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Review

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Efficacy and Safety of COVID-19 Vaccines in Adolescents: Systematic Review of Randomized Controlled Studies and Observational Studies

Soo-Han Choi,[1,*] **Su-Yeon Yu**,[2,*] **Jimin Kim**,[3] **Miyoung Choi**,[3] **Youn Young Choi**,[4] **Jae Hong Choi**,[5] **Ki Wook Yun**,[6] **Young June Choe**[7]

[1]Department of Pediatrics, Pusan National University Hospital, Pusan National University School of Medicine, Busan, the Republic of Korea
[2]Department of Pharmacy, College of Pharmacy, Kangwon National University, Chuncheon, the Republic of Korea
[3]Division of Healthcare Technology Assessment Research, National Evidence-based Healthcare Collaborating Agency, Seoul, the Republic of Korea
[4]Department of Pediatrics, National Medical Center, Seoul, the Republic of Korea
[5]Department of Pediatrics, Jeju National University School of Medicine, Jeju, the Republic of Korea
[6]Department of Pediatrics, Seoul National University College of Medicine, Seoul, the Republic of Korea
[7]Department of Pediatrics, Korea University Anam Hospital, Seoul, the Republic of Korea

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Correspondence to
Young June Choe
Department of Pediatrics, Korea University Anam Hospital, 73 Goryeodae-ro, Seongbuk-gu, Seoul 02841, the Republic of Korea.
Email: choey@korea.ac.kr

*Soo-Han Choi and Su-Yeon Yu contributed equally to the manuscript.

ORCID iDs
Soo-Han Choi
https://orcid.org/0000-0003-2449-3025
Su-Yeon Yu
https://orcid.org/0000-0001-5488-5068

ABSTRACT

The number of pediatric coronavirus disease 2019 (COVID-19) cases worldwide are increasing compared to the early phase of the pandemic, along with highly transmissible severe acute respiratory syndrome coronavirus variant and the increase in adult COVID-19 vaccination. We conducted a rapid systematic review and meta-analysis of published randomized clinical trials (RCTs) of the COVID-19 vaccines and the observational retrospective studies on adverse events after COVID-19 vaccination in adolescents. Seventeen studies were finally included in this systematic review. Meta-analysis showed that although vaccination in adolescents was significantly effective to prevent COVID-19 infection in retrospective studies (risk ratio [RR], 0.29; 95% confidence interval [CI], 0.22–0.37; I^2=100%), however the effect of preventing COVID-19 infection was lower than in RCTs (RR, 0.05; 95% CI, 0.01–0.27). In five retrospective studies, the pooled estimated proportion of participants with myocarditis and/or pericarditis was 2.33 per 100,000 of the population (95% CI, 0.97–5.61 per 100,000). Sub-group analysis with sex and vaccine doses showed that male (5.35 per 100,000) and the second dose (9.71 per 100,000) had significantly higher incidence of myocarditis and/or pericarditis than female (1.09 per 100,000) and the first dose (1.61 per 100,000), respectively. Our study showed that mRNA COVID-19 vaccines in adolescent recipients were favorable and effective against COVID-19 in RCT as well as observational studies. The safety findings of BNT162b2 vaccine in adolescents were explored and we found the difference of safety according to sex and vaccine doses. The occurrence of adverse events after mRNA COVID-19 vaccination should be monitored.

Keywords: COVID-19 vaccines; Adolescent; Systematic review; Meta-analysis

Jimin Kim
https://orcid.org/0000-0001-7375-4274
Miyoung Choi
https://orcid.org/0000-0002-2424-9965
Youn Young Choi
https://orcid.org/0000-0001-8749-0951
Jae Hong Choi
https://orcid.org/0000-0003-3284-9407
Ki Wook Yun
https://orcid.org/0000-0002-0798-6779
Young June Choe
https://orcid.org/0000-0003-2733-0715

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INTRODUCTION

As of December 29, 2022, the coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was responsible for more than 651 million cases and 6.6 million deaths globally.[1] Vaccination against SARS-CoV-2 is critical to ending COVID-19 pandemic. Mass vaccination against COVID-19 was implemented in many parts of the world since mid-December 2020.[1-3] An Israeli study on nationwide mass vaccination in people aged 16 years or older suggested that the BNT162b2 mRNA vaccine was effective for a wide range of COVID-19-related outcomes, a finding consistent with that of the randomized trial.[4]

In general, children are at low risk for severe illness from COVID-19 compared with adults. However, the incidence of pediatric COVID-19 cases worldwide increased compared to the early phase of the pandemic, this may be attributed to the highly transmissible SARS-CoV-2 variants and the increase in adult COVID-19 vaccination.[5-7] In the US, COVID-19 associated hospitalization rates among children and adolescents were 10 times higher among unvaccinated than among fully vaccinated adolescents.[8] In addition, multisystem inflammatory syndrome in children is a rare but serious condition associated with COVID-19.

According to the World Health Organization (WHO), as of November 11, 2022, 172 vaccines were being evaluated in the clinical development stage.[3] Thirteen COVID-19 vaccines were approved for emergency use by WHO.[9,10] On May 10, 2021, the US Food and Drug Administration expanded the emergency use authorization for BNT162b2 vaccine to include adolescents 12 to 15 years of age.[11] The European Medicines Agency (EMA) approved to expand the use of BNT162b2 in the 12 to 15 years of age group on May 28, 2021.[12] Vaccination of children and adolescents can prevent severe COVID-19 at some certain high-risk groups. The expansion of COVID-19 vaccination for a younger population would be a critical step in continuing to reduce the immense public health burden caused by the COVID-19 pandemic.[11]

There is a lack of comprehensive data regarding pediatric COVID-19 vaccination. It is imperative to analyze the safety and efficacy of COVID-19 vaccines in pediatric population. We conducted a rapid systematic review and meta-analysis of published clinical trials of the COVID-19 vaccines in children and adolescents. In addition, we reviewed studies that analyzed real-world data on adverse events after COVID-19 vaccination in adolescents.

Previous studies had provided evidence of the effectiveness[13,14] and the safety of COVID-19 vaccination. However, some of them were published before the emergence of Omicron variant, in 2021,[15-18] or only randomized controlled trials (RCTs) were included to review.[19,20] Moreover, there remains some uncertainty regarding the up-to-date reviews of COVID-19 mRNA vaccine effectiveness and safety in adolescents, including real-world evidence. Summary of observational real-world data can inform the effectiveness and safety which RCTs did not capture. Furthermore, novel variants of concern are emerging continuously, and new research evidence is being updated. Therefore, the purpose of our study was to evaluate the effectiveness and safety of COVID-19 mRNA vaccine in adolescents.

METHODS

We systematically reviewed studies reporting vaccine efficacy from RCTs and effectiveness from observational studies with the comparison group, respectively. Additionally, the safety profile such as myocarditis and/or pericarditis was obtained from observational studies without the comparison group, in adolescent population. The systematic review was conducted with a meta-analysis in accordance with the recommendations by the Cochrane Handbook and the preferred reporting items for systematic review and meta-analysis (PRISMA) statement.[21] The protocol for this review was prospectively registered in the International Prospective Register of Systematic Reviews under the registration number CRD42022343659.

1. Search strategy

We systemically searched articles initially on August 13 of 2021 and searched again to update new evidence on May 13 of 2022 in literature databases including ovid-MEDLINE, ovid-Embase, the Cochrane Library, and hand searching. These databases were searched for medical subheading terms and free-text keywords (**Supplementary Data 1**).

2. Eligibility criteria and study selection

The key question of this study was "Is COVID-19 vaccination safe and effective for pediatric population aged 12–17 years. Articles that met the following criteria were included: 1) the subjects included adolescents and children aged 12–17 years; 2) interventions of mRNA COVID-19 vaccines; 3) the comparator was placebo or no vaccination; 4) outcomes including symptomatic laboratory-confirmed COVID-19, myocarditis, pericarditis, and serious adverse events (SAE); 5) the study was designed as a RCT or observational studies excluding case or case series studies. Only English and Korean studies were included in the meta-analysis.

Two review authors (SC and SY) independently and in duplicate evaluated publications for inclusion based on their titles and abstracts; these evaluations were performed in duplicates., and then reviewed relevant full-text articles. Disagreements during the review process were addressed by consensus with the involvement of a third review author (MC or YC).

3. Data extraction and methodological quality assessment

Two review authors (SY and JK) extracted information from each included trial. These evaluations were carried out independently and yielded separate assessments. The disagreement was resolved by discussion and third opinion (SC). The data extraction form included the following information: the first author, time of publication, study design, characteristics of study subjects, types of COVID-19 vaccine, and outcomes. Efficacy/effectiveness outcome was symptomatic laboratory-confirmed COVID-19 infection, and was extracted from RCTs and observational comparative studies. Safety outcomes were myocarditis, pericarditis, and SAE, and were extracted from observational single-arm studies.

Two researchers (SC and SY) independently assessed the quality of the selected studies using the Cochrane Risk of Bias tool (RoB) for randomized studies and the RoB Assessment for Non-randomized Studies (RoBANS) for non-randomized studies.[22]

4. Data synthesis and analysis

Relative risk ratios (RRs) of SARS-CoV2 infection were pooled with Mantel-Haenszel random-effects analysis using RCTs and observational comparative studies. The pooled proportions of

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participants experiencing adverse events following COVID-19 vaccination were estimated with random-intercept logistic regression model using retrospective single-arm study. Because the outcomes reported in each study had different follow-up period, the random effects model was used for all analyses to generate conservative effect estimates. Subgroup analysis was performed based on sex (male, female) and dose times (the first dose, the second dose). All outcomes were reported with their associated 95% confidence interval (CI) and were analyzed in R software (version 4.2.1) and Review Manager Software version 5.4.

The heterogeneity of effects was evaluated using Higgins I^2 statistics (I^2>50% indicating substantial heterogeneity).[23]

RESULTS

1. Description of included studies

A total of 1,392 articles were retrieved from the databases, resulting in 1,168 articles after excluding duplicates. According to the selection criteria, 128 articles were selected for full review. All selection steps are presented as PRISMA flowchart (**Fig. 1**). Seventeen studies were finally included in this systematic review: two RCTs,[24,25] fifteen observational retrospective studies.[26-40] Two RCTs evaluated the efficacy and safety of each mRNA COVID-19 vaccine: BNT162b2 (adolescents aged 12–15 years in the US, phase 3) and mRNA-1273 (adolescents aged 12–17 years in the US, phase 2/3). fifteen retrospective studies evaluated the efficacy and safety of BNT162b2 and the countries were Denmark, France, Hong Kong, Israel, Malaysia, South Korea, and the US.

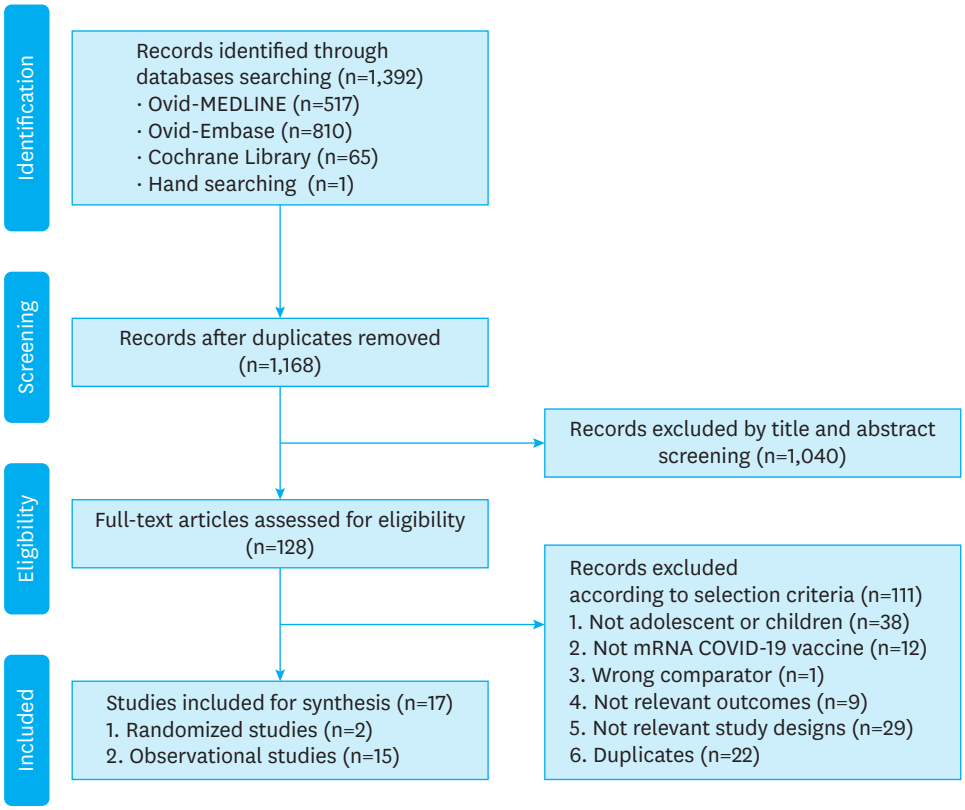

Fig. 1. Preferred reporting items for systematic reviews and meta-analyses study flowchart.
Abbreviation: COVID-19, coronavirus disease 2019.

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Table 1. Characteristics of included studies

Study	Study design	Vaccine (platform)	Study areas (countries)	Enrolled or vaccination periods	Age range	No. of adolescent participants (vaccine group) or study population	Predominant variant*	Analyzed outcomes
Frenck et al.[25] 2021	Randomized controlled trial (phase 3)	BNT162b2	US	2020.10.15–2021.01.12	12–15 yrs	2,260 (1,131)	Pre-Delta	Efficacy
Ali et al.[24] 2021	Randomized controlled trial (phase 2/3)	mRNA-1273	US	2020.12.09–2021.02.28	12–17 yrs	3,732 (2,489)	Pre-Delta	Efficacy
Fleming-Dutra et al.[27] 2022	Retrospective case-control	BNT162b2	US	2021.12.26–2022.02.21 (PCR test)	12–15 yrs ICATT	47,744 (22,977)	Omicron	Effectiveness
Husin et al.[29] 2022	Retrospective case-control	BNT162b2	Malaysia	2021.09.01–2021.12.31 (PCR test)	12–17 yrs	93,995 (28,703)	Delta	Effectiveness
Oliveira et al.[34] 2022	Retrospective case-control	BNT162b2	US	2021.06.01–2022.09.15 (PCR test)	12–18 yrs Connecticut	542 (154)	Delta	Effectiveness
Price et al.[38] 2022	Retrospective case-control	BNT162b2	US	2021.07.01–2022.02.17 (study)	12–18 yrs 31 hospitals in 23 states	2,275 (664)	Delta, Omicron	Effectiveness
Powell et al.[37] 2022	Retrospective case-control	BNT162b2	UK	2021.09.13–2022.01.12	12–17 yrs	842,969 (280,009)	Delta, Omicron	Effectiveness
Glatman-Freedman et al.[28] 2021	Retrospective case-control	BNT162b2	Israel	2021.06.02–2021.08.26 (vaccination)	12–15 yrs	15,657,205 (2,033,491)†	Delta	Effectiveness
Dorabawila et al.[26] 2022	Retrospective cohort	BNT162b2	US	2021.12.13–2022.01.21 (vaccination)	12–17 yrs New York	(852,384) 8,956,304	Omicron	Effectiveness
Veneti et al.[39] 2022	Retrospective cohort	BNT162b2	Norway	2021.08.25–2022.01.16 (vaccination)	12–17 yrs	372,179 (291,511)	Delta, Omicron	Effectiveness
Choe et al.[30] 2022	Retrospective cohort	BNT162b2	South Korea	2021.07.19–2021.09.25 (vaccination)	16–18 yrs	1,746,742 (883,401)	Delta	Effectiveness Myocarditis/ pericarditis Serious adverse events
Kim et al.[40] 2021	Retrospective cohort	BNT162b2	South Korea	2021.10.18–2021.11.20 (vaccination)	12–17 yrs	(1,084,478)	Delta	Myocarditis/ pericarditis Serious adverse events
Lai et al.[31] 2022	Retrospective cohort	BNT162b2	Hong Kong	2018.1.1–2021.09.30 (vaccination)	12–18 yrs	(131,418)	Delta	Serious adverse events
Lee et al.[17] 2022	Retrospective cohort	BNT162b2	Hong Kong	2021.03.10–2021.10.18 (vaccination)	12–17 yrs	(224,560)	Delta	Myocarditis/ pericarditis
Nygaard et al.[33] 2022	Retrospective cohort	BNT162b2	Denmark	2021.05.15–2021.09.15 (vaccination)	12–17 yrs	(261,334)	Delta	Myocarditis/ pericarditis
Ouldali et al.[36] 2022	Retrospective cohort	BNT162b2	France	2021.06.15–2022.01.01 (vaccination)	12–17 yrs	(8,113,058)	Delta	Myocarditis/ pericarditis
Oster et al.[35] 2022	Retrospective cohort	BNT162b2	US	2020.12–2021.08 (vaccination)	12–17 yrs VAERS	0.84–105.86‡	Delta	Myocarditis/ pericarditis

Abbreviation: PCR, polymerase chain reaction.
*If there was no information about variants of concern in the study, we cited the variants statistics by country and time (www.ourworldindata.org).
†Person year.
‡Reported cases per million doses of vaccine administered.

Specific characteristics of studies included are presented in **Table 1**. The results of the risk of bias summary are shown in **Supplementary Figs. 1** and **2**. RCTs showed low risks of bias, while most retrospective studies showed unclear risks of bias due to no blindness, incomplete outcome and selective outcome reporting.

2. Efficacy/effectiveness of COVID-19 vaccines

In RCTs, the efficacy of COVID-19 vaccination in adolescents was assessed in the two clinical trials of mRNA vaccine: BNT162b2 and mRNA-1273 respectively.[24,25] In a meta-analysis,

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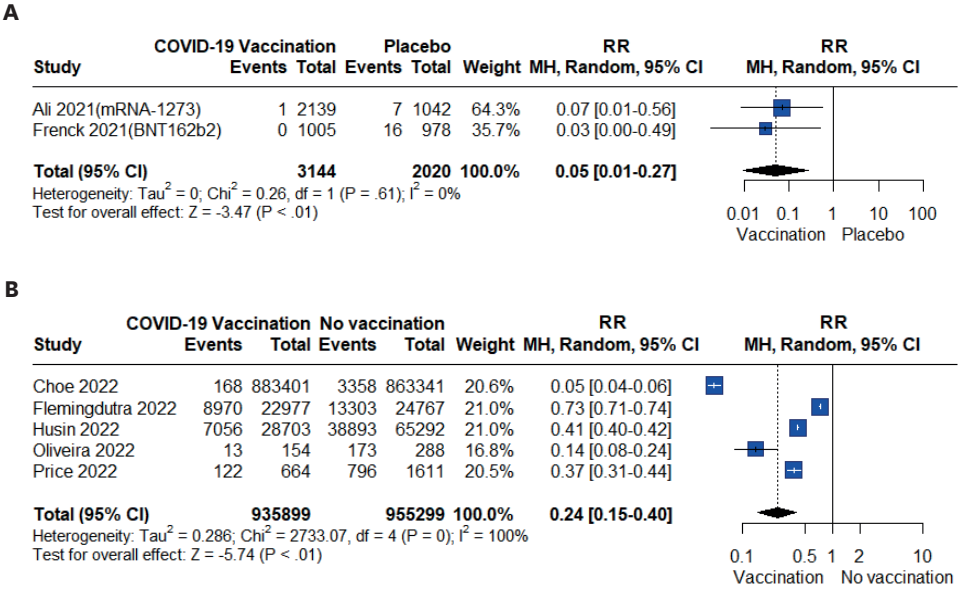

Fig. 2. Forest plot of symptomatic laboratory-confirmed COVID-19 from (A) randomized controlled trials; and (B) observational studies.
Abbreviations: COVID-19, coronavirus disease 2019; RR, risk ratio; CI, confidence interval.

symptomatic laboratory-confirmed COVID-19 cases in vaccine group was significantly lower than that in placebo group (RR, 0.05; 95% CI, 0.01–0.27), 95% as vaccine efficacy (**Fig. 2**).

Nine observational studies reported symptomatic laboratory-confirmed COVID-19 infection following BNT162b2 vaccination in adolescents, with the comparator group. Five studies among them provided raw data to be included in meta-analysis. Meta-analysis showed that although vaccination in adolescents was significantly effective in retrospective studies, however the effect of preventing COVID-19 infection was lower than in the RCTs (RR, 0.24; 95% CI, 0.15–0.40; I^2=100%) (**Fig. 3**).

There were four studies not included in meta-analysis and reported vaccine effectiveness from 53% to 85%, which were similar to our results from meta-analysis.[26,28,37,39]

3. Safety of COVID-19 vaccines in observational retrospective studies

Five retrospective studies reported myocarditis and/or pericarditis post-BNT162b2 vaccination in adolescents. The pooled estimated incidence of participants with myocarditis and/or pericarditis was 2.33 per 100,000 of the population (95% CI, 0.97–5.61 per 100,000; I^2=97%) (**Fig. 4**).

Sub-group analysis with sex and doses was followed. BNT162b2 vaccination showed different effects on myocarditis and/or pericarditis between male and female. Male subjects had significantly higher incidence of myocarditis and/or pericarditis than female subjects (*P*-value=0.028): male 5.35 per 100,000 (95% CI, 1.72–16.61 per 100,000; I^2=99%), female 1.09 per 100,000 (95% CI, 0.46–2.55 per 100,000; I^2=80%). In addition, while the proportion of myocarditis and/or pericarditis after the first dose was estimated to 1.61 per 100,000 (95% CI, 0.80–3.22 per 100,000; I^2=77%), the proportion after the second dose increased to 9.71 per 100,000 (95% CI, 3.10–30.44 per 100,000; I^2=97%) (*P*-value=0.008).

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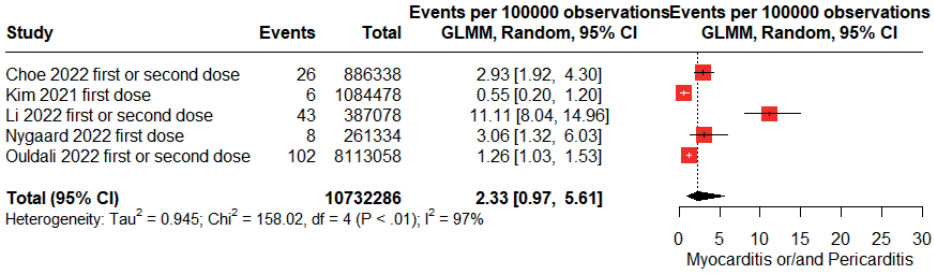

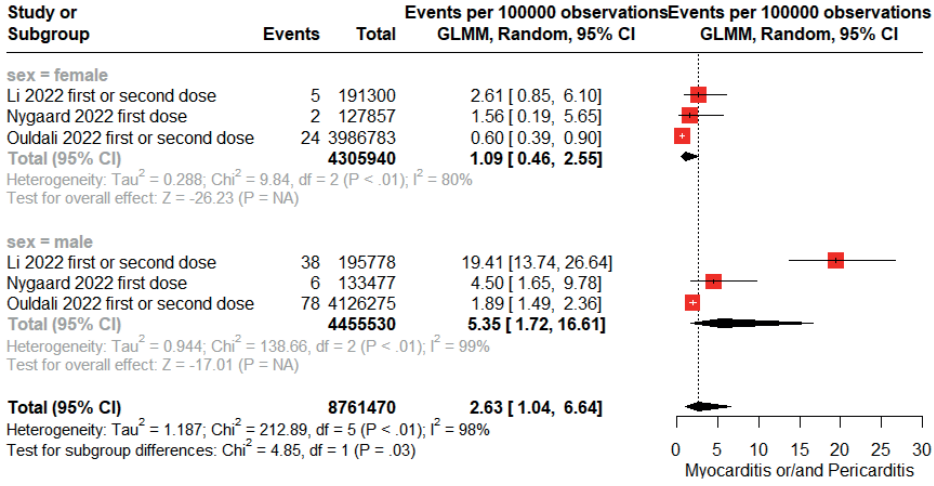

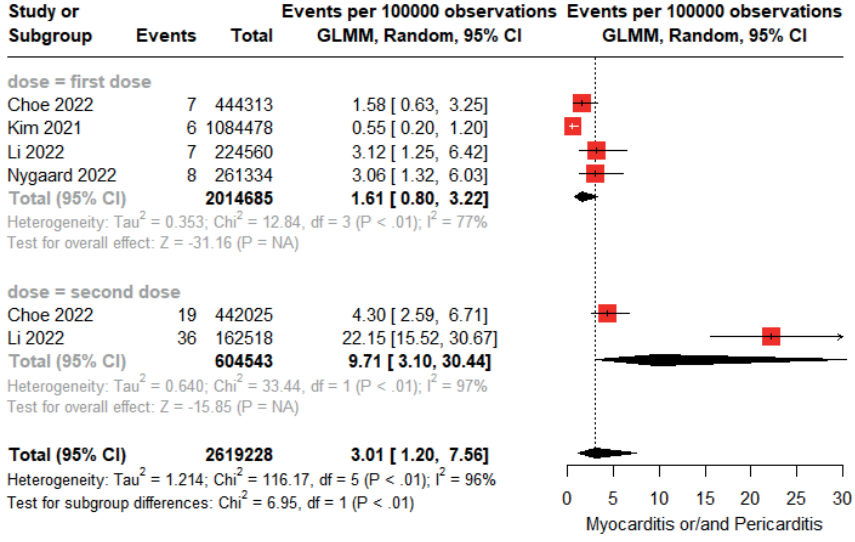

Fig. 3. Forest plot of myocarditis or/and pericarditis in observational studies for all population, by gender, and by number of doses.
Abbreviations: GLMM, generalized linear mixed model; CI, confidence interval.

SAE was reported in three retrospective single-arm studies. The pooled proportions of participants with SAE were 11.95 and 29.97 per 100,000 after the first dose and the second dose administered, respectively, which were not significantly different (the first dose: 95% CI, 4.86–29.3 per 100,000, I^2=97%; the second dose: 95% CI, 9.26–96.94; I^2 99%; *P*-value=0.222).

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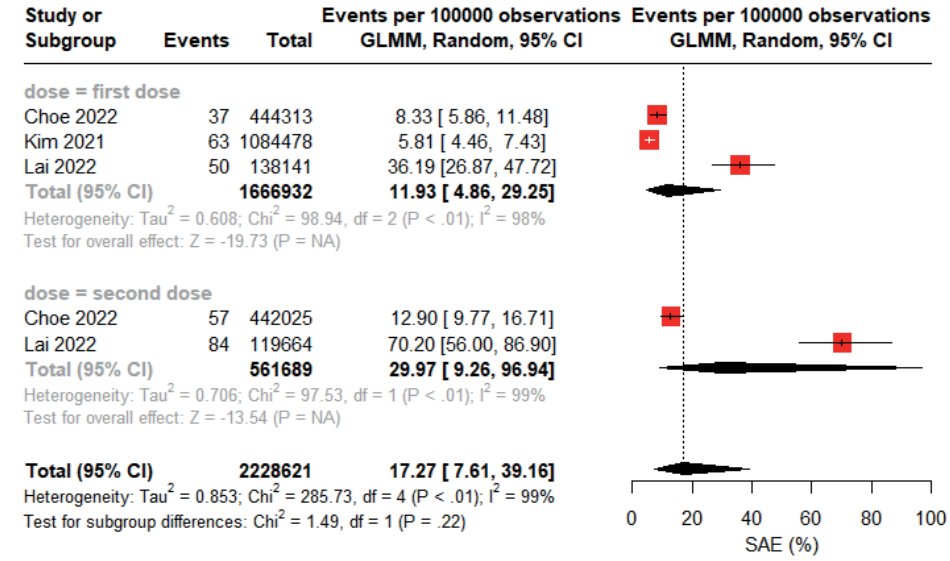

Fig. 4. Forest plot of serious adverse events in observational studies.
Abbreviations: GLMM, generalized linear mixed model; CI, confidence interval.

DISCUSSION

This study analyzed the efficacy, and safety of COVID-19 vaccines in adolescents aged 12–17 years using data of clinical trials and observational studies from real-world data reported by May 13, 2022. We performed the meta-analysis of data for comprehensive evaluation of mRNA vaccines in adolescents. Our research noted that COVID-19 vaccines in adolescent recipients produced effective against COVID-19, and the efficacy from clinical trials was higher than from observational study. In observational studies, the safety data of mRNA vaccines showed that myocarditis or pericarditis occurred more in male than female and more SAE occurred after the first dose of vaccine than the second dose.

As of May 13, 2022, among of the studies published the results of pediatric clinical trials data including 12–17 years old, only two studies of mRNA vaccines (BNT162b2 and mRNA-1273) reported phase 3 clinical trial results. In addition, the efficacy of two mRNA vaccines after the second dose was favorable and the safety profiles were acceptable in the studies.

The issues of the safety of COVID-19 vaccines have a significant impact on the vaccine hesitancy of parents and adolescents. The association between the development of myocarditis and mRNA COVID-19 vaccinations has been identified in multiple surveillance systems. Witberg et al.[41] reported that the estimated incidence per 100,000 person who had received at least one dose of BNT162b mRNA vaccine was 2.13 cases (95% CI, 1.56–2.70) in Israel and the highest incidence in male between the ages of 16–29 years. The Advisory Committee on Immunization Practices conducted a risk-benefit assessment, and the benefits still clearly outweigh the risks for COVID-19 vaccination in adolescents and young adults.[42]

From July 19 to September 25, 2021, COVID-19 vaccinations were conducted for high school seniors in South Korea. A total of 444,313 students received BNT162b2 vaccine, and 442,025 completed the second vaccination. A total of 3,981 AEs were reported, showing a 0.45% report rate of adverse reactions compared to the total number of vaccinations (0.29% of

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primary vaccinations and 0.61% of adverse reactions of secondary vaccinations). This was similar to the level of 0.45% to 0.48%, which is the level of reporting adverse reactions after BNT162b2 vaccination among young adults aged 20–39 years.[43]

As of October 6, 2021, 13 studies were registered on ClinicalTrials.gov with phase 2/3 or higher phase clinical trials for children and adolescents (including the age from 6 months).[44] Of these clinical trials, there were four types of vaccine platform (inactivated, RNA based [mRNA], protein subunit and non-replicating viral vector) and eight types of vaccine (inactivated: CoronaVac, BIBP-CorV, Covaxin and VLA2001; RNA based: BNT162b2 and mRNA-1273; protein subunit: NVX-CoV2373 [Novavax]; non-replicating viral vector: Gam-COVID-vac [Sputnik V]). The manufacture of BNT162b vaccine announced positive results from clinical trial in children aged 5–11 years on September 20, 2021.[45] The data from phase 2/3 study, which is enrolling children 6 months to 11 years of age, was for 2,268 participants who were 5 to 11 years of age and received a 10 μg dose level in a two-dose regimen. In the trial, the geometric mean titer of neutralizing antibody was 1,197.6 (95% CI, 1,106.1–1,296.6), demonstrating strong immune response in this cohort of children one month after the second dose and non-inferior comparing with participants ages 16 to 25 years old. Further, BNT162b2 vaccine was well tolerated in this age group, with side effects generally comparable to those observed in participants 16 to 25 years of age.

Although it varies depending on the countries or regions, the use of mRNA vaccines in children has been gradually expanding. The American Academy of Pediatrics recommends COVID-19 vaccination for all infants, children and adolescents 6 months of age and older who do not have contraindications for using a COVID-19 vaccine authorized for use for this age group.[46] Heath Canada authorized two mRNA COVID-19 vaccines, BNT162b2 and mRNA-1273, for youth aged 12 and older on May 5 and August 27, 2021, respectively. Canadian National Advisory Committee on Immunization recommends mRNA COVID-19 vaccine children 6 months of age and older who do not have contraindications to the vaccine.[47] In addition to BNT162b2 vaccine, the EMA approved an extension of indication for mRNA-1273 vaccine to include use in children aged 12–17 years in the European Union on July 23, 2021.[48] In the United Kingdom, the Joint Committee on Vaccination and Immunisation recommends BNT162b2 vaccine to all 5 to 17 years old.[49] In South Korea, approval of vaccination age for BNT162b2 was extended to 12 years or older on July 16, 2021,[50] and COVID-19 vaccinations had been sequentially implemented for children and adolescents aged 12 years or older since November, 2021.[51] For the decision of whether to include children and adolescents in national COVID-19 vaccination program, the government authorities usually consider a number of factors such as national prioritization strategies, the risks and benefits of COVID-19 vaccination in different age groups of adolescents, and the epidemiological situation.[52] Continued monitoring of adverse events after COVID-19 vaccination in children and adolescents would be important.

Our study had several limitations. First, there were only two RCTs to examine the effect of mRNA vaccination in adolescents' population. Therefore, we also included retrospective studies in our study and determined real-world health outcomes. Second, although the meta-analysis with two RCTs show less heterogeneity, there was a high degree of statistical heterogeneity with retrospective studies. This is likely due to study population, the timing of vaccination or outcome measure, and the types of COVID-19 variant. Therefore, we performed sub-group analysis to minimize the heterogeneity of the study subjects.

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CONCLUSIONS

Our systematic review and meta-analysis showed that while mRNA COVID-19 vaccines in adolescent recipients is highly preventive against COVID-19, the real-world effectiveness is lower than the efficacy reported in clinical trials. The safety findings of BNT162b2 vaccine in adolescents were also explored in observational studies and we found there were the difference of safety according to sex and vaccine doses. Given the current dynamic changes at the molecular level of SARS-CoV-2, the assessment of COVID-19 vaccination should be constantly updated.

SUPPLEMENTARY MATERIALS

Supplementary Data 1
Literature search strategies

Supplementary Fig. 1
Risk of bias: randomized controlled studies.

Supplementary Fig. 2
Risk of bias: non-randomized controlled studies.

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요약

본세계적으로 소아 코로나바이러스 감염 2019 (COVID-19) 환자 수가 질병 초기와 비교하여 증가하고 있으며, 이는 고도로 전염성이 있는 중증 급성 호흡기 증후군 코로나바이러스 변이와 성인 COVID-19 백신 접종 증가와 관련이 있다. 본 연구는 청소년 대상 COVID-19 백신 접종의 무작위 임상시험 (randomized controlled trial, RCT) 후향적 관찰연구를 대상으로 신속 체계적 문헌고찰과 메타 분석을 수행했다. 체계적 문헌고찰 결과, 17개의 연구가 최종적으로 포함되었다. 메타 분석 결과, 청소년 대상 예방접종은 후향적 관찰 연구에서 COVID-19 감염을 예방하는 데 유의미하게 효과적이었으나 (risk ratio [RR], 0.29; 95% confidence interval [CI], 0.22-0.37; I^2=100%), RCT보다 COVID-19 감염을 예방하는 효과가 낮았다 (RR, 0.05; 95% CI, 0.01-0.27). 5개의 후향적 관찰 연구에서, 국민 10만 명당 심근염 및/또는 심낭염 비율은 2.33명 (95% CI, 0.97-5.61 명)이었다. 성별 및 백신 접종 횟수에 따른 하위 그룹 분석 결과, 남성 (국민 10만 명당 5.35 명) 및 두 번째 접종 (국민 10만 명당 9.71명)은 여성 (국민 10만 명당 1.09명) 및 첫 번째 접종 (국민 10만 명당 1.61명)보다 심근염 및/또는 심낭염 발생률이 유의하게 높았다. 본 연구에서는 청소년을 대상으로 mRNA COVID-19 백신을 접종하는 것은 RCT 및 관찰연구 모두에서 COVID-19에 대해 효과적이었다. 또한 청소년 대상 BNT162b2 백신의 안전성 결과를 탐색하였으며, 성별 및 백신 접종 횟수에 따른 안전성의 차이를 확인했다. 향후 mRNA COVID-19 예방접종 후 부작용 발생은 계속 모니터링할 필요가 있다.

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