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Letter to the Editor

## Effectiveness of COVID-19 vaccine in children and adolescents with the Omicron variant: A systematic review and meta-analysis

Dear Editor,

We read with great interest the paper by Xu et al., which found that the Coronavirus Disease 2019 (COVID-19) vaccine for children is not only effective and safe but also more effective than the adult COVID-19 vaccine.[1] The emergence of the Omicron variant in November 2021 has further increased transmissibility and led to a significant increase in COVID-19 cases.[2] To date, many articles found that the effect of COVID-19 vaccine in children/adolescents with Omicron variant may be different due to the variations in the age and vaccine dose.[3–5] However, the results on the effect of COVID-19 vaccine in children and adolescents with the Omicron variant remain controversial. Therefore, a systematic review and meta-analysis is critical to evaluate the vaccine effectiveness (VE) of COVID-19 vaccines in children and adolescents with Omicron variant.

We comprehensively searched the MEDLINE, EMBASE, and Cochrane CENTRAL databases for articles published between November 1, 2021, and November 30, 2022. A combination of MeSH/Emtree and title/abstract keywords was used. The search terms were "COVID-19″, "COVID 19 vaccine", "sars cov2 vaccine", "omicron" (**Supplementary Table 1**). The inclusion criteria were as follows: (1) the children or/and adolescents were confirmed with Omicron variant infection who had previously been injected with COVID-19 vaccine; (2) the comparator arms were not injected with vaccine; (3) the studies measured the VE of the Omicron infection, hospitalization or symptomatic COVID-19; (4) the studies were observational studies and published in English. Any case reports, reviews, and preprints were excluded (**Supplementary Fig. 1**).

The relationship between children/adolescents with Omicron infection and the vaccine was evaluated through the random-effects models after pooling the VE and corresponding 95% confidence intervals (CIs) for each outcome. The $I^2$ and $P$ values were used to assess the heterogeneity, and potential publication bias by Funnel plots and Egger's tests (**Supplementary Figs. 2–9**), and the risk of bias was assessed using the Newcastle-Ottawa Scale (**Supplementary Table 2**). STATA 14.0 (College Station, Texas 77,845, USA, Serial number: 401,406,267,051) was used to perform all statistical analyses.

A total of 14 observational studies including 3793,543 patients were eligible to be included in this study, and the type of vaccines mainly included BNT162b2 mRNA vaccines and CoronaVac vaccines as well as the characteristics of the included articles and correspondent references are shown in the **Supplementary Table 3.** The pooled results showed that the overall VE for children with Omicron infection was 46.33% (95% CIs: 29.85–62.81, $p < 0.01$) (Fig. 1A). Subgroup analysis was performed according to the first and second vaccine doses, and the results showed the VE 18% (95% CIs: 0–36, $p = 0.05$) of the first dose was significantly lower than the VE 50.67% (95% CIs: 33.02–68.31, $p < 0.01$) of the second dose (Fig. 1A) among the children with Omicron infection. Moreover, the overall VE for adolescents was 54.35% (95% CIs: 43.49–65.20, $p < 0.01$) (Fig. 1B). Subgroup analysis showed that the VE 39.11% (95% CIs: 27.43–50.79, <0.05) of the first dose was lowest, and the second dose 60.59% (95% CIs: 41.31–79.86, $p < 0.01$) as well as the booster dose 63.38% (95% CIs: 48.59–78.17, $p < 0.01$) (Fig. 1B) were significantly higher than the first dose. Furthermore, the pooled VE for the COVID-19-related hospitalization was 70.43% (95% CIs: 56.71–84.15, $p < 0.01$) (Fig. 1C). Subgroup analysis suggested that the VE had no difference between children (70.98%) (95% CIs: 63.33–78.63, $p < 0.01$) and adolescents (70.17%) (95% CIs: 48.30–91.99, $p < 0.01$) (Fig. 1C). Additionally, the pooled VE for symptomatic COVID-19 in adolescents was 73.05% (95% CIs: 61.68–84.42, $p < 0.01$) which was higher than in children 45.18% (95% CIs: 29.96–60.40, $p < 0.05$) (Fig. 2A). The pooled VE for symptomatic COVID-19 after the first dose was 26.41% (95% CIs: 17.64–35.18, $p < 0.01$), which was lower than VE for second dose 59.72% (95% CIs: 42.93%−76.50%, $p < 0.01$) and the booster dose 71.10% (95% CIs: 66.0–76.20, $p < 0.01$) (Fig. 2B). Evaluating the safety of the vaccine is critical for children. The adverse reaction of vaccine was 0.02 (−0.01 to 0.04, $p > 0.05$) (Fig. 2C), which suggested that the vaccine was safe for children and adolescents with Omicron infection.

This meta-analysis included 14 studies and demonstrated that the COVID-19 vaccine for Omicron variant is safe and more effective in adolescents than in children. Moreover, the second dose as well as the booster vaccine were more effective than the first dose in protecting children and adolescents from the Omicron infection, especially those with symptomatic COVID-19. More importantly, different doses of the COVID-19 vaccine were higher VE in adolescents than in children with Omicron variant infection. Interestingly, like many the present articles,[4–6] most of the vaccines for Omicron infection in this study were BNT162b2 mRNA vaccines, only one study involved in CoronaVac vaccines[3] (showed in **Supplementary Table 3**). This may be caused by the Omicron strains have significantly reduced the VE, and 20% and 24% of BNT162b2 recipients had detectable neutralizing antibody against the omicron variant, but for the CoronaVac receptor, had almost no neutralizing antibody titer against Omicron strains.[7] A previous meta-analysis[6] suggested that the BNT162b2 vaccine could protect children and adolescents against COVID-19 infection, especially Delta variant and its complications, which is similar to the results with the Omicron strains in our study.

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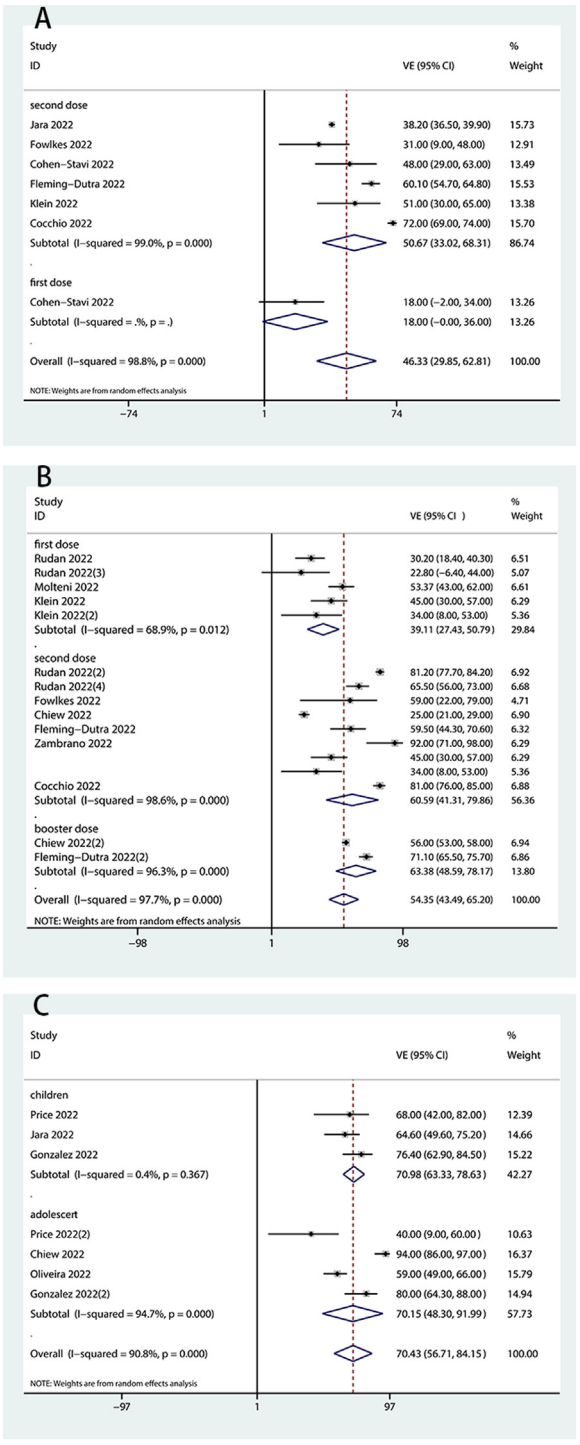


**Fig. 1.** Forest plot of VE and it's 95% CI for (A) children, (B) adolescents and (C) COVID-19-related hospitalization.

In summary, this was the first systematic review and meta-analysis to assess the relationship between COVID-19 vaccine and effectiveness in children and adolescents with Omicron variant infection. The findings suggested that the COVID-19 vaccine for Omicron variant was more effective in adolescents than in children, and the second dose and the booster vaccine were more effective than the first dose. Importantly, the second and booster doses were very important for protecting children and adolescents from COVID-19 infection.

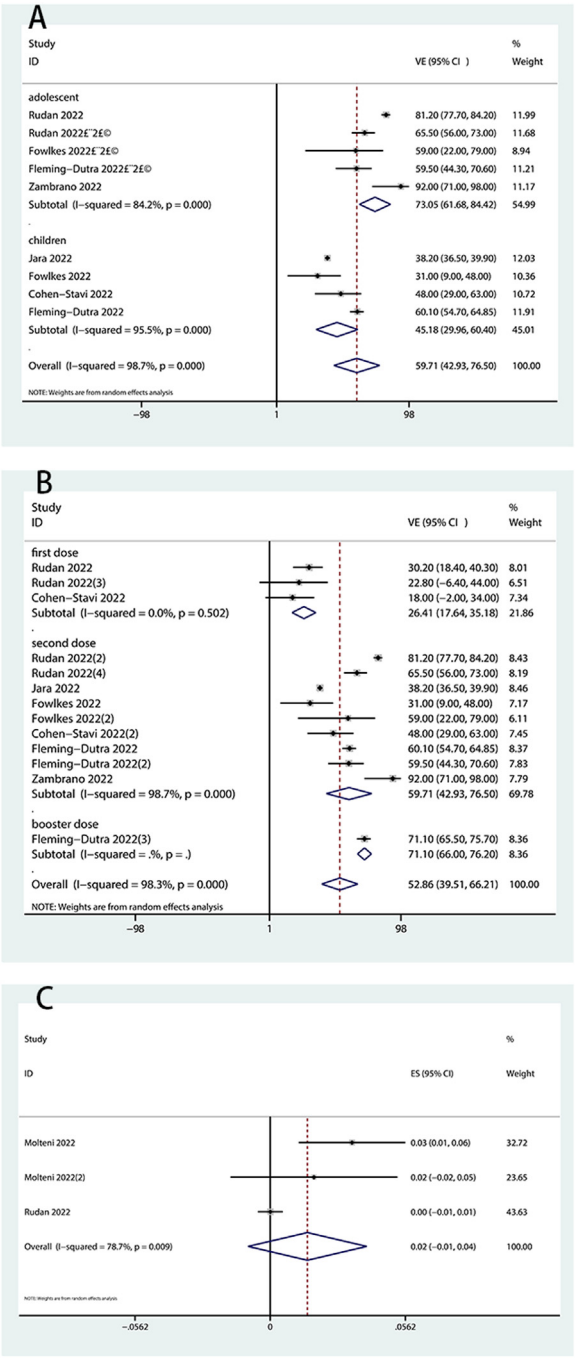


**Fig. 2.** Forest plot of VE and it's 95% CI for (A, B) symptomatic COVID-19 Omicron infection and (C) the adverse reactions of COVID-19 vaccine.

## Data sharing statement

Not available.

## Availability of data and materials

The datasets used and/or analyzed in the present study are available from the corresponding author on reasonable request.

## 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

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2023.01.001.

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