

# A Meta-Analysis on the Safety and Immunogenicity of COVID-19 Vaccines

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## Abstract

**Objective:** The presented meta-analysis (MA) aims at identifying the vaccine safety and immunogenicity in published trials about SARS-CoV-2 vaccines. **Methods:** All relevant publications were systematically searched and collected from different databases (Embase, Scopus, EBSCO, MEDLINE central/PubMed, Science Direct, Cochrane Central Register for Clinical Trials (CENTRAL), Clinical Trials.gov, WHO International Clinical Trials Registry Platform (ICTRP), COVID Trial, COVID Inato, Web of Science, ProQuest Thesis, ProQuest Coronavirus Database, SAGE Thesis, Google Scholar, Research Square, and Medrxiv) up to January 10, 2021. The pooled vaccine safety and immunogenicity following vaccination in phase 1 and 2 vaccine clinical trials, as well as their 95% confidence intervals (CI), were estimated using the random-effects model. **Results:** The predefined inclusion criteria were met in 22 out of 8592 articles. The proportion of anti-severe acute respiratory distress coronavirus 2 (SARS-CoV-2) antibody responses after 7 days among 72 vaccinated persons included in 1 study was 81% (95% CI: 70-89), after 14 days among 888 vaccinated persons included in 6 studies was 80% (95% CI: 58-92), after 28 days among 1589 vaccinated persons included in 6 studies was 63% (95% CI: 59-67), after 42 days among 478 vaccinated persons included in 5 studies was 93% (95% CI: 80-98), and after 56 days among 432 vaccinated persons included in 2 studies was 93% (95% CI: 83-97). Meta regression explains more than 80% of this heterogeneity, where the main predictors were; the inactivated vaccine type ( $\beta = 2.027$ ,  $P = 0.0007$ ), measurement of antibodies at week 1 ( $\beta = -4.327$ ,  $P < 0.0001$ ) and at week 3 of the first dose ( $\beta = -2.02$ ,  $P = 0.0025$ ). Furthermore, the pooled proportion adverse effects 7 days after vaccination was 0.01 (0.08-0.14) for fever, headache 0.23 (0.19-0.27), fatigue 0.10 (0.07-0.13), and 0.18 (0.14-0.23) for muscle pain. **Conclusion:** Immunogenicity following vaccination ranged from 63% to 93% depending on the time at which the antibody levels were measured.

## Keywords

COVID-19 vaccines, vaccine safety, immunogenicity, phase 1, phase 2, meta-analysis

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## Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) results in corona virus disease 2019 (COVID-19). COVID-19 pandemic emerged from Wuhan in 2019, the infection spread to more than 190 countries. According to the World Health Organization's (WHO) latest report on January 2, 2022, the disease affected a total of nearly 289 million subjects, and more than 5.4 million deaths globally.<sup>1,2</sup> This zoonotic disease has rapidly crossed species to humans, thereby making it a highly contagious disease transmitted through respiratory droplets, infected surfaces, or human contacts.<sup>3</sup> The virus attacks not only the lower respiratory system causing viral pneumonia but also affects other systems such as the gastrointestinal, renal, hepatic, and central nervous systems leading to a wide range of symptoms and potential organ failure.<sup>4</sup> The only recommended preventive measures are wearing masks, social distancing, caring for personal hygiene, and avoiding overcrowded and poorly aerated area.<sup>5,6</sup> The mental and economic burdens impose more pressure on the vaccine development industry to flatten the pandemic curve and regain normal life activities.<sup>7-9</sup>

Unrevealing the viral composition indicated 4 main structural proteins, namely spike (S), nucleocapsid (N), envelope (E), and membrane (M) proteins. The most important one among the 4 proteins is the S protein, which is responsible for viral attachment, fusion, and initiated endosome-mediated host entry.<sup>10</sup> Subsequently, all scientific efforts to design an effective vaccine depends on using the S protein to effectively deliver the viral antigens and induce host immunological responses.<sup>3</sup> According to the WHO latest report on January 18, 2022, the landscape of vaccine development included 140 COVID-19 vaccine studies in the different phases of clinical development. Additionally, 194 vaccines in preclinical studies were reported.<sup>11</sup> Data are available on 19 inactivated virus studies, 19 non-replicating viral vector studies, 23 RNA-based vaccine, 47 protein subunit vaccines, 16 DNA-based vaccines, 4 replicating viral vector, 6 virus like particle, 2 replicating viral vector with antigen presenting cell, 2 live attenuated virus, 1 nonreplicating viral vector with antigen presenting cell, and 1 bacterial antigen-spore expression vector. Each of which is at a variable randomized controlled trial (RCT) phase compared against placebo control groups with variable risks of bias.<sup>11</sup> Pfizer-BioNTech, Moderna, Sputnik V, Convidecia, Johnson & Johnson, EpiVacCorona, Sinopharm, and Sinovac vaccines are approved to be employed in distinct countries, and some of them are for limited use in emergencies only.<sup>12</sup> In December 2020, a mass vaccination program started, and as of January 20, 2022 and 9.8 billion doses have been administered globally, thereby representing 60.3% of the whole worldwide population.<sup>1,2,13</sup>

The WHO recommended the administration of COVID-19 vaccines for the high-risk population including older adults. The ideal vaccine should have a favorable safety

profile and proven efficacy measured by the prevention of virologically confirmed diseases or the transmission or both and should provide at least 6-month protection.<sup>14</sup> One of the chief markers of immunogenicity is anti-SARS-CoV-2 antibodies, which have been reported to predict disease severity and survival.<sup>15</sup> Anti-SARS-CoV-2 antibodies provide efficient sterilizing immunity in vaccinated individuals.<sup>16</sup>

A secondary vital outcome should involve a vaccine safety profile and reactogenicity. The fast-track evaluation of SARS-CoV-2 raises concerns about its full safety profile.<sup>17,18</sup> Most studies have reported pain, fever, injection site pain, and fatigue; however, more long-term follow up is recommended. Some occasional serious side effects or even deaths have also been reported with selected individuals during clinical studies and the marketing phase, which necessitate an overall evaluation of the vaccines' safety.<sup>19-21</sup>

Vaccine immunogenicity assays are performed under good clinical laboratory practices. In phase 1 and 2 vaccine studies, the standards of reporting immunogenicity data are guided by the European Medicine Agency guidelines, which include but are not limited to reporting the predetermined seroconversion rate, the change in geometric mean concentrations in the antibody titers, and the antigen-specific T-cell responses.<sup>22</sup>

Despite the high vaccine safety indication of the available first generation COVID-19 vaccines on healthy adults, several studies have reported product-related vaccine safety issues, such as adverse events following immunization, which might be linked or not to the vaccine administration. In addition, the vaccine trials have discussed adverse events of special interest, which are general pre-specified vaccine safety issues usually known as events after vaccination.<sup>23</sup> Safety of COVID-19 vaccines is one of the concerns affecting the acceptance of the population to be vaccinated. Studies on vaccine hesitancy found that the refusal or delaying the vaccination was affected by the population's trust in the safety and efficacy of vaccines.<sup>24</sup>

Therefore, the current work aims to reach elaborative evidence about vaccine immunogenicity and safety across various first-generation COVID-19 vaccines. This is to be achieved by a systematic review of the published studies with predefined inclusion criteria to include only phase 1 and 2 clinical trials on COVID-19 vaccine immunogenicity to SARS-CoV-2 and the associated product-related adverse events. Information on vaccine effectiveness is rapidly evolving and globally monitored, thus it is beyond the scope of this article.<sup>1,25</sup>

## Methods

This meta-analysis (MA) was guided by the 2019 Cochrane Handbook of Systematic Review and MA<sup>26</sup> with respect to the preferred reporting items of the systematic review and MA (PRISMA) checklist.<sup>27</sup>

## Data Sources

Search regarding the immunogenicity and safety of COVID-19 vaccination was conducted through the published and gray literature by using multiple databases: Embase, Scopus, EBSCO, MEDLINE central/PubMed, Science Direct, Cochrane Central Register for Clinical Trials (CENTRAL), Clinical Trials.gov, WHO International Clinical Trials Registry Platform (ICTRP), COVID Trial, COVID Inato, Web of Science, ProQuest Thesis, ProQuest Coronavirus Database, SAGE Thesis, Google Scholar, Research Square, and Medrxiv. The search terms were determined and approved after the consultation of PubMed help. The search terms included (“Coronavirus” OR “Coronavirus infections” OR “COVID 2019” OR “SARS2” OR “SARS-CoV-2” OR “SARS-CoV-19” OR “severe acute respiratory syndrome coronavirus 2” OR “coronavirus infection” OR “severe acute respiratory pneumonia outbreak” OR “novel CoV” OR “2019 ncov” OR “sars cov2” OR “cov2” OR “ncov” OR “COVID-19” OR “COVID19” OR “coronaviridae” OR “coronavirus”)AND(“Vaccin\*safety”OR“Vaccin\*immunogenicity”). Manual search was performed by tracking citations, references, and related articles for these eligible papers.<sup>28</sup>

The database search ended on January 10, 2021.

## Study Selection

Inclusion criteria: We included studies reporting COVID-19 immunogenicity or safety, which were published since 2019 with no language restriction. Thus, we included all studies with various COVID-19 vaccine types, doses, delivery, designs, mode of action, and different comparator groups (placebo, another vaccine, and distinct doses of the same vaccine). Moreover, we included studies reporting any gender of healthy adult populations (age above 18 years old). The inclusion criteria also incorporated no previous SARS-CoV-2 infection, no previous history of seizures, no febrile illness at the time of vaccination, participants who did not receive any blood products for the last 4 months, or no history of allergic reactions to any of the vaccine ingredients, and all types of clinical trials phases 1 and 2 only. Further, we excluded the abstract-only papers, research proposals, conference, editorial, author responses, all reviews, case reports, case series, books, and studies with data not accurately reliably extracted, duplicate, or overlapping data.

## Primary and Secondary Outcome

We mainly focused on the vaccine immunogenicity as our primary outcome. COVID-19 vaccine immunogenicity is defined as the ability of a vaccine to induce an immune response (antibody- and/or cell-mediated immunity) in a vaccinated individual.<sup>25</sup> Anti-SARS-CoV-2 antibodies were accessed at the baseline and at different periods of time according to each study.

Our secondary outcome was the vaccine safety, which was assessed by reporting any adverse events within 7 days after the vaccination or during other periods of time according to each vaccine type. The adverse events could be local or systemic, and the reported adverse effects varied between pain at the local injection site, rash, fever, chills, fatigue, muscle pain, hospitalization, mechanical ventilation, and death.

## Data Extraction and Selection Process

All the citations were imported into Endnote 18 to detect and remove the duplicates with 2 methods: title, author, year, and journal. Abstract screening, followed by full text screening phases, was started with articles extracted into an Excel sheet with the author’s name, publication year, journal, DOI, URL link, and abstract. The screening was performed independently by BK, NH, AK, MS, RS, SA, OR, AN, EE, YE, SG, and MB. The third part (HS, RA, OF) solved the disagreement between the reviewers. Additionally, the articles were extracted in an Excel sheet with the following predefined data: year of publication, author name, country, study design, inclusion, and exclusion criteria, reported immunogenicity, and reported adverse drug reactions. Full text eligibility was conducted by BK, NH, AK, MS, RS, SA, OR, AN, EE, YE, SG, and MB, and disagreement was solved by HS, RA, and OF. The Excel sheets were available online for reviewers through this link.

The agreement between reviewers was tested by the kappa Fleiss test,  $k = 0.86$ .

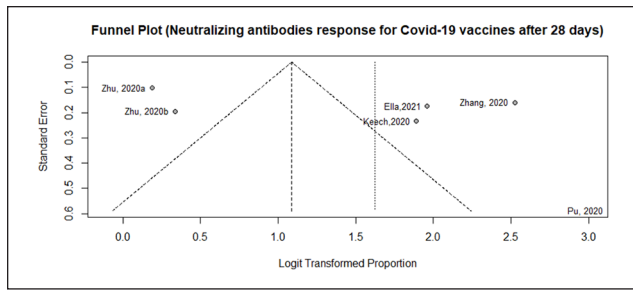
Measures of treatment effects: We calculated the pooled proportion with respective 95% confidence intervals (CIs) and performed the forest plots to show individual studies and pooled estimates.

## Investigations of Heterogeneity

Cochrane  $Q$  and  $I^2$  tests were utilized to assess and measure the heterogeneity between the studies, considering that  $I^2 \geq 75\%$  represents substantial heterogeneity and that the strength of evidence for heterogeneity is  $P \leq 0.05$  from the  $Q$  test according to the Cochrane Handbook for Systematic Reviews of Interventions.<sup>26</sup> In the case of substantial heterogeneity, the DerSimonian and Laird random-effects models were applied to pool the outcomes; otherwise, a fixed-effect model was used. The subgroup analysis and outlier removal were employed to resolve the heterogeneity. Metaregression was conducted to explain the significant predictors of remaining heterogeneity considering the type of used vaccine, weeks of antibodies measurement after first dose and the country.

## Publication Bias

The publication bias was assessed for our primary outcome (anti-SARS-CoV-2 antibodies after 28 days) by visual



**Figure 1.** Publication bias funnel plot. Egger’s test  $t = 1.365$ ,  $P$ -value = 0.24.

inspection of the funnel plot and statistically by the Begg’s modified funnel plot as presented in Figure 1.

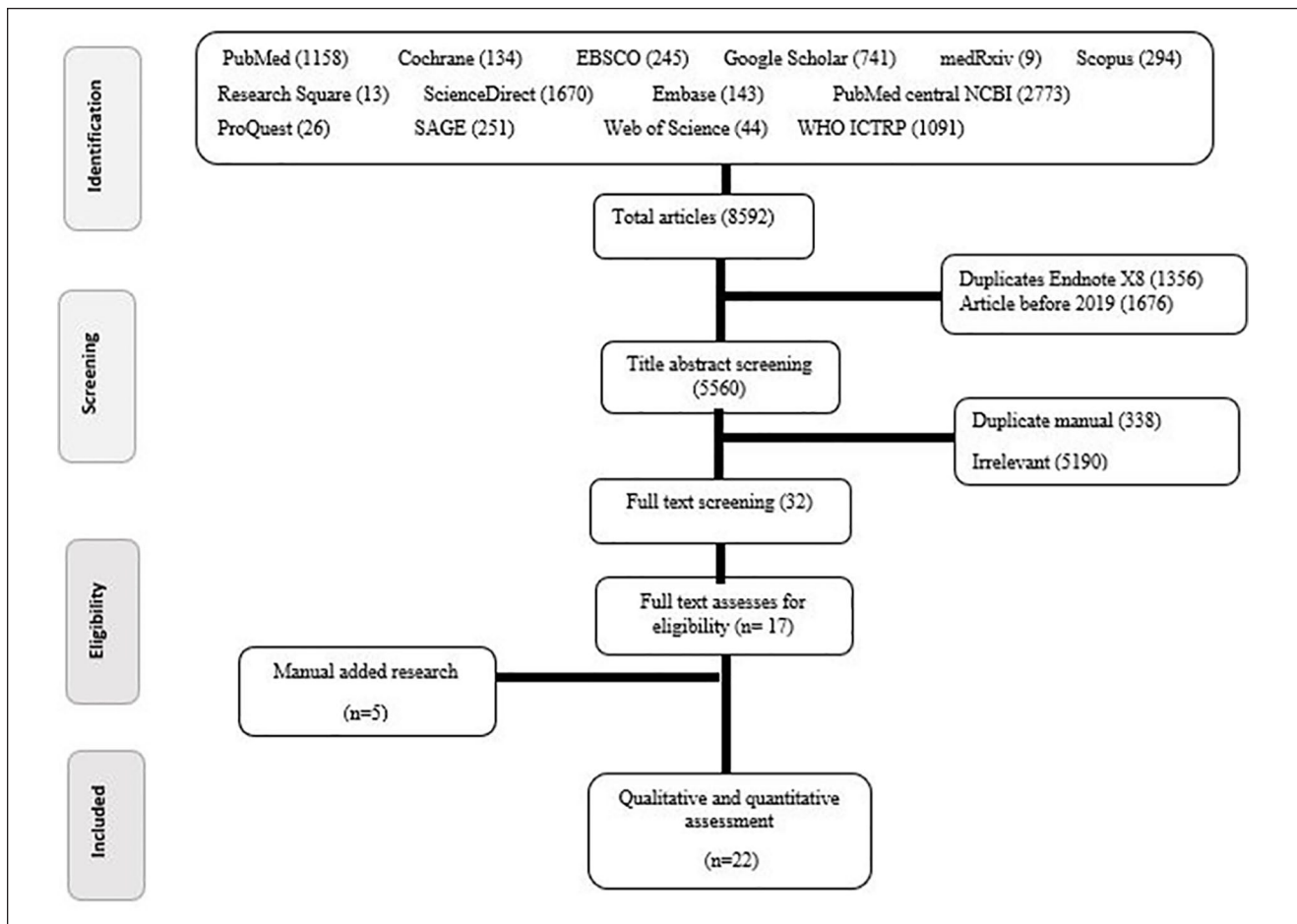
**Results**

Figure 2 depicts the flow diagram of the selection process. From a total of 8592 potentially relevant articles, 1356 duplicate articles were excluded by Endnote, and 1676

articles were excluded as they had been published before 2019. A total of 5560 articles were eligible for title abstract screening, and only 32 articles were eligible for full text screening after removing irrelevant (5190) and duplicate articles (338). In total, 17 articles were included for quantitative assessments after full text screening, and another 5 articles were added manually. Hence, 22 articles were included.

**Review of Literature**

The types of investigated studies encompassed double-blinded,<sup>29-36</sup> single-blinded,<sup>18,37-43</sup> or non-randomized,<sup>44-46</sup> some of them were open label.<sup>47-49</sup> They also included phase 1,<sup>29,30,32,42,43,46-49</sup> phase 2,<sup>18,29,36</sup> phase 1/2,<sup>33-35,37-41,44,45</sup> or phase 1/2a<sup>31</sup> randomized controlled trials. The age of most of the included subjects ranged from 18 to 60 years, except for some studies including older ages reaching 70,<sup>18</sup> 80,<sup>34</sup> and 85 years.<sup>42,43</sup> Male and female genders were equally distributed in the studies, except for the study of Ella et al.,<sup>29</sup> who included more male sex in their work. In addition, The types of vaccines investigated involved vectored,<sup>18,31,36-39,44,46</sup> inactivated



**Figure 2.** PRISMA flow chart of studies screened and included.

virus,<sup>29,30,33-35,40</sup> and mRNA vaccines.<sup>41-43,45,47,48</sup> The trial durations ranged from 2 weeks<sup>36</sup> to more than 3 months.<sup>43</sup>

The chief outcomes investigated in the clinical trials were vaccine immunogenicity, safety, and tolerability of distinct vaccines. Immunogenicity was determined via serological markers, such as measuring antibody titers,<sup>34,36,37,39,46,47</sup> geometric mean titers,<sup>41,47</sup> specific IgG responses,<sup>18,29,32,35,38,40-43,45,49</sup> and T-cell responses,<sup>35,36,46-48</sup> which included a strong CD4 cytokine response involving type 1 helper T-cells<sup>47</sup> while Zhang et al.<sup>35</sup> did not assess the T-cell responses in the phase 2 trial.

The adverse effects including, local, systemic, and unsolicited ones were examined at time points between day 7 until day 28,<sup>30,31,36,44</sup> and sometimes up to 8 weeks post-dose.<sup>38,40,49</sup> Most of the reported vaccines were well tolerated with high reactogenicity<sup>39</sup>; however, sometimes requiring booster doses (Tables 1-3).<sup>37</sup>

## Primary Outcome

### Level of Anti-SARS-CoV-2 Antibodies After 28 Days

The pooled proportion of anti-SARS-CoV-2 antibody response (AR) for COVID-19 vaccines after 28 days was 63% (95% CI: 59-67) among 1589 vaccinated individuals included in 6 studies ( $I^2=98%$ ,  $P\leq 0.01$ ) as presented in Figure 3. We performed a subgroup analysis based on the type of COVID-19 vaccines to investigate such significant heterogeneity. The pooled prevalence of AR for adenovirus vector vaccines was 56% (95% CI: 51-60,  $P\leq 0.5$ ) among 490 vaccinated individuals included in 2 studies ( $I^2=0%$ ). While non-adenovirus vectored vaccines exhibited higher immunogenicity, AR was 90% (95% CI: 86-93,  $P\leq 0.02$ ) among 1099 vaccinated individuals included in 4 studies ( $I^2=71%$ ). Figure 3 illustrates that the test for subgroup differences indicated that immunogenicity was significantly affected by the type of COVID-19 vaccines ( $P\leq 0.05$ ).

### Level of Anti-SARS-CoV-2 Antibodies After 7 Days

The pooled proportion of anti-SARS-CoV-2 antibody responses for COVID-19 vaccines after 7 days could not be calculated because only 1 paper studied the neutralizing antibodies response after 7 days. Among 72 vaccinated persons, 81% developed neutralizing antibodies in 7 days (95% CI: 70-89). See Supplemental Figure S1.

### Level of Anti-SARS-CoV-2 Antibodies After 14 Days

The pooled proportion of anti-SARS-CoV-2 antibody responses for COVID-19 vaccines after 14 days among

888 vaccinated persons included in 6 studies was 80% (95% CI: 58-92) with high heterogeneity ( $I^2=97%$ ),  $P<0.01$ . See Supplemental Figure S1. To identify the cause of this substantial heterogeneity, we conducted a subgroup analysis. The type of vaccine was employed for subgrouping, and the vaccines were sub-grouped into either adenovirus vectored vaccines or non-adenovirus vectored vaccines. The pooled prevalence of anti-SARS-CoV-2 antibody responses for adenovirus vectored COVID-19 vaccines after 14 days among 184 vaccinated persons included in 2 studies was 42% (95% CI: 26-60) ( $I^2=83%$ ),  $P=0.02$ . The pooled prevalence of anti-SARS-CoV-2 antibody responses for non-adenovirus vectored COVID-19 vaccines after 14 days among 704 vaccinated persons included in 4 studies was 91% (95% CI: 75-97) ( $I^2=95%$ )  $P<0.01$ .

### Level of Anti-SARS-CoV-2 Antibodies After 42 Days

The pooled proportion of anti-SARS-CoV-2 antibody responses for COVID-19 vaccines after 42 days among 478 vaccinated persons included in 5 studies was 93% (95% CI: 80-98) ( $I^2=84%$ ),  $P<0.01$ . See Supplemental Figure S1. We conducted subgroup analysis based on the type of vaccine, where vaccines were sub-grouped into either mRNA vaccines or non-mRNA vaccines, to identify the cause of such substantial heterogeneity. The pooled prevalence of anti-SARS-CoV-2 antibody responses for mRNA COVID-19 vaccines after 42 days among 158 vaccinated persons included in 3 studies was 94% (95% CI: 74-99) ( $I^2=78%$ ),  $P=0.01$ . The pooled prevalence of anti-SARS-CoV-2 antibody responses for non-mRNA COVID-19 vaccines after 42 days among 320 vaccinated persons included in 2 studies was 96% (95% CI: 25-100) ( $I^2=90%$ )  $P<0.01$ .

### Level of Anti-SARS-CoV-2 Antibodies After 56 Days

The pooled prevalence of anti-SARS-CoV-2 antibody responses for COVID-19 vaccines after 56 days among 432 vaccinated people included in 2 studies was 93% (95% CI: 83-97) ( $I^2=80%$ ),  $P=0.03$ . See Supplemental Figure S1.

### Meta Regression for Anti-SARS-CoV-2 Antibodies

We found substantial heterogeneity when we tried to combine all the reported anti-SARS-CoV-2 antibody studies ( $I^2=98%$ ). Thus, we conducted a meta regression model to explain the reason for this considerable heterogeneity. The main predictors of heterogeneity are the type of vaccine used and the time of anti-SARS-CoV-2 antibody measurement after the first dose of vaccine, and this model can explain

**Table 1.** Summary of the Characteristics of the Studies Included in Quantitative Analysis.

Study/country	Type of study/ study setting	Case definition	No. patients			Age (Mean + SD) (Median-IQR)	Sex (total m/%)	Duration (days)
			Intervention	Standard care				
Xia et al <sup>33</sup> China	RCT (double-blinded, placebo-controlled) Phase 1/2 (single-center)	Healthy adult aged 18-59 years old years*	(240) phase1, 72 (24 low dose, 24 medium, 24 high) phase2, 168 (84 gp 1, 84 gp2)	(80) phase1: 24 and phase2: 56	41.2 (9.6)years (phase 1 trial) 43.5 (9.1) years. (phase 2 trial)	38 m (39.6%) (phase 1) 82 m (36.6%) (phase 2)	21 days	
Zhu et al <sup>36</sup> China	RCT (double-blinded, placebo-controlled) Phase 2 (Single center)	Healthy adults aged 18 years or older, BMI (18.5-30) <sup>§,%,%,%,%</sup>	253 assigned to 1 × 10 <sup>11</sup> vp 129 assigned to 5 × 10 <sup>10</sup> vp	126 placebo	Mean age 39.7 years. (SD 12.5; range 18-83)	254 m (50%)	28 days	
Ward et al <sup>32</sup> Canada	RCT (partially-blinded) Phase 1 (Two sites)	Healthy adults 18-55 years of age*	180 subjects randomized into 9 groups (first dose) 178 subjects received both doses	CoVLP at three dose levels (3.75, 7.5, and 15 µg) unadjuvanted Comparator vaccine (MenACWY; n = 10).	18-55 years (34.3 ± 9.0) year	78 m (43.3%)	42 days	
Barrett et al <sup>37</sup> UK	RCT (participant-blinded) Phase 1/2 (Multicentre)	Healthy adults volunteers between the ages of 18 and 55 who had already received an initial standard dose of ChAdOx1 nCoV-19	Full-dose of the vaccine (SD/SD D56; n = 20) or half-dose (SD/LD D56; n = 32), 56 days from the prime vaccination Phase 1 n = 192 and phase2 n = 448	Phase 1 n = 8 in each dose gp Phase 2 n = 28 in each dose gp	18-55 years	N/A	84 days from priming dose (28 days from booster dose)	
Xia et al <sup>34</sup> China	RCT (double-blind, placebo-controlled, dose-escalating) Phase 1/2 (Single center)	Healthy people aged 18-80 years <sup>ar*s*:#,%,1,##,\$</sup>	Phase 1 n = 8 in each dose gp Phase 2 n = 28 in each dose gp	Phase 1 n = 8 in each dose gp Phase 2 n = 28 in each dose gp	phase 1 Age 18-59 and ≥60 years, phase2 Age 18-59 only	Phase 1 (m = 90/f = 102) Phase2 (m = 203/f = 245)	7 days for primary outcome and up to 42 days for immunogenicity	
Logunov et al <sup>44</sup> Russia	Non-randomized (Two open) Phase 1/2 (Two hospitals)	Adult volunteers of both sexes BMI 18.5-30 <sup>##</sup>	Total n = 76 and n = 38 in each study. Phase1 (rAd26-S) n = 9, (rAd5-S) n = 9 Phase2 (rAd26-S) n = 9, (rAd5-S) n = 20.	None	18-60 years	Gam-COVID-Vac (m = 32/f = 6) Gam-COVID-Vac-Lyo (m = 21/f = 17)	Phase 1 clinical and laboratory assessments on days 0, 2, and 14. Safety up to 28 days	

(Continued)

**Table 1.** (Continued)

Study/country	Type of study/ study setting	Case definition	No. patients		Age (Mean + SD) (Median-IQR)	Sex (total m/%)	Duration (days)
			Intervention	Standard care			
Ramasamy et al <sup>18</sup> [AstraZenca] UK	RCT (Single-blind, controlled) Phase 2 (multicentre)	Age-escalation manner: adults aged 18-55 years, then adults aged 56-69 years, and then adults aged 70 years and older <sup>%,**</sup>	[Low dose n = 300] Age 18-55 n = 100. Age 56-69 n = 80. Age >70 n = 120.	[Standard dose n = 260] Age 18-55 (n = 60) Age 56-69 (n = 80) Age >70 (n = 120)	18-55, 56-69, >70 years	Low dose Male n = 139 and female n = 156 (5 excluded). Standard dose Male n = 138 and female n = 119 (3 excluded did not receive booster)	Follow up safety and immunogenicity at min. 2 weeks after the booster dose
Tebas et al <sup>49</sup> Article in press USA	Open-label Phase 1 (multicentre)	Healthy adults aged between 18 and 50 years BMI 18-30 <sup>%,*,\$,**,*#</sup>	20 participants in each of 1.0 and 2.0 mg dose gps	None	Range 18-50 years Median age was 34.5 years	m (22, 55%)	8 weeks
Anderson et al <sup>47</sup> [Moderna] USA	Open-label trial, dose escalation Phase 1 (multicentre)	Participants: 18-55 years received 250-µg dose, 56 years of age or older received 25 or 100 µg doses. <sup>%,**</sup>	n = 40	None	56-70 and ≥71 years	m (19, 48%)	Follow up till 57 days for immunogenic effect
Sadoff et al <sup>31</sup> pre-print medRxiv[Johnson and Johnson] Belgium and USA	RCT (double-blinded, placebo-controlled clinical trial) Phase 1/2a (multicentre)	Healthy adults 18-55 years of age (cohort 1a and cohort 1b), 83 and >65 years of age (cohort 3) <sup>*</sup>	C1a n = 377, C1b n = 25, and C3 (all) n = 394	Placebo n = 77	Age 18-55 and ≥65 years	c1a (m179/f198), c1b (m111/f13), and c3 (m195/f199)	Follow up till 28 days for adverse effect and 29 days test for ELISA
Folegatti et al <sup>39</sup> preliminary UK	RCT (participant-blinded) Phase 1/2 (multicentre)	Healthy adult participants aged 18-55 years <sup>%,*,\$,**</sup>	ChAdOx1 n = 543	MenACWY n = 534	18-55 years	Male = 541 and Female = 536	Follow up till 42 days for immunogenic effect and day 56.
Walsh et al <sup>42</sup> USA	Placebo-controlled, observer-blinded, dose-escalation Phase 1 (N/A)	Healthy adults 18-55 years of age or 65-85 years of age. <sup>%,*,\$,**</sup>	156 (13 groups, 12/group)	39 (13 groups, 3/group)	BNT162b1 (18-55 gp: 36.9 ± 10.2, 65-85 gp: 29% m) 35 "19-45" (65-85 gp: 69.7 ± 4.3, 69 "65-82") BNT162b2 (18-55 gp: 36.7 ± 11.0, 37 "19-54" (65-85 gp: 69.3 ± 4.1, 68 "65-81")	BNT162b1 (18-55 gp: 57% m), (65-85 gp: 29% m) BNT162b2 (18-55 gp: 42% m) (65-85 gp: 38% m)	48 days

(Continued)

**Table 1.** (Continued)

Study/country	Type of study/ study setting	Case definition	No. patients		Age (Mean + SD) (Median-IQR)	Sex (total m/%)	Duration (days)
			Intervention	Standard care			
Zhu et al <sup>46</sup> China	Non-randomized, (dose-escalation, single-center, open-label) Phase I (hospital-based)	Healthy adults aged between 18 and 60 years <sup>*,*,\$,###,%%</sup>	108 (low, middle and high dose 36/group)	None	Low dose: 37.2 ± 10.7, middle dose: 36.3 ± 11.5, high dose: 35.5 ± 10.1	Low dose: 50% m middle dose: 53% m high dose: 50% m	11 days
Zhang et al <sup>35</sup> China	Randomized, (double-blind, placebo-controlled) Phase 1/2 (single-center)	Healthy participants aged 18-59 years <sup>#,*,*,\$,###,%%</sup>	96 (24 per group) (phase 1, 14-day interval), (phase 2, 28-day interval) (low->3 µg dose, high->6 µg dose) 600 (Phase 2)	48 (12/group)	Phase 1, 42.6 ± 9.4 phase 2, 42.1 ± 9.7	Phase 1, male 44% female 56% phase 2, male 49% female 51%	84 days (12 weeks)
Ewer et al <sup>38</sup> UK	RCT (single-blind) Phase 1/2 (5 centers in UK)	Healthy adults aged 18-55 years (n = 88)	44	44	N/A	N/A	56 days (8 weeks)
Keech et al <sup>40</sup> Australia	Randomized, (placebo-controlled) Phase 1/2/(2 sites)	Healthy participants 18-59 years of age, BMI 17-35 <sup>†,*,*,\$,###,%%</sup>	108 (4 groups) (n = 25) 25 µg rSARS-CoV-2, (n = 29) 5 µg rSARS-CoV-2 plus Matrix-MI (n = 28) 25 µg rSARS-CoV-2 plus Matrix-MI (n = 26) 25-µg single dose rSARS-CoV-2 plus Matrix-MI followed by a single dose of placebo	23	30.8 ± 10.20	Male 50.4%, Female 49.6%	2 months (60 days)
Sahin et al <sup>45</sup> Germany	Non-randomized CT Phase 1/2 (hospital-based)	Healthy participants 18-55 years (amended to add 56-85 of age) <sup>†,*,*,\$,###,%%</sup>	48 (5 groups, 1, 10, 20, and 30 µg, 12/group)	None	37.5 ± 10.91	50% both	43 days
Jackson et al <sup>48</sup> USA	Dose-escalation, open-label trial (clinical trial) Phase 1 (hospital-based)	Healthy adults 18-55 years of age Participants not screened for COVID before enrollment.	45 (3 groups, 25, 100, 250 µg, 15/group)	None	33.0 ± 8.5	49% males, 51% females	57 days
Mulligan et al <sup>41</sup> USA	Placebo-controlled, observer-blinded dose-escalation study Phase 1/2 (Clinical Trial)	Healthy participants aged 18-55 years <sup>†,\$,*,*,\$,###,%%</sup>	36 (3 groups, 10, 30, 100 µg, 12/group)	9 (3/group)	35.4 (range 19-54 years)	51.1% males, 48.9% females	45 days

(Continued)



**Table 1.** (Continued)

Study/country	Type of study/ study setting	Case definition	No. patients			Age (Mean + SD) (Median-IQR)	Sex (total m/f)	Duration (days)
			Intervention	Standard care				
Ella et al <sup>29</sup> India	RCT (double-blind, controlled) Phase I (11 hospitals)	Adult healthy aged 18-55 years <sup>%,*,%##</sup>	3 µg with Algel-IMDG n = 100, 6 µg with Algel-IMDG n = 100, 6 µg with Algel n = 100 (3 lost to follow up)	Algel only n = 75 (1 lost to follow up)	18-55 years	m = 297/f = 78	Immunogenic effect (28 days) Adverse events (0-7 days) for dose 1 and (14-21 days) for dose 2	
Zhu et al <sup>43</sup> China	RCT (observer-blind, placebo-controlled) Phase I (Clinical research center)	Healthy Chinese participants: younger (18-55 years of age) and older (65-85) adults. <sup>1,*,**</sup>	96 Younger participants aged 18-55 years: 10 µg (24), 30 µg (24) Older participants aged 65-85 years: 10 µg (24), 30 µg (24)	48 Younger participants aged 18-55 years: Placebo (24) Older participants aged 65-85 years: Placebo (24)	Adults mean 45.8 years (18 and 59 years) older adults (65 and 85 years)	72 m (50%)	43 days follow up the vaccine recipients for at least 6 months,	
Pu et al <sup>30</sup> China	RCT (double-blinded, placebo-controlled) Phase I (University Hospital)	Healthy volunteers 18-59 years of age. <sup>%,**</sup>	144 (72 at 0, 14 days schedule) and (72 at 0 and 28 days schedule)	*Schedule: Day 0, 14 Placebo group (n = 24) * Schedule: Day 0, 28 Placebo group (n = 24)	Schedule: Day 0, 14: 36.7 ± 10.69 Schedule: Day 0, 28: 37.0 ± 9.86	Schedule: Day 0, 14 (N = 96) 43 m (45%) Schedule: Day 0, 28 (N = 96) 43 m (45%)	90 days (2 vaccine schedules (0 and 14 days) and (0 and 28 days) with 28 days follow up post second vaccination)	

Abbreviations: BMI, body mass index; GMTs, geometric mean titers of RBD-specific ELISA antibody; IM, intramuscular; m, male; MNT50, micro neutralisation assay; N/A, not available; PBMCs, peripheral blood mononuclear cells; PRINT50, plaque reduction neutralisation test; Yp, viral particles/ml.

\*Patients without a history of SARS-CoV or SARS-CoV-2 infection or proven seronegative.

#Patients with locations or circumstances at the risk of SARS-CoV-2 infection, a high risk of severe Covid-19, or both.

\$HIV, HCV, HBV negative or stable condition.

%No flu symptoms or fever.

%%General good health by medical history and hospital examination and provided written informed consent.

\*\*\*Treatment with immunosuppressive therapy, or diagnosis with an immunocompromising condition.

!Pregnancy or lactation.

##Allergy to any ingredient in the vaccine.

\$\$History of seizures or mental illness; or being unable to comply with the study schedule.

**Table 2.** Summary of Types of Vaccines Used in the Intervention and Control Arm.

Study/country	Vaccine		Anti-SARS-CoV-2 antibodies
	Intervention	Control	
Xia et al <sup>33</sup> China	Inactivated whole-virus vaccine: Phase 1, 3 IM injections at days 0, 8, and 56.	Aluminum hydroxide (alum) adjuvant-only group	Neutralizing antibodies
Zhu et al <sup>36</sup> China	Phase 2, gp 0, 14 and gp 0, 21 Ad5-vectored COVID-19 vaccine a single injection of the vaccines of $1 \times 10^{11}$ and $5 \times 10^1$ vp, IM in arm	Placebo	Anti-spike protein and neutralizing antibody amounts against live SARS-CoV-2 and a pseudovirus were measured as humoral immunogenicity endpoints.
Ward et al <sup>32</sup> Canada	2 doses, 21 days apart (at day 21 and 42) of CoVLP doses of 3.75, 7.5, or 15 µg virus-like particle unadjuvanted or adjuvanted with AS03 or CpG1018 (randomized to 9 groups) (n = 20)	CoVLP at three dose levels (3.75, 7.5, and 15 µg) unadjuvanted	Neutralizing antibody responses assessed using a vesicular stomatitis virus (VSV) pseudovirion assay and interferon-gamma and interleukin-4, anti-spike antibody responses by ELISA and neutralizing antibodies measured by live virus plaque reduction neutralization test (PRNT) assay
Barrett et al <sup>37</sup> UK	ChAdOx1 nCoV-19 (Oxford Covid vaccine) (adenovirus vectored vaccine)	Comparator vaccine (MenACWY).	Anti-spike neutralizing antibody titers, as well as Fc-mediated functional antibody responses, including antibody-dependent neutrophil/monocyte phagocytosis, complement activation and natural killer cell activation
Xia et al <sup>34</sup> China	Phase I—BBIBP-CorV inactivated vaccine (2, 4, and 8 mg)	Saline with aluminum hydroxide adjuvants	Immunogenicity, assessed as the neutralizing antibody responses against SARS-Cov-2
Logunov et al <sup>44</sup> Russia	Intramuscular injection of two vector components, recombinant adenovirus type 26 (rAd26) and recombinant adenovirus type 5 (rAd5), Gam-COVID-Vac n = 38 and Gam-COVID-Vac-Lyo n = 38	N/A	Antigen-specific humoral immunity (SARS-CoV-2-specific antibodies)
Ramasamy et al <sup>18</sup> [AstraZenca] UK	ChAdOx1 nCoV-19 (adenovirus vectored vaccine)	MenACWY	IgG against RBD and trimeric spike protein, anti-ChAdOx1 neutralizing antibody
Tebas et al <sup>49</sup> Article in press USA	Intradermal DNA (INO-4800) Total n = 40, 1 mg group n = 20 and 2 mg group n = 19	*	Neutralization and/or binding antibodies to S protein (serum IgG binding titers to S1 + S2 spike protein)
Anderson et al <sup>47</sup> [Moderna] USA	IM mRNA-1273	*	SARSCoV-2 full-length spike glycoprotein trimer, S-2P, which has been modified to include 2 proline substitutions at the top of the central helix in the S2 subunit. The receptor-binding domain is the portion of the SARS-CoV-2 virus that is located on its spike domain and that links with body receptors to infect cells
Sadoff et al <sup>31</sup> pre-print medRxiv [Johnson and Johnson] Belgium and USA	IM Ad26.COV2.S (adenovirus vectored vaccine)	0.9% saline	S protein of SARS-CoV-2 specific antibody levels
Folegatti et al <sup>39</sup> preliminary UK	ChAdOx1 nCoV-19 (n = 543) (adenovirus vectored vaccine)	MenACWY (n = 534)	Neutralizing antibodies (seroconversion against non-spike proteins)

(Continued)

**Table 2.** (Continued)

Study/country	Vaccine		Anti-SARS-CoV-2 antibodies
	Intervention	Control	
Walsh et al <sup>42</sup> USA	BNT162b1: (10,20, 30 µg → 2 doses, 100 µg → 1 dose) BNT162b2 (10,20, 30 µg → 2 doses) mRNA	N/A	SARS-CoV-2 serum neutralizing geometric mean titers, S1-binding IgG, receptor-binding domain or BNT162b2 which encodes a membrane-anchored SARS-CoV-2 full length spike
Zhu et al <sup>46</sup> China	Ad5 vectored COVID-19 vaccine single dose (mild, middle, high doses)	N/A	RBD, the spike glycoprotein and neutralizing antibodies against live and pseudovirus
Zhang et al <sup>35</sup> China	inactivated SARS-CoV-2 vaccine 3, 6 µg	N/A	Receptor-binding domain (RBD)-specific IgG, S-specific IgG, and IgM
Ewer et al <sup>38</sup> UK	ChAdOx1 nCoV-19 (AZD1222) vaccine (5 × 10 <sup>29</sup> viral particles) (adenovirus vectored vaccine)	control vaccine (MenACWY)	Neutralizing antibodies and antigen-specific T cells against the SARS-CoV-2 spike protein.
Keech et al <sup>40</sup> Australia	NVX-CoV2373 recombinant nanoparticle technology	N/A	Anti-spike IgG, and wild-type SARS-CoV-2 microneutralization assay
Sahin et al <sup>45</sup> Germany	BNT162b1 (1, 10, 30, 50, 60 µg) mRNA	N/A	Neutralizing antibodies, S1- and RBD-binding IgG
Jackson et al <sup>48</sup> USA	mRNA-1273 vaccine (25, 100, 250 µg) 2 doses 28 days apart	N/A	Neutralizing antibodies and Binding antibody responses against S-2P and the isolated receptor-binding domain, located in the S1 subunit
Mulligan et al <sup>41</sup> USA	BNT162b1 (10, 30, 100 µg) mRNA	N/A	RBD-binding IgG concentrations and SARS-CoV-2-neutralizing titers
Ella et al <sup>29</sup> India	BBV152	Algel	SARS-CoV-2 wild-type neutralizing antibody
Zhu et al <sup>43</sup> China	mRNA drug substance encoding the trimerized SARS-CoV-2 spike glycoprotein RBD antigen, formulated with lipids to obtain the RNA-LNP drug product.	A commercial saline solution	Neutralizing antibodies, ELISA antibody responses to the receptor binding domain (RBD)
Pu et al <sup>30</sup> China	Inactivated SARS-COV 2 vaccine, Vero cell	Placebo	neutralizing antibodies, anti-spike, and (CTL) cytotoxic T lymphocytes response

\*The study was comparing 2 doses with no placebo group.

nearly 83% of this heterogeneity. Most significant predictors are inactivated COVID-19 vaccine ( $\beta=2.0272$   $P=0.0007$ ) and the measurement of antibodies at either week 1 ( $\beta=-4.327$ ,  $P\leq 0.0001$ ) or week 3 ( $\beta=-2.02$ ,  $P=0.0025$ ). See Table S2 in supplemental material.

## Secondary Outcomes

### Fever 7 Days After Vaccination

The pooled proportion of fever among inactivated COVID-19 vaccine receivers after 7 days among 2533 vaccinated persons included in 14 studies was 10% (95%

CI: 8-14) ( $I^2=95\%$ ),  $P<0.01$  after the outlier removal. See Figure 4.

### Headache After 7 Days

The pooled proportion of headache among COVID-19 vaccine receivers after 7 days among 2616 vaccinated persons included in 10 studies was 23% (95% CI: 19-27) ( $I^2=97\%$ ),  $P<0.01$ . See Figure 5. Subgroup analysis was performed to resolve the heterogeneity by the types of vaccines employed. The highest proportion was observed among individuals who received the adenovirus vectored and virus like particles vaccines (34%).

**Table 3.** Summary of the Primary Outcome and Main Findings.

Study/country	Primary outcomes	Findings
Xia et al <sup>33</sup> China	Humoral immunogenicity Safety outcome: 7 and 28 days after each injection.	Patients had a low rate of adverse reactions and demonstrated immunogenicity
Zhu et al <sup>36</sup> China	Immunogenicity endpoints GMTa, RBD-ELISA Ab, and neutralizing Ab responses at day 14, 28 post-vaccination, and specific T-cell responses at day 28 post-vaccination. Safety outcomes from days 0 to 28 after vaccination, serious adverse events up to 6 months	The Ad5-vectored vaccine at $5 \times 10^1$ viral particles is safe and induced significant immune responses after a single immunization.
Ward et al <sup>32</sup> Canada	Immunological outcomes (NAb) responses measured using VSV pseudovirion assay and IFN $\gamma$ and IL-4 cellular responses at D0, 21, and 42. Total anti-spike IgG responses by ELISA and NAb responses at Days 0, 21, and 42 and planned for 6-month post-vaccination.	CoVLP $\pm$ adjuvants was well-tolerated. Several adjuvanted formulations elicited strong humoral and T cell responses after dose 2. Even at the lowest CoVLP + AS03 dose, NtAb titers were $\sim 10$ -times higher than in convalescent serum with a balanced IFN $\gamma$ and IL-4 response.
Barrett et al <sup>37</sup> UK	Safety outcomes: Adverse Events for 7 days following vaccination Immunogenicity outcomes: (IFN- $\gamma$ ), (ELISpot) responses to SARS-CoV-2 spike protein; (seroconversion rates Abs against SARS-CoV-2 spike protein); (NAb) assays	ChAdOx1 nCoV-19 is well tolerated in a 2-dose regimen and induces multifunctional Ab responses that are enhanced by a booster dose, in addition to T cell responses.
Xia et al <sup>34</sup> China	Safety, tolerability, and immunogenicity	Inactivated BBIBP-CorV in the age group $\geq 18$ was safe and tolerable. The humoral response was active up to 42 days after receiving the second dose. Two escalating doses were better than a single dose in achieving a higher neutralizing antibody titer.
Logunov et al <sup>44</sup> Russia	Safety (local and systemic) and Immunogenicity at days (0, 14, and 28)	The good safety profile for heterologous rAd26 and rAd5 vector-based COVID-19 vaccine has induced strong cellular and humoral immune response in 100% of the volunteers.
Ramasamy et al <sup>18</sup> [AstraZenca] UK	Efficacy (symptomatic cases, confirmed virology testing). Safety (adverse events) Reactogenicity, and immunogenicity, efficacy against severe and non-severe COVID-19, death, and seroconversion	Safe and well-tolerated with a lower reactogenicity profile in older adults than in younger adults. Similar immunogenicity across age groups after booster vaccination.
Tebas et al <sup>49</sup> Article in press USA	Systemic and local administration site reactions up to 8 weeks post-dose 1. Immunology: Ag-specific binding Ab titers, neutralization titers, and antigen-specific (IFN-g) cellular immune responses after 2 doses of vaccine.	Phase I trial (safety, tolerability, and immunogenicity of INO-4800): well-tolerated Grade I AEs. Humoral and cellular immune responses: either or both neutralizing Abs or T cell responses were displayed following two doses of INO-4800 in 95% of participants in both doses and the corresponding GMTs were 102.3 and 63.5 for the 1.0 and 2.0 mg dose groups, respectively.
Anderson et al <sup>47</sup> [Moderna] USA	Safety and adverse effects. The geometric mean of antibody titers. Serum neutralizing activities were tested against the control from convalescent serum. CD4 cytokines involving type I helper T-cells.	Mild to moderate adverse effect. Higher doses yielded higher values of binding and neutralizing antibodies. Conduction of Phase3 is expected to conclude better outcomes.
Sadoff et al <sup>21</sup> pre-print medRxiv [Johnson and Johnson] Belgium and USA	safety, reactogenicity, and immunogenicity	Vaccine candidate Ad26.COV2.S has an acceptable safety and reactogenicity profile and is immunogenic at both titers. The vaccine candidate is less reactogenic in older adults, increases with the higher dose. S-binding Ab titers increased from baseline to Day 29 post-vaccination in 99% of the participants in cohort 1a and 100% of the first participants in cohort 3.

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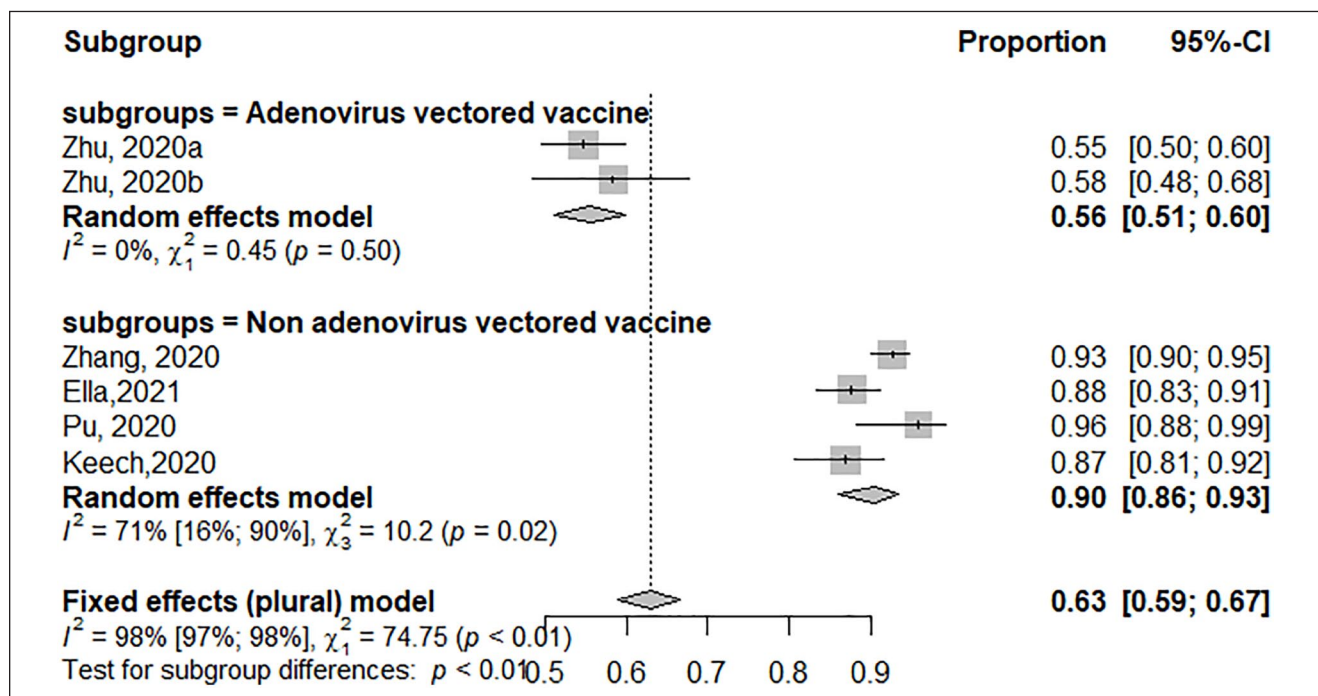
**Table 3.** (Continued)

Study/country	Primary outcomes	Findings
Folegatti et al <sup>39</sup> preliminary UK	Safety (adverse events) Efficacy asymptomatic virology confirmed cases. Reactogenicity, immunogenicity profile, and efficacy against hospital-attended COVID-19, death, and seroconversion	A single dose of ChAdOx1 nCoV-19 v was safe and tolerated, despite a higher reactogenicity profile than the control vaccine, MenACWY. Adverse events reported were mild or moderate in severity, all self-limiting, and no serious adverse reactions. A dose-response relationship with neutralizing Abs was observed.
Walsh et al <sup>42</sup> USA	RS-CoV-2 serum neutralizing titers, S1-binding IgG and RBD-binding IgG concentrations at baseline then at 7 and 21 days after the first dose, and at 7 days (ie, day 28) and 14 days (ie, day 35) after the second dose, GMTs, GMCs safety: local events within 7 days, unsolicited, and serious adverse events	Vaccination with 10 or 30 µg of BNT162b1 in adults 18-55 years of age suggested that it could be a promising Covid-19 vaccine candidate.
Zhu et al <sup>46</sup> China	Adverse reactions: 7 and 28 days after the vaccination, Specific ELISA Ab titers to RBD and the spike glycoprotein, and seroconversion post-vaccination.	The Ad5 vectored COVID-19 vaccine is tolerable and immunogenic at 28 days post-vaccination. Humoral responses against SARS-CoV-2 peaked at day 28 post-vaccination in healthy adults, and rapid specific T-cell responses were noted from day 14 post-vaccination.
Zhang et al <sup>35</sup> China	Adverse reactions 28 days after each dose, lab. measurements at day 3 and in s. inflammatory factors 7 days after each dose. Seroconversion of neutralizing Abs to live SARS-CoV-2 at day 14 after the last dose in the days 0 and 14 vaccination cohort, or day 28 after the last dose in the days 0 and 28 vaccination cohort. (GMTs) of neutralizing Abs to live SARS-CoV-2, RBD-specific IgG, S-specific IgG, and IgM. T-cell responses, post hoc, GMTs of neutralizing Abs to pseudovirus.	Two doses of CoronaVac at different concentrations and using different dosing schedules were well tolerated and moderately immunogenic in healthy adults aged 18-59 years.
Ewer et al <sup>38</sup> UK	Activation of lymphocyte populations, Immunoglobulin isotype responses, IgG subclass responses, T cell responses	An effective vaccine against COVID-19 will likely require both neutralizing antibodies and a Th1-driven cellular component.
Keech et al <sup>40</sup> Australia	Safety outcomes, immunogenicity responses	Safety outcomes: local and systemic reactogenicity (days 0-7 and days 21-28), laboratory values (s. chemistry and hematology) (days 7 and 28). Adverse events for 35 days Swab testing for SARS-CoV-2 on day 35 or any time they reported symptoms. Immunogenicity outcome (anti-spike IgG ELISA to rSARSCoV-2 protein Ags (days 0, 7, 21, 28, and 35)
Sahin et al <sup>45</sup> Germany	Immunogenicity (safety and tolerability profiles)	Concurrent production of neutralizing antibodies was observed, in addition to activation of virus-specific CD4+ and CD8+ T cells, and robust release of immunomodulatory cytokines such as IFN $\gamma$ , which represents a coordinated immune response to counter a viral intrusion.
Jackson et al <sup>48</sup> USA	Safety and immunogenicity (SARS-COV-2 binding Ab responses, neutralizing responses, T-cell responses)	The mRNA-1273 vaccine-induced anti-SARS-CoV-2 immune responses in all participants, and no trial-limiting safety concerns were identified.
Mulligan et al <sup>41</sup> USA	The adverse effect after 7 days of each dose, immunogenicity (SARS CoV IgG GMC, GMTs)	RBD-binding IgG concentrations and SARS-CoV-2 neutralizing titers in sera increased with the dose level and after a second dose. Geometric mean neutralizing titers reached 1.9-4.6-fold that of a panel of COVID-19 convalescent human sera, which were obtained at least 14 days after a positive SARS-CoV-2 PCR.

(Continued)

**Table 3.** (Continued)

Study/country	Primary outcomes	Findings
Ella et al <sup>29</sup> India	Reactogenicity events at 2 h and 7 days after vaccination and throughout the full study duration, including serious adverse events. Immunogenicity (GMTs) and seroconversion rate of neutralizing Abs, from baseline to days 14, 28, 42, 104, and 194.	Interim findings from the phase I clinical trial of BBV152, a whole-virion inactivated SARS-CoV-2 vaccine. The vaccine was well tolerated in all dose groups with no vaccine-related serious adverse events. Both humoral and cell-mediated responses were observed in the recipients of the Adgel-IMDG-based vaccines.
Zhu et al <sup>43</sup> China	Safety evaluation within 14 days post-vaccination, and until 28 days. Immunogenicity (GMT), seroconversion rates, and fold increase of virus-neutralizing antibody, or ELISA IgG antibodies measured at days 8, 22 after each vaccination.	The tolerability and favorable immunogenicity profile of the RNA-based SARS-CoV-2 vaccine candidate BNT162b1 was confirmed and expands reporting of BNT162b1 and other RNA-based vaccine candidates from clinical trials
Pu et al <sup>30</sup> China	Adverse reactions: 0-28 days postimmunization. Serological evidence of immunogenicity of the vaccine.	No severe adverse reactions (redness, itching, and swelling at the inoculation site) and few cases of slight fatigue. The immune functions were upregulated in comparison with the placebo group.

**Figure 3.** Pooled proportion of neutralizing antibodies response for COVID-19 vaccines after 28 days.

### Fatigue 7 Days After Vaccination

The pooled proportion of fatigue among COVID-19 vaccine receivers after 7 days among 32 678 vaccinated persons included in 10 studies was 10% (95% CI: 7-13) ( $I^2=99\%$ ),  $P<0.01$ . See Figure 6. Subgroup analysis was performed to resolve the heterogeneity by the type of vaccine utilized, and 56% was the proportion among the

mRNA vaccinated participants, which was the highest proportion. See Figure 6.

### Muscle Pain 7 Days After Vaccination

The pooled proportion of muscle pain among Adenovirus vectored COVID-19 vaccine recipients after 7 days among 3237 vaccinated persons included in 9 studies was 18%

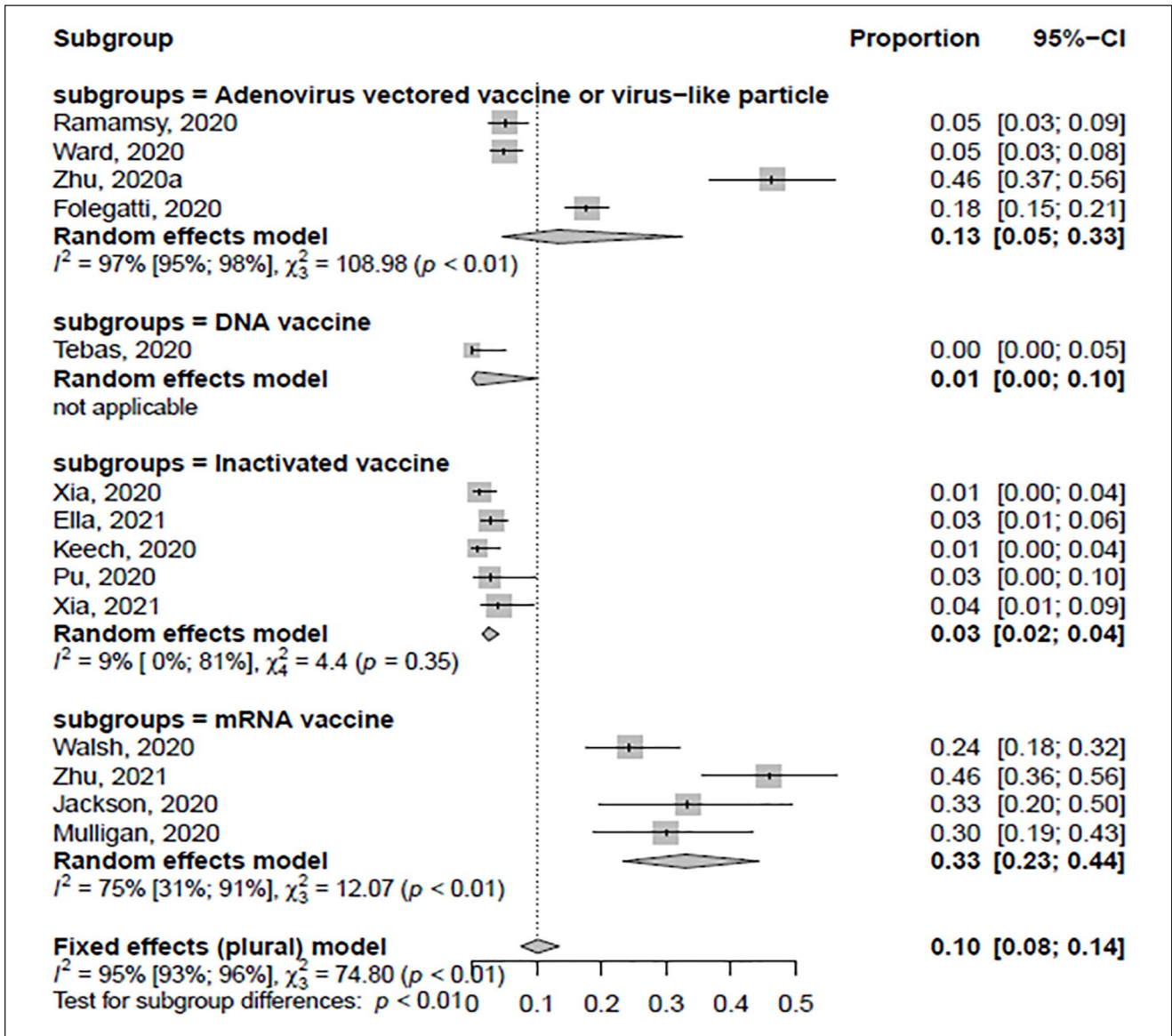


Figure 4. Fever 7 days after vaccination.

(95% CI: 14-23) with heterogeneity ( $I^2=96\%$ ),  $P=0.57$ . See Figure 7.

While in mRNA vaccine, the pooled prevalence of muscle pain among COVID-19 vaccine recipients after 7 days included in 2 studies was 17% (95% CI: 12-23) ( $I^2=0\%$ ),  $P=0.92$ . See Figure 7.

### Discussion

This study provides empirical evidence for the safety and immunogenicity of COVID-19 vaccines, and this is crucial as demonstrating the safety and benefits of COVID-19 vaccines is critical to enhance public trust in COVID-19 vaccination, particularly in countries with high rates of vaccine

hesitancy.<sup>24,50</sup> Moreover, results from this analysis will provide information about the number of days required for the development of anti-SARS-CoV-2 antibodies developed from the sequential immunization strategy. Information on the duration of the development of the commonly reported vaccine adverse effects across various vaccine technology platforms.

Some of the criteria considered to develop new vaccines are animal immunogenicity, toxicity data, immunogenicity response in adults, possible impact on public health, chances of acceptance by the community, cost-effectiveness, and the preexistence of a vaccine with a satisfactory risk-benefit profile. The immune response primarily measured during the early stages of vaccine development (phase 1/2) should

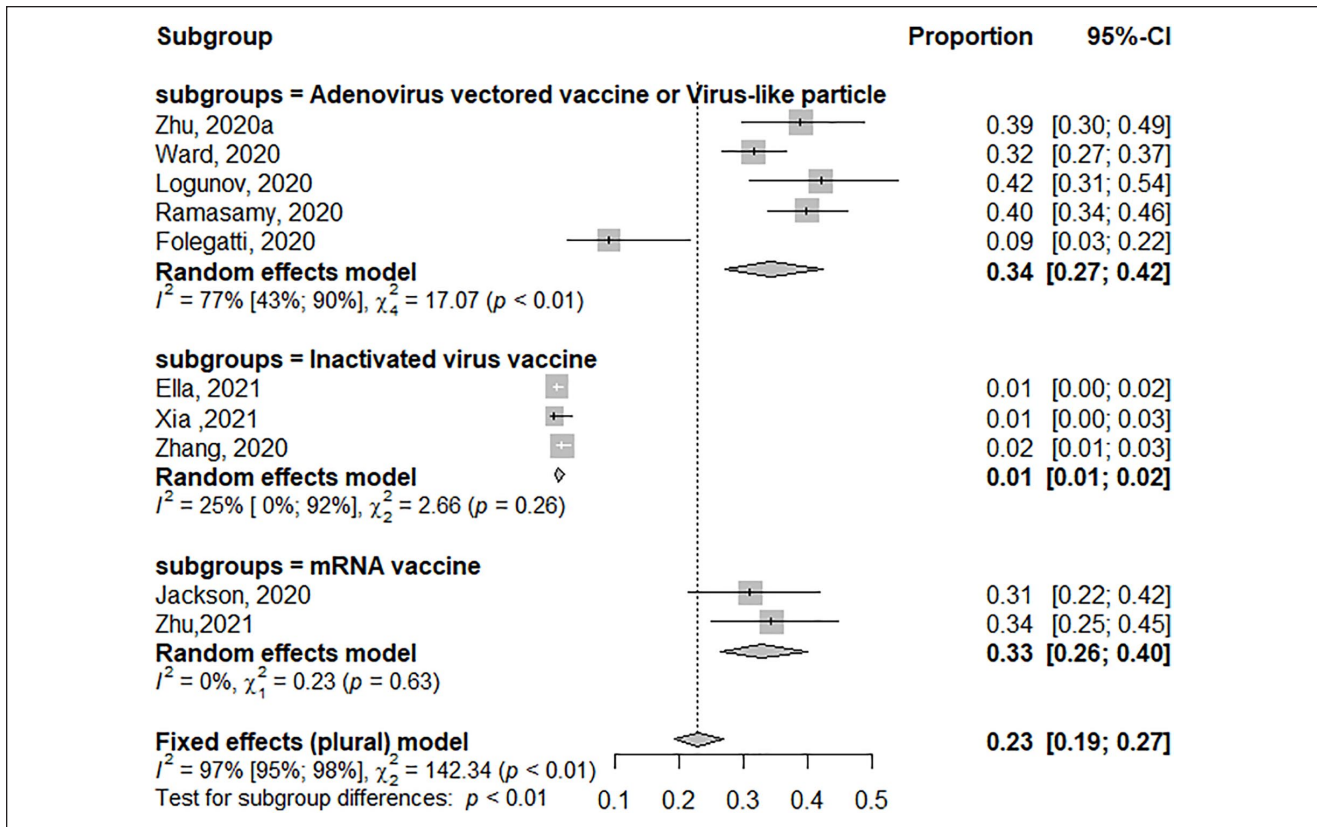


Figure 5. Headache after 7 days.

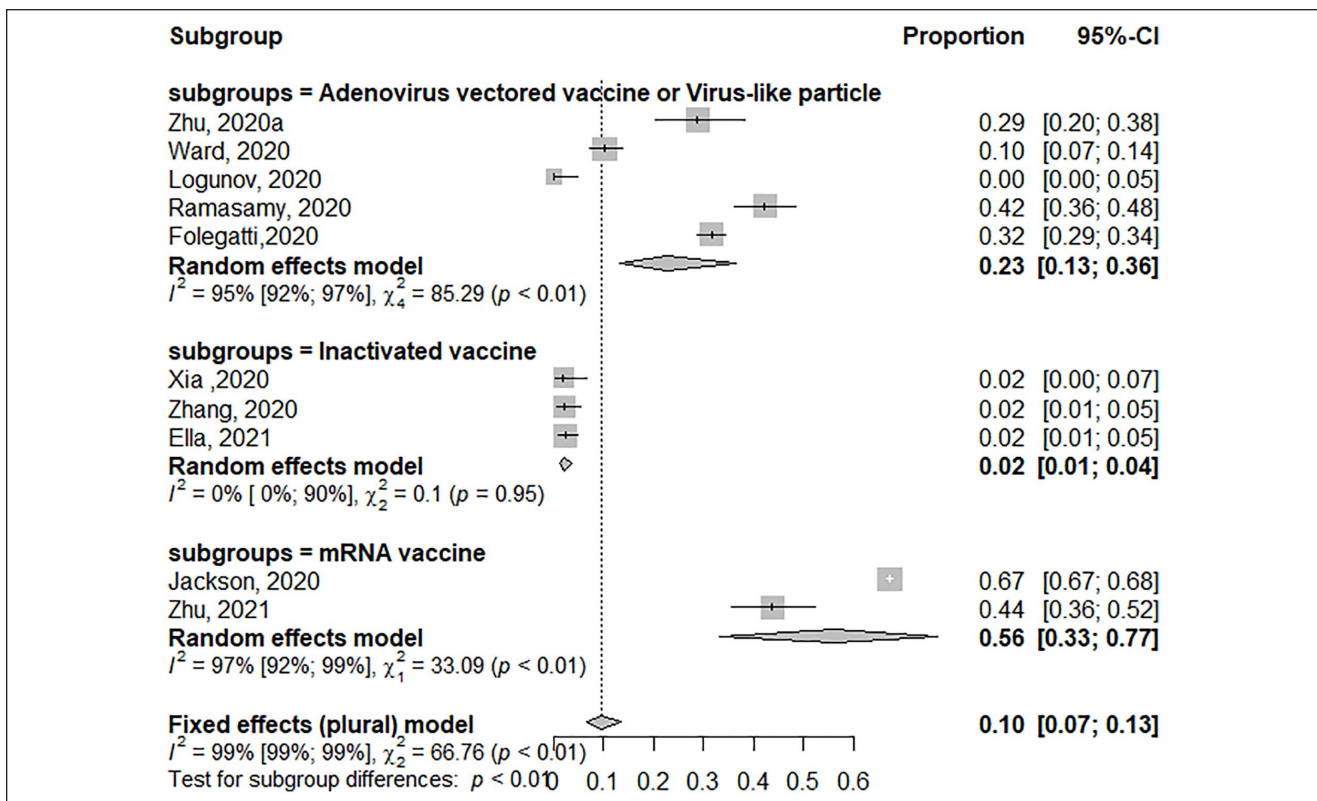


Figure 6. Fatigue 7 days after vaccination.



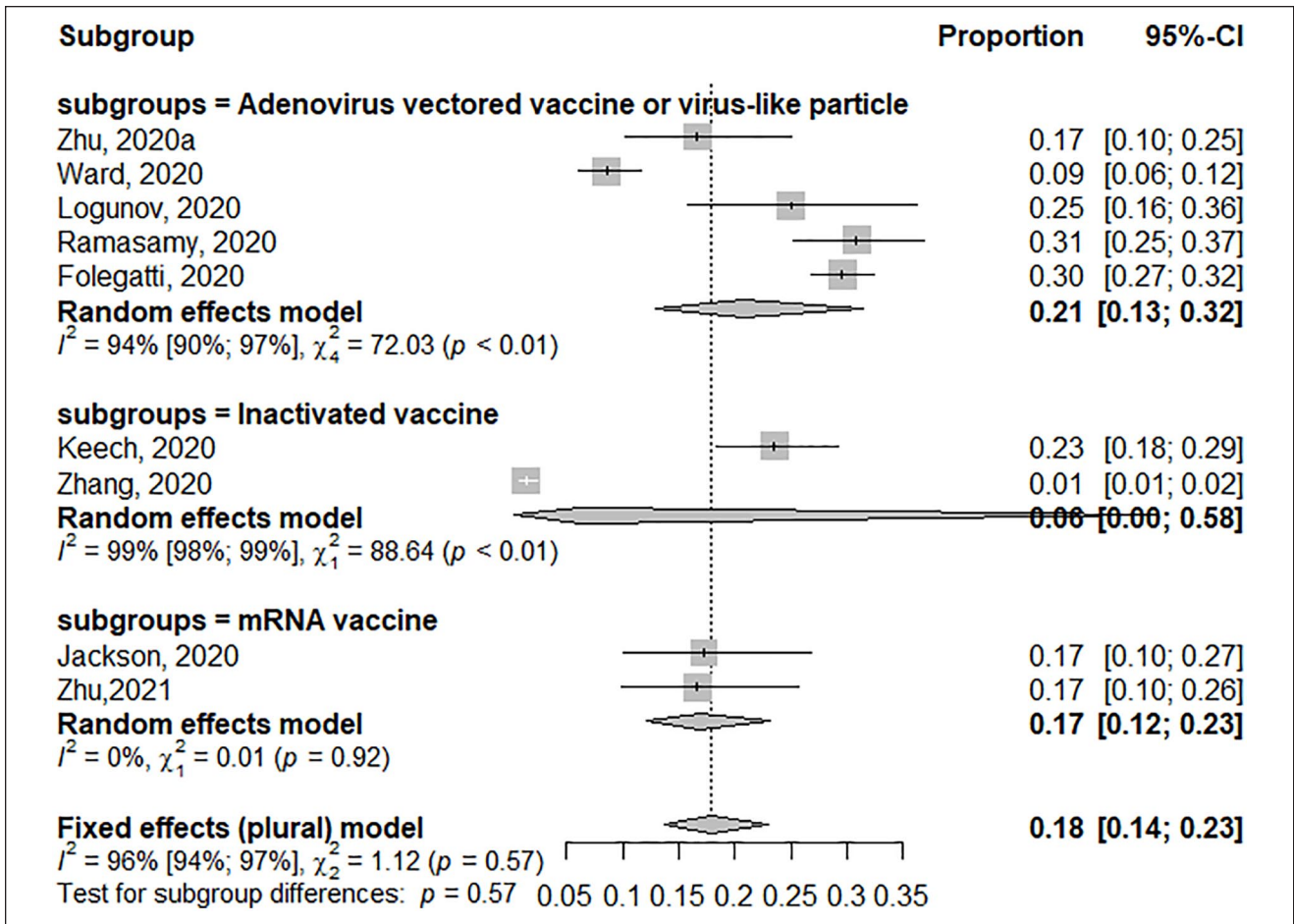


Figure 7. Muscle pain 7 days after vaccination.

evaluate the following: amount, class, subclass, and function of each specific antibody.<sup>22</sup> Phase 1 aims to evaluate vaccine safety, reactogenicity, and the collection of immune responses. Generally, the dose, immunization schedule, and mode of vaccine administration are also assessed, while the objective of phase 2 is to identify the vaccine preparation, optimal dose, and schedule.<sup>51</sup>

This MA includes 22 studies; 7 were conducted in China,<sup>30,33-36,43,46</sup> 5 in the USA,<sup>41,42,47-49</sup> 4 in the UK,<sup>18,37-39</sup> 1 in India,<sup>29</sup> 1 in Germany,<sup>45</sup> 1 in Australia,<sup>40</sup> 1 in Canada,<sup>32</sup> 1 in Russia,<sup>44</sup> and 1 in Belgium and the USA.<sup>31</sup> The sample size varies from 39 participants<sup>49</sup> who received the vaccination to 1077.<sup>39</sup> The types of vaccines administered were different, and different doses were used. The duration of the study varies from 11 days<sup>46</sup> in China to 194 days<sup>29</sup> in India. Age limitations of the studied population in each study were variable. No participant below 16 years old was included in any study, and randomization was performed in 19 studies.

The  $I^2$  statistics values have shown a substantial heterogeneity in Figure 3, which can be attributed to variability in gender and age. Various studies have validated that age and

sex are the determinants of different immune responses, especially to viral vaccines, which may vary between males and females in some of the immunogenic parameters, such as humoral responses and cell-mediated immunity. None of the MA studies have included participants below 16 years of age. For the immune responses of older individuals, it has been interpreted as with previous multiple exposures to diseases, and the elderly were more likely to show a high diversity of immune responses to viruses more than what is observed among the younger population.<sup>52-54</sup>

Regarding vaccine development platforms and formulation, our review included 8 studies on replication-defective adenovirus vector vaccines, 6 studies on mRNA vaccines, 1 study on synthetic peptide/virus-like particle vaccines, 1 on DNA-based vaccines, and 6 studies on inactivated vaccines as shown in Table 2. Most of the included studies reported immunogenic responses on the 28th day post-vaccination. A similar number of studies reported immunogenic responses at day 42 post-vaccination.<sup>30,32,34,35,37-43,45,47-49</sup> The shortest reported duration of immunogenic responses was at day seven post-vaccination, which was observed in 1 study.<sup>30</sup>

The proportion of anti-SARS-CoV-2 antibody responses for COVID-19 vaccines after 7 days among 72 vaccinated persons was 81%, and the proportion of anti-SARS-CoV-2 antibody responses for COVID-19 vaccines after 14 days among 888 vaccinated persons was 80%. Furthermore, the proportion of anti-SARS-CoV-2 antibody responses for COVID-19 vaccines after 28 days among 1589 vaccinated persons included in 6 studies was 63%. After 42 days, the proportion of anti-SARS-CoV-2 antibody responses for COVID-19 vaccines among 478 vaccinated persons included in 5 studies was 93%, and the proportion of anti-SARS-CoV-2 antibody responses for COVID-19 vaccines after 56 days among 432 vaccinated persons included in 3 studies was 93%. The observed escalation in the proportion of anti-SARS-CoV-2 antibodies supports the role of a sequential immunization strategy in producing high levels of anti-SARS-CoV-2 antibodies, especially among mRNA vaccine recipient groups. Nonetheless, He et al<sup>55</sup> verified that the immune response was not strong with the inactivated vaccine nor with adenovirus vaccine recipients. Even though the WHO International Standard for anti-SARS-CoV-2 immunoglobulin with a unit of 250 IU/ampoule, is available (anti-SARS-CoV-2 antibody activity). Anti-SARS-CoV-2 immunoglobulin units have yet to be assigned by the first WHO International Reference Panel. As a result, there is a knowledge gap in determining the immune response cut-off points in various phases 1 and 2 randomized controlled trial (RCT), and vaccine trials.

Within the included studies, we assessed the following adverse effects: fever, headache, fatigue, and muscle pain. The findings presented the proportion of fever 7 days after the vaccine administration at 10%, and this was reported in 3% and 13% in inactivated and adenovirus vectored or virus-like particle vaccine recipients, respectively. This relatively low adverse event is supported by the findings reported by Logunov et al<sup>56</sup> phase 3 RCT about the safety of adenovirus (rAd)-based COVID-19 vaccine, which includes flu-like illness, reaction at the site of injection, headache, and fatigue.

After 7 days, fatigue incidence was 10% and is mostly reported among mRNA vaccine recipients. Findings are consistent with the review conducted by Kaur et al<sup>57</sup> in March 2021, who reported about the mRNA vaccine adverse reactions that included mild to moderate intensity effects, such as headache, chills, fatigue, myalgia, and pain at the site of injection. Local adverse reactions were mostly pain at the site of injection.

The proportion of headache 7 days after the vaccine administration was at 23% and mostly caused by adenovirus vectored vaccine. Headache was found to be a common presentation after all forms of COVID-19 vaccine administration.<sup>56,57</sup>

Our findings affirmed that 7 days post-vaccination, muscle pain prevalence was slightly higher among adenovirus

vectored vaccine recipients than mRNA vaccinated individuals at 21% and 17%, respectively. Our MA findings exhibited relatively high statistical heterogeneity in fatigue at various types of vaccines studies as presented in Figure 1.

Finally, the highest observed heterogeneity can be related to the publication bias in which non-statistically significant results are usually not published.

## Strengths and Limitations

Our MA was unable to provide a definitive conclusion on vaccine efficacy as most of the included studies were phase 1 and 2 novel vaccine studies. Additionally, the immunogenicity against the variant strains of SARS-CoV-2 was not assessed in this study. Figure 2 depicts that a robust criterion followed in identifying and including the relevant articles to answer the PICO; however, this MA has limitations. The included phase 1 and phase 2 studies are lacking the control arms. Moreover, the short duration of the reported immunogenicity within some of the included studies makes the analysis subjected to latency bias.<sup>58</sup> Given that non-statistically significant results are usually not published, the publication bias may impact the current analysis. Nevertheless, the results from this review will provide information on the days required for the development of the anti-SARS-CoV-2 antibodies developed from the sequential immunization strategy. Moreover, it provides information on the duration of the development of the commonly reported vaccine adverse effects across various vaccine technology platforms. More community-based vaccine efficacy studies on COVID-19 are essential to articulate the relative risk reduction across various COVID-19 vaccines.<sup>59</sup> The development of second generation COVID-19 vaccines is critical to address the issues of viral mutations.<sup>55</sup>

## Conclusions

The immunogenicity, following phase 1 and 2 novel vaccine studies, ranged from 63% to 93% depending on the time at which antibodies level was measured. The safety and immunogenicity data from this MA will provide information on the days required for the development of anti-SARS-CoV-2 antibodies developed from the sequential immunization strategy. The adverse events were mostly mild and appeared to be well tolerated. The safety and immunogenicity data, from the phase 1 and 2 trials, needs to further ascertain its safety and protection efficacy against COVID-19.

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## Authors Contributions

RA: title and abstract reviewing, full text screening, data extraction, quality assessment, writing methodology. OR: Database search, title and abstract screening, full text screening, data extraction revision, analysis of the outcomes and writing results and part of the discussion. NH: introduction, data extraction and literature search, collection of summary table, revising the manuscript and corresponding author. MA: database search, abstract and title screening, literature search, data extraction, quality assessment. YM: database search, title and abstract screening, collection of common outcomes. SA: Introduction, literature search, data extraction, summary table, discussion. SE: data extraction, introduction, collection of common outcomes. OE: title and abstract reviewing, text screening (data extraction), quality assessment, methodology. G: summary of outcomes, database search, follow chart of the study, literature search, title and abstract screening, full text screening, data extraction, quality assessment. AN: methodology, abstract, data extraction, collection of common outcomes. AK: database search, title and abstract screening, data extraction, collection of common outcomes. HE: responsible for the data bases collection, confirming the eligible studies and part of the analysis. EE: Database search, abstract and full paper screening, data extraction and writing the manuscript. RS: database search, title and abstract screening, data extraction. RMG: conceptualization of research idea, data base search, statistical analysis, writing manuscript.

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## Supplemental Material

Supplemental material for this article is available online.

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