Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Reactogenicity and immunogenicity of heterologous prime-boost immunization with COVID-19 vaccine

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ABSTRACT

Background: The objective of the present work was to assess the reactogenicity and immunogenicity of heterologous COVID-19 vaccination regimens in clinical trials and observational studies.
Methods: PubMed, Cochrane Library, Embase, MedRxiv, BioRxiv databases were searched in September 29, 2021. The PRISMA instruction for systemic review was followed. Two reviewers independently selected the studies, extracted the data and assessed risk of bias. The quality of studies was evaluated using the New Castle-Ottawa and Cochrane risk of instrument. The characteristics and study outcome (e.g., adverse events, immune response, and variant of concern) were extracted.
Results: Nineteen studies were included in the final data synthesis with 5 clinical trials and 14 observational studies. Heterologous vaccine administration showed a trend toward more frequent systemic reactions. However, the total reactogenicity was tolerable and manageable. Importantly, the heterologous prime-boost vaccination regimens provided higher immunogenic effect either vector/ mRNA-based vaccine or vector/ inactivated vaccine in both humoral and cellular immune response. Notably, the heterologous regimens induced the potential protection against the variant of concern, even to the Delta variant.
Conclusions: The current findings provided evidence about the higher induction of robust immunogenicity and tolerated reactogenicity of heterologous vaccination regimens (vector-based/mRNA vaccine or vector-based/ inactivated vaccine). Also, this study supports the application of heterologous regimens against COVID-19 which may provide more opportunities to speed up the global vaccination campaign and maximize the capacity to control the pandemic.

1. Introduction

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in a global pandemic in late 2019 [1]. As of 10th Jan 2022, there have been over 3.0 million confirmed cases of COVID-19, with 5,464,532 deaths reported worldwide [2], prompting unprecedented efforts to contain the virus [1,3,4]. Covid-19 has not only killed more than five million people worldwide but has also left at least 1.5 million orphans, leading to a dramatic burden on the healthcare system and social security [5]. Globally, vaccination programmes have proved to be safe, effective and save lives [6,7]. However, most vaccines do not confer 100% protection potential, and it is not known how the current vaccines will prevent future transmission of SARS-CoV-2 [8], given emerging variants [9]. But vaccination is an effective tool to reach herd immunity and to interrupt the spreading of the disease against current and future variants [9,10]. The SARS-Cov-2 vaccines were developed in different platforms such as inactivated virus, protein subunit, vector-based and mRNA-based vaccines [3]. Heterologous

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vaccination refers to the use of booster and priming vaccines developed with different platforms. Heterologous vaccination against COVID-19 should be considered under some circumstances. There are some reasons for using heterologous regimen in clinical practices: (1) intermittent supply shortages of vaccines due to limited capacity in vaccine production and logistic challenge of distributing the right vaccines into the right people at the right time; (2) rare but severe adverse events of vector-based vaccines (e.g., thromboembolism in Oxford-AstraZeneca ChAdOx1-S COVID-19 vaccine); (3) emerging SARS-Cov-2 variants lead to demand for alternative second vaccination. Heterologous vaccine regimens were applied for other diseases including tuberculosis, yellow fever, and influenza [11,12]. Matching two different vaccine platforms could increase efficacy and elicit a strong and long-lasting immune response [13]. Heterologous prime-boost vaccination against SARS-Cov-2 was used in several countries although evidence of safety and robust immunogenicity to support the application of the heterologous regimens was scarce. We conducted this systematic review to investigate and point out the reactogenicity and immunogenicity of heterologous vaccine regimens for preventing COVID-19 disease.

2. Methods

2.1. Eligibility criteria

We included clinical trials and observational studies that examined the reactogenicity and immunogenicity of heterologous regimens of COVID-19 vaccine in healthy adults (uninfected human subjects). We considered published articles in peer-reviewed journals or preprints in English up until September 29, 2021.

3. Search strategy

We searched PubMed, Cochrane Library, Embase, and pre-print servers (Medrxiv and Biorxiv) to identify the relevant studies. Databases were searched with pre-specified keywords including "COVID-19″, "SARS-CoV-2″, "Coronarivus", "prime-boost", "vaccine", "immunization", "inoculation", "heterologous", "mix", "match", and "combination". The complete search strategy is detailed in Supplement file.

3.1. Study selection

After removing exact duplicates, two authors (T.T.N and G.V.V) independently screened the titles and abstracts of the articles to identify the potentially eligible studies. For those selective studies, the two authors independently assessed the full-text articles for eligibility for inclusion in this review. Disagreements between the authors on the inclusion of a given study were resolved by discussion between T.T.N and G.V.V to clarify eligibility. If no consensus was reached, the article was further evaluated by the third author (T.H.T.Q).

3.2. Data extraction and statistical analysis

Following PRISMA guideline, two authors (N.T.T and V.V.G) independently extracted the following data: general study information (authors, year of publication, and location of study), study characteristics, subgroup of study, sample size, description of vaccine, vaccination regimens, reactogenicity, immunology, and information to assess the quality of the study. Because of heterogeneity of quantifications, criteria for positivity vary in different studies, reported outcomes; comparison between trials are impossible for direct meta-analysis. Therefore, we conducted the network meta-analysis using the extracted data for reactogenicity of vaccination.

3.3. Quality assessment

Two reviewers (N.T.T and V.V.G) independently assessed study quality and discussed if disagreements occurred. If no agreement was reached, the study quality was evaluated by an additional reviewer (T.H.T.Q). The Cochrane risk of bias instrument was used to assess the risk of bias for clinical trials. We classified a clinical trial as high risk of bias if at least one category was rated as high risk of bias [14]. The Newcastle-Ottawa quality assessment scale was used to assess the risk of bias for observational studies. We classified observation studies with ≥ 7 stars as low risk of bias, 5 or 6 stars as medium risk of bias, and less than 5 stars as high risk of bias [15] (Table S1).

4. Results

4.1. Study selection and description

A total of 7288 papers were found based on the search strategy (2341 PubMed, 1604 EMBASE, 96 Cochrane library, 1481 MedRxiv, 1766 BioRxiv). After exclusion of exact duplicates, we screened titles and abstracts of 6333 articles to identify 76 potentially eligible articles. Of 76 articles, 21 articles met eligibility criteria and were included. Of 21 eligible studies, two papers were excluded because one study was third dose study [16] and another did not get the suitable outcome [17]; 19 studies were included in this review with 5 clinical trials and 14 observational studies (Fig. 1). The description of chosen studies was detailed in Table 1 with all the studies are conducted in 2021 year.

4.2. Risk of bias

Of 5 clinical trials, two studies were high risk of bias. One trial did not blind outcome assessment [18] and another trial was lack of random sequence and blindness of participants and personnel [19]. The remaining 3 clinical trials were low of bias although they did not provide sufficient information to evaluate blindness of participants and personnel, blindness of outcome assessment, or selective reporting (Table S2). Of the 14 observational studies, 12 were low risk of bias. The other two studies were medium because of the unrepresentativeness of the exposed cohort and inadequacy of following up [20,21] (Table S1).

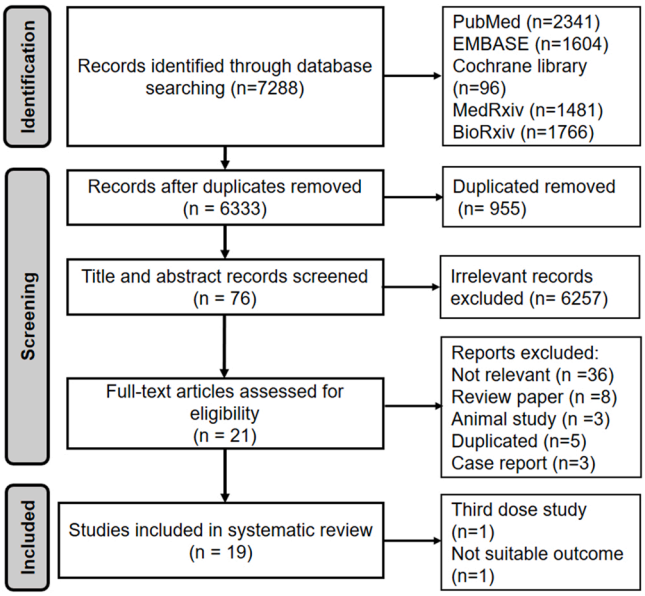

Fig. 1. Flowchart of the searching protocol and the final articles for systematic review. There studies were excluded because of third dose study [16], not suitable outcome [17], case report [23,54,55]. These studies did not get the inclusion criteria although the studies conducted in combination of the COVID—19 vaccines.

Table 1
Summary of included studies on heterologous COVID-19 vaccination.

Author	Country	Study design	Vaccine regimens†	Time period after boosting	Mean of age (range of age)	Gender Female (%)	Vaccine regimen	Sample size
Borobia[22]	Spain	Open label, randomized controlled trial	**ChAd/BNT** ChAd/no boost	14 days	43.98 (18–60 years)	56.5%	ChAd, BNT	676
Liu[28]	UK	Single-blind, randomized non-inferiority trial	**ChAd/BNT** ChAd/ChAd	28 days	57.8 (≥50 years)	45.8%	ChAd, BNT	830
Shaw[18]	UK	Multi-center, single-blind, randomized non-inferiority trial	**ChAd/** **BNT**BNT/BNT**BNT/** **ChAd**ChAd/ChAd	28 days	57.8 (≥50 years)	45.8%	ChAd, BNT	830
Li[26]	China	Randomized, controlled, observer-blinded trial	**CoVac/Convidecia**CoVac/CoVac	28 days	44.25	41%		299
Tenbusch[19]	Germany	Non-blinded non-randomized study	ChAd/ChAd**ChAd/BNT**BNT/BNT	2 weeks	42.5 (31–55)	90.2%	ChAd, BNT	642
Hillus[23]	Germany	Prospective cohort study	ChAd/ChAd**ChAd/BNT**BNT/BNT	3 weeks	35	66.6%	ChAd, BNT	380
Groβ[24]	Germany	Prospective cohort study	**ChAd/BNT**	14–19 days	30.5 (25–46 yrs)	61.5%	ChAd, BNT	26
Barros[30]	Germany	Prospective cohort study	ChAd/ChAd**ChAd/BNT**BNT/BNT	17 days	39	75%	ChAd, BNT	129
Behrens[31]	Germany	Prospective cohort study	ChAd/ChAd**ChAd/BNT**	16.3 days	39	21.7	ChAd, BNT	23
Benning[32]	Germany	Prospective cohort study	ChAd/ChAd**ChAd/BNT**BNT/BNT	20 days	ChAd/ChAd 55 (33–60 yrs)ChAd/ BNT 30 (24–45 yrs) BNT/BNT 45 (33–56 yrs)	81%	ChAd, BNT	134
Dimeglio[34]	France	Prospective cohort study	ChAd/ChAd**ChAd/BNT**BNT/BNT	28 days	37 (20–55 yrs)	74%	ChAd, BNT	132
Fabricius[35]	Germany	Prospective cohort study	BNT/BNTmRNA1273/ mRNA1273ChAd/BNT**CHAd/** **mRNA1273**ChAd/ChAd	2 weeks	44	62%	ChAd, mRNA 1273	116
Hammerschmidt [20]	Germany	Prospective cohort study	ChAd/ChAd**ChAd/BNT**BNT/BNT	17 days	NA	75%	ChAd, BNT	115
Kant[25]	India	Retrospective cohort study	**ChAd/Covaxin**ChAd/ ChAdCovaxin/Covaxin	3 weeks	≥ 50 yrs	49%	ChAd, Covaxin	98
Normark[29]	Sweden	Prospective cohort study	ChAd/ChAd**ChAd/mRNA1273**	30 days	43 (23–62 yrs)	NA	ChAd, mRNA1273	88
Schmidt[33]	UK	Prospective cohort study	ChAd/ChAd**ChAd/** **mRNA1273**mRNA1273/ mRNA1273	13 days	47.1	69.9%	ChAd, mRNA1273	213
Valiee[21]	France	Prospective cohort study	**ChAd/BNT**BNT/BNT	30 days	34.5	69.1%	ChAd, BNT	197
Yorsaeng[36]	Thailand	Prospective cohort study	CoVac/CoVac**CoVac/** **ChAd**ChAd/ChAd	32 days	41.5	62.7%	ChAd, Covac	214
Schmidt[27]		Prospective cohort study	ChAd/ChAd**ChAd/** **mRNA1273**mRNA1273/ mRNA1273	14 days	54.5	65.5%	ChAd, mRNA1273	110

†Bold text indicates the heterologous regimens.
mRNA: messenger RNA; mRNA1273: Vaccine from Moderna company; ChAd: Astrazeneca, vector (Covisheld) vaccine; BNT: Pfizer mRNA vaccine; Convidecia: recombinant adenovirus type-5-vectored vaccine; CoronaVac: inactivated SARS-CoV-2 vaccine (CoVac); Covaxin: inactivated whole virion BBV152 vaccine; NA: not available;

4.3. Reactogenicity

Of the nine studies reported the safety of vaccine, the local reactions including injection site pain [18,22–26], redness [18,22,23,26], pruritus [18,22,26], hardness [18,22], swelling [18,23,26], and urticarial [22] were reported. One study conducted in solid organ transplant recipients, and showed the lower incidence of adverse events than healthy controls [27]. Overall, the local adverse events were mild or moderate and receded by several days after boosting. A higher occurrence of solicited injection site was observed in heterologous vaccination than homologous vaccination (Table 1c). The local and systemic events in females were more frequent than males while there was no different in subgroups of age [22,24].

In term of systemic reactions, feverishness [18,23–26], fatigue [18,23,24,26], diarrhea [18,23], myalgia [18,22,23,24,26], arthralgia [18,22,23], malaise [18,22,25], chill [18,22,24,27], headache [18,22,23,24,26,27], and nausea [18,22,23,26] were reported. No serious adverse events were reported in studies investigated reactogenicity. Although one study reported serious events in 4 participants, it was not related to the vaccination [28]. The result from network meta–analysis showed that the incidence of fever symptom was higher in the heterologous vaccination of vector-based and mRNA vaccine compared to homogenous vaccination. In case of vector-based vaccine and inactivated vaccine, the feverishness was the same between two groups (Fig. 2). The pyrexia events were managed by administration of antipyretic medication to reduce symptoms within several days post vaccination [18,25,23]. Table S3 was detailed systemic reactions through the participants.

4.4. Immunogenicity

4.4.1. Heterologous regimens of vector-based and mRNA-based vaccine

In general, the immunogenicity induced by heterologous ChAd/BNT

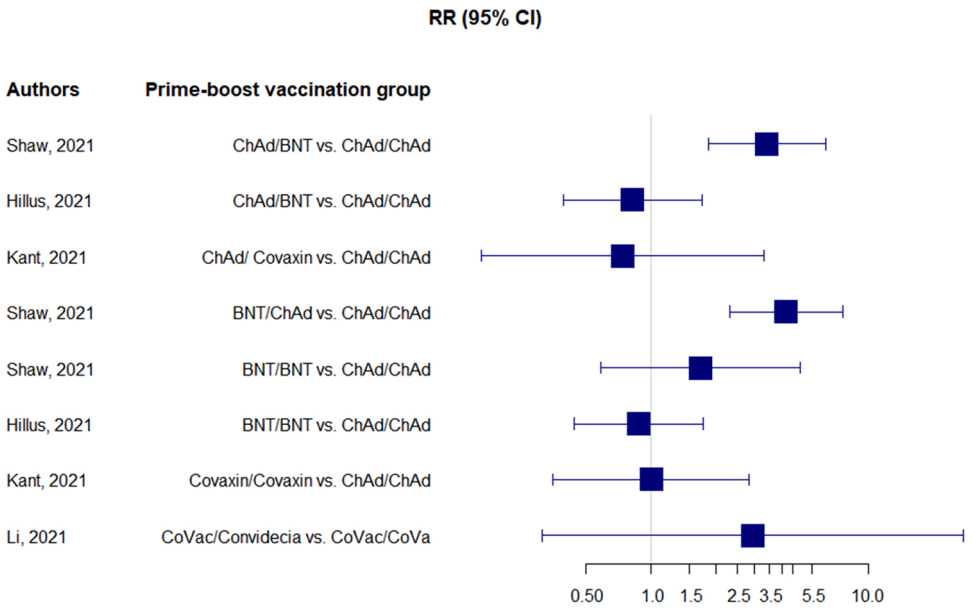

Fig. 2. Forest plot analysis of feverishness event by network meta-analysis in both random clinical trials and observational studies.

vaccination was more potent compared to homologous ChAd/ChAd vaccination in most of studies (Table 2). These findings were similar in both humoral and cellular immune response. Particularly, the anti-spike S antibody response in group vaccinated with heterologous regimens was high [22,24,21,29] and higher than groups vaccinated with homologous regimens [28,30–32]. Only two studies showed that the anti-spike S antibody response in group vaccinated with heterologous regimens was the same as groups vaccinated with homologous regimens [23,33]. Additionally, the receptor-binding domain (RBD) specific antibody was high in two studies [29,22,23]. The neutralizing antibody of group vaccinated with heterologous regimens was high [22,24,29] and higher than groups vaccinated with homologous regimens [23,28, 34,33]. Only two studies showed that neutralizing antibody of heterologous group was the same as groups vaccinated with homologous regimens [32,35]. In term of cellular response, the T cell response in group receiving heterologous regimens was high [22,24] [27,35] and higher than group receiving homologous regimen [23,28,30]. Only one study showed the same T cell response between heterologous and homologous regimens [33]. Notably, the B cell response was investigated in one study and showed similar extent in expansion of spike-specific memory B across regimens [30]. While evaluating combination vector-based/mRNA and BNT/BNT vaccination, the immunogenic effect was not consistent across studies. The spike protein Ab level was less than or equal; in contrast to, the T cell response had trend forwards to higher than or equal in heterologous group [23,28,30,32,34,21]. Different immunogenicity was not significantly influenced by age or sex [21,30].

When mRNA vaccine platform derived from different company (Pfizer or Moderna), the immunological activity was consistent in the previous review with the higher immune response being observed in heterologous compared to homologous ChAd/ChAd vaccination (Table 2). These findings supported the mRNA booster vaccination in ChAd prime individuals in order to solve the shortage of vaccine delivery.

4.4.2. Heterologous regimen of vector-based and inactivated vaccine

Because of emergency vaccine program, the heterologous vaccine regimens combined different vaccine platforms in different orders (e.g., vector-based prime/inactivated boost or inactivated prime/vector-based boost). Although the consideration of anxiety, safety, and efficacy was raised, the heterologous vaccine strategies were demonstrated the higher antibody response compared to inactivated prime-boost vaccine. Particularly, the spike protein antibody was higher in heterologous vaccination group compared to homologous vaccination of vector-based vaccine [25] or homologous vaccination of inactivated vaccine [36]. The neutralizing antibody response and RBD antibody response were higher in participants vaccinated with heterologous vaccination than participants vaccinated with homologous vaccination [26]. In contrast, the RBD antibody was lower among group vaccinated with heterologous regimen than group vaccinated with homologous regimen of vector-based vaccine [25]. Moreover, the T cell response was reported in covaxin/covaxin and ChAd/ChAd groups with the forward higher response was in ChAd/ChAd vaccination [25] (Table 3). On the other hand, while evaluating the IgG1/IgG4 response of CoVac and Convidecia vaccine, the heterologous group induced more potent response than homologous group [26]. Interestingly, the combination of vector and inactivated virus vaccine could offer potent immune memory in individuals, this might be the effect of immunodominance hierarchy which focusing to the insert in inactivated vaccine group [37,38].

4.4.3. Effect of heterologous regimens on SAR-Cov-2variants

The heterologous regimens showed more potent immunogenicity against the variant of concern α, β, and γ. The antibody responses against the Delta variant in heterologous regimens were higher than homologous regimen [20,2425]. The greater immune response was reported in combination between vector-based/mRNA vaccine and vector-based/inactivated vaccine [25] (Table 4). These studies reported the evaluation of geometric mean titerss of neutralizing antibody against the variants. The spread of new variant also raised a huge concern due to the reduction of vaccine protection or efficacy of drug therapy. Therefore, the superior immunogenicity of heterologous vaccine regimens supported the application of the heterologous regimens in the nationwide vaccine programs.

5. Discussion

The present work evaluated reactogenicity and immunogenicity of SARS-CoV-2 heterologous vaccination regimens in comparison to homologous vaccination regimens to provide scientific evidence in determination of vaccine strategy for the pandemic. In regard to the reactogenicity, the local and systematic reactions were well tolerated and there were no severe events occurring by vaccination. There was

Table 2
Immunogenicity of heterologous regimens including vector-based and mRNA-based vaccines (ChAd/BNT or ChAd/mRNA-1273).

Vaccine platform	Studies	Outcomes	ChAd/BNT (Mean (95% CI))	ChAd/ChAd (Mean (95% CI))	BNT/BNT (Mean (95% CI))	Major results
ChAd and BNT	Borobia [22]	Spike protein Ab	3684.87 BAU/ml (3851.58–4920.85),Ratio was 36.41-fold increase from baseline	ChAd prime only: 101.2 BAU/ml (82.45–124.22)	NA	Heterologous vaccination induced robust response
		RBD Ab	The number was higher compared with ChAd prime: 7756.68 BAU/ml (7371.53–8161.96)	99.84 BAU/ml (76.93–129.59)		
		Neutralizing Ab	GMT: increased 45-times, from 41.84 to 1905.69 (1625.65–2233.98)	41.81 (27.18–64.32)		
		T cell response	IFN-γ significantly increased with GMT: 521.22 pg/ml (422.44–643.09)	122.67 pg/ml (88.55–169.95)		
	Liu[28]	Spike protein Ab	12,906 ELU/ml (11,404–14,604)	1392 ELU/ml (1188–1630)	14,080 ELU/ml (12,491–15,871)	The higher immunogenicity of mixing vaccination compared with ChAd/ChAd was demonstrated
		Neutralizing Ab	Pseudotype virus neutralizing Ab (NT_{50}): 515 (430–617)	61(50–73)	574 (475–694)	
		T cell response	SFC per million PBMCs: 184 (152–223)	48 (37–61)	80 (63–101)	
	Hillus[23]	Serum Ab avidity	100% (88.6–100)	83% (66.4–92.7)	90% (74.4–96.5)	The heterologous improved immunogenicity compared with homologous ChAd/ChAd
		RDB Ab	5.6 S/Co (5.1–6.1)	4.9 S/Co (4.3–5.6)	5.4 S/Co (4.8–5.9)	
		Neutralizing Ab	Reactive neutralizing Ab: 100% (96.1–100)	88% (71.9–95.0)	99% (94.6–99.5)	
		T cell response	INF-γ concentration: 4762 mIU/ml (IQR: 2723–8403)	1061 mIU/ml (IQR: 599–2274)	2026 mIU/ml (IQR 1459–4621)	
	Groβ[24]	Spike protein Ab	Median IgG titers increased 135-fold (63.9 U/ ml, 4.27–2005→8815 U/ml, 1206–19,046)	NA	NA	The heterologous ChAd/BNT was potent humoral immune response and elicits T cell reactivity
		Neutralizing Ab	Median ACE2 neutralization increased after BNT booster (62%, 32–95–>98%, 89–98)			
		T cell response	100% participants developed CD4 +T cells and 89% produced CD8 + T cells			
	Barros [30]	Spike protein Ab	Ab IgG: 625.7 RU/mlAb IgA: 3.76 RU/ml	Ab IgG: 160.9 RU/ mlAb IgA: 0.87 RU/ml	Ab IgG: 574.1 RU/mlAb IgA: 5.06 RU/ml	Mixing vaccination provided potent higher immune response to ChAd/ChAd group. Boosting with BNT induced higher frequency of T cells response
		T cell response	A significant higher T cell response in ChAd/ BNT group			
		B cell response	Similar extent in expansion of spike-specific memory B in all groups			
	Behrens [31]	Spike protein Ab	611.o RU/ml (SD: 104.5)	171.9 RU/ml (SD: 121.8)	NA	Study supported for heterologous boost vaccination of individuals with completed homologous ChAd vaccination
	Benning [32]	Spike protein Ab	116.2 9IQR 61.84–170)	13.09 (IQR 7.03–29.02)	145.5 (IQR 100–291.1)	Heterologous induced strong and broad humoral response
		Neutralizing Ab	Percent of inhibition 96.8 (IQR 96.7–96.9)	93.5 (88.6–96.7)	97.0 (96.1–98.0)	
	Dimeglio [34]	Neutralizing Ab	95.4%	63.6%	68.2%	ChAd/BNT heteroglous regimen provided a stronger Ab response than either of the homologous regimens
	Valiée [21]	Spike protein Ab	7268.6 (6501.3–8128.3)	NA	10,734.9 (9141.1–12,589.3)	Applying heterologous second dose of BNT was associated with decrease of Ab response levels compared to homologous BNT vaccination
ChAd, mRNA, BNT			**ChAd/mRNA**	**mRNA/mRNA**	**ChAd/ChAd**	
In these two studies, the mRNA was mRNA 1273-vaccine from Moderna company	Fabricius [35]	Neutralizing Ab	‘ > 85% participants exhibited stronger neutralizing capacity		‘> 90% vaccinated individuals exhibited no or medium level neutralization capacity	Heterologus vaccination booster regimens with mRNA could allow enhanced protection against SARS-CoV-2
		T cell response	Peak IFN-γ secretion was significant stronger			
	Normark [29]	Spike protein Ab	115 time as high as. 128,108	NA	4320	Potent induction of SARS-CoV-2 immune response had trend to be higher in heterologous group
		RBD Ab	125 times as high as, 41,680	NA	1224	

(*continued on next page*)

Table 2 (*continued*)

Vaccine platform	Studies	Outcomes	ChAd/BNT (Mean (95% CI))	ChAd/ChAd (Mean (95% CI))	BNT/BNT (Mean (95% CI))	Major results
		Neutralizing Ab	Reciprocal serum neutralization titer 20 times as high as			
In these two studies, the mRNA was either BNT and mRNA1273from Moderna	Schmidt cellular [27]	Humoral response	In transplant recipients, the heterologous regimen led to significant induction in IgG level and neutralizing activity			
		T cell response	CD4 T cell levels was reported a significant increase in mixing boosting compared to mRNA boosting			
	Schmidt [33]	Spike protein Ab	3630 BAU/ml (IQR 3721)	4932 (IQR 4239)	404 (IQR 510)	Heterologous strategy led to a strong induction of both antibodies and T cells and approximately tenfold higher than hom0ologous vector vaccination
		Neutralizing Ab	Majority of individuals had 100% inhibitory activity		This number was lower	
		T cell response	Median % was 0.17 (IQR 0.13%)	0.16 (IQR 0.19%)	0.04 (IQR 0.04%)	

cell; Ab: antibody; RBD: receptor binding domain; IQR: presented as median; SD: standard deviation; GMT: Geometric mean titerss; SFC: spot-forming units; PMBC: peripheral blood mononuclear; NA: Not available; CI: confidence interval; mRNA: messenger RNA; mRNA1273: Vaccine from Moderna company; ChAd: Astrazeneca, vector (Covisheld) vaccine; BNT: Pfizer mRNA vaccine

Table 3
Immunogenicity in different prime/boost regimen with vector and inactivated vaccine type in included studies.

Studies	Type of vaccine	Spike protein Ab	RBD Ab	Neutralizing Ab	T cell response	Major results
Kant[25]	ChAd/ Covaxin	1145 (520.7–2520)	1866 (1003–3472)	NA		Immunization with combination of an vector-based type and inactivated whole virus vaccine elicited better immunogenicity
	Covaxin/ Covaxin	742.4 (485.8–1134)	710 (461–1092)		39.4 (IQR 33.87–49.27)	
	ChAd/ChAd	353.7 (219.9–568.9)	2260 (1881–2716)		47.66 (IQR 40.03–55.02)	
Li[26]	CoVac/ Convidecia	NA	941.8 (663.9–1336.1)	49.6 (35.1–70.2)	IgG1/IgG4: 24.4 (17.7–33.6)	Heterologous prime-boost regiment with ChAd after priming with CoronaVac induced significantly immunogenic than homogenous boost with CoronaVac
	CoVac/CoVac		154.1 (116.3–203.3)	10.6 (8.3–13.5)	IgG1/IgG4: 3.8 (3.1–4.6)	
	CoVac/CoVac/ Convidecia		3090.1 (2636.1–3622.3)	150.3 (128.6–175.7)	IgG1/IgG4: 42.4 (35.6–50.6)	
	CoVac/CoVac/ CoVac		369.0 (304.2–447.5)	35.3 (29.4–42.4)	IgG1/IgG4: 6.1 (5.2–7.1)	
Yorsaeng [36]	CoVac/ChAd	797.2 U/ml (598.7–1062)	NA	NA	NA	ChAd boosting after CoVac priming provided better antibody response than two doses of CoVac
	CoVac/ CoVac	96.4 U/ml (76.1–122.1)				
	ChAd/ ChAd	818.1 U/ml (662.5–1010)				

ChAd: Astrazeneca, vector (Covisheld); Convidecia: recombinant adenovirus type-5-vectored vaccine; CoronaVac: inactivated SARS-CoV-2 vaccine (CoVac); Covaxin: inactivated whole virion BBV152 vaccine

inconsistent between the total results of adverse reactions as equal reactions [22,23], higher reactions [18,32,25,26] in mixing vaccination group. The explanation for more frequency of systemic reactogenicity in heterologous groups might be the higher reactions in young age group with ChAd and BNT [39,40] or the variety in interval of prime-boost vaccination time [41]. In contrast, after the second dose vaccination, the adverse events in individuals immunized with the vector-based vaccine was more frequent compared to mRNA vaccines [42]. The systemic events were generally less frequent in individuals receiving heterologous regimen than individuals receiving homologous regimen [27,43]. However, in solid transplant recipients, the systemic events in individuals receiving heterologous regimen was more frequent than individuals receiving homologous regimen. In term of heterologous regimen of vector-based vaccine and inactivated vaccine, the similar document was cited of the slightly higher incidences of injection-site and systemic reactions. One study reported differences between male and female in reactogenicity because of stronger immune response among females than males [44]. The remaining studies did not observe the difference in subgroup analysis.

Immunological data suggested that either heterologous regimens of vector-based/mRNA or vector-based/ inactivated vaccine might be highly effective in preventing COVID-19. These findings were observed in the study conducted on animal [45]. The mechanism for this action could be that using different platforms has induced protection from different pathways. The mRNA vaccine elicited extremely high neutralizing and binding antibody titers while the vector-based vaccine produced polyclonal antibodies [46,47]. Additionally, the enhancer immunogenic effect might be related to the different natural immune response activated by the inactivated vaccine and the vector-based vaccine [37,48]. Furthermore, the differences in innate immunity after the first and second dose of vaccination and the potential role of trained innate cells might partially explain the improvement of immunogenicity in heterologous injection [49]. Notably, the combination of different vaccine platforms increased the cellular immunity responses while the second dose of ChAd failed to improve the cellular response obtained after an initial dose [39]. Another benefit of the heterologous approach was to prevent the development of immunity by the virus against a particular viral vector-based vaccine [13]. These results were consistent with the previous studies in animal models, that the heterologous of ChAd and BNT induced IgG specific titers and robust T cell helper responses in mice [45]. A combination of inactivated virus vaccine with other platform vaccine as adenovirus vectored could improve neutralizing antibody and T cell response [50]. Furthermore, heterologous immunization strategy with adenovirus vectored vaccine followed by

Table 4
Immunogenicity in different variants of concern in reported studies.

Study	Type of vaccine	Outcomes	Type of variant			
Hillus[23]	ChAd/BNT	The Geometric mean of 50% inhibitory dose (95% CI)	**α (B.1.1.7)** 956.6 (835.6–1095)	**β (B,1.351)** 417.1 (349.3–498.2)	**γ (B.1.1.28.1)** NA	**δ (B.1.617.2)** NA
	ChAd/ChAd		212.5 (131.2–344.4)	48.5 (28.4–82.8)		
	BNT/BNT		369.2 (310.7–438.6)	72.4 (60.5–86.5)		
Groβ[24]	ChAd/BNT	Neutralizing activities median titer of serum samples	2744 (209.8–8985)	1297 (252–6523)	NA	1309 (150–13,252)
	BNT/BNT	Compared to ChAd/BNT group	Lower ($p < 0.001$)	Lower ($p < 0.05$)		Lower (not significant)
Barros[30]	ChAd/BNT	Neutralization capacity of Ab	All participants	All participants	All but two participants	NA
	ChAd/ChAd		Increased in some individuals	No effect	No effect	
Behrens[31]	ChAd/ BNTWith ChAd/ChAd	50% neutralization titers (NT_{50})	ChAD/BNT induced higher levels against all type of variants compared to ChAd/ChAd group.$NT_{50} \geq 100$ in 85% of vaccines in delta variant			
Hammeschmidt [20]	ChAd/BNT with ChAd/ ChAd	Surrogate virus neutralization tests	NA	NA	NA	ChAd/BNT vaccination induced ninefold increase in neutralizing titers compared to ChAd/ ChAd group.
Fabricius[35]	ChAd/mRNA	Mean neutralization capacity individuals	87%	85%	71%	NA
	mRNA/mRNA		76%	73%	56%	
	ChAd/ChAd		48%	57%	15%	
Normark[29]	ChAd/mRNA	Neutralizing Ab		Induced Ab could neutralize the β variant		
	ChAd/ChAd			Did not induce potent Ab against this variant		
Kant[25]	ChAd/covaxin	Geometric mean titers with 95% confidence interval (CI)	396.1 (199.1–788)	151 (80.21–284.3)	NA	241.2 (74.99–775.9)
	ChAd/ChAd		122.7 (59.36–253.7)	48.43 (19.71–119)		51.99 (19.65–137.6)
	Covaxin/ Covaxin		112.4 (76.56–164.9)	52.09 (34.9–77.73)		54.37 (27.26–108.4)

NA: Not available; CI: confidence interval

inactivated/recombinant subunit/mRNA vaccine vaccination increased levels of neutralizing antibodies and promoted the modulation of antibody responses [51].

With emerging variants of concern, current evidence indicated that the higher immune response in heterologous regimens compared to homogenous regimens against the current type of variants (α, β, γ, δ). The efficacy of heterologous regimens against variants was observed in both humoral and cellular immune response and thus was suggested as a suitable strategy to contain emerging SAR-CoV-2 variants [52]. Besides that, some studies have been conducted to evaluate the third dose application, the result were consistent about the robust immunogenic effect in heterologous vaccination [16,26].

In contrast to the previous articles, we conducted a systematic study has been updated the status of heterologous strategy for not only prime vector/ boost mRNA vaccination but also the prime/boost vector/ inactivated vaccination [41,53]. Moreover, this is the first time the studies about matching vaccine was assessed by powerful tools for systematic study as Risk of bias 2 from Cochrane assessment for clinical trials and NewCastle- Ottawa assessment scales for cohort studies. We also used more source of data from printed and preprinted papers to entirely evaluated the matching vaccination. Additionally, the consideration for immunogenicity against the variants have been pointed out as the evidence for potent immune response of mixing vaccination. Thus, this systematic review was essential, important to give comprehensive, completed evaluation of heterologous vaccine strategy. Because of the variety of outcome quantified numbers, the network meta-analysis used the same outcome of previous review, however the method to calculate was different and this result was more intuitive to evaluate the reactogenicity. Besides that, the local and systemic reactions were assessed and pointed out to demonstrate the effect of heterologous or homogenous vaccination to the participants in studies (Table S3, S4).

The present study has several strengths. This review followed the PRISMA construction for conducting the assessment. Although the direct meta-analysis was impossible, the network meta-analysis was carried out to evaluate the reactogenicity of heterologous vaccination in term of fever symptoms which frequently occurred by COVID-19 vaccines. The risk of bias was assessed separately for clinical trials and observational studies by using Cochrane assessment and NewCastle- Ottawa assessment scales.

This systematic review was subjected some limitations. We cannot compare directly between studies because of the diversity of quantitative methods for antibody responses. Therefore, the work has lack of direct meta-analysis result. The interval of prime-boost injections varied between studies and has been not pointed out because of complication and the supplier contradiction.

6. Conclusion

The systematic review provided assessment and evidence about the higher induction of robust immunogenicity and tolerated reactogenicity of heterologous regimens (vector-based/mRNA vaccine or vector-based/ inactivated vaccine). The heterologous vaccination regimens might be an effective tool to contain the COVID-19 pandemic and the emergence of new variants. A future studies should investigate the efficacy and effectiveness of heterologous vaccination regimens.

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CRediT authorship contribution statement

TTN, THTQ, TMT, HTN, TKV and GVV involved in conceptualization; TTN, TMT, and GVV performed literature search and screen. TTN, THTQ, TMT, TKV and GVV performed quality assessment and analysis; TTN, THTQ, TMT, HNP, HTN and GVV were responsible for methodology and software; TTN, THTQ and GVV wrote the first draft. TTN, TKV and GVV supervised and revised the manuscript. All authors have read and agreed to the published version of the manuscript.

Declaration of conflicting interests

The authors declare no conflict of interest.

Data availability

The datasets used for the analysis in the present study are available from the corresponding author on reasonable request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.biopha.2022.112650.

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