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Ethics of age de-escalation in pediatric vaccine trials: Attending to the case of COVID-19

Ami Harbin [a,*], Naomi Laventhal [b,c], Mark Navin [a,d,e]

[a] Department of Philosophy, Oakland University, Rochester, MI, USA
[b] Department of Pediatrics, University of Michigan, Ann Arbor, MI, USA
[c] Center for Bioethics and Social Sciences in Medicine, University of Michigan, Ann Arbor, MI, USA
[d] Department of Foundational Medical Studies, Oakland University William Beaumont School of Medicine, Rochester, MI, USA
[e] Clinical Ethics Consultation Service, Department of Spiritual Care, Corewell East, Southfield, MI, USA

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ABSTRACT

In the development of new vaccines, many trials use *age de-escalation*: after establishing safety and efficacy in adult populations, progressively younger cohorts are enrolled and studied. Age de-escalation promotes many values. The responsibility to protect children from potential risks of experimental vaccines is significant, not only given increased risks of adverse effects but also because parents and medical professionals have a moral responsibility to protect children from harms associated with novel, uncertain interventions. Further, given that young children cannot provide informed consent, acceptable risks for research requiring proxy consent are lower than for adults making decisions for themselves. Although age de-escalation approaches are widely used in vaccine trials, including notably in the recent development of pediatric COVID-19 vaccines, ethicists have not addressed the benefits and risks of these approaches. Their benefits are largely assumed and unstated, while their potential risks are usually overlooked. There are no official ethics guidelines for the use of age de-escalation in clinical research. In this paper, we provide a systematic account of key moral factors to consider when employing age de-escalation. Analyzing pediatric COVID-19 vaccine development as our key case study, we clarify the benefits, risks, and trade-offs involved in age de-escalation approaches and call for the development of evidence-based best practice guidelines to identify when age de-escalation is likely to be an ethical strategy in vaccine development.

1. Introduction: Age de-escalation in vaccine development

Typically, vaccine development requires phase I, II, and III clinical trials, which evaluate, respectively, the safety, immunogenicity, and protective efficacy of a vaccine in advance of its licensure [1]. When these phases are completed, the safety of vaccines can be further observed in post-licensure studies to observe the performance of the vaccine in population use.

In the development of new vaccines, many trials use *age de-escalation:* following the establishment of safety and efficacy in a larger adult population, progressively younger cohorts are enrolled and studied [2–4]. Sometimes referred to as a *step-down* approach, age de-escalation can involve, for example, first testing a vaccine found effective in adults on a cohort of teenagers, followed by elementary school-aged children, followed by preschoolers, toddlers, and then infants [5].

Recent studies that have used age de-escalation include trials of vaccine candidates for anthrax [6], typhoid [7,8], enterovirus [9], malaria [10], HPV [11] and, most notably for our purposes, COVID-19 [12]. Age de-escalation strategies are also used in development of other treatments/interventions, such as in pediatric oncology [13,14], treatment for malaria [15], and treatment for flu [16]. Not all vaccine or treatment trials for children have followed an age de-escalation process [17], but many have.

In pediatric vaccine development, age de-escalation promotes many values including protecting children from predictable kinds of adverse effects of experimental vaccines, shifting uncertain outcomes to older populations, and limiting risks to those who cannot consent to research participation. Although age de-escalation is widely used, including in the recent development of pediatric COVID-19 vaccines, ethicists have not explicitly addressed its benefits and risks, and there are no formal, published ethics guidelines for the use of age de-escalation in clinical research. We provide the first systematic account of key moral factors to consider when employing age de-escalation, in ways that should inform the work of vaccine developers, trial designers, and IRBs. We call for the

* Corresponding author at: Department of Philosophy, Oakland University, 2200 N. Squirrel Rd, Rochester, MI 48309, USA.
E-mail address: aharbin@oakland.edu (A. Harbin).

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development of evidence-based best practice guidelines to identify future contexts in which these approaches should be used.

2. Age de-escalation in COVID-19 vaccine development

Consider the case of the development of COVID-19 vaccines for children under five years old. In May 2020, Kao and colleagues noted with concern a lack of discussion about moving COVID vaccine trials to children, and urged for immediate planning and implementation of such trials in pediatric populations, recommending the commonly used age de-escalation approach with the goal of ensuring early identification of safety signals while minimizing risks and determining appropriate dosages [18–20]. Pfizer and Moderna's COVID-19 vaccine trials eventually followed an age de-escalation protocol, first expanding from adults to adolescents, then to elementary school-aged children, and then to preschoolers, toddlers, and infants [21,22]. Alternative approaches *could have* been employed. For example, it may have been appropriate to conduct trials on younger children prior to studying effects on adults, if children had been at especially high risk of COVID-19. However, children initially seemed less likely to become infected with that disease, and infected children generally experienced less serious symptoms than adults. Accordingly, adherence to age de-escalation in COVID-19 vaccine trials made epidemiologic sense.

Pfizer's COVID-19 vaccine for children five years and older received Emergency Use Authorization in October 2021, with the promise that younger children would not be far behind. Children under five years old were the last to benefit from Early Use Authorization for COVID vaccine in the U.S., when both the Pfizer 3-dose series and the Moderna 2-dose series were authorized in June 2022. Children under five remained ineligible for COVID-19 vaccination during the Omicron surge of December 2021 and experienced the largest increase in hospitalization rates during that time. This was largely due to their unvaccinated status, close contact with unvaccinated individuals (e.g., in childcare settings), and the inability of some children in this age group to wear masks (not recommended for children under age 2). While young children generally are at low risk of serious COVID-19 disease and death, according to the CDC's Data Tracker as of January 2023, child cases represent over 16.2 million cases (17.2%) of cumulative cases in the US, with over 3.3 million cases in children under 5, including 651 deaths (33 % of child COVID deaths), and 2,370 cases of MIS-C (25.4% of all child MIS-C cases). The Omicron surge demonstrated that infants and children *can* be susceptible to highly transmissible variants. And, crucially, the low absolute risk of clinically significant COVID disease fails to account for the full impact of infection in children. Over time, we will be able to better quantify the prevalence of "long COVID" for pediatric patients, and the potential connection between COVID infection and pediatric diabetes and hepatitis. For now, the full impact of COVID infection for children remains poorly understood; we have yet to fully contend with the societal cost of having excluded young children from vaccination for so long.

3. Ethical reasons for age de-escalation

Age de-escalation in vaccine trial design is ethically desirable in part because of the special vulnerabilities of children. Age de-escalation aims to protect young children from three chief risks.

3.1. Protecting young children from adverse effects of vaccine

The physical immaturity of younger children, who are in a rapid phase of growth and development, renders them more susceptible to adverse effects of medications. Age de-escalation protects the youngest trial participants from undue risk of participating in a trial with a new vaccine, and from needing to do so in high numbers. Risks to children associated with a new vaccine are presumed to be greater than risks to adults insofar as less is known about how children's bodies will respond to vaccines. Further, children have a longer future ahead of them during which they might experience ill effects. Unlike treatments or interventions that aim to ameliorate illness or injury, vaccines are received by healthy individuals and thus the threshold for safety must be high. Age de-escalation ensures that most of the information about possible safety signals has already been gathered in the larger adult reference groups. Note that risks are not so much reduced in an absolute sense by age de-escalation approaches as they are *shifted* from younger participants to older ones.

3.2. Protecting young children from uncertainty of novel intervention

A further reason to employ age de-escalation in vaccine trial design is less tangible: we generally view it as our collective moral responsibility to protect our youngest and most vulnerable from risk and uncertainty. Adults rather than children, it seems, should be on the frontline of any uncertain intervention [23]. While the previous point focuses on protecting children from predictable or even known risks, the concern here is to shield children from *unknown* effects of novel interventions. An age de-escalation protocol not only shifts the greater magnitude of adverse events to adults, but it also shifts uncertainty itself onto older groups and away from children.

3.3. Limiting risks to those who cannot consent

Finally, young children lack the maturity to provide informed consent, the foundational principle of research ethics. Although parents have the moral and legal authority to consent on their children's behalf, acceptable risks for research requiring proxy consent are lower than for adults making decisions for themselves [24].

4. Ethical concerns with age de-escalation approaches

Benefits notwithstanding, age de-escalation approaches also impose risks on children and others. They sometimes may not be clinically appropriate, and even when there is a *clinical* justification for an age-de-escalation approach, other ethical concerns can be present. We thus contend that researchers have a moral obligation to weight the benefits *and risks* of age de-escalation protocols against those of other clinical research strategies. In particular, we call for the development of evidence-based guidelines for best practices in use of age de-escalation in trial design. Our list of the benefits and risks of age de-escalation approaches can provide useful resources for such guidelines.

4.1. Clinical complications of age de-escalation

In some cases, contextual clinical realities indicate that age de-escalation is not scientifically appropriate, and recruitment of children to phase I trials may be justifiable. This is the case if the new vaccine would likely cause problems in adults but not in children, because of prior immunity in adults (e.g., as in the case of DTP vaccine) [3]. Also, if a new vaccine is only needed for infants, trials in older age groups may expose them to unnecessary risks without potential to benefit (e.g., rotavirus vaccines). In some cases, adults may be used as participants only in preliminary safety studies (in principle with altruistic motivations), but it may be clinically appropriate to move directly to efficacy studies in children (bypassing adults) [3].

Even when clinically appropriate, age de-escalation models can be difficult to implement: children's immune systems are developing and cannot be straightforwardly compared to adults [17]. Children have differences in size, fat distribution, muscle mass, and other factors that can impact dosing [25]. Immune responses can be age-dependent (e.g., in the case of polysaccharide vaccines), and immunogenicity results in adults can thus be of limited relevance in predicting pediatric outcomes. It is often advisable for additional pediatric safety data to be used since the risks to children can be different (ICH E11 (2000) section II.D (2.4)). To determine whether extrapolation will be appropriate in a particular case of developing pediatric vaccines, researchers must carefully evaluate what evidence supports the understanding of the disease similarity in the reference and pediatric populations, the strength of the evidence of efficacy in the reference population, and uncertainties about the existing reference data (FDA 2018 E11(R1) Addendum). It is not always clear exactly what level of antibody response should be taken as the threshold for having demonstrated protection [17]. Vaccine development can be further complicated in the youngest cohorts, in which there is a greater likelihood of other vaccines being received in the weeks and months surrounding trial vaccines, and therefore higher possibility of interference during co-immunization. Even taking all these considerations into account, age de-escalation approaches are seen as well-established for pediatric vaccine development which, when clinically possible (even if complicated), have all the benefits outlined in the previous section. The existing recommendations regarding the use of age de-escalation exist in the form of status quo norms of use more than in formalized and evidence-based recommendations. We see the norms of use articulated both by government agencies [12], and in publications from health researchers, for instance when urging the earlier development of pediatric COVID-19 vaccines and outlining how such vaccine trials should be designed [18–20].

4.2. Tension of protection

As demonstrated by the COVID-19 case, one ethical concern about age de-escalation approaches is a *tension of protection*. On the assumption that the timeline for *licensing* of vaccines follows the timeline for vaccine *studies*, age de-escalation in trial design will result in the youngest populations being the last to be eligible for vaccine protection. That is, there is a tension between protecting children from known and unknown risks of vaccine studies and protecting them from the diseases that new vaccines protect against. In the COVID-19 case, the result of age de-escalation in vaccine studies was that young children were without access to vaccine protection for much longer than older cohorts. Similar concerns have been raised regarding the delayed inclusion of pregnant participants in vaccine research [26].

4.3. Moving target problem

Consider further a *moving target problem*: as new strains of viruses emerge or become dominant, studies of vaccines that were designed for earlier variants will provide less potential benefit to younger populations if an age de-escalation protocol is followed. This was an issue in the case of pediatric COVID-19 vaccine development. By the time the youngest cohorts were receiving trial doses of vaccines, the dominant variants of the virus were no longer the same as the ones present when older children received study doses. A vaccine that had been shown highly effective at preventing symptomatic illness with previous variants was now less effective at doing so (while still effective at preventing severe outcomes). This lag created complications in evaluating dosage, as well as in public perception of whether the vaccine was successful and worth taking.

4.4. Problem of narrow conception of risk

Consider further a *problem of narrow conception of risk*: typically, the primary risks in view during pediatric vaccine development are the risks of infection (both for individual children and for their potential to transmit the virus) and the risks of adverse vaccine effects. These are the chief risks that age de-escalation studies aim to avoid, and these are the risks that are in 'tension' in the 'tension of protection'. But the costs of delayed access to vaccines include more than delayed protection against infection or the reception of an inferior vaccine. They may also include various social harms. In the case of COVID-19 vaccine access, age de-escalation had ripple effects for daycare and preschool closures, and for quarantine or isolation. Young children lost in a one-two punch during the COVID-19 pandemic: they were harmed by being excluded from early childhood education *and* by the stress and financial instability that the lack of reliable childcare brought into their homes. It was common during the early pandemic to think of child health and child education / social development as separate areas of concern. But this failed to acknowledge that, in light of young children's rapid emotional, social, and cognitive development, access to education is a fundamental component of child health. The deleterious physical and mental health impacts of social isolation and sedentary lifestyle were clear, as were the tangible realities that follow disruptions in childcare. The *social value* of vaccine research reflects all these harms: those of avoiding infection, illness, and transmission, as well as those of persistent isolation for young children, and its impact on families. When considering risk/benefit analyses in future age de-escalation approaches—which propose to develop vaccines for the youngest children last—we need to take a broad view of the harms/risks of not having the vaccine available. Children are harmed not only when they lack access to disease protection, but also by social and educational disruption, in addition to emotional, financial, social, and professional harms to their family units.

4.5. Problem of assumed rather than actual sources of vaccine hesitancy

Further, we must consider a *problem of assumed rather than actual sources of vaccine hesitancy*: vaccines are only effective if people use them. The full benefit of vaccines for protecting individuals and communities depends in large part on public trust of the mechanisms and institutions which develop, authorize, and distribute vaccines. If a certain approach to vaccine development and authorization (e.g., age de-escalation) is *perceived* as prioritizing the safety of the most vulnerable, that might generate greater vaccine acceptance. The benefits of increased vaccine acceptance may outweigh any harms associated with delaying children access to the vaccine. In particular, some might worry that forgoing age de-escalation—for example, by 'skipping' a cohort in studying or authorizing a vaccine (e.g., studying or authorizing a vaccine for use in 6–24 month olds before studying or authorizing a vaccine for use in 2–4 year olds)—would undermine confidence in the vaccine for the skipped cohort. However, there is no evidence that 'cohort skipping' generates vaccine hesitancy, and, unfortunately, we have reason to expect vaccine hesitancy about authorized COVID-19 vaccines for *all ages*, regardless of whether the vaccine approval process follows age de-escalation.

4.6. Concerns about age de-escalation in review, authorization, and approval

Finally, consider *concerns about age de-escalation in review, authorization, and approval*. Following successful vaccine trials in the US context, pharmaceutical companies typically submit their data to

the FDA for review. In the case of COVID-19 vaccines, the FDA's Center for Biologics Evaluation and Research (CBER) made decisions regarding approvals and Emergency Use Authorizations, supported by the Vaccines and Related Biological Products Advisory Committee (VRBPAC). Following FDA/VRBPAC review and decision, the Advisory Committee on Immunization Practices (ACIP) provided expert advice to the CDC in the form of recommendations.

When vaccine trials go well, pharmaceutical companies typically submit their data to the FDA as they become available. Age de-escalation in vaccine trials thus have the potential to create a norm of age de-escalation in the FDA's review and approval process, as though this is a moral imperative. However, the FDA does not mandate age de-escalation for its review process. Rather, FDA characterizes it as a *permitted and typical* consequence of age de-escalation in research:

> Due to the age de-escalation approach typically undertaken for vaccine development in pediatric populations. . .licensure or emergency use authorization of COVID-19 vaccines for use in pediatric age groups may proceed in a similarly stepwise fashion [12].

Ethical concerns might arise in a number of scenarios. For instance, if a *procedural* norm of age de-escalation delays the review, authorization, or approval of a vaccine shown safe and effective for a younger cohort due to there being outstanding questions of its safety or efficacy in an older cohort, this constitutes a moral failure. For instance, some parents and pro-vaccine advocacy groups voiced concerns following Pfizer's December 17, 2021 earnings call, when the company reported that noninferiority had been met for the 2 dose pediatric COVID vaccine in the 6–24 month old population (i.e., two doses were shown to generate an immune response comparable to that found in 16–25 year olds), but not in the 2–4 year old population (in whom two doses had shown an inferior response to that measured in 16–25 year olds), and that the company would nonetheless be testing a third dose series in *both* age groups before seeking licensure [27]. Exactly why the two-dose data in 6–24 month olds, which demonstrated both safety and efficacy, were not submitted for review at that point was the subject of significant concern and speculation [28].

There are more potentially good reasons to prioritize review, authorization, or approval of a vaccine in a younger cohort *before* an older cohort for reasons related to the safety or efficacy of the vaccine and/or the needs of different populations. Ethical concerns should arise if a norm of age de-escalation delays the review, authorization, or approval of a vaccine that is urgently needed in a younger cohort (e.g., due to particular medical vulnerabilities in that age group – e.g., potential higher risk of hepatitis), while the vaccine is less urgently needed in older cohorts. If a norm of age de-escalation takes priority in such instances, the principles of research ethics have been misapplied.

If pharmaceutical companies' data demonstrate that a vaccine is safe and effective for younger children, they should not delay submitting those data for FDA review simply because they have not yet submitted data from older cohorts. Nor should the FDA delay in reviewing such data until it authorizes investigational vaccines for older groups of children. Age de-escalation in research might protect vulnerable children, but age de-escalation in the review and approval process, particularly during public health crises, heightens children's vulnerability by prolonging their susceptibility to vaccine-preventable illness. Delaying submission or review

Table 1
Ethical concerns with age de-escalation approaches.

Ethical concern	Description	Application in COVID-19 age de-escalation trial
Tension of protection	Approach to vaccine development protects a population from some risk(s) while subjecting it to others	From an understandable desire to protect them from undue risk, youngest populations were subject to the risk of being without vaccine protection for much longer than older cohorts.
Moving target problem	Clinical conditions change during the time it takes to wait for age group's involvement in research trial	By the time youngest cohorts were receiving trial doses of vaccines, dominant variants of the virus were no longer the same as those present when older children received study doses. A vaccine that had been shown highly effective at preventing symptomatic illness with previous variants was now less effective at doing so (while still effective at preventing severe outcomes). This lag creates complications in evaluating dosage, as well as in public perception of whether the vaccine is successful and worth taking.
Problem of narrow conception of risk	Risk/benefit of vaccine trials focuses largely on risks of serious illness in individuals and populations, sometimes to the exclusion of risks to social, emotional, and educational health	Risk/benefit analyses of COVID vaccines for young children typically focused on risk of infection, serious illness, and transmission. Insufficient attention was paid to the ways delayed vaccine access prompted social and educational disruption, and also emotional, financial, social, and professional harms to family units, and thereby also to children.
Problem of assumed rather than actual sources of vaccine hesitancy	Public trust in vaccines must be prioritized for vaccines to receive uptake, but sources of vaccine hesitancy are sometimes assumed rather than empirically confirmed	If age de-escalation is *perceived* as prioritizing the safety of children, thus resulting in more public uptake for a given vaccine once authorized, the benefits of greater uptake might outweigh harms of delaying access to the vaccine. But in fact, we have reason to expect vaccine hesitancy and low uptake about authorized vaccines for *all ages*, regardless of whether the vaccine development process follows age de-escalation.
Concerns about age de-escalation in review, authorization, and approval	Age de-escalation can be a formal part of trial design, but should not be an informal part of review, authorization or approval.	In the pediatric Pfizer vaccine trial, December 2021 data showed that the two-dose series met the noninferiority standard desired in 6–24 month olds, but the vaccine was not reviewed for that age group. Review was not pursued until after third dose data was collected in children 6 months-4 years of age.

of data from younger cohorts due to adherence to an age de-escalation process unnecessarily delays the granting of pre-approval access, which excludes vulnerable populations of young children from the benefits of vaccination. In the review and pre-approval access authorization for vaccines, strict adherence to age de-escalation potentially constitutes moral *failure* Table 1.

5. Conclusion: Call to develop age de-escalation research ethics guidelines

There are clear ethical advantages to age de-escalation approaches in vaccine development, but the potential risks involved in such approaches suggest that vaccine researchers should not default to them uncritically. Prospective use of age de-escalation in vaccine trial design should be more carefully and formally reviewed to consider all the risks and benefits of such approaches and the situations in which they are appropriate. For instance, had all the social, emotional, and educational risks been taken into account for the youngest age groups, it might have been more appropriate to enroll them in COVID-19 vaccine trials concurrently with the 5–11 year olds. The absence of published recommendations or guidelines in advance of the COVID-19 vaccine trials may have contributed to a default to an age de-escalation strategy, based on an implicit moral norm, rather than as an evidence-based or even expert-consensus best practice. As we look ahead to future vaccine development in urgent conditions, we need clear, *a priori*, rather than *post hoc* assessment of the ethical dimensions of these approaches.

Vaccine research would benefit from the development of a set of guidelines for the use of age de-escalation approaches in pediatric vaccine trial design. Such guidelines can help researchers to identify the benefits, potential harms, and the tradeoffs of age de-escalation. They can help researchers determine whether age de-escalation is clinically and ethically appropriate for their studies. We lack the expertise in vaccine development to propose a full set of such guidelines, however, we suggest that those guidelines should focus on the considerations we have proposed in this paper.

Data availability

No data was used for the research described in the article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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