EDITORIAL

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Research Article

VACCINATION OF CHILDREN AGAINST CORONAVIRUS INFECTION CAUSED BY SARS-CoV-2

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The novel coronavirus infection (COVID-19) is currently a widespread disease in all countries of the world. The adult population is predominantly involved in the epidemic process. In children, the disease proceeds, as a rule, in asymptomatic, mild and moderate forms. However, severe forms of the disease with the development of adverse outcomes are possible. Severe forms of infection are more likely to develop in children under the age of 1 year and older than 12 years. The risk group for a non-smooth course and adverse outcomes are children with concomitant diseases: genetic, neurological, metabolic disorders, congenital heart defects, obesity, diabetes mellitus, bronchial asthma and other chronic lung diseases, sickle cell anemia, oncopathology, immunodeficiency states. At present, various types of vaccines are used for specific prevention in the world: based on M-RNA technologies, vectorial, inactivated. These vaccines are effective and safe in reducing the burden of disease in eligible adolescents. Despite the emergence of new strains of circulating viruses, vaccines continue to be effective in preventing severe infections, hospitalization and death.

Keywords: COVID-19; children; vaccination; efficacy; safety.

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Научная статья

ВАКЦИНАЦИЯ ДЕТЕЙ ПРОТИВ КОРОНАВИРУСНОЙ ИНФЕКЦИИ, ВЫЗВАННОЙ SARS-CoV-2

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Новая коронавирусная инфекция (COVID-19) в настоящее время — широко распространенное заболевание во всех странах мира. В эпидемический процесс преимущественно вовлечено взрослое население. У детей заболевание протекает, как правило, в бессимптомной, легкой и среднетяжелой формах. Однако возможны тяжелые формы болезни с развитием неблагоприятных исходов. Тяжелые формы инфекции чаще развиваются у детей в возрасте до 1 года и старше 12 лет. Группу риска по негладкому течению и неблагоприятным исходам составляют дети с сопутствующими заболеваниями: генетическими, неврологическими, метаболическими нарушениями, врожденными пороками сердца, ожирением, сахарным диабетом, бронхиальной астмой и другими хроническими легочными заболеваниями, серповидно-клеточной анемией, онкопатологией, иммунодефицитными состояниями. В настоящее время для специфической профилактики в мире применяют различные варианты вакцин: на основе мРНК-технологий, векторные, инактивированные. Данные вакцины эффективны и безопасны для снижения бремени болезни в группах подростков, подлежащих вакцинации. Несмотря на появление новых штаммов циркулирующих вирусов, вакцины продолжают сохранять эффективность по предупреждению случаев тяжелого течения инфекции, госпитализации и смерти.

Ключевые слова: COVID-19; дети; вакцинация; эффективность; безопасность.

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INTRODUCTION

Since the beginning of the pandemic, the situation with the new coronavirus infection i.e., coronavirus disease 2019 (COVID-19) has not been of particular concern to pediatric services. At the beginning of the pandemic, in 2020, it was believed that children accounted for no more than 2% of cases [40]. In the structure of registered COVID-19 cases in the Russian Federation, the proportion of children did not exceed 6%–7% [4, 9]. According to the US Centers for Disease Control and Prevention (CDC), the number of children aged 0–9 years increased from 2.3% to 4% and those aged 10–19 years from 5.1% to 11.1% among cases from May to August 2020. [17]. "Pediatric" COVID-19 can be asymptomatic, mild, or, much less frequently, moderately severe [12]. Three hypotheses have been suggested as to why disease severity and incidence differ in children compared with adults: (1) probably less ACE2 receptor presence in children's lungs; (2) less prior endothelial damage than in adults, especially those with pre-existing cardiovascular or metabolic pathology (e.g., diabetes); (3) "trained immune system" — first-line defense against SARS-CoV2 — congenital immunity. Congenital immunity in children is "trained" not only by frequent viral infections but also by repeated injections of vaccines during routine vaccination [23, 31]. In the same period, the role of children in the transmission of infection was widely discussed because most carry the disease asymptomatically or in a mild form and can become a source of infection for older family members [28, 29].

However, since the beginning of the pandemic, severe cases of multisystemic inflammatory syndrome and lethal outcomes have been described in children. Severe infections were more common in children aged <1 year and >12 years. The risk group included children with concomitant pathologies, i.e., those with genetic, neurological, and oncohematological diseases, metabolic disorders, congenital heart diseases, obesity, diabetes mellitus, bronchial asthma, and other chronic lung diseases, sickle cell anemia, and immunodeficiency states [2, 3, 6–8, 10, 30].

With the emergence of COVID-19 virus variants by the fall of 2021, the involvement of children in the epidemic process increased, including hospitalization for moderate, and severe disease forms, especially in the group aged >7 years [14]. The emergence of another highly invasive omicron strain in January 2022 led to a dramatic increase in the incidence in the pediatric population compared with that in the same period in 2021. Thus, the incidence in children aged <4 years increased 2.6-fold [11, 20].

In addition to the increased morbidity, the possibility of life-threatening conditions in children and adults, i.e., post-COVID syndrome, has been described [19, 33]. The post-COVID syndrome is more frequently noted in school-age children, both after mild and asymptomatic COVID-19 [1, 13].

Taking into account all these points, the increased involvement of children and adolescents in the epidemic process, risk of a severe course, formation of a postvaccination syndrome, and participation in the transmission of the pathogen, including children in mass vaccination is justified.

CHARACTERISTICS OF VACCINES TO PREVENT COVID-19 IN CHILDREN

Currently, different variants of vaccines are actively used in children, i.e., mRNA-based, vector-based, and inactivated vaccines.

The use of mRNA vaccines was approved by the US Advisory Committee on Immunization Practices (ACIP) in May 2021 for adolescents aged 12–16 years [38] and in November 2021 for children aged 5–11 years. Supplemental and booster doses were also recommended in November [39]. For children aged 5–11 years, a high efficacy has been shown to prevent symptomatic laboratory-confirmed COVID-19 in the absence of strong evidence of risk (grade I validity). The clinical efficacy in adolescents before the delta and omicron variants was up to 100% (95% CI 75.3%–100%) in preventing symptomatic, laboratory-confirmed COVID-19. The immune response to two doses of Pfizer-BioNTech vaccine in adolescents aged 12–15 years without previous SARS-CoV-2 infection was no less than that of individuals aged 16–25 years. In children aged 5–11 years, the efficacy in reducing symptomatic infection was 90.9% (95% CI 68.3%–98.3%). Local or systemic reactions occurred in adolescents within 7 days of vaccination, with 90.9% of vaccine recipients reporting any local reaction and 90.7% reporting some symptoms of a general reaction, more often after the second dose, mostly mild to moderate. Reactions occurred on average on days 1–4 after receiving the vaccine and resolved in 1–2 days on average. The most common symptoms were fatigue, fever, headache, chills, and injection site pain [34, 36]. In children aged 5–11 years, local reactions within 7 days of vaccination were noted in 86.2%, and general reactions in 66.6%, more often after the second

dose. The vast majority had mild-to-moderate manifestations and were recorded less frequently than those aged 16–25 year. Severe local and systemic reactions (grade III or higher, defined as impaired activities of daily living) were observed in 2.7% of vaccine recipients and 1.1% of placebo recipients. An expanded safety cohort of 2379 children (including 1591 vaccine recipients) was added to monitor serious adverse events, with an average follow-up period of 2–4 weeks after the second dose [15, 16, 26].

The coronavirus mRNA vaccine Moderna COVID-19 (mRNA-1273; ModernaTX, Inc; Cambridge, Massachusetts) was approved for use in the United States on December 18, 2020. [32]. Data on vaccine efficacy in children were evaluated in a clinical trial involving 3,000 adolescents aged 12–17 years. It was shown to be comparable in preventing infection and antibody production to adults aged 18–25 years. The vaccine was registered in the European Union on January 6, 2021, authorized with the new name Spikevax on June 22, 2021, and authorized for use in individuals from the age of 12 years [35]. When evaluating the efficacy and safety of vaccines in real-world practice settings, the association between mRNA vaccines and the occurrence of myocarditis was suspected, predominantly in young men aged 16–30 years and more pronounced in those aged 16–19 years. In most cases, myocarditis had a mild course and passed within a few days [27]. As of June 11, 2021, approximately 296 million doses of mRNA vaccine against COVID-19 had been used in the United States, with 52 million doses given in individuals aged 12–29 years, of which 30 million were first and 22 million were second doses. Vaccine adverse event reports were received, with 1,226 reports of myocarditis after mRNA vaccination between December 29, 2020, and June 11, 2021. Among those with myocarditis after mRNA vaccination, the mean age was 26 (range 12–94) years, 923 were men, and 289 were women. Among 1,094 cases with a refined vaccine dose, 76% cases of myocarditis occurred after the second dose of mRNA vaccines, both Pfizer-BioNTech, and Moderna. Men aged 12–17 and 18–24 years had the highest rates (62.8 and 50.5 reported cases of myocarditis per million second doses of mRNA administered, respectively). ACIP looked at the individual benefit–risk ratio of mRNA vaccines in adolescents and young adults, compared the benefits (prevention of severe COVID-19 disease) to the risks (number of myocarditis cases), and concluded that vaccination should continue. The balance of benefit and risk varied by age and sex. Per one million-second doses of COVID-19 mRNA vaccine given to men aged 12–29 years, 11,000 cases of COVID-19, 560 hospitalizations, 138 admissions in the intensive care unit, and 6 deaths were prevented, compared with 39–47 expected cases of myocarditis after COVID-19 vaccination. This analysis did not include the potential benefit of preventing long COVID and multisystem syndrome. European researchers evaluated the excess risk of myocarditis after a second dose of Moderna vaccine. A study reported approximately 1,316 (95% CI 1,299–1,333) additional cases of myocarditis in men aged 12–29 years per 10,000 persons compared with unvaccinated persons within 7 days of the second dose. In another study, 1.88 (95% CI 0.956–2.804) additional cases of myocarditis occurred in men aged 16–24 years per 10,000 compared with unvaccinated individuals within 28 days of the second dose [35]. No cases of myocarditis were fatal.

On June 17, 2022, the Food and Drug Administration amended the Emergency Use Authorization for COVID-19 mRNA vaccines to include children 6 months of age to 4 years of age to receive BNT162b2 [Pfizer-BioNTech, 3 doses of 3 μg (0.2 mL) each] and children 6 months to 5 years of age to receive mRNA1273 [Moderna, 2 doses of 25 μg (0.25 mL) each]. In the clinical trial of the Pfizer-BioNTech vaccine, 3013 children aged 6 months to 4 years were vaccinated, and the Moderna vaccine was given to 5011 children aged 6 months to 5 years. The most reported adverse events were mild to moderate and had no serious consequences [18, 22]. The CDC reviewed adverse events and health effects after Pfizer-BioNTech and Moderna vaccination, and v-safe reports of vaccine adverse events from June 18 to August 21, 2022, in 599,457 children aged 6 months to 4 years who received the Pfizer-BioNTech vaccine and 440,773 children aged 6 months to 5 years who received the Moderna vaccine. The v-safe program received 23,266 reports. Irritability or crying was most frequently reported in approximately half of the children aged 6 months to 2 years. Among children aged >3 years, systemic reactions were less frequent; however, pain at the injection site was most frequent in children of this age. Local reactions were noted in 900 (19.0%) children aged 6 months to 2 years; in 1078 (28.4%) children aged 3–4 years after the first dose of Pfizer-BioNTech vaccine; in 1601 (19.2%) children aged 6 months to 2 years and in 2072 (32.4%) children aged 3–5 years after the first dose of Moderna. Systemic reactions occurred

in 2,649 (55.8%) children aged 6 months to 2 years and in 1,220 (32.2%) children aged 3–4 years after the first dose of Pfizer-BioNTech. When Moderna vaccine was administered, they occurred in 4,647 (55.7%) children aged 6 months to 2 years and in 2,204 (34.5%) children aged 3–5 years after the first dose. Parents of approximately 1,323 (5.7%) and 803 (6.5%) children aged 6 months to 5 years reported that their children were unable to perform normal daily activities for 1 week after the 1st and 2nd doses of any vaccine, respectively. Approximately 741 (2%) children reported seeking medical care within 1 week of vaccination, and most care services were received on an outpatient basis (450; 1.3%; four children were hospitalized after vaccination; two respondents indicated that hospitalization was not related to vaccination). Observational data concluded that vaccination was safe for children from 6 months to 5 years of age [25].

Inactivated vaccines. Sinovac-CoronaVac is whole-virion vaccine with aluminum hydroxide adjuvant recommended by the WHO. The vaccine is given twice (0.5 mL) at 2–4 weeks apart. The WHO recommends an interval of 4 weeks. The efficacy of the vaccine in phase 3 clinical trials in Brazil showed that two doses administered 14 days after the second vaccination had efficacy of 51% (95% CI 36%–62%) against symptomatic COVID-19 and 100% (95% CI 17%–100%) against severe COVID-19 and hospitalization. A prospective national cohort study in Chile involving 10.2 million people aged >16 years from February 2 to May 1, 2021, showed efficacy against infection of 65.9% (95% CI 65.2–66.6%), against the hospitalization of 87.5% (95% CI 86.7%–88.2%), against severe course with intensive care of 90.3% (95% CI 89.1%–91.4%), and against death of 86.3% (95% CI 84.5%–87.9%). The vaccine is used in children from the age of 3 years in China and in some Southeast Asian countries; immunization of children from 7 months of age is currently being completed [21, 24]. Studies have also been conducted on the use of Covaxin vaccine (BBV152) in children aged 2–18 years. The vaccine has been evaluated as a low reactogenic. The efficacy (humoral response) was identical to that of other inactivated SARS-CoV-2 vaccines. The need to immunize younger age groups, the researchers believe, will help interrupt the transmission [37].

Vaccines based on adenovirus vectors. The domestic vaccine Gam-KOVID-Vac-M ("Sputnik M") for adolescents aged 12–18 years is based on Gam-KOVID-Vac ("Sputnik V") is also used twice with an interval between injections of 21 days. It has five times lower antigen concentration. According to the provisional guidelines "Procedure for vaccination against new coronavirus infection (COVID-19," GAM-COVID-VAC-M vaccine is designed to prevent COVID-19 in adolescents aged 12–17 years (inclusive) [5]. Vaccination against COVID-19 is included in the calendar of preventive vaccinations for epidemic indications. Priority should be given to the vaccination of children aged >12 years at a high risk of severe and complicated COVID-19. These include the following categories: patients with organic lesions of the central nervous system; patients with orphan diseases, with Budd–Chiari syndrome, with malformations of the cardiovascular and bronchopulmonary system; patients with cancer and oncohematological diseases, long-term recipients of immunosuppressive, corticosteroid therapy, and treatment with sex hormones; patients with a history of thrombotic events (stroke, thrombosis of the heart cavities, thrombosis of the veins of the limbs and pelvis, and pulmonary embolism in patients and their close relatives). Data from clinical trials of Sputnik M demonstrate that it is just as safe for use. No serious adverse events have been reported. However, further studies are underway to identify possible rare adverse events of the vaccine.

CONCLUSION

According to the WHO, despite the lower risk of severe COVID-19, children, and adolescents have been disproportionately affected by COVID-19 measures. The most important indirect effects are related to school closure. Vaccines approved by stringent regulatory authorities to children and adolescents are safe and effective in reducing the burden of disease in these age groups.

Although vaccines have declined in effectiveness because of the emergence of new strains of circulating viruses, they continue to be effective in preventing severe infection, hospitalization, and death.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

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