ISSN: 2573-9611

Research Article

Journal of Pediatrics & Neonatal Biology

Safety and Efficacy of Covid-19 Vaccine in Children less than 12 Years of Age: a Scoping Review

Tashkandi A.A[1,2*], D. Alammari[2], A. El-Metwallyb and Othman A[1,2]

[1]*Emergency Medicine Department, Prince Mohammed Bin Abdulaziz National Guard Hospital, Al-Madinah Al-Munawarah, Saudi Arabia*

[2]*College pf Public Health and Health Informatics, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia.*

[*]Corresponding Author
Abdulhadi Tashkandi, Emergency Department, Prince Mohammed Bin Abdulaziz National Guard Hospital, Al-Madinah Al-Munawarah.

Submitted: 19 Mar 2023; **Accepted:**25 Mar 2023; **Published:**19 Apr 2023

Citations: Tashkandi, A. A., Alammari, D., El-Metwally, A., Othman, A. (2023). Safety and Efficacy of Covid-19 Vaccine in Children less than 12 Years of Age: a Scoping Review. *J Pediatr Neonatal Biol, 8*(2), 179-184.

Abstract

The continuous evolving and the emerging of different SARS-CoV2 strains making it difficult to control the pandemic even with vaccines availability. COVID-19 infection has been reported in children with different ages ranging from 1 day to 15 years. This age group necessitate more attention particularly with the reported relative increase in the incidence of myocarditis and its possible correlation to COVID-19 vaccines. Data assessing efficacy and safety of the existing CoVid-19 vaccines are very limited in this age group and mostly were reported from adult and adolescent studies. This study aimed to summarize and review all researches published from January 2020 to December 2021 assessing the safety and efficacy of the COVID-19 vaccine among children and adolescents. As a conclusion of this review, more studies are needed, especially phase-3 trials with adequate follow up period to provide more data on vaccine safety and efficacy. Although the current available information recommend administration of vaccination in this age group, as well it showed reduction in severity of COVID-19 infection and its related hospitalization, with no severe side effects re reported to be different from adult population.

Keywords: Scoping Review, Vaccine Efficacy, Vaccine Safety, Sars-Cov2, Covid-19, Children

Introduction

Since the initial outbreak of coronavirus disease (COVID-19) in 2019, a global pandemic have been declared by World Health Organization (WHO) on 30 January 2020, following the spread of the disease beyond the boundaries of China [1,2]. The rapid spread of this infectious disease have posed a threat to the healthcare system. The COVID-19 pandemic is caused by a single-stranded RNA virus that belongs to the coronavirus family responsible for severe acute respiratory syndrome (SARS-CoV-2). This virus shares more than 70% of its sequence with SARS-CoV and around 50% with the coronavirus responsible for Middle Eastern respiratory syndrome (MERS-CoV). Human coronaviruses were discovered in the 1960s causing varieties of diseases, infection can be undetectable or can manifest as mild upper respiratory tract symptoms (81%) while (14%) develop severe symptoms and (5%) develop critical complicated multisystem inflammatory syndrome or fatal multi-organ dysfunction. Older age group patient at higher risk in developing severe symptoms and complications as well special patient population carry higher risk too like immunocompromised as well pregnant women [15].

Based on international statistics, the proportion of COVID-19 cases around the world was 530 million infections and more than 6 million deaths worldwide as of June 2022. Children also affected with this pandemic representing around 19% of total confirmed cases as reported in the US as per the health department, with 8.7% occurring among 5-11-year-old [1,16,22]. Although many reports have indicated that the overall prevalence of the infection among children is low compared to adults, other studies indicated a severe impact of the disease on children and adolescents, especially those with comorbidity. Thus, studies reported that children who suffering from underlying medical comorbidities, specifically chronic lung disease, congenital heart disease, and metabolic and neurological disorders (Obesity and feeding tube dependence were associated with increased risk of severe disease). Additionally, the reported symptoms in the literature suggest variation in the clinical presentation that range from nausea and vomiting, diarrhea, dyspnea, nasal symptoms, rashes, fatigue and abdominal pain. Most children with COVID-19 recover within 1 to 2 weeks [10,12,18]. COVID-19 associated hospitalizations and deaths also reported and some cases COVID-19 symptoms may continue for weeks to months after their initial illness. Asymptomatic infection can hap-

pen estimate vary from 15 to 50% of infections and is of great concerns because they can act as a disease transmitter to the community and older population contributing to the undesirable spread of the disease [9,12]. The mean age of children with COVID-19 has been reported to be 6.7 years (range: 1 day to 15 years) .Disease presentations in children varies with variable presentations most commonly presenting with non-specific upper respiratory tract symptoms including sore throat, cough and fever [12,18]. Reported the cough, fever and weakness are the most common presenting symptoms with severity ranging from mild to moderate. In view of time required in producing safe and effective vaccines with the urgency to do so keeping in mind all the concerns related to the necessity, safety, efficacy and the life-long side effects especially in children. Knowing there is significant lack of research studies to address all those concerns.

Vaccines are considered as an effective way to prevent and control disease infections, stimulating the human immune system to produce antibodies, thus increasing immunity to the disease and generating protection for the immunized individual. Vaccination aims to curb the spread of the disease and helps to potentially achieve herd immunity. Several international organizations and countries have also developed guidelines for different aspects of COVID-19 vaccination, including vaccination of special populations, management of adverse reactions, and cautions for vaccination. However, the efficacy of protection and adverse effects of COVID-19 vaccines in children and adolescents remains unclear despite a large number of clinical trials being conducted. In December 2020 in US after the emergency use authorization of COVID-19 vaccines cases and deaths declined sharply during the first half of 2021; however, beginning in late June 2021 a rise in cases was observed, including in children, associated with the highly transmissible virus variants [4,20]. Yet more studies and data are needed to review exact rate of complications, hospitalization and mortality related to the disease in children less than 12 years of age as well the lifelong side effects of Corona virus disease or its related vaccines. As of 2021, twenty-two COVID-19 vaccines worldwide have been approved with very limited knowledge about the vaccine's efficacy and safety in children. On October 2021, the Food and Drug Administration (FDA) amended the Emergency Use Authorization (EUA) for Pfizer-BioNTech COVID-19 (BNT162b2) mRNA vaccine to expand its use to children aged 5– 11 years, administered as 2 doses (10 µg, 0.2mL each) 3 weeks apart [1,9]. As of December 19, 2021, only the Pfizer-Biotech COVID-19 vaccine is authorized for administration to children aged 5–17 years [1,3]. The Centers for Disease Control and Prevention recommended use of the vaccine among children in this age group on November 2, 2021. In preauthorization clinical trials, PfizerBioNTech COVID-19 vaccine was administered to 3,109 children aged 5–11 years; most adverse events were mild to moderate, and no serious adverse events related to vaccination were reported [4]. By the end of 2021, twenty-two COVID-19 vaccines are approved worldwide. (Table-1) demonstrates time line of COVID-19 vaccines approvals.

In view of the recent relative increase in the incidence of myocarditis and it's possible correlation to COVID-19 vaccines [8,21]. The overall incidence of myocarditis following COVID-19 infection is low; patients with COVID-19 have a nearly 16-fold increase in risk for myocarditis, compared to individuals without COVID-19. The risk is lowest among individuals 25-39 years and higher in persons less than 16 years and older than 50 years of age [22]. Myocarditis may also present as part of the multisystem inflammatory syndrome in children (MIS-C), usually 3 to 5 weeks after a SARS-CoV-2 infection. MIS-C is a rare but serious COVID-19-associated condition that occurs in less than 1% of children with confirmed SARS-CoV-2 infection [1,21].

Currently, published studies on vaccine safety and efficacy in this group are lacking. This study aimed to summarize the safety and efficacy of the COVID-19 vaccine among children and adolescents and the finding of this review would help in providing reliable evidence for clinical decision regarding application of the vaccine and any further recommendations.

Table: 1

DATE	Country	Region	Vaccine name
May 2021	Canada	first country to approve vaccine for use in children aged 12-15	Pfizer's vaccine
June 2021	UAE	offering vaccine to 12 to 15-year-olds	Pfizer-BioNtech vaccine
Sept 2021		China, UAE & Venezuela announced plans to vaccinate younger children, Cuba is the first to do so.	Cuban-madre vaccines: Abdala, Soberana-2, and Soberana-plus
October 2021	USA (FDA)	children aged 5– 11 years,	Pfizer-BioNTech COVID-19 (BNT162b2) mRNA vaccine
	Bahrain	approved for young kids	Sinopharm vaccine (Chinese-made)
November, 2021	USA (CDC)	preauthorization clinical trials, was administered to 3,109 children aged 5–11	PfizerBioNTech COVID-19 vaccine
	Saudi (FDA)	children between the ages of 5 and 11	
December, 2021		authorized for administration to children aged 5–17 years	Pfizer-BioNTech COVID-19 vaccine

Materials and Methods

Search Strategy

Three English bibliographic databases PubMed, EBSCO AND ProQuest were searched to retrieve studies related to COVID-19 vaccines safety and efficacy in children less than twelve years of age. Search was restricted to studies published between January 2020 to December 2021.

Search Terms

Three set of search terms are used based on (PCC) Population, Concept, and Context.

The main search terms included according to the search strategy are: COVID-19 Vaccines, SARS-CoV-2, 2019 novel, coronavirus, vaccines, vaccination, COVID-19 vaccines, Vaccine Efficacy, Patient Safety, Product Safety and result were filtered specifically for children less than 12 years of age.

Study Eligibility Criteria

Studies about safety and efficacy of COVID-19 vaccine in children were screened. The study population consisted of children below age of 12. English published studies from January 2020 and December 2021 were included. Articles with incomplete or incorrect content, repeated data studies, editorials, correspondence, news and commentaries were excluded from this review to improve its quality.

Study Selection

Study selection process was conducted in phases: identifying the eligible studies, screening title and abstract followed by full article review. Non eligible and duplicate studies were excluded during all articles review process. Relevant data from each study were extracted from each eligible study including data on study's first author, study setting, study time, country, study population, sample size, age, and COVID-19 vaccination.

Results

According to the literature screening flowchart shown in figure 1, total of 64 articles were retrieved from the three searches databases. 6 duplicate records were removed then 20 of the 58 articles reviewed also were excluded. 38 articles were sought for retrieval and 13 of which was not able to be retrieved. During the screening process for eligibility 16 articles out of the 25 were excluded because of population didn't meet criteria (11 articles) or not meeting study designs (5 articles). At the end 9 articles were identified meeting this scoping review main aim.

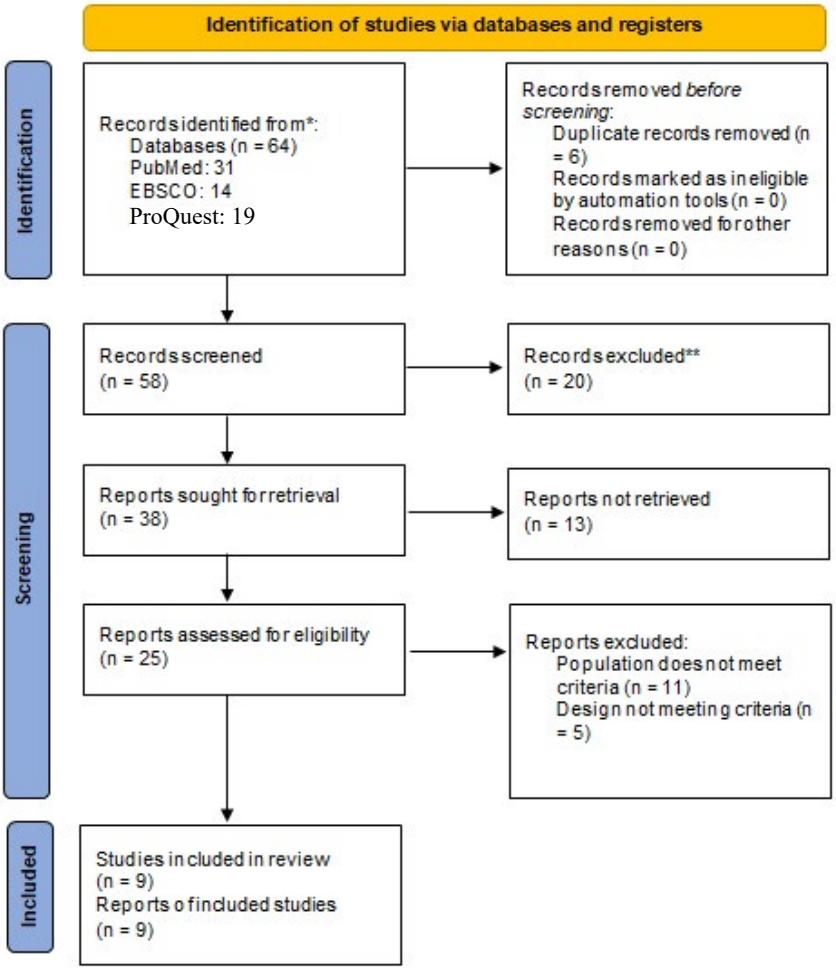

Figure 1: "PRIAMA" Study selection process

Total of nine articles were identified meeting search criteria and included in the review. Two clinical trials and seven review articles [2,3,5-7,9,13,15,22]. The two clinical trials had a total of 2818 participant aged less than 12 years. 1953 received various doses of COVID-19 vaccines (either CoronaVac or BNT162b2) and 865 of them received placebo. The summary of the included studies is shown in (Table 2).

Both clinical trials in their phase-1, evaluated the most suitable dose to be given and considered effective in inducing immunogenicity with less side effects. Then in subsequent phase the immunogenicity, seroconversion, efficacy and safety were furtherly evaluated [2,6]. The data from both studies shows that the vaccines were well tolerated with no vaccine-related major serious adverse events. On the other hand, it was also noted that 3•0μg dose of CoronaVac induced more neutralizing antibody titers than 1•5μg dose. The reported vaccine efficacy is 90.7% [6].

Table 2: Clinical trials summary

	Author	Design	Objective	Sample size	Intervention	Outcome	Results
1	Bihua Han et al,	Double-blind, randomized, controlled, phase 1/2 clinical trial	Assess the safety, tolerability, and immunogenicity of a candidate COVID-19 vaccine	550 (n=71 for phase 1 n=479 for phase 2	- Group1 (219) CoronaVac 1•5 μg - Group2 (217) CoronaVac 3•0 μg, - Group3 placebo(114)	-adverse reactions at 28 days -seroconversion rate of neutralizing antibody to live SARS-CoV-2 at 28 days	Adverse effect: • 26% participants in the 1•5μg group • 29% participants in the 3•0μg group • 24% in the alum-only group
2	Walter et al.	Randomized, controlled trial - phase 1, dose-finding study - phase 2–3 randomized trial	to investigate the safety, immunogenicity, and efficacy of 2 doses of the BNT162b2 vaccine administered 21 days apart in children 6 months to 11 years of age	- phase 1: 48 children - phase 2–3: 2268 children	phase 2–3: 2268 children -1517 received BNT162b2 vaccine - 751 children received placebo	-Vaccine efficacy against Covid-19 at ≥ 7 days -Vaccine safety, immunogenicity and efficiency	- 90.7% vaccine efficacy - No cases of severe disease -No vaccine-related serious adverse events

Studying details of the seven review articles, it was found that infants and neonates are more vulnerable to severe COVID-19 disease and there is lack of sufficient data regarding safety and efficacy between different vaccine types. It is difficult to predict or anticipate vaccines related side effects from adult studies.

It is also noted children below age of 12 years were not included in most of the phase 3-trials and because the recent onset of the disease long-term vaccine effects is not yet revealed. But it's observed vaccinating children may limit spread of infection to adult besides providing immunity to them. The summary of the included studies is shown in (Table 3). No severe side effects or disease were reported to COVID-19 vaccines different than adult population but most reviews concluded that more studies, especially phase-3 trials with adequate follow up period are needed to provide sufficient data on safety, efficacy and vaccines related effects in children less than age of 12 years according to different vaccines type.

Table 3: Review articles summary

	Author	Objective(s)	No of articles	Results/ COMMENTS
1	Christiane S, et al. 2020	Role for childhood vaccination against COVID-19	NA	- Most of the phase 3 trials DID NOT include children <12 years
2	Deniz Aygün, 2020	Coronavirus infections in childhood and vaccine studies	NA	-Phase III trials are needed to confirm safety and efficacy of COVID vaccines in children <12 years

3	Erin Wilson, 2021	Importance of Pediatric Studies in SARS-CoV-2 Vaccine Development	NA	- Lack safety and efficacy data between different vaccines in children <12 years
4	Hyun Mi Kang, 2021	Updates on the coronavirus disease 2019 vaccine and consideration in children	NA	- Deficiency of long-term Vaccines side-effects in children - Ongoing clinical trials for population <12 years • "Pfizer-BioNTech" phase 1/2/3 clinical study • "KidCove study" mRNA-1273 phase 2/3 clinical • AZD1222 phase-2 clinical trial • Ad26.COV2.S clinical trial is strategized.
5	Meng Lv. et al. 2021	To identify the safety, immunogenicity, and protective efficacy of COVID-19 vaccines in children and adolescents	• 28 clinical studies • 2852 children and adolescents	-3 µg CoronaVac dose induced stronger immune response than with 1.5 µg. - Immune response to BNT162b2 in adolescents aged 12–15 years was non-inferior to that in young people aged 16–25 years, -Further studies are needed with longer follow-up, larger sample size, and a greater variety of vaccines.
6	Nicoletta Luxi, 2021	Recommendations and Pre- and Post-Marketing Evidence for Vaccine Efficacy and Safety	NA	- infants and neonates are more vulnerable to severe COVID-19 disease -special population (pregnant and breastfeeding women, children/adolescents, immunocompromised) were excluded from most of researches - COVID-19 vaccination for children and adolescents is still debated - ongoing large-scale studies will provide clinically relevant data
7	William J. , 2021	Pediatric COVID-19 Vaccines: What's needed to know	NA	- Vaccinations protect children, decrease spread to adult - Adverse effects similar to older children and adults in frequency and severity

Discussion

To date, COVID-19 pandemic not fully controlled in many countries around the world as new emerging variants of SARS-CoV2 strains still evolving. Given the special nature of the children and adolescents population, many factors need to be considered prior the administration of the vaccine to gain immunity against COVID-19 pandemic. The efficacy and safety of vaccine among this age group is still controversial and point of concern to many parents. Authorization to vaccinate children <12yrs based on the two highlighted clinical trials (for CoronaVac & Pfizer-BioNTech) and its reported that COVID-19 vaccine is well tolerated, safe and well induce humoral responses in children. Risk of myocarditis is reported to be less than adolescent and other older age group. Introducing COVID-19 vaccines in pediatric population can interrupt and minimize viral transmission to the community and older patients. This review have showed that in general the COVID-19 vaccines has good safety in the child and adolescent populations as most of the adverse effect were mild or moderate adverse event.

On the other hand, efficacy is an important point related to COVID-19 vaccine among children and adolescent population. During the pandemic, two type of RNA vaccines have been approved for children aged 5-11 years, Pfizer-BioNTech COVID-19 (BNT162b2) mRNA vaccine and mRNA-1273 developed by Moderna. The introducing of vaccine triggers sequential immune response resulting in antibody production and T-cell mobilization resulting in further protection against SARS-CoV-2 infection. In this review, RNA vaccine had around 90.7% efficacy after second dose. This supports the recommendation of administration of vaccination among this population. Adding to this, many studies have indicated that RNA vaccine provided efficacious reduction in severity of COVID-19 disease and its related hospitalization.

Limitations

This review has some limitations mainly the lacking of available studies with complete data on vaccine efficacy in pediatric, as most of this age group were not included in most of the phase 3 trials. Adding to this point, the literature lack longer-term follow-up data to assess the duration of immune responses, efficacy, and safety. In addition, concomitant administration of BNT162b2 with other vaccines was not assessed lack of longer-term follow-up.

Further studies are needed with longer follow-up, larger sample size, and a greater variety of vaccines. Knowing that as of June 2022, 38 COVID vaccines are approved in 197 countries and 722 vaccine trials are ongoing in 76 countries (24), hopefully many of

the inquiries related to COVID-19 vaccines effect on children can be addressed as well the concomitant administration of COVID-19 vaccines with other vaccines to be evaluated.

References

1. Hause, A. M., Baggs, J., Marquez, P., Myers, T. R., Gee, J., Su, J. R., ... & Shay, D. K. (2021). COVID-19 vaccine safety in children aged 5–11 years—United States, November 3–December 19, 2021. Morbidity and Mortality Weekly Report, 70(51-52), 1755.
2. Bihua Han. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy children and adolescents: a double-blind, randomised, controlled, phase 1/2 clinical trial. Lancet Infect Dis 2021; 21: 1645–53.
3. Christiane S. Is there a role for childhood vaccination against COVID-19?: A review article. Pediatr Allergy Immunol. 2020;00:1–8.
4. Davies A. Uptake, effectiveness and safety of COVID-19 vaccines in children and young people in Scotland: Protocol for early pandemic evaluation and enhanced surveillance of COVID-19 (EAVE II). JOGH, vol.11.
5. Aygün, D., Önal, P., Apaydın, G., & Çokuğraş, H. (2021). Coronavirus infections in childhood and vaccine studies. Turkish Archives of Pediatrics, 56(1), 10.
6. E.B. Walter, et al. Evaluation of the BNT162b2 Covid-19 Vaccine in Children 5 to 11 Years of Age. N Engl J Med 2022;386:35-46.
7. Wilson, E., Girotto, J., Passerrello, N., Stoffella, S., Shah, D., Wu, A., ... & Cash, J. (2021). Importance of pediatric studies in SARS-CoV-2 vaccine development. The Journal of Pediatric Pharmacology and Therapeutics, 26(4), 418-421.
8. Hoffmann M, Kleine-Weber H, Schroeder S, et al.. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020; 181:271–280.e8.
9. Kang, H. M., Choi, E. H., & Kim, Y. J. (2021). Updates on the coronavirus disease 2019 vaccine and consideration in children. Clinical and Experimental Pediatrics, 64(7), 328.
10. Kate R. W. The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Pfizer-BioNTech COVID-19 Vaccine in Children Aged 5–11 Years. MMWR / November 12, 2021 / Vol. 70 / No. 45.
11. Lalitphat T. Current data on Covid-19 vaccine in pediatrics: A review article. Pharm Sci Asia 2022; 49(1), 15-21
12. Ludvigsson, J. F. (2020). Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. Acta paediatrica, 109(6), 1088-1095.
13. Lv, M., Luo, X., Shen, Q., Lei, R., Liu, X., Liu, E., & Chen, Y. (2021). Safety, immunogenicity, and efficacy of COVID-19 vaccines in children and adolescents: a systematic review. Vaccines, 9(10), 1102.
14. Mohammad A. Parental coronavirus disease vaccine hesitancy for children in Bangladesh: a cross-sectional study [version 2; peer review: 3 approved]. F1000Research 2022, 11:90 Last updated: 16 MAR 2022
15. Luxi, N., Giovanazzi, A., Capuano, A., Crisafulli, S., Cutroneo, P. M., Fantini, M. P., ... & Trifirò, G. (2021). COVID-19 vaccination in pregnancy, paediatrics, immunocompromised patients, and persons with history of allergy or prior SARS-CoV-2 infection: overview of current recommendations and pre-and post-marketing evidence for vaccine efficacy and safety. Drug safety, 44(12), 1247-1269.
16. Nicola P. Reasons in favour of universal vaccination campaign against COVID-19 in the pediatric population. Ital J Pediatr. 2022; 48: 4.
17. Noura A. Willingness, beliefs, and barriers regarding the COVID-19 vaccine in Saudi Arabia: a multiregional cross-sectional study. Family Practice (2021) 22:247
18. Önal P, Kılınç AA, Aygün F, Durak C, Çokuğraş H. COVID-19 IN Turkey: A tertiary center experience. Pediatr Int 2020;
19. Moghadas, S. M., Vilches, T. N., Zhang, K., Wells, C. R., Shoukat, A., Singer, B. H., ... & Galvani, A. P. (2021). The impact of vaccination on coronavirus disease 2019 (COVID-19) outbreaks in the United States. Clinical Infectious Diseases, 73(12), 2257-2264.
20. Seyed M. Simulated identification of silent COVID-19 infections among children and estimated future infection rates with vaccination.
21. Walls, A. C., Park, Y. J., Tortorici, M. A., Wall, A., McGuire, A. T., & Veesler, D. (2020). Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell, 181(2), 281-292.
22. William J. M. Pediatric COVID-19 Vaccines: What Parents, Practitioners, and Policy Makers Need to Know. JAMA. 2021 Dec 14;326(22):2257-2258.
23. Perez, Y., Levy, E. R., Joshi, A. Y., Virk, A., Rodriguez-Porcel, M., Johnson, M., ... & Swift, M. D. (2022). Myocarditis following coronavirus disease 2019 mRNA vaccine: a case series and incidence rate determination. Clinical Infectious Diseases, 75(1), e749-e754.
24. COVID-19 tracker.