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LETTER TO THE EDITOR

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Immunogenicity and safety of different platforms of COVID-19 vaccines given as a third (booster) dose in healthy adults

To the Editor,

The development and distribution of anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines are considered the most promising approach for curbing the COVID-19 pandemic. However, the disappointing immunologic response induced by CoronaVac and messenger RNA (mRNA) vaccination after a two-dose schedule of COVID-19 vaccines has given rise to great concern.[1]

Interestingly, in this journal, Petrelli et al.[2] reviewed 30 published studies on the efficacy and safety of the third dose of SARS-CoV-2 vaccine, which enlightened us to evaluate the published data on the immunogenicity and safety of different platforms of COVID-19 vaccines given as a third (booster) dose in healthy adults. To the best of our knowledge, no comprehensive meta-analysis focusing on this assessment has yet been published. Web of Science, PubMed, EMBASE, and Cochrane Library databases were searched to detect articles published from December 15, 2019 to March 18, 2022. The following combinations were used as search terms: SARS-CoV-2, COVID-19, vaccine, clinical trial, randomized controlled study efficacy, observational study, safety, efficacy, effectiveness, and side effects. Studies were included in this meta-analysis if they reported the immunogenicity and safety of different platforms of COVID-19 vaccines given as a third dose in phase I/phase II/phase III clinical trials. Analysis was carried out using Review Manager 5.3 (RevMan; Cochrane Collaboration). The randomized controlled trials included in the review are depicted in the preferred reporting items for systematic reviews and meta-analyses flowchart (Supporting Information: Figure 1).

After searching the Web of Science and other databases, three eligible publications[3–5] involving 3150 participants who have previously received two doses of the same COVID-19 vaccines including viral vector vaccine ChAdOx1 nCov-19 (ChAd; AZD1222; Oxford–AstraZeneca; hereafter referred to as AZD1222), mRNA vaccine BNT162b2 (Pfizer-BioNtech), or the inactivated COVID-19 vaccine, CoronaVac (Sinovac Biotech Co., Ltd.) were included under the inclusion criteria.

To date, evidence has been accumulated that antibody-mediated immunity plays a critical role in protection against SARS-CoV-2 infection.[3,6] As shown in Table 1, these studies reported that vaccinated by 1) inactivated SARS-CoV-2 virus VLA2001 (Valneva; hereafter referred to as VLA), mRNA vaccine mRNA1273 (Moderna; hereafter referred to as m1273), mRNA vaccine CVnCov (CureVac; hereafter referred to as CVn), AZD1222, nanoparticle vaccine NVX-CoV2373 (Novavax; hereafter referred to as NVX), or replication-deficient adenovirus vector vaccine Ad26.COV2.S (Janssen; hereafter referred to as Ad26) after BNT162b2/BNT162b2; 2) BNT162b2, m1273, CVn, NVX, or Ad26 after AZD1222/AZD1222; 3) inactivated vaccine BBIBP-CorV (Sinopharm; hereafter referred to as BBIBP), BNT162b2, and AZD1222 after CoronaVac/CoronaVac could all significantly boost antibody responses at Day 28 post the third dose. Exceptionally, the participants received BNT162b2/BNT162b2 as the initial schedule did not show an increased level of anti-spike immunoglobulin G antibodies at Day 28 post-VLA vaccination, evaluated by the pre-established criteria of minimal clinically important difference.

Like B cells, which produce antibodies, T-cell immunity plays an important role to protect against infection and to fight a SARS-CoV-2 infection.[7] The ability of the different platforms of COVID-19 vaccines as a booster dose to induce T-cell-mediated immunity among healthy adults was also assessed (Table 1). Among the three studies, the T-cell-boosting effects of the half dose boost of NVX previously received BNT162b2/BNT162b2 and the 1/5 dose boost of BNT162b2 previously received CoronaVac/CoronaVac groups were not statistically higher than the control treatment or the baseline. All of the other vaccines induced higher T-cell responses among participants who had previously received different vaccines (Table 1).

To evaluate the safety of different platforms of COVID-19 vaccines given as a third dose in healthy adults, we calculated the rates of Grade 3 and Grade 4 adverse events (Grade 3: severe: marked limitation in activity, some assistance usually required; medical intervention/therapy required. Grade 4: potentially life-threatening: requires assessment in the emergency department or hospitalization)[3] in the overall population (Figure 1). Serious adverse effects were well documented in one report[3] and two reports have made an explicit statement that no serious events had occurred after vaccination.[4,5] Fatigue, headache, and pain at the injection site were the most common systemic and local reactions in all three studies. Evaluation of Grade 3 and Grade 4 adverse events in participants who have previously received BNT162b2/BNT162b2 or AZD1222/AZD1222 as a subgroup reveals that a different booster vaccination following two doses of BNT162b2 was associated with a higher risk of Grade 3 and Grade 4 adverse events (risk ratio [RR], 1.97; 95% confidence interval [CI], 1.17–3.33), while no statistical difference was found

TABLE 1 Immunogenicity and safety of different platforms of COVID-19 vaccines given as a third (booster) dose

Study	Third dose type	Previous vaccine type	Time from second to third dose	Age groups (years) in trials	Country	Setting/median follow-up	No. of participants	Antibody titer before third dose (baseline)	Antibody titer post third dose (timing)	T-cell response, spot forming cells per 10^6 peripheral blood mononuclear cells before third dose	T-cell response, spot forming cells per 10^6 peripheral blood mononuclear cells post third dose (timing)	T-cell responses, IFN-γ $CD4^+$ (IU/ml) before third dose (baseline)	T-cell responses, IFN-γ $CD4^+$ (IU/ml) post-third dose (timing)
Munro et al./2021[3]	Control	Viral vector vaccine (AZD1222), 0.5 ml IM	78 days	<70 57 (52.3%); ≥70 52 (47.7%)	UK	General population	109	1237	841 (Day 28)	52.8	56.1 (Day 28)	–	–
	Nanoparticle vaccine (NVX), 0.5 ml IM	Viral vector vaccine (AZD1222), 0.5 ml IM	76 days	<70 63 (54.8%); ≥70 52 (45.2%)	UK	General population	115	1053	4791 (Day 28)	25.3	104.5 (Day 28)	–	–
	Nanoparticle vaccine (NVX), 0.25 ml IM	VIral vector vaccine (AZD1222), 0.5 ml IM	77 days	<70 59 (54.6%); ≥70 49 (45.4%)	UK	General population	108	1073	4959 (Day 28)	37.1	171.5 (Day 28)	–	–
	Control	mRNA vaccine (BNT162b2), 0.3 ml IM	104.5 days	<70 66 (55.9%); ≥70 52 (44.1%)	UK	General population	118	3482	2415 (Day 28)	37.9	33.2 (Day 28)	–	–
	Viral vector vaccine (AZD1222), 0.5 ml IM	mRNA vaccine (BNT162b2), 0.3 ml IM	110 days	<70 64 (58.7%); ≥70 45 (41.3%)	UK	General population	109	3196	13708 (Day 28)	57.9	116.4 (Day 28)	–	–
	Nanoparticle vaccine (NVX), 0.5 ml IM	mRNA vaccine (BNT162b2), 0.3 ml IM	104.5 days	<70 65 (57%); ≥70 49 (43%)	UK	General population	114	3512	8754 (Day 28)	56.9	75.0 (Day 28)	–	–
	Nanoparticle vaccine (NVX), 0.25 ml IM	mRNA vaccine (BNT162b2), 0.3 ml IM	100 days	<70 67 (59.8%); ≥70 45 (40.2%)	UK	General population	112	4469	10171 (Day 28)	25.8	39.8 (Day 28)	–	–
	Control	Viral vector vaccine (AZD1222), 0.5 ml IM	78 days	<70 48 (45.3%); ≥70 58 (54.7%)	UK	General population	106	1276	867 (Day 28)	56.6	50.0 (Day 28)	–	–
	mRNA vaccine (BNT162b2), 0.3 ml IM	Viral vector vaccine (AZD1222), 0.5 ml IM	77 days	<70 50 (46.7%); ≥70 57 (53.3%)	UK	General population	107	1443	21824 (Day 28)	44.2	129.4 (Day 28)	–	–
	Inactivated SARS-CoV-2 Virus (VLA), 0.5 ml IM	Viral vector vaccine (AZD1222), 0.5 ml IM	79 days	<70 51 (46.8%); ≥70 58 (53.2%)	UK	General population	109	1211	1599 (Day 28)	31.7	54.2 (Day 28)	–	–

TABLE 1 (Continued)

Study	Third dose type	Previous vaccine type	Time from second to third dose	Age groups (years) in trials	Country	Setting/median follow-up	No. of participants	Antibody titer before third dose (baseline)	Antibody titer post third dose (timing)	T-cell response, spot forming cells per 10^6 peripheral blood mononuclear cells before third dose	T-cell response, spot forming cells per 10^6 peripheral blood mononuclear cells post third dose (timing)	T-cell responses, IFN-γ $CD4^+$ (IU/ml) before third dose (baseline)	T-cell responses, IFN-γ $CD4^+$ (IU/ml) post-third dose (timing)
	Inactivated SARS-CoV-2 virus (VLA), 0.25 ml IM	Viral vector vaccine (AZD1222), 0.5 ml IM	77 days	<70 51 (45.9%); ≥70 60 (54.1%)	UK	General population	111	1334	1537 (Day 28)	35.9	64.4 (Day 28)	–	–
	Replication-deficient adenovirus vector vaccine (Ad26), 0.5 ml IM	Viral vector vaccine (AZD1222), 0.5 ml IM	77 days	<70 50 (46.3%); ≥70 58 (53.7%)	UK	General population	108	1555	5673 (Day 28)	36.7	102.7 (Day 28)	–	–
	Control	mRNA vaccine (BNT162b2), 0.3 ml IM	101 days	<70 62 (56.9%); ≥70 47 (43.1%)	UK	General population	109	4483	3209 (Day 28)	36.6	35.7 (Day 28)	–	–
	Inactivated SARS-CoV-2 virus (VLA), 0.5 ml IM	mRNA vaccine (BNT162b2), 0.3 ml IM	105.5 days	<70 63 (57.3%); ≥70 47 (42.7%)	UK	General population	110	3352	4428 (Day 28)	32.9	88.6 (Day 28)	–	–
	Inactivated SARS-CoV-2 virus (VLA), 0.25 ml IM	mRNA vaccine (BNT162b2), 0.3 ml IM	101.5 days	<70 61 (55.5%); ≥70 49 (44.5%)	UK	General population	110	3460	3500 (Day 28)	31.5	39.1 (Day 28)	–	–
	Replication-deficient adenovirus vector vaccine (Ad26), 0.5 ml IM	mRNA vaccine (BNT162b2), 0.3 ml IM	106 days	<70 59 (55.7%); ≥70 47 (44.3%)	UK	General population	106	4181	18631 (Day 28)	42.1	153.2 (Day 28)	–	–
	Control	Viral vector vaccine (AZD1222), 0.5 ml IM	77.5 days	<70 54 (47.4%); ≥70 60 (52.6%)	UK	General population	114	712	600 (Day 28)	45.1	48.8 (Day 28)	–	–
	mRNA vaccine (BNT162b2), 0.15 ml IM	Viral vector vaccine (AZD1222), 0.5 ml IM	78 days	<70 55 (47. 0%); ≥70 62 (53.0%)	UK	General population	117	1485	13951 (Day 28)	47.1	123.5 (Day 28)	–	–
	mRNA vaccine (m1273), 0.2 ml IM	Viral vector vaccine (AZD1222), 0.5 ml IM	79 days	<70 55 (49.1%); ≥70 57 (50.9%)	UK	General population	112	1265	23771 (Day 28)	48.4	148.6 (Day 28)	–	–
	mRNA vaccine (CVn), 0.6 ml IM	Viral vector vaccine (AZD1222), 0.5 ml IM	78 days	<70 58 (48.7%); ≥70 61 (51.3%)	UK	General population	119	920	4241 (Day 28)	47.6	65.1 (Day 28)	–	–

(Continues)

TABLE 1 (Continued)

Study	Third dose type	Previous vaccine type	Time from second to third dose	Age groups (years) in trials	Country	Setting/median follow-up	No. of participants	Antibody titer before third dose (baseline)	Antibody titer post third dose (timing)	T-cell response, spot forming cells per 10^6 peripheral blood mononuclear cells before third dose	T-cell response, spot forming cells per 10^6 peripheral blood mononuclear cells post third dose (timing)	T-cell responses, IFN-γ $CD4^+$ (IU/ml) before third dose (baseline)	T-cell responses, IFN-γ $CD4^+$ (IU/ml) post-third dose (timing)
	Control	mRNA vaccine (BNT162b2), 0.3 ml IM	93.5 days	<70 60 (53.6%); ≥70 52 (46.4%)	UK	General population	112	2761	2094 (Day 28)	38.3	26.9 (Day 28)	–	–
	mRNA vaccine (BNT162b2), 0.15 ml IM	mRNA vaccine (BNT162b2), 0.3 mlIM	107.5 days	<70 62 (56.4%); ≥70 48 (43.6%)	UK	General population	110	4060	27498 (Day 28)	42.0	107.0 (Day 28)	–	–
	mRNA vaccine (m1273), 0.2 ml IM	mRNA vaccine (BNT162b2), 0.3 ml IM	101.5 days	<70 62 (55.9%); ≥70 49 (44.1%)	UK	General population	111	3271	30654 (Day 28)	28.3	140.4 (Day 28)	–	–
	mRNA vaccine (CVn), 0.6 ml IM	mRNA vaccine (BNT162b2), 0.3 ml IM	98 days	<70 58 (54.7%); ≥70 48 (45.3%)	UK	General population	106	4175	8385 (Day 28)	56.6	68.8 (Day 28)	–	–
Intapiboon et al./ 2021 [4]	mRNA vaccine (BNT162b2). 0.3 ml IM	Inactivated SARS-CoV-2 virus (CoronaVac)	73 days	40.8	Thailand	Healthy adults	30	52	2622 (28 days)	32.0	49.0 (Day 14)	–	–
	mRNA vaccine (BNT162b2). 0.15 ml IM	Inactivated SARS-CoV-2 virus (CoronaVac)	73 days	40.6	Thailand	Healthy adults	30	52	1952 (28 days)	32.0	52.0 (Day 14)	–	–
	mRNA vaccine (BNT162b2). 0.06 ml ID	Inactivated SARS-CoV-2 virus (CoronaVac)	73 days	38.4	Thailand	Healthy adults	31	52	1205 (28 days)	32.0	34.0 (Day 14)	–	–
Kanokudom et al./ 2022 [5]	Inactivated vaccine (BBIBP), 0.5 ml IM	Inactivated SARS-CoV-2 virus (CoronaVac)	3–4 Monthsafter receipt of the first dose	42.7	Thailand	Healthy adults	60	42.76	164.1 (28 days)	–	–	0.050	0.085 (28 days)
	Viral vector vaccine (AZD1222), 0.5 ml IM	Inactivated SARS-CoV-2 virus (CoronaVac)	3–4 Monthsafter receipt of the first dose	41.6	Thailand	Healthy adults	57	41.13	1736 (28 days)	–	–	0.030	0.260 (28 days)
	mRNA vaccine (BNT162b2), 0.3 ml IM	Inactivated SARS-CoV-2 virus (CoronaVac)	3–4 Monthsafter receipt of the first dose	44.2	Thailand	Healthy adults	60	48.99	2584 (days)	–	–	0.035	0.790 (28 days)

Abbreviations: IFN-γ, interferon-γ; mRNA, messenger RNA; NVX, Novavax; SARS-CoV-2,severe acute respiratory syndrome coronavirus 2; VLA, Valneva.

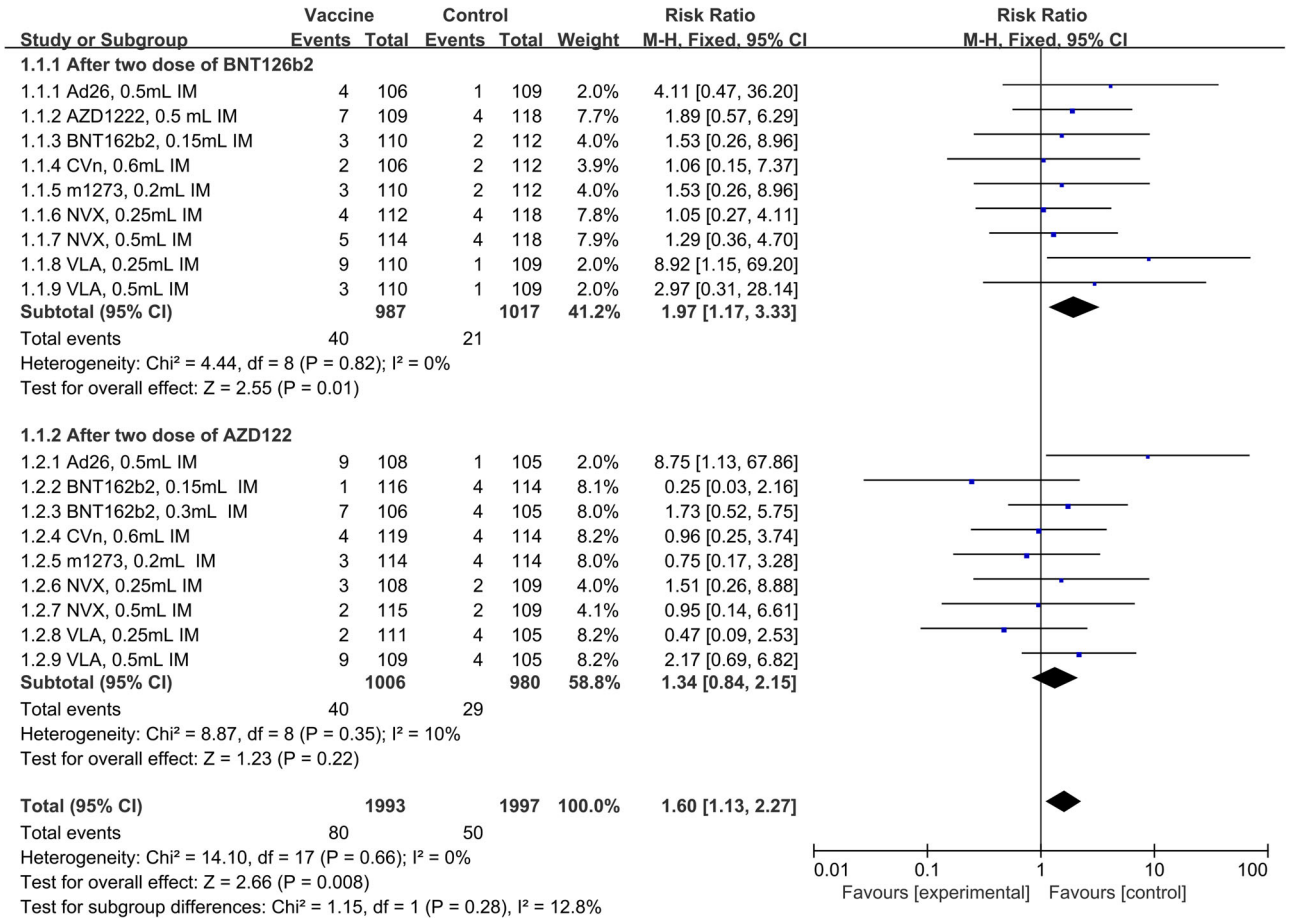

FIGURE 1 Forest plot for any Grade 3 or 4 adverse event with relative risk random effects. Grades 3 and 4 among 3990 participants who have previously received BNT162b2/BNT162b2 or AZD1222/AZD1222 vaccination were assigned a different booster vaccination or some trial treatment. CI, confidence interval, M-H, Mantel–Haenszel.

in a different booster vaccination following two doses of AZD1222 compared with control (RR, 1.34; 95% CI, 0.84–2.15) (Figure 1). In all these studies, no deaths associated with the booster COVID-19 vaccines were documented. All the booster vaccination showed acceptable side-effect profiles in the three studies, although some schedules were more than others.

In conclusion, the current study presented an integrated overview of the immunogenicity and safety of different platforms of COVID-19 vaccines given as a third dose in healthy adults. In this meta-analysis, we detected that the potential of all vaccines tested (inactivated SARS-CoV-2 virus VLA2001 [Valneva], mRNA vaccine mRNA1273 [Moderna], mRNA vaccine CVnCov [CureVac], AZD122 [Oxford–AstraZeneca], nanoparticle vaccine NVX-CoV2373 [Novavax], replication-deficient adenovirus vector vaccine Ad26.COV2.S [Janssen], and inactivated vaccine BBIBP [Sinopharm]) to enhance immunity as a booster dose in healthy adults. Furthermore, systemic adverse reactions among participants who received the third dose were generally acceptable. The immunogenicity and safety of heterologous vaccine regimens could provide guidelines for vaccination practice and increase the global reach of the finite vaccine supply.

AUTHOR CONTRIBUTIONS

Zemin Lin, Shijun He, and Jianping Zuo conceived the study protocol. Zemin Lin, Shijun He, Jianping Zuo, Xiaoqian Yang, and Fenghua Zhu participated in the literature search and data collection. Mengnan Cheng analyzed the data. Zemin Lin and Shijun He drafted the manuscript. All authors read and approved the final manuscript.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in One of the included study at doi:10.1016/2FS0140-6736(21)02717-3, reference number 3. All the data that support the finding of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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