INPLASY PROTOCOL

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None declared.

Efficacy of the third dose of COVID-19 vaccine: a systematic review and meta-analysis

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Review question / Objective: **To investigate the immune response and related clinical outcomes of healthy adults who received coronavirus vaccine booster compared with those who did not receive the vaccine booster.**
Condition being studied: **The COVID-19 pandemic, which has spread since 2019, has created a huge disease and economic burden on the world. A large number of clinical trials have verified the effectiveness of COVID-19 vaccine. Previous studies have found that the serum conversion rate and antibody level of those vaccinated after the first two doses of COVID-19 vaccine continue to decrease, and the efficacy of the vaccine will decrease over time after the first two doses. Therefore, in order to maintain the protective efficacy of the vaccine, The need for a vaccine booster shot to achieve the expected goal of long-term effective prevention of the novel coronavirus has become a focus of discussion around the world.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 23 November 2022 and was last updated on 23 November 2022 (registration number INPLASY2022110114).

INTRODUCTION

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METHODS

Search strategy: Relevant studies were searched in PubMed, Embase, and Web of Science from January 1, 2021 to September 7, 2022 using a combination of comprehensive keywords, such as 'COVID', 'SARS-CoV-2,' 'third', 'three','four', 'boost', 'vaccination,' and 'vaccine' with Boolean operators and MeSH terms.

Participant or population: Healthy adults.

Intervention: People receiving the third dose of COVID-19 vaccine.

Comparator: People who received the first two doses of COVID-19 vaccine.

Study designs to be included: Randomized controlled trials、prospective cohort study、retrospective cohort study.

Eligibility criteria: Published papers were eligible for inclusion if they met the inclusion criteria: (1) studies were observational studies (prospective or retrospective cohort) or randomized trials with a minimum of ten adult participants in any subject group, (2) studies involved the third dose of COVID-19 vaccination, (3) studies had full COVID-19 vaccination (two doses) as the control group, (4) studies reported at least one of the outcomes of interest after boosting vaccination: serum antibodies against different SAS-CoV-2 fragments, neutralizing antibody, cell-mediated immune outcome, laboratory confirmed infection, COVID-19–related hospitalization, COVID-19–related ICU admission, death.

Information sources: All intended information came from electronic databases (Pubmed, Web of Science and Embase).

Main outcome(s): Differences in immune response and clinical events in healthy adults who received and did not receive the COVID-19 vaccine booster.

Quality assessment / Risk of bias analysis: The Risk Of Bias (ROB) tool used to assess the risk of bias for randomized controlled trials. The quality of the included studies was evaluated using the ROBINS-I risk of bias assessment tool for non-randomized studies of interventions . Seven domains were covered including confounding and selection of participants for the study, classifcation of interventions, deviations from intended interventions, missing data, measurement of out comes and selection of the reported result.

Strategy of data synthesis: Data extraction - Two researchers (LXQ and ZLY) extracted data according to a predetermined proforma in Microsoft Excel Version 15.0. All key extracted data were reviewed and quality checked at the end of the data extraction phase by the same two researchers.
Data on study characteristics included country, primary and secondary outcomes, study design, sample size, dropout and non-response rates, age of participants, and gender. Data related to the intervention included vaccine type and brand, dosing schedule, number of participants receiving each type and brand of vaccine, and median or mean of dosing intervals. Outcome-related data included type of assay, antibodies measured, method of measurement, time interval between sample collection and number of measurements, and number of clinical outcome events.
Data analysis - We used the DerSimonian and Laird random effects model to estimate the pooled risk ratios and corresponding 95% confidence intervals for the primary outcomes of interest. A risk ratio <1 indicates that participants who

received booster shots had a lower risk of clinical outcome events than those who did not receive booster injections or that participants receiving booster shots had higher antibody levels than those who did not receive booster shots. Statistical heterogeneity of the results in the included studies was assessed by χ2 test and I2 statistic. We considered heterogeneity to be significant when the P value by χ2 test was <0.10, or the I2 statistic was ≥50%.

Assessment for publication bias was both qualitative, through visual inspection for funnel plot asymmetry, and quantitative, using Egger's test. We performed a subgroup analysis to determine if the results were affected by different types of vaccination regimens. Interaction tests were used to compare the differences between estimates from different subgroups.

We conducted a separate meta-analysis of the incidence of clinical outcome events (critical hospitalization rate, mortality, infection rate) after vaccination.

Small study effects were assessed both qualitatively, through visual inspection for funnel plot asymmetry, and quantitatively, using Egger's test. We conducted all analyses on R (version 4.0.3) using the meta and metafor packages. Unless specified otherwise, we considered a two sided P value of <0.05 to be statistically significant.

When publication bias was suspected based on either the Egger's regression-intercept test of bias or visual inspection for funnel plot asymmetry, we conducted a sensitivity analysis using the trim-and-fill method (R0 estimator, fixed random effects models) to re-estimate the pooled effect size after imputing potentially missing studies. The trim-and-fill method shows a normal distribution of effect sizes around the centre of the funnel plot if publication bias is absent.

Subgroup analysis: Predetermined subgroup analysis was performed stratifying by types of booster vaccines and the counterpart full vaccination strategy to explore the SARS CoV-2 prevention efficacy in various vaccine strategies.

Sensitivity analysis: Sensitivity analysis will not be conducted in this meta analysis.

Country(ies) involved: China.

Keywords: COVID-19；vaccine；booster；full vaccination；clinical event；Nabs.

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