

Immunogenicity and Safety Analysis of Inactivated Virus Vaccine against SARS-CoV-2: A Systematic Review of Phase 1/2 Clinical Trials

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Introduction The lingering Severe Acute Respiratory System-Coronavirus-2 (SARS-CoV-2) pandemic worldwide has called scientists to accelerate vaccine production and reduce the spread of the virus. The inactivated virus vaccine has been administered widely due to its potency. Following its recent public use, we aim to summarize the efficacy and safety of the inactivated vaccine, especially following Indonesia's settlement on the SinoVac vaccine.

Materials and Methods A systematic review was performed, searching for randomized controlled trials, according to the PRISMA statement throughout four online databases with studies published up to 2 February 2021. Critical appraisal was further conducted utilizing the Cochrane Risk of Bias Tool 2.0.

Results and Discussions The search yielded six phase 1/2 clinical trials with a total of 3251 subjects. The outcome was obtained in seroconversion rates (%) after two doses of vaccine. Four studies administered the CoronaVac inactivated vaccine and resulted in a high seroconversion rate, ranging from 89–90%. The other two studies administered the BBV152 and BBIBP-CorV inactivated vaccine and showed similar results. Furthermore, a dose-dependent relation is shown with higher doses showing higher seroconversion rates. The safety analysis reported injection site pain as an insignificant but most prevalent local adverse reaction, with other adverse reactions being mild to moderate respiratory tract infections.

Conclusion The inactivated vaccine's efficacy has been proven to stimulate antibody response regardless of dosage, period of administration, and age, with insignificant adverse

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effects. Further phase 3 clinical trials and widespread administration with the help of non-governmental and medical student organizations are recommended.

Keywords *COVID-19, SARS-CoV-2, viral vaccine*

Introduction

As of February 16th, 2021, the Severe Acute Respiratory System-Coronavirus-2 (SARS-CoV-2) virus that started in Wuhan, China, has caused 2,396,408 deaths and 108,579,352 confirmed cases worldwide.¹ The race to fight off the pandemic has resulted in the acceleration of vaccine development worldwide. World Health Organization (WHO) has reported a total of 66 vaccine candidates on clinical trials and 176 vaccine candidates on pre-clinical trials, with 10 being inactivated virus vaccine on clinical trials by 12th of February 2021.² Despite the current state of an ongoing clinical trials, the effort to slow down the spread of the virus remains an urgent priority. The vaccination effort was first conducted on the 8th of December, 2020.³ Since then, the administration of vaccine worldwide has accelerated, with an estimation of 20 million people being fully vaccinated against coronavirus disease-2019 (COVID-19) by the 14th of February 2021.⁴

Inactivated viral vaccine has been used for centuries, with examples including the inactivated poliovirus vaccine (IPV), pertussis vaccine, rabies vaccine, hepatitis A vaccine, and most influenza vaccines.^{5,6} Nonetheless, the certainty of efficacy and safety of inactivated COVID-19 vaccine has not yet been universally proven because of the novelty of the vaccine. The adverse events following the administration of the vaccine must also be included in the consideration of the vaccine's safety. Following Indonesia's choice of SinoVac which is an inactivated vaccine, in this review, we aim to summarize the efficacy

(in the form of seroconversion rates) of inactivated virus vaccine to fight off the SARS-CoV-2 through previously conducted clinical trials. Furthermore, safety is discussed using the adverse effects of the vaccine administration in a variety of ages, ranging from 18 years to 60 years and above. We also correlate the impact of COVID-19 vaccine to support the Sustainable Development Goals (SDG) in the aspects of good health and wellbeing (SDG Number 3) and poverty (SDG Number 1), especially in Indonesia, with the hopes to repair the indirect impact the pandemic has caused to the nation.

Materials and Methods

Search strategy

In this study, literature search was conducted based on the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA). In obtaining the relevant studies, we used the following keywords: "COVID-19 OR SARS-CoV-2" AND "Inactivated vaccine" AND "Immunogenicity OR Safety OR Tolerability", altogether with known synonyms and applying the use of Mesh Terms where appropriate. The search strategy was carried out in 4 databases namely PubMed/MEDLINE, Science Direct, CENTRAL/Cochrane, and Wiley Online Library for peer-reviewed studies that were published up to 2 February 2021.

Inclusion and exclusion criteria

Throughout the creation of this review, we applied inclusion criteria as follows: (1) phase 1/2 clinical trials; (2) using inactivated virus vaccine for immunization; (3)

outcome in seroconversion rates and adverse effects; (4) population being healthy adults 18-59 years and ≥ 60 years of age. The exclusion criteria applied were: (1) studies with irretrievable full text; (2) articles such as reviews, commentaries, letters, conference abstracts; (3) incomplete RCTs with unpublished results; (4) studies in languages other than Bahasa Indonesia or English.

Data extraction and study outcomes

Three independent reviewers performed data extraction, with discrepancies adjudicated by consensus with the fourth investigator. The details extracted from the reviewed articles include: (1) authors and year of publication; (2) subject characteristics: sample size & mean age; (3) study characteristics: study design and country of origin. (3) vaccine characteristics which include type, dose, and cohort. The main outcomes observed in this review include indicators for safety and immunogenicity of the various inactivated COVID-19 vaccine, which are (1) incidence of adverse events for safety; (2) seroconversion rates for indicators of immunogenicity.

Risk of bias assessment

Risk of bias (ROB) assessment was carried out using the Cochrane risk-of-bias tool for randomized controlled studies 2.0 to evaluate methodological quality.⁷ The ROB tool consists of 5 main domains, which addressed bias arising from: the randomization process, deviations from intended, missing outcome data, measurement of outcome, and selection of the reported results. Response options

of the individual domains include: *Yes, Probably Yes, Probably No, No, and Not Included* which were used to evaluate each domain to show low, some, or high risk of bias according to Agency for Healthcare Research and Quality (AHRQ). The assessment was performed by four independent investigators, with discrepancies being resolved in mutual agreement and accordance.

Results and Discussions

Search results

Search from the four international databases using the set keywords yielded 426 studies and additionally one study was included for separate individual searches. The 427 studies were then screened according to their title and abstract relevancy, resulting in 27 studies and 21 studies after duplicates were excluded. Full-text screening were then conducted resulting in 15 studies being excluded with 10 studies having irretrievable full-text and 5 studies having an incompatible study design. The visual comprehensive selection process is shown as **Figure 1**.

Characteristics of included studies

Rigorous screening according to the inclusion and exclusion criteria yielded 6 double-blinded RCTs with 1 study only conducting phase 1, 1 study only conducting phase 2, and 4 studies conducting both phase 1 and phase 2 clinical trials all in 2020. In total, 3251 subjects were tested (879 in phase 1 and 2372 in phase 2) with 4 studies evaluating healthy adults 18-59 years, 1 study evaluating ≥ 60 years, and 1 study

evaluating both in separate cohorts. 4 studies used CoronaVac (SinoVac) as its vaccine of choice, while the other 2 used a variation of BBV152 and BBIBP-CoV vaccines. However, both types were administered in 0/14- or 0/28-days cohort and outcome was procured in seroconversion rates (%) and adverse effects (%) reported. The included studies were reviewed using the Cochrane risk-of-bias tool 2, with all studies reflecting good quality. The full summary table of included

Current State of COVID-19 and the Urgency of Vaccines

The ongoing progression of the COVID-19 pandemic has been a worrisome burden for multiple stakeholders worldwide.¹⁴ Various interventions and policies have been implemented which are pivotal in flattening the curve.^{14,15} However, their sustainability is questionable. Restricting public movement led to the stagnation of global economic growth with developing countries such as Indonesia being the

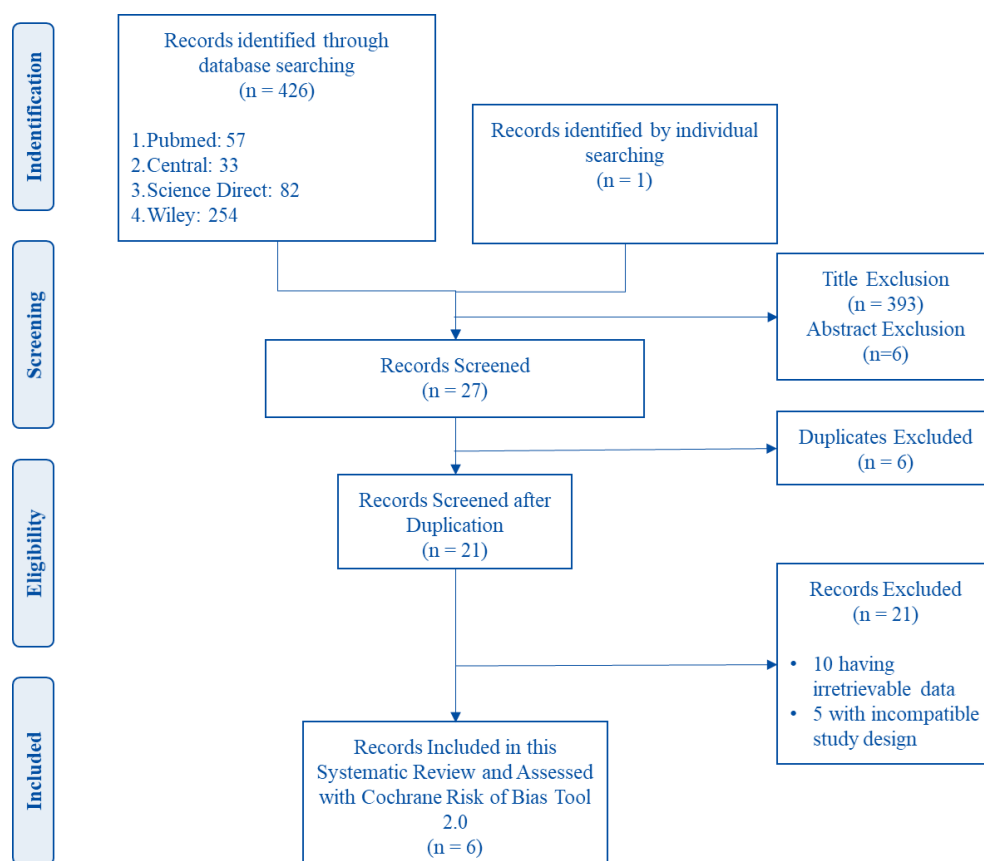


Figure 1 PRISMA Flow Chart of Search Strategies

studies is shown as **Table 1**. while summary of risk-of-bias assessment and the full justification are attached as **Table 2**. and **Appendix 1**. respectively.⁸⁻¹³

most affected with economic growth projected to decline severely from 5% initially to 1% in 2020.^{16,17} Hence, with an increasing global interest in preventing

other multi-sectoral damages, the adoption of living a 'new normal' is currently preferred.^{14,17,18}

Entering the new normal era, the increasing contact rate yields the possibility of a second wave of COVID-19 spike - deterring the initial efforts in pressing the curve.¹⁸ During the course of the pandemic, vaccine development has remained within the periphery until phase 2 clinical trials started.⁸ Firstly initiated by the United Kingdom, vaccine administration has sporadically accelerated with countries even opting for a premature vaccination plan for workers in healthcare.¹⁹⁻²¹ In response to the loosening restrictions, the urgency for a wide scale preventive health measure has peaked in importance. This rationale is further exacerbated by the elusive nature of COVID-19 infections with 45% of COVID-19 carriers being asymptomatic.¹⁹ Moreover, the Center of Disease Control (CDC) reported that only 28% IgG seroconversion was achieved following a mild infection of COVID-19, leading to the possibility of reinfection.^{19,21,22}

Mechanism of Inactivated Vaccines

An inactivated vaccine is produced by exposing the virus to physical (e.g. pH & temperature) or chemical agents (e.g. formaldehyde & glutaraldehyde), to eliminate its infective capabilities whilst retaining immunogenicity.^{23,24} Several rationales lie in using this vaccine design instead of live-attenuated ones, which are generally known to elicit stronger immune responses, such as the case in influenza vaccines, where live-attenuated version

actually produce a broader and longer-lasting cellular & humoral response.²⁵ With particular interest to the current COVID-19 pandemic, the rapid development of an efficacious vaccine is needed, which is usually demonstrated by an inactivated vaccine, e.g. BBIBP-CorV, which places it as a promising COVID-19 vaccine development strategy. Furthermore, BBIBP-CorV immunized macaques demonstrated protection towards intratracheal challenge with SARS-CoV-2, by showing significantly lower viral load in throat swabs and lungs pathology, when compared to the placebo group.²⁶ The need for large amounts of antigen to elicit adequate immune response from inactivated vaccines is a major disadvantage when compared to live-attenuated vaccines.²³ However, this problem could be solved through incorporating "booster" doses within the primary vaccination course.^{23,25} This theory is further supported by study results on immunization schedules from a phase 2 study of BBIBP-CorV by Xia et al., where participants who receive two doses on either day 0 & 14, 0 & 21 or 0 & 28 elicited greater reciprocal neutralizing antibody (NAb) titre than those who receive a single dose.¹¹ The promising results on BBIBP-CorV illustrated beforehand, is further supported looking back at previous experiences in managing viral outbreaks with the use of inactivated vaccines, as summarized by Stuurman et al on the benefits of mass vaccination program using a monovalent inactivated vaccine against hepatitis A. The review summarized multiple studies that illustrated the importance of achieving

herd immunity to consequently produce a marked decline in incidence, in both vaccinated and non-vaccinated groups, with the decline occurring post-outbreaks being unable to be attributed to other factors, e.g., improvement in water sanitation infrastructure.²⁷ Other instances which we can learn from is the use of killed Oral Cholera Vaccine (OCV). Islam et al had illustrated the intermediate efficacy of OCV from various studies.²⁸ Nonetheless, Islam et al and Lopez et al had also pressed the urgency of utilizing the short-term protection conferred from such vaccines as a strategy to contain outbreaks, further boosting the confidence in the mass use of inactivated COVID vaccines as a principal strategy to manage the ongoing pandemic.^{28,29}

Immunogenicity of Inactivated Vaccines for COVID-19

The primary immunological outcome of the six included studies were in the form of Neutralizing Antibodies (Nab) response against the virus.⁸ All the studies required the participants having no NAb response beforehand against SARS-CoV-2 to ensure seroconversion rates could be calculated with minimal error.^{11,12} NAb is defined as an antibody that protects the host from an infectious particle (SARS-CoV-2) via a neutralising mechanism, rendering it to be non-infectious or non-pathogenic.³⁰ The number of NAb induced by the inactivated vaccine is represented in geometric mean titre (GMT) with seroconversion rates (%) being stated as the primary outcome.³⁰ Seroconversion rates were mostly tested on the 14th or 28th day following the second or last dose of the vaccine

depending on the vaccination cohort and immunization procedure.

Studies conducted by Xia et al, Zhang et al, Wu et al, and Che et al administered CoronaVac inactivated vaccines with mostly showing above 90% seroconversion rates following the second immunization.^{8,9,12,13} There are no significant outcome differences between phase 1 and phase 2 clinical trials with a few exceptions, specifically in Zhang et al's study.⁹ The study administered low dose CoronaVac at 3 µg and medium dose at 6 µg with a 0/14-days vaccination cohort for its phase 1 clinical trials.⁹ Despite both showing subpar results (45.8% for 3 µg and 50.0% for 6 µg), the outcome is not significant ($p=0.77$) and further deterred by phase 2 results of the same study which yielded above 90% seroconversion rate ($p=0.03$) and Che et al's study which yielded 89% seroconversion rate ($p<0.001$).^{2,6} Other than CoronaVac, studies conducted by Xia et al and Ella et al used BBV152 and BBIBP-CorV inactivated vaccines.^{10,11} Both studies showed impressive seroconversion rates following the second dose and showed a dose-dependent relation similar to Coronavac.⁸⁻¹³ Moreover, better seroconversion rates was achieved with a higher vaccination dose and 0/28-days vaccination cohort, supported in Zhang et al, Wu et al, and Che et al.^{9,12,13} Additionally, this is further supported by the meta-analysis (Preprint) conducted by Yuan et al on the immunogenicity of COVID-19 vaccines in general, with vaccines administered 0/28 days being more significant ($p<0.00001$) than 0/14 days ($p=0.0004$).³

Table 1. Summary of Study Characteristics

Author Year	Study location	Study Design		Study population			Vaccine type [dose]	Vaccination cohort	Immunogenicity		Adverse effect	
		Blinding, control	Phase	Sample size	Characteristics of study population	Mean age, years (SD)			Value (95% CI)	p	Value	p
							LD vaccine [2.5 µg antigen protein content per dose] (n=24)		24/24 (100%; 60-100) for 2.5 µg		5/24 (20.8%) for 2.5 µg	
Xia; 2020 ⁸	Wuhan Institute of Biological Products Co Ltd and Henan Provincial CDC & CDC of Wuzhi Country, Henan Province	Randomized, double-blind, placebo-controlled	1	96	Healthy adults aged 18-59 years	41.2 (9.6) years	MD vaccine [5 µg antigen protein content per dose] (n=24)	0, 28, and 56 days	23/24 (95.8%; 56.7-100) for 5 µg	NA	4/24 (16.7%) for 5 µg	NA
						HD vaccine [10 µg antigen protein content per dose] (n=24)	24/24 (100%; 60-100) for 10 µg		6/24 (25%) for 10 µg			
						Control [aluminum hydroxide (alum) adjuvant only] (n=24)	0/0 (0%; 0-0) for alum		3/24 (12.5%) for alum			
						2	224		43.5 (9.1) years		MD vaccine [5 µg antigen protein content per dose] (n=168), Control [aluminum hydroxide (alum) adjuvant only] (n=56)	
			0 and 21 days	16/84 (19%) for 5 µg, 5/28 (17.9%) for alum								
			Zhang; 2021 ⁹	Suining County of Jiangsu province, China	double-blind, placebo controlled	1	144	healthy adults aged 18-59 years	42.6 (9.4) for Day 0 and 14, 42.1 (9.7) for Day 0 and 28		LD CoronaVac [3 µg per 0.5 mL of aluminium hydroxide diluent per dose] (n=48), HD CoronaVac [6 µg per 0.5 mL of aluminium hydroxide diluent per dose] (n=48), placebo (n=47)	0 and 14 days
0 and 28 days	20/24 (83.3%; 62.6-95.3) for 3 µg, 19/24 (79.2%; 57.9-92.9) for 6 µg, 1/23 (4.4%; 0.1-22.0) for placebo	<0.0001							3/24(13%) for 3 µg, 4/24 (17%) for 6 µg, 3/23 (13%) for placebo	NA		

			2	600			LD CoronaVac [3 µg per 0.5 mL of aluminium hydroxide diluent per dose] (n=240), HD CoronaVac [6 µg per 0.5 mL of aluminium hydroxide diluent per dose] (n=240), placebo (n=120)	0 and 14 days 109/118 (92.4%; 86.0–96.5) for 3 µg 117/119 (98.3%; 94.1–99.8) for 6 µg 2/60 (3.3%; 0.4–11.5) for placebo	0.03	40/120 (33%) for 3 µg, 42/120 (35%) for 6 µg, 13/60 (22%) for placebo	site symptoms (p=0.02) and -site pain (p=0.04)
								0 and 28 days 114/118 (97.4%; 92.7–99.5) for 3 µg 118/118 (100%; 96.9–100) for 6 µg 0/59 (0.0%; 0.0–6.1) for placebo	0.12	23/120 (19%) for 3 µg, 23/120 (19%) for 6 µg, 11/60 (18%) for placebo	
Ella; 2021¹⁰	Multiple Institutes in India	Randomized, double-blind, multicentre, Placebo-controlled	1	375	Healthy adults aged 18-55 years	N/A	LD BBV152 vaccine [3 µg with Algel-IMDG] (n=100)	87.9% (95% CI 79.8-94.3) for MNT50, 93.4% (83.7-97.8) for PRNT50	NA	5/99 (5%; 1.9 - 11.8) for solicited local reaction, 5/99 (5%; 1.9 - 11.8) for solicited systemic reaction,	NA
							HD BBV152 vaccine [6 µg with Algel-IMDG] (n=100)	91.9% (84.6-96.0) for MNT50, 86.4% (75.1-93.2) for PRNT50		5/99 (5%; 1.9-11.8) for solicited local reaction, 14/99 (14%; 8.1-22.7) for solicited systemic reaction	
							HD BBV152 vaccine [6 µg with Algel only] (n=100)	82.8% (73.7-89.2) for MNT50, 86.6% (74.3-93.6) for PRNT50		1/93 (1%; 0.05-6.2) for solicited local reaction, 8/93 (8%; 3.8-15.6) for solicited systemic reaction	
							Control group [Algel only] (n=75)	8% (3.6-17.2) for MNT50		3/73 (3%; 1.04-12.03) for solicited local reaction, 7/73 (7%; 1.04-12.03) for solicited systemic reaction	

Xia; 2020 ¹¹	Shangqiu City Liangyuan District CDC in Henan Province, China	randomized, double-blind, placebo-controlled	1	96	Healthy adults aged 18-59 years reactions	53.7 (15.6)	LD BBIBP-CorV [2 µg per 0.5 mL of aluminium hydroxide adjuvant per dose] (n=24), medium dose BBIBP-CorV [4 µg per 0.5 mL of aluminium hydroxide adjuvant per dose] (n=24), HD BBIBP-CorV [8 µg per 0.5 mL of aluminium hydroxide adjuvant per dose] (n=24), placebo (n=24), for both 18-59 years age group and ≥60 years age group	days 0 & 28	Seroconversion at day 14 9/24 (79%) for 2µg group 21/24 (87%) for 4µg group 23/24 (96%) for 8µg group	N/A	11/24 (46%) for 2 µg , 3/8 (38%) in placebo group 8/24 (33%) for 4 µg 2/8 (25%) in placebo group 11/24 (46%) for 8 µg 1/8 (13%) for placebo group	p>0.99 in 2 µg and 4µg cohort p = 0.2 in 8 µg cohort
				96	Healthy adults aged ≥60 years				Seroconversion at day 28 24/24 (100%) for 2µg group 24/24 (100%) for 4µg group 24/24 (100%) for 8µg group			
			2	448	Healthy adults aged 18-59 years	41.7 (9.9)	HD BBIBP-CorV [8 µg per 0.5 mL of aluminium hydroxide adjuvant per dose] n=84, placebo (n=28)	day 0 (n=112)	Reciprocal neutralising antibody titre 14.7 (11.6-18.8)	N/A	Injection site adverse reaction (pain) 53/336(16%) for vaccine group 4/112 (4%) for placebo group	p = 0.008
								days 0 & 14 (n=112)	Reciprocal neutralising antibody titre 169.5 (132.2-217.1)			
							MD BBIBP-CorV [4 µg per 0.5 mL of aluminium hydroxide adjuvant per dose], placebo (n=84)	days 0 & 21 (n=112)	Reciprocal neutralising antibody titre 282.7 (221.2-361.4)		88/97 (90.7% [78.1-99]) for 1.5 µg, 96/98 (98% [92.8-99.8]) for 3 µg, 97/98 (99% [94.5-100]) for 6 µg	N/A
								days 0 & 28 (n=112)	Reciprocal neutralising antibody titre 218.0 (181.8 - 261.3)			

Wu; 2021 ¹²	Renqiu (Hebei, China)	double-blind, placebo-controlled	1	72	healthy adults aged 60 years	65.8 (4.8)	LD CoronaVac [3 µg per 0.5 mL of aluminium hydroxide] (n=24), HD Coronavac [6 µg per 0.5 mL of aluminium hydroxide] (n=24), placebo [aluminium hydroxide only] (n=24)	0 and 28 days	24/24 (100% [85.8-100]) for 3 µg, 22/23 (95.7% [78.1-99.9]) for 6 µg	0.558	mild to moderate 20/200 (20%) for 1.5 µg, 25/125 (25%) for 3 µg, 27/123 (22%) for 6 µg, 15/73 (9%) for placebo	0.981
			2	350		66.6 (4.7)	LD CoronaVac [1.5 µg per 0.5 mL of aluminium hydroxide] (n=100), MD Coronavac [3 µg per 0.5 mL of aluminium hydroxide] (n=100), HD Coronavac [6 µg per 0.5 mL of aluminium hydroxide] (n=99), placebo [aluminium hydroxide only] (n=50)	0 and 28 days	88/97 (90.7% [78.1-99]) for 1.5 µg, 96/98 (98% [92.8-99.8]) for 3 µg 97/98 (99% [94.5-100]) for 6 µg	0.489	severe adverse events unrelated to vaccine adm 4/100 (4%) for 1.5 µg, 1/125 (1%) for 3 µg, 2/123 (2%) for 6 µg	
Che Y; 2021 ¹³	Gejiu and Mile County, China	double blinded, placebo-controlled	2	750	Healthy adults aged 18-59 years	41.4 (10.84) MD, 40.3 (10.55) HD, 41.8 (9.75) P for Day 0 and 14	HD [100-150 EU inactivated viral agent in alumunium hydroxide] (n=300), MD (n=300), placebo [alumunium hydroxide only] (n=150)	0 and 14 days	Seroconversion at day 14 89% for MD group 96% for HD group	<0.001	Adverse reactions 24% for MD group 27.3% for HD group 17.3% for placebo	N/A
						37.3 (9.82) MD, 37.8 (9.58) HD, 36.9 (9.63) placebo for Day 0 and 28		0 and 28 days	Seroconversion at day 28 92% for MD group 96% for HD group		Systemic adverse reactions 10% for MD group 13% for HD group 14.7% for placebo	
Legend		CDC; Center of Disease Control and Prevention, LD; Low Dose, MD; Medium Dose, HD; High Dose, MNT ₅₀ ; Microneutralisation assay, PRNT ₅₀ ; Plaque-reduction neutralisation assay, Algel-IMDG; Aluminium hydroxide (Algel) Imidazoquinoline molecule chemisorbed to Algel										

Table 2. Cochrane Risk of Bias Assessment 2.0 Summary

Xia et al, 2020⁸						
Zhang et al, 2021⁹						
Ella et al, 2021¹⁰						
Xia et al, 2020¹¹						
Wu et al, 2021¹²						
Che et al, 2021¹³						
	 Low risk of bias	Bias arising from the randomization process Bias due to deviations from intended Bias due to missing outcome data Bias in measurement of the outcome Bias in selection of the reported results Overall bias				
	 Some concerns					
	 High risk of bias					

Safety Analysis Based on Adverse Reactions Reported

The studies reviewed within this paper considers the occurrence of injection site adverse events as well as systemic adverse reactions after a said period of time as the primary safety outcome that is analysed. For the two studies carried out by Xia, et.al 2020 in Wuzhi County⁸ and Shangqiu City Liangyuan District Center for Disease Control and Prevention¹¹, the occurrence of adverse reactions was recorded within 7 days post-vaccination, and for studies carried out by Ella et al, Zhang et al, and Wu et al, the said reactions were recorded after 28 days post vaccination schedule. Assessment of the 5 different primary safety outcomes revealed injection site pain as the most prevalent local adverse reaction.⁸⁻¹² Study results from Ella et al and Xia et al on the safety of BBV152 and

BBIBP-CorV respectively, identified fever as the most common systemic adverse reaction. However, these 2 studies, as well as studies by Wu et al and the phase 2 stage of CoronaVac study on adults aged 18-59 years old had stated that these adverse reactions are not significant in comparison to the placebo group.⁹⁻¹² To further illustrate, the phase 2 study carried out by Zhang et al concluded injection site symptoms & pain as statistically insignificant ($p=0.02$ and $p=0.04$ respectively).⁹ Statistically insignificant mild to moderate adverse event is also reported in the study by Wu et al.¹² Interestingly, the phase 2 study on BBIBP-CorV by Xia et al noted the appearance of injection site adverse reaction as statistically significant. ($p=0.008$) However, further investigation consisting of respiratory symptoms monitoring and laboratory measurements revealed neither upper respiratory tract infection nor clinically significant abnormal changes respectively.¹¹ Furthermore, Xia et al and Ella et al noted how the incidence of adverse events in inactivated vaccines was lower when compared to vaccine candidates of different types, suggesting a better safety profile for inactivated vaccines.^{8,10} Wu et al highlighted the absence of dose-related aggravation of adverse events in healthy adults aged more than 60 years old.¹² The findings within the studies that we reviewed are in line to the findings summarized by Yuan et al, that reported the findings of mild to moderate adverse event are mainly contributed by local, non-harmful adverse events, supporting inactivated vaccines as safe candidates for clinical use.³¹

Strength and Limitations

The strengths of this systematic review include the following: Firstly, the studies reviewed were all RCTs, often referred to as the gold standard for evidence-based medicine. The studies are further strengthened through double blinding eliminating the risk of selection, observational, as well as participant bias.³ The large sample sizes encompass a broad range of ages (18-59 years; 60 years or older), allowing researchers to observe the humoral response of the vaccine elicited in different age groups. Finally, the longitudinal nature of the studies, involving periodical scheduled visits accompanied with few participant withdrawals helps establish the difference in seroconversion rate and geometric mean titre between single and double dose vaccination.⁸⁻¹²

The systematic review has several limitations. Although the sample size was large, a much bigger one is needed for the results to be globally representative. The locations of the studies reviewed do not vary.³¹ Out of the 5 studies reviewed, 4 (Xia et al, Zhang et al, Wu et al, and Xia et al) were conducted in China, while 1 (Ella et al) in India, rendering the results hard to generalize. Furthermore, few or completed phase 3 clinical trials have been found, with a majority being phase 1/2 clinical trials.⁸⁻¹²

Conclusion and Recommendation

In summary, the use of inactivated vaccines from the studies have proven to elicit an antibody response within

participants regardless of dosage, period of administration, and age, with insignificant adverse effects. However, there are several limitations that should be considered. Firstly, due to the limited data from RCTs, little is known on whether the double dose vaccine can evoke long term immunity. Second, from an economical perspective, the distribution and administration of vaccines may be costly and time-consuming. Lastly, Indonesia's vaccination program administers vaccine based on priority groups, thus only a small percentage of the population has been vaccinated to date, which are mostly primary health workers. Thus, it is difficult to determine the effectiveness of the vaccine given the rate of vaccination and the uncertainty of compliance from the public due to multiple dosage administration.

For future studies, we recommend conducting phase 3 clinical trials to examine the effectiveness of the inactivated virus vaccine on participants or pilot clinical trials on patients with significantly mutated strains of SARS-CoV-2. Furthermore, upcoming RCTs should explore a wider demographic to examine the vaccines effects on children, populations of different ethnicities, and adverse effects that arise from both study populations, allowing for a more globally generalized data. Lastly, we suggest that the Indonesian government collaborate with NGOs and medical student organizations to increase the outreach, distribution, and vaccination attempts. Hopefully, these recommendations could help in further lowering COVID-19

transmission thus fulfilling our contribution towards the SDG 2030.

Conflict of Interest

The authors declare no competing interests.

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None were received

References

1. WHO. WHOcoronavirus disease (COVID-19) dashboard [Internet]. Geneva: World Health Organization; date unknown [updated 2021 Feb 16]. Available from: https://covid19.who.int/?gclid=Cj0KCQIAiKiBBhCcARIsAPWqoSoQfWyDTfnCGyXZXxLXjhPeI5bL6yQPMnuT2kLiDijlFAXl7eTJSvlaAsIDEALw_wcB
2. WHO. Draft landscape and tracker of COVID-19 candidate vaccines [Internet]. Geneva: World Health Organization; 2021 Feb 16. Available from: <https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines>
3. RCN. The nurse who gave world's first COVID-19 vaccine [Internet]. London: Royal College of Nursing; 2020 Dec 24. Available from: <https://www.rcn.org.uk/magazines/bulletin/2020/dec/may-parsons-nurse-first-vaccine-covid-19>
4. Oxford. Number of people fully vaccinated against COVID-19 [Internet]. Oxford: University of Oxford; date unknown. Available from: <https://ourworldindata.org/grapher/people-fully-vaccinated-covid?tab=chart&stackMode=absolute®ion=World>
5. Nunnally BK, Turula VE, Sitrin RD. Vaccine analysis: strategies, principles, and control. 1st ed. Heidelberg: Springer; 2015; p1-665.
6. Gao Q, Bao L, Mao H, Wang L, Xu K, Yang M, Li Y, Zhu L, Wang N, Lv Z, Gao H. Development of an inactivated vaccine candidate for SARS-CoV-2. Science [Internet]. 2020 Jul 3 ;369(6499):77-81. Available from: <https://science.sciencemag.org/content/369/6499/77.abstract>
7. Cochrane. RoB 2: A revised Cochrane risk-of-bias tool for randomized trials [Internet]. London: Cochrane; date unknown . Available from: <https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials>
8. Xia S, Duan K, Zhang Y, Zhao D, Zhang H, Xie Z, Li X, Peng C, Zhang Y, Zhang W, Yang Y. Effect of an inactivated vaccine against SARS-CoV-2 on safety and immunogenicity outcomes: interim analysis of 2 randomized clinical trials. Jama [Internet]. 2020 Sep 8;324(10):951-60. Available from: <https://pubmed.ncbi.nlm.nih.gov/32789505/>
9. Zhang Y, Zeng G, Pan H, Li C, Hu Y, Chu K, Han W, Chen Z, Tang R, Yin W, Chen X. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18–59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. The Lancet Infectious Diseases [Internet]. 2020 Nov 17; 21(2):181-192. Available from: <https://pubmed.ncbi.nlm.nih.gov/33217362/>
10. Ella R, Vadrevu KM, Jogdand H, Prasad S, Reddy S, Sarangi V, Ganneru B, Sapkal G, Yadav P, Abraham P, Panda S. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: a double-blind, randomised, phase 1 trial. The Lancet Infectious Diseases [Internet]. 2021 Jan 21. Available from:

- <https://www.sciencedirect.com/science/article/pii/S1473309920309427>
11. Xia S, Zhang Y, Wang Y, Wang H, Yang Y, Gao GF, Tan W, Wu G, Xu M, Lou Z, Huang W. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBIBP-CorV: a randomised, double-blind, placebo-controlled, phase 1/2 trial. *The Lancet Infectious Diseases* [Internet]. 2021 Jan; 21(1):39-51. Available from: <https://www.sciencedirect.com/science/article/pii/S1473309920308318>
 12. Wu Z, Hu Y, Xu M, Chen Z, Yang W, Jiang Z, Li M, Jin H, Cui G, Chen P, Wang L. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy adults aged 60 years and older: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. *The Lancet Infectious Diseases* [Internet]. 2021 Feb 3. Available from: <https://www.sciencedirect.com/science/article/pii/S1473309920309877>
 13. Che Y, Liu X, Pu Y, Zhou M, Zhao Z, Jiang R, Yin Z, Xu M, Yin Q, Wang J, Pu J. Randomized, double-blinded and placebo-controlled phase II trial of an inactivated SARS-CoV-2 vaccine in healthy adults. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America* [Internet]. 2020 Nov. Available from: <https://pubmed.ncbi.nlm.nih.gov/33165503/>
 14. Pradhan D, Biswasroy P, Ghosh G, Rath G. A review of current interventions for COVID-19 prevention. *Archives of Medical Research* [Internet]. 2020 Apr 30; 51(5):363-74. Available from: <https://www.sciencedirect.com/science/article/abs/pii/S0188440920306159>
 15. Kaur SP, Gupta V. COVID-19 Vaccine: A comprehensive status report. *Virus Research* [Internet]. 2020 Aug 13; 198114. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7423510/>
 16. Shrestha N, Shad MY, Ulvi O, Khan MH, Karamehic-Muratovic A, Nguyen US, Baghbanzadeh M, Wardrup R, Aghamohammadi N, Cervantes D, Nahiduzzaman KM. The impact of COVID-19 on globalization. *One Health* [Internet]. 2020 Oct;100180. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7553059/>
 17. Suryahadi A, Al Izzati R, Suryadarma D. The impact of COVID-19 outbreak on poverty: An estimation for Indonesia. *The SMERU Research Institute* [Internet]. 2020 Apr. Available from: <http://www.smeru.or.id/en/content/impact-covid-19-outbreak-poverty-estimation-indonesia#:~:text=The%20economic%20impact%20is%20expected,lead%20to%20a%20global%20recession.&text=The%20economic%20impact%20is%20also,between%201%20and%204%20percent>
 18. Papageorgiou AT. The new normal. *International Journal of Obstetrics and Gynaecology* [Internet]. 2020 May 14; 127(7): 779-780. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7273111/>
 19. Ophinni Y, Hasibuan AS, Widhani A, Maria S, Koesnoe S, Yuniastuti E, Karjadi TH, Rengganis I, Djauzi S. COVID-19 vaccines: current status and implication for use in indonesia. *Acta Medica Indonesiana* [Internet]. 2020 Dec 28; 52(4):388. Available from: <http://www.actamedindones.org/index.php/ijim/article/view/1648/pdf>
 20. Raja AT, Alshamsan A, Al-Jedai A. Status of the current COVID-19 vaccine candidates: implications in the saudi population. *Saudi Pharmaceutical Journal* [Internet]. 2020 Nov 10. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7654289/>
 21. Bartsch SM, O'Shea KJ, Wedlock PT, Strych U, Ferguson MC, Bottazzi ME, Randall SL, Siegmund SS, Cox SN, Hotez PJ, Lee BY. The

- Benefits of vaccinating with the first available COVID-19 coronavirus vaccine. *American Journal of Preventive Medicine* [Internet]. 2021 Jan 19. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7817395/>
22. CDC. Reinfection with COVID-19 [Internet]. Atlanta: Center for Disease Control and Prevention; date unknown [updated 2020 Oct 27]. Available from: <https://www.cdc.gov/coronavirus/2019-ncov/your-health/reinfection.html>
 23. Burrell CJ, Howard CR, Murphy FA. Fenner and White's Medical Virology. Academic Press; 2016 Nov 9.
 24. Delrue I, Verzele D, Madder A, Nauwynck HJ. Inactivated virus vaccines from chemistry to prophylaxis: merits, risks and challenges. *Expert Review of Vaccines* [Internet]. 2012 Jun 1; 11(6):695-719. Available from: <https://www.tandfonline.com/doi/full/10.1586/erv.12.38>
 25. Sridhar S, Brokstad KA, Cox RJ. Influenza vaccination strategies: comparing inactivated and live attenuated influenza vaccines. *Vaccines* [Internet]. 2015; 3(2):373-89. Available from: <https://www.mdpi.com/2076-393X/3/2/373>
 26. Wang H, Zhang Y, Huang B, Deng W, Quan Y, Wang W, Xu W, Zhao Y, Li N, Zhang J, Liang H. Development of an inactivated vaccine candidate, BBIBP-CorV, with potent protection against SARS-CoV-2. *Cell* [Internet]. 2020 Aug 6;182(3):713-21. Available from: <https://www.sciencedirect.com/science/article/abs/pii/S0092867420306954>
 27. Stuurman AL, Marano C, Bunge EM, De Moerloose L, Shouval D. Impact of universal mass vaccination with monovalent inactivated hepatitis A vaccines—A systematic review. *Human Vaccines & Immunotherapeutics* [Internet]. 2017 Mar; 13(3):724-36. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5360128/>
 28. Islam MT, Chowdhury F, Qadri F, Sur D, Ganguly NK. Trials of the killed oral cholera vaccine (Shanchol) in India and Bangladesh: Lessons learned and way forward. *Vaccine* [Internet]. 2020 Feb 29; 38:A127-31. Available from: <https://www.sciencedirect.com/science/article/pii/S0264410X19308709>
 29. Lopez AL, Deen J, Azman AS, Luquero FJ, Kanungo S, Dutta S, Von Seidlein L, Sack DA. Immunogenicity and protection from a single dose of internationally available killed oral cholera vaccine: a systematic review and metaanalysis. *Clinical Infectious Diseases* [Internet]. 2018 Jun 1; 66(12):1960-71. Available from: <https://academic.oup.com/cid/article/66/12/1960/4645296?login=true>
 30. Jiang S, Hillyer C, Du L. Neutralizing antibodies against SARS-CoV-2 and other human coronaviruses. *Trends in Immunology* [Internet]. 2020 May 1; 41(5):355-9. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7129017/>
 31. Yuan P, Ai P, Liu Y, Ai Z, Wang Y, Cao W, Xia X, Zheng JC. Safety, Tolerability, and immunogenicity of COVID-19 vaccines: A systematic review and meta-analysis [Internet]. 2020 Nov 4. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7654888/>
 32. Booth CM, Tannock IF. Randomised controlled trials and population-based observational research: partners in the evolution of medical evidence. *British Journal of Cancer* [Internet]. 2014 Feb; 110(3):551-5. Available from: <https://www.nature.com/articles/bjc2013725>