

Reflections on the use of COVID-19 vaccines in children and adolescents

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COVID-19 has less impact on children and adolescents, when compared to adults. Cases in the pediatric age group are estimated to account for between 1% and 5% of all confirmed cases. Although milder or asymptomatic clinical forms predominate among children and adolescents, they are not exempt from the occurrence of more severe forms, such as severe acute respiratory syndrome (SARS) and COVID-19-associated multisystem inflammatory syndrome in children (MIS-C), these being possible and important causes of morbidity and mortality in this population. Also noteworthy are cases of long COVID-19 and its consequences, especially with regard to cognitive, nutritional and safety aspects.^{1,2}

In view of this scenario, this article aimed to discuss the importance of vaccination against COVID-19 in the pediatric age group and the need for follow-up of possible adverse events.

Epidemiology

According to the Brazilian Ministry of Health, of the 1,487,502 SARS cases reported up until September 18, 2021, 73.5% (1,093,423) were confirmed as COVID-19 cases; of these, 17,299 were children and adolescents in the 0-19 age group, corresponding to 1.6% of the total number of cases of the disease in the country. 1,245 deaths were reported in this age group, accounting for 0.4% of the 346,554 SARS deaths in Brazil as at that date.³

With regard to MIS-C cases occurring between June 2020 and September 18, 2021, 2,264 suspected cases temporally associated with COVID-19 were reported in children and adolescents. After investigation by the

epidemiological surveillance service, 1,307 (57.7%) cases were confirmed as having MIS-C, and of these, 81 died (6.2% fatality rate), 1,080 were discharged from hospital, and 146 remained with an open outcome as at September 12-18, 2021 (Epidemiological Week 37).³

Another important aspect to note is evidence of persisting symptoms (long COVID-19) in children and adolescents after the acute phase of the disease. Fatigue, headache, sleepiness, loss of concentration and anosmia have been frequent.²

Although the risk factors for COVID-19 complications in children and adolescents are not well defined, the existence of more vulnerable groups is suggested. A Brazilian study assessed more than 10,000 children and adolescents hospitalized due to COVID-19 and found that risk of infection was two times greater among those up to 2 years old and those aged 12 or over compared to children who were 2 to 11 years old.⁴ Pre-existing medical conditions, geopolitical region and indigenous ethnicity were shown to be factors associated with higher risk of death from COVID-19.⁴

Certain social, economic and demographic characteristics, as well as the presence of comorbidities, have also been shown to be associated with greater disease severity in children. In the United States, comorbidities associated with COVID-19 deaths in those over 21 years of age, in order of frequency, were: obesity; asthma or bronchial hyperreactivity; and neurological diseases.⁵ It is also important to note that the COVID-19 mortality rate among children and adolescents in Brazil is much higher than the corresponding rates in the United States and the United Kingdom.⁴

With the accelerated development of COVID-19 vaccines and their administration in adults, studies

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with adolescents and children have become a natural consequence of this process. According to Plotkin & Levy,⁶ there are practical, immunologic, ethical and social reasons to justify vaccination of children and adolescents. However, it is understood that use of COVID-19 vaccines in this group should be based on studies that meet the requirements for vaccine licensing, i.e. immunogenicity, efficacy and safety.⁶

COVID-19 vaccines in children and adolescents

In Brazil, up until the time this article was approved for publication, the only vaccine licensed by the National Health Surveillance Agency (ANVISA) for use in adolescents 12 years of age or older is the one produced by the Pfizer-BioNTech laboratory, with messenger RNA (mRNA) technology as its development platform.⁷ The concept of these nanoparticle vaccines is relatively new: the mRNA that encodes the SARS-CoV-2 Spike protein is injected into the individual and the individual endogenously produces the viral antigen, inducing an immune response.⁸

Regarding children, there is, however, no vaccine licensed for use in Brazil. Studies are ongoing, but phase 3 clinical trials need to be completed to ensure that vaccines are safe and efficacious in this population.

The release of the Pfizer-BioNTech vaccine for use by adolescents aged 12-17 years old was supported by clinical studies. A randomized, placebo-controlled, phase 3 trial conducted in the United States evaluated the safety, immunogenicity and efficacy of this vaccine in healthy adolescents aged 12-15 years old. Its comparator was a cohort aged 16-25 years, enabling non-inferiority analysis of immunogenicity.⁹ A total of 2,260 adolescents were included: 1,131 received the vaccine and 1,129 received the placebo. The Pfizer-BioNTech BNT162b2 vaccine had a favorable safety and adverse event profile, with mild to moderate transient reactogenicity: 79%-86% injection site pain, 60%-66% fatigue, and 55%-65% headache; no vaccine-related serious adverse events were observed. The mean neutralizing antibody titers after the second dose met the non-inferiority criterion and indicated an even greater response in the 12-15 year cohort. That trial also found eight cases of COVID-19, all in the placebo group.⁹ Similar results were obtained from a phase 2 and 3 clinical trial, also conducted in the United States,

with adolescents aged 12-17 years who received the mRNA vaccine manufactured by Moderna.¹⁰

Chinese phase 1 and 2 trials using the Coronavac® vaccine with 743 children and adolescents aged 3-17 years have demonstrated its safety and immunogenicity in this population.¹¹ Based on that publication, the Butantan Institute requested ANVISA to authorize emergency use of the inactivated Coronavac® vaccine in the 3-17 year-old age group. This was not accepted in principle because the data presented were considered to be insufficient to establish the vaccine's immunogenicity and safety profile in the pediatric population.¹² In Chile, the same vaccine was recently approved for children and adolescents over 6 years old.¹³

The results of COVID-19 vaccine studies in adolescents have several implications. Vaccination confers the direct benefit of disease prevention plus indirect benefits, including community protection. Although frequency of symptomatic COVID-19 is generally lower among children than among adults, school activities, youth sports and other community gatherings can be important sources of outbreaks and transmission, even among vaccinated adults. Vaccinating adolescents will allow them to safely reintegrate into society and resume classroom learning, given the severe effects of the COVID-19 pandemic on the mental health of this population.⁹

Adverse mRNA vaccine events in adolescents

In May 2021, the United States Centers for Disease Control and Prevention (U.S. CDC) recommended use of the Pfizer-BioNTech mRNA vaccine for adolescents aged 12 and over. As part of ongoing safety monitoring, the U.S. CDC have evaluated cases of myocarditis and/or pericarditis in adolescents and young adults following its use.¹⁴

Up until August 11, 2021, the United States Vaccine Adverse Event Reporting System received 1,306 reports of myocarditis or pericarditis associated with COVID-19 vaccines. Case follow-up led to 760 reports being confirmed, most of them relating to male adolescents, over 16 years of age, and young adults (up to 30 years old), following the second dose of the vaccine and, typically, within the first week following vaccination. Response to treatment was positive and recovery was rapid, for most individuals. The U.S. CDC continue

to recommend the Pfizer-BioNTech COVID-19 mRNA vaccine for adolescents, as it considers that in the current epidemiological situation, with the more transmissible SARS-CoV-2 Delta variant in circulation, the benefits of vaccination outweigh the risks of any rare adverse events related to these vaccines.¹⁴

Recommendations of the National Immunization Program and the Brazilian Pediatrics Society

The Ministry of Health recommends that people between 12 and 17 years old, whether or not they have comorbidities, be vaccinated against COVID-19 exclusively using the Pfizer-BioNTech Comirnaty vaccine, and that those who have comorbidities should be prioritized initially.¹⁵

In turn, the Brazilian Pediatrics Society recommends that the Pfizer-BioNTech mRNA COVID-19 vaccine be administered to all adolescents aged 12 or over, based on clinical trials on administration of the vaccine in this age group, its having been licensed by ANVISA for use in Brazil and the experiences of other countries.¹⁶

It is important to note: full as adult vaccination progresses, severe COVID-19 cases (hospitalizations and deaths) tend to be concentrated in unvaccinated populations, and there is a natural shift in age group, with a percentage increase in cases in the pediatric population.

Although, at the time this article was authorized for

publication, the vaccine has been shown to be safe for adolescents, continuous monitoring of adverse events is recommended and any such events should be duly reported to the competent authorities.

We consider that the adolescent vaccination strategy should be organized by government bodies, at their different levels (federal, state, municipal), sequentially to the vaccination of adults. Ideally, vaccination should, in its initial stages, prioritize adolescents with risk factors, using criteria similar to those already adopted for adults,¹⁷ as shown in Box 1.

We conclude that vaccination of adolescents will be critical for reducing COVID-19 transmission in the general population and providing a safer return to school and social activities. There is great potential that both mRNA technology vaccines and inactivated vaccines will soon be authorized by the U.S. Food & Drug Administration and by ANVISA for use in pediatrics. These are important decisions for contributing to the reduction of virus circulation in the community and the effective control of the pandemic.

Author contributions

Fonseca Lima EJ, Faria SM and Kfourri RA contributed equally to the concept, drafting and critical reviewing of the manuscript. They have reviewed and approved the final version and declare themselves to be responsible for all aspects of this paper.

Box 1 – COVID-19 vaccination priority list for adolescents

Risk factor to be prioritized:

- Diabetes *mellitus*
- Chronic pulmonary diseases
- Cardiovascular diseases
- Chronic liver disease
- Chronic kidney disease
- Chronic neurological disease
- Immunosuppression (congenital or acquired, including HIV/AIDS)
- Hemoglobinopathies
- Down syndrome
- Obesity (score $z > +3$)
- Pregnant and postpartum adolescents

Source: Adapted from the scientific document entitled 'Vacinas Covid-19 em crianças e adolescentes' [COVID-19 vaccines in children and adolescents], published by the Sociedade Brasileira de Pediatria [Brazilian Pediatrics Society].

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