Seroconversion rates among different designs of COVID-19 vaccines: a network meta-analysis of randomized controlled trials

by Gatot Soegiarto

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SYSTEMATIC REVIEW

Seroconversion rates among different designs of COVID-19 vaccines: a network meta-analysis of randomized controlled trials [version 1; peer review: awaiting peer review]

Gatot Soegiarto[1], Jonny Fajar[2], Laksmi Wulandari[3], Muhammad Anshory[4], Muhammad Ilmawan[5], Anisa Asmiragani[5], Himma Illiyana[6], Azaria Adam[7], Sutini Lamadi[5], Umi Sa'adah[8], Tubagus Yuantoko[6], Esi Nanda[6], Farida Rachmawati[8], Nabila Rahmadani[5], Randy Talilah[9], Madyline Katipana[10], Sharon Susanto[11], Maria Hindom[12], Ufi Anjasari[11], Nur Hidayah[13], Nanda Fadilla[14], Vanela Lekatompessy[8], Uzi Phoenna[15], Fredo Tamara[2], Dessy Kartini[5], Aditya Mahendra[2], Andi Permana[5], Erwin Pasaribu[5], Kuldeep Dhama[16], Harapan Harapan[17]

[1]Division of Allergy & Immunology, Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, East Java, 60286, Indonesia
[2]Brawijaya Internal Medicine Research Center, Department of Internal Medicine, Faculty of Medicine, Universitas Brawijaya, Malang, East Java, 65145, Indonesia
[3]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, East Java, 60286, Indonesia
[4]Division of Allergy & Immunology, Department of Internal Medicine, Faculty of Medicine, Universitas Brawijaya, Malang, East Java, 65145, Indonesia
[5]Faculty of Medicine, Universitas Brawijaya, malang, East Java, 65145, Indonesia
[6]Faculty of Public Health, Universitas Indonesia, Jakarta, Jakarta, 10430, Indonesia
[7]Department of Psychiatry, Faculty of Medicine, Universitas Airlangga, Surabaya, East Java, 60286, Indonesia
[8]Department of Biology, Faculty of Mathematics and Natural Sciences, Universitas Brawijaya, malang, East Java, 65145, Indonesia
[9]Faculty of Nursing, Universitas Indonesia, jakarta, Jakarta, 10430, Indonesia
[10]Department of Anesthesiology and Intensive Care, Faculty of Medicine, Universitas Udayana, Denpasar, Bali, 80361, Indonesia
[11]School of Pharmacy, Institut Teknologi Bandung, bandung, East Java, 40132, Indonesia
[12]Department of Child Health, Faculty of Medicine, Public Health and Nursing, University of Gadjah Mada, Yogyakarta, Yogyakarta, 55281, Indonesia
[13]Faculty of Animal Science, Universitas Brawijaya, malang, East Java, 65145, Indonesia
[14]Faculty of Mathematics and Natural Sciences, Universitas Negeri Malang, Malang, East Java, 65145, Indonesia
[15]Department of Clinical Pathology, Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Central Java, 57126, Indonesia
[16]Division of Pathology, Indian Veterinary Research Institute, Izatnagar, Uttar Pradesh, 243122, India
[17]Medical Research Unit, School of Medicine, Universitas Syiah Kuala, Banda Aceh, Aceh, 23111, Indonesia

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Abstract

BACKGROUND: The COVID-19 vaccination program, which uses

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various types of vaccines, has been applied since the beginning of 2021. However, the efficacy in the context of seroconversion rate remains unclear.
OBJECTIVE: To assess the seroconversion rates among different COVID-19 vaccines using a network meta-analysis approach.
METHODS: A network meta-analysis of randomized controlled trials (RCTs) was conducted during the study period. Data of interest, such as seroconversion rate and the type of COVID-19 vaccine, were extracted from each study. The analysis was performed using single-arm analysis by calculating the cumulative seroconversion rate. A network meta-analysis was conducted using the Bayesian method.
RESULTS: A total of 31 RCTs were included in our analysis. Our pooled calculation revealed that the seroconversion rates of inactivated messenger ribonucleic acid (mRNA), protein subunit, and vector COVID-19 vaccines during the follow-up periods were 93.2%, 93.9%, 65.3%, and 54.7%, respectively, at ≤ 15 days; 96.0%, 94.8%, 91.2%, and 89.7%, respectively, between days 16–30; and 98.5%, 98.6%, 98.5%, and 96.2%, respectively, between days 31–60.The indirect comparison revealed that in the follow-up periods of ≤ 15 and 16–30 days, the inactivated and mRNA COVID-19 vaccines had superior seroconversion rates compared with those of the protein subunit and vector vaccines. In the follow-up period of 31–60 days, the highest seroconversion rates were found in the inactivated, mRNA, and protein subunit COVID-19 vaccines.
CONCLUSION: This study provides valuable information regarding the comparison of seroconversion rates of COVID-19 vaccines.

Keywords
COVID-19; vaccine; seroconversion; efficacy; immunization.

Corresponding authors: Gatot Soegiarto (gatot_soegiarto@fk.unair.ac.id), Jonny Fajar (gembyok@gmail.com)

Author roles: Soegiarto G: Conceptualization, Formal Analysis, Investigation, Methodology, Resources, Supervision, Validation, Writing – Review & Editing; **Fajar J**: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Resources, Software, Supervision, Validation, Writing – Original Draft Preparation, Writing – Review & Editing; **Wulandari L**: Conceptualization, Formal Analysis, Investigation, Methodology, Supervision; **Anshory M**: Conceptualization, Formal Analysis, Investigation, Methodology, Supervision; **Ilmawan M**: Formal Analysis, Investigation, Methodology, Software; **Asmiragani A**: Formal Analysis, Investigation, Methodology, Software; **Illiyana H**: Project Administration, Resources; **Adam A**: Data Curation, Formal Analysis, Software; **Lamadi S**: Data Curation, Project Administration, Resources; **Sa'adah U**: Data Curation, Project Administration, Resources; **Yuantoko T**: Data Curation, Project Administration, Resources; **Nanda E**: Data Curation, Project Administration, Resources; **Rachmawati F**: Data Curation, Project Administration, Resources; **Rahmadani N**: Data Curation, Project Administration, Resources; **Talilah R**: Data Curation, Project Administration, Resources; **Katipana M**: Data Curation, Project Administration, Resources; **Susanto S**: Data Curation, Project Administration, Resources; **Hindom M**: Data Curation, Project Administration, Resources; **Anjasari U**: Data Curation, Project Administration, Resources; **Hidayah N**: Data Curation, Project Administration, Resources; **Fadilla N**: Data Curation, Project Administration, Resources; **Lekatompessy V**: Data Curation, Project Administration, Resources; **P[illegible]nna U**: Data Curation, Project Administration, Software; **[illegible]nara F**: Data Curation, Project Administration, Resources; **Kartini D**: Data Curation, Project Administration, Resources; **Mahendra A**: Data Curation, Project Administration, Resources; **Permana A**: Data Curation, Project Administration, Resources; **Pasaribu E**: Data Curation, Project Administration, Resources; **Dhama K**: Data Curation, Project Administration, Resources; **[illegible]rapan H**: Data Curation, Project Administration, Resources

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Introduction

COVID-19 remains a global challenge.[1] While the incidence of COVID-19 was reported to have decreased in recent months, recent reports have suggested that there has been a rising trend in COVID-19 incidence.[2] This fluctuating incidence might be affected by the variants of concern,[3] in which COVID-19 management also remained challenging,[4] and the management of new variants of concern might differ from that of previous variants.[5] The guidelines for COVID-19 management have been periodically published and updated.[6] However, the efficacy of each treatment was inconclusive, particularly in the case of severe or critical illness.[7–9] Therefore, the proper treatment of COVID-19 remains under investigation. While the potential of new drugs has been explored,[10] the vaccination program appears to have the potential to end this pandemic.[11]

The COVID-19 vaccination program was introduced in early 2021 and implemented worldwide.[12] This vaccination program was initially targeted to health workers, a population with high risk of infection, and continued to the public.[12,13] To date, a wide variety of COVID-19 vaccines have been available, such as inactivated, messenger ribonucleic acid (mRNA), protein subunit, and vector vaccines.[14] However, efficacy differs between vaccines, and the results from each study have varied.[15] In this circumstance, conflict between pharmaceutical companies might occur. Therefore, the question of which vaccine has the best efficacy remains. In the content of vaccination, seroconversion was used to assess the early response of neutralizing antibody production.[16] However, the report of seroconversion of COVID-19 vaccines varied in each study, particularly in the special cases with comorbidity.[17–19] Moreover, to date, no study has directly compared the efficacy of COVID-19 vaccines. Therefore, the present study aimed to assess the indirect comparison of seroconversion rates among different COVID-19 vaccines using a network meta-analysis approach. Our present study provides preliminary evidence regarding potential COVID-19 vaccines.

Methods

Study design

A meta-analysis, following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) protocols,[20] was conducted to compare the seroconversion rates of different COVID-19 vaccine designs. To formulate a comprehensive comparison, the relevant articles were collected from PubMed, Embase, and Scopus, and the information of interest was extracted to compare the seroconversion rates among different COVID-19 vaccine designs.

Eligibility criteria

Articles were included in our analysis if they met the following inclusion criteria: (1) assessed the seroconversion rate of a COVID-19 vaccine; and (2) provided standardized data to determine the seroconversion rate of a COVID-19 vaccine. The following articles were excluded: reviews, commentaries, letters to the editor, non-randomized controlled trials (RCTs), and double publications.

Search strategy and data extraction

As of January 10, 2022, we searched for potential articles in PubMed, Scopus, and Web of Science. We determined potential COVID-19 vaccine designs to be involved in our study prior to searching the primary outcomes (seroconversion rate). We used the keywords adapted from medical subject headings: “COVID-19 vaccine” or “inactivatedCOVID-19 vaccine” or “mRNACOVID-19 vaccine” or “protein subunit COVID-19 vaccine” or “vector COVID-19 vaccine” and “efficacy” or “seroconversion”. The search was limited to RCTs and articles published in English. If a double publication was found, only articles with a larger sample size were included. We also browsed the reference list of relevant systematic reviews to obtain additional references. Subsequently, the following information of interest from the potential articles was extracted by two independent investigators: (1) first author name, (2) publication year, (3) study design, (4) age of patients, (5) sample size, (6) design of COVID-19 vaccine, (7) trade name of COVID-19 vaccine, (8) dosage of COVID-19 vaccine, (9) modified JADAD scale, and (10) seroconversion rate.

Assessment of the methodological quality

Prior to inclusion in our analysis, articles were appraised for quality using the modified JADAD scale. The scores ranged from 0 to 7. Scores of 5–7, 3–4, and 0–2 indicated high-, moderate-, and low-quality papers, respectively.[21] Low-quality articles were excluded from the analysis. Using a pilot form, quality assessment was performed by two independent authors (JKF & MI). Discrepancies between the two authors were resolved by discussion.

Outcome measure

The primary outcome was the seroconversion rate of the COVID-19 vaccine, defined as the level of geometric mean titer (GMT) of neutralizing antibodies of greater than or equal to four-fold from the baseline. The predictors were different COVID-19 vaccine designs. To identify the potential COVID-19 vaccine designs, an initial evaluation of the available data in PubMed, Scopus, and Web of Science was performed. Of those, inactivated, mRNA, protein subunit, and vector COVID-19 vaccines were available for the analysis.

Statistical analysis

Before analyzing the data, the potential publication bias and heterogeneity across the studies was assessed. Publication bias was assessed using an Egger test, and a p-value < 0.05 indicated a publication bias. Heterogeneity among the studies was evaluated using the Q test. A p-value < 0.1 suggested that heterogeneity existed among studies, and that a random effect model should be applied for the data analysis. Otherwise, a fixed-effect model should be used. The cumulative seroconversion rate of COVID-19 vaccines was determined using a single arm model meta-analysis by calculating the pooled seroconversion events from the total sample size. The effect size was presented using the seroconversion percentage and 95% confidence interval (CI). The data were analyzed using R package software (R package, MA, US, RRID:SCR_001905). The pooled seroconversion rates are summarized in a forest plot. The seroconversion rates between different designs of COVID-19 vaccines were compared by calculating the effect size of each COVID-19 vaccine design. The highest seroconversion rate was considered the highest efficacy, and the Confidence in Network Meta-Analysis software version 1.9.1 (Bern, Switzerland, RRID:SCR_016488) was used to outline the network diagram of comparison among COVID-19 vaccines.

Results

Study selection

We collected 8,070 potential papers from the databases. Of these, 23 duplication papers were found, and 7,966 papers had irrelevant topics; therefore, those papers were excluded. Subsequently, 81 papers were included for further full-text reviews. Among these, 19 reviews and 32 papers with insufficient data and were excluded. Finally, a total of 31 papers were analyzed to compare the seroconversion rates among COVID-19 vaccines.[22–52] The process of article selection in our study is presented in Figure 1, and the characteristics of the papers included in our analysis are summarized in Table 1.

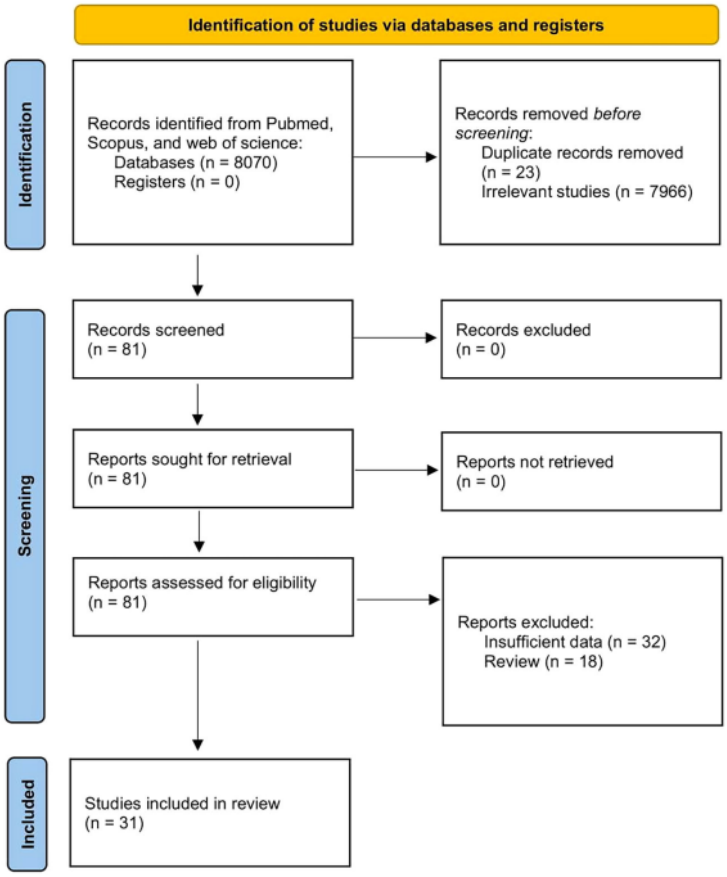

Figure 1. A PRISMA flow chart of study selection.

Table 1. Baseline characteristics of study included in our meta-analysis.

Author	Age (±SD)	Sample size	Type of vaccine	Merk vaccine	Dose of vaccine	Jadad Modified Scale
Al Kaabi et al 2021 [2]	36.2 (9.2)	40832	Inactivated	WIV04, HB02, alum–only	WIV04 = 5 μg/dose; HB02 = 4 μg/dose; alum-only = 0.5mg	6
Ali et al 2021	14.2 (1.6)	3732	mRNA	mRNA-1273	200 μg	5
Baden et al 2021	51.3 (24.7)	30420	mRNA	mRNA-1273	200 μg	4.5
Che et al 2020	41.4 (10.84)	750	Inactivated	Inactivated SARS-CoV-2 vaccine	50 EU, 100 EU, 150 EU	6
Ella et al 2021	32.5 (24)	375	Inactivated	BBV152	Algel-IMDG = 3 μg; Algel-IMDG = 6 μg v[illegible]; Algel = 6 μg [17]	7
Fadlyana et al 2021 (1)	35.6 (11.3)	1620	Inactivated	Inactivated SARS-CoV-2 vaccine [15]	3 μg	6.5
Falsey et al 2021 [2]	64.8 (21.4)	32379	Vector vaccine	AZD1222 (ChAdOx1 nCoV-19) [10]	5×10^{10} viral particles	7
Feng et al 2021	N/A	809	Inactivated	Inactivated SARS-CoV-2 vaccine	3 μg	5.5
Formica et al 2021	38.9 (12.40)	1288	Protein subunit vaccine	NVXCoV2373	5 μg, 25 μg [7]	6.5
Han et al 2021	8.4 (4.2)	550	Inactivated	CoronaVac	1.5 μg, 3 μg	6
Jackson et al 2020	36.7 (7.9)	45	mRNA	mRNA-1273	25 μg, 100 μg, 250 μg	4.5
Kremsner et al 2020	38.6 (12.9)	248	mRNA	CVnCoV	2-12 μg	5.5
Li et al 2021	37.9 (9.6)	144	mRNA	BNT162b1	10 μg, 30 μg	7
Liu et al 2021	58.2 (4.81)	830	mRNA	ChAd, BNT	ChAd = 0.5 mL, BNT = 0.3 mL	6.5
Melo-González et al 2021 [2]	N/A	94	Inactivated	CoronaVac	3 μg	5.5
Pan et al 2021	38.0 (9.5)	560	Inactivated	KCONVAC	5 μg, 10 μg	7
Polack et al 2020	N/A	43448	mRNA	BNT162b2	30 μg	5.5
Pu et al 2021	18-59	96	Inactivated	NA	NA	5.5

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Table 1. *Continued*

Author	Age (±SD)	Sample size	Type of vaccine	Merk vaccine	Dose of vaccine	Jadad Modified Scale
Richmond et al 2021	37.6 (11.9)	148	Protein subunit vaccine	SCB-2019	3 µg, 9 µg, 30 µg	7
Sadoff et al 2021	36.1 (10.1)	805	Vector vaccine	Ad26.COV2.S	5×10^{10}, 1×10^{11} viral particles	5.5
Shu et al 2021	43.9 (11.3)	880	Protein subunit vaccine	V-01	10 µg, 25 µg	7
Tanriover et al 2021	N/A	10218	Inactivated	CoronaVac	3 µg	7
Thomas et al 2021	N/A	44060	mRNA	BNT162b2	30 µg	5.5
Wu et al 2021	65.6 (4.3)	395	Inactivated	CoronaVac	1.5 µg, 3 µg, 6 µg	7
Xia et al 2020 (a)	36.0 (8.5)	320	Inactivated	Inactivated SARS-CoV-2 vaccine	2.5 µg, 5 µg, 10 µg	6
Xia et al 2020 (b)	42·7 (8·1)	640	Inactivated	BBIBP-CorV	2 µg, 4 µg, 8 µg	7
Yang et al 2020	32.6 (9.41)	950	Protein subunit vaccine	ZF2001	25 µg, 50 µg	6
Zeng et al 2021	45.2 (9.1)	540	Inactivated	CoronaVac	1.5 µg, 3 µg, 6 µg	7
Zhang et al 2020	41.8 (9.4)	744	Inactivated	CoronaVac	3 µg, 6 µg	6
Zhang et al 2021	40.0 (9.2)	180	Protein subunit vaccine	V-01	10 µg, 25 µg, 50 µg	7
Zhu et al 2020	37.2 (10.7)	108	Vector vaccine	Ad5 vectored COVID-19 vaccine	5×10^{10}, 1×10^{11}, $1{\cdot}5 \times 10^{11}$ viral particles	4

Note: NA, not available; SD, standard deviation; mRNA, messenger ribonucleic acid.

The seroconversion rates among different COVID-19 vaccines

In the follow-up period of ≤ 15 days, 24 papers assessing the seroconversion rate of COVID-19 vaccines were collected. In total, the seroconversion rate was 91.1% (Figure 2A). The seroconversion rates of inactivated (Figure 2B), mRNA

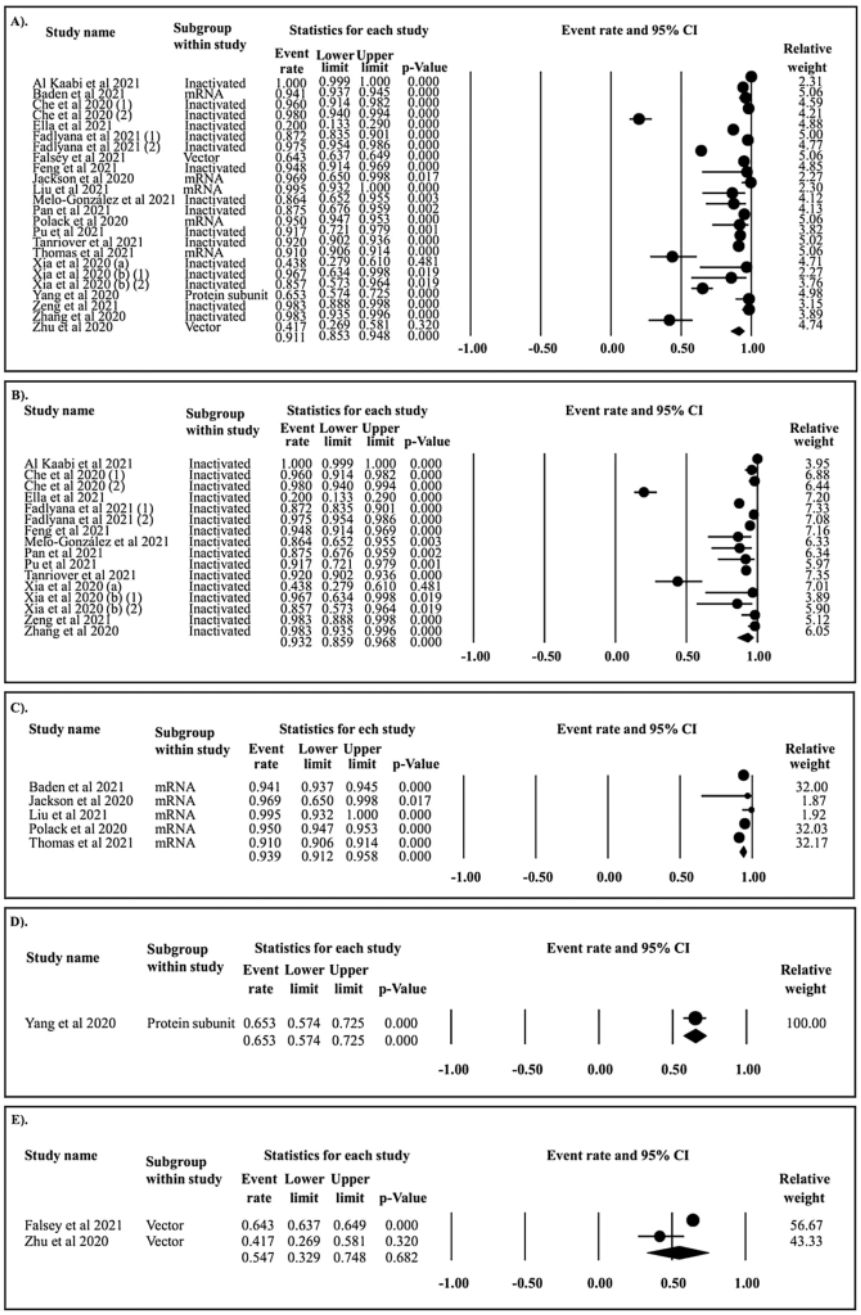

Figure 2. A forest plot of the seroconversion rate among different type of COVID-19 vaccines at day ≤15. A). All vaccine types; B). Inactivated vaccine; C). mRNA vaccine; D). Protein subunit vaccine; and E). Vector vaccine.

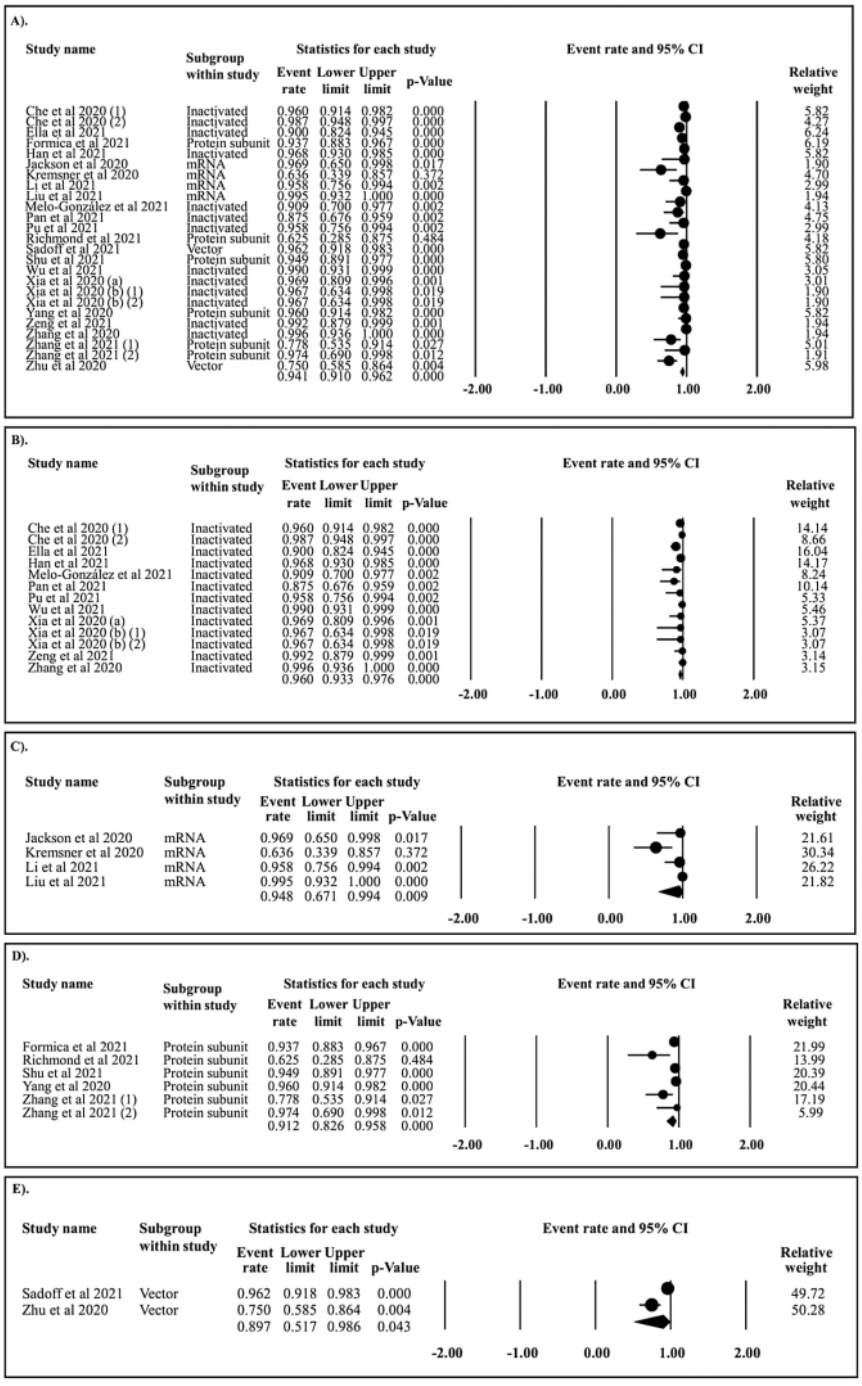

Figure 3. A forest plot of the seroconversion rate among different type of COVID-19 vaccines at day 16-30. A). All vaccine types; B). Inactivated vaccine; C). mRNA vaccine; D). Protein subunit vaccine; and E). Vector vaccine.

(Figure 2C), protein subunit (Figure 2D), and vector COVD-19 vaccines (Figure 2E) were 93.2%, 93.9%, 65.3%, and 54.7%, respectively. Subsequently, in the follow-up period of 16–30 days, the cumulative seroconversion rate of COVID-19 vaccines was 94.1% (Figure 3A). The seroconversion rates of inactivated (Figure 3B), mRNA (Figure 3C), protein subunit (Figure 3D), and vector COVID-19 vaccines (Figure 3E) were 96.0%, 94.8%, 91.2%, and 89.7%, respectively. Alternatively, in the follow-up period of 31–60 days, the pooled seroconversion rate of COVID-19 vaccines was 98.0% (Figure 4A). The seroconversion rate of inactivated (Figure 4B), mRNA (Figure 4C), protein subunit (Figure 4D), and vector COVID-19 vaccines (Figure 4E) were 98.5%, 98.6%, 98.5%, and 96.2%, respectively.

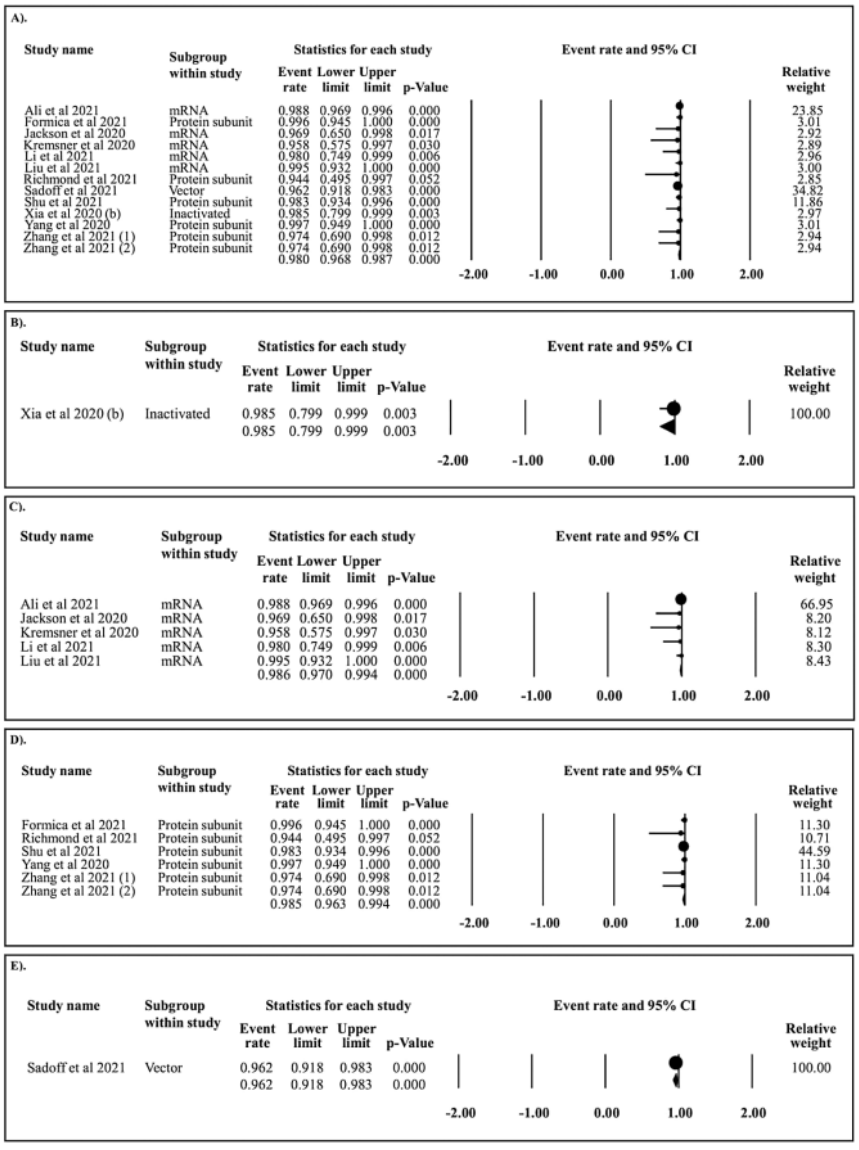

Figure 4. A forest plot of the seroconversion rate among different type of COVID-19 vaccines at day 31-60. A). All vaccine types; B). Inactivated vaccine; C). mRNA vaccine; D). Protein subunit vaccine; and E). Vector vaccine.

The indirect comparison of seroconversion rates among different COVID-19 vaccines

In the follow-up period of ≤ 15 days (Figure 5A), the seroconversion rates of inactivated and mRNA COVID-19 vaccines were superior to those of the protein subunit and vector COVID-19 vaccines. In the follow-up period of 16–30 days (Figure 5B), the seroconversion rates of inactivated and mRNA COVID-19 vaccines were significantly higher than those of protein subunit and vector COVID-19 vaccines. In the follow-up period of 31–60 days (Figure 5C), the seroconversion rate of the vector COVID-19 vaccine was inferior to that of the inactivated, mRNA, and protein subunit COVID-19 vaccines. The network diagrams of seroconversion rates among different COVID-19 vaccine designs are presented in Figure 5D, 5E, and 5F for the follow-up periods of ≤ 15, 16–30, and 31–60 days, respectively. The summary of indirect comparison of seroconversion rate among COVID-19 vaccines is outlined in Table 2.

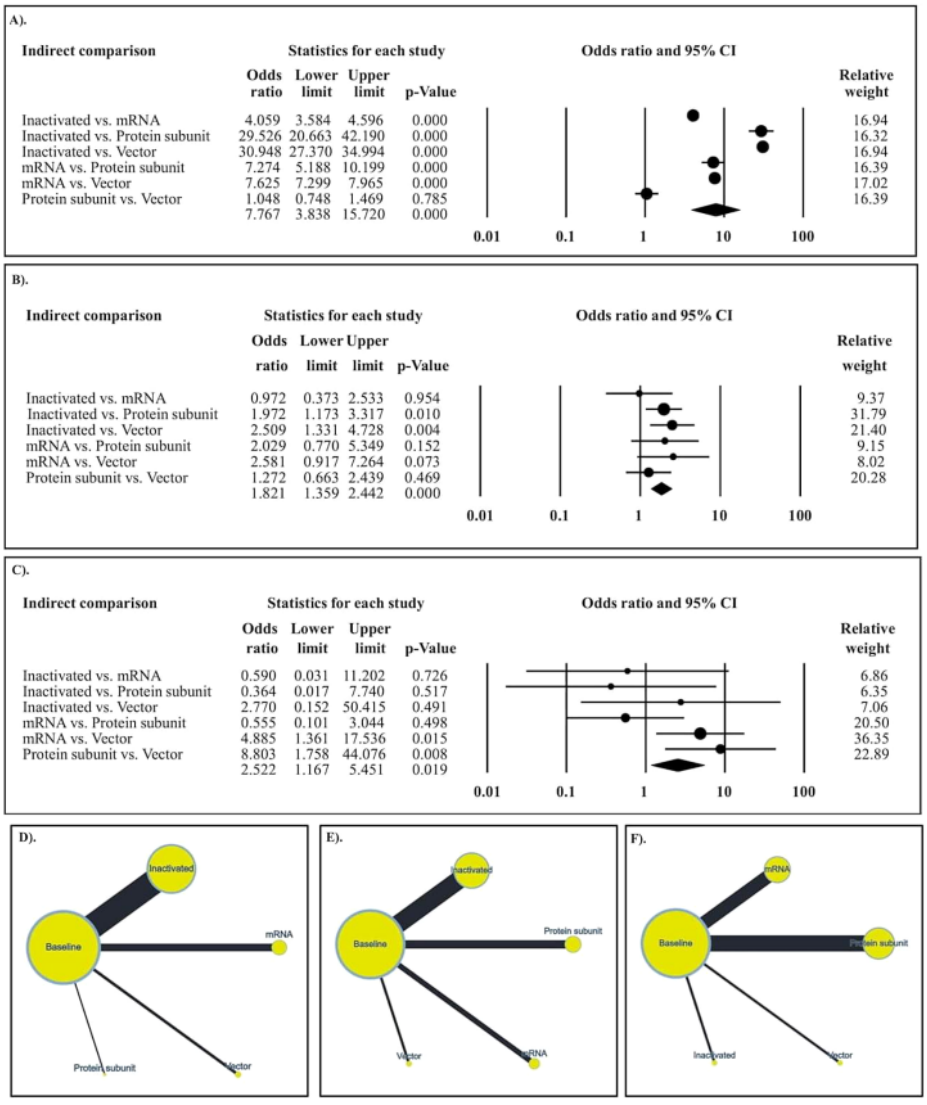

Figure 5. The indirect comparison between different types of COVID-19 vaccines. A). Follow up period at day ≤15; B). Follow up period at day 16-30; C). Follow up period at day 31-60; D). The networking among studies at day ≤15; E). The networking among studies at day 16-30; and F). The networking among studies at day 31-60.

Table 2. The summary of analysis on the indirect comparison of seroconversion rate between different types of COVID-19 vaccines.

Indirect comparison	NS	Sample size	OR	95%CI	p
Follow up at day ≤15					
Inactivated *vs.* mRNA	16 *vs.* 5	15464 *vs.* 53454	4.06	3.58 – 4.60	<0.0001
Inactivated *vs.* protein subunit	16 *vs.* 1	15464 *vs.* 150	29.53	20.66 – 42.19	<0.0001
Inactivated *vs.* vector	16 *vs.* 2	15464 *vs.* 21623	30.95	27.37 – 34.99	<0.0001
mRNA *vs.* protein subunit	5 *vs.*1	53454 *vs.* 150	7.27	5.19 – 10.20	<0.0001
mRNA *vs.* vector	5 *vs.* 2	53454 *vs.* 21623	7.63	7.30 – 7.97	<0.0001
Protein subunit *vs.* vector	1 *vs.* 2	150 *vs.* 21623	1.05	0.75 – 1.47	0.7850
Follow up at day 16-30					
Inactivated *vs.* mRNA	13 *vs.* 4	990 *vs.* 159	0.97	0.37 – 2.53	0.9540
Inactivated *vs.* protein subunit	13 *vs.* 6	990 *vs.* 453	1.97	1.17 – 3.32	0.0100
Inactivated *vs.* vector	13 *vs.* 2	990 *vs.* 194	2.51	1.33 – 4.73	0.0040
mRNA *vs.* protein subunit	4 *vs.* 6	159 *vs.* 453	2.03	0.77 – 5.35	0.1520
mRNA *vs.* vector	4 *vs.* 2	159 *vs.* 194	2.58	0.92 – 7.26	0.0730
Protein subunit *vs.* vector	6 *vs.* 2	453 *vs.* 194	1.27	0.66 – 2.44	0.4690
Follow up at day 31-60					
Inactivated *vs.* mRNA	1 *vs.* 5	32 *vs.* 499	0.59	0.03 – 11.20	0.7260
Inactivated *vs.* protein subunit	1 *vs.* 6	32 *vs.* 448	0.36	0.02 – 7.74	0.5170
Inactivated *vs.* vector	1 *vs.* 1	32 *vs.* 158	2.77	0.15 – 50.42	0.4910
mRNA *vs.* protein subunit	5 *vs.* 6	499 *vs.* 448	0.56	0.10 – 3.04	0.4980
mRNA *vs.* vector	5 *vs.* 1	499 *vs.* 158	4.89	1.36 – 17.54	0.0150
Protein subunit *vs.* vector	6 *vs.* 1	448 *vs.* 158	8.80	1.76 – 44.08	0.0080

Note: NS, number of studies; OR, odd ratio; CI, confidence interval; mRNA, messenger ribonucleic acid.

Source of heterogeneity

In the follow-up period of ≤ 15 days, evidence of heterogeneity (p heterogeneity > 0.05) was observed in the models of analyses for all COVID-19 vaccines, inactivated COVID-19 vaccines, mRNA COVID-19 vaccines, and vector COVID-19 vaccines. Therefore, a random effect model was used. In the follow-up period of 16–30, evidence of heterogeneity was observed in all models of analyses; therefore, a random effect model was used. In the follow-up period of 31–60 days, all analyses were performed using a fixed effect model, because no evidence of heterogeneity was found **(Supplementary files)**.[20]

Discussion

Our study reported on the seroconversion rate among different COVID-19 vaccines in the follow-up periods of ≤ 15, 16–30, and 31–60 days. We revealed that, in the follow-up period of ≤ 15 days, the highest seroconversion rate was that of the inactivated vaccine. In the follow-up period of 16–30 days, the highest seroconversion rates were those of the inactivated and mRNA vaccines. Conversely, in the follow-up period of 31–60 days, the highest seroconversion rates were those of the inactivated, mRNA, and protein subunit vaccines. To date, our study is the first to report on the seroconversion rates among different COVID-19 vaccines; therefore, comparisons among meta-analyses were not discussed. However, similar meta-analyses have been performed to assess the efficacy of COVID-19 vaccines. In total, nine meta-analysis studies have been conducted.[53–61] While the majority of these studies focused on side effects of the vaccine, they also reported the efficacy of COVID-19 vaccines by assessing the reduced risk of infection, mortality, hospitalization, and admission to the ICU. The findings revealed that the mRNA vaccine had the highest efficacy in preventing COVID-19 infection.[59] Those previous meta-analyses support our findings that, besides the mRNA vaccine, the inactivated vaccine had a higher seroconversion rate than that of the protein subunit and vector COVID-19 vaccines.

The theory underlying the comparison of the efficacy of COVID-19 vaccines remains debatable. It has been widely proposed that various vaccines have various immunogens and may be engulfed, processed, and presented by antigen-presenting cells (APCs) along with MCH antigens to CD4+ T cells. Resultingly, cytokine synthesis may occur and may

activate humoral and cellular responses, including antibody production, CD8+ T cell activation, and macrophage stimulation. Subsequently, B lymphocytes may differentiate into plasma cells and produce specific antibodies to protect against the infection.[62,63] In the inactivated vaccine, the immunogenic property is a killed or modified virus containing the whole pathogen, virus fragments, or virus epitope.[64] In the mRNA vaccine, the mRNA will be taken up by APC and translated into protein in situ. The mRNA encodes the full-length, pre-fusion stabilized spike protein (S) of SARS-CoV-2.[14] In the protein subunit vaccine, the immunogenic property is specific isolated proteins from SARS-COV2 virus (S glycoprotein), which is responsible for receptor binding to cellular ACE-2.[65–67] This type of vaccine is similar to a vector vaccine, in which the S protein is produced to confer protection against COVID-19.[68] Of those possible mechanisms, the inactivated vaccine may target a wide variety of epitopes,[69] and therefore, this type of vaccine may have a wide protection against COVID-19 variants of concern compared to other types of COVID-19 vaccines. However, vaccine specificity may differ, which requires evaluation by comparing the total GMT levels.

To the best of our knowledge, the present study is the first to report a comparison of seroconversion rates among different COVID-19 vaccine designs. Our study provided valuable evidence that inactivated and mRNA vaccines provided an early seroconversion rate, and the protein subunit vaccine achieved a similar seroconversion rate to that of inactivated and mRNA vaccines in the follow-up period of 31–60 days. The results of our research may be used as a basis for evaluating the development of COVID-19 vaccines in the future.[13] We hope that future vaccine development may take into account the results of seroconversion rates between different vaccine designs, as we reported in our study. Therefore, the expected protective effects of the vaccine could be achieved. However, our present study only assessed the seroconversion rate in a short follow-up period. Further studies assessing a long-term follow-up period are required.

Our current study had several important limitations. First, we did not include potential confounding factors in assessing the efficacy of COVID-19 vaccines, such as comorbidity, nutritional status, and transmission area. Therefore, the probability of the dependent effect remains open to discussion. Second, the different report formats among studies required manual calculation for the precise seroconversion rate information. Therefore, there is the possibility of human error in interpreting seroconversion rates. Third, the vaccine and booster dosages varied among the studies. Therefore, false-positive findings might exist. Fourth, we only focused on the seroconversion rate, in which this evaluation was only effective in assessing the sensitivity of vaccines. Further studies evaluating cumulative GMTs might be required. Fifth, in the current study, vaccine safety was not evaluated. Therefore, further studies assessing safety are needed.

Conclusion

Our study revealed that the inactivated and mRNA COVID-19 vaccines provided the highest seroconversion rates at early follow-up. The protein subunit COVID-19 vaccine achieved a seroconversion rate similar to that of the inactivated and mRNA vaccines at the follow-up period of 31–60 days. Our study might contribute to better insight into the seroconversion rates of different COVID-19 vaccines.

Data availability

All data underlying the results are available as part of the article and no additional sources of data are required.

Reporting guidelines

Figshare. PRISMA checklist. DOI: https://doi.org/10.6084/m9.figshare.19236714.v2[20]

Competing interests

No competing interests were declared.

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Author contribution

Idea/concept: GS, JKF. Design: GS, JKF, LW. Control/supervision: GS, LW, MA, KD, HH. Data collection/processing: MI, AA, HI, AAA, SL, US, TDY, EDN, FR, NR, RT, MVK, SS, MCH, UA, NH, NBF, VCL, UMP, FT, DAK, AIM, AP, EAP. Extraction/Analysis/interpretation: JKF, MI. Literature review: GS, JKF, MI. Writing the article: GS, JKF, MI. Critical review: GS, LW, MA, KD, HH. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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