INPLASY PROTOCOL

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Minimum number of vaccine doses required to protect against long COVID symptoms: a systematic review and meta-analysis of observational studies

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Review question / Objective: **Following the COVID-19 global outbreak, Long Covid is currently the most urgent global health problem. Primary clinical research have produced widely varying findings demonstrating the protective and even counterproductive effects of immunization against extended Covid. We used a systematic review and meta-analysis to examine the impact of pre- and post-Covid immunization for the prevention of extended Covid.**
Condition being studied: **The main result is whether long Covid is present or absent, which is determined by whether one or more long Covid symptoms have persisted for more than three weeks following infection. The secondary result is whether or not each unique long-term Covid symptom is present. ICD10-CM was used to classify and define symptoms since research utilized several names for the same symptom. To ensure validity, we only examined long-lasting Covid symptoms mentioned in three or more research. We asked the authors of publications that merely provided information on the presence or absence of extended Covid to provide information on specific symptoms. We also wanted data that was stratified by the number of vaccine doses for studies that pooled data from pre-Covid vaccinations given in 1-dose and 2-dose regimens.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 28 October 2022 and was last updated on 28 October 2022 (registration number INPLASY2022100115).

INTRODUCTION

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against extended Covid. We used a systematic review and meta-analysis to examine the impact of pre- and post-Covid immunization for the prevention of extended Covid.

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METHODS

Participant or population: From each study that met the predetermined criteria, we took the study characteristics (study population, action taken, response rate, country), subject characteristics (sample size, age, sex, baseline characteristics, ethnicity), intervention (comparison group, vaccine brand, follow-up period after infection, follow-up period after vaccination), outcome (mode of assessment, framework of questionnaire or interview, symptoms measured, outcome measures), and data (raw data or OR). Since we want to find out how vaccinating long Covids affects them, here's how we define the experimental and control groups: The people who weren't vaccinated and got Covid are in the control group. There are 3 experimental groups, which are made up of people who were infected with Covid and got either (1) a 1-dose vaccination before Covid, (2) a 2-dose vaccination before Covid, or (3) a 1-dose vaccination after Covid. Google Sheets is used to get data and figure out the chance of bias. Supplemental Table 3-10 has information about all the studies that were included and those that were not included.

Intervention: Studies that compare long-term Covid symptoms in people who got vaccinated and people who didn't get vaccinated were included. Only studies that said how many doses were given were used. We took the study's characteristics and data and used the DerSimonian and Laird random effects model to figure out the summary odds ratio (OR).

Comparator: We searched the following databases and preprint servers without language restrictions: Cochrane Library, Medline (Ovid), Medline (PubMed), PubMed Central, Global Health (Ovid), PsycInfo (Ovid), Scopus (Elsevier), Embase (Ovid), Academic Search Ultimate (Ebsco), CINAHL Ultimate (Ebsco), WHO Covid database (including preprint databases such as medRxiv and bioRxiv), Web of Science, and ScienceDirect. The list of databases and search terms are provided in Supplementary Table 1. We also inspected the reference list of included studies to look for more studies.

Study designs to be included: The effects of 1-dose pre-Covid, 2-dose pre-Covid and 1-dose post-Covid vaccination were computed separately. Data which combined 1-dose and 2-dose pre-Covid vaccination are excluded from analysis. Test for subgroup difference is evaluated by random effects meta-regression model (the rma function with treatment group as the moderator).

Eligibility criteria: Studies were included if they met all the following inclusion criteria: (1) investigate one or more long covid symptoms among covid patients; (2) compare between vaccinated and unvaccinated groups; 3) subjects received vaccinations either before or after infected with covid; (4) the number of doses received by participants is specified; (5) original article; (6) sample size more than

or equal to 30; (7) report raw data or odds ratios.

Information sources: We searched the following databases and preprint servers without language restrictions: Cochrane Library, Medline (Ovid), Medline (PubMed), PubMed Central, Global Health (Ovid), PsycInfo (Ovid), Scopus (Elsevier), Embase (Ovid), Academic Search Ultimate (Ebsco), CINAHL Ultimate (Ebsco), WHO Covid database (including preprint databases such as medRxiv and bioRxiv), Web of Science, and ScienceDirect.

Main outcome(s): The primary outcome is presence or absence of long Covid, which is defined by having one or more long Covid symptoms persisting for more than three weeks since infection. The secondary outcome is presence or absence of individual long Covid symptoms. Since studies used different names for the same symptom, ICD10-CM was used for the classification and definition of symptoms. . We only analysed long Covid symptoms reported by 3 or more studies to ensure validity. For studies which only reported data for presence or absence of long Covid, we requested data for individual symptoms from the authors. For studies which combined data of 1-dose and 2-dose pre-Covid vaccination, we also requested data stratified by number of vaccine dose.

Quality assessment / Risk of bias analysis: The Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) framework63 was used to measure the risk of bias. The average of all the scores was taken. Based on the average score, studies were put into four groups: low, medium, serious, or critical risk of bias. Then, we did sensitivity analysis, but only for studies with a low risk of bias. A funnel plot and Egger's test were used to check for publication bias. The GRADE method was used to figure out how sure the evidence was. All steps (selection of abstracts and titles, data extraction, and risk of bias assessment) were done by two authors on their own. Disagreements are solved by talking about them.

Strategy of data synthesis: The R language's metafor package is used to analyze data. We used the escalc function56 to figure out the log odds ratio and standard error for each study that reported raw data. For calculations, we turned the odds ratio (OR) and 95% confidence interval (CI) from the studies that gave them into log OR and standard error. When a study gave both "raw data" and "adjusted odds ratios," we used the "adjusted odds ratios" because they are less likely to be messed up. For studies that broke down the people who took part into subgroups, we added up all the subgroups and used the total for our analysis. After figuring out the ORs for each study, we used the rma function from the DerSimonian and Laird random effects model to figure out the summary OR. When p 0.05, this is called statistical significance. To figure out how different the statistics were, the restricted maximum likelihood estimator was used. The effects of the 1-dose pre-Covid, 2-dose pre-Covid, and 1-dose post-Covid vaccinations were calculated separately. Data that included both 1-dose and 2-dose pre-Covid vaccinations are not looked at. The random effects meta-regression model (the rma function with the treatment group as the moderator)60 is used to test if there are differences between subgroups. The forest function in the metafor package and the forestplot function in the forestplot package were used to make forest plots. In the forest plot, the number of people who took part in some studies was replaced by "NA," which stands for "Not Available." This is because these studies gave adjusted odds ratios instead of raw data.

Subgroup analysis: For studies that broke down the people who took part into subgroups, we added up all the subgroups and used the total for our analysis. After figuring out the ORs for each study, we used the rma function from the DerSimonian and Laird random effects model to figure out the summary OR58. When p 0.05, this is called statistical significance. To figure out how different the statistics were, the restricted maximum likelihood estimator59 was used. The

effects of the 1-dose pre-Covid, 2-dose pre-Covid, and 1-dose post-Covid vaccinations were calculated separately. Data that included both 1-dose and 2-dose pre-Covid vaccinations are not looked at. The random effects meta-regression model is used to evaluate the test for subgroup difference (the rma function with treatment group as the moderator).

Sensitivity analysis: Then, we did sensitivity analysis, but only for studies with a low risk of bias. A funnel plot and Egger's test were used to check for publication bias. The GRADE method was used to figure out how sure the evidence was. All steps (selection of abstracts and titles, data extraction, and risk of bias assessment) were done by two authors on their own. Disagreements are solved by talking about them.

Language restriction: English.

Country(ies) involved: Hong Kong.

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