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COVID in Pediatric Age: an opinion paper

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ABSTRACT

The incidence of COVID in pediatrics was underestimated during the first months of the pandemic due to the oligo-symptomatic nature of the infection in many children and the scarcity of diagnostic tests applied to this population. It is now accepted that children are infected and transmit the disease in the same way as adults. On the contrary, children have less severe and less lethal COVID, probably due to a lower maturity of the child's immune system, a lower number of ACE₂ receptors and the lower presence of comorbidities in this population group.

The development of a multisystemic inflammatory syndrome after SARS-CoV-2 infection in children, despite its rarity, is a very serious condition that frequently requires intensive care. Other less severe post-COVID manifestations have been described in children but are not yet well defined.

COVID has had and continues to have a significant psychological impact on the children themselves, on their caregivers and on the exacerbation of pre-existing psychiatric conditions.

We apply adult therapeutic principles to children but with very low levels of evidence. Information on the tolerability

of the available medications in this population group is still scarce. The mortality of COVID in children is very low and generally affects children with significant comorbidities.

There are, at present, three vaccines licensed for pediatric use which are compatible with all other vaccines applicable to children.

In these circumstances, there has been much speculation about the indication for vaccination in the pediatric age group, but given its good tolerance, there are clinical and ethical reasons that, in our opinion, justify it.

Keywords: COVID-19, SARS-CoV2, treatment, vaccination, omicron, delta, ethics, inflammatory syndrome, pediatric population, pediatrics

COVID en la edad pediátrica: un documento de opinión

RESUMEN

La incidencia de COVID en pediatría ha estado infraestimada durante los primeros meses de la pandemia por el carácter oligosintomático de la infección en muchos niños y por la escasez de pruebas diagnósticas aplicadas a esta población. Hoy se admite que los niños se infectan y transmiten la enfermedad igual que los adultos. Por el contrario, los niños tienen cuadros clínicos menos graves y letales lo cual parece relacionado con una menor madurez del sistema inmune del niño, una menor cantidad de receptores ACE₂ y la menor presencia de comorbilidades en este grupo de población.

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El desarrollo de un síndrome inflamatorio multisistémico tras la infección por SARS-CoV-2 en niños, pese a su rareza, es un cuadro muy grave que frecuentemente requiere cuidados intensivos. Se han descrito otros cuadros post-COVID en niños, menos graves, pero todavía no muy bien definidos.

La COVID-19 ha tenido y tiene un importante impacto psicológico en los propios niños, en sus cuidadores y en la exacerbación de cuadros psiquiátricos pre-existentes.

Aplicamos a los niños los principios terapéuticos de los adultos pero con niveles muy bajos de evidencia y la tolerancia de los medicamentos disponibles en este grupo de población es todavía mal conocida. La mortalidad de la COVID en niños es muy baja e incide generalmente en niños con importantes comorbilidades.

Hay, en el momento presente, tres vacunas autorizadas para el uso pediátrico y las vacunas frente a SARS-CoV-2 son compatibles con el resto de las vacunas aplicables a niños.

En estas circunstancias se ha especulado mucho sobre la indicación de vacunación en la edad pediátrica pero dada su buena tolerancia, existen, en nuestra opinión, razones clínicas y éticas que la justifican.

Palabras clave: COVID-19, SARS-CoV2, tratamiento, vacunación, ómicron, delta, ética, síndrome inflamatorio, edad pediátrica

INTRODUCTION

At the present time, in the midst of the expansion of the sixth wave of SARS-CoV-2 infection and its variant Omicron in Spain, the situation of COVID-19 in pediatric age group (under 18 years of age) is a matter of concern.

The Illustrious Official College of Physicians of Madrid (ICOMEM) has received different consultations regarding infection and disease in children and the COVID-19 Committee itself has had frequent discussions on this important population subgroup.

At the time of writing (January 17, 2022) PubMed responds to the query about articles containing the words COVID-19 or SARS-CoV-2 or Coronavirus in the title with the figure of 165,881 publications. When the pediatric age filter is introduced, 12,286 articles focus on pediatric age patients.

For all these reasons, we thought it appropriate to ask ourselves and try to answer a series of specific questions that are asked on a daily basis, not only by professionals related to the health sector, but also by the general population. Below we present the information we have been able to collect on this subject with the intention of providing the state of the art on different issues on the subject.

WHAT HAS BEEN THE REAL INCIDENCE OF COVID-19 IN PEDIATRICS?

At the beginning of the pandemic (2020), pediatric infection was thought to be less frequent than in adults, but the data in children during that period were probably underesti-

mated [1], given the scarcity of diagnostic tests available at that time and the peculiarities of the COVID-19 in pediatrics [1].

For example, the prevalence of IgG antibodies against SARS-CoV-2 in a population-based sample in Spain in 2020 was lower in those under 20 years of age than that observed in the general population. Moreover, in them, the infection was very often asymptomatic (44.9%) [2], which facilitated that in clinical studies, it was under-diagnosed [3,4].

The most recent serological studies in symptomatic or asymptomatic children show that susceptibility to infection is similar in all age groups [5,6] and that the difference between them is due more to different behavioral habits than to other causes.

It is now recognized that children are infected and transmit the disease in a similar way to adults, although the actual incidence of SARS-CoV-2 infection in pediatrics is difficult to know exactly. European seroprevalence studies show that 15-31% of children under 12 years of age have been infected with the virus and this situation is increasing in recent months throughout Europe [7]. Initially affecting adolescents, it is now increasing preferentially in younger children, aged 5-11 years, who are not yet fully vaccinated. As of December 9, 2021, the incidence in Spain in children under 11 years of age was 533 cases per 100,000 inhabitants, the highest of all population groups and almost 4 times higher than that of persons over 80 years of age [8].

WHAT HAVE BEEN THE REASONS FOR LOWER DISEASE SEVERITY IN THIS POPULATION?

There is evidence-based consensus on the lower severity of COVID-19 in children and adolescents. The lower maturity of the immune system makes children more vulnerable to certain infections [9], but it may also make less likely the proinflammatory state that is associated with much of the morbidity and mortality observed in COVID-19. [3,10]. On the other hand, the expression of the ACE₂ receptor, to which SARS-CoV-2 binds, is lower in children [9,10], who also tend to have been exposed to environmental toxins and tobacco for a shorter time than adults, which increase the expression of these receptors [11]. Having fewer receptors to which the virus binds would make children less susceptible to severe infection, and less prone to a proinflammatory response. Finally, the lower prevalence of comorbidities and risk factors associated with worse outcome (obesity, diabetes and hypertension among others) may also explain the lower severity of COVID-19 in pediatric age [12-15].

WHAT DO WE KNOW ABOUT TRANSMISSIBILITY OF SARS-COV-2 INFECTION IN CHILDREN?

During the course of the epidemic, we have learned that the capacity of children to become infected, to generate viral loads in the upper respiratory tract and to transmit viruses is

comparable to that of adults [5]. The greater biological transmissibility of the latest strains, already evident in the delta and notably in the omicron, has highlighted the vulnerability of children to infection and their role as transmitters. The lower vaccination rate in this age group may have marked the differences in incidence compared to adults.

The airborne route, in the home, seems to be the main source of infection and transmission [16,17]. In schools, mainly the younger children's classes, have not been the focus of major epidemic outbreaks and, in fact, the outbreaks described at the beginning of the pandemic showed more involvement of infected teachers in the origin of the secondary cases than of the student body [18].

As age increases, transmission behavior becomes more similar to that of adults, and the lack of school-based prevention measures also increases the rate of transmission in this environment.

Vertical transmission is a mechanism of transmission in the newborn and during breastfeeding, although it seems to carry a low risk of transmission [19].

WHAT IS THE SYMPTOMATOLOGY OF COVID-19 IN CHILDREN?

Symptoms, respiratory support therapy requirements and evolution vary depending on whether we are dealing with a general casuistry or if we specifically review data from children and adolescents, collected in emergency departments and hospital records, but the figures are very concordant when the circumstances are similar [20-22].

The symptoms in children, in addition to fever, are respiratory symptoms, cough, pharyngeal erythema and rhinorrhea, but also fatigue, vomiting and diarrhea, and alterations of taste and smell. It is necessary to take into account the possibility of renal, cardiovascular, neurological, cutaneous, hematological, hepatic and ocular alterations [23].

In one of the first systematic reviews of the literature published in 2020, 90% of cases in children corresponded to asymptomatic, mild or moderate forms and only 6% of cases were severe or critical [20]. Only 2 to 5% showed oxygen saturation of less than 92%, although imaging tests revealed 18% of pneumonias and 80% of the CT scans performed showed alterations. The results reported in a cohort of 582 children with a confirmed diagnosis of COVID-19, of whom 13% were recruited in primary care and the rest in hospital institutions of different levels, are of great interest, as this is a European multicenter study with broad Spanish participation. Sixteen percent were asymptomatic and although 62% were admitted, only 12% could be considered severe as they required some type of respiratory support treatment and only 5% required admission to the ICU. Mortality was 0.69% [24].

These data were confirmed in reviews throughout the development of the pandemic and already in a study carried out in a pediatric population of 135,794 subjects, 5,374 cases were

found, of which 5,015, more than 90%, were asymptomatic or had mild symptoms. Seven percent were hospitalized and of these 28% were admitted to the ICU and 9% required invasive mechanical ventilation. Overall mortality was 0.2%. [25].

The data do not differ much from those found in studies with smaller numbers of cases, but limited to children requiring emergency department care. In a study of 422 children seen in an emergency department, 78 cases of SARS-CoV-2 infection were found, of which 87% were asymptomatic or mild cases, 13% were moderate and only 1.2% were considered severe [26]. In this study, 7.7% of the children required oxygen therapy, 1.3% CPAP treatment and none required invasive mechanical ventilation, with no deaths.

With respect to severity risk factors leading to hospitalization with or without admission to the ICU, age under 2 years, comorbidity and the presence of onco-haematological disease seem to be associated with greater severity [27,28]. In the aforementioned European multicenter study [24], in addition to comorbidity and younger age, the presence of pneumonia at the time of diagnosis was also a higher risk factor.

WHAT HAS BEEN THE INCIDENCE AND CLINICAL MANIFESTATIONS OF POST-COVID-19 MULTISYSTEMIC INFLAMMATORY SYNDROME (MIS-C) IN CHILDREN?

Pediatric Multisystem Inflammatory Syndrome (MIS-C, MIS-C) is a rare and severe post-infectious complication of SARS-CoV-2 infection that mainly affects children and adolescents. It is defined by WHO as an illness in a pediatric-aged patient (0 to 18 years) presenting with fever for a period ≥ 3 days, with elevated biomarkers of inflammation (CRP, ESR or procalcitonin) and with at least two clinical signs of multisystem involvement. Such signs include: rash, bilateral nonpurulent conjunctivitis, mucocutaneous inflammation (oral, hands or feet), hypotension or shock, cardiac dysfunction, pericarditis, valvulitis, coronary anomalies, elevated troponin/BNP, evidence of coagulopathy or acute gastrointestinal symptoms (diarrhea, vomiting or abdominal pain), with no other obvious microbial cause of inflammation (including bacterial sepsis or toxic shock syndrome) and with evidence of previous SARS-CoV-2 infection [29].

Data on incidence are limited. In a cohort study of 248 persons with MIS-C in U.S. children under 21 years of age, the incidence was 316 persons/ 10^6 SARS-CoV-2 infections. In addition, the adjusted incidence estimate was 5.1 cases/ 10^6 person-months [30]. Incidence did not differ significantly by sex, but was significantly lower in persons aged 16-20 years compared with children aged 5 years or younger. The incidence was 9 times higher among Blacks, Hispanics, or Latinos and 3 times higher among Asians or Pacific Islanders [30].

Regarding clinical manifestations, several systematic reviews have been published including studies on MIS-C that have provided an overview of the clinical signs, laboratory findings, imaging test characteristics, treatments and out-

comes of patients with MIS-C [31-34]. It generally has a heterogeneous clinical spectrum and none of the clinical manifestations or signs appear to be sensitive or specific for MIS-C [32]. The median age of those with the disease is 8 years. Fever is present in almost all cases and gastrointestinal symptoms are predominant (65-90%), mainly abdominal pain (58-73%), vomiting (57-68%) and diarrhea (50%). Cardiac involvement is frequent (79%) with tachycardia (76.7%), myocarditis (41.4%) and mild or moderate decrease in left ventricular ejection fraction (LVEF between 30 and 55%; 40%) [31]. Echocardiographic abnormalities are found in more than half of the cases, the most common being a depressed left ventricular ejection fraction (LVEF) (45.1%) [32]. Half of the patients present cardiogenic shock and severe cardiovascular complications such as LVEF below 30% (7%), coronary dilatation (11.6%) and aneurysm formation (10%) [31]. Overall, 30-50% of MIS-C sufferers have respiratory symptoms, including upper respiratory tract symptoms (24%), dyspnea (27%) and multiple radiological infiltrates (26-55%) [32]. Non-purulent conjunctivitis (47-82%) and skin eruptions (57-74%) such as rash or polymorphous exanthema (55%) are frequently observed [31].

MIS-C cases present with significant laboratory abnormalities: neutrophilia and lymphopenia, significantly elevated cardiac markers (troponin and brain natriuretic peptide), increased inflammatory biomarkers (C-reactive protein, procalcitonin, ferritin, interleukin-6), and substantially increased coagulation markers, including D-dimer and D-lymphopenia [31-35].

The clinical manifestations of patients with MIS-C vary according to age. Younger children (0 to 4 years), present a lower proportion of severe manifestations and fewer admissions to the ICU, with more frequent conjunctival findings, skin rash and abdominal pain [34,35]. Patients aged 18 to 20 years were more likely to have pneumonia, dyspnea, myocarditis, and cardiac dysfunction [31,34,35].

The onset of MIS-C follows peaks of SARS-CoV-2 infection, with a median of 4 weeks (range 2 to 5 weeks) and usually following asymptomatic or mildly symptomatic COVID-19 cases [36]. Despite the potential severity of the disease, with two-thirds of patients requiring ICU admission for a median of 5 days (range: 4-8 days), most recover with a fairly low reported mortality rate (1.3-2%) [31-33,35,36]. Death usually results from shock and/or myocardial dysfunction.

Although MIS-C has clinical features in common with Kawasaki disease or toxic shock syndrome and half of the patients with MIS-C meet the diagnostic criteria for these conditions, they are distinct entities [37-41].

IS THERE A PEDIATRIC POST-COVID-19 SYNDROME?

There is increasing evidence and knowledge of post COVID-19 syndrome in adults, initially described in Italy [42] and later in China (Wuhan) in which they found that up to 76% of cases can be symptomatic 6 months after diagnosis [43].

This is not the case in pediatrics, where data are, even today, scarce to be able to define and diagnose post-COVID-19 syndrome or prolonged pediatric COVID-19. We do not know its incidence, disease burden or long-term sequelae. First pediatric cases described (year 2021) [44] are a series of 5 Swedish children, mean age 10.4 years, with symptoms similar to adult post-COVID-19 syndrome, who persist symptomatic 2-6 months after acute infection. More recent studies include cohorts of children with prolonged post-COVID-19 sequelae in Italy [45], Sweden [44], Russia [46], Spain [47] and the United Kingdom [48]. They share as risk factors for developing this post-COVID-19 syndrome, having a history of allergic diseases and being older than 6 years. The most frequently reported characteristics are: age between 10.4 and 12 years, fatigue, dyspnea, chest pain, difficulty concentrating and sleep disturbances that persist for several months after the acute infection. Management is not clearly protocolized and treatment is symptomatic.

Prolonged follow-up of symptomatic children by specialized multidisciplinary teams (physicians, physical rehabilitators, psychologists and psychiatrists) is important in order to better understand the disease and the care and social needs it may generate.

Several groups are proposing novel forms of monitoring [49] and care of these patients, grouping patients and resources in specialized units [50]. It is essential to have a good knowledge of this new pathology and to be able to foresee the care and social needs derived from it and its future long-term evolution.

WHAT IS THE REAL PSYCHOLOGICAL IMPACT OF COVID-19 ON CHILDREN?

Children are not immune, nor are they indifferent, to the adverse psychological effects of the pandemic and quarantine measures. Children as young as 2 years old are aware of the changes around them and are affected by them [51]. The child/youth population is not only afraid of infection, but is also very concerned about the consequences it may have on their families. Adolescents are also concerned about the interruption of their studies [52], limitations in their personal relationships, etc. Many studies have focused on the psychological consequences in this age group (depression, stress, anxiety, inattention, irritability, etc.) as well as on the aggravation of previous psychiatric diseases. In a meta-analysis by Panda et al. [53] the authors divided the studies on the subject into three categories: those on previously healthy children/adolescents, those on children with pre-existing behavioral comorbidities and, finally, those on the impact on caregivers confined to the children at home/hospital.

In the group of healthy children, the work of Duan et al [52] shows that anxiety levels are very high in both adolescents and younger children, but depression is higher in adolescents, mainly determined by factors such as addiction to the Internet and smartphones. In our environment, in a survey conducted

in Spain and Italy [54], on the impact of confinement on the 3-18 years age group, the authors report that the most frequent problems were: difficulty concentrating (76.6%), irritability (39%), boredom (52%), restlessness (38%), feeling lonely (31%), nervousness (38%), discomfort (30%), worries (30%), anxiety (28%), anger (25%), apathy (24%), sadness (23%) and fear (23%). These data are very similar to those found in other studies [53].

Positive reinforcement and healthy emotional interaction among family members is a simple but effective measure to alleviate stress, although many will need psychological intervention.

In those with pre-existing psychiatric problems, there is a high likelihood of worsening of their behavioral symptoms [53,55]. To mitigate this negative impact, it is necessary to apply multifaceted, age- and developmentally appropriate strategies to be taken by health authorities.

In the third category, regarding confined caregivers, 52.3% and 27.4% developed anxiety and depression, respectively, when isolated with the children [56,57].

WHAT IS THE CORRECT PHARMACOLOGICAL TREATMENT OF COVID-19 IN CHILDREN?

There are no data from randomized clinical trials to establish firm recommendations on the optimal pharmacological treatment of COVID-19 in pediatric patients. For this reason, recommendations are largely based on efficacy and safety data obtained in adults and on the risk of disease progression in children [58,59]. It seems reasonable to follow the recommendations made for adults the older the child is or the more severe the disease.

However, as pandemic waves have occurred, experience has been gained in the treatment of children that allow reasonable recommendations to be made, which vary according to the clinical picture:

1.- Children with mild disease that does not require hospitalization. In most cases the administration of symptomatic and supportive treatment is sufficient.

2.- Children with moderate or severe disease requiring hospitalization. In this case, the administration of the following may be considered:

- Remdesivir: is approved for children >12 years and weighing >40 kg. It is also available under an FDA Urgent Use Authorization (EUA) for the treatment of COVID-19 in hospitalized pediatric patients weighing between 3.5 kg and <40 kg or who are less than 12 years old and weigh more than 3.5 kg. [60]. It could be recommended for all hospitalized children requiring oxygen therapy, regardless of age and weight, with less than 7 days of symptoms [61]. The recommendation is strongest for children >12 years with need for oxygen therapy and who have risk factors for disease progression to severe forms and for children >16 years with need for oxygen therapy, even

if they do not have risk factors for progression [62]. In most cases the evolution is good without the need to initiate treatment with remdesivir.

- Dexamethasone: would be recommended in children requiring high-flow oxygen, noninvasive ventilation, invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) [63]. Given the efficacy of its treatment in adults, its use in children requiring oxygen therapy and who have pneumonia has been widely extended.

Other drugs approved and recommended in adults, such as other antiviral drugs, immunomodulators (tocilizumab, sarilumab, anakinra) or drugs with anti-inflammatory activity (baricitinib, tofacitinib) lack information to be able to recommend their routine use in children. Tocilizumab has been the most commonly used immunomodulator in critically ill patients, generally in intensive care units, especially if elevated IL-6 levels are confirmed. Both tocilizumab and baricitinib are currently being evaluated in clinical trials in children.

3.- Children with multisystemic inflammatory syndrome (MIS-C). There are only data from observational studies. Hemodynamic and respiratory support treatment is a fundamental therapeutic tool. Intravenous immunoglobulins and/or steroids are used as first-line treatments [64,65]. In some refractory cases, IL-1 (anakinra) or IL-6 (tocilizumab) inhibitors have been used successfully [66]. The best option or appropriateness of combination therapy is unknown, although some studies have shown greater benefit from co-administration of immunoglobulins and steroids than immunoglobulins alone [67].

4.- Children with underlying disease at high risk for severe disease. There are no data to support the use of neutralizing monoclonal antibodies or antiviral drugs in children who do not require hospitalization but who have risk factors for progression to severe disease [68]. In these cases, use could be considered, especially in cases with more than one criterion or age >12 years. In fact, bamlanivimab + etesevimab, casirivimab + imdevimab and sotrovimab have been approved for use in high-risk children aged >12 years and weighing >40 kg. It is important to note that only the monoclonal sotrovimab has been shown to be effective for the omicron variant. At present time, there is very limited availability of these drugs in Spain, which must be requested through the AEMPS. Remdesivir has been tested in a clinical trial of early administration, although only 1.4% of patients were between 12 and 18 years of age [69], however, the use of 3 doses on an outpatient basis in patients at risk could be considered as an option.

WHAT IS THE MORTALITY RATE OF COVID-19 IN THE PEDIATRIC AGE GROUP?

It is not easy to provide data on the mortality of the disease, which has also been changing as time has passed in the pandemic. Of 24,778 deaths from any cause quantified as excess over the expected deaths that occurred in Spain up to June 2020, there were only 65 deaths in children under 19

years of age [70]. It should also be noted that in the population base of the English National Health System there was no excess mortality in the pediatric population in 2020 that could be attributed to SARS-CoV-2 infection [71].

About 1% of infected children require hospitalization, less than 0.02% require intensive care, and mortality is very low. Generally, occurs in children with comorbidities [72].

In a review carried out by the Committee of Evidence-Based Pediatrics of the Spanish Association of Pediatrics and the Spanish Association of Primary Care Pediatrics, it is established with a low level of evidence that mortality in pediatric patients admitted for COVID-19 is 413/100.000 patients and, in series that also include non-hospitalized patients, from 104 to 208/100,000 cases. Most of the deaths are due to complications of serious chronic diseases, and the direct causality of COVID-19 is unclear [73].

The estimated mortality in the pediatric population in a recent systematic review is 0.12% [4], sharply lower than that of the general population of 2.22% worldwide in February 2021 [74].

Factors related to ICU admission (46.3%) were age, fever, multisystem inflammatory syndrome (MIS-C) and seizures [75].

WHAT ARE THE REASONS FOR THE PROPOSAL OF VACCINATION IN THE PEDIATRIC AGE GROUP?

Vaccination in the pediatric age group responds to the common pandemic vaccination response. It has benefits both for the potential pediatric patient with COVID-19 and for society as a whole. From the individual point of view, although the risk of severe COVID-19 in the child is lower than in the adult [76,77], vaccination would further reduce this possibility, even from a theoretical point of view due to new circulating variants. Therefore, a first benefit would be the reduction of severe infection. Also, in the case of symptomatic infection, the vaccinated child's recovery should be much faster, which would bring as a second benefit the reduction of the period of non-schooling or, at least, of the time in which socialization would not be possible due to isolation after infection by SARS-CoV-2. As a third benefit, derived from the previous one, a better mental health would be achieved [78]. Also, since the immune response is more efficient and longer lasting in children than in adults, including the humoral response, vaccination at this age would generate a higher quality response [79].

At the collective level, vaccination of children would increase the vaccination rates of the entire population in general and, therefore, of the so-called herd immunity. It would limit the possibilities of transmission between children and drift towards severe disease, and from child to adult, also reducing in this group the probabilities of acquisition of COVID-19.

Since the selection factor for new variants lies in the number of people infected with SARS-CoV-2, broad vaccination of this group would reduce the likelihood of the emergence of new variants [76]. Also, the absence of new variants would al-

low to maintain the current diagnostic strategies (antigen test, PCR, serology, ...) since modifications would not be necessary.

WHAT IS THE VACCINE EFFICACY AND SAFETY OF VACCINES IN CHILDREN?

At present there are 3 vaccines available for vaccination of children and adolescents. In young children (5 - 11 years) only the vaccine Comirnaty 10 mcg/dose (Pfizer & BioNTech) is licensed [80,81]. In older children and adolescents (12-17 years), Comirnaty 30 mcg/dose (Pfizer & BioNTech) and Spikevax (Moderna) are used [80].

These vaccines contain a messenger RNA molecule that facilitates the production of the virus spike protein; it is recognized by the immune system, generating an antibody response against SARS-CoV-2.

The vaccines approved in the pediatric age group have demonstrated high immunogenicity and safety in phase 3 clinical studies. Their effectiveness in preventing severe symptomatic forms of disease and lethality is expected, although long-term effectiveness data are lacking.

The dose administered in children aged 5-11 years is one-third of that received by adults, because their antibody response to SARS-CoV-2 at the 10 µg dose was similar to that seen in 16- to 25-year-olds at the 30 µg dose.

They are administered in the deltoid muscle with a schedule of two doses separated by at least 8 weeks. The patterns are different in immunosuppressed children or those under immunosuppressive treatment [82].

Other vaccines are under development in clinical trials in this age group and may be licensed in the future.

HOW ARE THE USUAL VACCINES COMPATIBLE WITH THE SARS-COV-2 VACCINE IN CHILDREN?

The Interterritorial Council of the Spanish Government published on December 7, 2021 the recommendations for vaccination against COVID-19 in children aged 5-11 years [83].

Childhood vaccination against SARS-CoV-2 has been included for the first time in the Children's Systematic Vaccination Calendar of the Spanish Association of Pediatrics 2022 [82].

Although there is insufficient data on co-administration with other vaccines, given their characteristics and mechanism of action, it is expected that there will be no incompatibility with the vaccines of the children's calendar. They can be administered simultaneously (in the same medical visit) as the rest, or sequentially (on a different day), always respecting the rules of administration (different anatomical site, syringe and needle). It is not necessary to respect a certain time between COVID-19 vaccines and any other vaccine of the calendar.

There is recent information recommending the interval to be respected between previous SARS CoV-2 infection and the administration of the vaccines, which is at least 8 weeks for children aged 5-11 years, and 4 weeks for adolescents aged 12-17 years.

There is no data on the interchangeability of the authorized mRNA vaccines, so in primary vaccination it is recommended to use the same vaccines. In patients under treatment with other biological products (convalescent plasma or monoclonal antibodies) it is recommended to delay the vaccine for 3 months.

In case of special situations: immunosuppression, allergy, etc., the vaccination of each patient will be assessed individually [82].

WHAT IS THE EXPECTED IMPACT OF ANTI-COVID-19 VACCINATION IN CHILDREN ON COMPLIANCE WITH THE SCHOOL CALENDAR?

During the first wave of the pandemic (until September 2020), school closures and their impact on the mental health of schoolchildren have been reviewed by Viner et al. [84]. The authors searched 11 databases and identified 36 studies on the subject in 11 countries, with a total of 79,781 children and adolescents. The duration of school closure ranged from 1 week to 3 months. The studies reported a relationship between school closure and mental health disturbances and health behaviors among children and adolescents [84,85].

In Spain, López-Bueno et al. have also reported the consequences of school closure with not only socio-affective alterations but also a decrease in physical activity in schoolchildren and excessive exposure to screens [86]. Consequences such as weight gain in schoolchildren have been demonstrated [87], the progression of myopia [88, 89] and the increase in sedentary lifestyles [90].

On the other hand, school closures have not been shown to clearly decrease transmission and therefore, at the present time, it appears that the advantages of keeping schools open outweigh the disadvantages [91].

An ECDC modeling study has shown that vaccination of children aged 5-11 years in a country like Spain, with high adult vaccination rates, can reduce transmission by up to 15%. Therefore, the vaccination schedule of the Spanish Association of Pediatrics (CAV-AEP) believes that restoring normal school life to children is a priority objective, which has a direct impact on their health, and can only be achieved through childhood vaccination [82].

WHAT ETHICAL ISSUES ARE RAISED BY COVID-19 IN CHILDREN AND ITS PROPHYLACTIC AND THERAPEUTIC MANAGEMENT?

The ethical considerations of vaccination in this age group are supported by an assessment of the direct and indirect effects that the COVID-19 pandemic has had and continues to have on the health and well-being of children [92]. The relatively low risk posed by acute COVID-19 in children, accompanied by the small but existing uncertainty about the relative harms of vaccination and disease, make the risk-benefit balance of vaccination in the pediatric age more complex [93].

In this sense, the direct benefits are clear, if safe and effective vaccinations such as the current ones can prevent deaths and serious illness in children, there is a clear ethical justification for vaccination. Indirect benefits would also support such a justification and include protection of others through reduced spread, reduced overall stress on children from school closures and social distancing, and reduced economic cost to families.

Thus, the main ethical arguments in support of COVID 19 vaccination include the following [92-95]:

1. Consistency in relation to respect for autonomy. Generally, when the range of risk is narrow, the decision is a matter of personal choice. Between the two risks, which one should caregivers choose? Current evidence suggests that the risk of refusal of childhood vaccination is greater than the risk of vaccinating children against COVID-19.

2. Local justice. Children from low socioeconomic and ethnic minority backgrounds are especially prone to COVID-19 morbidity and the harms of social distancing. Vaccination could mitigate these disparities.

3. Global justice. The greater the number of people vaccinated, the closer the society is to herd immunity and protection of the most vulnerable in it. Delaying vaccination of children can hinder recovery from the pandemic and can deepen socioeconomic gaps.

4. Utilitarian considerations. Currently, a major concern is the emergence of mutations. When adults are already vaccinated, selection pressure will operate in a pediatric reservoir, thus cultivating variants that spread among children, and even undermine herd immunity.

Therefore, it would not be fair to deprive the child population of the benefits of vaccination, which are already enjoyed by those over 12 years of age (although the health objectives are different) [82]. Children's access to the vaccine is a public responsibility and the final choice is a matter of pediatric informed consent.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest

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