a large pediatric medical center, I am regularly tasked with reviewing requests to prescribe FDA approved medications "off-label" when that use is not common. Off label prescribing is quite common in medicine and even more common in pediatrics.[16] When I receive these requests, I review the information provided by the requester regarding the currently known risks and benefits of the drug and the circumstances of the individual patient. I then perform a literature review of the drug and especially its use for the indication in the requested patient. Finally, if the information is not compelling, I will consult uninvolved clinical expert(s). This is especially important if the clinical problem or the medication is new and the literature is small or rapidly changing.

I follow an algorithm developed by Gazarian, Kelly, McPhee, et al. for appropriateness of off-label medicine use[17] and consider the principles outlined by Fitzgerald and O'Malley.[18] Using the algorithm, this request is for an FDA approved indication, but not an FDA approved age group, making the request off-label. There is not high-quality evidence supporting the vaccine's use in this population; the response in children <12 years of age may certainly be different than older children, just as adverse effects in teens and young adults may be dissimilar to older

adults.[19] In this case, participation in a formal research study was considered, but Jane was not a candidate for unspecified reasons.

Gazarian and colleagues recommend exceptional use, if "there is a serious underlying disease or condition; AND there is some evidence to support potential beneficial effect; AND **potential benefits outweigh potential risks;** AND standard therapy has been trialled (sic) or is inappropriate; AND use has been approved by institutional drug committee; AND written informed consent obtained (Box 2, bold added)."[17]

In this case, the vaccine would be used for prevention of a potentially serious condition. FDA approval for patients only slightly older provides some evidence of a potential beneficial effect. "Standard" therapy would be mitigating strategies like masking (which is not universally required at Jane's school) and social distancing, and treating the illness if it occurred. The vaccine has been approved by our Pharmacy and Therapeutics Committee and written informed consent could certainly be obtained. This leaves the question of whether the potential benefits outweigh the potential risks.

There is an abundance of literature on this disease and the vaccination. These papers uniformly note that most COVID-19 cases in pediatrics are mild, but there are rare patients who develop serious complications and even die. The literature on factors associated with severe disease is complicated by the diversity of factors considered and the ways in which they are classified. While obesity has been consistently associated with risk of severe disease, findings regarding

other comorbidities have been inconsistent.[20] Kompaniyetes et al., for example, did not include a category of chronic lung disease and did not find an association between asthma or neurodevelopmental disorders and severe illness.[9] As for the risk of complications from the vaccine, information about children less than 12 years is forthcoming. It would seem reasonable that the risk would not be substantially higher than for a child only one year older. The balance of the benefits and risks depends on any special benefits of the vaccine to Jane based on her medical conditions.

Because the clinical problem is out of my area of expertise, the vaccine and the disease are new, and the literature is being updated daily, I asked a virologist with extensive experience with COVID-19 and the vaccines to review the case. He responded that "while this child has a myriad of medical issues, she is at no particular increased risk for moderate-severe COVID-19 infection (personal communication)."

As a representative of the hospital, legal liability also needs to be considered. COVID-19 vaccinations are not typical drugs and federal restrictions require providers to follow Centers for Disease Control and Prevention (CDC) recommendations which do not allow off-label prescribing.[7,21] Disobeying these recommendations could potentially jeopardize the hospital's ability to administer these vaccines and potentially result in other penalties. In addition, legal liability from the adverse effects of the vaccine also needs to be considered.

I understand the rationale for the request and empathize with the patient and her family. Assuming that Jane does not have any significant unlisted comorbidities such as obesity, I do not believe that she is at substantially increased risk for severe disease if she unfortunately contracts COVID-19. As such, I would deny the request at this time. Further information may soon become available which may change the risk-benefit ratio, or the vaccine may be authorized for younger individuals soon making off-label prescribing unnecessary in her case.

Govind Persad, Patricia J. Zettler, and Holly Fernandez Lynch, bioethicists and lawyers, comment

As the Delta variant casts its shadow over another pandemic school year, children ages 12 and up can be protected against COVID-19 through vaccination. However, the path to vaccination remains murky for younger children not yet covered by either the BLA or EUA for the Pfizer-BioNTech vaccine as of September 24, 2021, even as authorization in children ages 5-11 seems imminent.[22] In our view, the universal recommendations against "off-label" pediatric use of Comirnaty issued by the FDA, CDC, and AAP are overbroad.[6-8] Especially for higher-risk children nearing age 12, vaccination can be ethically justified even before FDA authorization or approval for this group – and similar reasoning is relevant for even younger patients. Legal risks can also be managed, although the FDA, CDC, and Department of Health and Human Services (HHS) should move quickly to provide clarity.

In the case presented, an 11-year-old girl, Jane, is reasonably perceived to face higher-than-typical risk for severe COVID-19 based on the available evidence.[23] However, she would attend

a school without a mask mandate and could not enroll in a vaccine trial. If Jane's trial participation would have presented unacceptable individual risk, vaccination outside the trial clearly should be avoided. But if she was excluded due to full enrollment or narrow criteria intended to simplify data analysis, off-label vaccination could be ethically reasonable depending on an individualized assessment of expected benefits and risks.

Though some uncertainty remains, ongoing trials of Comirnaty in children between 6 months and 11 years provide important insight. With rare exceptions, pediatric trials that pose more than minimal risk, such as trials of a novel vaccine, legally must "hold out the prospect of direct benefit" and have risks "justified by the anticipated benefit to the subjects." In addition, "the relation of the anticipated benefit to the risk" must be "at least as favorable to the subjects as that presented by available alternative approaches."[24] This is not equivalent to the demonstrated safety and effectiveness necessary for full marketing approval, but it is a more demanding standard than for adult trials, in which individual risk can exceed anticipated individual benefit so long as social value is sufficient.[25] Therefore, for children like those in the trial and with similar monitoring, the expected benefits of Comirnaty vaccination following the same trial dose and schedule are likely to exceed the risks. This conclusion is further supported by Pfizer and BioNTech's announcement via press release on September 20, 2021 that the vaccine is "safe, well tolerated and showed robust neutralizing antibody responses" in children 5 to 11 years of age.[26]

Beyond these clinical considerations, off-label access typically poses at least two important ethical concerns, although we think both are reduced here. First, off-label vaccination must not be allowed to hinder pediatric trials, which provide key data about risks and benefits for regulatory and clinical decision-making in this unique population. Accordingly, off-label vaccination should be considered only when trials are fully enrolled or participation is not otherwise possible, as is the case for Jane – and many other children on waitlists for oversubscribed COVID-19 vaccine trials.[27] Second, extensive off-label use can threaten FDA's role in assuring safety and effectiveness and in incentivizing companies to produce rigorous evidence about their products.[28] However, evidence of Comirnaty's safety and effectiveness in marginally older children, as well as the topline trial results recently reported in children Jane's age, both stand in contrast to many off-label uses that lack evidentiary support.[29] Moreover, off-label prescribing is generally unrestricted and widely-accepted, especially in pediatrics.[3] Indeed, CDC has recommended off-label Hepatitis A vaccination for infants traveling to some settings,[30] and has provided guidance on off-label pediatric Japanese encephalitis vaccination.[31] Given this, a broad ban on off-label Comirnaty vaccination of any patient under 12, no matter their individual risk, seems disproportionate.

Assuming Jane's physician agrees that vaccination is clinically and ethically appropriate, several legal considerations remain. Absent restrictions in a Risk Evaluation and Mitigation Strategy (REMS), FDA approval of a product typically enables off-label use. Unlike most products, however, COVID-19 vaccines are currently subject to federal agreements requiring providers to abide by "all requirements and recommendations of CDC and CDC's Advisory Committee on Immunization Practices (ACIP)."[21] As of mid-September 2021, the CDC not only recommended

against "any" off-label use of COVID-19 vaccines, it also signaled possible sanctions for violating provider agreements.[7] As a result, Jane's physician may worry that vaccinating her could jeopardize their future access to COVID-19 vaccines through the federal government, and perhaps even prompt civil or criminal penalties. In practice, however, a single violation (or even a few) seems unlikely to spur enforcement, particularly given that some entities are openly providing off-label boosters in similar violation of the provider agreements without apparent consequence.[32]

The CDC has also previously warned that off-label administration of Comirnaty "may not" be shielded from liability by the Public Readiness and Emergency Preparedness (PREP) Act and that off-label recipients "may not" be eligible for compensation under the Countermeasures Injury Compensation Program (CICP).[7] We think both outcomes are unlikely and note that these specific warnings no longer appear on the CDC's COVID-19 Vaccine FAQs for Healthcare Professionals which were revised on September 22, 2021.[33] Those generally authorized to administer vaccines, including physicians, differ from those authorized to do so only for COVID-19, including certain pharmacists and pharmacy interns. The latter group may only administer vaccinations "according to ACIP's COVID-19 vaccine recommendations(s)," and would otherwise lose their status as "covered persons" under the PREP Act.[34] Physicians, however, remain "covered persons" even if administering an approved COVID-19 vaccine off-label—for instance, a pediatric off-label vaccination or off-label adult booster—and would not be engaged in unprotected "willful misconduct" when the benefits of off-label vaccination are likely to outweigh risks. Approved vaccines also appear to remain "covered countermeasures"

under the PREP Act and CICP even when used off-label for COVID-19, although this is not explicitly addressed.[35]

To provide certainty to patients and the health care community, HHS should clarify PREP Act and CICP coverage for off-label use and CDC should amend its provider agreements, announce enforcement discretion, or otherwise walk back its warnings about possible sanctions to permit appropriate flexibility. This would be in line with other countries that are permitting case-by-case access for children in the 5-11 age group.[36]

If Pfizer agreed, FDA might also consider the possibility of expanded access ("compassionate use") for high-risk children currently unable to access vaccination or trial participation, on an individual basis or through a broader program, until authorization of an EUA or approval of a BLA is extended to younger ages. Although expanded access is atypical for either prophylactics or off-label uses absent a restrictive REMS, expanded access to vaccines is not without precedent[37] and the CDC provider agreement operates analogously to a REMS.[38] Importantly, an expanded access program could provide additional regulatory oversight, clarify liability and injury compensation, and promote equity, such that off-label vaccine access for high-risk children may not depend as heavily on parental privilege and persistence.

Short of these efforts, physicians who provide off-label vaccination to children like Jane upon express request and full disclosure of risks would still face relatively low chance of tort liability for vaccine injury.[39,40] Most medical interventions are provided without a liability shield –

physicians are simply expected to behave as a reasonable physician would. Although the AAP and federal agencies have recommended against off-label pediatric vaccination for COVID-19,[6-8] this is not dispositive. Vaccination may nevertheless be reasonable for a specific patient, particularly if facing high risk and given the same dose as in a pediatric trial.

Especially in light of Pfizer's reports of positive trial results, many expect FDA to issue a vaccine EUA for 5–11-year-olds in Fall 2021. Against the backdrop of a surging pandemic, and the legitimate medical and psychosocial concerns facing families like Jane's, legal barriers intended to universally exclude younger children from off-label COVID-19 vaccination should be quickly removed. In the meantime, we believe those barriers are not so high that a physician should necessarily be dissuaded from vaccinating Jane, and that it would be ethically acceptable for them to do so.

Outcome of the Case

While sympathetic to the parents' request, you decline to prescribe the vaccine due to uncertainty regarding dosing, safety, and efficacy as well as legal concerns.

Armand H. Matheny Antommaria, Section Editor, comments

Off label prescription is legal and common in pediatrics. Prescribing a COVID-19 vaccine off label to children under 12 does not appear to be categorically different from other forms of off label prescription. It is unlikely to interfere with the completion of clinical trials in children or to

cause domestic vaccine shortages. Rather than focus on the absolute risk of severe COVID-19 in unvaccinated children, the focus should be on the relative risk in unvaccinated and vaccinated children. Providers should consider potential risks of and alternatives to vaccination such as the possibility that the vaccine will be less or in-effective in children or children may experience previously unknown side-effects. These risks may be greater the younger the child. The potential benefits appear to be sufficiently proportionate to the risks that they should be evaluated within shared decision making with parents. Parents should be educated about the potential risks and provide adequately informed consent. Providers should also consider the implications of off label prescription for themselves, their practices, and society. These potential risks include liability. Legal barriers preventing off label access to COVID-19 vaccines should be minimized as exceptionalism in this case is not justified. Similar issues should be considered in decision making for age groups in which the vaccine remains unauthorized as FDA authorizations and approvals move into progressively younger populations.

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