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Immunologic response, Efficacy, and Safety of Vaccines against COVID-19 Infection in Healthy and immunosuppressed Children and Adolescents Aged 2 – 21 years old: A Systematic Review and Meta-analysis

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ABSTRACT

Children and adolescents form a large proportion of societies and play an important role in the transmission of COVID-19. On the other hand, their education, mental and physical wellness, and safety are compromised which makes vaccination a crucial step to return to normal life. In the current systematic review, the COVID-19 vaccination was evaluated in a total of 50,148 children and adolescents in 22 published studies and 5,279 participants in two ongoing clinical trials. The study was registered in the PROSPERO with the ID# CRD42022303615. Data were collected about multiple vaccines including BNT162b2 (Pfizer), mRNA-1273 (Moderna), JNJ-78436735 (Johnson and Johnson), CoronaVac (Sinovac), BBIBP-CorV (Sinopharm), adenovirus type-5-vectored vaccine, ZyCov-D, and BBV152 (COVAXIN). The immune response and efficacy of such vaccines were 96% – 100% in healthy children and adolescents and were also acceptable in those with underlying diseases and suppressed immune systems. The current systematic review revealed favorable safety profiles of employed vaccines in children and adolescents; however, adverse reactions such as myocarditis and myopericarditis were reported which were transient and resolved entirely. Consequently, vaccinating children and adolescents aged 2 – 21 years old is beneficial to abort the COVID-19 pandemic. Moreover, the risk-benefit assessments revealed favorable results for vaccinating children and adolescents, especially those with underlying diseases and immunosuppressed conditions, alongside adults to prevent transmission, severe infection, negative outcomes, and new variants formation. Also, according to the meta-analysis, the efficacy and immune response of vaccines after the first and second doses were 91% and 92%, respectively. Meanwhile, overall immune response for all vaccines was 95% and 91% for Pfizer vaccine.

Abbreviations: SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analysis; Ab, antibodies; Ad5, adenovirus type-5; CVID, common variable immunodeficiency; unPAD, unclassified pediatric antibody deficiency; IBD, Inflammatory bowel disease; JNJ, Johnson & Johnson; KTRs, kidney transplant recipients; JIA, juvenile inflammatory arthritis.

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1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is caused by coronavirus 2019 (COVID-19) and was announced as a global pandemic on March 11, 2020 [1]. Children and adolescents are at risk of COVID-19 infection as likely as other age groups; however, children may manifest milder symptoms than adults [2]. Although the clinical manifestation of COIVD-19 involves lots of organs [3–7] and its course is smoother in pediatrics, the disease can escalate to severe pulmonary involvement especially in those with underlying medical conditions [8]. Multiple trials evaluated the efficacy and safety of vaccines against COVID-19 in healthy grown-ups as well as adults with comorbidities [9–14]. Likewise, vaccination against coronavirus can prevent serious outcomes or hospitalization following the natural infection [15]. Of note, children and adolescents have their education, safety, mental and physical wellness negatively affected which it makes vaccination crucial for them [16]. All children and adolescents should be considered for COVID-19 vaccination for their own protection against the infection and its difference outcomes, and more importantly because they are part of the COVID transmission cycle [3-7, 17-19].

Several clinical trials supported the favorable immune response, effectiveness, and safety profiles of COVID-19 vaccines in healthy children and adolescents, and those with underlying medical conditions [20–23]. In the current study, we aimed to collect all the data about immunogenicity, efficacy, and safety of available COVID-19 vaccines to guide health care workers and families on vaccinating the younger population (2 – 21 years old).

2. Method and Materials

The current systematic review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) (Table S1 and Table S2). The study was registered in the PROSPERO with the ID# CRD42022303615.

2.1. Search Strategy

A systematic search was performed on databases including Ovid Medline, Cochrane Library, Scopus, Web of Sciences, Embase, Google Scholar, and ClinicalTrials.gov website until December 7th, 2021. The combination of employed keywords and MeSH terms is attached in the supplementary data (Table S3). A total of 9,369 publications were found in the primary search and 5,540 duplicates were removed in the first screening phase and 3,829 published studies entered the next phase of screening. PRISMA flow diagram can be found in supplementary data (Fig. S1).

2.2. Literature Screening

For the entire screening process, EndNote software, version 20, was utilized. In the first phase of screening, 5,540 duplicates were detected by EndNote and removed. In the second phase of screening, two investigators independently reviewed all the literature by reading titles and abstracts to ensure their quality to be included in data extraction, and remained duplicates were removed manually. Disagreements were resolved with discussion or the consensus of the corresponding investigator. In the last phase of screening, full texts were reviewed by one investigator and 22 publications plus two ongoing clinical trials, with released interim results, were selected for data extraction

2.3. Inclusion and Exclusion Criteria

Criteria for inclusion of studies comprised full text, English language, human studies, pediatric and adolescent population (21 years old or younger), clinical trials, observational studies, cohort, case series and case reports. Further, criteria excluding studies out of the review included trials about adults (older than 21 years old), studies on animals or *in vitro/ex vivo,* reviews, consensus, or guidelines, and articles which were not about COVID-19 vaccination.

2.4. Data Extraction

Extracted data from studies that were included in the current review are (i) study characteristics (author, year, design of study, county, name, and type of the vaccine), (ii) participants characteristics (age, sample size, and underlying medical conditions), and [24] results (immune response, efficacy, safety, and adverse reactions). Microsoft Word software, version 16.56, was utilized for data extraction. Two investigators performed the data collection process.

2.5. Bias Assessment and Quality Evaluation

Methodological quality of the included studies and risk of bias were independently assessed by two investigators. For these assessments, the National Institute of Health (NIH) Quality Assessment Tool for Observation Cohort and Cross-Sectional Studies [25] and the NIH Quality Assessment Tool for Clinical Trials [26] were utilized and the results can be found in supplementary data table S4.

2.6. Data Analysis

The main measure of the effect/effect size was efficacy of vaccine (ratio of effectiveness to the total vaccinated children). Cochrane's test (Q-test) (showing significant heterogeneity in the meta-analysis) and I_2 (showing the amount of heterogeneity, ranged from 0% to 100 %) were used to assess the heterogeneity among the studies. The random-effects model was used for the frequency outcome under study. Random-effects meta-analysis was performed for estimating the main index, which was the pooled prevalence, at the 95% confidence interval. A forest plot was used to present the efficacy of vaccine sorted by type of vaccine. Publication bias was assessed using Begg's test. The analysis was performed using Stats version 13.

2.7. Ethics Consideration

This review study is not individual-based study and we used peer-reviewed published studies data with ethic codes.

3. Results

3.1. Results of meta-analysis and basic findings

A total of 3,829 publications remained after removing duplicates. Among these numbers, 3,616 studies did not meet the inclusion criteria and were excluded out of the study. A total of 207 publications were entered the last phase of screening and ultimately 22 studies were selected for data extraction. Meanwhile, two ongoing clinical trials with the released interim results met the criteria to be included. Consequently, data extraction revealed the results of vaccination of a total of 50,848 children and adolescents for the current systematic review. In the meta-analysis section, **Fig. 2**, **3**, **4**, **5** present the immune response of vaccines in children in whom the efficacy after first and second dose was 91% and 92%, respectively. Immune response was 95% for all vaccines and 91% for Pfizer. **Fig. 6** shows the assessment of publication bias ($p>0.05$).

3.2. Immunogenicity of COVID-19 Vaccines in Pediatrics and Adolescents

A total of 12 publications plus two ongoing clinical trials investigated the immunogenicity of COVID-19 vaccines in participants aged 2 - 21 years old. Two other studies extended the age of their participants to 26 and 26.8 years old while assessing the immunologic response of the

Table 1
Characteristics of included published studies (n=22).

StudyID	Country	Study design	Sample size	Age	Name of vaccine	Vaccine type	Immune Response	Efficacy	Adverse reactions and safety (n or %)	Special consideration
Alamer [43]	Saudi Arabia	Cross-sectional	965	12 – 18 y/o	BNT162b2[1]	mRNA	N/A	N/A	60% reported at least 1 side effect	10% had type 1 diabetes mellitus, sickle cell anemia or asthma
Ali and Berman [29]	USA	RCT[2]	3,732	12 – 17 y/o	mRNA-1273[3]	mRNA	98.8% serologic response	93.3% (after second dose)	Injection site pain, headache, fatigue	None
Amodio [35]	Italy	Observational	21 (only one adolescent entered to the current review)	16 y/o	BNT162b2	mRNA	Significant lower Ab[4] titer than healthy individual	N/A	Injection site pain	CVID[5] and Burkitt lymphoma in remission
Bickel [45]	USA	Observational	31	16 – 25 y/o	BNT162b2	mRNA	N/A	N/A	Mild adverse reactions (83.9% after the first dose and 74.2% after the second dose)	Long care facility residents
Dailey [27]	USA	Cohort	33	2 – 26 y/o	JNJ-78436735[6] (n=5) BNT162b2 (n=21) mRNA-1273 (n=7)	Viral vector, mRNA	15-fold higher serologic response post-vaccination compared to wild infection	N/A	N/A	IBD[7] receiving infliximab or vedolizumab
Dimopoulou [46]	Greece	Observational	21	16 – 21 y/o	BNT162b2	mRNA	N/A	N/A	Injection site reaction (74%), urticaria, no exacerbation of JIA[8]	JIA controlled with TNF inhibitor at least for one year
Frenck [30]	USA	RCT	2,260 (1,131 received vaccine, 1,129 received placebo)	12 – 15 y/o	BNT162b2	mRNA	Greater response in adolescents than in younger adults	100% after 2 doses, 3 cases of Covid between the first and second dose	Injection site pain, fatigue, headache, and fever	None
Han [31]	China	RCT	552	3 – 17 y/o	CoronaVac (Sinovac)	Inactivated virus	Over 96% of serologic response after both doses	N/A	Injection site pain (13%), fever (25%)	None
Haskin [28]	Israel	Observational	38	13.5 – 26.8 y/o	BNT162b2	mRNA	63% serologic response after both doses. A high proportion of patients with GFR[9]<30 or previously treated with rituximab did not develop Ab	N/A	Injection site reaction, fever, fatigue, headache, non-significant decrease in GFR after vaccination	Kidney transplant recipients
Jara [41]	Chile	Cohort	38,225 (8,192 received 1 dose and 30,033 received both doses)	16 – 19 y/o	CoronaVac	Inactivated virus	N/A	65.5% prevents of covid-19 infection, 87.5% of hospitalization, 90.3% of ICU admission, and 86.3% of covid-related death	N/A	None
King [47]	UK	Observational	27	12 – 15 y/o	BNT162b2	mRNA	N/A	N/A	Severe fatigue and discomfort combined with increased agitation, change in seizure type becoming clusters	Neurologic conditions
Macedoni [38]	-	Observational	20	16 – 22 y/o	BNT162b2	mRNA	Acceptable serologic response	N/A	Injection site reaction and pain, fever	Type 1 diabetes mellitus
Mark [44]	Canada	Cohort	32	12 – 17 y/o	BNT162b2	mRNA	N/A	N/A	No allergic reactions	History of acute lymphoblastic leukemia and

(*continued on next page*)

Table 1 (*continued*)

StudyID	Country	Study design	Sample size	Age	Name of vaccine	Vaccine type	Immune Response	Efficacy	Adverse reactions and safety (n or %)	Special consideration
										allergy to PEG[10]-asparaginase
Moeller [48]	USA	Observational	33	12 – 17 y/o	BNT162b2	mRNA	N/A	N/A	No adverse effects were reported from patients	Mental illness
Qin [39]	USA	Cohort	57	12 – 18 y/o	BNT162b2	mRNA	Ab titers 56.8% positive after the first dose and 73.3% positive after the second dose	2 patients tested positive for mild Covid-19 (the first infected between 2 doses, the second 46 days after second dose)	N/A	Solid organ transplant recipients on multiple immunosuppressants and anti-metabolites
Revon-Riviere [40]	France	Cohort	13 (3 patients did not receive the second dose)	16 – 21 y/o	BNT162b2	mRNA	Ab titers were positive in 8/10 after the first dose and positive in 9/10 after the second dose	No patients developed Covid after immunization	Injection site pain [6], fever and chills	Solid tumor malignancy on chemotherapy, targeted therapy, or immunotherapy
Shire ([37, 40])	Canada	Cohort	42 (26 patients received second dose)	12 – 17 y/o	BNT162b2	mRNA	Acceptable Ab response after vaccination	N/A	N/A	IBD treated with TNF[11] inhibitors
Spencer [36]	USA	Cohort	340	≤21 y/o	JNJ-78436735 BNT162b2 mRNA-1273	Viral vector, mRNA	20 Patients checked for Ab after vaccination and those received Moderna had significantly higher titer of Ab	N/A	N/A	IBD on immunosuppressor
Walter [32]	USA	RCT	2,268 (1,517 received vaccine and 751 received placebo)	5 – 11 y/o	BNT162b2	mRNA	99.2% of participants achieved serologic response 1 month after the second dose	90.7% effective (3 cases of Covid-19 reported 7 days or more after the second dose)	Fever (1 case was severe), injection site reaction and pain (71 – 74%), severe fatigue (0.9%), headache (0.3%), chills (0.1%)	12% of participants had obesity and 8% had asthma
Xia [33]	China	RCT	288 (phase 1), and 720 (phase 2)	3 – 17 y/o	BBIBP-CorV (sinopharm)	Inactivated virus	100% serologic response on day 56 post-vaccination	Protection efficacy against Covid-19	Moderate fever (n=32), and cough (n=22)	None
Zhu [34]	China	RCT	150 (100 received vaccine and 50 received placebo)	6 – 17 y/o	Ad5-vectored COVID-19 vaccine	recombinant adenovirus type-5 (Ad5)-vectored	Higher Ab titers in pediatrics than in adults, 98% - 100% serologic response after 84 days	N/A	Fever, headache, fatigue, injection site pain (overall in 82%), 3 patients had severe fever, 1 had abdominal pain	None
Zydus Cadila company (42)	India	RCT	1,000	12 – 18 years-old	ZyCov-D	Plasmid DNA	N/A	66.6% (first dose) 100% (third dose)	100%	None

[1] Pfizer;
[2] Randomised Clinical Trial;
[3] Moderna;
[4] Antibody;
[5] Combined Variable Immunodeficiency;
[6] Jahnson & Johnson;
[7] Inflammatory Bowel Disease;
[8] Juvenile Inflammatory Arthritis;
[9] Glomerular Infiltration Rate;
[10] Polyethylene Glycol;
[11] Tumor Necrosis Factor

Table 2
Characteristics of ongoing clinical with released interim results (n=2).

Clinical trial number	Country	Study design	Sample size	Age	Name of vaccine	Vaccine type	Immune Response	Efficacy	Adverse reactions and safety (n or %)	Special consideration
NCT04918797 [76]	India	Clinical trial	526	2 – 18 y/o	BBV152 (COVAXIN)	Inactivated virus	Over 90% serologic response	Suggested protection like adults	Suggested safety like adults	Interim results were released
NCT04796896 [77]	USA	Clinical trial	4,753	6 months – 12 y/o	mRNA-1273[2]	mRNA	99.3% serologic response one month after the second dose	N/A	Mild to moderate fatigue, headache, fever, and injection site pain	Continue enrolling children 6 months to 6 y/o

1Moderna

vaccination in pediatric groups [27, 28]. Ali and Berman et al. [29] reported 98.8% serologic response to mRNA-1273 (Moderna) vaccine in contributors aged 12 – 17 years old compared to 98.6% seroresponse in younger adults, and neutralizing antibodies (Ab) titers implied no inferiority in younger ages than in older. Frenck et al. [30] conducted a randomized clinical trial (RCT), studying the effect of BNT162b2 (Pfizer) in participants aged 12 – 15 years old and found a greater post-vaccination Ab titer compared to vaccinated younger adults and control group. Han et al. [31] Also announced over 96% serologic response 28 days after two doses of CoronaVac (Sinovac) injection to individuals aged 3 – 17 years old. Meanwhile, they noticed a higher Ab detection with 3.0μg dose of vaccine injection than 1.5μg dose. Walter [32] revealed that 99.2% of Pfizer recipients aged 5 – 11 years old achieved serologic response a month after the second dose injection. Moreover, a study conducted by Xia et al. [33] on the effect of BBIBP-CorV (Sinopharm) among participants aged 3 – 17 years old reported 100% serologic response 56 days after vaccination. Noteworthy that produced Ab following the injection of 4μg and 8μg of Sinopharm were significantly higher than 2μg dosage. Furthermore, Zue et al. [34] enrolled an RCT about recombinant adenovirus type-5 (Ad5)-vectored COVID-19 vaccine which revealed 98% - 100% immunologic response 84 days post-vaccination in the 6 – 17-year-old age group. The robust Ab response to Ad5-vectored vaccine was higher in pediatrics than in adults (Table 1).

Interim results of an ongoing RCT (*NCT04918797*) on BBV152 (COVAXIN) revealed over 90% serologic response following vaccination in 2 – 18 years old contributors. Another ongoing RCT (*NCT04796896*) has been evaluating Moderna vaccine in 4,753 individuals aged 6 months – 12 years old, and the interim results reported 99.3% immunologic response one month after the second shot of vaccine (Table 2). Additional data related to dosage of vaccines, antibody titers, type of assay for antibody titration, and the relationship between time of vaccination and immunogenicity were reported in Table 3.

3.2.1. Immunogenicity of COVID-19 Vaccines in Pediatrics and Adolescents with Underlying Conditions

Multiple studies evaluated the immunologic response to COVID-19 vaccines in pediatrics and adolescents with underlying clinical conditions as well as in healthy individuals. Amodio et al. [35] in a case series of 21 patients, reported the effect of Pfizer vaccine in eight adolescents aged 16 – 21 years old, seven patients with common variable immunodeficiency (CVID), and one patient with unclassified Ab deficiency (unPAD). The serologic response in such patients after two doses of vaccine was significantly lower than in healthy individuals. Dailey et al. [27] compared the serologic response of the natural COVID-19 infection to the immunogenicity of the several COVID-19 vaccines in inflammatory bowel disease (IBD) patients. All patients in the latter study were under the treatment with infliximab, vedolizumab, or methotrexate and the employed vaccines were Pfizer, Moderna, and Johnson & Johnson (JNJ). The serologic response was 10 folds greater post-COVID vaccination compared to natural COVID-19 infection. In another study on adolescents with IBD, Spencer et al. [36] observed that Moderna recipients developed a greater Ab response compared to Pfizer and JNJ recipients disregarding the type of immunosuppressant medication. Shire et al. [37] also performed a study on 12 – 17-year-old patients with IBD treated with TNF-inhibitors. Patients received Pfizer vaccine and showed an acceptable Ab titer on follow-ups. Haskin et al. [28] found 63% serorespose after two doses of Pfizer among kidney transplant recipients (KTRs) aged 13.5 – 26.8 years old. Noteworthy that a high proportion of patients without an acceptable Ab response had an eGFR<30 mL/min/1.73m^2 and formerly received rituximab. Interestingly, KTRs with a history of natural COVID-19 infection developed higher immunologic responses compared to vaccinated KTRs. Macedoni et al. [38] reported an acceptable serologic response after Pfizer vaccine in 16 – 22-year-old patients with type-1 diabetes mellitus. A total of 57 of Solid organ transplants aged 12 – 18 years old in a cohort study conducted by Qin et al. [39], received Pfizer vaccine while were on multiple immunosuppressants and anti-metabolites. Serologic response was reported 56.8% after the first dose and 73.3% after the second dose of vaccine. Revon-Riviere et al. [40] revealed 80% and 90% seropositive response in patients with solid tumor malignancy after the first and second dose of Pfizer, respectively. The age of patients ranged 16 – 21 years old and they were on chemotherapy, targeted therapy, or immunotherapy.

3.3. Efficacy of COVID-19 vaccines in Pediatrics and Adolescents

The efficacy of Pfizer vaccine in participants aged 5 – 11 years old was reported 90.7% after the second dose [32] and in individuals aged 12 – 15 years old was 100% [30]. In a study, assessing the effectiveness of Pfizer in 12 – 18—year-old adolescents, among 57 participants, only two patients were tested positive for COVID-19 infection, one patient before receiving the second dose and another one 46 days after the second dose [39]. In the category of Pfizer recipients with underlying medical conditions, adolescents with solid tumor malignancy did not develop COVID-19 infection after full immunization [40].

Other vaccines such as Moderna, CoronaVac, and ZyCov-D were reported 93.3%, 65.5%, and 100% protection against COVID-19 infection in 12 – 19 years old participants, respectively [29, 41, 42]. Additionally, studies on Sinopharm and COVAXIN (*NCT04918797*) suggested protection efficacy against COVID-19 among 2 – 18-year-old individuals [33].

3.4. Safety of COVID-19 Vaccines in Pediatrics and Adolescents

Reported adverse reactions were mild-to-moderate and self-limiting. The most common adverse reactions following vaccination of children and adolescents comprised injection site pain and erythema, headache, fatigue, fever, and chills ([29-33, 35, 38, 40, 43]). In the meanwhile, no allergic reactions were reported in patients with a history of allergy to PEG-asparaginase and acute lymphoblastic leukemia after receiving Pfizer vaccine [44].

Table 3
Antibody titers after vaccination.

StudyID	Study design	Sample size	Age group (y/o)	Sex (F:M)n	Name of vaccine	Vaccine Dosage (μg)	RBD*-specific Ab (GMT**)	Neutralizing Ab (GMT) After Vaccination	Ab Measurement Method	Time of Ab measurement
Ali and Berman [29]	RCT	3,732(2489 received vaccine and 1234 received placebo)	12 – 17	1811:1915	mRNA-1273	100	807	1401.7	ELISA	One month after the second dose
			18 - 25				740	1301.3		
Walter[32]	RCT	2,268 (1,517 received vaccine and 751 received placebo)	5 – 11	1086:1182	BNT162b2	10	–	1197.6	–	One month after the second dose
			16 - 25			20		1146.5		
Frenck[30]	RCT	2,260 (1,131 received vaccine, 1,129 received placebo)	12 – 15	1108:1152	BNT162b2	30	–	1239.5	Serum neutralization assay and receptor-binding domain [RBD]–binding or S1-binding IgG direct Luminex immunoassays)	One month after the second dose
			16 - 25					705.1		
Han[31]	RCT	552	3 – 17	253:297	CoronaVac (Sinovac)	1.5	–	86.4	Serology (microcytopathogenic effect assay)	28 days after the second dose
						3		142.2		
Xia[33]	RCT	240	3 – 5	121:119	BBIBP-CorV	2	–	143.55	Serology (Microneuralisation assay)	28 days after the 3rd dose
						4		199.11		
						8		224.39		
		240	6 - 12	118:122	BBIBP-CorV	2	–	126.99		
						4		184.78		
						8		175.78		
		240	13 - 17	107:133	BBIBP-CorV	2	–	150.73		
						4		198.98		
						8		192.14		
Zhu[34]	RCT	150 (100 received vaccine and 50 received placebo)	6 – 17	46:54	Ad5-vectored COVID-19 vaccine	–	1037.5 (889.3-1210.5)	168.0 (95% CI: 143.3, 197.1)	ELISA	28 days after the second dose
						–	1091.6 (95% CI: 873.7, 1363.7)	96.6 (76.8, 121.4)		28 days after a 1st dose

Table 4
Myo/pericarditis events following the Covid-19 vaccination.

Author name and year	Study design	Mean age or (age range) and M/F ratio	Type of Vaccine	Dose of vaccine	Reaction of interest	Mean or interval days between vaccination and reaction
Ambati, 2021	Case report	24.5, 2	Pfizer-BioNTech	Second	Myopericarditis	2.5
Li, 2021	Population-based	N/A, 2.7	Pfizer-BioNTech, Moderna, Janssen	First 36.53%, second 63.47 %	Myocarditis and pericarditis	N/A
Minocha, 2021	Case report	17, 1/0	Pfizer-BioNTech	Second	Myocarditis	1
Jain, 2021	Retrospective multicenter study	15.6, 5.2	59 Pfizer, 9 Moderna	All after second dose, except for one patient	Myocarditis	2.1 ± 1.3
Schauer, 2021	Retrospective electronic medical record review	15, 12/1	Pfizer	Second	Myopericarditis	3
Snapiri, 2021	Case series	16–18, 7/0	BNT162b2	In 6 of the 7 patients, following the 2nd dose and in 1 patient following the 1st dose.	Perimyocarditis	2.1
Das, 2020	Cross-sectional study	2-18, 22/3	Pfizer-BioNTech	In 3 of the 25 patients, following the 1st dose and in 22 patients following the second dose.	Myopericarditis	2
McLean, 2021	Case report	16, 1/0	Pfizer-BioNTech	Second	Myopericarditis	1
Marshal, 2021	Case series	16.7, 7/0	Pfizer-BioNTech	Second	Myocarditis	4
Fleming, 2021	Case series	20.12, 8/0	Pfizer-BioNTech	Second	Myopericarditis	3
Tano, 2021	Case series	16.6, 8/0	Pfizer-BioNTech	1 patient after the first and second dose. On patient after the first dose. Six patients after the second dose.	Perimyocarditis	4
Marshal, 2021	Case series	16.7, 7/0	Pfizer-BioNTech	Second	Myocarditis and myopericarditis	4
Truong, 2021	Retrospective study	15.8, 126/13	Pfizer-BioNTech (n=131), Moderna (n=5), Janssen (n=1), unknown (n=2)	(n=12) first dose, (n= 128) second dose	Myocarditis	2
Snapiri, 2021	Case series	16.8, 7/0	BNT162b2 vaccine	In 6 of the 7 patients, symptoms began following the 2nd dose and in 1 patient following the 1st dose.	Perimyocarditis	2.1
Park, 2021	Case report	15.5, 2/0	BNT162b2 vaccine	One after first dose, one after second dose	Myocarditis	2.5
Pfajfer, 2021	Case report	17, 3/0	BNT162b2	Two after first dose and one case after the second.	Myocarditis	6.33
Azir, 2021	Case report	17, 1/0	BNT162b2	Second	Focal myocarditis	1

In 16 – 25-year-old patients who were residents of a long care facility and received Pfizer, after the first dose 83.9% and following the second dose of vaccine 74.2% of patients presented mild adverse reactions such as discomfort/agitation, nausea/emesis, diarrhea, fever, chills, headache, and injection site erythema [45]. Further, Pfizer was administered in patients with juvenile inflammatory arthritis (JIA) aged 16 – 21 years old and no exacerbation of JIA was reported [46]. Among KTRs aged 13.5 – 26.8 years old, a non-significant decrease in eGFR were reported after vaccination with Pfizer [28]. Increased agitation and changed seizure pattern (becoming cluster) were observed transiently in Pfizer recipients aged 12 – 15 years old with underlying neurologic conditions [47]. Pfizer vaccine was also injected to 12 – 17-year-old patients with mental illness and no adverse reactions were reported from patients [48].

4. Discussion

Mass vaccination of children and adolescents against coronavirus can be the endgame for the current pandemic [49, 50]. Trials about the immunogenicity of mRNA vaccines (Moderna and Pfizer) against COVID-19 revealed a great humoral immunity and more interestingly cell-mediated response in adults and children [51, 52]. AstraZeneca, JNJ, and Novovax demonstrated a lower humoral response than mRNA vaccines [52]. The immune response in pediatric age groups was reported 90% - 100% which was also higher and more durable than natural COVID-19 infection [29, 31, 32]. Therefore, vaccination of children and adolescents is recommended.

Immunogenicity among children and adolescents with underlying conditions such as malignancy, IBD, transplant recipients, inherited immunodeficiency, and those on immunosuppressant and immunomodulator medications was revealed to be lower than healthy individuals [28, 38, 53, 54]. This finding can be justified because of the relative immune system suppression. However, it was still an acceptable immune response to vaccinate this group of children and adolescents as they are more prone to show more severe forms of COVID-19 disease and its negative outcomes [54].

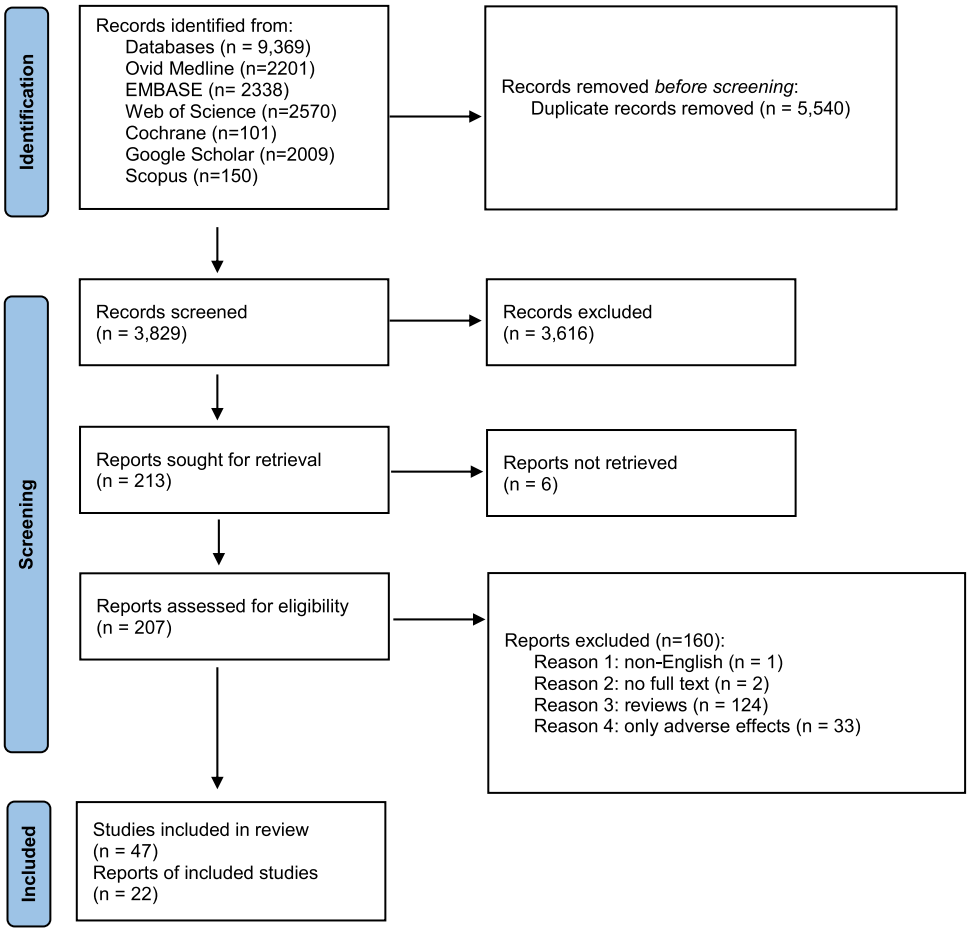

Fig. 1. Flow chart of included studies in this systematic review and meta-analysis.

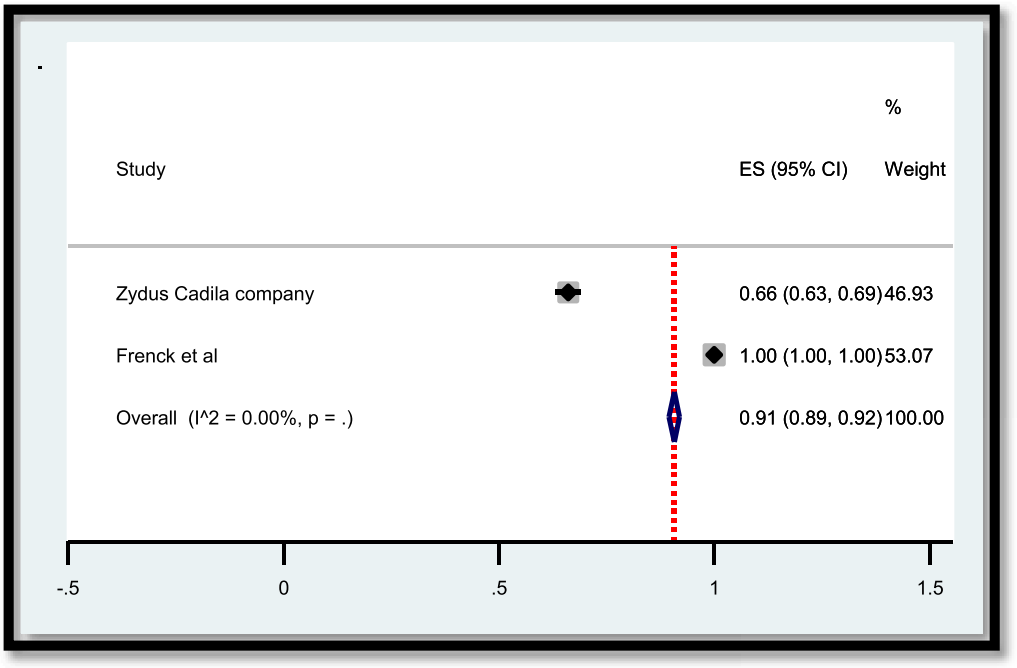

Fig. 2. Efficacy of vaccine after the first dose in children.

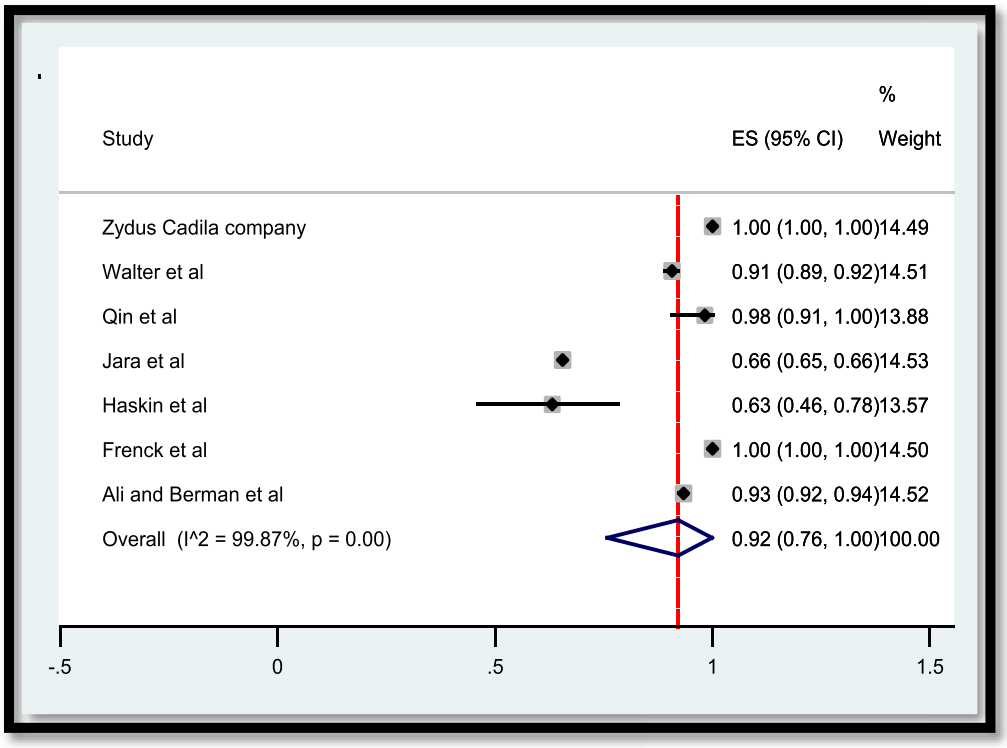

Fig. 3. Efficacy of vaccine after the second dose in children.

Full vaccination of people aged 16 years and older with mRNA vaccines provided over 90% and partial vaccination with such vaccines provided over 80% efficacy on protection against COVID-19 [13,55-57]. Other vaccines for adults such as virus-vectored vaccines (Ad26.COV2.S [58], AZD1222 [59], Ad5-vectored [60], inactivated vaccines (BBV152 [61], CoronaVac [62]), recombinant particles or nanoparticle [63] (V-01 [64], Novavax [65], CoVLP [66] reported also a significant efficacy in protection against moderate to severe COVID-19 infection.

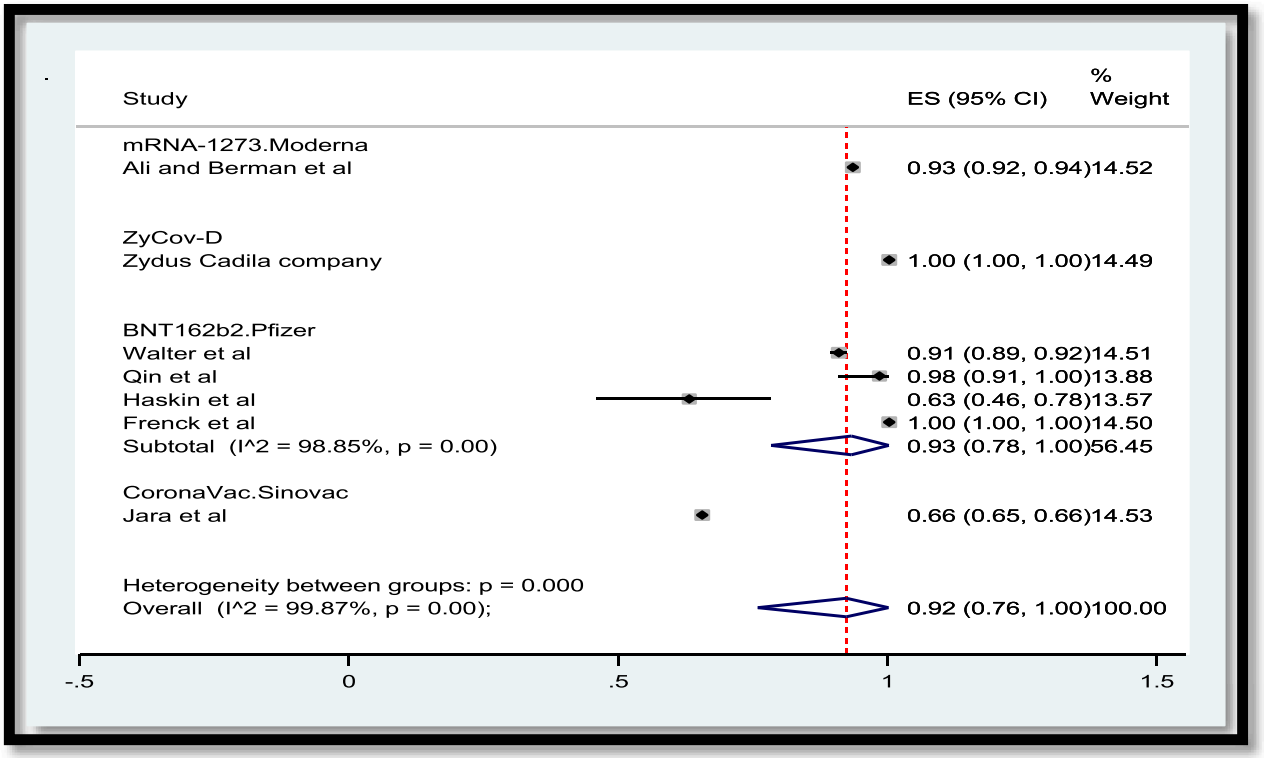

Fig. 4. Efficacy of vaccine after the second dose in children by vaccine.

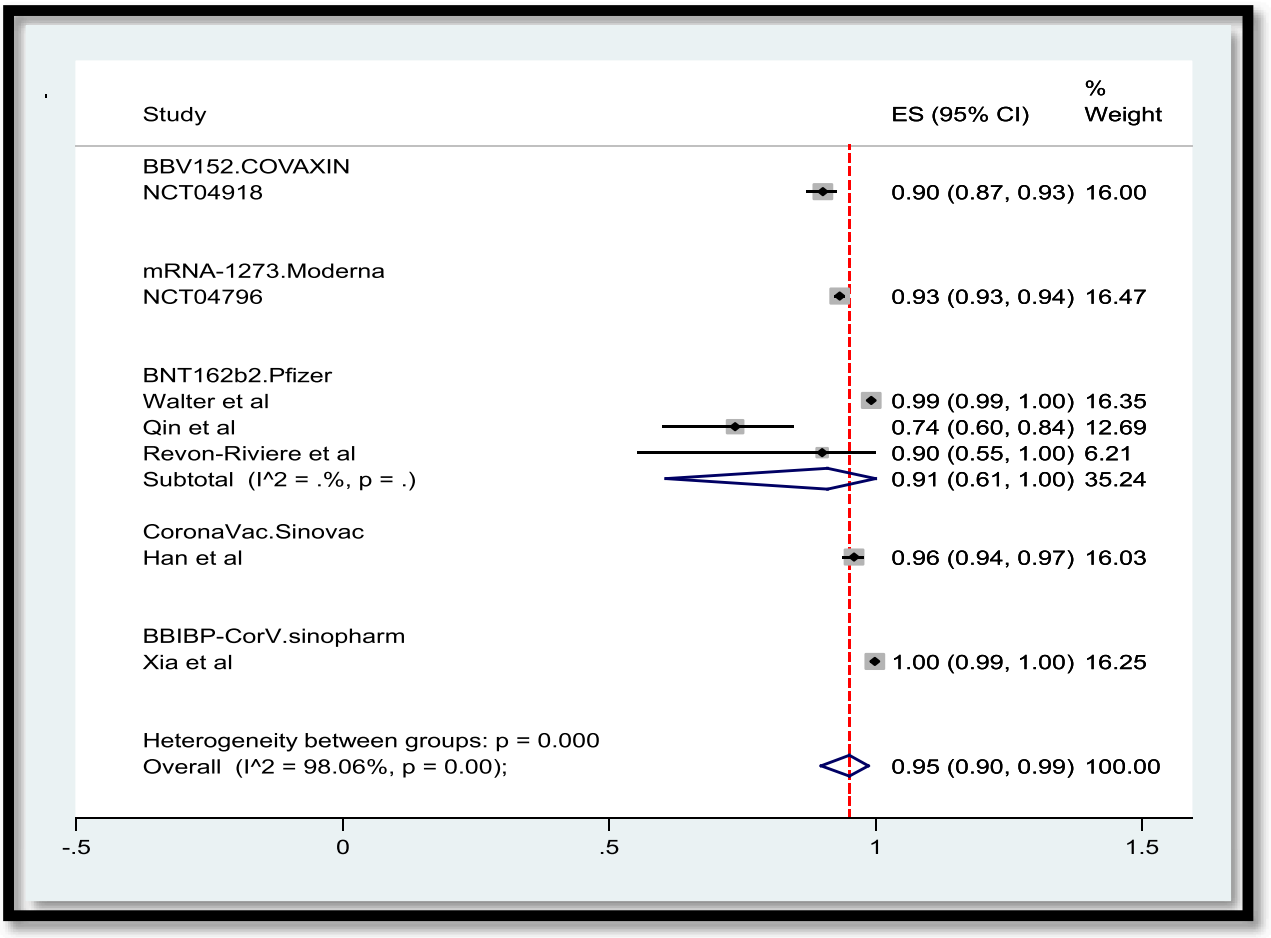

Fig. 5. Immune response of vaccine after both doses in children by vaccine.

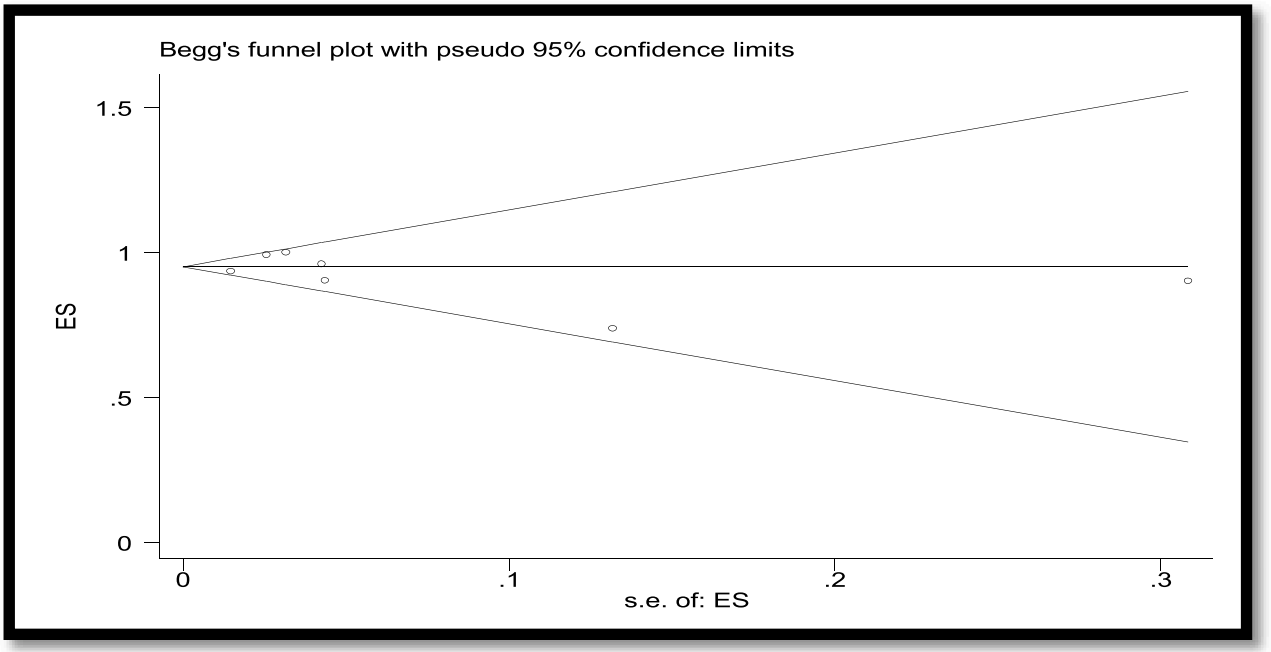

Fig. 6. Funnel plot to assess publication bias.

Meanwhile, vaccination of children and adolescents was reported approximately 100% effective. Vaccination in 12 – 18-year-old participants has been decreased the rate of hospitalization due to COVID-19 and its consequences among these age groups [15, 67].

The most common adverse reactions following COVID-19 vaccination in adult and pediatric age groups have been fatigue, body pain, injection site pain and erythema, headache, myalgia, nausea/emesis/diarrhea, fever, and joint pain [43, 68-70]. More serious adverse effects such as transient myocarditis and myopericarditis have been primarily reported in male adolescents; however, the incidence of such reactions is rare and most of the patients fully recovered without treatment [71–73]. Myo/pericarditis mostly was seen following Pfizer vaccine 1 – 7 days post-vaccination, especially after the second shot. Table 4 gathered data regarding the interval between the vaccination and occurrence of the myo/pericarditis, mean age of vaccine recipients, type of vaccine, and the relation of myo/pericarditis to the dose of vaccine. Risk-benefit assessment for vaccination against COVID-19 determined an acceptable balance for vaccinating children and adolescents of both sexes [71, 73-75].

5. Conclusion

The current systematic review on 22 publications plus the interim results of two ongoing clinical trials about vaccinating children and adolescents aged 2 – 21 years-old that provided an overall result about the serologic response, efficacy, and safety of available vaccines. Vaccinating younger age groups can be helpful to end the current pandemic as kids have been a part of the COVID-19 transmission cycle. Moreover, broad vaccination of all age groups can help us to prevent other COVID-19 variants to be formed. The safety profiles of such vaccines are acceptable and make them great options to prevent COVID-19 infection in healthy children and adolescents or patients with underlying conditions such as malignancy. According to the meta-analysis, immune response of vaccines after the first and second dose was 91% and 92%, respectively. The overall immune response was 95% for all vaccines and 91% for Pfizer.

6. Limitation and Recommendation

All reviewed studies about COVID-19 vaccines, especially in pediatric groups, are new and need more time to be evaluated about their long-term efficacy and safety. Further, more studies are required to assess the long-lasting immunity of such vaccines among pediatrics and the need for booster shots.Fig. 1

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Ethical Approval

Not applicable.

Transparency declaration

Authors declare that the manuscript is an honest, accurate, and transparent. No important aspect of the study is omitted.

Patients and Public Partnership

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Data Availability Statement

All data produced in the present study are available upon reasonable request to the authors.

Authors Contribution

Contributions to the current study are SS in the design, database search, screening publications, literature review, quality evaluation, and bias assessment, and drafting the manuscript. YK in screening publications, literature review, quality evaluation, and bias assessment, and drafting the manuscript, and AG, RV, S. Shokri, MF, and NN in drafting, reviewing, and revising the manuscript critically for importance intellectual content. All authors have read and approved the final version to be published and agreed to be accountable for all aspects of the work. All authors agreed on the order in which their names are listed in the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

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