

Meta-Analysis: The Effect of Vaccination on the COVID-19 Infection

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ABSTRACT

Background: The Indonesian government has determined that COVID-19 is a public health emergency and a non-natural national disaster that requires multi-strategy management. Strategies such as implementing health protocols and vaccination efforts to break the chain of transmission of COVID-19 must continue to be carried out massively. This study aims to analyze the effect of vaccination on COVID-19 infection.

Subjects and Method: This study is a systematic review and meta-analysis, with PICO as follows Population= population aged ≥ 18 years. Intervention= Vaccination. Comparison= Not vaccinated. Outcome= COVID-19 infection. The articles used in this study were obtained from several databases including PubMed, Google Scholar, and Scopus. These articles were collected over 2 months. The keywords to search for articles are as follows “Vaccine OR Vaccination AND (Infection OR Transmission) AND COVID-19 OR SARS-CoV-2”. The articles included in this study were full-text articles with a retrospective or prospective cohort study design. Articles are collected using PRISMA flow diagrams. Articles were analyzed using the Review Manager 5.3 application.

Results: A total of 10 articles reviewed in this meta-analysis study originating from England, Spain, France showed that COVID-19 vaccination is effective in reducing the risk of COVID-19 infection. People who were given the COVID-19 vaccine had a 0.22 times risk of being infected compared to those who were not vaccinated, and the reduced risk was statistically significant (aHR= 0.22; 95% CI= 0.13 to 0.36; $p < 0.001$).

Conclusion: COVID-19 vaccination is effective in reducing the risk of COVID-19 infection.

Keywords: vaccination, infection, COVID-19, SARS-COV-2

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BACKGROUND

The Indonesian government has determined that COVID-19 is a public health emergency and a non-natural national disaster that requires multi-strategy management. Strategies such as implementing health protocols and vaccination efforts to break the chain of transmission of COVID-19 must continue to be carried out massively. The vaccination program as one of the government's efforts

to overcome the COVID-19 pandemic for the community requires the role of various parties. This vaccination activity aims to provide protection for a person by generating active immunity against SARS Cov-2 infection so that it can prevent the severity if one day is exposed to the disease. In addition, it is hoped that by giving vaccinations to the entire community, community immunity (herd immunity) will be obtained (Kemen-

kes RI, 2021). As of 23 August 2022, a total of 12,449,443,718 doses of vaccine have been administered (WHO, 2022).

The COVID-19 vaccine is effective and is important for controlling the pandemic. However, no vaccine is 100% effective at preventing the disease. Some fully vaccinated people will fall ill, and some will even be hospitalized or die from COVID-19. However, there is evidence that vaccination can make the disease milder for individuals who are vaccinated and are still sick. The risk of infection, hospitalization, and death is lower in vaccinated individuals compared to those who are not vaccinated (CDC, 2021).

For example, the Corona-virus Disease 2019 (COVID-19) mRNA vaccine has shown high effectiveness in preventing severe COVID-19 symptoms from hospitalization to death. However, a small proportion of vaccinated individuals may become infected and experience significant morbidity (Pollett, 2022).

Findings from a journal of the CT Department of Public Health (2021) state that many factors affect the severity of symptoms of COVID-19 infection, more than a quarter of fully vaccinated people experience severe to critical symptoms, which had causative factors, including: the emergence of a variant of SARS-CoV-2 which may lead to decreased vaccine effectiveness and ineffective immune response to vaccines or a history of comorbidities such as older age, obesity, use of immunosuppressive agents, presence of comorbid diseases, secondary infections, and increased inflammatory indicators in the blood (Ruan et al., 2020).

This study aimed to analyze previous primary studies in assessing the effect of vaccination on COVID-19 infection. This study will use a systematic review and meta-analysis approach to analyze the effect of vaccination on COVID-19 infection. Systematic review includes quantitative techni-

ques (meta-analysis) which is carried out by combining several research results statistically on the same test so as to obtain quantitative results.

SUBJECTS AND METHOD

1. Study Design

This research is a systematic review and meta-analysis, using PRISMA diagrams using databases including PubMed, Google Scholar, and Scopus. These articles were collected over 2 months. The keywords to search for articles are as follows: "Vaccine OR Vaccination AND (Infection OR Transmission) AND COVID-19 OR SARS-CoV-2". There were 10 studies with cohort research designs that met the inclusion criteria. Analysis was performed with Review Manager (revMan) 5.3.

2. Steps of Meta-Analysis

Meta-analysis is carried out through 5 steps as follows:

- 1) Formulate research questions using the PICO model (PICO as follows Population= population aged ≥ 18 years. Intervention= Vaccination. Comparison= Not vaccinated. Outcome = COVID-19 infection).
- 2) Search primary study research articles from electronic databases and libraries, such as PubMed, Science Direct, and Google Scholar.
- 3) Conduct screening and quality assessment of primary research articles.
- 4) Extracting and analyzing data into the RevMan 5.3 application.
- 5) Interpret the results and draw conclusions.
- 6) Interpretation the results and draw conclusions

3. Inclusion Criteria

The inclusion criteria in this study included research subjects who were adults aged ≥ 18 years, full paper articles with cohort observational studies (retrospective or prospec-

tive), the effect size used was the adjusted Hazard Ratio (aHR), and the study outcome was infection with COVID-19 patients.

4. Exclusion Criteria

Exclusion criteria were articles non-English languages and articles other than cohort study design.

5. Operational Definition of Variables

Vaccines are biological products which given to someone will generate active specific immunity against COVID-19 disease. The research instrument was an intramuscular injection, with a categorical measurement scale.

COVID-19 infection is defined as confirmation status in the population aged ≥ 18 years. Infections were categorized as infected with COVID-19 and not infected with COVID-19. The measurement instrument is RT-PCR (Swab-Test), with a categorical measurement scale.

6. Study Instruments

The quality assessment in this study used the assessment criteria from the Cohort Study Checklist published by CASP (Critical Appraisal Skills Program).

7. Data Analysis

The articles in this study were collected using the PRISMA diagram and analyzed using the RevMan 5.3 application by calculating effect sizes and heterogeneity to determine the combined research model and form the final results of the meta-analysis.

RESULTS

The initial search process in the database yielded 1,314 articles, after the process of deleting published articles, 876 were found, with 59 of them meeting the requirements for a full text review. A total of 12 articles with cohort studies can be seen in Figure 1.

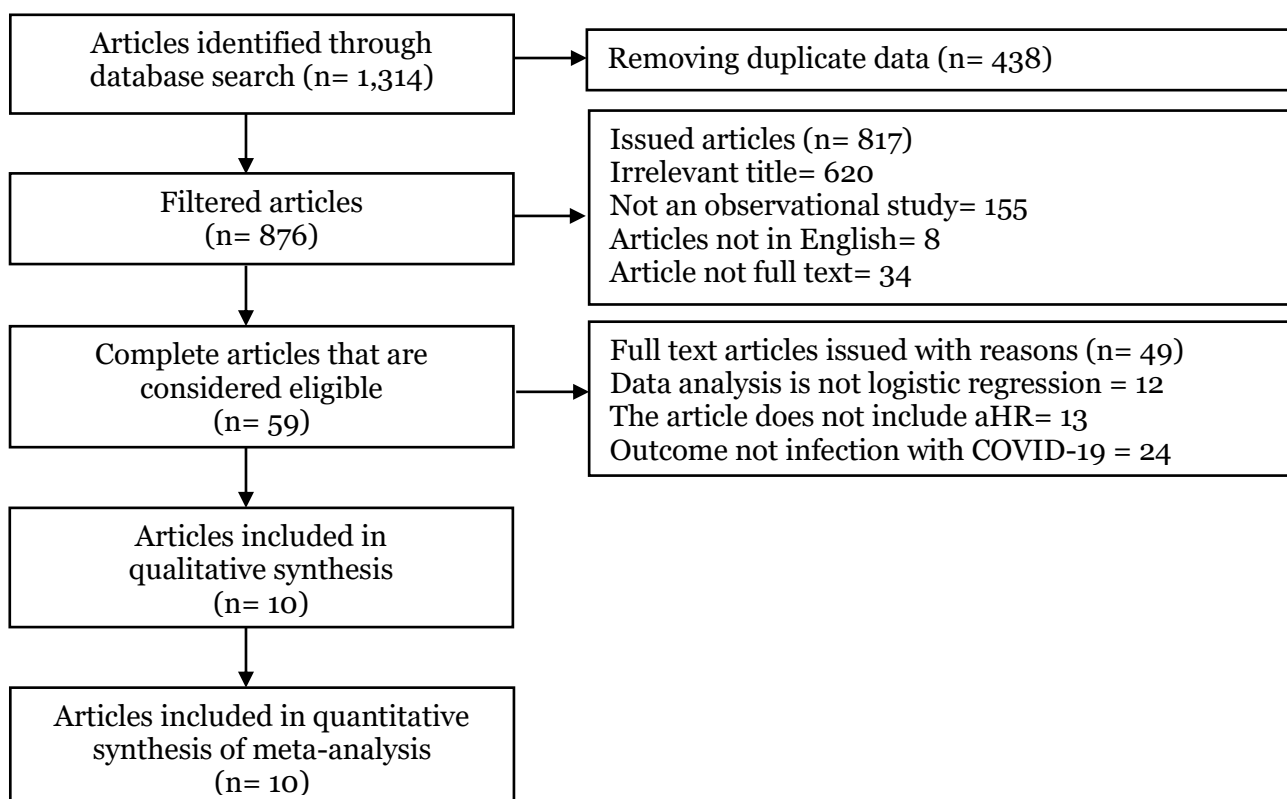


Figure 1. PRISMA Flowchart



Figure 2. Research areas on the effect of vaccination on covid-19 infection

The regional map in Figure 2 shows the distribution of primary study articles on the European continent consisting of 4 studies from England, 2 studies from Spain, 2 studies from Denmark, 1 study from Italy, and 1

study from France (Figure 2). Assess the quality of research using Critical Appraisal Questions for Cohort Study published by CASP (Critical Appraisal Skills Program) which consists of 12 questions.

Table 1. Results of the quality assessment of the cohort study on the effect of vaccination on COVID-19 infection

Author (Year)	Question Criteria												Total	
	1	2	3	4	5	6	7	8	9	10	11	12		
Cabezas et al. (2021)	2	2	2	2	2	2	2	2	2	2	2	2	2	24
Emborg et al. (2021)	2	2	2	2	2	2	2	2	2	2	2	2	2	24
Fabiani et al. (2021)	2	2	2	2	2	2	2	2	2	2	2	2	2	24
Glampson et al. (2021)	2	2	2	2	2	2	2	2	2	2	2	2	2	24
Hall et al. (2021)	2	2	2	2	2	2	2	2	2	2	2	2	2	24
Hall et al. (2022)	2	2	2	2	2	2	2	2	2	2	2	2	2	24
Monge et al. (2021)	2	2	2	2	2	2	2	2	2	2	2	2	2	24
Moustsen-Helms et al. (2021)	2	2	2	2	2	2	2	2	2	2	2	2	2	24
Paris et al. (2021)	2	2	2	2	2	2	2	2	2	2	2	2	2	24
Shrotri et al. (2021)	2	2	2	2	2	2	2	2	2	2	2	2	2	24

Description of the question criteria:

- 1 = Does the cohort study clearly address the clinical problem?
- 2 = Were the cohort (exposed and unexposed groups) selected in the right way?
- 3 = Is exposure to COVID-19 accurately measured to minimize bias?
- 4 = Was the result (COVID-19 infection) accurately measured to minimize bias?
- 5 = Did the researcher identify all important confounding factors? Did the researcher account for confounding factors in the design and/or analysis?
- 6 = Does the research subject complete the research time in full? Were the research subjects followed up for a sufficiently long time?
- 7 = Are the results of this study reported in the aHR?

- 8 = What is the precision of the results?
 9 = Are the results reliable?
 10 = Are the results applicable to the local (local) population?
 11 = Are the results of this study compatible with the available evidence?
 12 = What are the implications of this research for practice?

Answer score description:

- 0 = No
 1 = Can't tell
 2 = Yes

Table 2. Summary of primary cohort study articles with each PICO

Author (Year)	Country	Total Sampel	P	I	C	O
Cabezas et al. (2021)	Spain	864,096	Residents of nursing homes, nursing home staff, and health workers	Pfizer/BioNTech Vaccination (BNT162b2)	No Vaccination	COVID-19 infection
Emborg et al. (2021)	Denmark	864,096	Residents and health workers aged > 65 years	Pfizer/BioNTech Vaccination (BNT162b2)	No Vaccination	COVID-19 infection
Fabiani et al. (2021)	Italy	6,423	Hospital workers have an average age of 30 – 49 years	Prizer/BNT162b2 /BioNTech Vaccination	No Vaccination	COVID-19 infection
Glampson et al. (2021)	English	2,183,939	Patients aged >18 to 80 years	Prizer/BioNTech Vaccination	No Vaccination	COVID-19 infection
Hall et al. (2021)	English	23,324	Hospital staff aged >18 years	Prizer/BNT162b2 vaccination	No Vaccination	COVID-19 infection
Hall et al. (2022)	English	35,768	Hospital staff aged >18 years	Prizer/BNT162b2 vaccination	No Vaccination	COVID-19 infection
Monge et al. (2021)	Spain	573,533	Residents recorded in the COVID-19 laboratory registration	Pfizer/BioNTech Vaccination (BNT162b2)	No Vaccination	COVID-19 infection
Moustsen-Helms et al. (2021)	Denmark	370,079	Patients and health workers aged 84 years (77 – 90 years)	Prizer/BNT162b2 vaccination	No Vaccination	COVID-19 infection
Paris et al. (2021)	French	8,165	Hospital workers have an average age of 42 years	Prizer/BNT162b2 vaccination	No Vaccination	COVID-19 infection
Shrotri et al. (2021)	English	10,412	Residents of nursing homes aged >65 years	Prizer/BNT162b2 vaccination	No Vaccination	COVID-19 infection

Tabel 3. Adjusted Hazard Ratio (aHR) study of the effect of vaccination on COVID-19 infection

Studies	aHR	95%CI	
		Lower Limit	Upper Limit
Cabezas et al. (2021)	0.12	0.10	0.14
Emborg et al. (2021)	0.06	0.04	0.09
Fabiani et al. (2021)	0.42	0.33	0.53
Glampson et al. (2021)	0.15	0.04	0.56
Hall et al. (2021)	0.22	0.18	0.27
Hall et al. (2022)	0.43	0.42	0.44
Monge et al. (2021)	0.17	0.04	0.72
Moustsen-Helms et al. (2021)	0.05	0.01	0.25
Paris et al. (2021)	0.49	0.20	1.20
Shrotri et al. (2021)	0.86	0.27	2.74

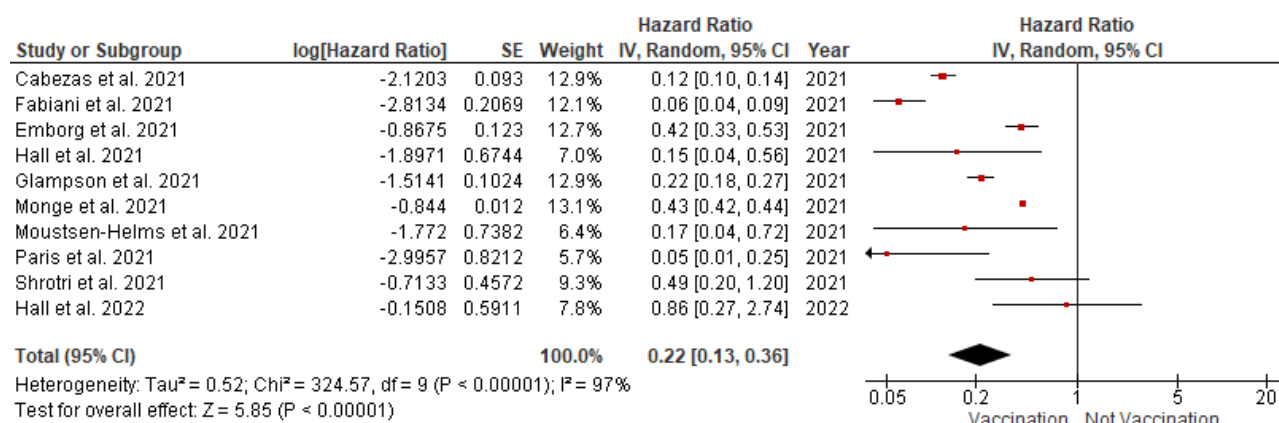


Figure 3. Forest plot of the effect of vaccination on COVID-19 infection

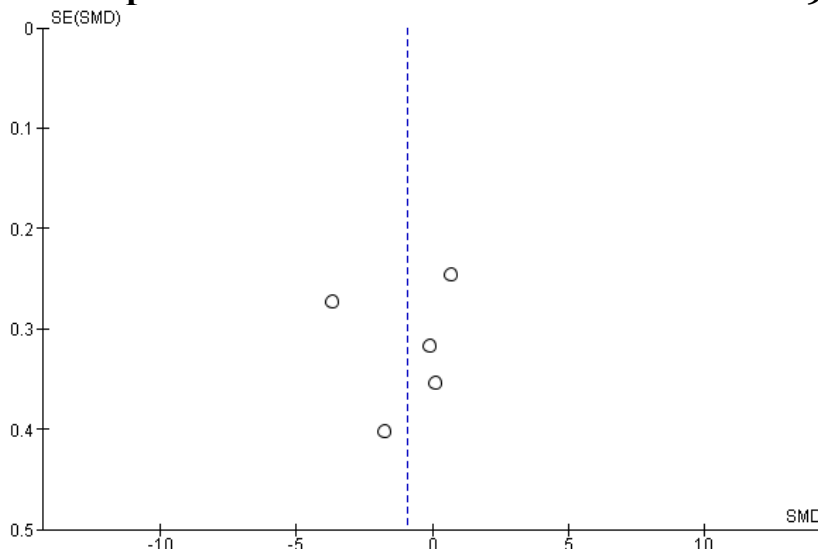


Figure 4. Funnel plot of the effect of vaccination on COVID-19 infection

DISCUSSION

COVID-19 is a global pandemic with more than 158,129 million deaths worldwide with 438,360,363 doses of vaccine (WHO, 2022).

The clinical symptoms of individuals infected with COVID-19 range from no symptoms to severe illness requiring prolonged hospitalization, invasive mechanical ventilation

and possible death. Evaluation of the effectiveness of the COVID-19 vaccine conducted by the Health Research and Development Agency of the Indonesian Ministry of Health, proved that vaccines can reduce the risk of being infected with COVID-19, as well as reduce treatment and death for health workers (Kemenkes RI, 2022).

Vaccine effectiveness against asymptomatic SARS-CoV-2 infection was 90-92% for AZD1222 and BNT162b2 against unspecified strains (Shah et al., 2021). Among pregnant women, one or two doses resulted in 78% effectiveness against the original strain and 96% against Alpha, respectively. Previous studies focused on 6 years in people, but a retrospective cohort of adolescents aged 12–15 years in Israel also reported a high 91.5% efficacy against Delta infection (Glatman-Freedman et al., 2021).

In terms of effectiveness, the efficacy of the Si-novac vaccine in Indonesia is only around 65.3%. This value is lower than Turkey (91.25%) and Brazil (78%). Even though there is no evidence that Sinovac protects someone from COVID-19, based on phase three clinical trials, this vaccine can provide a three times lower risk of experiencing symptomatic COVID-19 (confirmed case). When compared to the efficacy of the Pfizer vaccine, Sinovac is still far below Pfizer. The difference in efficacy is very natural. It depends on three things, namely the host (human), agent (vaccine) and environment (environment). Several post-immunization adverse events (AEFI) that may occur after the vaccine include pain, irritation, swelling, redness, myalgia, arthralgia, fatigue, fever and dizziness (Marwan, 2021).

The second vaccine used in Indonesia is Astrazeneca. This vaccine is produced by the UK. News about this vaccine has spread around the world. AEFIs caused by Astrazeneca include fever for 1-3 days, nausea, vomiting, dizziness, weakness, pain, swell-

ing, redness at the injection site, even the worst is death caused by blood clots. However, the Astrazeneca company itself has provided guidance regarding this vaccine. Astrazeneca is a vaccine intended for people aged 18 and over, especially for the elderly. There are two doses that have an injection period of three months. If there are AEFI symptoms, it is advisable to immediately take pain relievers and contact the health service if there are more severe symptoms (Widayanti and Kusumawati, 2021).

A literature study in 33 countries by Sallam in 2021 regarding the COVID-19 vaccine which states that countries with the highest vaccine acceptance rates include Ecuador (97.0%), Malaysia (94.3%), Indonesia (93.3%) and China (91.3%). Meanwhile, countries with the lowest acceptance rates included Kuwait (23.6%), Jordan (28.4%), Italy (53.7), Russia (54.9%), Poland (56.3%), US (56.9%), and France (58.9%) (Sallam, 2021).

A total of 10 cohort observational research articles as a source of meta-analysis of the effect of vaccination on COVID-19 infection. This study shows that vaccination has a statistically significant effect on infection in COVID-19 patients. The forest plot results show that vaccination reduces the risk of COVID-19 infection. Individuals with vaccinations were protected from the risk of being infected with COVID-19 by 0.22 times compared to individuals who did not have vaccinations, and this result was statistically significant (aHR= 0.22; 95% CI= 0.13 to 0.36; $p < 0.001$). The heterogeneity of study data showed $I^2 = 97\%$, which means that the effect estimates between primary studies in this meta-analysis varied. Thus, the calculation of the average effect estimate is carried out using the random effect model approach.

Vaccination can reduce COVID-19 infection, this result is in accordance with

the hypothesis. Liu et al. (2021) reported that among individuals infected with COVID-19, vaccination significantly reduced the risk of death (aHR= 0.20; 95% CI= 0.08 to 0.49; p= 0.005).

Previous study has shown that Moderna or Pfizer vaccines provide excellent protection against severity in the general population (Baden et al., 2021; Pollack et al., 2020; Xia et al., 2020; Havers et al., 2021). This protection consists of prevention of infection and prevention of severe outcomes after individuals are infected, although it is currently not well reported whether vaccines reduce the likelihood of developing severe outcomes after individuals are already infected.

Tande et al. (2022) demonstrated that vaccination using an mRNA vaccine could decrease the rate of asymptomatic SARS-CoV-2 infection among individuals tested during pre-procedural molecular screening. These studies demonstrated a significant reduction in asymptomatic infection, similar results to those in clinical trials evaluating symptomatic infection prevention after vaccination with mRNA vaccines (Polack et al., 2020; Voysey et al., 2021).

This study concludes that the COVID-19 vaccination is effective in reducing the risk of COVID-19 infection. This study recommends that researchers conduct further research regarding the effect of vaccination on COVID-19 infection, the severity and even death in individuals infected with COVID-19.

AUTHOR CONTRIBUTION

Farida Nurhayati as the main researcher who chose the topic, conducted a search for data collection in this study. Setyo Sri Raharjo and Bhisma Murti conducted data analysis and reviewed research documents.

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The study was self-funded.

CONFLICT OF INTEREST

There is no conflict of interest in this study.

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