

## REVIEW

# Safety and efficacy of COVID-19 vaccines in children and adolescents: A systematic review of randomized controlled trials

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**Abstract**

To systematically review and synthesize the safety and efficacy of coronavirus disease-2019 (COVID-19) vaccines in children and adolescents. PubMed, EMBASE, Web of Science, Cochrane Library databases, the International Clinical Trials Registry Platform (ICTRP), the Chinese Clinical Trials Registry (ChiCTR), and [ClinicalTrials.gov](https://www.clinicaltrials.gov) website were searched to collect accessible randomized controlled trials (RCTs) about the safety and efficacy of human COVID-19 vaccines in children and adolescents until May 1, 2022. Three steps, including duplicate removal, title and abstract screening, and full-text review, were used to screen the studies. The Cochrane risk-of-bias tool for RCTs was used to assess the bias risk of the included studies. Microsoft Excel 16.57 (2021) software was used for data extraction and analysis. (PROSPERO Code No: CRD42021295422). COVID-19 vaccines were evaluated in a total of 10 950 children and adolescents in seven published studies and over 49 530 participants in 26 ongoing randomized controlled trials. Descriptive findings of the included published studies were reported stratified by vaccine type. The overall, local, and systemic adverse events following immunization (AEFIs) reported in most trials were similar between the vaccine and placebo groups. Most of the reactions reported were mild to moderate, whereas a few were severe. The common adverse events were injection-site pain, fever, headache, cough, fatigue, and muscle pain. Few clinical trials reported serious adverse events, but most of them were unrelated to vaccination. In terms of efficacy, the investigated messenger RNA (mRNA) vaccine was found to be 90.7%–100% efficacious in preventing COVID-19 among children and adolescents, revealing good efficacy profiles in this age group. Among children and adolescents, the safety of current COVID-19 vaccines is acceptable, and studies have suggested that mRNA vaccines can provide high protection against COVID-19 infection in pediatric age groups.

**KEYWORDS**

children and adolescents, COVID-19 vaccines, efficacy, safety, systematic review

[Correction added on 5 July 2022, after first online publication: Zhaoyan Chen has been included as third author.]

Fangyuan Tian and Ruonan Yang contributed equally to this study.

## 1 | INTRODUCTION

Since its initial outbreak in December 2019, the novel coronavirus disease (COVID-19) pandemic had a devastating impact on people throughout the world. According to statistics from the World Health Organization, as of February 7, 2022, there have been 394.3 million confirmed cases of COVID-19 worldwide, including 5.7 million deaths.<sup>1</sup> Compared with the adult group, the proportion of COVID-19 cases in the child and adolescent groups was lower. National statistics from countries in Asia, Europe, and North America showed that pediatric cases account for 2.1%–20.2% of confirmed COVID-19 cases.<sup>2–5</sup> However, the impact of this novel disease on children and adolescents has been significantly severe. According to the Centers for Disease Control and Prevention (CDC), COVID-19 ranks as one of the top ten causes of death for children and adolescents in the United States at present.<sup>6</sup> Additionally, children who become infected with COVID-19 can also develop serious complications, such as multisystem inflammatory syndrome (MIS-C), a condition where different body parts become inflamed, including the heart, lungs, kidneys, brain, skin, eyes, or gastrointestinal organs.<sup>7</sup> Since the pandemic began, more than 2300 cases of MIS-C have been reported in children ages 5–11 years.<sup>6</sup> In addition to the physical harm, the pandemic also affected their physical, intellectual, and emotional development. It was estimated that approximately 1.5 billion young people worldwide had been obliged to stay at home, negatively influencing their health and social functioning.<sup>8</sup> Therefore, there is an urgent need for a vaccine to provide some protection against COVID-19 for pediatric age groups.

Vaccination is an effective way to fight against COVID-19, which can help to reduce the rate of severe illness and mortality, to curb further spread of the disease, and potentially to achieve herd immunity. With the shared effort of governing authorities, pharmaceutical enterprises, and the scientific community, a variety of COVID-19 vaccines have been widely used in the adult population, and some of them have also received conditional approval for mass vaccinations in the younger generation in some regions/countries. For example, inactivated virus vaccines from Beijing Institute of Biological Products, Wuhan Institute of Biological Products, and Sinovac Biotech have been granted conditional approval for vaccination to the pediatric population aged between 3 and 11 years in China.<sup>9</sup> The messenger RNA (mRNA) vaccine BNT162b2, which was collaboratively developed by Pfizer and BioNTech, has been authorized for use in children aged over 5 years in the United States.<sup>6</sup> In July 2021, the European Medicines Agency (EMA) also granted an extension of indication for the mRNA vaccine Spikevax in children aged between 12 and 17 years.<sup>10</sup>

Even though over 26.6 million COVID-19 vaccinations were given to 0.22 million people aged between 5 and 17 years as of February 2022 in the United States,<sup>11</sup> the topic of whether COVID-19 vaccination should be recommended for children and adolescents is still under debate. Children and adolescents, as a special population, are usually excluded from clinical trials, and

more importantly, published studies on safety and efficacy in this group are lacking. Based on this situation, more high-quality clinical trials and research are urgently required to answer this question.

To date, no systematic review to our knowledge has reported the safety and efficacy profile of COVID-19 vaccines in children and adolescents based on high-quality RCTs. Consequently, this article will summarize and analyze the safety and protective efficacy of the COVID-19 vaccine in clinical trials among children and adolescents to provide more reliable evidence for further clinical application.

## 2 | METHODS

### 2.1 | Eligibility criteria

Inclusion criteria required for searching included the following: human studies; children and adolescent population (aged < 18 years); published and ongoing RCT studies determining the safety or/and efficacy of the COVID-19 vaccine. Furthermore, the exclusion criteria were as follows: studies on animals or in vitro/ex vivo; adult population (aged ≥ 18 years); published clinical studies without the full text or without original data, including reviews, editorials, case reports, and comments; and ongoing clinical studies whose basic information or protocol was unavailable.

### 2.2 | Search strategy

We followed PRISMA guidelines to conduct this systematic review.<sup>12</sup> Systematic literature retrieval was performed on the Medline (via PubMed), EMBASE (via OvidSP), Web of Science, and Cochrane Library databases until May 1, 2022. Medical subject headings and free words such as “vaccine,” “COVID-19,” “SARS-CoV-2,” “COVID-19 Vaccines,” “children and adolescents,” and “randomized controlled trial” were used for the search and were adjusted depending on the database retrieved. No additional filters were used. All search strategies were developed and implemented independently by two investigators and then cross-checked. In addition to the literature databases, the International Clinical Trials Registry Platform (ICTRP), the Chinese Clinical Trials Registry (ChiCTR), [ClinicalTrials.gov](https://www.clinicaltrials.gov) website, and reference lists of identified articles were also searched to avoid missing potentially relevant studies.

### 2.3 | Literature screening

The following steps were conducted for literature selection: First, one investigator removed duplicates from the retrieved records; after that, two investigators used the titles and abstracts of all identified records to eliminate the studies irrelevant to our topic; finally, the remaining identified records and the records that were difficult to judge by reading their titles and abstracts were screened by two

investigators by reading the full text. The third investigator would join the discussion and make the final decision if there was a disagreement. We used Endnote 20.3 software during the entire screening process.

## 2.4 | Risk of bias assessment

Using the Cochrane risk-of-bias tool for RCTs<sup>13,14</sup> to assess the methodological quality of the included RCTs, the following seven aspects were included: correct random sequence generation, allocation concealment, blind application of subjects and investigators, blinded evaluation results, completeness of information, whether selective reporting was used, and any other risk of bias implementation.

## 2.5 | Data extraction

With the help of Microsoft Excel 16.57 (2021) software, one investigator extracted the information we needed into two pre-designed tables. One sheet designed for completed studies consisted of three parts: (1) the basic characteristics of the included studies, including the first author, publication year, clinical trial registration number, phase of clinical trial, location, name and type of vaccine, follow-up duration, and immunization schedule; (2) the characteristics of participants, including age, sex, and sample size; (3) the results of the included studies, including safety (the incidence of overall, local and systemic adverse events following immunization (AEFIs) and efficacy ( $100 \times (1 - IRR)$ ; IRR: the incidence of COVID-19 cases). The other sheet designed for ongoing studies extracted information about clinical trial number, recruitment status, phase of clinical trial, center information, location, name and type of vaccine, age range, and sample size.

## 2.6 | Data analysis

We systematically synthesized and reviewed extracted information about the safety and efficacy of COVID-19 vaccines in children and adolescents from high-quality RCTs. Microsoft Excel 16.57 (2021) software was utilized for data processing and analysis.

# 3 | RESULTS

## 3.1 | Study characteristics

The search resulted in 602 studies, including 344 published studies from four databases and 258 ongoing studies from other sources. After screening the titles, abstracts, and full texts, 456 studies were excluded. Finally, a total of 33 studies that met the eligibility criteria were obtained. The study selection process is shown in Figure 1.

Of these, seven randomized clinical trials (10950 participants) were officially published.<sup>15–21</sup> The participants of the included studies were restricted to children and adolescents who varied between 6 months and 18 years of age. The included studies contained 22 kinds of vaccines, and they could be classified into seven vaccine types based on different technology platforms: inactivated virus vaccines, viral vector vaccines, RNA vaccines, DNA vaccines, recombinant vaccines, subunit vaccines, and multipeptide protein/peptide vaccines. Among them, 27 studies were conducted in one country (14 in China, 3 in India, 2 each in the United States and Thailand, 1 each in Brazil, Colombia, Cuba, Iran, Turkey, and the Russian Federation), four studies were from a global multicenter, and two studies did not report their location. The characteristics of the included published and ongoing studies are summarized in Tables 1 and 2, respectively.

## 3.2 | Quality assessment

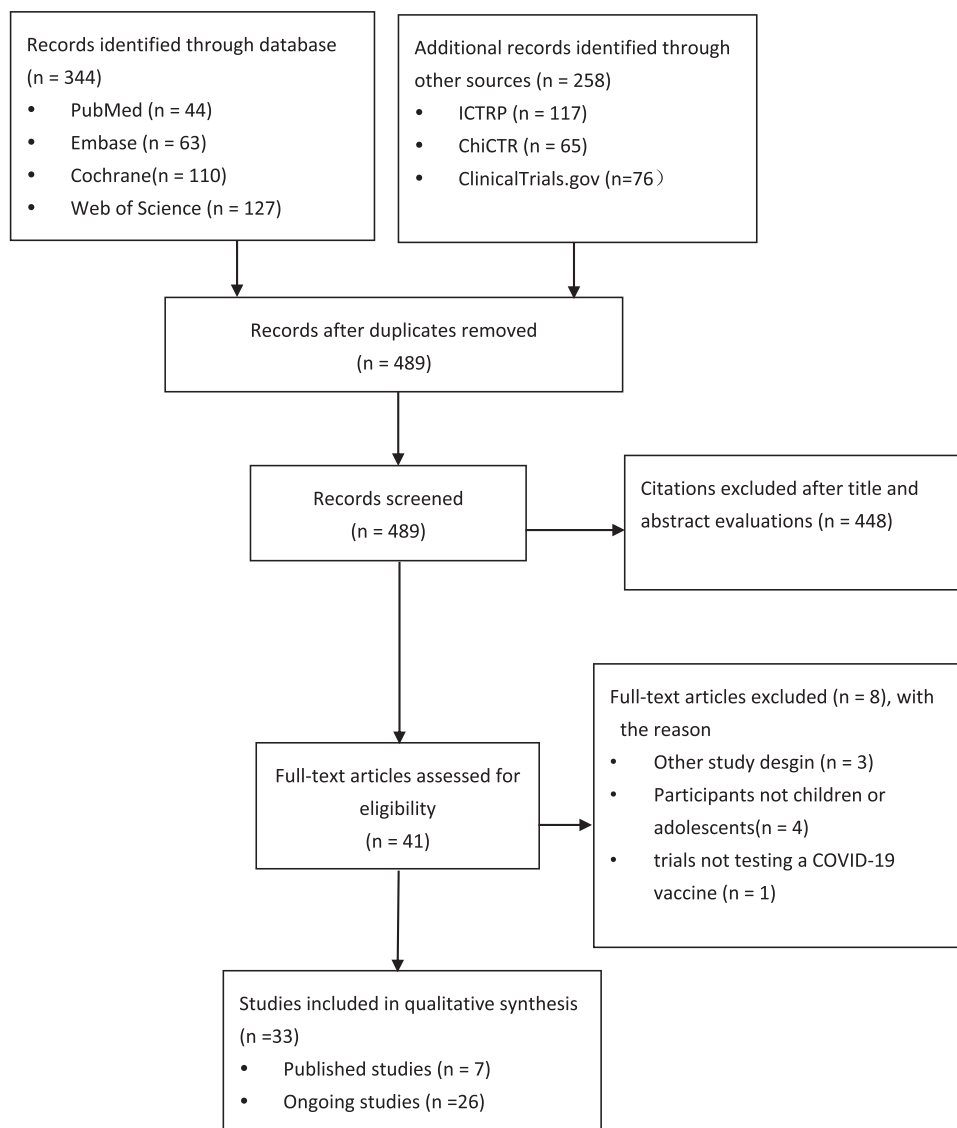
We performed a quality assessment of the included completed studies, and their bias risks are shown in Table 3. In some studies, incomplete outcome data reporting led to an unclear risk of attrition bias. However, all identified studies showed low risks of selection, performance, detection, and reporting biases as a result of the appropriate implementation of these RCTs, such as the use of interactive response technology systems, blinding of participants and investigators, and predesigned study protocols and outcome endpoints. In conclusion, the methodological quality of the included studies was high, and the risk of bias was low.

## 3.3 | Safety and efficacy of the COVID-19 vaccines

### 3.3.1 | RNA vaccines

We pooled three published studies evaluating the safety and efficacy of mRNA vaccines against COVID-19 in participants aged 5–17 years old, which contained two studies on the BNT162b2 vaccine and one study on the mRNA-1273 vaccine.

Frenck et al.<sup>15</sup> reported that the incidence of overall AEFI in the BNT162b2 vaccine and placebo groups was 6.0% and 5.9%, respectively. Similarly, Walter et al.<sup>16</sup> reported a 10.9% overall AEFI incidence in the BNT162b2 vaccine group compared to 9.2% in the placebo group. Two studies both indicated that there existed similar rates of overall AEFI between the BNT162b2 and placebo group, though they didn't provide the exact P-values. In the mRNA-1273 vaccine group, Ali et al.<sup>17</sup> found a significantly increased incidence of adverse reactions after vaccination in mRNA-1273 vaccine recipients (Dose 1: 95.9%; Dose 2: 97.1%) compared with placebo recipients (Dose 1: 65.1%; Dose 2: 55.7%). Each included study showed that mRNA vaccine recipients reported more local and systemic events than placebo recipients. We also found that common systemic events were generally reported more often after mRNA vaccine Dose 2 than after Dose 1. The most common local and systemic events of children



**FIGURE 1** Diagram of the literature selection.

and adolescents comprised injection site pain, fatigue, and headache. Most adverse events were mild and moderate in severity and typically lasted transiently (resolved within 4 days, mRNA-1273 vaccine > BNT162b2 vaccine). No case reports of a multisystem inflammatory syndrome in children (MIS-C), myocarditis, pericarditis disease, or death were noted.

Efficacy was obtained by monitoring the incidence of COVID-19 cases after the second dose. Of the two RCTs on the efficacy of the BNT162b2 vaccine,<sup>15,16</sup> one study observed 100% (95% CI = 75.3–100, without evidence of the previous infection<sup>17</sup>; 95% CI = 78.1–100, with or without evidence of previous infection) efficacy, and the other study reported 90.7% (95% CI = 67.7–98.3, without evidence of the previous infection; 95% CI = 67.4–98.3, with or without evidence of previous infection) efficacy. Additionally, an RCT on the mRNA-1273 vaccine<sup>17</sup> reported 93.3% (95%

CI = 67.7–98.3) protection against COVID-19 infection among an aged 12–17 per-protocol population.

### 3.3.2 | Inactivated virus vaccine

Two published studies examined the safety of inactivated vaccines in children and adolescents. They were both conducted in China and targeted the pediatric population aged 3–17 years old, but the inactivated vaccine they used for the vaccine group was different (CoronaVac vs. BBIBP-CorV vaccine).

The results of Han's study<sup>18</sup> showed that the incidence of overall AEFI ranged from 18% to 35% after vaccination within 28 days and was highest in participants aged 12–17 years, but there was no significant difference in the incidence of overall AEFI between the

TABLE 1 Characteristics of the included published studies (n = 7)

Article	Clinical trials registration	Phase	Location	Vaccine name	Vaccine type	Age range	Sample size		Male(%)	Follow-up duration	Number of doses & schedule
							Intervention group	Control			
Freneck, et al. <sup>15</sup>	NCT04368728	III	The United States	BNT162b2	RNA vaccine	Aged 12–15 years	1131	1129	51.00	4.7 months	2 doses Day 0, 21
Walter, et al. <sup>16</sup>	NCT04816643	I/II/III	the United States, Spain, Finland, Poland	BNT162b2	RNA vaccine	Aged 5–11 years	1565	751	52.10	2.3 months	2 doses Day 0, 21
Ali, et al. <sup>17</sup>	NCT04649151	II/III	The United States	mRNA-1273	RNA vaccine	Aged 12–17 years	2489	1243	51.00	4.6 months	2 doses Day 0, 28
Han, et al. <sup>18</sup>	NCT04551547	I/II	China	CoronaVac	Inactivated vaccine	Aged 3–17 years	436	114	53.80	4.1 months	2 doses Day 0, 28
Xia, et al. <sup>19</sup>	ChiCTR2000032459	I/II	China	BBIBP-CoV	Inactivated vaccine	Aged 3–17 years	755	252	52.08	NR*	3 doses Day 0, 28, 56
Zhu, et al. <sup>20</sup>	NCT04566770	IIb	China	Ad5-nCoV	Adenovirus vaccine	Aged 6–17 years	100	50	52.67	NR	2 doses Day 0, 56
Khobragade, et al. <sup>21</sup>	CTRI/2021/01/030416	III	India	ZyCov-D	DNA vaccine	Aged 12–17 years	448	487	NR	11 months	3 doses Day 0, 28, 56

\*Not reported.

TABLE 2 Characteristics of included ongoing studies (n = 26)

Clinical trials registration	Status	Phase	Center	Location	Vaccine name	Vaccine type	Age range	Sample size
NCT05013983	Not yet recruiting	I/II	Single-center	China	Sf9 Cells	Recombinant vaccine	Aged 6-17 years	600
NCT05330871	Not yet recruiting	II	Single-center	China	Ad5-nCoV	Adenovirus vaccine	Aged 6-17 years	410
NCT04961359	Recruiting	I	Single-center	China	CHO cell	Recombinant vaccine	Aged 3-17 years	75
NCT04869592	Recruiting	I/II	Single-center	China	CHO cell	Recombinant vaccine	Aged 3-17 years	NR
NCT05193279	Not yet recruiting	II/III	Multicenter	Colombia	SCB-2019	Recombinant vaccine	Aged <18 years	3820
NCT05107557	Recruiting	IV	NR	China	Vero cell/EV71	Inactivated vaccine	Aged 3-5years	520
NCT04992260	Recruiting	III	Multicenter	Chile, Malaysia, Philippines, South Africa, Turkey	CoronaVac	Inactivated vaccine	Aged 6 months to 17 years	14 000
NCT04884685	Active, not recruiting	II	Single-center	China	CoronaVac	Inactivated vaccine	Aged 3-17 years	500
NCT05003479	Not yet recruiting	I	Single-center	China	Vero Cell	Inactivated vaccine	Aged 3-17years	84
NCT04551547	Active, not recruiting	I/II	Single-center	China	Vero Cell	Inactivated vaccine	Aged 3-17 years	552
NCT05003466	Not yet recruiting	II	Single-center	China	Vero Cell	Inactivated vaccine	Aged 3-17 years	480
NCT05230940	Recruiting	IIb	Multicenter	Turkey	TURKOVAC/CoronaVac	Inactivated vaccine	Aged 16-18 years	644
NCT05225285	Recruiting	III	Single-center	Brazil	Coronavac/BNT162b2	Inactivated vaccine/mRNA vaccine	Aged 3-17 years	960
NCT05298644	Not yet recruiting	II/III	NR	NR	VLA2001	Inactivated vaccine	Aged 2-12 years	1720
NCT04954092	Recruiting	II/III	NR	Russian Federation	GamCOVID-Vac M	Combined Vector Vaccine	Aged 12-17 years	3000
NCT05345873	Not yet recruiting	II	NR	NR	SCTV01E/mRNA-1273	RNA vaccine	Aged 12-17 years	300
NCT04796896	Recruiting	II/III	Multicenter	United States, Canada	mRNA-1273	RNA vaccine	Aged 6 months to 12 years	13 575
NCT04951388	Active, not recruiting	II	Multicenter	China	MVC-COV1901	Subunit vaccine	Aged 12-18 years	399
NCT04773067	Active, not recruiting	II	Multicenter	China	UB-612	Multitope Protein/Peptide Vaccine	Aged 12-18 years	385
TCTR2020125002	Not yet recruiting	II	NR	Thailand	BNT162b2	RNA vaccine	Aged 5-12 years	400
TCTR20210917004	Recruiting	II	NR	Thai	BNT162b2	RNA vaccine	Aged 12-18 years	120
IRCT20171122037571N3	Recruiting	I/II	Single-center	Iran	CovIran-Barkat	Inactivated vaccine	Aged 12-18 years	500

(Continues)

TABLE 2 (Continued)

Clinical trials registration	Status	Phase	Center	Location	Vaccine name	Vaccine type	Age range	Sample size
CTRI/2021/10/037564	Not yet recruiting	II/III	Multicenter	Argentina, Brazil, Colombia, India, Mexico, South Africa, Turkey	Ad26. COV2.S	Recombinant vaccine	Aged 12–17 years	4350
CTRI/2021/10/037066	Recruiting	II/III	Single-center	India	CORBEVAX	Subunit vaccine	Aged 7–18 years	624
CTRI/2021/02/031554	Recruiting	II/III	Multicenter	India	COVOVAX	Recombinant vaccine	Aged 2–17 years	920
RPCEC00000381	Not yet recruiting	I/II	NR	Cuba	ABDALA	Recombinant vaccine	Aged 3–18 years	592

CoronaVac vaccine and control groups in each age group. Xia et al.<sup>19</sup> reported that the incidence of overall AEFI was less than 35% for each age group, but there was a higher risk of AEFI in the BBIBP-CorV vaccine group (6–12 years group: 25.79%; 13–17 years group: 34.13%) than in the control group (6–12 years group: 5.95%; 13–17 years group: 17.86%) in participants aged 6–17 years old. The most common adverse events for the inactivated vaccine were mild and moderate injection site pain, fever, and cough. Except for a higher prevalence of injection site pain in the vaccine group than in the placebo group, the prevalence of other local and systemic adverse events between groups was not observed to be significantly different in either study. In addition, no deaths or related serious adverse events were reported. The included RCTs on inactivated vaccines did not assess vaccine efficacy.

### 3.3.3 | Adenovirus vector vaccine

One published study was included in this article. This is a Phase 2b RCT conducted in China evaluating the safety of an adenovirus vector vaccine (Ad5-nCoV) in 150 participants aged 6–17 years.<sup>20</sup> From this article, a 69% overall AEFI incidence was observed within 14 days after vaccination, and the rate of overall AEFI in the vaccine group was significantly higher than that in the placebo group (22%). In contrast to the RNA vaccine, fewer adverse events were reported in the adenovirus vector vaccine group following Dose 2 than after Dose 1. The most common adverse events were injection-site pain, fever, headache, and fatigue. Most adverse events were not severe and self-limiting. Among local and systemic adverse events, only the prevalence of injection site pain, fever, and headache were higher in the vaccine group than in the placebo group. A few related serious adverse events, such as severe fever and gastrointestinal disorders, were reported in the vaccine group. In addition, we also found an ongoing single-center, open-label RCT that aims to determine the safety and immunogenicity of Ad5-nCoV vaccines for booster use in children and adolescents aged 6–17 years. The included RCTs on adenovirus vector vaccine vaccines did not assess vaccine efficacy.

### 3.3.4 | DNA vaccine

One published study from India was identified. It is a multicenter Phase 3 double-blind, randomized, placebo-controlled trial.<sup>21</sup> The interim results of healthy participants aged 12–17 years ( $n = 935$ ) were analyzed to report the safety of ZyCoV-D in this age group.

The occurrence of overall AEFI in the ZyCoV-D groups was 3.13% after the first dose, which was no different compared with the placebo group (1.44%). After vaccinations, the most frequently reported solicited local adverse reactions were of mild to moderate intensity (including injection-site pain, redness, swelling, and itching). Systemic adverse reactions were of mild to moderate intensity, and the most reported events comprised headache, fever, muscle pain, and fatigue. These events were similar between the ZyCoV-D and



**TABLE 3** Quality assessment of included studies

Study	Selection bias		Performance bias Blinding of participants and personnel	Detection bias Blinding of outcome assessment	Attrition bias Incomplete outcome data	Reporting bias		Total score (max = 7)
	Random sequence generation	Allocation concealment				Selective reporting	Other bias	
Frenck et al. <sup>15</sup>	+	+	+	+	?	+	+	6
Walter et al. <sup>16</sup>	+	+	+	+	?	+	+	6
Ali et al. <sup>17</sup>	+	+	+	+	+	+	+	7
Han et al. <sup>18</sup>	+	+	+	+	+	+	+	7
Xia et al. <sup>19</sup>	+	+	+	+	+	+	?	6
Zhu et al. <sup>20</sup>	+	+	+	+	+	+	-	6
Khobragade et al. <sup>21</sup>	+	+	+	+	+	+	?	6

placebo groups. In the vaccine group, fewer common local and systemic adverse events were reported after Doses 2 and 3 than after Dose 1. Fifteen serious adverse events and two deaths were reported, and the serious adverse events were reported in both groups, but none of them was considered causally related to vaccination.

Efficacy will be assessed based on the number of COVID-19 infections. In this study, the efficacy of the ZyCoV-D vaccine in 12- to 17-year-old adolescents was not reported, but for participants included in the effectiveness assessment, 66.6% (95% CI = 47.6–80.7) efficacy was reported after the whole vaccination procedure.

## 4 | DISCUSSION

Although more than two years have passed away, the COVID-19 pandemic has not been fully controlled and remains a huge threat to global public health. To date, numerous variants of SARS-CoV-2 strains are frequently emerging and evolving, especially the Omicron variant, which plays a dominant role, making the situation more complicated.<sup>22</sup> Compared with healthy peers, children and adolescents who are infected with SARS-CoV-2 are more likely to develop complications such as MIS-C and diabetes.<sup>23</sup> Therefore, it is necessary to vaccinate children and teens against COVID-19 so that they can gain immunity. However, more influencing factors should be considered when administering vaccines to this age group given their special nature. Generally, vaccine safety and efficacy are the most important considerations for young people and their parents.<sup>24</sup> To examine the safety and efficacy of COVID-19 vaccines in this vulnerable population, our study conducted a comprehensive review using specific data from published and ongoing high-quality RCTs, which will promote the massive use of COVID-19 vaccines among children and adolescents.

An adverse event following immunization (AEFI) is a common indicator of vaccine safety. It may be any unfavorable or unintended

sign, abnormal laboratory findings, symptoms, or disease.<sup>25</sup> According to the location of occurrence, AEFIs can be classified into local adverse events and systemic adverse events, and according to the severity, they can be classified into common, minor events, or rare and more serious events.<sup>25</sup> Currently, in clinical application, AEFIs are inevitable with any vaccine, and the exact mechanism of the adverse events by vaccination is unclear, although some studies emphasized that it might be related to nonspecific immune responses by the components of vaccines (e.g., adjuvant, stabilizers, or preservatives).<sup>26</sup> Therefore, it is very important to demonstrate a good safety profile before administering COVID-19 vaccines to children and adolescents. In this review, we synthesized the safety data of seven published RCTs and found that COVID-19 vaccines have shown good safety in the child and adolescent populations. The overall, local, and systemic AEFIs reported in most trials were similar between the vaccine and placebo groups, suggesting that adverse events after injection probably had no correlation with COVID-19 vaccines. Most adverse reactions were mild and moderate, with few severe reactions that were unrelated to the test vaccine. The common adverse events were injection-site pain, fever, headache, cough, fatigue, and muscle pain. Serious adverse events were reported in two trials: adenovirus vector vaccine (Ad5-nCoV)-two related to the testing vaccine and DNA vaccine (ZyCoV-D)-17 with none related to the vaccine. The above conclusions can also be found in other clinical trials and published papers limited to the general population,<sup>26–29</sup> suggesting that there is great similarity in the safety of COVID-19 vaccines between young people and adults.

Efficacy is an important indicator of the protection of a vaccine. Due to the limited quantity of included studies, our article only explored the efficacy of RNA vaccines against COVID-19 among children and adolescents. RNA vaccines, for their advantages, such as high versatility, rapid adaptation, and ease of manufacture, have received widespread attention in the development of COVID-19 vaccines.<sup>27,30</sup> As of March 2022, 25 anti-SARS-CoV-2 candidate RNA vaccines have been tested in clinical trials.<sup>31</sup> Of them, mRNA-1273 (developed by Moderna) and BNT162b (developed by Pfizer and BioNTech Ltd.) was the first vaccines



approved for emergency use in many countries.<sup>32</sup> They are lipid nanoparticle-formulated, nucleoside-modified RNA vaccines that encode a full-length SARS-CoV-2 spike protein.<sup>33,34</sup> Essentially, a piece of the sequenced genetic code of the virus is encoded within a fat molecule. This instructs the cell to make the spike protein displayed on the surface of SARS-CoV-2 cells (antigen), thus initiating an immune response resulting in antibody production and mobilization of T cells, conferring protection against further exposure to SARS-CoV-2.<sup>35</sup> A previous study showed that full vaccination of adults with mRNA vaccines provided 91% and partial vaccination with such vaccines provided 81% efficacy on protection against COVID-19.<sup>36</sup> In this review, RNA vaccines exhibited over 90% efficacy after the second dose in clinical trials of young people aged 5–17 years,<sup>15–17</sup> demonstrating that the policy of mass vaccination of children and adolescents is reasonable and feasible. Additionally, the BNT162b vaccine was found to be 92%, 93%, and 91% efficacious in preventing SARS-CoV-2 infection, COVID-19 hospitalization, and multi-system inflammatory syndrome among people aged 12–18 years based on data from real-world conditions.<sup>37–39</sup>

This study's key strength is that it is the first, as far as we know, a systematic review of high-quality RCTs on the safety and efficacy of COVID-19 vaccination in children and adolescents. Compared with other related reviews, more complete published and ongoing RCTs were included in this article. In addition, we conducted rigorous quality assessment procedures to reduce occasional bias. However, this review also has some limitations. Due to the lack of available clinical trials, vaccine efficacy data in the pediatric age group for the inactivated adenovirus vector and DNA vaccines could not be included. We could also not assess the long-term safety and efficacy against SARS-CoV-2 in the vaccinated young population. Furthermore, due to the heterogeneity in different trials, we could not perform a meta-analysis. Therefore, the safety and efficacy of COVID-19 vaccination in children and adolescents still require large and high-quality studies for further confirmation.

## 5 | CONCLUSION

Based on the systematic analysis of the published safety data of the four COVID-19 vaccines, we concluded that the safety of current COVID-19 vaccines for children and adolescents is acceptable. The mRNA vaccine exhibited high efficacy in this age group.

### AUTHOR CONTRIBUTIONS

Ruonan Yang: Developing design, literature search, and manuscript writing. Ruonan Yang and Fangyuan Tian: Developing design, literature search, manuscript writing, and analysis of results. All authors read and approved the final manuscript.

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### CONFLICT OF INTEREST

The authors declare no conflict of interest.

### DATA AVAILABILITY STATEMENT

The data set will be available upon request unless there are legal or ethical reasons for not doing so.

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