IJTID. Volume 12 No 2 May-August 2024 e-ISSN: 2356-0991; p-ISSN:2085-1103
Sinta 2 (Decree No: 105/E/KPT/2022) Available online at https://e-journal.unair.ac.id/IJTID

Review Article

IJTID

(INDONESIAN JOURNAL OF TROPICAL AND INFECTIOUS DISEASE)

Scientific Journal of Tropical and Infectious Disease

Effectiveness of Vaccines Booster Against Infection, Severe Disease and Death Related to COVID-19 : A Systematic Review and Meta-Analysis

Mujahidah Khalisha[1], Melvanda Gisela Putri[1], Zulfa Nurfitri Ramadhani[1], Paulus Parholong Siahaan[1], Rafi Alfian Razan[1], Ratna Devi Antari[1], Adiba Hasna Hanifah[1], Budi Utomo[1*], Shifa Fauziyah[2] , Pandaram Muthu[3]

[1]Department of Public Health and Preventive Medicine, Faculty of Medicine, Universitas Airlangga, Tambaksari, Surabaya, East Java, Indonesia
[2]Doctoral Program of Medical Science, Faculty of Medicine, Universitas Airlangga, Tambaksari, Surabaya, East Java, Indonesia
[3]Department of Biomedical Engineering, College of Engineering and Technology, SRM Institute of Science and Technology, Tamilnadu, India

OPEN ACCESS

ARTICLE INFO

Received: May 21, 2024
Accepted: May 29, 2024
Published: August 30, 2024
Available online: August 30, 2024

*) Corresponding author:
E-mail: budiutomo@fk.unair.ac.id

Keywords:
Vaccine
Booster
BNT162B2
m-RNA 1723
COVID-19

Abstract

COVID-19 is an infectious disease as a result of a type of corona virus. COVID-19 is now a pandemic affecting many countries. This study aims to know the effectiveness of booster vaccines to reduce the severity of illness, confirm infection, hospitalization, death in humans infected with COVID-19. The specific purpose was to analyze the severity of COVID-19 disease in humans by booster and without booster. The design of this study was a systematic review and meta-analysis based on observational studies, published in databases such as PubMed, Embase, MedRxiv, Nature and Scopus. In the search for articles, the limitations of 2021 to 2022 are used. This research was analyzed quantitatively through the Review Manager 5.4.1 program. Study was taken from 13 journals that met the criteria for a meta-analysis. With the population aged over 18 years, and using the type of vaccine BNT162b2 or mRNA. The population of this study came from Israel, Italy, England, Qatar, Brazil, Turkey, Puerto-Rico, Northern Bangkok, Vicinities and Thailand. Significant results were obtained for each outcome. The OR values of BNT162b2 booster vaccine against confirmed infection OR 0.16 (95% CI 0.06 – 0.45), against symptomatic disease 0.22 (95% CI 0.11 – 0.44), against asymptomatic disease OR 0.72 (95% CI 0.69 – 0.74), against hospitalization OR 0.12 (95% CI 0.06 – 0.22), against severe disease OR 0.15 (95% CI 0.07 – 0.33), and against death OR 0.10 (95% CI 0.04 – 0.31). Administration booster vaccines are effective in reducing infection rates, disease severity, and deaths from COVID-19.

Cite this as: Khalisha, M., Putri, M. G., Ramadhani, Z. N., Siahaan, P. P., Razan, R. A., Antari, R. D., Hanifah, A. H., Utomo, B., Fauziyah, S., Muthu, P. (2024). Effectiveness of Vaccines Booster Against Infection, Severe Disease and Death Related to COVID-19 : A Systematic Review and Meta-Analysis. *Indonesian Journal of Tropical and Infectious Disease*, 12(2) : 132–150. https://doi.org/10.20473/ijtid.v12i2.45606

INTRODUCTION

In December 2019, a local epidemic of COVID-19 was reported in Wuhan, China after it was caused by SARS-CoV-2. Since 2020, COVID-19 has outspread globally and is now affecting many countries. Over 346 million confirmed cases and beyond 5.5 million deaths have been announced throughout the world as of January 23, 2022. The death rate from COVID-19 in Indonesia reached 147,342 of the total positive cases of COVID-19, with the Case Fatality Rate (CFR) reaching 3.15% as of February 24, 2021. Carrying out a complete dose of vaccination is one of the prevention strategies for dealing with the transmission of the SARS-Co-2 virus.[1]

Beyond 409 million confirmed infections and 5.8 million deaths were reported universally in February 2022. At the geographical level, the Western Pacific Region showed a 19% improvement in new weekly cases, whereas the rest of the world saw a drop: Southeast Asia (37%), and the Americas (33%). the two most populous regions in the world (32%), and region of the Eastern Mediterranean (12 %).[2]

The pandemic has been going on for a couple years, but so far, no effective therapy has been found. The therapy used for COVID-19 is an antiviral that is not specific for the SARS-CoV-2 strain. The existing therapies are divided into several groups, namely viral protease inhibitors such as lopinavir, RNA virus inhibitors such as favipiravir which is commonly used for influenza therapy, immunomodulatory inhibitors of the virus, improvement of host immunity, inhibitors of fusion of virus with host cells such as bromhexine, and inhibitors of entry. virus in host cells such as convalescent plasma therapy.[3] This convalescent plasma therapy still raises the pros and cons of experts. According to Joyner et al. (2020)[4] covalent plasma donor therapy is still less significant for medication of COVID-19 patients.[4]

However, based on research by Salazar et al (2020), this therapy increased the clinical improvement of patients.[5] In addition, COVID-19 patients are also given symptomatic therapy only to treat existing symptoms. Therefore, a strategy is needed in dealing with the transmission of the SARS-CoV-2 virus, namely through prevention.

The infection cases have risen since the appearance of Omicron, the new variant of SARS-CoV-2. There are 26 to 32 variants found in the spike region of Omicron, some of which are worrisome and may be a source of immune escape and high communicability. The situation remains uncertain, however. Due to the presence of mutations that can confer the potential for evading immunity as well as increased transmissibility, Omicron likely has the potential for wider global spread. Given these characteristics, it is possible there will be spikes in COVID-19 cases in the future, depending on a number of factors, which could lead to the major consequences. The overall global risk associated with Omicron's new variant of concern is considered very high.[6] Omicron's global resurgence has raised serious concerns. In countries with good vaccination coverage, Omicron has led to a fresh wave of illnesses. Around 30 mutations in Omicron are identical to the earlier variation of concerns, which might reduce VE. As a result, the appearance of Omicron is anticipated to pose a serious threat to public health and might change the course of COVID-19 vaccinations.[7]

Previous study shows that 56% of the 210 persons in this cohort research who had seroconversion evidence during a regional Omicron variant increase denied having recently having had an Omicron

variant infection.[8] The evidence in the literature demonstrates that these eight vaccinations are quite successful in defending the populace against deadly illnesses, yet there are some concerns about their safety and side effects. Additionally, booster injections and immunizations tailored to certain variants would be necessary.[9]

One of preventive actions that could be taken in order to decrease infection cases is with a booster dose vaccine. So far, the relationship between booster vaccines on the incidence of confirmed infection, death, hospitalization and disease severity is still unknown. Furthermore, the data regarding the impact of booster vaccines are considered to be lacking. This study aims to determine the effectiveness of booster vaccines on disease severity, confirmed infections, hospitalizations and deaths.[1]

MATERIALS AND METHODS

Search Strategy

This study collects retrospective or prospective case-control and cohort observational studies, which will then synthesize data and/or analyze data from these studies to create a meta-analysis produce meta-analysis and/or systematic review. This analysis uses the priority report item recommendations in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement as a reference for the method procedure looking[7]. The research sources came from the literature obtained from the online databases PubMed (n = 50), Medrxiv (n = 508), Embase (n = 176), Nature (n = 50), and Scopus (n = 44). The data collection technique in this research is scientific research from English-language journal publications using the keywords “Vaccine” AND (“booster” OR “third dose”) AND ('COVID-19” OR “Sars-CoV-2”) AND (“severe illness" OR "severe disease" OR "hospitalization" OR "mortality" OR "death"). Article searches used the 2021 to 2022 limits. Based on the search results using the relevant keywords on a predetermined search engine, then the articles were chosen based on its abstract and title then selected based on the inclusion and exclusion criteria. Next was data grouping based on the variables to be discussed and then data synthesis to obtain a systematic study related to the effectiveness of booster vaccines against disease severity and mortality due to COVID-19.

Study Selection

Articles were first reviewed by three independent authors (MK, MGP, PPS) based on the title and abstract. All inappropriate publications were removed. Then the full text of the remaining articles was reviewed. Three independent reviewers evaluated articles as potentially suitable. After that, the reviewers discussed until the suitability of the article to be used was obtained.

Eligibility and Inclusion Criteria

The research design used in this study is observational research and includes cross-sectional, case-control, and both retrospective and prospective cohorts. The population studied were all ages that had been received booster vaccinations; studies with COVID-19 booster vaccine interventions, studies with a population comparator that had not received a booster vaccine (non-booster group), research on the vaccine’s booster effectiveness against severe disease, confirmed infection, and mortality related to COVID-19, and studies in English were all included.

Exclusion Criteria

Studies that are not observational, systematic review and/or meta-analysis,

studies that go into duplication, vaccine effectiveness data that do not match the outcome, and studies in a language other than English.

Data Extraction

The data extraction consist of author's name; year of publication; research design; research location; the population under study; total number of samples and gender; average age of the sample with standard deviation; statistical analysis used in the literature; types of primary vaccine; the timing of the booster vaccine is different from the second vaccine; types of booster vaccines.

Quality Assessment

Evaluation of the quality of studies from the literature collected was using The Newcastle-Ottawa Scale (NOS) which assesses through three major parts, namely: selection, comparability, and exposure. In this study, the assessment based on NOS scores is [10] : (1) Good quality: 7-9 points; (2) Fair quality: 4-6 points; (3) Low quality : 0-3 points.

Analysis

After data extraction, data processing in the Review Manager (RevMan) version 5.4 program was performed. A random effect model was used to approximate the combined odds ratio (OR) for the incidence of confirmed infection, high morbidity, and COVID-19-related death attributable to the booster and non-booster groups with 95% confidence intervals. Then heterogeneity between the statistically tested studies test 2 and I2, with $p<0.10$ and 50%, sequentially, was reviewed as an indicator of diversity. The effectivity of vaccine is marked as the OR, along with the 95% confidence interval.

RESULTS AND DISCUSSION

Characteristics of Included Studies

Researchers conducted a search for predetermined keywords, through the PubMed, Medrxiv, Embase, Nature, and Scopus databases. After conducting a search, the researcher obtained a total of 828 available literatures. The researcher conducted an examination with the same title in the 386 studies, and excluded as many as 34 duplicates, so that there were 794 studies without the same title. Then the first stage of screening was carried out to find the availability of full text from the literature, and it was found that one study was not available in full text, so that there were 793 studies left. In the second stage of screening, the researchers carried out the first stage of the screening process, and obtained 760 titles and abstracts that did not match so that there were 33 studies remaining. The researcher then continued with the third stage of the screening process, and 17 studies were excluded because the desired outcome was not obtained, so that the remaining 16 could be included in the systematic review and 13 could be included in the meta-analysis. The results of this filtering process are shown in Figure 1. The characteristics of sixteen observational studies are summarized in Table 1.

A total of 828 publications were screened for Effectiveness of Booster Vaccines COVID-19. A total of 13 journals met the criteria for the meta-analysis. All included studies were reported during the 2021 publication year. All journals are in English, with the population aged over 18 years, and using the type of vaccine BNT162b2 or mRNA. The population of studies came from Israel, Italy, England, Qatar, Brazil, Turkey, Puerto-Rico, Northern Bangkok, Vicinities, and Thailand. Significant results were obtained for each

outcome. The studies were used to explain the difference in outcome between the population that was given a booster and that was not given a booster. Six studies explain the effectiveness of boosters against confirmed infection, as many as five journals explain the effectiveness of boosters against symptomatic disease. Three studies explain the effectiveness of boosters against asymptomatic disease, six studies explain s the effectiveness of boosters against hospitalization, seven studies explain the effectiveness of boosters against severe disease and seven studies describe the effectiveness of boosters against death.

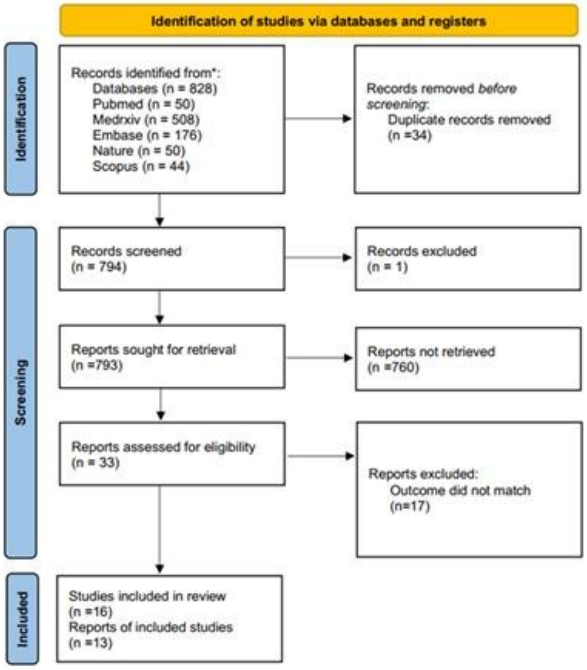

Figure 1. Literature screening chart using PRISMA 202011. Of the 16 studies included in the inclusion, a systematic review was carried out and 13 were subject to a meta-analysis.

Table 1. Characteristics of the included studies and the results.

Author & Year	Study Location	Study Design	Population/Age Range	Duration time of Research	Type of Vaccine Booster/Result
Muhsen et al.[11]	Israel	Observational retrospective cohort study	41,623 participants/Observed group: >60 years old, Control group: all ages	July-September 2021	BNT162b2 **Symptomatic disease**: Incidence Rate Ratio (IRR) 0.29 ; relative rate reduction 71% **Hospitalization**: IRR 0,20; relative rate reduction 80% **Death**: decrease from 0.3 per 1000 population in week 34 to 0.1 per 1000 population in week 36

Spitzer et al.[12]	Tel Aviv, Israel	Prospective cohort study	1,928 participants/Aged 18 years old and older	August 8 and 19 - September 20, 2021.	BNT162b2 **Confirmed infection**: adjusted Hazard Ratio (aHR) 0.07 (95% CI, 0.02-0.20); 44 participants (5 booster group, 39 non-booster group) **Symptomatic disease**: 31/44 (70.5%)
Mattiuzzi and Lippi[13]	Italia	Case-control	5.2 million participants/Older (>60 y.o), fragile people, booster vs. non-booster group	October-December 2021	BNT162b2 **Confirmed infection**: Vaccine Effectiveness (VE) 65% **Hospitalization**: VE 69% **Severe disease (ICU admission)** : VE 67% **Death**: VE 97%
Mattiuzzi and Lippi[13]	Italia	Case- control	1,549,747 participants/60 years old and older	October-December 2021	BNT162b2 **Confirmed infection**: 75% lower risk **Hospitalization & ICU admission**: 82-83% lower risk **Death**: 81% lower risk
Berec[14]	Czech Republic	Retrospective Cohort study	10,701,777 participants/Various age	March 1 2020 (first detected case) - November 20 2021	Comirnaty, Spikevax **Confirmed Infection**: Comirnaty booster: VE 92% **Hospitalization**: Comirnaty booster: VE 95%; Spikevax booster: 98% **Death**: VE Comirnaty booster: 97%; Spikevax: close to 100%
Spitzer et al.[15]	Israel	Observational retrospective cohort study	5,065,502/≥ 60 years old	July 30 - October 10 2021	BNT162b2 **Confirmed infection**: Rate Ratio 12.3 (95% CI 11.8-12.8) **Severe disease**: Rate Ratio 17.9 (95% CI 15.1-21.2) **Death**: Rate Ratio 14.7 (95% CI 10.0-21.4)
Bar-On[16]	Israel	Observational restrospective cohort study	1.137.804/≥ 60 years old	July 30 - August 31 2021	BNT162b2 **Confirmed infection**: aHR 11.3 (95% CI 10.4012.3) **Severe disease**: aHR 19.5 (12.9-29.5)

Andrews et al.[17]	England	Test-Negative Case-Control design	271,747/>50 years old	September 13 - October 29, 2021	BNT162b2 **Symptomatic disease**: VE 87.4% (primary vaccine ChAdOx1s: Vaxzefria, Astra Zeneca); VE 84.4 % (primary vaccine BNT162b2 (Comirnaty, Pfizer-BioNTech)
Abu Raddad[18]	Qatar	Retrospective cohort studies	2,232,224/All ages	January 5, 2021 and January 9, 2022	BNT162b2, mRNA-1273 **Symptomatic disease**: BNT162b2: aHR 0.50 (95% CI 0.47-0.53); mRNA-1273 aHR 0.49 (95% CI 0.43-0.57)
Silva, T C et al,[19]	Brazil	Test-negative design case control	14 million/All ages	18 January to 11 November 2021	BNT162b2 **Confirmed infection**: VE 92.7% **Hospitalization**: VE 97.3%
Andrews et al.[17]	England	Test-negative case-control design	aged 18 years and over	13 September 2021 to 5 December 2021	BNT162b2, mRNA-1273 **Symptomatic infection**: VE 94-97% **Hospitalization**: VE 99.2% (primary vaccine ChAdOx1s); VE 98.6% (primary vaccine BNT162b2) **Death**: VE 97.8% (primary vaccine ChAdOx1s); VE 98.7% (primary vaccine BNT162b2)
Barda et al.[20]	Israel	Retrospective cohort studies	1,158,269/37-68 years old	July 30, 2020, and Sept 23, 2021	BNT162b2 **Hospitalization**: VE 03% **Severe disease**: VE 92% **Death**: VE 81%
Uzun et al.[21]	Turkey	Retrospective cohort studies	1,401/General populations	August 1-August 10 2021	BNT162b2 **Hospitalization:** lower hospitalization in booster group (11/1,401 = 0.8%)
Robles-Fontán[22]	Puerto-Rico	Case Control	540,140/General populations	December 2020 - November 28, 2021	BNT162b2, mRNA-1273 **Hospitalization:** VE 89% **Death:** VE 94%

Sritipsukho[23]	Northern Bangkok	A test-negative case-control design	3,353/Adults ≥18 years old	25 July 2021 to 23 October 2021.	BNT162b2, ChAdOx1s **Confirmed infection**: VE 98% (BNT162b2 booster); VE 86% (ChAdOx1s booster) **Asymptomatic disease**: 3/1118 (ChAdOx1s booster); 0/1118 (BNT162b2 booster) **Hospitalization**: **Mild**: 9/1118 (ChAdOx1s booster); 1/1118 (BNT162b2 booster) **Moderate**: 0/1118 (ChAdOx1s booster); 0/1118 (BNT162b2 booster) **Severe disease**: 0/1118 (ChAdOx1s booster); 0/1118 (BNT162b2 booster) **Critical**: 0/1118 (ChAdOx1s booster); 0/1118 (BNT162b2 booster)
Arbel et al.[24]	Israel	Retrospective cohort studies	758,118/≥ 50 years	August 6-September 2021	**Death**: aHR 0.10 (95% CI 0.07-0.14; P<0.001)

Quantitative Analysis of the Effectiveness of Booster Vaccines Against Deaths

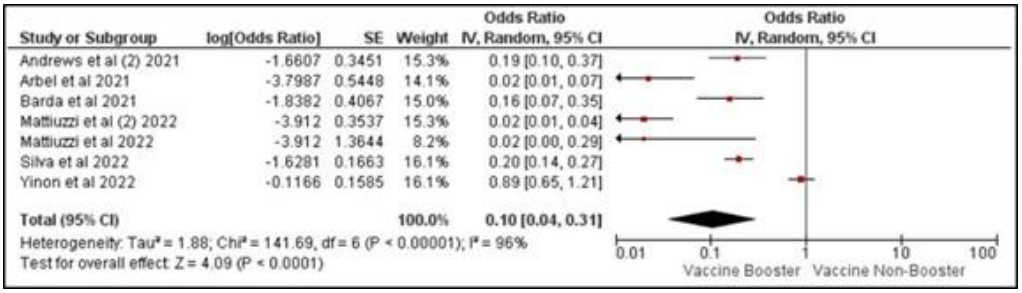

Figure 2. Forest Plot with outcome against confirmed infection by BNT162b2 vaccine booster.

From the six studies that we used to assess the BNT162b2 effectiveness of booster vaccine to prevent infection of SARS CoV-2, the results were significant with OR 0.16 (95% CI 0.06 – 0.45) and P = 0.0004 (Figure 2). The heterogeneity of the six studies was above 50% (I2: 100%, P < 0.00001), which means there was a high level of heterogeneity. So, using the random effect model (REM) analysis model , from the results of the funnel plot (Figure 3), it appears that there are four journals on the left and two on the right, so it looks asymmetrical due to bias.

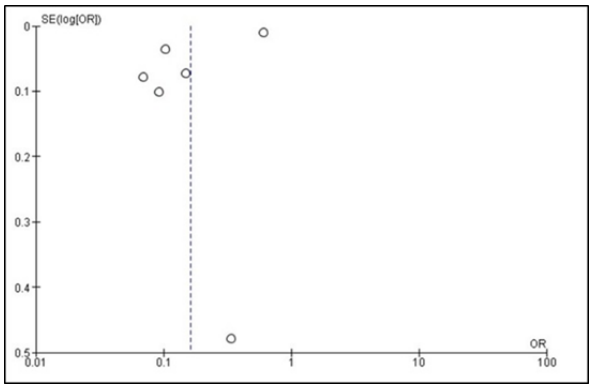

Figure 3. Funnel Plot with outcome against confirmed infection by BNT162b2 vaccine.

Quantitative Analysis of the Effectiveness of Booster Vaccines Against Symptomatic Disease

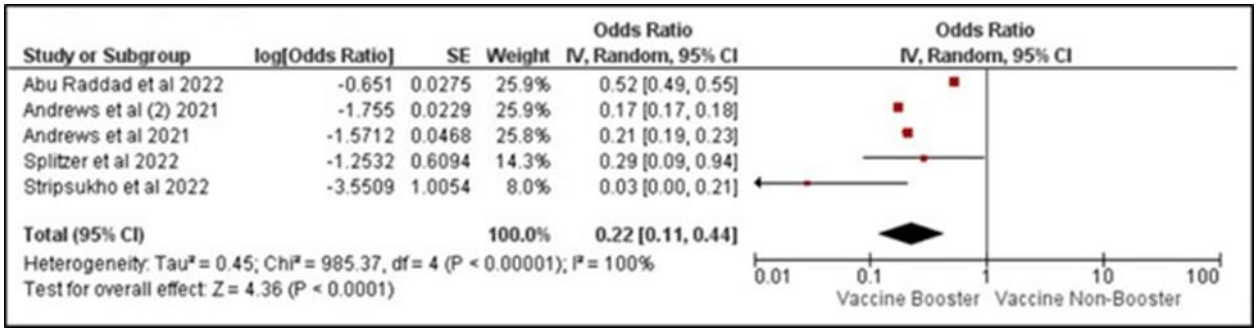

Figure 4. Forest Plot with outcome against symptomatic disease by BNT162b2 vaccine booster.

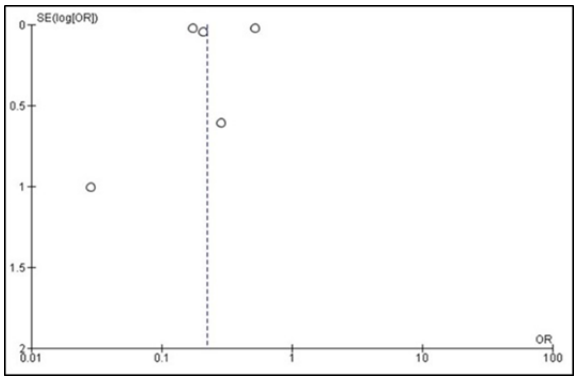

Figure 5. Funnel Plot with outcome against symptomatic disease by BNT162b2. vaccine

For this study, we used five publications to assess the BNT162b2 booster vaccine effectiveness to prevent symptoms for SARS-CoV-2 infection. The results were significant with OR 0.22 (95% CI 0.11 – 0.44) and P < 0.0001 (Figure 4). The heterogeneity of the five studies was above 50% (I2: 100%, P < 0.00001), which means it had a high level of heterogeneity. So, using the random effect model (REM) analysis model from the results of the funnel plot (Figure 5), it appears that there are three journals on the left side and two on the right, so it looks asymmetrical due to bias.

From the three studies that we used to assess the BNT162b2 booster vaccine effectiveness to prevent asymptomatic infection of SARS CoV-2, the results were significant with OR 0.72 (95% CI 0.69 – 0.74) and P < 0 .00001 (Figure 6). For three studies, heterogeneity was below 50% (I2: 0%, P 0.57), which means they had a low level of heterogeneity.

Quantitative Analysis of the Effectiveness of Booster Vaccines Against Asymptomatic Disease

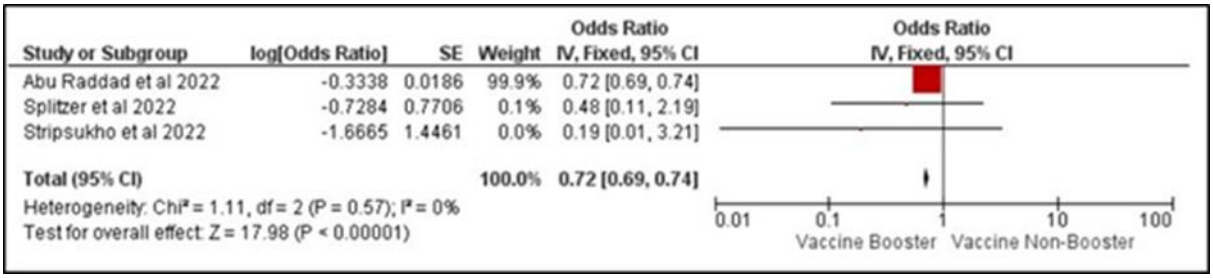

Figure 6. Forest Plot with outcome against asymptomatic disease by BNT162b2 vaccine booster.

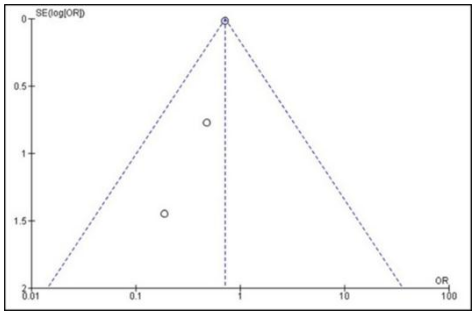

Figure 7. Funnel Plot with outcome against asymptomatic disease by BNT162b2 vaccine booster.

had a low level of heterogeneity.

So. using the fixed model (FM) analysis model, from the results of the funnel plot, it appears that there are two journals on the left side which appear asymmetrical due to bias (Figure 7).

Quantitative Analysis of the Effectiveness of Booster Vaccines Against Hospitalizations

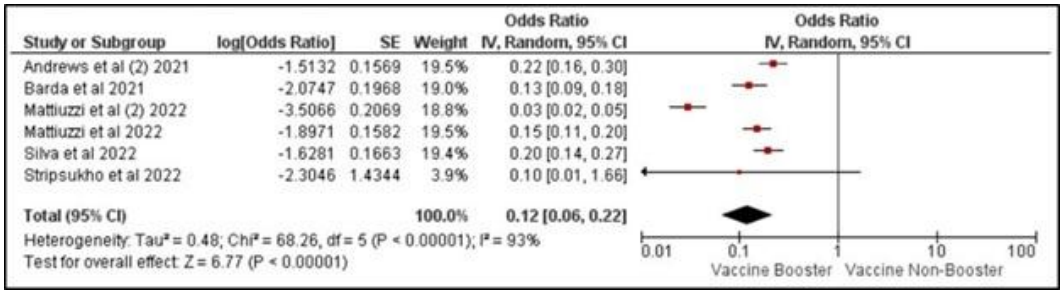

Figure 8. Forest Plot with outcome against hospitalization by BNT162b2 vaccine booster.

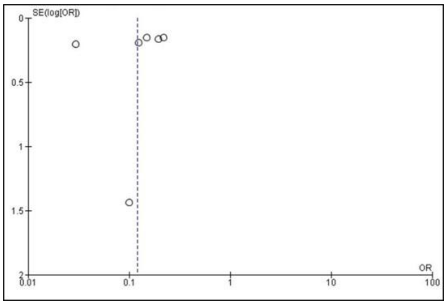

Figure 9. Forest Plot with outcome against hospitalization by BNT162b2.

From the six studies that we used to analyze the BNT162b2 booster vaccine effectiveness to prevent hospitalization, the results were significant with OR 0.12 (95% CI 0.06 – 0.22) and P <0.00001 (Figure 8). From six studies, heterogeneity was above 50% (I2: 93%, P 0.00001), which means there was a high degree of heterogeneity.

So, using the random effect model (REM) analysis model, from the results of the funnel plot, it appears that there are two journals on the left side, one in the middle, and the other three on the right side, so it looks asymmetrical due to bias (Figure 9).

Quantitative Analysis of the Effectiveness of Booster Vaccines Against Severe Diseases

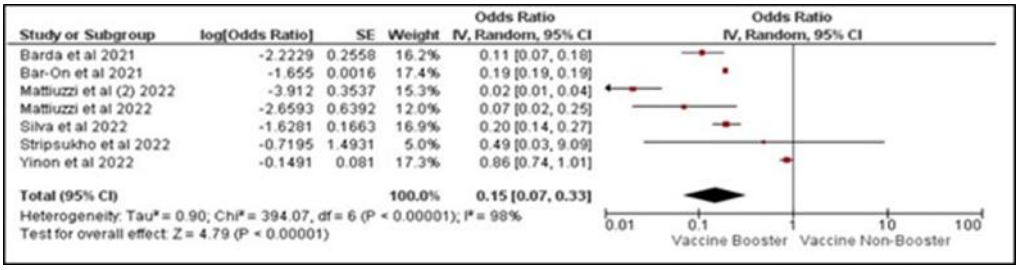

Figure 10. Forest Plot with outcome against severe disease by BNT162b2 vaccine booster.

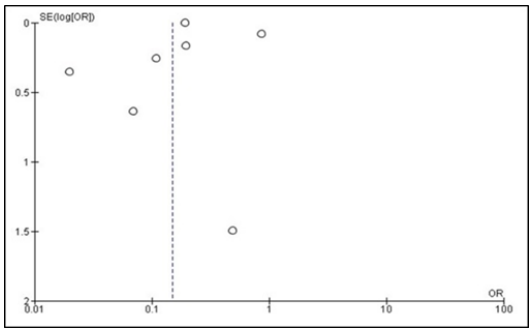

Figure 11. Funnel Plot with outcome against severe disease by BNT162b2 vaccine booster.

From the seven studies that we used to analyze the BNT162b2 booster vaccine effectiveness to prevent severity, the results were significant with OR 0.15 (95% CI 0.07 – 0.33) and P < 0.00001(Figure 10). The heterogeneity of the seven literatures was above 50% (I2: 98%, P 0.00001), which means there was a high degree of heterogeneity. So, using the random effect model (REM) analysis model, from the results of the funnel plot, it appears that there are three journals on the left side, and the other four on the right side, so it looks asymmetrical due to bias (Figure 11).

Quantitative Analysis of the Effectiveness of Booster Vaccines Against Death

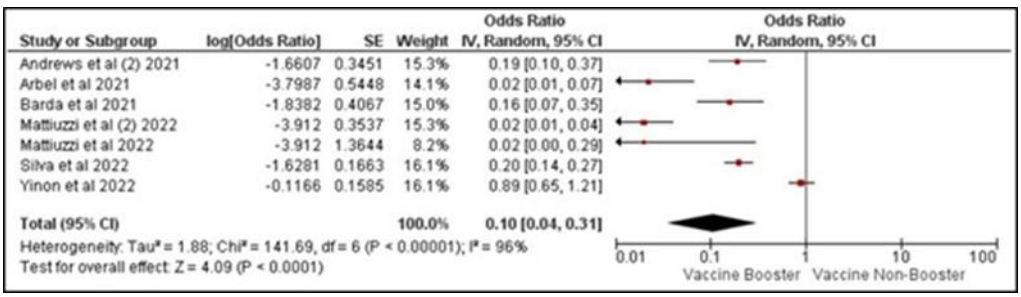

Figure 12. Forest Plot with outcome against death by BNT162b2 vaccine booster.

Figure 12 shows Vaccine Booster BNT612b2 Against Death. The urgency of vaccine to prevent death is high. The two doses of vaccine are essential, but over time the effectiveness wanes. Booster vaccine is there to help. Study showed that in people given BNT162b2 vaccine had 90%lower mortality than those who were not. The study was done on people who were 50 years old age and older, with deaths totaling 65 and 137 in both booster and non-booster participants respectively at 54 days' time (95%CI, 0.07-0.14; p<0.001)[29]. This finding is also supported by other research in individuals of 50 years old of age, which showed that vaccine effectiveness was 97.8 over 14-34 days after booster was injected (95%CI, 94.4-99.1).

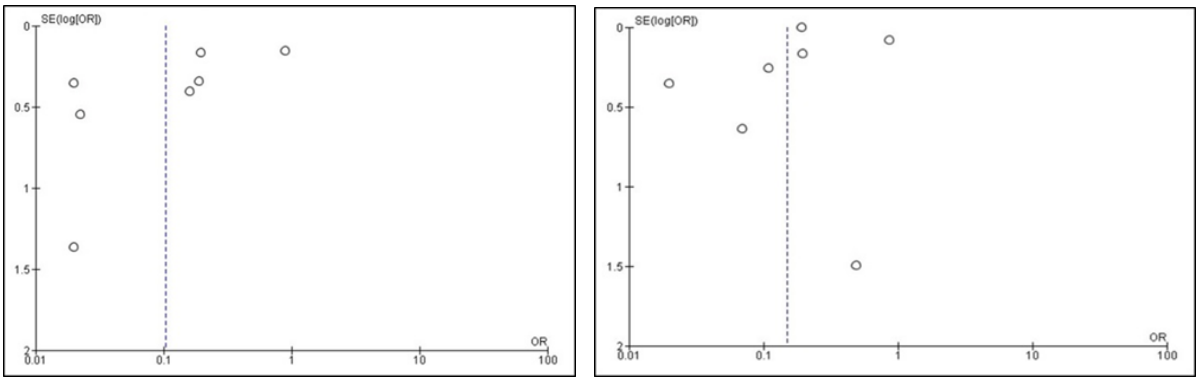

Figure 13. Funnel Plot with outcome against death by BNT162b2 vaccine booster.

Figure 13 indicates that there is no publication bias, because the structure of the image is symmetrical between right and left. Publication bias can be influenced by several factors. Here are some common ones:

Editorial Preferences: Journal editors play a crucial role in deciding which studies get published. Their preferences, biases, and interests can impact the selection process[12].

Selective Reporting: Researchers may choose not to submit or publish studies with negative findings (often called "negative studies"). They might perceive these results as less interesting or consider their research to have "failed" if the effects are not statistically significant.

Funding Influences: Financial interests, conflicts of interest, or pressure from funders can affect the decision to publish certain results. Researchers may suppress negative findings from clinical trials to maintain funding or align with specific agendas.

Publication bias distorts the overall body of evidence and can impact decision-making across various fields. It's essential to recognize and address these factors to ensure a more balanced representation of research outcomes.

DISCUSSION

The high number of infections from the coronavirus necessitates accelerated efforts in providing vaccination coverage. The waning protection from the vaccine against COVID-19 and the introduction of SARS-CoV-2 Omicron (B.1.1.529) variant have prompted efforts to scale up COVID-19 booster immunization. Booster doses are given to people who have already been vaccinated and have completed their primary period of prevention (presently first and second doses of vaccine against COVID-19 based on the type of vaccine).

Boosters can help to protect the clinically susceptible and unvaccinated by lowering infection. This study provides an analysis related to the effectiveness of the booster vaccine against many aspects that have not been carried out by other journals, namely confirmed infections, against symptomatic disease and asymptomatic disease, also severity and death[12,13].

There are 16 observational studies (Muhsen et al., 2022[14]; Spitzer et al., 2022[15]; Mattiuzzi et al., 2022[16]; Mattiuzzi et al., 2022[17]; Berec et al., 2021[18]; Bar-On et al., 2021[19]; Bar- On et al., 2021[20]; Andrews et al., 2021[21]; Abu Raddad et al., 2022[22]; Silva et al., 2022[23]; Andrews et al., 2022[24]; Barda et al., 2021[25]; Uzun et al., 2022[26]; Robles-Fontan et al., 2021[27]; Sritipsukho et al., 2021[28]; Arbel et al., 202[29]) which were analyzed qualitatively with a systematic review. The studies were carried out in nine different countries. Of the 16 studies, only 13 were analyzed quantitatively by meta-analysis.

Vaccine booster BNT162b2 Against Confirmed Infection

Our meta-analysis of six studies found booster vaccine became powerful in reducing the quantity of infections. This study showed the number of confirmed SARS COV-2 infections was decreased with the booster against the non-booster. Giving a booster of BNT162b2 vaccination can increase antibody neutralization. Increased neutralization titers will provide protection against infection. The infection rate in the booster group was lower than the non-booster group by a factor of 11.3 (95% confidence interval [CI], 10.4 to 12.3). The number of infections was lower on days 12 to 25 post-booster compared to four to six days post-booster [20]. This is also supported by a study conducted by Omer and Malani (2021) who compared the incidence of infection in the mRNA booster group, two doses of mRNA vaccine and those without vaccine[30]. In this study, bias was found, which may be caused by data sources, the presence of comorbidities, differences in behavior to seek help in the booster and non-booster groups. In addition, it could be caused by the limited sample, the low incidence of asymptomatic infection, and some patients who did not perform the PCR test.

A study conducted in Israel assessed the effectiveness of a booster dose of the BNT162b2 vaccine (Pfizer-BioNTech) against SARS-CoV-2 infection and showed a value of 96.8% for people aged 16-59 years and 93.1% for people over 60 years in week three. However, there was a decrease in vaccine effectiveness after eight weeks in the 16-59 year age group and 11 weeks in the over 60 year age group. This decline became more pronounced in the final 2-3 weeks of evaluation, with estimates of vaccine effectiveness reaching 77.6% and 61.3% for people aged 16-59 years and over 60 years, respectively. This decrease occurred at the same time as the activity of the Omicron variant increased. Despite this, vaccines continue to provide moderate to high protection against cases of abuse, including reductions in cases, hospitalizations, and deaths associated with COVID-19[31].

Vaccine Booster BNT162b2 Against Symptomatic Disease

Based on the results of meta-analysis of five studies, it was found that BNT162b2 booster was effective against symptomatic disease-related COVID-19, with a significant association ($P < 0.05$). The heterogeneity of the study was 100%, with an OR 0.22 (95% CI 0.11-0.44). The results of a study evaluating the third dose of BNT162b2 effectivity in the United States unified health order show that vaccine effectivity declines following two

doses of BNT162b2 and that obtaining dose number three gives different protection against the infection of SARS-CoV-2 COVID-19 in-patients than only receiving two doses. Given that 91% of the infections were symptomatic, the study found no significant differences in the adjusted effectiveness of three BNT162b2 dosages against symptomatic COVID-19 (90 %[95% CI 88-92])[32]. Our review also has limitations. Of the study variants, two were case-control observational studies and the other three were cohort studies.

A prospective cohort study was conducted in Hong Kong to measure the effectiveness of BNT162b2 and CoronaVac vaccines against asymptomatic and symptomatic SARS-CoV-2 omicron infections. The study involved 8636 individuals aged 5 years and older, who were enrolled from all 18 districts of Hong Kong. The primary outcomes were the incidence of SARS-CoV-2 infection and the vaccine effectiveness of BNT162b2 and CoronaVac vaccines. The study found that statistically significant protection against asymptomatic and symptomatic SARS-CoV-2 omicron infection was found only for those who received a BNT162b2 or CoronaVac booster dose, with a vaccine effectiveness of 41.4% and 32.4%, respectively. The vaccine effectiveness of BNT162b2 and CoronaVac boosters was further increased to 50.9% and 41.6% for symptomatic omicron infections. A similar pattern of vaccine effectiveness was also conferred after receipt of a BNT162b2 booster by individuals who received a CoronaVac primary vaccination series[33].

Vaccine Booster mRNA-1273 Against Symptomatic Disease

From the two studies that we reviewed to assess mRNA-1273 booster vaccine effectivity to avert the occurrence of symptomatic infection of SARS CoV-2, the results were significant with OR 0.30 (95% CI 0.10 – 0.94) and P value = 0.04. Using the random effect model (REM) analysis model, the heterogeneity of the two studies was above 50% (I2: 97%, P < 0.00001), which means that it has a high level of heterogeneity. One of the included studies, by Andrews et al. (2021) also found mRNA booster vaccines against symptomatic disease in the age group 50 years and above are effective against symptomatic disease[21]. According to research studies from Doria-Rose et al. (2021), dose number three of mRNA-1273 can increase neutralization of the Omicron titer and can substantially decrease the possibility of disease with symptoms in COVID-19 infection[32]. In this study, publication bias was found because there were differences in study designs, namely case control vs retrospective cohort studies, differences in population size, differences in age groups compared, and differences in the time span of booster vaccines after the second vaccine.

Vaccine Booster BNT612b2 Against Asymptomatic Disease

SARS-CoV-2 contaminations are frequently symptomless and can present a possibility to susceptible people, making them rare breakthrough infections with contagious potential that pose a unique issue[33]. Identifying their possibility to disseminate the agent along a period of time of direct contact with an infected person along the general communal, decreases the possibility of contagious contamination, This may take place among patients with symptomless contamination or some period of time prior to the onset of the signs, and is mostly principal among health control employees, initial staff, also further important and forefront staff[34]. The noteworthy findings were based on a three

literature reviews of BNT162b2 effectivity booster doses in order to prevent asymptomatic infection of SARS-CoV-2. This outcome is more consistent with earlier research. The Moderna mRNA and Pfizer-BioNTech vaccines against COVID-19 were around 90% successful in order to prevent asymptomatic and symptomatic contamination with SARS-CoV-2 32, according to a web of prospective cohorts between forefront staff. The Pfizer–BioNTech BNT162b2 messenger RNA vaccine has also been demonstrated to lower the incidence of asymptomatic illness and the related infectivity [33].

Vaccine Booster against Hospitalization

In terms of COVID-19-related urgent care/emergency room (UC/ER) for in-patients and visits, vaccine effectiveness (VE) increased after dose number three much more than after dose number two but decreased slowly since vaccination. In the time of mainly Omicron variant, the effectivity of vaccines against COVID-19 associated urgent care/emergency room in-patients and visits were 97% and 91%. But throughout the two months after booster dose, this dropped to 66% and 78% in the fourth month after booster dose[35]. This meta-analysis consisting of six studies of BNT162b2 booster vaccine shows that booster vaccine is effective in terms of reducing hospitalizations. The result is significant (P<0.000) and the heterogeneity of the study is 93% with an OR of 0.12 (95% CI 0.06-0.22).

Vaccine Booster BNT612b2 Against Severe Disease

Bar-On et al. (2021) compared COVID-19 confirmation rates and severe illness rates in individuals who had had a booster injection at least 12 days before (booster group) with those who had not had a booster shot (non-booster group) in the primary study. The verified rate of serious illness was reduced by a factor of 19.5 (95% CI, 12.9–29.5) at least 12 days following the booster dose. Those who had a booster (third) dose of BNT162b2 vaccination had significantly reduced rates of confirmed COVID-19 and severe illness, according to Bar-On et al. (2019) [19]. From the seven studies that we used to evaluate the effectiveness of the BNT162b2 booster vaccine to prevent severity, the results were significant with OR 0.15 (95% CI 0.07 – 0.33) and P<0.00001. The heterogeneity of the seven studies was above 50% (I2: 98%, P <0.00001), which means there was a high degree of heterogeneity.

Vaccine Booster BNT612b2 Against Death

The urgency of vaccine to prevent death is high. The two doses of vaccine are essential, but over time the effectiveness wanes . Booster vaccine is there to help. Study showed that people given BNT162b2 vaccine had 90% lower mortality than those who were not. The study was done on people who were 50 years old age and older, with total deaths of 65 and 137 in both booster and non-booster participants, respectively, at 54 days' time. (95%CI, 0.07-0.14; p<0.001)[29]. This finding is also supported by other research on individuals of 50 years old of age, which showed that vaccine effectiveness was 97.8 over 14-34 days after booster injection (95%CI, 94.4-99.1)[24].

STRENGTH AND LIMITATION

There are numerous limitations in this research. First, there are limitations in study period. Second, there may be unmeasured confounding factors such as sociodemographic factors, behavioral factors, and testing rate. Third, exploring

potential adverse effect may be concerned as limitations. Fourth, the under-reporting of patients with confirmed COVID-19 infection (whether they had a booster vaccination or not), especially when the health system is occupied, as well as the accessibility and capacity to examine and evaluate COVID-19 incidence rates for different outcomes. Fifth, there are significant population differences included in various studies regarding number of cases, gender, ethnicity, age, geographic area, level of vaccine population coverage, etc. Sixth, there were limitations in the amount of issued study literature researches. Seventh, there were limitations in the time of investigation following the vaccine booster doses. Eighth, the included studies used a variety of methods.

We used journals with four different methods (cohort, cross-sectional, retrospective cohort, case control) which guarantees the carefulness of the results interpretation. Ninth, serious occasions and more possible to have medical awareness and therefore be recorded and caught, which is the major key for monitoring severe disease and vaccine efficacy. Lastly, there are analysis limitations because of numerous research biases, similar study bias, and diversity. We performed a sub-population analysis to perceive the roots of diversity. The study described several features of the study as well as confirmed infection, severe illness, hospitalization, and death. To prevent language bias, we only used articles in English. To prevent publication influences, we looked for numerous sites and obtained data from credible sources to obtain issued works. Nevertheless, diversity and bias are unpreventable in systematic reviews and meta-analytical research. Thus, all limitations have to be reviewed during interpretation of the results.

CONCLUSIONS

From 16 observational studies conducted by systematic reviews, it was concluded that the booster vaccine group had lower rates of confirmed infections and lower severity of illness related to hospitalization and mortality. Then from the 16 observational studies that were carried out, a systematic review was carried out, followed by a meta-analysis of 13 observational studies.

From the outcomes of the meta-analysis, it was found that the booster vaccine is effective in reducing the severity of disease and preventing death in patients infected with COVID-19 with a protective Odds Ratio (OR) value < 1. The OR value of the BNT162b2 booster vaccine effectivity against confirmed infections is OR 0, 16, BNT162b2 booster vaccine against symptomatic disease is 0.22, mRNA-1273 booster vaccine against symptomatic disease is 0.30, BNT162b2 booster vaccine against asymptomatic disease is 0.72, BNT162b2 booster vaccine hospitalization is 0.12, booster vaccine BNT162b2 against severe disease is 0.15, and booster vaccine BNT162b2 against death is 0.10 This will speed up the handling of the COVID-19 disease by knowing the various conditions of the disease Fast handling of COVID-19 in accordance with the state of the disease will reduce deaths.

ACKNOWLEDGMENT

The authors thank the Department of Public Health and Preventive Medicine, Faculty of Medicine, Universitas Airlangga.

FUNDING

This research did not receive any funding.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTION

MK contributed to manuscript writing and literature collection; MGP contributed to data analysis and manuscript writing; ZNR contributed to statistical analysis and grammatical check; PPS contributed to methodology; RAR contributed to literature collection; RDA contributed to investigation; AHH contributed to methodology; BU contributed to manuscript writing and as supervisor; SF contributed to manuscript writing and as supervisor.

REFERENCES

1. WHO. Coronavirus disease (COVID-19): Vaccines. 2022.
2. WHO. Coronavirus. 2022.
3. Şimşek-Yavuz S, Komsuoğlu Çelikyurt FI. An update of anti-viral treatment of COVID-19. Turkish J Med Sci. 2021 Dec;51(SI-1):3372–90.
4. Joyner MJ, Wright RS, Fairweather D, Senefeld JW, Bruno KA, Klassen SA, et al. Early safety indicators of COVID-19 convalescent plasma in 5000 patients. J Clin Invest. 2020 Sep;130(9):4791–7.
5. Salazar E, Perez KK, Ashraf M, Chen J, Castillo B, Christensen PA, et al. Treatment of Coronavirus Disease 2019 (COVID-19) Patients with Convalescent Plasma. Am J Pathol. 2020 Aug;190(8):1680–90.
6. WHO. Enhancing response to Omicron SARS-CoV-2 variant. 2022.
7. Burhan E, Rachmadi RA. Omicron surge and the future of COVID-19 vaccinations. Med J Indones. 2022;31(1):80–4.
8. Joung SY, Ebinger JE, Sun N, Liu Y, Wu M, Tang AB, et al. Awareness of SARS-CoV-2 Omicron Variant Infection among Adults with Recent COVID-19 Seropositivity. JAMA Netw Open. 2022;5(8):E2227241.
9. Aggarwal A, Mehta S, Gupta D, Sheikh S, Pallagatti S, Singh R, et al. Clinical & immunological erythematosus patients characteristics in systemic lupus Maryam. J Dent Educ [Internet]. 2012;76(11):1532–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23144490
10. GA Wells, B Shea, D O'Connell, J Peterson, V Welch, M Losos PT. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2021.
11. PRISMA. PRISMA Flow Diagram. 2020.
12. Liu Q, Qin C, Liu M, Liu J. Effectiveness and safety of SARS-CoV-2 vaccine in real-world studies: a systematic review and meta-analysis. Infect Dis Poverty. 2021;10(1):132.
13. Zheng C, Shao W, Chen X, Zhang B, Wang G, Zhang W. Real-world effectiveness of COVID-19 vaccines: a literature review and meta-analysis. Int J Infect Dis. 2022;114:252–60.
14. Muhsen K, Maimon N, Mizrahi A, Varticovschi B, Bodenheimer O,

Gelbshtein U, et al. Effects of BNT162b2 Covid-19 Vaccine Booster in Long-Term Care Facilities in Israel. N Engl J Med. 2022;386(4):399–401.
15. Spitzer A, Angel Y, Marudi O, Zeltser D, Saiag E, Goldshmidt H, et al. Association of a Third Dose of BNT162b2 Vaccine with Incidence of SARS-CoV-2 Infection among Health Care Workers in Israel. JAMA - J Am Med Assoc. 2022;327(4):341–9.
16. Mattiuzzi C, Lippi G. Primary COVID-19 vaccine cycle and booster doses efficacy: analysis of Italian nationwide vaccination campaign. Eur J Public Health. 2022;1–12.
17. Mattiuzzi C, Lippi G. Efficacy of COVID-19 vaccine booster doses in older people. Eur Geriatr Med. 2022;
18. Berec L, Šmíd M, Přibylová L, Májek O, Pavlík T, Jarkovský J, et al. Real-life protection provided by vaccination, booster doses and previous infection against covid-19 infection, hospitalisation or death over time in the Czech Republic: A whole country retrospective view. medRxiv. L. Berec, Centre for Mathematical Biology, Institute of Mathematics, Faculty of Science, University of South Bohemia, Branišovská 1760, České Budějovice, Czech Republic; 2021.
19. Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Freedman L, Alroy-Preis S, et al. Protection Across Age Groups of BNT162b2 Vaccine Booster against Covid-19. medRxiv. 2021 Jan;2021.10.07.21264626.
20. Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Freedman L, Kalkstein N, et al. Protection of BNT162b2 Vaccine Booster against Covid-19 in Israel. N Engl J Med. 2021;385(15):1393–400.
21. Andrews N, Stowe J, Kirsebom F, Gower C, Ramsay M, Bernal JL. Effectiveness of BNT162b2 (Comirnaty, Pfizer-BioNTech) COVID-19 booster vaccine against covid-19 related symptoms in England: test negative case-control study. medRxiv. 2021 Jan;2021.11.15.21266341.
22. Abu-raddad LJ, Chemaitelly H, Ayoub HH. Effectiveness of BNT162b2 and mRNA-1273 COVID-19 boosters. 2022;
23. Cerqueira-Silva T, Katikireddi S V, de Araujo Oliveira V, Flores-Ortiz R, Júnior JB, Paixão ES, et al. Vaccine effectiveness of heterologous CoronaVac plus BNT162b2 in Brazil. Nat Med. 2022;
24. Andrews N, Stowe J, Kirsebom F, Toffa S, Sachdeva R, Gower C, et al. Effectiveness of COVID-19 booster vaccines against covid-19 related symptoms, hospitalisation and death in England. Nat Med. 2022;
25. Barda N, Dagan N, Cohen C, Hernán MA, Lipsitch M, Kohane IS, et al. Effectiveness of a third dose of the BNT162b2 mRNA COVID-19 vaccine for preventing severe outcomes in Israel: an observational study. Lancet. 2021;
26. Uzun O, Akpolat T, Varol A, Turan S, Bektas SG, Cetinkaya PD, et al. COVID-19: vaccination vs. hospitalization. Infection. 2022;
27. Robles-Fontán MM, Irizarry RA. Effectiveness of different booster regimens for preventing infection and adverse outcomes in Puerto Rico. medRxiv. R.A. Irizarry, Dana-

Farber Cancer Institute,; 2021.
28. Sritipsukho P, Khawcharoenporn T, Siribumrungwong B, Damronglerd P, Suwantarat N, Satdhabudha A, et al. Comparing real-life effectiveness of various COVID-19 vaccine regimens during the delta variant-dominant pandemic: a test-negative case-control study. Emerg microbes & Infect. 2022;11(1):585–92.
29. Arbel R, Hammerman A, Sergienko R, Friger M, Peretz A, Netzer D, et al. BNT162B2 vaccine booster and mortality due to covid-19. N Engl J Med. 2021;385(26):2413–20.
30. Omer SB, Malani PN. Booster Vaccination to Prevent COVID-19 in the Era of Omicron: An Effective Part of a Layered Public Health Approach. Vol. 327, JAMA. United States; 2022. p. 628–9.
31. Glatman-Freedman A, Bromberg M, Hershkovitz Y, Sefty H, Kaufman Z, Dichtiar R, Keinan-Boker L. Effectiveness of BNT162b2 vaccine booster against SARS-CoV-2 infection and breakthrough complications, Israel. Emerging infectious diseases. 2022; 28(5), 948.
32. Tartof SY, Slezak JM, Puzniak L, Hong V, Frankland TB, Ackerson BK, et al. Effectiveness of a third dose of BNT162b2 mRNA COVID-19 vaccine in a large US health system: A retrospective cohort study. Lancet Reg Heal Am. 2022 Feb;100198.
33. Tsang, NNY, So, HC, Cowling BJ, Leung GM, Ip DKM. Effectiveness of BNT162b2 and CoronaVac COVID-19 vaccination against asymptomatic and symptomatic infection of SARS-CoV-2 omicron BA. 2 in Hong Kong: a prospective cohort study. The Lancet Infectious Diseases. 2022; 23(4), 421-434.
34. Doria-Rose NA, Shen X, Schmidt SD, O'Dell S, McDanal C, Feng W, et al. Booster of mRNA-1273 Strengthens SARS-CoV-2 Omicron Neutralization. medRxiv : the preprint server for health sciences. 2021.
35. Bergwerk M, Gonen T, Lustig Y, Amit S, Lipsitch M, Cohen C, et al. Covid-19 Breakthrough Infections in Vaccinated Health Care Workers. N Engl J Med. 2021;385(16):1474–84.
36. Thompson MG, Burgess JL, Naleway AL et al. Interim Estimates of Vaccine Effectiveness of BNT162b2 and mRNA-1273 COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Health Care Personnel, First Responders, and Other Essential and Frontline Workers — Eight U.S. Locations, December 2020–March. MMWR Morb Mortal Wkly Rep 2021. 2021.
37. Ferdinands JM, Rao S, Dixon BE, Mitchell PK, DeSilva MB, Irving SA, et al. Waning 2-Dose and 3-Dose Effectiveness of mRNA Vaccines Against COVID-19-Associated Emergency Department and Urgent Care Encounters and Hospitalizations Among Adults During Periods of Delta and Omicron Variant Predominance - VISION Network, 10 States, Aug. MMWR Morb Mortal Wkly Rep. 2022;71(7):255–63.