COVID-19 vaccines: a look at the ethics of the clinical research involving children

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ABSTRACT

Currently, millions of minors are being inoculated against SARS-CoV-2 in many countries in the world. Ethical concerns about clinical research involving children have barely been addressed in the literature, despite the fact that the paediatric population is particularly vulnerable within this context. Children should be included in the research plans for COVID-19 vaccines. Nevertheless, it is necessary to critically assess to what extent clinical trials are being conducted according to methodological and ethical criteria that allow us to conclude that the results are valid and, in consequence, how far the vaccination plans for children are scientifically justified.

The principal aim of this article is to analyse critically the process of clinical research on COVID-19 vaccines involving children, highlighting the ethical concerns that arise, including the need to stratify the results from older adolescents separately for analysis before proceeding, if further research is warranted, in descending age order. The development of COVID-19 vaccines is examined, with a special look at the participation of children throughout their clinical development, including a review of the clinical trials registered in three international databases. We also offer some additional considerations about the inclusion of minors in vaccination plans. Finally, we conclude with some recommendations, with particular emphasis on the following ethical duties: research in children should be carried out only once the relevant research in adults has previously been conducted; issues that concern children's needs and rights should be specifically addressed; and, therefore, the highest standards of ethical and scientific quality should be met.

INTRODUCTION

The SARS-CoV-2 pandemic poses a major challenge for humanity, affecting many aspects of our lives. Despite the huge number of people affected throughout the world, we do not yet know its real scope. Nor do we understand the degree to which certain factors influence whether the disease presents itself or not, its seriousness and how it develops clinically, even in groups that share common characteristics (age, sex, pathologies, concurrent pathologies and/or associated treatment). This situation makes the therapeutic and preventive approach to COVID-19 even more difficult. Nevertheless, to date, we do know that older people, especially men over 60, and persons living with comorbidities, obesity or overweight, tend to suffer from more severe forms of the disease and higher mortality. We also know that the clinical manifestation of COVID-19 in children tends to be more moderate than in adults.[1]

In the first months of the pandemic, many attempts were made both to search for effective treatments for the symptoms and to extrapolate from the in vitro activity of the drugs under study, without due coordination. This situation had consequences for the patients themselves and the validity of the studies, in terms of time lost and wasted resources, overload of review bodies such as the Institutional Review Boards (IRBs) and resultant inefficiency in the hospitals where the research was usually being organised and carried out.[2] Generally, these experiments, poorly planned and sometimes without adequate justification, generated little scientific knowledge beyond demonstrating their low utility, because they lacked the methodological rigour of randomised double-blind clinical trials.[3] Meanwhile, sequencing the whole SARS-CoV-2 genome in record time, together with a global approach that has prioritised vaccine research, has enabled the availability of different classes of vaccines, approved on a temporary basis for emergency use in numerous countries in the world.

Surprisingly, ethical concerns about clinical research involving children have hardly been addressed in the scholarly literature. Instead, in high-income countries, once the vaccination rate in adults has reached a significant level and the pandemic seems to be subsiding, vaccination plans for minors are being implemented in a rush, attracting great attention in both the literature and the media. Indeed, even in high-impact scientific journals, attention has been directed almost exclusively to the controversy generated by vaccination itself (see, for example, https://doi.org/10.1136/bmj.n1687). For these reasons, in this article we focus our attention on the process prior to plans for the vaccination of minors, as a starting point for discussion.

THE DEVELOPMENT PROCESS OF COVID-19 VACCINES

The clinical development of vaccines is a well-established four-phase process, with clear objectives associated with each phase. The fundamental difference from the development of drugs is that—since the aim is to prevent disease not to cure it or treat its symptoms—although the participants in vaccine trials are, like those in drug trials, volunteers, they must not have had the disease or developed an immune response to it. On the basis of the results obtained from research in animal and laboratory models (preclinical studies to test aspects such as toxicity and immune response), the first human studies are intended to confirm the initial tolerability and safety of the vaccine in a small group of

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volunteers (phase 1). The primary objective of the subsequent studies is to explore preliminary efficacy in a small group of participants with very similar characteristics and to search for the most appropriate dosage (phase 2). The efficacy and safety studies that follow are the most important, as their outcome will determine whether or not the vaccine can be authorised for sale under the conditions set out (phase 3). Monitoring of the effects of the vaccine once it has been put on the market is carried out in phase 4.

The development of a new drug is a technically complex process, rigorously regulated in each of its stages; it is long and financially risky (in great measure due to the high fixed costs and the numerous failures) and, therefore, very costly. These traits are even more pronounced when dealing with the development of a new vaccine.[4 5] Developing a conventional human vaccine takes 15–20 years between discovery and market introduction and carries a cost of approximately US$1 billion.[6] Other sources estimate a timescale of 5–10 years for the traditional process of vaccine development.[7] From any perspective, this timescale is far removed from the period of less than a year spent in obtaining the first available vaccine against SARS-CoV-2 infection.

As regards attaining herd immunity and contributing to the advancement of scientific and technological knowledge to combat future—and potentially pandemic—infectious diseases, vaccines can be considered public goods, characterised by positive externalities. These are benefits reaching uninvolved people, whose welfare is positively impacted through channels outside the market. Unlike private goods, public goods are non-rivalrous (available to society and not limited to a particular consumer or user) and non-excludable (it is not possible to exclude those who do not pay for them) (see https://plato.stanford.edu/entries/public-goods/#PublGoodExte). Vaccines can be considered a public good insofar as they provide a private benefit (the advantages of immunisation are internalised individually by each person) and an external benefit (the fact of being vaccinated contributes to the protection of others). Arguably, activities that generate positive externalities (such as immunisation) deserve public support because transactions made exclusively by individual decisions in the market will leave out external benefits that are not bid for, as exclusion is not possible. In cases where positive externalities are not limited to the inhabitants of a particular country, but can affect the population of the world as a whole, we can speak of global public goods. In a pandemic context, insofar as externalities transcend borders between countries, immunisation qualifies as a global public good. All this justifies the public support that the development of COVID-19 vaccines requires and is, in fact, receiving internationally.

The development of a vaccine to combat a new disease such as SARS-CoV-2 infection in record time has been a major global challenge for humanity. The massive efforts made on multiple fronts—including actors from outside the pharmaceutical industry and unprecedented public–private partnership—have been rewarded with the achievement of this major goal in less than a year. Given the exceptional circumstances of the pandemic, virtually every step taken in the development of COVID-19 vaccines has been unprecedented, and these include partially overlapping phases, regulatory speed, massive financing by actors outside the industry and advance purchase agreements, as well as different formulas for authorising emergency use prior to licensing. The 'new pandemic paradigm' deviates from linear sequence and involves, for example, testing the vaccine candidate in humans and animals at the same time (or even skipping animal studies), simultaneous phase 1 and phase 2 clinical trials and very early large-scale commercial manufacture.[8]

The great speed attained in obtaining vaccines against SARS-CoV-2 infection was made possible, to a great extent, by previous scientific knowledge, including previous studies on other human coronaviruses of zoonotic origin (SARS-CoV-1 and Middle East respiratory syndrome coronavirus). Other factors relate to the fusion of computing power with recombinant DNA technology, advances in whole-genome sequencing and biological and genomic big data available in databanks.[9]

Some shortcuts in the pathway to vaccine development are justified and ethically desirable, and certainly when supported by scientific evidence and/or related to eliminating dead time. However, other shortcuts may raise ethical concerns.[10] One major concern relates to children, as potential subjects in clinical research and, in consequence, in vaccination plans.

CHILDREN AS SUBJECTS IN CLINICAL RESEARCH ON COVID-19 VACCINES

The term 'children' here refers to minors under the age of 18, the legal age for being considered an adult in most countries in the world—as considered in the United Nations Convention on the Rights of the Child (UNCRC)—and, therefore, for giving informed consent.

The paediatric population is particularly vulnerable within the context of clinical research, in terms of both minors' exclusion from and participation in clinical trials. Leaving minors out of clinical research has meant that most drugs approved by regulatory agencies lack sufficient information about their potential use in children. In consequence, they are used by analogy (ie, dose/kg) in the paediatric population. The administration of off-label drugs, which happens occasionally with adults, is the rule with children. Extrapolating from results obtained in adults to the paediatric population can have serious consequences for children's health, as children are not small adults. They have their own distinctive physiological characteristics, which include a higher proportion of body water, the immaturity of some enzyme systems and of other response mechanisms to various forms of attack, such as the immune system. In addition, these characteristics differ in different age subgroups, depending on the stage of growth and development. Therefore, there is an ethical obligation to carry out research involving this population group in a planned way, once safety has been proven in adults capable of both understanding the implications of the research and giving their unequivocal consent to participate in a study. Moreover, since minors are not able to give informed consent, in addition to the consent given by their parents or legal guardians, it is necessary to obtain the minors' own assent, provided that they are considered capable of understanding the information and communicating their opinion.

From this premise, and considering the gaps in our understanding of different aspects related to COVID-19—including the disease course and the novel mechanism of action of messenger RNA (mRNA)-based vaccines, which have never before been tested in humans[11]—it follows that the inclusion of minors in clinical trials of vaccines against SARS-CoV-2 should be planned after assessing the results in adults. This approach is consistent with the criterion that '…research risks should be allocated to adults rather than to children whenever feasible', established as an ethical recommendation by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.[12] In addition, depending on the results obtained, planning should generally proceed in descending age order, including older adolescents first, then younger children. This general approach reflects the older teenagers' greater autonomy

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in decision-making, and that younger children have greater difficulty in accurately reporting their physiological and emotional state. Note that, otherwise, the youngest minors would be placed at greater risk than others participating in the same research.[12]

There are many recommendations from different international organisations (including the WHO, the Council for International Organizations of Medical Sciences, the World Medical Association Declaration of Helsinki and the UNCRC), as well as consensus documents from scientific societies, legislation from various countries and further bibliographic sources, all of which establish ethical requirements that need to be met to justify research involving human participants. These include social value and scientific validity (eg, the hypothesis is plausible and the methodology is correct); fair participant selection (not including the most vulnerable because they are easy to recruit, nor excluding those who could also benefit from the results), with eligibility criteria guided by valid scientific reasons (eg, both high-incidence/transmission rates of an infection) and warranting that the groups bearing the risks also potentially enjoy the benefits; and favourable benefit-risk ratio (eg, minimising potential risks and maximising potential benefits). In the case of minors, the same requirements must be met as in any other type of research involving human participants. However, given their vulnerability, clinical research with children requires special attention to their needs and rights. For example, all the requirements must always be supported by a favourable report from an independent review body, such as an IRB, and the IRB must assess whether both surrogate consent and, where appropriate, the minor's assent can be considered valid, while also bearing in mind the added complexity that the conditions may vary from country to country.

Despite the emergency circumstances, with respect to research in humans, the basic ethical principles remain the same,[13] especially when children are involved. That is to say, minors should undoubtedly be included in the research plans for vaccines against COVID-19, provided that the plans are carried out according to methodological and ethical criteria that allow us to conclude that the results have internal and external validity, as well as to guarantee that human subjects' rights have been respected. It appears that neither the incidence nor severity of SARS-CoV-2 infection is very high in the paediatric population,[14–17] so that the scientific data available so far reinforce the ethical approach outlined above, proceeding with adults before children and planning a staggered schedule of experimentation on minors.

In order to find out how the research involving children is being conducted and to be able to give a broad outline of the approaches and trends involved in the clinical trials undertaken, we carried out a search of COVID-19 vaccine clinical trials involving the paediatric population, which is presented concisely in the following section.

CLINICAL TRIALS OF COVID-19 VACCINES INVOLVING CHILDREN

The databases consulted were the ClinicalTrials.gov database, the European Union Clinical Trials Register and the International Standard Randomized Controlled Trial Number platform. We identified 19 trials registered from the beginning of the pandemic to May 2021 (see table 1). The trials identified reflect the strategies in the development of COVID-19 vaccines in the general population, both regarding the technologies being applied (given the classes of vaccines tested), and the nationality of the sponsors leading the research, with the USA and China

Table 1 Clinical trials of COVID-19 vaccines involving children*

NCT number	**NCT04551547**
S	Sinovac Research and Development
EA	3–17 years
PC	China
NCT number	**NCT04471519**
S	Bharat Biotech International
EA	12–65 years
PC	India
NCT number	**NCT04683484**
S	Nanogen Pharmaceutical Biotechnology Joint Stock
EA	12–75 years
PC	Vietnam
NCT number	**NCT04566770**
S	CanSino Biologics
EA	6 years and older
PC	China
NCT number	**NCT04535453 (Postponed. See text)†**
EudraCT number	**2020-002584-63 (children not eligible in EU countries)**
S	Janssen Vaccines & Prevention (subsidiary of Johnson & Johnson)
EA	12 years and older 18 years and older (until 3 December 2020)
PC	Brazil, Canada, Germany, Netherlands, Spain, UK, USA
EudraCT number (2021)	**2020-005720-11**
S	Janssen Vaccines & Prevention
EA	From birth to 17 years; 18–55 years
PC	Sites planned: Argentina, Australia, Brazil, Canada, Colombia, Finland, Italy, Mexico, Poland, South Africa, Spain, Sweden, Turkey, UK, USA
ISRCTN	**ISRCTN90906759**
NCT number	**NCT04400838**
EudraCT number	**2020-001228-32 (UK—only adults)**
S/C	University of Oxford/AstraZeneca
EA	18 years and older (participants aged 5–12 no longer eligible) 5–12 years; 18 years and older (until early December 2020)
ISRCTN (2021)	**ISRCTN15638344 (Postponed. See text)‡**
S/C	University of Oxford/National Institute for Health Research (UK); AstraZeneca
EA	6–17 years
PC	UK
NCT number	**NCT04299724**
S	Shenzhen Geno-Immune Medical Institute
EA	6 months to 80 years
PC	China
NCT number	**NCT04276896**
S	Shenzhen Geno-Immune Medical Institute
EA	6 months to 80 years
PC	China
NCT number	**NCT04368728**
EudraCT number	**2020-002641-42 (children not eligible in the EU)**
S/C	BioNTech/Pfizer
EA	12 years and older 16 years and older (from 25 September 2020 to 13 October 2020); 18 years (until 24 September 2020)
PC	Argentina, Brazil, Germany, South Africa, Turkey, USA
NCT number (2021)	**NCT04713553**
S/C	BioNTech/Pfizer

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Table 1 Continued

EA	12–50 years 18–55 years (until 8 February 2021)
PC	USA
NCT number (2021)	**NCT04816643**
S/C	BioNTech/Pfizer
EA	6 months to 11 years
PC	USA
NCT number	**NCT04649151**
S	ModernaTX
EA	12–17 years
PC	USA
NCT number (2021)	**NCT04796896**
S	ModernaTX
EA	6 months to 11 years
PC	USA
NCT number (2021)	**NCT04863638**
S	China National Biotec Group
EA	3 years and older
PC	China
NCT number (2021)	**NCT04800133**
S	The University of Hong Kong
EA	11 years and older
PC	Hong Kong Special Administrative Region of China
NCT number (2021)	**NCT04611802**
S	Novavax
EA	12 years and older 18 years and older (until 26 April 2021)
PC	Mexico, USA (paediatric extension not applicable to Puerto Rico)
NCT number (2021)	**NCT04773067**
S	United Biomedical, Asia
EA	12–85 years
PC	Taiwan

Data current as of 1 May 2021.
*Created by the authors. Data sources: ClinicalTrials.gov database (https://clinicaltrials.gov/ct2/home); EU Clinical Trials Register-EudraCT database (www.clinicaltrialsregister.eu/); and ISRCTN registry (www.isrctn.com/). The search terms were 'vaccine' and 'vaccination', combined with 'COVID-19' and 'SARS-CoV-2'. In the ISRCTN registry database, the search term used was 'infections and infestations'. The lists of projects obtained were refined in order to exclude passive immunity strategies (convalescent plasma and monoclonal antibodies) and treatments with substances of chemical origin, as well as other activities, such as vaccine-promoting initiatives. The searches were conducted twice: on 1 January 2021 and 1 May 2021. The criteria followed, in the order of presentation of the studies listed in this table, are as follows: in the first instance, the degree of technological innovation (from inactivated vaccines to messenger RNA (mRNA)-based ones, with no intention of establishing any comparative ranking of vaccines within the same class); in the second instance, chronological order (2020, then 2021), except when the same sponsor had already registered a trial in children during 2020, in which case the 2021 trial is listed immediately below that sponsor's earlier trial.
†Suspended from 16 April 2021 to 8 July 2021, according to the history of changes at the ClinicalTrials.gov registry. From 9 July to 28 September 2021: active, not recruiting.
‡Ongoing, not currently recruiting.
EA, eligible ages; EU, European Union; EudraCT number, EU Clinical Trials identifier; ISRCTN, International Standard Randomized Controlled Trial Number; NCT number, ClinicalTrials.gov identifier; PC, participating countries; S, sponsor; S/C, sponsor/collaborators.

being the countries that are currently sponsoring most trials in children.

During 2020, the minimum eligible age for including children in trials was 12 years in all participating countries, except China. Currently, trials that project enrolling infants from birth to 1 year of age are being conducted in other countries (see table 1). This situation is taking place in parallel with a process of paediatric extensions initiated at the end of 2020, in some cases within very short periods of time (see table 1).

We were able to verify compliance with the order of preference in the selection of classes of subjects in the vast majority of trials, but not in all (namely the trials identified as NCT04299724 and NCT04276896 in table 1). Even so, given the short observation periods, in all cases, the research in children has been conducted with the support of preliminary results obtained in adults or in minors situated in older age ranges. In April 2021, two trials of viral vector vaccines in children were suspended, postponing vaccination, at the same time that vaccination in adults was stopped (at least for some age ranges and, primarily, first doses), while their potential link to rare cases of blood clots, especially in young adults, was being reviewed.

It is not possible to discuss each of the trials identified in table 1 individually. However, we will refer specifically to two situations, insofar as they are likely to arise frequently in the near future, and require methodological decisions with ethical implications. The BNT162b2 vaccine (NCT04368728 in table 1) requires special attention in this respect, as it was the first one to be temporarily authorised for use in adolescents aged 16–17 in many countries simultaneously. Although the results publicly presented prior to temporary authorisation were analysed by subgroups, the stratification established put the adolescents aged 16–17 into a single group consisting of those aged 16–55. We consider that preliminary outcomes referring to adolescents aged 16–17 should be analysed separately, since the teenagers are in the process of growth and have different biological characteristics. In this regard, uncertainties or doubts could arise regarding both the statistical significance and the clinical validity of the results in relation to the population concerned, especially given the small number of adolescents inoculated and the short observation period. Furthermore, it is necessary to take into account that this population group is taken as a reference point for all the other minors in further trials. Another situation worth mentioning with a view to the design of clinical trials in minors relates to the trials that plan to recruit children from birth to less than 1 year of age. The findings regarding the fact that the breast milk of women who have been infected or vaccinated contains antibodies that can be transmitted to the infant[18 19] should be taken into account to the extent that, in case vaccination was indicated in infants, the breast milk would provide protection from infection, at least for the period that passive immunisation lasts.

ADDITIONAL CONCERNS ABOUT INCLUDING CHILDREN IN COVID-19 VACCINATION PLANS

For mass vaccination to control the pandemic situation, it is necessary not to have a very large population group susceptible to infection by the disease and therefore able to transmit it. Besides, affecting children as it does, the pandemic situation itself justifies the need to include them in clinical research, assuming that all the methodological and ethical requirements that guarantee the validity of the results are followed. However, as Obaro points out, the approach to the formulation of vaccines for immunising children against SARS-CoV-2 should take some further considerations into account.[20] First, the current lack of knowledge about the pathogenesis of multisystem inflammatory syndrome in children (MIS-C), and its possible relationship to the immune response in minors, could put otherwise healthy children at greater risk if the same criteria used to evaluate COVID-19 vaccines in adults are followed, because the incidence of MIS-C could be increased by the vaccination itself inducing the immune response.[20 21] Second, from a public health perspective, the vaccination of minors would be justified

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if they transmitted the disease (ie, acted as reservoirs) and the vaccine could prevent this, both of which are as yet undemonstrated.[14 20 22] Finally, from an ethical point of view, the benefit-risk ratio of vaccinating children indiscriminately provides little direct benefit to minors (ie, marginal benefit), while the medium-term to long-term risk is still unknown.[14 20] Furthermore, if a global perspective is adopted, the benefit to society is not justified as long as there are many adults at higher risk in middle-income and low-income countries without access to vaccines. Since, by definition, pandemic does not respect borders and immunisation can therefore be considered a global public good, this is the perspective we consider it appropriate to adopt. In other words, even assuming that the research plans respect all the methodological and ethical requirements, in this context, the design of the vaccination plans should not ignore the concept of global public good.

In any case, as far as the paediatric population is concerned, transparency (eg, the release of adequately broken down raw data from clinical trials), inclusiveness and validity (accurate and reproducible results) should be the guiding principles in decision-making without exception. Among other criteria, the results of the clinical studies, both in adult and older paediatric populations, should guide health authorities to design the research plans oriented towards younger children. Stratification in descending age order is followed so as to avoid extrapolating indications (from adults to the paediatric population and between different subgroups of the latter) and in order to use the results (in this case, interim results) obtained in the preceding clinical studies to give continuity to research in younger population strata. The results obtained from the trials in younger age groups should be the basis for the indications and conditions of use within these age groups, if and when it is finally considered appropriate to administer vaccines against COVID-19 to these subgroups of the population. Lastly, insofar as the long-term outcomes of COVID-19 vaccines are currently unknown, in terms of their effectiveness, safety, as well as the durability of their effects, monitoring of their long-term effects is key to decision-making in general and, particularly, in relation to both clinical research and vaccination plans involving the paediatric population.

To date, in the Western world, priority is being given to the vaccination of older populations and those with associated risk factors. In other words, in most countries and regions in the world that could afford vaccination, so far it has not been considered necessary to include the paediatric population in general in priority plans for vaccination (in the absence of specific underlying health conditions). Recently, vaccination of adolescents aged 16–17 has started in numerous countries. In the USA, vaccination is recommended for everyone aged 12 years and older. In Cuba, the media have announced the imminent vaccination of children from the age of 2. If carried out, Cuba would be the only country in the world where such young children were vaccinated to date.

The possibilities for comparing vaccine outcomes are limited due to the dynamics and genetic mutations of the SARS-CoV-2 lineages; the differing levels of incidence and prevalence of COVID-19 in the research locations; and, as Hodgson *et al* point out,[23] the absence of a gold standard to evaluate the different efficacy endpoints. Even if the vaccines made possible by novel platform technologies seem to have yielded generally promising results at the time of writing, potential safety problems with some viral vector vaccines are being studied. Concerning mRNA-based vaccines, their main advantage is that they can be produced fully synthetically. Nevertheless, their major disadvantage is that none had been authorised for human use prior to the COVID-19 vaccines, so there are still gaps in our understanding of both their mechanism of action and their long-term performance.[11] Meanwhile, cases of myocarditis and pericarditis are being reported as probably associated with mRNA vaccination, above all, after second dose was administered to young men and, especially, to minors in the upper age range. Logically, the (rare though serious) cases are being detected in those countries where the vaccination of adolescents is more advanced, such as Israel[14] and the USA.[24] This evidence upsets the underlying benefit-risk ratio in the vaccination plans for adolescents. In fact, the UK has recommended delaying the administration of the second dose to people aged 16–17, while the recommendation of two doses for children aged 12–15 with specific underlying health conditions has been retained.[25] In addition, as mentioned earlier, the detection of cases of blood clots potentially linked to immunisation of adults with viral vector vaccines led to the suspension of two trials of this class of vaccines involving children.

The enthusiasm generated by the authorisation of the first COVID-19 vaccines has tended to overshadow the fact that other public health strategies also deserve attention as complementary ways to fight SARS-CoV-2. Indeed, there is concern regarding the possibility that, once the vaccination process is underway, other strategies will be neglected, such as social distancing or educational interventions, in particular those aimed at young people. In this context, we consider it necessary to implement a comprehensive strategy. For instance, to soften isolation measures, when deemed necessary, it would be worth evaluating the promising potential of initiatives that promote more outdoor activities and splitting classes into smaller groups. The full potential benefits of these initiatives include a way to facilitate social distancing and thus reduce risk, and an opportunity to move towards alternative pedagogical models. A comprehensive strategy, obviously including prioritised vaccination of adults and other vulnerable persons, could alleviate the undesirable impact of isolation on the education and emotional well-being of minors, permitting adults to protect minors and not the reverse.

RECOMMENDATIONS

Including under-represented groups in clinical research, as is the case with children, is an ethical obligation, as is the establishment of and respect for basic guidelines for research on children. As a corollary, the following recommendations could be considered as ethical duties in research on COVID-19 vaccines involving children: research in the paediatric population should be carried out only once the relevant research has previously been conducted in adults; issues that concern children's needs and rights should be specifically addressed; and, therefore, the highest standards of ethical and scientific quality should be met.

Furthermore, in the current circumstances, monitoring both the course of the disease across all age groups and the impact of newly emerging variants is crucial, as is gaining a deeper understanding of MIS-C.[17] Meanwhile, given the pace at which vaccination plans are being implemented in several high-income countries, the comprehensive strategy suggested here would facilitate a more global and equitable approach to the pandemic. That is, it would be possible to release vaccine doses to the more vulnerable people in countries with difficulties in accessing them, enabling a more equitable and efficient manner to the control of pandemic, insofar as immunisation against SARS-CoV-2 is a global public good. In parallel, pharmacovigilance and seroprevalence studies (researching the immune response both to administration of the vaccine and also to the disease itself in children

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who have had it) are particularly relevant in this context. Clinical trials in phase 4 should be encouraged at international level, which will undoubtedly help to better protect the general population and, in particular, the paediatric population, as well as to better define the benefit-risk ratio, which is in principle less favourable for children than for adults.

Finally, we must insist that the emergency situation we are experiencing cannot justify circumventing ethical requirements and a consensus that it has taken a great deal of effort to reach. We must learn from past mistakes and avoid excluding children from research as we did until a few decades ago, but we must also ensure that, as a society and through the relevant institutions, the agreed criteria and standards are respected, otherwise the risks may also be high.

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