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Article Title:

Comparative Immunogenicity, Safety and Efficacy Profiles of four COVID-19 Vaccine types in healthy adults: Systematic Review cum Meta-analysis of Clinical Trial data

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Abstract

Four principal types of authorised COVID-19 vaccines include inactivated whole-virus vaccines, protein subunit vaccines, viral-vector vaccines and nucleic acid (mRNA and DNA) vaccines. Despite numerous Randomised Controlled Trials (RCTs), comprehensive systematic review and comparative meta-analysis have not been performed to validate the immunogenicity, safety and efficacy of COVID-19 vaccines in the healthy adult population. We aim to fulfil this unmet void. We searched for peer-reviewed articles about RCTs of the COVID-19 vaccines on healthy adults (18-64 years) available in eight major bibliographic databases (PubMed, EMBASE, Web of Science, Cochrane Library, Scopus, ScienceDirect, POPLINE, HINARI) till August 28, 2022. The Risk of Bias (RoB) was assessed using the Cochrane RoB-2. Random effects meta-analysis was conducted by pooling dichotomous outcomes using risk ratios (safety outcomes) and continuous outcomes using standardised mean differences (immunogenicity outcomes). Efficacy outcomes were summarised narratively. Moderate to high-quality evidence suggests that those receiving COVID-19 vaccines had significantly higher immune responses compared to placebo. Serious adverse events were rare, confirming that COVID-19 vaccines were safe and immunogenic for the healthy adult population. Remarkably, adverse events were the least common in inactivated vaccines, and nucleic acid vaccines were the most immunogenic. The efficacies of COVID-19 vaccines ranged from 21.9% to 95.9% in preventing COVID-19. We endorse all four types of COVID-19 vaccines for public health policy implementing taskforces. Yet, meta-analyses based on individual patient data are warranted for more extensive measurement of differential impacts of COVID-19 vaccines on different genders, ethnicities, comorbidities and types of vaccine jabbed.

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1. Introduction

The Coronavirus Disease 2019 (COVID-19) is an infectious respiratory communicable disease caused by Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2), originating in Wuhan, China, in early December 2019 [1]. World Health Organization (WHO) announced the outbreak as a global pandemic on March 11, 2020 [2]. COVID-19 is a systemic disease with both short-, intermediate- and long-term physical and mental health impacts [3, 4]. Majority of patients experience mild to moderate symptoms and 5–10% suffer from severe or debilitating disease. Therefore, the development of effective and safe vaccines and novel therapeutics is deemed a global exigency [5].

SARS-CoV-2 belongs to the genus *Betacoronavirus* under the *Coronaviridae* family and has four primary structural proteins, viz. Spike (S), Membrane (M) and Envelope (E) proteins in the viral surface, and Nucleocapsid (N) protein in the ribonucleoprotein core [6]. S proteins bind with a host cell receptor, angiotensin-converting enzyme 2 (ACE2), which is extensively expressed in pulmonary alveolar cells, cardiac myocytes, vascular endothelium and various other cell types, leading to viral invasion [7]. Most COVID-19 vaccines innovated so far have targeted the S protein. S protein consists of a membrane-distal S1 moiety and a membrane-proximal S2 moiety and presents on the viral envelope as a homotrimer (S1-S2 and S2′). The S1 subunit

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facilitates ACE2 recognition via its receptor-binding domain (RBD), whereas the S2 subunit enables membrane fusion during viral entry [8].

Four major types of COVID-19 vaccines are in clinical trials and/or have received emergency use authorisation globally: inactivated whole-virus vaccines, protein subunit vaccines, viral vector vaccines and nucleic acid (mRNA and DNA) vaccines. Inactivated whole-virus vaccine candidates contain attenuated SARS-CoV-2 viruses that induce immune responses similar to their real counterparts without causing disease. Protein subunit vaccines contain antigenic parts of the SARS-CoV-2 virus rather than the whole virus to trigger an immune response. Viral vector vaccines utilise modified viruses such as adenoviruses to deliver antigen-encoding genes which encode the surface spike proteins found on the virus and are delivered into human cells. Nucleic acid vaccines contain viral genetic material to provide immunity against the virus particles by encoding the viral antigen [9]. Vaccines offer protection against COVID-19 disease by eliciting both humoral and cellular immune responses [10], which work synergistically to ultimately induce neutralising antibodies crucial for virus clearance by targeting the S protein, thus preventing infection and risk reduction of severe COVID-19 disease [6, 11].

Meta-analyses on immunogenicity, safety and efficacy of COVID-19 vaccine trials among adults published till date have pooled trial data without differentiating between age groups and accounting for comorbidities [12–15], although these covariates markedly influence vaccine efficacy and immune response. With the rapid development of COVID-19 vaccine candidates, clinicians, policymakers and the public at large experienced confusion in deciding which vaccines/vaccine type would be more effective and which would be safer. A multitude of meta-

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analyses focused on patient groups with various comorbidities and in the younger population [16–20]. To the best of our knowledge, no meta-analysis has been conducted on the effects of COVID-19 vaccines in the healthy adult population. Due to the rapid development and publication of COVID-19 vaccine trial data, an updated systematic review and meta-analysis is needed. Hence, the current systematic review and meta-analysis aimed to compare the immunogenicity, safety, and efficacy of different types of COVID-19 vaccines in healthy adults.

2. Methods

We reported this systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [21]. The protocol was registered on PROSPERO (CRD42022314578).

2.1. Study selection criteria

We included peer-reviewed studies evaluating COVID-19 vaccine candidates irrespective of language and publication date. They must be randomised controlled trials (RCT) (Phase I-IV). Preclinical studies, and those of other study designs (e.g., quasi-experimental, reviews, opinion articles), publication types (e.g., conference abstracts, letters to editor etc.) and non-peer-reviewed articles (e.g., preprints, grey literature) were excluded.

Participants who were non-pregnant, non-lactating, healthy adults (18-64 years old) were included. When RCTs reported data on mixed populations, e.g., those with comorbidities or adults aged 65 years and above, we extracted data concerning only the subgroups of interest to our review. We excluded the trial if less than 90% of participants met the inclusion criteria (e.g.,

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studies which mainly recruited participants aged <18 and >64 years old, >10% of participants had comorbidities which put them at risk of severe COVID-19 infection or immunosuppression, e.g., cancer, uncontrolled diabetes, cardiovascular disease, obesity). Given many vaccines are under development, this review focused on vaccines with potential clinical applicability; hence vaccines which ceased further development, or Phase I trials with very small sample sizes (with less than 20 participants in the intervention arm) were excluded unless the vaccine had been investigated in further trials.

In terms of intervention, all four types of COVID-19 vaccine candidates at any RCT phase (nucleic acid, viral vector, inactivated virus, and protein subunit vaccines) were eligible. Comparators were as defined by trials, which included placebo (e.g., saline, vaccine adjuvant or vaccine protecting for other diseases such as meningococcal conjugate vaccine) or no vaccine. However, studies on co-administering different vaccines were excluded, e.g., a COVID-19 vaccine and influenza vaccine.

Studies which evaluated at least one outcome (immunogenicity, safety and/or efficacy) were included in the review. Immunogenicity outcomes included humoral immunity [(geometric mean titres (GMT) and 95% confidence interval (CI)] of anti-RBD IgG, anti-S protein IgG and neutralising antibodies) and cell-mediated immunity (T-cell response). Safety outcomes of COVID-19 vaccine candidates included any adverse events, local, systemic, and serious adverse events. Efficacy outcomes included the number of COVID-19 infections, hospitalisations, ICU admissions, severe illness, and deaths due to COVID-19.

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2.2. Search strategy

The detailed search strategy is presented in Supplementary File 1. We systematically searched 8 principal databases (PubMed, EMBASE, Web of Science, Cochrane Library, Scopus, ScienceDirect, POPLINE, HINARI) using keywords such as 'safety', 'immunity', 'vaccine efficacy' and "covid 19 vaccine' for eligible articles on 18-19 April 2022. We also hand-searched the New England Journal of Medicine for relevant articles, as many COVID-19 vaccine RCTs were published in this journal. We searched trial registries (ClinicalTrials.gov, WHO International Clinical Trials Registry Platform) to ensure that all relevant published studies were included. Finally, reference lists of relevant studies and reviews were assessed. Initial search results were uploaded into EndNote X20, where duplicates were removed automatically and manually. Screening of titles and abstracts was done by PB and SQY using Rayyan (http://rayyan.qcri.org). They then independently assessed full texts for eligibility. Discrepancies were discussed until a consensus was reached. Given the rapid publication of COVID-19 vaccine trials, we checked regularly for peer-reviewed articles for relevant articles. The final cutoff date for inclusion into the review was August 28, 2022.

2.3. Data extraction

Data were extracted using a pre-piloted data extraction sheet by SQY and PB. Discrepancies were discussed until a consensus was reached. Information extracted includes author, year, country, study design, participant characteristics, vaccine characteristics, type of placebo, immunogenicity, safety, and efficacy outcomes.

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2.4. Quality appraisal

Risk of bias (ROB) was independently assessed by PB and SQY for each study using the Revised Risk of Bias tool, and discrepancies were discussed until a consensus was reached [22]. ROB was assessed using 5 domains (bias arising from randomisation process, deviations from intended interventions, missing outcome data, outcome measurement, selection of reported results), and each domain was rated as 'low risk of bias', 'high risk of bias', or 'some concerns'. We assessed deviations from interventions based on the effect of assignment to intervention (the intention-to-treat effect). Overall ROB for each study was evaluated accordingly, and ratings were visualised using Robvis [23].

The overall quality of evidence was rated following Grading of Recommendations, Assessment, Development and Evaluations (GRADE) guidelines and justifications were provided in Evidence Profile tables generated using GRADEproGDT software [24].

2.5. Synthesis approach

Meta-analyses were performed using Review Manager Version 5.4.1. The random-effects model was used for all analyses as it accounts for between-study heterogeneity. Meta-analysis was conducted only at timepoints which were investigated by 3 or more studies. For immunogenicity outcomes, standardised mean differences (SMD) of log-transformed geometric mean titers were selected as different assays were used, and that meta-analysis of skewed data can be performed using a natural log transformation [25, 26]. When geometric median titers were reported, we

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transformed them into geometric means using established formulas if possible [27]. For safety and efficacy outcomes, dichotomous data were pooled using risk ratios (RR) as the effect size. When meta-analysis was not possible (e.g., dissimilar outcomes, timepoints, inadequate data for meta-analysis, only descriptive/graphical data available), outcomes were summarised narratively.

Cochran's Q test and I^2 statistics were used to evaluate heterogeneity. Statistically significant heterogeneity was set at $p < 0.10$. Heterogeneity was unimportant when $I^2 = 0–40\%$, moderate when $I^2 = 30–60\%$, substantial when $I^2 = 50–90\%$ and considerable when $I^2 = 75–100\%$. If there were more than 10 studies in a meta-analysis and significant heterogeneity was found, subgroup and sensitivity analysis were used to investigate sources of heterogeneity [26]. We predefined subgroups to be based on age, sex and vaccine type (nucleic acid, viral vector, inactivated virus and protein subunit vaccines). There was a significant subgroup difference when $p < 0.10$ [28]. Sensitivity analysis was done by excluding each study. If results remain consistent, they were construed as robust. When results differed, they were treated with caution. If there were more than 10 studies in a meta-analysis, publication bias was assessed using visual inspection of funnel-plot asymmetry, Begg's and Egger's test [26] using Jamovi version 1.6.

3. Results

3.1. Search findings

The initial search yielded 20482 articles. After the removal of duplicates, 13112 articles were screened using titles and abstracts. Full texts of 113 articles were assessed, and finally, 41 RCTs were included in the systematic review [29–69]. The PRISMA diagram is shown in Figure 1.

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3.2. Characteristics of included studies

Studies were published from 2020 to 2022 across 25 countries, most commonly in China (n = 14), US (n = 8) and Japan (n = 5) (Table 1). Forty-one studies on 26 vaccines were included, of which 14 studies were on protein subunit vaccines, 12 on inactivated vaccines, 9 on viral vector vaccines and 6 on nucleic acid vaccines. Most were phase 1-2 RCTs, and there were 6 phase 3 RCTs [35, 42, 47, 54, 57, 65]. There was a total of 118 377 participants, with sample sizes ranging from 15 to 37594.

3.3. Risk of bias

Most studies had some concerns (n = 31) with high ROB, while the rest had low ROB (n = 15). We rated the studies according to the RCT phase if possible; hence the total number does not add up to 41. Studies were rated with some concerns commonly due to the lack of information on allocation sequence concealment, and some studies did not specify the method of randomisation (Figure 2).

3.4. GRADE assessment

Of the 16 outcomes assessed in the meta-analyses, 14 had moderate or high certainty of evidence. Certainty of evidence was downgraded most commonly due to high heterogeneity (inconsistency) and/or insignificant effect sizes (imprecision), and some outcomes were upgraded due to large effect sizes. The detailed GRADE assessment for each outcome is presented in Supplementary File 2.

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3.5. Synthesis findings

Subgroup analysis was conducted based on vaccine type only, as age and sex were not possible due to inadequate information reported. Unless otherwise specified, sensitivity analysis confirmed the robustness of the results as the significance of the effect size remained unchanged.

3.5.1. Immunogenicity outcomes

Cellular immune responses to COVID-19 vaccines are summarised in Table 2. All immunogenicity outcomes in the following meta-analyses refer to the number of days after the completion of the primary vaccine series (either two or three doses).

3.5.1.1. Neutralising antibodies (live virus neutralisation)

Four studies reported neutralising antibody levels at 7 days after vaccination (n = 281) [34, 38, 44, 67], which was significantly higher in the vaccinated group compared to the control group (SMD = 2.51, 95% CI 1.58-3.44, $p < 0.00001$). Heterogeneity was considerable ($I^2 = 84\%$, $p = 0.0004$) (Figure 3a).

At 14 days after vaccination (n = 1409, 11 studies) [29–31, 34, 38, 39, 43, 45, 46, 67, 68], neutralising antibodies were significantly higher in the vaccinated group than in the control group (SMD = 4.30, 95% CI 3.54-5.07, $p < 0.00001$). Heterogeneity was also considerable ($I^2 = 94\%$, $p < 0.00001$), and there was a significant subgroup difference ($I^2 = 80.2\%$, $p = 0.02$). Protein subunit vaccines induced higher levels of neutralising antibodies (SMD = 5.01, 95% CI

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4.10-5.92, $p < 0.00001$) than inactivated vaccines (SMD = 3.39, 95% CI 2.30-4.47, $p < 0.00001$) (Figure 3b). Publication bias is likely as both Begg's ($p = 0.007$) and Egger's test ($p < 0.001$) were significant (Supplementary File 3 Figure S1)

At 28 days after vaccination (n = 1494, 8 studies) [30, 38, 45, 46, 58, 63, 64, 68], neutralising antibodies were significantly higher in the vaccinated group than in the control group (SMD = 4.70, 95% CI 3.55-5.85, $p < 0.00001$). Heterogeneity was considerable ($I^2 = 97\%$, $p < 0.00001$) (Figure 3c).

3.5.1.2. Neutralising antibodies (pseudovirus neutralisation)

Five studies reported neutralising antibodies at 28 days after vaccination [38, 45, 58, 59, 69], which was significantly higher in the vaccinated group than the control group (SMD = 3.41, 95% CI 2.48-4.34, $p < 0.00001$). Heterogeneity was considerable ($I^2 = 91\%$, $p < 0.00001$) (Figure 3d).

3.5.1.3. Anti-RBD IgG

Log-transformed anti-RBD IgG levels 14 days after vaccination (n = 1130, 8 studies) [34, 43–46, 58, 67, 69] were also significantly higher in the vaccinated group compared to the control group (SMD = 5.68, 95% CI 3.95-7.42, $p < 0.00001$) with considerable heterogeneity ($I^2 = 99\%$, $p < 0.00001$) (Figure 4a).

Log-transformed anti-RBD IgG levels 28 days after vaccination (n = 2326, 8 studies) [36, 38, 46, 49, 56, 58, 59, 69] was also significantly higher in the vaccinated group compared to the control group (SMD = 4.31, 95% CI 3.21-5.42, $p < 0.00001$). Heterogeneity was considerable ($I^2 = 98\%$, $p < 0.00001$) (Figure 4b).

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3.5.1.4. Anti-S IgG

Three studies reported anti-S IgG levels at 7 days after vaccination (n = 198) [29, 39, 44], and anti-S IgG levels were significantly higher in the vaccinated group than the control group (SMD = 3.71, 95% CI 1.01-6.42, p = 0.007) with considerable heterogeneity (I^2 = 96%, p < 0.00001) (Figure 4c).

At 14 days after vaccination (n = 2006, 9 studies) [29–31, 43, 44, 51, 56, 63, 64], pooled SMD for anti-S IgG levels was 5.48 (95% CI 3.66-7.29, p < 0.00001) with considerable heterogeneity (I^2 = 99%, p < 0.00001) (Figure 4d).

3.5.2 Safety outcomes

3.5.2.1. Seven days after the first dose

Twelve studies reporting local adverse events seven days after the first dose of a COVID-19 vaccine were included in the meta-analysis (n = 1301) [31–33, 37, 39, 43, 44, 49, 51, 55, 64, 67], and those in the vaccine arm had a significantly higher risk of local adverse events compared to the control (pooled RR = 2.88, 95% CI 1.78-4.67, p < 0.0001). Heterogeneity was substantial (I^2 = 71%, p < 0.00001). There was a significant subgroup difference based on vaccine type (p = 0.03, I^2 = 65.7%), and only the inactivated vaccines subgroup showed an insignificant pooled RR of 1.43 (95% CI 0.60-3.41, p = 0.42), indicating that risk of local adverse events was similar between vaccine and control groups (Figure 5a). Publication bias is unlikely as Egger's regression (p = 0.471) and Begg's test (p = 0.638) were insignificant (Supplementary File 3 Figure S2). When the article by Mohraz et al. [44] was excluded during sensitivity analysis, heterogeneity became insignificant (I^2 = 17%, p = 0.28).

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Ten studies reporting systemic adverse events seven days after the first dose of a COVID-19 vaccine were pooled (n = 1144) [31, 32, 37, 43, 44, 49, 51, 55, 64, 67], and the risk of systemic adverse events was similar between vaccine and control groups (pooled RR = 1.30, 95% CI 0.89-1.91, p = 0.17). Heterogeneity was substantial (I^2 = 63%, p = 0.004). There was also a significant subgroup difference based on vaccine type (p = 0.03, I^2 = 67.8%) (Figure 5b). Publication bias is unlikely as Egger's regression (p = 0.452) and Begg's test (p = 0.484) were insignificant (Supplementary File 3 Figure S3).

3.5.2.1. Seven days after the second dose

Ten studies reporting local adverse events seven days after the second dose of a COVID-19 vaccine were pooled (n = 1193) [31–33, 37, 39, 43, 44, 55, 64, 67]. Similarly, RR was higher in the vaccine group (pooled RR = 2.61, 95% CI 1.38-4.90, p = 0.003), and heterogeneity is considerable (I^2 = 80%, p < 0.00001). A significant subgroup difference was found (p = 0.0003, I^2 = 84.2%), with only inactivated vaccines reporting an insignificant effect size (pooled RR = 1.05, 95% CI 0.48-2.28, p = 0.90) (Figure 6a). Publication bias is unlikely as Egger's regression (p = 0.608) and Begg's test (p = 0.862) were insignificant (Supplementary File 3 Figure S4).

Seven studies reported systemic adverse events seven days after the second dose of a COVID-19 vaccine (n = 1005) [31, 32, 37, 43, 55, 64, 67], and the risk ratio was higher in the vaccinated group (pooled RR = 2.24, 95% CI 1.61-3.11, p < 0.00001). Heterogeneity was insignificant (I^2 = 35%, p = 0.16) (Figure 6b).

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3.5.2.2. One month after the first dose

Six studies reporting any adverse events 1 month after the first dose were pooled (n = 397) [29, 32–34, 44, 67], and there were no significant differences between groups receiving vaccine or control (pooled RR = 1.04, 95% CI 0.66-1.65, p = 0.87). Heterogeneity was moderate (I^2 = 48%, p = 0.09) (Figure 7a).

3.5.2.3. One month after the second dose

Seven studies reporting any adverse events 1 month after the second dose were pooled (n = 529) [32–34, 44, 61, 62, 67], and there were also no significant differences between the groups receiving vaccine or control (pooled RR = 1.20, 95% CI 0.63-1.73, p = 0.34). Heterogeneity was insignificant (I^2 = 0%, p = 0.89) (Figure 7b).

3.5.2.4. Overall adverse events

Eight studies reported overall adverse events after 7 days (n = 1603) [38, 40, 41, 50, 52, 63, 66, 68], and the risk of adverse events was significantly higher in the vaccinated group (pooled RR = 1.68, 95% CI 1.21-2.34, p = 0.002). Heterogeneity was substantial (I^2 = 70%, p = 0.0001) (Figure 8a).

Nine studies reported overall adverse events after 1 month (n = 2235) [38, 40, 41, 45, 46, 50, 55, 59, 68], and the risk of adverse events was significantly higher in the vaccinated group (pooled RR = 1.19, 95% CI 1.01-1.40, p = 0.04). Heterogeneity was insignificant (I^2 = 26%, p = 0.17) (Figure 8b).

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3.5.2.5 Serious adverse events

Serious adverse events, defined as Grade 3 or worse, were reported in 19 studies [29, 31, 35, 40, 42, 44, 48, 52, 54–57, 59, 60, 63–67]. However, they were rare, and many studies did not specify if these were related to the vaccine. Nonetheless, the studies concluded that the vaccines had an acceptable safety profile.

3.5.3. Efficacy outcomes

Efficacy outcomes were summarised in Table 1, and 6 studies reported efficacy outcomes [35, 42, 47, 54, 57, 65] ranging from 21.9% (95% CI −49.9 to 59.8) against mild-moderate COVID-19 [57] to 95.9% in preventing COVID-19 [65]. However, they were based on previous circulating variants of concern; hence the findings would not be representative of its efficacy in the current COVID-19 situation in which Omicron is the predominant strain, with subvariants such as BA.4 and BA.5 making up most of the world's COVID-19 cases [70].

4. Discussions

This systematic review and meta-analysis found that the vaccinated individuals had significantly immunogenic to COVID-19 compared to the placebo. Although our meta-analyses confirmed that vaccines induce significantly higher immune responses compared to placebo up to 28 days after completion of the primary vaccination series, this does not necessarily correlate with better disease outcomes [6]. Efficacy outcomes in healthy adults, which were rarely reported in this review, should still be relied upon to assess the clinical utility of a vaccine.

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COVID-19 vaccines in healthy adults, as assessed in this review, were relatively safe with minimal serious adverse events, which is consistent with previous large-scale observational studies and reviews [71–74] . Subgroup analyses suggest that inactivated vaccines may result in the lowest risk of adverse events among the four major vaccine genres. Similar incidences of adverse events concur with other observational studies as well [75, 76]. Due to misinformation, there is significant vaccine hesitancy worldwide. This review provides empirical evidence that vaccines are usually safe, countering the misconception-led vaccine hesitancy [77].

All meta-analyses conducted in this review found that immune responses (neutralising antibodies, anti-RBD and anti-S IgG) were significantly higher than the placebo group after vaccination. However, these measures may not all contribute to establishing immunity to COVID-19 infection and reducing the severity of COVID-19 disease [11]. Nonetheless, neutralising antibody levels are predictive of their protective efficacy, and we found that neutralising antibody levels were the highest in the nucleic acid vaccines subgroup (Figure 4D), which correlates to their high efficacy in preventing COVID-19 infection, as established by previous studies [11, 78]. In the context of the current COVID-19 pandemic, it was found that neutralising antibody levels were reduced by at least $1/10^{th}$ against the Omicron variant compared to the original strain [11]. Hence, the findings of this outcome should be interpreted with caution as most included studies were conducted when previous strains, such as the Alpha, Beta and Delta strains were more prevalent [79]. Immune responses and actual protection against COVID-19 infection and severe disease would thus be lower in real-world conditions. A large-scale observational study found that homologous primary vaccination with 2 doses of ChAdOx1 nCoV-19, BNT162b2 or mRNA-1273 resulted in vaccine effectiveness of 48.9% (95% CI 39.2

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to 57.1), 65.5% (95% CI 63.9-67.0) and 75.1% (95% CI 70.8 to 78.7) respectively at 2-4 weeks against symptomatic disease against the Omicron variant [80].

We have also descriptively summarised the cellular immune responses of COVID-19 vaccines in Table 2, which shows that they predominantly induce a Th1-mediated immune response. Studies included in the review utilised a variety of assays and outcomes; hence meta-analysis was not possible. A recent study performing head-to-head comparisons of the immune responses of those receiving mRNA-1273, BNT162b2, Ad26.COV2.S or NVX-CoV2373 vaccines found that while antibody titers declined over 6 months, memory T cells and B cells were comparatively stable, suggesting that immune memory from vaccination remains intact [81]. T-cell responses also remain robust against the Omicron variant [82], suggesting that while vaccinations may be less effective in preventing infection due to less neutralising antibodies generated against emerging variants, they are still paramount in reducing disease severity through SARS-CoV-2 specific T cells facilitating early recognition of COVID-19 virus and mediating antiviral responses [83]. Recent COVID-19 vaccine research has thus focused on the effectiveness of heterologous and homologous boosters to make up for the natural decay of antibody levels over time [84].

To the best of our knowledge, this is the first systematic review and meta-analysis that focuses on the effects of COVID-19 vaccines in the healthy adult population and provides comprehensive evidence that current vaccines are safe and immunogenic in the healthy adult population, unlike early meta-analyses on COVID-19 vaccines which had pooled outcomes without accounting for the differences in participant characteristics between studies. In addition,

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we have included the most recent RCTs which were not included in the latest meta-analyses published [85, 86].

However, our review was not devoid of limitations. First, numerous studies could not be included in the review or be pooled in the meta-analysis as they did not provide subgroup analyses of the RCT results on the healthy adult population. Our meta-analyses thus had relatively small sample sizes, with most included studies being Phase 1 or 2 trials where sample sizes are smaller. Our subgroup analyses should be interpreted with caution as there was an uneven distribution of studies in each subgroup [28]. Second, we only included English language studies and could have missed out on studies in other languages. Third, due to the varied outcomes investigated and poor reporting of information by some studies, some findings could not be included in the meta-analyses (e.g., no 95% CI reported, different timepoints for outcome measurement).

5. Conclusions

Overall, this systematic review and meta-analysis show that COVID-19 vaccines are safe and immunogenic in the healthy adult population. Future individual patient data-driven meta-analyses should be conducted to fully utilise the available RCT data and provide a more comprehensive analysis of the effects of COVID-19 vaccines according to different patient characteristics (e.g., gender, ethnicities, comorbidities). Thorough longitudinal designs calibrating exposure to SARS-CoV-2 vaccine-mediated adaptive immunity in relation to the consequential long-term advantageous and detrimental impact on diverse ethnic populations can

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assist in refurbishing preemptive policies against the future occurrence and outbreak of COVID-19.

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Declarations

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Ethics approval: This is a systematic review and meta-analysis using publicly available data from peer-reviewed articles reposited in bibliographic databases; hence, no ethical approval is needed.

Author contributions: All authors attest that they meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship. Si Qi Yoong: Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Visualisation. Priyanka Bhowmik: Conceptualisation, Investigation, Writing – review & editing. Debprasad Dutta: Conceptualisation, Writing – review & editing, Supervision.

References

[1] Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med* 2020; 382: 727–733.

[2] World Health Organisation. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020, https://www.who.int/director-

medRxiv preprint doi: https://doi.org/10.1101/2023.08.10.23293964; this version posted August 12, 2023. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. It is made available under a CC-BY 4.0 International license .

general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020 (2020, accessed 1 September 2022).

[3] Dutta D. Neurological Impact of Covid-19 Pandemic: Lessons & Cautions. *COVID-19 Pandemic Update* 2020; 73–83.

[4] Walia N, Lat JO, Tariq R, et al. Post-acute sequelae of COVID-19 and the mental health implications. *Discov Craiova Rom* 2021; 9: e140.

[5] Terpos E, Trougakos IP, Karalis V, et al. Kinetics of Anti-SARS-CoV-2 Antibody Responses 3 Months Post Complete Vaccination with BNT162b2; A Prospective Study in 283 Health Workers. *Cells* 2021; 10: 1942.

[6] Pang NY-L, Pang AS-R, Chow VT, et al. Understanding neutralising antibodies against SARS-CoV-2 and their implications in clinical practice. *Mil Med Res* 2021; 8: 47.

[7] Beyerstedt S, Casaro EB, Rangel ÉB. COVID-19: angiotensin-converting enzyme 2 (ACE2) expression and tissue susceptibility to SARS-CoV-2 infection. *Eur J Clin Microbiol Infect Dis* 2021; 40: 905–919.

[8] Dai L, Gao GF. Viral targets for vaccines against COVID-19. *Nat Rev Immunol* 2021; 21: 73–82.

[9] Rahman MdM, Masum MdHU, Wajed S, et al. A comprehensive review on COVID-19 vaccines: development, effectiveness, adverse effects, distribution and challenges. *VirusDisease* 2022; 33: 1–22.

[10] Jeyanathan M, Afkhami S, Smaill F, et al. Immunological considerations for COVID-19 vaccine strategies. *Nat Rev Immunol* 2020; 20: 615–632.

[11] Kent SJ, Khoury DS, Reynaldi A, et al. Disentangling the relative importance of T cell responses in COVID-19: leading actors or supporting cast? *Nat Rev Immunol* 2022; 22: 387–397.

[12] Cheng H, Peng Z, Luo W, et al. Efficacy and Safety of COVID-19 Vaccines in Phase III Trials: A Meta-Analysis. *Vaccines* 2021; 9: 582.

[13] McDonald I, Murray SM, Reynolds CJ, et al. Comparative systematic review and meta-analysis of reactogenicity, immunogenicity and efficacy of vaccines against SARS-CoV-2. *Npj Vaccines* 2021; 6: 1–14.

[14] Pormohammad A, Zarei M, Ghorbani S, et al. Efficacy and Safety of COVID-19 Vaccines: A Systematic Review and Meta-Analysis of Randomised Clinical Trials. *Vaccines* 2021; 9: 467.

[15] Sharif N, Alzahrani KJ, Ahmed SN, et al. Efficacy, Immunogenicity and Safety of COVID-19 Vaccines: A Systematic Review and Meta-Analysis. *Front Immunol* 2021; 12: 714170.

medRxiv preprint doi: https://doi.org/10.1101/2023.08.10.23293964; this version posted August 12, 2023. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. It is made available under a CC-BY 4.0 International license .

[16] Chen J-J, Lee TH, Tian Y-C, et al. Immunogenicity Rates After SARS-CoV-2 Vaccination in People With End-stage Kidney Disease: A Systematic Review and Meta-analysis. *JAMA Netw Open* 2021; 4: e2131749.

[17] Mehrabi Nejad M-M, Moosaie F, Dehghanbanadaki H, et al. Immunogenicity of COVID-19 mRNA vaccines in immunocompromised patients: a systematic review and meta-analysis. *Eur J Med Res* 2022; 27: 23.

[18] Teh JSK, Coussement J, Neoh ZCF, et al. Immunogenicity of COVID-19 vaccines in patients with hematologic malignancies: a systematic review and meta-analysis. *Blood Adv* 2022; 6: 2014–2034.

[19] Xu W, Tang J, Chen C, et al. Safety and efficacy of the COVID-19 vaccine in children and/or adolescents:A meta-analysis. *J Infect* 2022; 84: 722–746.

[20] Chou OHI, Mui J, Chung CT, et al. COVID-19 vaccination and carditis in children and adolescents: a systematic review and meta-analysis. *Clin Res Cardiol* 2022; 111: 1161–1173.

[21] Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021; 372: n71.

[22] Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; 366: l4898.

[23] McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualising risk-of-bias assessments. *Res Synth Methods* 2021; 12: 55–61.

[24] GRADEpro GDT: GRADEpro Guideline Development Tool, https://www.gradepro.org/ (2022, accessed 1 June 2022).

[25] Olivier J, Johnson WD, Marshall GD. The logarithmic transformation and the geometric mean in reporting experimental IgE results: what are they and when and why to use them? *Ann Allergy Asthma Immunol* 2008; 100: 333–337.

[26] Higgins JPT, Thomas J, Chandler J (eds). *Cochrane Handbook for Systematic Reviews of Interventions*. 2nd ed. John Wiley & Sons, https://blackwells.co.uk/bookshop/product/Cochrane-Handbook-for-Systematic-Reviews-of-Interventions-by-Julian-P-T-Higgins-editor-Cochrane-Collaboration-issuing-body/9781119536628 (2019, accessed 22 December 2022).

[27] Wan X, Wang W, Liu J, et al. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014; 14: 135.

[28] Richardson M, Garner P, Donegan S. Interpretation of subgroup analyses in systematic reviews: A tutorial. *Clin Epidemiol Glob Health* 2019; 7: 192–198.

medRxiv preprint doi: https://doi.org/10.1101/2023.08.10.23293964; this version posted August 12, 2023. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. It is made available under a CC-BY 4.0 International license .

[29] Keech C, Albert G, Cho I, et al. Phase 1–2 Trial of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine. *N Engl J Med* 2020; 383: 2320–2332.

[30] Masuda T, Murakami K, Sugiura K, et al. Safety and immunogenicity of NVX-CoV2373 (TAK-019) vaccine in healthy Japanese adults: Interim report of a phase I/II randomised controlled trial. *Vaccine* 2022; 40: 3380–3388.

[31] Formica N, Mallory R, Albert G, et al. Different dose regimens of a SARS-CoV-2 recombinant spike protein vaccine (NVX-CoV2373) in younger and older adults: A phase 2 randomised placebo-controlled trial. *PLOS Med* 2021; 18: e1003769.

[32] Duc Dang A, Dinh Vu T, Hai Vu H, et al. Safety and immunogenicity of an egg-based inactivated Newcastle disease virus vaccine expressing SARS-CoV-2 spike: Interim results of a randomised, placebo-controlled, phase 1/2 trial in Vietnam. *Vaccine* 2022; 40: 3621–3632.

[33] Pitisuttithum P, Luvira V, Lawpoolsri S, et al. Safety and immunogenicity of an inactivated recombinant Newcastle disease virus vaccine expressing SARS-CoV-2 spike: Interim results of a randomised, placebo-controlled, phase 1 trial. *eClinicalMedicine* 2022; 45: 101323.

[34] Liao Y, Li Y, Pei R, et al. Safety and immunogenicity of a recombinant interferon-armed RBD dimer vaccine (V-01) for COVID-19 in healthy adults: a randomised, double-blind, placebo-controlled, Phase I trial. *Emerg Microbes Infect* 2021; 10: 1589–1597.

[35] Hager KJ, Pérez Marc G, Gobeil P, et al. Efficacy and Safety of a Recombinant Plant-Based Adjuvanted Covid-19 Vaccine. *N Engl J Med* 2022; 386: 2084–2096.

[36] Hernández-Bernal F, Ricardo-Cobas MC, Martín-Bauta Y, et al. Safety, tolerability, and immunogenicity of a SARS-CoV-2 recombinant spike RBD protein vaccine: A randomised, double-blind, placebo-controlled, phase 1-2 clinical trial (ABDALA Study). *eClinicalMedicine* 2022; 46: 101383.

[37] Iwata S, Sonoyama T, Kamitani A, et al. Phase 1/2 clinical trial of COVID-19 vaccine in Japanese participants: A report of interim findings. *Vaccine* 2022; 40: 3721–3726.

[38] Meng F-Y, Gao F, Jia S-Y, et al. Safety and immunogenicity of a recombinant COVID-19 vaccine (Sf9 cells) in healthy population aged 18 years or older: two single-center, randomised, double-blind, placebo-controlled, phase 1 and phase 2 trials. *Signal Transduct Target Ther* 2021; 6: 1–11.

[39] Ryzhikov AB, Б PA, Ryzhikov EA, et al. A single blind, placebo-controlled randomised study of the safety, reactogenicity and immunogenicity of the "EpiVacCorona" Vaccine for the prevention of COVID-19, in volunteers aged 18–60 years (phase I–II). *Russ J Infect Immun* 2021; 11: 283–296.

[40] Yang S, Li Y, Dai L, et al. Safety and immunogenicity of a recombinant tandem-repeat dimeric RBD-based protein subunit vaccine (ZF2001) against COVID-19 in adults: two

medRxiv preprint doi: https://doi.org/10.1101/2023.08.10.23293964; this version posted August 12, 2023. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. It is made available under a CC-BY 4.0 International license .

randomised, double-blind, placebo-controlled, phase 1 and 2 trials. *Lancet Infect Dis* 2021; 21: 1107–1119.

[41] Guo W, Duan K, Zhang Y, et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18 years or older: A randomised, double-blind, placebo-controlled, phase 1/2 trial. *eClinicalMedicine* 2021; 38: 101010.

[42] Al Kaabi N, Zhang Y, Xia S, et al. Effect of 2 Inactivated SARS-CoV-2 Vaccines on Symptomatic COVID-19 Infection in Adults: A Randomised Clinical Trial. *JAMA* 2021; 326: 35–45.

[43] Ella R, Vadrevu KM, Jogdand H, et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: a double-blind, randomised, phase 1 trial. *Lancet Infect Dis* 2021; 21: 637–646.

[44] Mohraz M, Salehi M, Tabarsi P, et al. Safety and immunogenicity of an inactivated virus particle vaccine for SARS-CoV-2, BIV1-CovIran: findings from double-blind, randomised, placebo-controlled, phase I and II clinical trials among healthy adults. *BMJ Open* 2022; 12: e056872.

[45] Pan H-X, Liu J-K, Huang B-Y, et al. Immunogenicity and safety of a severe acute respiratory syndrome coronavirus 2 inactivated vaccine in healthy adults: randomised, double-blind, and placebo-controlled phase 1 and phase 2 clinical trials. *Chin Med J (Engl)* 2021; 134: 1289–1298.

[46] Zhang Y, Zeng G, Pan H, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18–59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. *Lancet Infect Dis* 2021; 21: 181–192.

[47] Bueno SM, Abarca K, González PA, et al. Safety and Immunogenicity of an Inactivated Severe Acute Respiratory Syndrome Coronavirus 2 Vaccine in a Subgroup of Healthy Adults in Chile. *Clin Infect Dis* 2021; ciab823.

[48] Fadlyana E, Rusmil K, Tarigan R, et al. A phase III, observer-blind, randomised, placebo-controlled study of the efficacy, safety, and immunogenicity of SARS-CoV-2 inactivated vaccine in healthy adults aged 18–59 years: An interim analysis in Indonesia. *Vaccine* 2021; 39: 6520–6528.

[49] Pu J, Yu Q, Yin Z, et al. The safety and immunogenicity of an inactivated SARS-CoV-2 vaccine in Chinese adults aged 18–59 years: A phase I randomised, double-blinded, controlled trial. *Vaccine* 2021; 39: 2746–2754.

[50] Che Y, Liu X, Pu Y, et al. Randomized, Double-Blinded, Placebo-Controlled Phase 2 Trial of an Inactivated Severe Acute Respiratory Syndrome Coronavirus 2 Vaccine in Healthy Adults. *Clin Infect Dis Off Publ Infect Dis Soc Am* 2021; 73: e3949–e3955.

[51] Zakarya K, Kutumbetov L, Orynbayev M, et al. Safety and immunogenicity of a QazCovid-in® inactivated whole-virion vaccine against COVID-19 in healthy adults: A single-

medRxiv preprint doi: https://doi.org/10.1101/2023.08.10.23293964; this version posted August 12, 2023. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. It is made available under a CC-BY 4.0 International license .

centre, randomised, single-blind, placebo-controlled phase 1 and an open-label phase 2 clinical trials with a 6 months follow-up in Kazakhstan. *eClinicalMedicine* 2021; 39: 101078.

[52] Sadoff J, Le Gars M, Shukarev G, et al. Interim Results of a Phase 1-2a Trial of Ad26.COV2.S Covid-19 Vaccine. *N Engl J Med* 2021; 384: 1824–1835.

[53] Stephenson KE, Le Gars M, Sadoff J, et al. Immunogenicity of the Ad26.COV2.S Vaccine for COVID-19. *JAMA* 2021; 325: 1535–1544.

[54] Sadoff J, Gray G, Vandebosch A, et al. Final Analysis of Efficacy and Safety of Single-Dose Ad26.COV2.S. *N Engl J Med* 2022; 386: 847–860.

[55] Asano M, Okada H, Itoh Y, et al. Immunogenicity and safety of AZD1222 (ChAdOx1 nCoV-19) against SARS-CoV-2 in Japan: a double-blind, randomised controlled phase 1/2 trial. *Int J Infect Dis* 2022; 114: 165–174.

[56] Folegatti PM, Ewer KJ, Aley PK, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. *The Lancet* 2020; 396: 467–478.

[57] Madhi SA, Baillie V, Cutland CL, et al. Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B.1.351 Variant. *N Engl J Med* 2021; 384: 1885–1898.

[58] Zhu F-C, Guan X-H, Li Y-H, et al. Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomised, double-blind, placebo-controlled, phase 2 trial. *The Lancet* 2020; 396: 479–488.

[59] Zhu F, Jin P, Zhu T, et al. Safety and immunogenicity of a recombinant adenovirus type-5-vectored COVID-19 vaccine with a homologous prime-boost regimen in healthy participants aged 6 years and above: a randomised, double-blind, placebo-controlled, phase 2b trial. *Clin Infect Dis Off Publ Infect Dis Soc Am* 2022; 75: e783–e791.

[60] Zhu F, Zhuang C, Chu K, et al. Safety and immunogenicity of a live-attenuated influenza virus vector-based intranasal SARS-CoV-2 vaccine in adults: randomised, double-blind, placebo-controlled, phase 1 and 2 trials. *Lancet Respir Med* 2022; 10: 749–760.

[61] Haranaka M, Baber J, Ogama Y, et al. A randomised study to evaluate safety and immunogenicity of the BNT162b2 COVID-19 vaccine in healthy Japanese adults. *Nat Commun* 2021; 12: 7105.

[62] Walsh EE, Frenck RW, Falsey AR, et al. Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates. *N Engl J Med* 2020; 383: 2439–2450.

[63] Masuda T, Murakami K, Sugiura K, et al. A phase 1/2 randomised placebo-controlled study of the COVID-19 vaccine mRNA-1273 in healthy Japanese adults: An interim report. *Vaccine* 2022; 40: 2044–2052.

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[64] Chu L, McPhee R, Huang W, et al. A preliminary report of a randomised controlled phase 2 trial of the safety and immunogenicity of mRNA-1273 SARS-CoV-2 vaccine. *Vaccine* 2021; 39: 2791–2799.

[65] Baden LR, El Sahly HM, Essink B, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med* 2021; 384: 403–416.

[66] Chen G-L, Li X-F, Dai X-H, et al. Safety and immunogenicity of the SARS-CoV-2 ARCoV mRNA vaccine in Chinese adults: a randomised, double-blind, placebo-controlled, phase 1 trial. *Lancet Microbe* 2022; 3: e193–e202.

[67] Shu Y-J, He J-F, Pei R-J, et al. Immunogenicity and safety of a recombinant fusion protein vaccine (V-01) against coronavirus disease 2019 in healthy adults: a randomised, double-blind, placebo-controlled, phase II trial. *Chin Med J (Engl)* 2021; 134: 1967–1976.

[68] Xia S, Zhang Y, Wang Y, et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBIBP-CorV: a randomised, double-blind, placebo-controlled, phase 1/2 trial. *Lancet Infect Dis* 2021; 21: 39–51.

[69] Song JY, Choi WS, Heo JY, et al. Safety and immunogenicity of a SARS-CoV-2 recombinant protein nanoparticle vaccine (GBP510) adjuvanted with AS03: A randomised, placebo-controlled, observer-blinded phase 1/2 trial. *eClinicalMedicine* 2022; 51: 101569.

[70] Mahase E. Covid-19: What we know about the BA.4 and BA.5 omicron variants. *BMJ* 2022; 378: o1969.

[71] Singh A, Khillan R, Mishra Y, et al. The safety profile of COVID-19 vaccinations in the United States. *Am J Infect Control* 2022; 50: 15–19.

[72] Wu Q, Dudley MZ, Chen X, et al. Evaluation of the safety profile of COVID-19 vaccines: a rapid review. *BMC Med* 2021; 19: 173.

[73] Kaur RJ, Dutta S, Bhardwaj P, et al. Adverse Events Reported From COVID-19 Vaccine Trials: A Systematic Review. *Indian J Clin Biochem* 2021; 36: 427–439.

[74] Cai C, Peng Y, Shen E, et al. A comprehensive analysis of the efficacy and safety of COVID-19 vaccines. *Mol Ther* 2021; 29: 2794–2805.

[75] Al Khames Aga QA, Alkhaffaf WH, Hatem TH, et al. Safety of COVID-19 vaccines. *J Med Virol* 2021; 93: 6588–6594.

[76] Lounis M, Rais MA, Bencherit D, et al. Side Effects of COVID-19 Inactivated Virus vs. Adenoviral Vector Vaccines: Experience of Algerian Healthcare Workers. *Front Public Health* 2022; 10: 896343.

[77] Biswas MR, Alzubaidi MS, Shah U, et al. A Scoping Review to Find Out Worldwide COVID-19 Vaccine Hesitancy and Its Underlying Determinants. *Vaccines* 2021; 9: 1243.

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[78] Khoury DS, Cromer D, Reynaldi A, et al. Neutralising antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nat Med* 2021; 27: 1205–1211.

[79] Siddiqui S, Alhamdi HWS, Alghamdi HA. Recent Chronology of COVID-19 Pandemic. *Front Public Health* 2022; 10: 778037.

[80] Andrews N, Stowe J, Kirsebom F, et al. Covid-19 Vaccine Effectiveness against the Omicron (B.1.1.529) Variant. *N Engl J Med* 2022; 386: 1532–1546.

[81] Zhang Z, Mateus J, Coelho CH, et al. Humoral and cellular immune memory to four COVID-19 vaccines. *Cell* 2022; 185: 2434-2451.e17.

[82] Chen Z, Zhang Y, Wang M, et al. Humoral and Cellular Immune Responses of COVID-19 vaccines against SARS-Cov-2 Omicron variant: a systemic review. *Int J Biol Sci* 2022; 18: 4629–4641.

[83] Agrati C, Carsetti R, Bordoni V, et al. The immune response as a double-edged sword: The lesson learnt during the COVID-19 pandemic. *Immunology* 2022; 167: 287–302.

[84] Du Y, Chen L, Shi Y. Booster COVID-19 vaccination against the SARS-CoV-2 Omicron variant: A systematic review. *Hum Vaccines Immunother* 2022; 18: 2062983.

[85] Ghazy RM, Ashmawy R, Hamdy NA, et al. Efficacy and Effectiveness of SARS-CoV-2 Vaccines: A Systematic Review and Meta-Analysis. *Vaccines* 2022; 10: 350.

[86] Graña C, Ghosn L, Evrenoglou T, et al. Efficacy and safety of COVID-19 vaccines. *Cochrane Database Syst Rev*. Epub ahead of print 2022. DOI: 10.1002/14651858.CD015477.

Table 1. Characteristics of included studies

Author (year) Country/ Settings	Study design	Vaccine information				Baseline participant characteristics				Outcomes assessed		
		Vaccine description	Intervention included in systematic review	Placebo	No. of doses / Route / Duration between doses	Sample size (Male /Female)	Age cohort included	Co-morbidities (if any)	History of COVID-19 infection/ serostatus	Immunogenicity	Safety	Efficacy
Protein subunit vaccines												
Keech et al. (2020) [29] Australia (2 sties)	Phase 1-2 study - Study reported phase 1 results (up to day 35) 3-arm RCT	NVX-CoV2373 - nanoparticle vaccine trimeric full-length SARS-CoV-2 spike glycoprotein and Matrix-M1 adjuvant Other arms - B: 25µg rSARS-Cov2 (2 doses) - D: 25µg rSARS-Cov2 + 50µg adjuvant (2 doses) - E: 25µg rSARS-Cov2 + 50µg adjuvant (1 dose)	C: 5µg rSARS-Cov2 + 50µg adjuvant (2 doses) (selected formulation for phase 3 trials)	A: 0.9% normal saline	2 doses IM deltoid 21 days apart	A = 23 (11/12) C = 29 (13/13)	18-59	Likely none	No history of COVID-19 infection	✓	✓	Not assessed
Masuda et al. (2022) [30] Japan	Phase 1/2 study 2-arm RCT	NVX-CoV2373	5µg NVX-CoV2373 + Matrix M 50µg	Saline	2 doses IM deltoid 21 days apart	Intervention = 100 (54/46) Placebo = 40 (23/17)	20-64	None	No history of COVID-19 infection	✓	✗ (not reported for placebo < 65 years old)	Not assessed
Formica et al. (2021) [31] US (8 sites) and Australia (9 sites)	Phase 2 study 5-arm RCT	NVX-CoV2373 Other arms - C: 5µg + M1 / placebo - D: 25µg + M1 (2 doses) - E: 25µg + M1 / placebo	B: 5µg + M1 (2 doses) (selected formulation for phase 3 trials)	A: 0.9% NaCl	2 doses IM 21 days apart	A = 139 B = 140	18-59	Included those with clinically stable chronic conditions	No history of COVID-19 infection Seropositive participant included	✓	✓	Not assessed
Dang et al. (2022) [32] Vietnam (Hanoi Medical University)	Phase 1-2 (interim) - study reports phase 1 results 5-arm RCT	NDV-HXP-S (COVIVAC) - Inactivated recombinant Newcastle disease virus vaccine expressing SARS-CoV-2 spike Other arms - 1µg S - 1µg S + CpG1018 - 10µg S	3µg S (selected formulation for phase 2 trials)	Saline	2-dose IM 28 days apart	3µg S = 25 (14/11) Placebo = 20 (10/10)	18-59	Likely none	No history of COVID-19 infection 5 were seropositive	✗ (no 95% CI)	✓	Not assessed

Pitisuttithum et al. (2022) [33] Thailand	Phase 1 dose-escalation study (interim) 6-arm study	NDV-HXP-S Other arms - 1µg S - 1µg S + 1.5 µg CpG1018 adjuvant	- 3 µg S (selected formulation for phase 2 trials) - 3 µg S + 1.5 µg CpG1018 adjuvant (selected formulation for phase 2 trials)	Saline	2 doses IM 28 days apart	3 µg S = 35 (7/28) 3 µg S + 1.5 µg CpG1018 = 35 (15/20) Placebo = 35 (14/21)	18-59	Likely none	No history of COVID-19 infection All seronegative at baseline	✗ (no placebo)	✓	Not assessed
Liao et al. (2021) [34] Gaozhou, China (Guangdong Provincial Center for Disease Control and Prevention)	Phase 1 4-arm RCT	V-01 - recombinant fusion protein vaccine using RBD dimer as antigen (2-dose IM arm) - 0.5ml of vaccine and Al(OH)3 as adjuvant Other arms - 25µg - 50µg	10µg (selected formulation for phase 3 trials)	Al(OH)3 in solution buffer identical to the vaccine	2 doses IM 21 days	Intervention (10µg) = 24 (6/18) Placebo = 18 (10/8)	18-59	None	No history of COVID-19 infection All seronegative at baseline	✓	✓	Not assessed
Shu et al. (2021) [67] Guangdong, China (Haozhou Centre for Disease Control and Prevention)	Phase 2 study 4-arm RCT	V-01 Other arms - V-01 (1-dose): 50µg - V-01 (2-dose): 25µg	2-dose 10µg (selected formulation for phase 3 trials)	Al(OH)3 in solution buffer	1-2 doses IM 21 days apart	10µg (2-dose) = 120 (56/64) Placebo = 40	18-59	None	No history of COVID-19 infection	✓	✓	Not assessed
Hager et al. (2022) [35] Argentina, Brazil, Canada, Mexico, UK, US (85 sites)	Phase 3 2-arm RCT	CoVLP+AS03	CoVLP+AS03 - 3.75µg CoVLP and AS03 adjuvant	0.5ml phosphate-buffered saline with polysorbate-80	2-dose IM deltoid 21 days apart	Intervention: 12074 (6107/5966) Control: 12067 (6186/5880)	18-64	None	No history of COVID-19 infection Seropositive participants included	✗ (reported but not age and co-morbidity segregated)	✗ (reported but not age and co-morbidity segregated)	Symptomatic COVID-19 in healthy adults aged 18-64: 68.9% (95% CI 55.0-78.9)
Hernandez-Bernal et	Phase 1-2 study	Abdala - based on recombinant RBD	50µg, 0-14-28 days	Not specified	3-dose IM 14/28 days	Phase 1 - 50µg = 22	19-54	well-controlled	No history of COVID-	✓	✗ (reported but did not	Not assessed

al. (2022) [36] Cuba (1 hospital)	3-arm RCT	subunit of spike protein produced in Pichia pastoris yeast, adjuvanted to alumina Other arm - 25µg	schedule (selected formulation for phase 3 trials)		apart - phase 1: 0-14-28 days (short schedule) and 0-28-56 days (long schedule) - phase 2: short schedule	(13/9) - Placebo = 22 (11/11) Phase 2 (19-54 years old) - 50µg = 151 (75/76) - Placebo = 153 (77/76)			19 infection		indicate length of follow-up)	
Iwata et al. (2022) [37] Japan	Phase 1-2 study (interim) 3-arm RCT	S-268019-b - contains S-910823 antigen, a modified recombinant spike protein of SARS-CoV-2 produced using baculovirus expression system in rhabdovirus- free insect cells, with a a squalene-based adjuvant (A-910823) in oil-in-water emulsion) Other arm - 5µg S-910823 with A-910823	10 µg S-910823 with A-910823 (selected formulation for phase 2/3 trials)	Saline	2-doses 21 days apart	- 10 µg S-910823 with A-910823 = 24 (13/11) - Placebo = 12 (5/7)	20-64	None	No history of infection or previous COVID-19 vaccination	✗ (reported but no 95% CI)	✓	Not assessed
Meng et al. (2021) [38] China (Taizhou for phase 1, Sheyang for phase 2)	Phase 1 and 2 4-arm RCT	Sf9 cells - recombinant COVID-19 vaccine (Sf9 cells) expressing SARS-CoV-2 spike protein RBD - Al(OH)3 adjuvant Other arms (Phase 1) - low dose 20µg (0, 28 days) - high dose 40µg (0, 28 days) Other arms (Phase 2) - low dose 20µg (0, 21 days) - high dose 40µg (0, 21 days) - low dose 40µg (0, 14, 28 days)	Phase 1 - high dose 40µg (0, 14, 28 days) (selected formulation for phase 3 trials) Phase 2 - high dose 40µg (0, 14, 28 days) (selected formulation for phase 3 trials)	Consistent with vaccine except for vaccine antigen	2-3 IM doses 14-21 days apart	high dose 40µg (0, 14, 28 days) - Phase 1 = 24 (9/15) - Phase 2 = 100 (42/58) Placebo: - Phase 1 = 24 (15/9) - Phase 2 = 80 (26/54)	18-55	None	No history of COVID-19 infection All seronegative at baseline	✓	✓	Not assessed
Song et al. (2022) [69] South Korea (14 centres)	Phase 1/2 trial 5-arm RCT	GBP510 with/without AS03 - recombinant protein vaccine containing self-assembling, two-component nanoparticles (RBD-16GS-I53-50) displaying RBD of SARS-CoV-2 Other arms - Group 1: 10µg GBP510+AS03	Group 3: 25µg GBP510 + AS03	Not specified	2 doses IM 28 days apart	Intervention = 92 Placebo = 56	19-64	Likely none	No history of COVID-19 infection	✓	✗ (reported but not age-segregated)	Not assessed

		- Group 2: 10µg GBP510 - Group 4: 25µg GBP510										
Ryzhikov et al. (2021) [39] Russia (Federal State Budgetary Health Institution)	Phase 2 2-arm RCT	EpiVacCorona - composition of chemically synthesised peptide immunogens of S protein of SARS-CoV-2 coronavirus conjugated to a carrier protein and adsorbed on Al(OH)3	225µg/0.5ml	NaCl 0.9% solution for injection	2 doses IM deltoid 21 days apart	n = 86 (43 each arm) - Men 60.5% - Women 39.5%	18-60	Likely none	No history of COVID-19 infection All seronegative at baseline	✓	✓	Not assessed
Yang et al. (2021) [40] China - Phase 1 (2 university hospitals in Chongqing and Beijing) - Phase 2 (Hunan Provincial Centre for Disease Control and Prevention in Xiangtan)	Phase 1 and 2 3 (Phase 1) and 6-arm RCT (Phase 2)	ZF001 - RBD-dimer protein produced in Chinese hamster ovary cells adjuvanted with Al(OH)3 Other arms - 50 µg	25µg (selected formulation)	Al(OH)3 in buffer	3 doses IM 30 days apart (selected formulation)	Phase 1 - Placebo 3 doses = 10 (5/5) - 25 µg 3 doses = 20 (14/6) Phase 2 - Placebo 3 doses = 150 (74/76) - 25 µg 3 doses = 150 (71/79)	18-59	Likely none	No history of COVID-19 infection	✗ (reported but no 95% CI)	✓	Not assessed
Inactivated vaccines												
Guo et al. (2021) [41] China	Phase 1/2 study (ongoing) 4 (Phase 1) and 2-arm (Phase 2) RCT	WIVO4 (2 or 3 IM doses) - WIV04 strain was isolated from a patient - vaccine was adsorbed to 0.5mg-alum and packed in 0.5ml-sterile phosphate-buffered saline Phase 1 (received doses on day 0, 28, 56) - 2.5µg - 5µg - 10µg Phase 2 (received doses on day 0 and 14, or 0 and 21, or 0 and 28) - 5µg	Selected regimen for phase 3 trials: 5µg 2 doses 21 or 28 days apart	Sterile phosphate-buffered saline and alum adjuvant	3 doses IM 28 days apart 2 doses IM 14, 21 or 28 days apart	Phase 1 - 5µg = 84 (35/49) - Placebo = 84 (29/55) Phase 2 2 doses 21 days apart - 5µg = 84 (32/52) - Placebo = 28 (9/19) 2 doses 28 days apart	18-59	No severe comorbidities	No history of infection All seronegative at baseline	✗ (no placebo)	✓	Not assessed

						- 5µg = 84 (37/47) - Placebo = 28 (12/16)						
Kaabi et al. (2021) [42] United Arab Emirates and Bahrain (medical centers and hospital)	Phase 3 study (interim and ongoing) 3-arm RCT	WIVO4 (2 IM doses) - 5µg/dose, alum adjuvant HBO2 (2 IM doses) - 4µg/dose, alum adjuvant	WIVO4 HBO2	Al(OH)3	21 days	WIVO4 (n = 12530) HBO2 (n = 12525) Al(OH)3 (n = 12 539)	18-59	None	No history of infection	✗ (reported but not age-segregated)	✗ (reported but not age-segregated)	Efficacy for <60 years old - WIV04: 72.8% (58.0-82.4) - HB02: 78.1% (64.9-86.4)
Xia et al. (2021) [68] China	Phase 1/2	BBIBP-CorV - created using HB02 strain isolated from a patient, with Al(OH)3 adjuvant Phase 1 (2 IM doses) - 2µg - 4µg - 8µg Phase 2 - 4µg (2 IM doses) - 8µg (1 IM dose)	Selected formulation for phase 3 trials: 4µg 2 doses 21 days apart	Not specified	Phase 1: 28 days apart Phase 2: 14, 21 or 28 days apart for 4µg doses	Phase 2 - 4µg day 0 and 21 = 112 (53/59)	18-59	Likely none	No history of infection All seronegative at baseline	✓	✓	Not assessed
Ella et al. (2021) [43] India (11 hospitals)	Phase 1 (interim) 4-arm RCT	BBV152 - based on strain NIV-2020-770 (spike variant Asp14Gly) - 0.5ml dose with virus antigen with toll-like receptor 7/8 agonist molecule adsorbed to alum (Algel IMDG) Other arm: 3µg + Algel-IMDG	6µg + Algel-IMDG (selected formulation for phase 3 trials) - 6µg + Algel	Algel only	2 dose IM deltoid 14 days apart	6µg + Algel-IMDG = 100 (82/18) Placebo = 75 (61/14)	18-55	Likely none	No history of infection All seronegative at baseline	✓	✓	Not assessed
Mohraz et al. (2022) [44] Iran (single centre)	Phase 1 (18-50 years old) and 2 (not age-segregated) 3-arm RCT for Phase 1, 2-arm RCT for Phase 2	BIV1- CovIran - virus isolated from infected patient - alhydrogel as adjuvant (maximum 500µg) Other arm: 3µg	5µg (selected formulation for phase 3 trials)	Alhydrogel diluted by phosphate-buffered solution	2 IM doses 14 days apart	Stage 1 Phase 1 - Placebo = 8 (4/4) - 5µg = 24 (18/6)	18-50 - Stage 1 in Phase 1	Stage 1 Phase 1: those with increased risk for COVID-19 excluded	No history of infection	✓	✓	Not assessed

Pan et al. (2021) [45] China	Phase 1 and 2 3-arm RCT	KCONVAC - 19nCov-CDC-Tan-Strain03 isolated from patient - 0.25mg of Al(OH)3 adjuvant Other arm: - 10µg	5µg, 2 doses 28 days apart (selected formulation for phase 3 trials)	Al(OH)3	2 IM doses - phase 1: 14 days apart - phase 2: 14 or 28 days apart	Phase 2 - 5µg group = 100 (38/62) - Placebo = 50 (25/25)	18-59	None	No history of infection Seronegative at baseline (IgG, IgM)	✓	✓	Not assessed
Zhang et al. (2021) [46] China (Jiangsu Provincial Centre for Disease Control and Prevention)	Phase 1/2 3-arm RCT	CoronaVac - inactivated CZ02 strain with Al(OH)3 adjuvant, phosphate-buffered saline and NaCl Other arm: 10µg	3µg 14 or 28 days apart (selected formulation)	Al(OH)3	2 doses IM 14 or 28 days apart	14 days apart - 3µg group = 144 (67/77) - Placebo = 84 (40/44) 28 days apart - 3µg group = 144 (69/75) - Placebo = 83 (38/45)	18-59	None	No history of infection Seronegative at baseline (IgG, IgM)	✓	✓	Not assessed
Bueno et al. (2021) [47] Chile (8 sites)	Phase 3 (interim) (subgroup of healthy adults) 2-arm RCT	CoronaVac	3µg	0.5ml of aqueous suspension for injection with Al(OH)3 and excipients	2 doses IM left deltoid 14 days apart	Intervention = 245 Control = 152	18-59	Well-controlled chronic conditions included	No history of infection All anti SARS CoV-2 IgG negative	✗ (only geometric median and 95% CI reported)	✗ (did not report total/local/ systemic adverse events for 7 days/1 month)	Not assessed
Fadlyana et al. (2021) [48] Indonesia	Phase 3 (interim) 2-arm RCT	CoronaVac	3µg/0.5ml dose	Water for injection in ampoules (0.5ml/dose)	2 doses IM left deltoid 14 days apart	Intervention = 811 (505/305) Control = 809 (541/269)	18-59	Excluding serious and uncontrolled co-morbidities	No history of infection All seronegative at baseline	✗ (only geometric median and 95% CI reported)	✗ (did not report timepoint)	65.3% effective in preventing symptomatic infection 14 days after 2nd dose
Pu et al. (2021) [49] China	Phase 1 study 4-arm RCT	Virus strain (KMS-1) was isolated from patient and has a D614G mutation in the S protein - inactivated viral antigen adsorbed to 0.25mg of Al(OH)3 adjuvant and suspended in 0.5ml of buffered saline Other arms: 50 and 100 EU	150 EU 14 days apart (selected formulation)	Al(OH)3 in buffer	2 IM doses 14 or 28 days apart	0, 14 schedule - 150 EU = 24 (10/14) - Placebo = 24 (14/10)	18-59	None	Not specified	✗ (no 95% CI)	✓	Not assessed
Che et al. (2021) [50]	Phase 2 study	KMS-1 Other arm: 100 EU	150 EU 14 days apart (selected	Al(OH)3 in buffer	2 IM doses 14 or 28 days apart	0, 14 schedule - 150 EU =	18-59	Only specified that they were	Not specified	✗ (no 95% CI)	✓	Not assessed

China	3-arm RCT		formulation)			150 (56/94) - Placebo = 75 (33/42)		healthy				
Zakarya et al. (2021) [51] Kazakhstan	Phase 1 and Phase 2 study with 6 months follow-up 2-arm RCT	QazCovid-in - virus strain isolated SARS-CoV2/human/KAZ/KZ_Almaty/2020 - Al(OH)3 adjuvant (only phase 1 study results included as phase 2 has no control)	5µg	0.9% NaCl	2 IM deltoid 21 days apart	Phase 1 - vaccine = 22 (17/5) - placebo = 22 (12/10)	18-50	None	No history of infection Seronegative at baseline (IgG, IgM)	✓	✓	Not assessed
Virus vector vaccines												
Sadoff et al. (2021) [52] Belgium and US (12 centres)	Phase 1 and 2a (interim) - reported results from cohort 1a, 1b and cohort 3 5-arm RCT	Ad26.COV2.S - recombinant, replication-incompetent human adenovirus type 26 vector encoding a full-length, membrane bound SARS-CoV-2 spike glycoprotein spike protein in a prefusion stabilised conformation - low dose ($5x10^{10}$ viral particles/ml) - high dose ($1x10^{11}$ viral particles/ml) Other arms - Low + low - high + high - high + placebo - placebo + placebo	Low + placebo (selected formulation for phase 3 trials: single shot vaccine)	Not specified	Single dose or 2 doses IM 56 days apart	Low dose group = 162 (78/84) Placebo group = 82 (49/51)	18-55	No	2% seropositive	✗ (no placebo)	✓	Not assessed
Stephenson et al. (2021) [53] US (medical centre in Boston)	Phase 1b trial (part of Phase 1-2a trial) - reported results from cohort 1b 5-arm RCT	Ad26.COV2.S - low dose: $5x10^{10}$ viral particles/ml - high dose: $1x10^{11}$ viral particles/ml Other arms - low + low - high + high - high + placebo (single shot vaccine) - placebo + placebo	- Low + placebo (selected formulation for phase 3 trials: single shot vaccine)	1ml 0.9% NaCl solution	56 days apart or as a single shot vaccine	Low dose group = 10 (5/5) Placebo group = 5 (3/2)	18-55	No	No history of COVID-19 infection All seronegative at baseline	✗ (no 95% CI)	Not assessed	Not assessed
Sadoff et al. (2022) [54] United States,	Final analysis (crossover vaccination occurred in control	Ad26.COV2.S (single dose IM injection)	$5x10^{10}$ viral particles	Saline injection (0.5ml)	Single dose IM	Intervention = 14564 Control = 14553	18-59	Included those with high risk for severe COVID-19, but efficacy	Seropositive individuals included but efficacy analysis	Not assessed	✗ (reported but not age and co-morbidity segregated)	Moderate to severe-critical COVID-19 - onset at least 14

South Africa, Brazil, Columbia, Argentina, Peru, Chile, Mexico	group) of Phase 3 trial 2-arm RCT							for healthy adult population available	included those only seronegative at baseline			days after vaccination: 57.0% (95% CI 49.99-63.03) - onset at least 28 days after: 55.2% (47.52-61.82) Severe-critical COVID-19 - 14 days: 69.1% (51.84-80.70) - 28 days: 71.9% (54.79-83.12)
Asano et al. (2022) [55] Japan (5 centres)	Phase 1/2 trial 2-arm RCT	AZD1222 (ChAdOx1 nCoV-19) - replication-deficient simian adenovirus-vectored vaccine encoding the full-length SARS-CoV-2 spike glycoprotein spike protein	$5x10^{10}$ viral particles	Saline	2 IM doses 4 weeks apart	Intervention = 96 (71/25) Control = 32 (24/7)	18-55	Mild/moderate, well-controlled comorbidities were allowed (23/128 had hypertension)	No history of COVID-19 infection Seronegative at baseline	✗ (no placebo)	✓	Not assessed
Folegatti et al. (2020) [56] UK (5 trial sites)	Phase 1/2 study (preliminary findings) 2-arm RCT	AZD1222 (ChAdOx1 nCoV-19)	$5x10^{10}$ viral particles	Meningococcal conjugate vaccine (MenACWY)	Single IM dose	Intervention = 533 Control = 533	18-55	None	No history of COVID-19 infection Some had high-level anti-spike antibodies at baseline	✓	✗ (some received prophylactic paracetamol)	Not assessed

Madhi et al. (2021) [57] South Africa	Phase 1b-2 study (against B.1.351 variant) 2-arm RCT	AZD1222 (ChAdOx1 nCoV-19)	$5x10^{10}$ viral particles	0.9% NaCl	2 IM doses deltoid 21-35 days apart	Overall safety population = 1978 Seronegative efficacy population = 1206	18-64	No or well-controlled chronic conditions (hypertension, chronic respiratory condition, diabetes < 10%)	No history of COVID-19 infection Some seropositive	✗ (no control group)	✗ (did not specify timepoint)	Did not show protection against mild-moderate COVID-19 (against B.1.351 variant only): 21.9% (95% CI −49.9 to 59.8)
Zhu et al. (2020) [58] China (single centre in Wuhan, Hubei province)	Phase 2 3-arm RCT	Ad5-vectored COVID-19 vaccine - replication-defective Ad5 vectors expressing full-length spike gene based on Wuhan-hu-1 Other arm: $1x10^{11}$ viral particles/ml	$5x10^{10}$ viral particles/ml (selected formulation for phase 3 trial)	Vaccine excipients only, no virus particles	Single dose IM arm	$5x10^{10}$ viral particles = 112 Placebo = 112	18-54	5.49% with underlying disease	No history of COVID-19 infection	✓	✗ (not age-segregated)	Not assessed
Zhu et al. (2022) [59] China (Taizhou, Jiangsu Province)	Phase 2b 2-arm RCT	Ad5-vectored COVID-19 vaccine	$5x10^{10}$ viral particles per 0.5ml	Not specified	2 IM doses 56 days apart	Intervention = 20 (7/13) Control = 10 (5/5)	18-55	None	All seronegative (IgG, IgM) at baseline	✓	✗ (reported adverse events 14 days after each dose)	Not assessed
Zhu et al. (2022) [60] China (Dongti Center for Disease Control and Prevention)	Phase 1 and 2 study 2-arm RCT	dNS-1 RBD - live-attenuated influenza virus-vector	10^6 plaque-forming units of CA4-dNS1-nCoV-RBD per ml (0.2ml per dose)	IN diluent	2 doses IN 14 days apart	Intervention = 51 (23/28) Placebo = 12 (7/5)	18-59 (Phase 1 study only)	Included only those stable chronic diseases	No history of COVID-19 infection All seronegative at baseline	✗ (GMT and 95% CI not reported)	✓	Not assessed
Nucleic acid vaccines												
Haranaka et al. (2021) [61] Japan (1 hospital and 1 clinic)	Phase 1/2 (ongoing)	BNT162b2 - mRNA drug substance encoding the SARS-CoV-2 spike glycoprotein RBD antigen, formulated with lipids to obtain the RNA-LNP drug product	30µg	Saline	2 IM doses deltoid 21 days apart	Intervention = 97 (50/47) Control = 33 (17/17)	20-64	Included those with stable preexisting disease	No history of COVID-19 infection	✗ (GMT and 95% CI not reported)	✓	Not assessed

Walsh et al. (2020) [62] US	Phase 1	BNT162b2 - 10µg - 20µg - 100µg BNT162b1 - 10µg - 20µg - 30µg - 100µg	BNT162b2: 30µg (selected formulation for phase 3 trials)	Not specified	2 IM doses deltoid 21 days apart	30µg BNT162b2 = 12 (5/7) Control = 12 (7/5)	18-55	None	No history of COVID-19 infection All seronegative (IgG, IgM) at baseline	✗ (no 95% CI)	✓	Not assessed
Masuda et al. (2022) [63] Japan (2 sites)	Phase 1/2 study (interim)	mRNA-1273	0.5ml of 100µg of vaccine	Saline	2 IM doses 28 days apart	Intervention = 100 (54/46) Placebo = 40 (21/19)	20-64	None	No history of infection	✓	✓	Not assessed
Chu et al. (2021) [64] US (8 sites)	Phase 2 study 3-arm RCT	mRNA-1273 - other arm: 50µg	100µg (selected formulation for phase 3 trials)	Saline	2 doses IM 28 days apart	100µg = 100 (47/53) Placebo = 100 (40/60)	18-55	Likely none	No history of infection	✓	✓	Not assessed
Baden et al. (2021) [65] US (99 centres)	Phase 3 study 2-arm RCT	mRNA-1273 - a LNP-encapsulated mRNA vaccine expressing the pre-fusion-stabilised spike glycoprotein	0.5ml of 100µg of vaccine	Saline	2 doses IM 28 days apart	Intervention = 8189 Placebo = 8200	18-64	None	No history of infection All seronegative at baseline	✗ (not age and co-morbidity segregated)	✗ (not age and co-morbidity segregated)	Prevention of COVID-19 in healthy adult population aged 18-64: 95.9% (90-98.3%)
Chen et al. (2022) [66] China	Phase 1 dose-escalation study	ARCoV - encodes the SARS-CoV-2 spike glycoprotein RBD Other arms: 5, 10, 20, 25µg	15 µg (selected formulation for phase 3 trials)	0.9% NaCl	2 doses IM 28 days apart	15 µg = 20 (14/6) Placebo = 20 (15/5)	18-59	Hypertension (n = 1)	No history of infection All seronegative at baseline	✗ (no 95% CI)	✓	Not assessed

Abbreviations: RCT (randomised controlled trial), ✓ (outcome included in the meta-analysis), ✗ (outcome excluded from meta-analysis), IM (intramuscular), CI (confidence interval), IN (intranasal), GMT (geometric mean titre

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Table 2. Cellular immune responses of different COVID-19 vaccines

Vaccine	Author (year)	Assay methods	Findings
Protein Subunit Vaccines			
NVX-CoV2373	Keech et al. (2020) [29]	Intracellular cytokine staining of antigen-specific CD4+ T cells	- Adjuvanted regimens induced antigen-specific polyfunctional CD4+ T-cell responses reflected in IFN-γ, IL-2 and TNF-α production on spike protein stimulation (strong bias towards Th1 phenotype) - Th2 responses minimal (IL-5 and IL-13 cytokines)
NDV-HXP-S	Pitisuttithum et al. (2022) [33]	IFN-γ, IL-5 using ELI-Spot kit	IFN-γ/IL-5 ratio strongly skewed to Th1 response relative to the prevaccination baseline, suggesting the vaccine-induced T-cell memory capable of an antiviral response
S-268019-b	Iwata et al. (2022) [37]	IFN-γ, IL-2, IL-4, IL-5 in CD4+ or CD8+ cells using intracellular cytokine staining by flow cytometry, IFN-γ ELISpot assay	- Both vaccine regimens induced antigen-specific polyfunctional CD4+ T-cell responses reflected in IFN-γ, IL-2, IL-4 production on spike protein stimulation - Strong bias towards Th1 phenotype - Th2 responses minimal (IL-4 and IL-5) - Substantial increase in IFN-γ levels observed on day 36 and 50 for those receiving vaccine
Sf9 cells	Meng et al. (2021) [38]	Enzyme-linked immunospot (ELISpot)	- In the phase 1 trial, the positive rate of IFN-γ peaked at 14 days than that at 28 days after the last dose vaccination. - Among three vaccine groups, no significant difference was found in the positive rate of IFN-γ at 14 days after the last dose vaccination, with 50% in the adult low dose group (0, 28 days), 88% in the adult high dose group (0, 28 days), 88% in the adult high dose group (0, 14, 28 days), and 8% in the adult placebo group.
GBP510 with/without AS03	Song et al. (2022) [69]	Intracellular cytokine staining using SARS-CoV-2 RBD	- GBP510 adjuvanted with AS03 induced stronger CD4+ T-cell responses with higher percentages of IFN-g, TNF-a, and IL-2 expression compared to unadjuvanted GBP510. - IL-4 was inconsistent and IL-5 was nearly inexistent across all groups.
Inactivated Vaccines			
BBV152	Ella et al. (2021) [43]	- ELISpot - Intracellular cytokine staining	- IFN-γ ELISpot responses against SARS-CoV-2 peptides peaked at about 100–120 spot-forming cells per million peripheral blood mononuclear cells in all vaccinated groups on day 28. - The Algel-IMDG groups elicited CD3+, CD4+, and CD8+ T-cell responses that were reflected in the IFN-γ production - a minimal detection of less than 0·5% of CD3+, CD4+, and CD8+ T-cell responses in the 6 μg with Algel group and the Algel group (placebo).

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CoronaVac	Bueno et al. (2021) [47]	ELISPOT and flow cytometry assays were performed using isolated peripheral blood mononuclear cells (PBMCs).	- Immunisation with CoronaVac induces a T-cell response polarised toward a Th1 immune profile, as the secretion of interleukin-4 by T cells was mainly undetected. - Modest increases in the expression of activation-induced markers were detected for both MP-CD8A and MP-CD8B.
inactivated SARS-CoV-2 vaccine	Pu et al. (2021) [49]	- Human IFN-c ELISpot Kit - Bio-Plex Pro Human Cytokine 48-Plex	- The specific positive cytotoxic T lymphocyte (CTL) responses against the S protein, N protein and virion in the ELISpot assay indicated a distinct increase at day 28 after the booster for both schedules. These results suggest that the vaccine elicits a synchronous dynamic response involving antibodies and CTLs against the viral antigens. - There were no significant differences between the vaccine and placebo groups with regard to the counts of various T cell populations in the peripheral blood.
Virus Vector Vaccines			
Ad26.COV2.S	Sadoff et al. (2021) [52]	Intracellular cytokine staining with the use of two pools of S-peptide pools of 15 mers overlapping by 11 amino acids	- In cohort 1a, Th1 response to S peptides was detected in 76% (95% CI 65-86) of low-dose recipients and in 83% (95% CI, 73 to 91) of high-dose recipients; the corresponding values in cohort 3 were 60% (95% CI 46-74) and 67% (95% CI 53-79), respectively. - In cohort 1a, the median CD4+ Th1 response to S peptides increased from an undetectable level at baseline to a median of 0.08% (IQR 0.05-0.16) in low-dose recipients and 0.11% (IQR, 0.07-0.16) in high-dose recipients on day 15; in cohort 3, the corresponding values were 0.09% (IQR 0.04-0.17) and 0.11% (IQR 0.04-0.15), respectively. - S-specific CD8+ T-cell responses, as identified by the expression of interferon-γ or interleukin-2 cytokines on S-peptide stimulation. On day 15 in cohort 1a, CD8+ T-cell response was detected in 51% of participants (95% CI 39-63) in the low-dose group and in 64% (95% CI 52-75) in the high-dose group, with a median S-specific CD8+ T-cell response of 0.07% (IQR 0.03-0.19) and 0.09% (IQR, 0.05-0.19), respectively. - In cohort 3, CD8+ T-cell responses were lower, with an incidence of 36% (95% CI 23-51) in the low-dose group and 24% (95% CI 13-37) in the high-dose group, with a median response of 0.06% (IQR 0.02-0.12) and 0.02% (IQR 0.01-0.08), respectively.
Ad26.COV2.S	Stephenson et al. (2021) [53]	- IFN-γ and IL-4 ELISPOT assays - Multiparameter ICS assays	- IFN-γ ELISPOT responses were observed in 65% (13/20) of vaccine recipients by day 15 and in 84% (16/19) of vaccine recipients by day 71, with no significant differences among groups - No IL-4 responses were observed, indicating aTH1-biased cellular immune response. - Multiparameter ICS assays confirmed the

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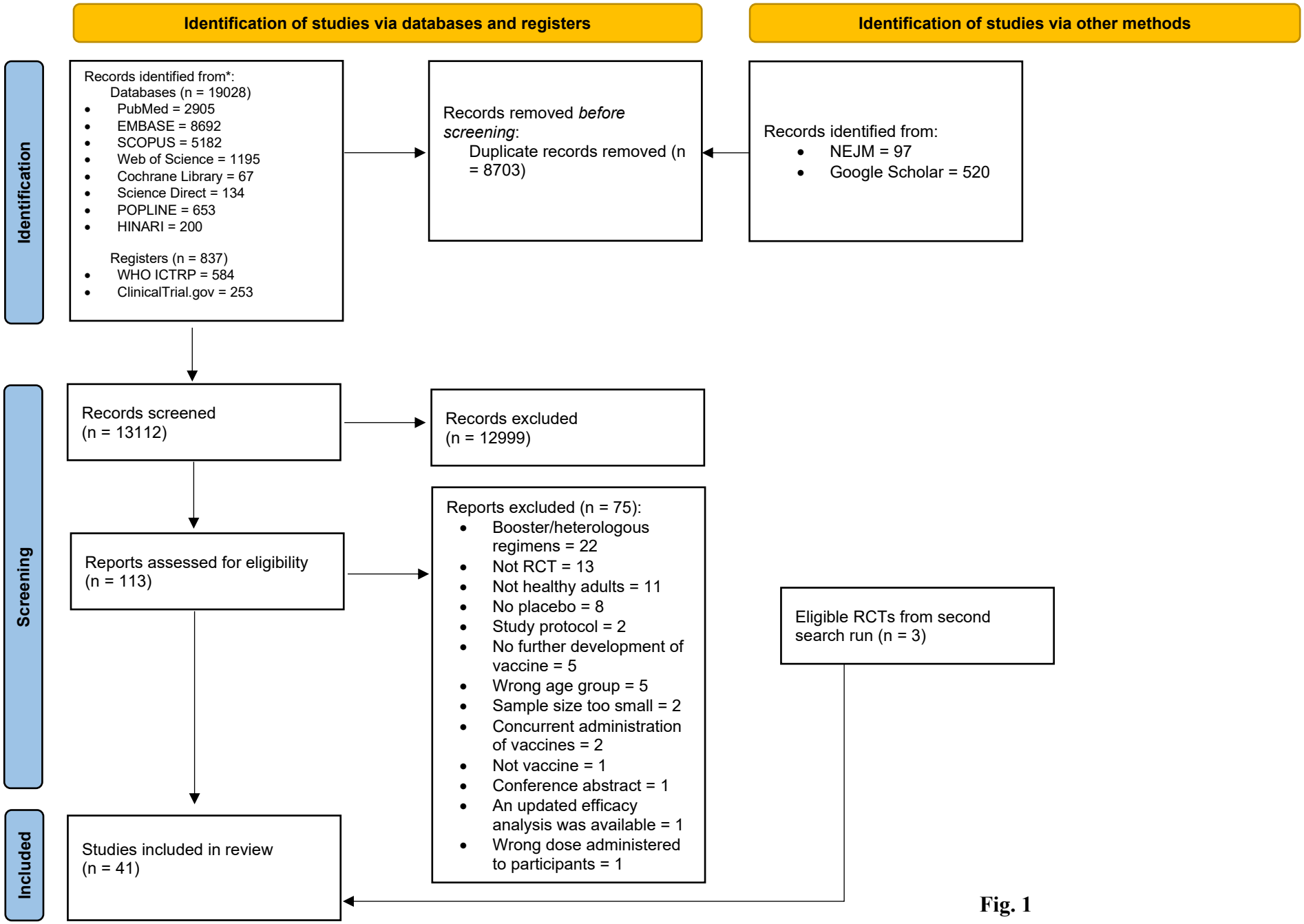
			induction of central memory CD27+/CD45RA−/CD4+ and CD8+ T-cell responses.
AZD1222 (ChAdOx1 nCoV-19)	Folegatti et al. (2020) [56]	Ex-vivo interferon-γ ELISpot assay	- Interferon-γ ELISpot responses against SARS-CoV-2 spike peptides peaked at 856 spot-forming cells per million peripheral blood mononuclear cells (IQR 493–1802; n=43) at day 14, declining to 424 (221–799; n=43) by day 56 after vaccination.
AZD1222 (ChAdOx1 nCoV-19)	Madhi et al. (2021) [57]	ImmunoSEQ® Assay	- The ChAdOx1 nCoV-19 vaccine caused the expansion of CD4+ and CD8+ T lymphocytes to specific epitopes of the spike protein. - D215G mutation found in the B.1.351 variant is within a region that had prevalent T-cell antigen responses
Ad5-vectored COVID-19 vaccine	Zhu et al. (2020) [58]	IFN-γ ELISpot	- Significant activation in postvaccination T-cell responses in terms of spot-forming cells observed both in participants with high and low pre-existing neutralising antibodies at day 28. - Baseline ELISpot T-cell responses were negative in 506 (>99%) of 508 participants. Ad5-vectored COVID-19 vaccine induced significant SARS-CoV-2 spike glycoprotein-specific IFN-γ ELISpot responses in 227 (90%, 95% CI 85–93) of 253 participants receiving the 1×10^{11} viral particles dose, and 113 (88%, 81–92) of 129 participants receiving the 5×10^{10} viral particles dose at day 28. - A median of 11·0 spot-forming cells (IQR 5·0–25·0) and 10·0 spot-forming cells (6·0–21·0) per 1×10^{5} peripheral blood mononuclear cells in participants in the 1×10^{11} viral particles and 5×10^{10} viral particles dose groups, respectively, were observed at day 28, with increases of more than 10-times in both dose groups. - The IFN-γ-ELISpot responses were not significantly different between the dose groups at day 28. - No positive IFN-γ ELISpot T-cell responses were detected in the placebo group postvaccination.
dNS-1 RBD	Zhu et al. (2022) [60]	INF- γ ELISpot	- No specific T-cell responses were detected in PBMCs from vaccinators 1 month after the participants had received the second dose.
Nucleic Acid Vaccines			
ARCoV	Chen et al. (2022) [66]	ELISpot	- Following the first vaccination, only a small proportion of participants in each vaccine group was positive for IFN-γ-expressing cells. However, after the second vaccination, all participants in the 5 µg, 10 µg, 15 µg, and 20 µg groups were positive for IFN-γ- expressing cells. - All participants were positive with IL-2-expressing cells at day 7 after the second vaccination.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Identification of studies via other methods
Identification
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SCOPUS = 5182
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Science Direct = 134
POPLINE = 653
HINARI = 200
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ClinicalTrial.gov = 253
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Google Scholar = 520
Screening
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(n = 13112)
Records excluded
(n = 12999)
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Reports excluded (n = 75):
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Not RCT = 13
Not healthy adults = 11
No placebo = 8
Study protocol = 2
No further development of vaccine = 5
Wrong age group = 5
Sample size too small = 2
Concurrent administration of vaccines = 2
Not vaccine = 1
Conference abstract = 1
An updated efficacy analysis was available = 1
Wrong dose administered to participants = 1
Eligible RCTs from second search run (n = 3)
Included
Studies included in review
(n = 41)

Fig. 1

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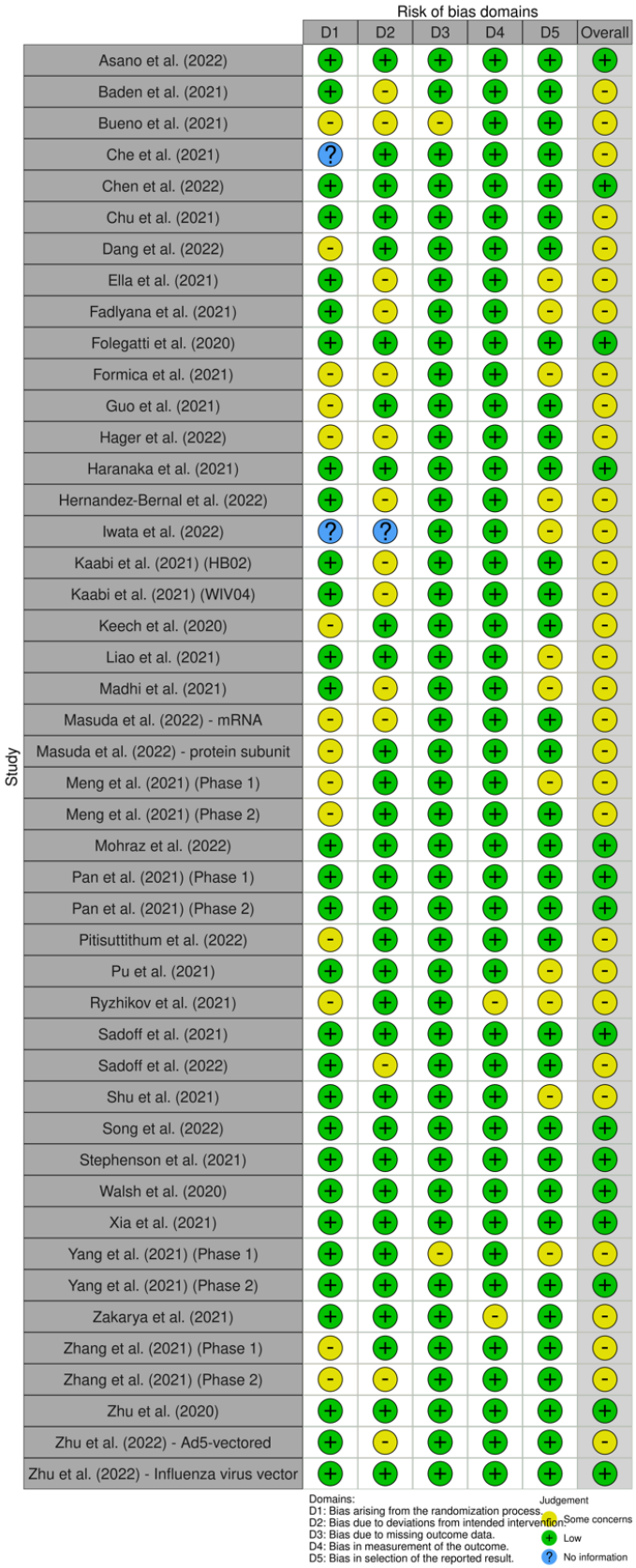
a



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b

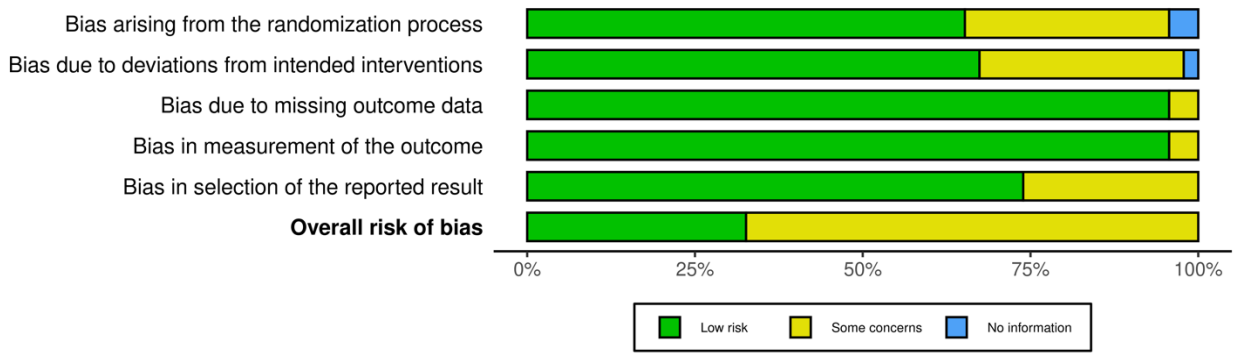
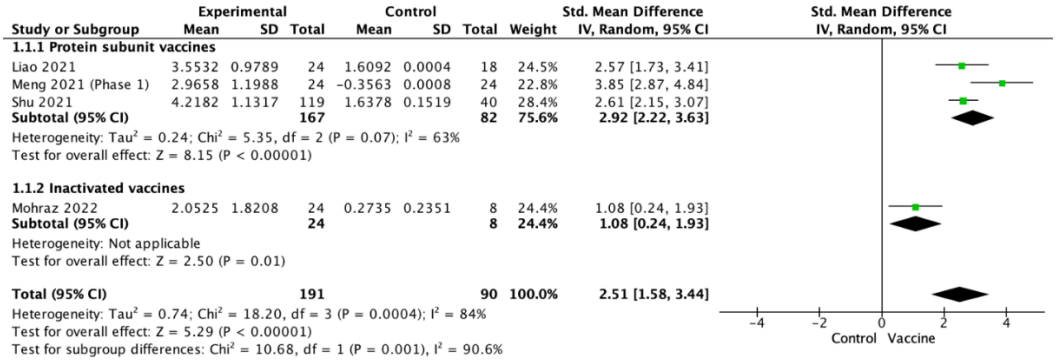


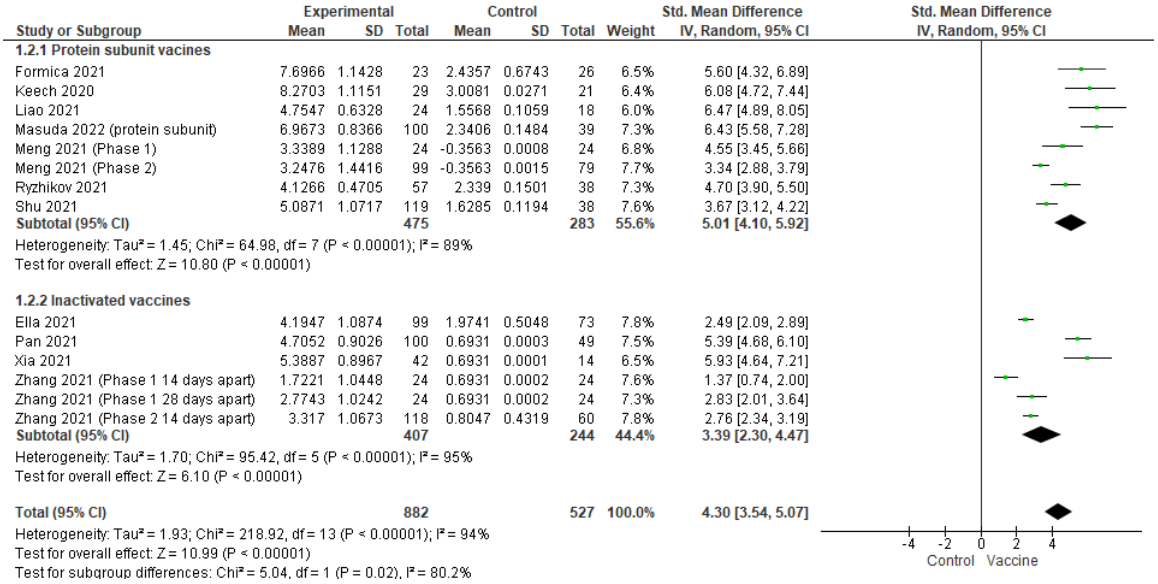
Fig. 2

a



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.1 Protein subunit vaccines								
Liao 2021	3.5532	0.9789	24	1.6092	0.0004	18	24.5%	2.57 [1.73, 3.41]
Meng 2021 (Phase 1)	2.9658	1.1988	24	−0.3563	0.0008	24	22.8%	3.85 [2.87, 4.84]
Shu 2021	4.2182	1.1317	119	1.6378	0.1519	40	28.4%	2.61 [2.15, 3.07]
Subtotal (95% CI)			**167**			**82**	**75.6%**	**2.92 [2.22, 3.63]**
Heterogeneity: Tau² = 0.24; Chi² = 5.35, df = 2 (P = 0.07); I² = 63%								
Test for overall effect: Z = 8.15 (P < 0.00001)								
1.1.2 Inactivated vaccines								
Mohraz 2022	2.0525	1.8208	24	0.2735	0.2351	8	24.4%	1.08 [0.24, 1.93]
Subtotal (95% CI)			**24**			**8**	**24.4%**	**1.08 [0.24, 1.93]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.50 (P = 0.01)								
Total (95% CI)			**191**			**90**	**100.0%**	**2.51 [1.58, 3.44]**
Heterogeneity: Tau² = 0.74; Chi² = 18.20, df = 3 (P = 0.0004); I² = 84%								
Test for overall effect: Z = 5.29 (P < 0.00001)								
Test for subgroup differences: Chi² = 10.68, df = 1 (P = 0.001), I² = 90.6%								

b



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.2.1 Protein subunit vacines								
Formica 2021	7.6966	1.1428	23	2.4357	0.6743	26	6.5%	5.60 [4.32, 6.89]
Keech 2020	8.2703	1.1151	29	3.0081	0.0271	21	6.4%	6.08 [4.72, 7.44]
Liao 2021	4.7547	0.6328	24	1.5568	0.1059	18	6.0%	6.47 [4.89, 8.05]
Masuda 2022 (protein subunit)	6.9673	0.8366	100	2.3406	0.1484	39	7.3%	6.43 [5.58, 7.28]
Meng 2021 (Phase 1)	3.3389	1.1288	24	-0.3563	0.0008	24	6.8%	4.55 [3.45, 5.66]
Meng 2021 (Phase 2)	3.2476	1.4416	99	-0.3563	0.0015	79	7.7%	3.34 [2.88, 3.79]
Ryzhikov 2021	4.1266	0.4705	57	2.339	0.1501	38	7.3%	4.70 [3.90, 5.50]
Shu 2021	5.0871	1.0717	119	1.6285	0.1194	38	7.6%	3.67 [3.12, 4.22]
Subtotal (95% CI)			**475**			**283**	**55.6%**	**5.01 [4.10, 5.92]**
Heterogeneity: Tau² = 1.45; Chi² = 64.98, df = 7 (P < 0.00001); I² = 89%								
Test for overall effect: Z = 10.80 (P < 0.00001)								
1.2.2 Inactivated vaccines								
Ella 2021	4.1947	1.0874	99	1.9741	0.5048	73	7.8%	2.49 [2.09, 2.89]
Pan 2021	4.7052	0.9026	100	0.6931	0.0003	49	7.5%	5.39 [4.68, 6.10]
Xia 2021	5.3887	0.8967	42	0.6931	0.0001	14	6.5%	5.93 [4.64, 7.21]
Zhang 2021 (Phase 1 14 days apart)	1.7221	1.0448	24	0.6931	0.0002	24	7.6%	1.37 [0.74, 2.00]
Zhang 2021 (Phase 1 28 days apart)	2.7743	1.0242	24	0.6931	0.0002	24	7.3%	2.83 [2.01, 3.64]
Zhang 2021 (Phase 2 14 days apart)	3.317	1.0673	118	0.8047	0.4319	60	7.8%	2.76 [2.34, 3.19]
Subtotal (95% CI)			**407**			**244**	**44.4%**	**3.39 [2.30, 4.47]**
Heterogeneity: Tau² = 1.70; Chi² = 95.42, df = 5 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 6.10 (P < 0.00001)								
Total (95% CI)			**882**			**527**	**100.0%**	**4.30 [3.54, 5.07]**
Heterogeneity: Tau² = 1.93; Chi² = 218.92, df = 13 (P < 0.00001); I² = 94%								
Test for overall effect: Z = 10.99 (P < 0.00001)								
Test for subgroup differences: Chi² = 5.04, df = 1 (P = 0.02), I² = 80.2%								

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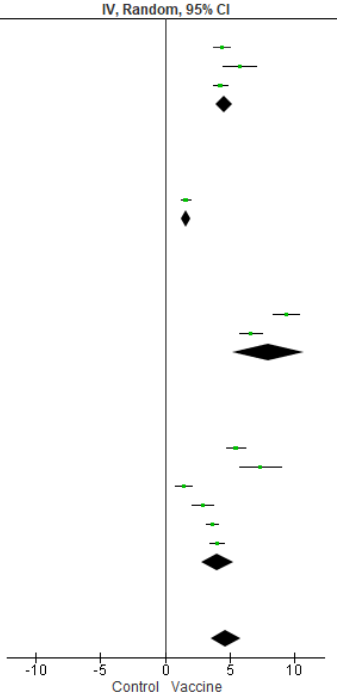
c

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.3.1 Protein subunit vaccines								
Masuda 2022 (protein subunit)	6.3636	1.0519	100	2.3542	0.1903	39	8.5%	4.43 [3.79, 5.08]
Meng 2021 (Phase 1)	4.6342	1.2046	24	-0.3937	0.0878	24	7.8%	5.79 [4.46, 7.13]
Meng 2021 (Phase 2)	4.6313	1.5598	99	-0.3937	0.1654	79	8.6%	4.28 [3.74, 4.82]
Subtotal (95% CI)			**223**			**142**	**24.9%**	**4.59 [3.96, 5.23]**
Heterogeneity: Tau² = 0.16; Chi² = 4.25, df = 2 (P = 0.12); I² = 53%								
Test for overall effect: Z = 14.15 (P < 0.00001)								
1.3.2 Virus vector vaccines								
Zhu 2020 (18-44 years old)	3.0541	1.4075	80	1.4098	0.2151	77	8.7%	1.61 [1.25, 1.97]
Subtotal (95% CI)			**80**			**77**	**8.7%**	**1.61 [1.25, 1.97]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 8.74 (P < 0.00001)								
1.3.3 Nucleic acid vaccines								
Chu 2021	7.4336	0.3175	95	3.8818	0.4275	92	8.2%	9.42 [8.41, 10.42]
Masuda 2022	7.4545	0.5445	98	4.3804	0.0012	39	8.3%	6.62 [5.75, 7.50]
Subtotal (95% CI)			**193**			**131**	**16.5%**	**8.01 [5.27, 10.75]**
Heterogeneity: Tau² = 3.67; Chi² = 16.80, df = 1 (P < 0.0001); I² = 94%								
Test for overall effect: Z = 5.73 (P < 0.00001)								
1.3.4 Inactivated vaccines								
Pan 2021	4.8802	0.9285	98	0.6931	0.0003	49	8.4%	5.48 [4.76, 6.21]
Xia 2021	5.6444	0.7574	39	0.6931	0.0001	13	7.5%	7.39 [5.78, 8.99]
Zhang 2021 (Phase 1 14 days apart)	1.6864	0.9602	24	0.6931	0.0001	24	8.5%	1.44 [0.80, 2.08]
Zhang 2021 (Phase 1 28 days apart)	2.9454	0.8648	24	0.8087	0.5232	23	8.3%	2.92 [2.08, 3.77]
Zhang 2021 (Phase 2 14 days apart)	3.1709	0.8255	118	0.6931	0.0004	60	8.6%	3.67 [3.17, 4.16]
Zhang 2021 (Phase 2 28 days apart)	3.7857	0.9251	117	0.7175	0.1338	59	8.6%	4.02 [3.50, 4.55]
Subtotal (95% CI)			**420**			**228**	**49.9%**	**4.05 [2.81, 5.28]**
Heterogeneity: Tau² = 2.19; Chi² = 96.17, df = 5 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 6.43 (P < 0.00001)								
Total (95% CI)			**916**			**578**	**100.0%**	**4.70 [3.55, 5.85]**
Heterogeneity: Tau² = 3.96; Chi² = 409.55, df = 11 (P < 0.00001); I² = 97%								
Test for overall effect: Z = 7.99 (P < 0.00001)								
Test for subgroup differences: Chi² = 86.46, df = 3 (P < 0.00001), I² = 96.5%								



d

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.2.1 Protein subunit vaccines								
Meng 2021 (Phase 1)	4.6827	0.7479	24	2.7413	0.1755	24	15.7%	3.52 [2.59, 4.44]
Song 2022	7.10826	0.88376	85	2.971439	0.4121	53	16.6%	5.56 [4.81, 6.31]
Subtotal (95% CI)			**109**			**77**	**32.2%**	**4.56 [2.55, 6.56]**
Heterogeneity: Tau² = 1.91; Chi² = 11.32, df = 1 (P = 0.0008); I² = 91%								
Test for overall effect: Z = 4.46 (P < 0.00001)								
2.2.2 Virus vector vaccines								
Zhu 2020 (18-44 years old)	4.0642	1.078	80	1.6988	0.4826	77	17.8%	2.80 [2.36, 3.24]
Zhu 2020 (45-54 years old)	4.026	1.3294	32	1.6378	0.1414	35	17.0%	2.56 [1.90, 3.21]
Zhu 2022 (Ad5 vector)	3.8076	1.275	20	1.5848	0.5047	10	15.6%	1.99 [1.06, 2.92]
Subtotal (95% CI)			**132**			**122**	**50.4%**	**2.59 [2.20, 2.99]**
Heterogeneity: Tau² = 0.02; Chi² = 2.45, df = 2 (P = 0.29); I² = 18%								
Test for overall effect: Z = 12.85 (P < 0.00001)								
2.2.3 Inactivated vaccines								
Pan 2021	5.1204	0.7996	98	2.1482	0.6063	49	17.3%	3.99 [3.41, 4.56]
Subtotal (95% CI)			**98**			**49**	**17.3%**	**3.99 [3.41, 4.56]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 13.58 (P < 0.00001)								
Total (95% CI)			**339**			**248**	**100.0%**	**3.41 [2.48, 4.34]**
Heterogeneity: Tau² = 1.22; Chi² = 58.14, df = 5 (P < 0.00001); I² = 91%								
Test for overall effect: Z = 7.17 (P < 0.00001)								
Test for subgroup differences: Chi² = 17.45, df = 2 (P = 0.0002), I² = 88.5%								

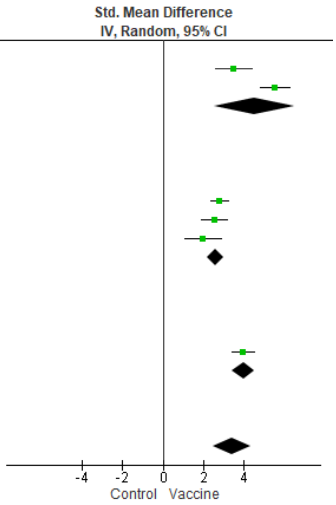


Fig. 3

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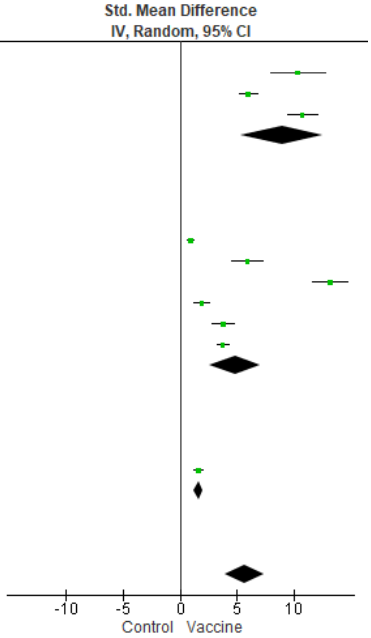
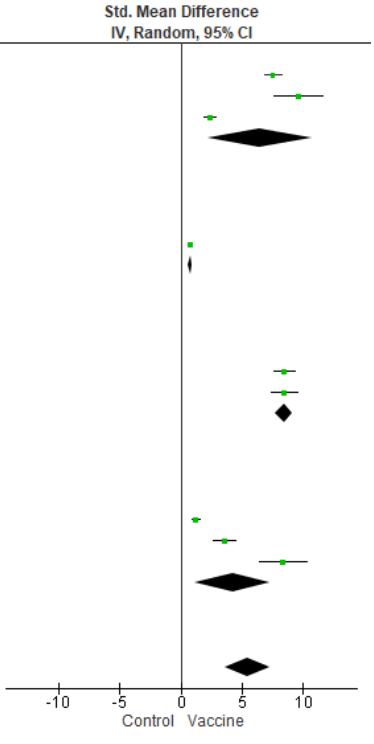
a

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.2.1 Protein subunit vacines								
Liao 2021	8.1051	0.7711	24	1.7562	0.2201	18	8.7%	10.35 [7.94, 12.75]
Shu 2021	8.2588	1.2208	119	1.7516	0.2899	38	10.3%	6.03 [5.26, 6.79]
Song 2022	7.9291	0.5365	85	2.3389	0.4824	53	9.9%	10.76 [9.43, 12.10]
Subtotal (95% CI)			**228**			**109**	**28.8%**	**8.97 [5.36, 12.59]**
Heterogeneity: Tau² = 9.53; Chi² = 42.52, df = 2 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 4.86 (P < 0.00001)								
3.2.2 Inactivated vaccines								
Ella 2021	8.0515	0.6663	99	7.3911	0.74	73	10.4%	0.94 [0.62, 1.26]
Mohraz 2022	2.025	0.6904	24	-2.1203	0.6813	24	9.8%	5.94 [4.58, 7.31]
Pan 2021	4.5689	0.1829	100	2.3216	0.1366	49	9.7%	13.22 [11.66, 14.77]
Zhang 2021 (Phase 1 14 days apart)	6.1438	1.2259	24	4.4398	0.1968	24	10.3%	1.91 [1.22, 2.60]
Zhang 2021 (Phase 1 28 days apart)	7.2124	1.0202	24	4.381	0.0023	23	10.1%	3.82 [2.83, 4.81]
Zhang 2021 (Phase 2 14 days apart)	6.9979	0.838	115	4.3941	0.0931	57	10.4%	3.77 [3.25, 4.28]
Subtotal (95% CI)			**386**			**250**	**60.7%**	**4.83 [2.59, 7.07]**
Heterogeneity: Tau² = 7.57; Chi² = 327.26, df = 5 (P < 0.00001); I² = 98%								
Test for overall effect: Z = 4.23 (P < 0.0001)								
3.2.3 Viral vector vaccine								
Zhu 2020 (18-44 years old)	4.6633	1.424	80	3.0078	0.1197	77	10.4%	1.62 [1.25, 1.98]
Subtotal (95% CI)			**80**			**77**	**10.4%**	**1.62 [1.25, 1.98]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 8.76 (P < 0.00001)								
Total (95% CI)			**694**			**436**	**100.0%**	**5.68 [3.95, 7.42]**
Heterogeneity: Tau² = 7.49; Chi² = 623.49, df = 9 (P < 0.00001); I² = 99%								
Test for overall effect: Z = 6.42 (P < 0.00001)								
Test for subgroup differences: Chi² = 23.13, df = 2 (P < 0.00001), I² = 91.4%								



b

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
4.2.1 Protein subunit vaccines								
Formica 2021	11.0824	0.903	127	4.8197	0.754	135	11.4%	7.53 [6.83, 8.22]
Keech 2020	11.0534	0.7704	29	4.7317	0.4233	21	10.1%	9.59 [7.55, 11.63]
Masuda 2022 (protein subunit)	7.4941	1.107	100	4.9906	0.8394	39	11.5%	2.39 [1.93, 2.86]
Subtotal (95% CI)			**256**			**195**	**33.0%**	**6.43 [2.17, 10.69]**
Heterogeneity: Tau² = 13.78; Chi² = 172.74, df = 2 (P < 0.00001); I² = 99%								
Test for overall effect: Z = 2.96 (P = 0.003)								
4.2.2 Virus vector vaccines								
Folegatti 2020	9.40282	9.32868	482	3.9902	3.96068	485	11.6%	0.76 [0.63, 0.89]
Subtotal (95% CI)			**482**			**485**	**11.6%**	**0.76 [0.63, 0.89]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 11.35 (P < 0.00001)								
4.2.3 Nucleic acid vaccines								
Chu 2021	5.4775	0.3894	95	1.8198	0.4688	92	11.3%	8.47 [7.55, 9.38]
Masuda 2022	5.0304	0.6986	98	-0.4271	0.471	39	11.1%	8.44 [7.36, 9.52]
Subtotal (95% CI)			**193**			**131**	**22.4%**	**8.46 [7.76, 9.15]**
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.98); I² = 0%								
Test for overall effect: Z = 23.76 (P < 0.00001)								
4.2.4 Inactivated vaccines								
Ella 2021	8.6606	0.9305	99	7.6009	0.8126	73	11.5%	1.20 [0.87, 1.52]
Mohraz 2022	4.2544	0.5846	24	-1.1775	2.0432	24	11.2%	3.56 [2.62, 4.49]
Zakarya 2021	10.3394	1.0703	22	3.911	0.0023	22	10.3%	8.34 [6.42, 10.26]
Subtotal (95% CI)			**145**			**119**	**33.0%**	**4.21 [1.13, 7.29]**
Heterogeneity: Tau² = 7.03; Chi² = 70.03, df = 2 (P < 0.00001); I² = 97%								
Test for overall effect: Z = 2.68 (P = 0.007)								
Total (95% CI)			**1076**			**930**	**100.0%**	**5.48 [3.66, 7.29]**
Heterogeneity: Tau² = 7.36; Chi² = 938.72, df = 8 (P < 0.00001); I² = 99%								
Test for overall effect: Z = 5.93 (P < 0.00001)								
Test for subgroup differences: Chi² = 462.82, df = 3 (P < 0.00001), I² = 99.4%								



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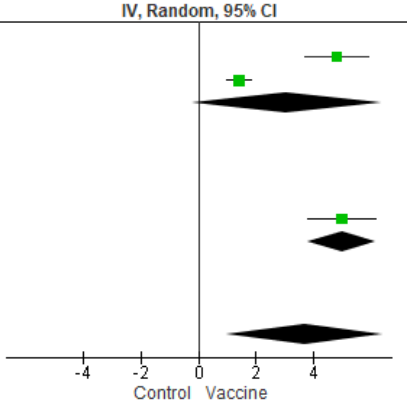
c

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
4.1.1 Protein subunit vaccines								
Keech 2020	9.6368	1.2597	29	4.7057	0.4596	21	32.8%	4.82 [3.69, 5.95]
Ryzhikov 2021	4.3984	0.4531	57	3.907	0.0163	43	34.5%	1.42 [0.98, 1.87]
Subtotal (95% CI)			**86**			**64**	**67.4%**	**3.08 [-0.25, 6.41]**
Heterogeneity: Tau² = 5.58; Chi² = 29.93, df = 1 (P < 0.00001); I² = 97%								
Test for overall effect: Z = 1.81 (P = 0.07)								
4.1.2 Inactivated vaccines								
Mohraz 2022	4.0045	0.9761	24	-0.8179	0.9143	24	32.6%	5.02 [3.83, 6.21]
Subtotal (95% CI)			**24**			**24**	**32.6%**	**5.02 [3.83, 6.21]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 8.26 (P < 0.00001)								
Total (95% CI)			**110**			**88**	**100.0%**	**3.71 [1.01, 6.42]**
Heterogeneity: Tau² = 5.47; Chi² = 53.79, df = 2 (P < 0.00001); I² = 96%								
Test for overall effect: Z = 2.69 (P = 0.007)								
Test for subgroup differences: Chi² = 1.15, df = 1 (P = 0.28), I² = 13.1%								



d

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.3.1 Protein subunit vaccines								
Hernandex-Bernal 2022 (Phase 1)	5.0446	1.3811	22	0.6803	0.0514	22	7.7%	4.39 [3.26, 5.51]
Hernandez-Bernal 2022 (Phase 2)	4.5882	1.6489	151	0.7623	0.4961	153	8.3%	3.14 [2.81, 3.48]
Meng 2021 (Phase 1)	7.1562	1.3875	24	2.9831	0.03	24	7.8%	4.18 [3.14, 5.22]
Meng 2021 (Phase 2)	7.0029	1.5177	99	3.4195	1.9822	79	8.3%	2.05 [1.69, 2.42]
Song 2022	7.6371	0.4762	85	2.5265	0.5265	53	7.5%	10.25 [8.97, 11.52]
Subtotal (95% CI)			**381**			**331**	**39.4%**	**4.71 [2.99, 6.42]**
Heterogeneity: Tau² = 3.62; Chi² = 161.47, df = 4 (P < 0.00001); I² = 98%								
Test for overall effect: Z = 5.38 (P < 0.00001)								
3.3.2 Virus vector vaccines								
Folegatti 2020	8.243563	8.29302381	482	2.9687037	2.80375	485	8.3%	0.85 [0.72, 0.98]
Zhu 2020 (18-44 years old)	6.5512	1.0596	80	3.0078	0.1197	77	8.1%	4.63 [4.03, 5.24]
Zhu 2022 (Ad5 vector)	6.4098	1.038	20	3.1699	0.5467	10	7.6%	3.47 [2.26, 4.67]
Subtotal (95% CI)			**582**			**572**	**24.0%**	**2.97 [0.10, 5.83]**
Heterogeneity: Tau² = 6.26; Chi² = 158.26, df = 2 (P < 0.00001); I² = 99%								
Test for overall effect: Z = 2.03 (P = 0.04)								
3.3.3 Inactivated vaccines								
Pu 2021	7.374	0.4111	23	2.3258	0.0845	12	4.3%	14.54 [10.86, 18.23]
Zhang 2021 (Phase 1 14 days apart)	6.1438	1.1378	24	4.4975	0.3918	24	8.1%	1.90 [1.21, 2.59]
Zhang 2021 (Phase 1 28 days apart)	6.9525	0.8786	24	4.432	0.1184	23	7.8%	3.91 [2.91, 4.92]
Zhang 2021 (Phase 2 14 days apart)	6.96	0.7801	114	4.382	0.0001	60	8.2%	4.06 [3.53, 4.59]
Zhang 2021 (Phase 2 28 days apart)	7.4864	0.8758	117	4.4568	0.4485	59	8.2%	3.97 [3.44, 4.49]
Subtotal (95% CI)			**302**			**178**	**36.5%**	**4.45 [3.06, 5.84]**
Heterogeneity: Tau² = 2.06; Chi² = 62.06, df = 4 (P < 0.00001); I² = 94%								
Test for overall effect: Z = 6.30 (P < 0.00001)								
Total (95% CI)			**1265**			**1081**	**100.0%**	**4.31 [3.21, 5.42]**
Heterogeneity: Tau² = 3.81; Chi² = 759.64, df = 12 (P < 0.00001); I² = 98%								
Test for overall effect: Z = 7.65 (P < 0.00001)								
Test for subgroup differences: Chi² = 1.08, df = 2 (P = 0.58), I² = 0%								

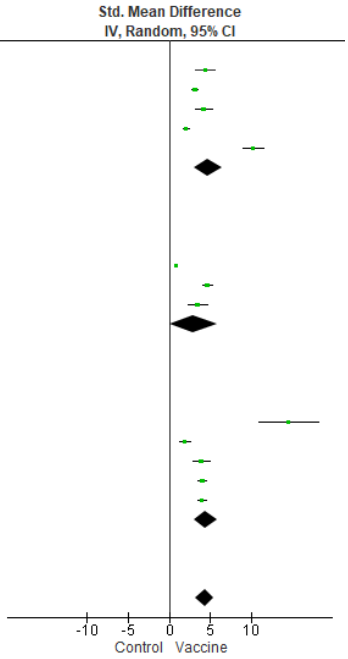


Fig. 4

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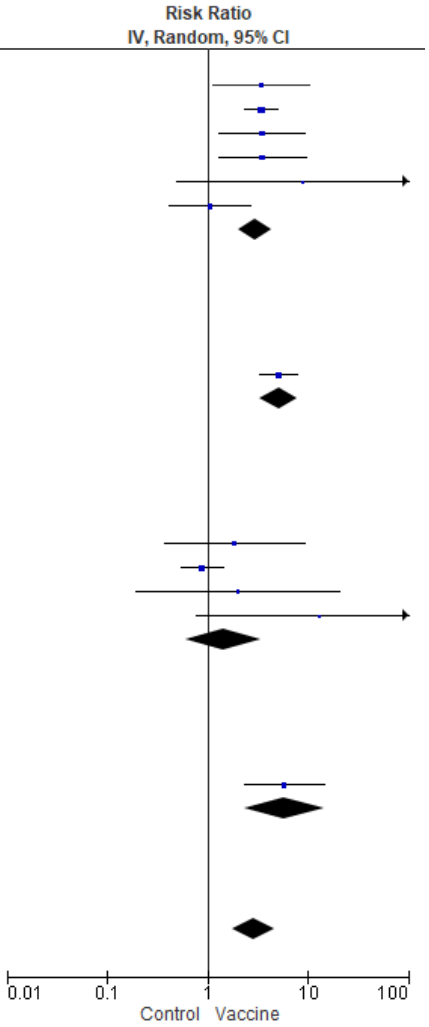
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
1.1.1 Protein subunit vaccines						
Dang 2022a	13	25	3	20	8.4%	3.47 [1.14, 10.51]
Formica 2021a	87	139	25	138	13.8%	3.45 [2.37, 5.04]
Iwata 2022	21	24	3	12	9.2%	3.50 [1.30, 9.43]
Pitisuttithum 2022 (3µg S)	14	35	4	35	9.1%	3.50 [1.28, 9.59]
Ryzhikov 2021	4	43	0	43	2.3%	9.00 [0.50, 162.22]
Shu 2021	16	120	5	40	9.6%	1.07 [0.42, 2.73]
Subtotal (95% CI)		**386**		**288**	**52.4%**	**2.99 [2.05, 4.37]**
Total events	155		40			
Heterogeneity: Tau² = 0.04; Chi² = 5.96, df = 5 (P = 0.31); I² = 16%						
Test for overall effect: Z = 5.66 (P < 0.00001)						
1.1.2 Nucleic acid vaccines						
Chu 2021	87	100	17	100	13.4%	5.12 [3.30, 7.94]
Subtotal (95% CI)		**100**		**100**	**13.4%**	**5.12 [3.30, 7.94]**
Total events	87		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 7.28 (P < 0.00001)						
1.1.3 Inactivated vaccines						
Ella 2021a	5	100	2	75	5.6%	1.88 [0.37, 9.40]
Mohraz 2022	16	24	6	8	13.0%	0.89 [0.54, 1.45]
Pu 2021	2	24	1	24	3.3%	2.00 [0.19, 20.61]
Zakarya 2021	6	22	0	22	2.5%	13.00 [0.78, 217.61]
Subtotal (95% CI)		**170**		**129**	**24.4%**	**1.43 [0.60, 3.41]**
Total events	29		9			
Heterogeneity: Tau² = 0.27; Chi² = 4.30, df = 3 (P = 0.23); I² = 30%						
Test for overall effect: Z = 0.81 (P = 0.42)						
1.1.4 Viral vector vaccines						
Asano 2022	70	96	4	32	9.7%	5.83 [2.31, 14.71]
Subtotal (95% CI)		**96**		**32**	**9.7%**	**5.83 [2.31, 14.71]**
Total events	70		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.74 (P = 0.0002)						
Total (95% CI)		**752**		**549**	**100.0%**	**2.88 [1.78, 4.67]**
Total events	341		70			
Heterogeneity: Tau² = 0.40; Chi² = 38.56, df = 11 (P < 0.0001); I² = 71%						
Test for overall effect: Z = 4.30 (P < 0.0001)						
Test for subgroup differences: Chi² = 8.75, df = 3 (P = 0.03), I² = 65.7%						



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b

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
1.2.1 Protein subunit vaccines						
Dang 2022a	6	25	12	20	11.2%	0.40 [0.18, 0.88]
Formica 2021a	68	139	55	138	19.1%	1.23 [0.94, 1.60]
Iwata 2022	13	24	2	12	6.0%	3.25 [0.87, 12.14]
Shu 2021	11	119	4	40	7.8%	0.92 [0.31, 2.74]
Subtotal (95% CI)		**307**		**210**	**44.1%**	**1.01 [0.50, 2.04]**
Total events	98		73			
Heterogeneity: Tau² = 0.33; Chi² = 9.71, df = 3 (P = 0.02); I² = 69%						
Test for overall effect: Z = 0.04 (P = 0.97)						
1.2.2 Nucleic acid vaccines						
Chu 2021	52	100	30	100	17.8%	1.73 [1.22, 2.47]
Subtotal (95% CI)		**100**		**100**	**17.8%**	**1.73 [1.22, 2.47]**
Total events	52		30			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.05 (P = 0.002)						
1.2.3 Inactivated vaccines						
Ella 2021a	14	100	7	75	10.3%	1.50 [0.64, 3.53]
Mohraz 2022	13	24	5	8	13.1%	0.87 [0.45, 1.66]
Pu 2021	0	24	2	24	1.5%	0.20 [0.01, 3.96]
Zakarya 2021	1	22	0	22	1.4%	3.00 [0.13, 69.87]
Subtotal (95% CI)		**170**		**129**	**26.2%**	**1.04 [0.63, 1.72]**
Total events	28		14			
Heterogeneity: Tau² = 0.00; Chi² = 2.61, df = 3 (P = 0.46); I² = 0%						
Test for overall effect: Z = 0.14 (P = 0.89)						
1.2.4 Viral vector vaccines						
Asano 2022	65	96	6	32	11.9%	3.61 [1.73, 7.53]
Subtotal (95% CI)		**96**		**32**	**11.9%**	**3.61 [1.73, 7.53]**
Total events	65		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.43 (P = 0.0006)						
Total (95% CI)		**673**		**471**	**100.0%**	**1.30 [0.89, 1.91]**
Total events	243		123			
Heterogeneity: Tau² = 0.18; Chi² = 24.37, df = 9 (P = 0.004); I² = 63%						
Test for overall effect: Z = 1.36 (P = 0.17)						
Test for subgroup differences: Chi² = 9.33, df = 3 (P = 0.03), I² = 67.8%						

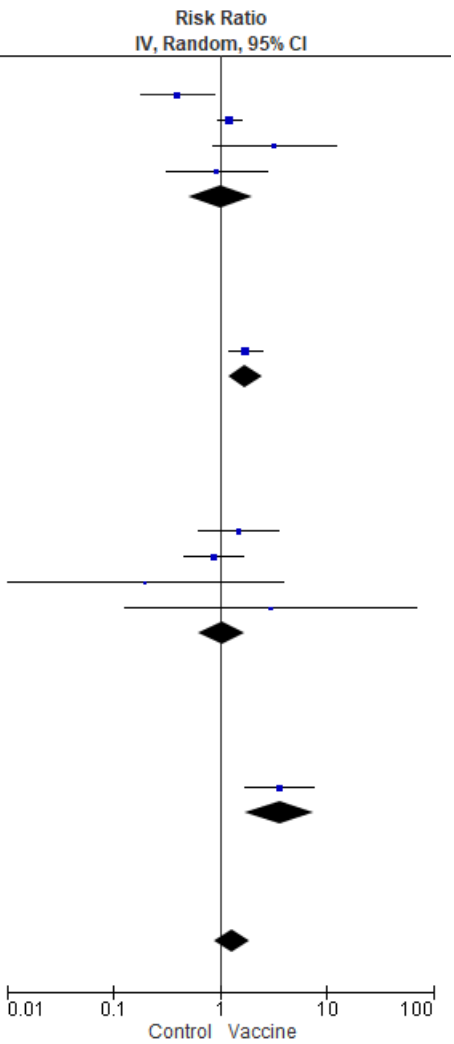

Fig. 5

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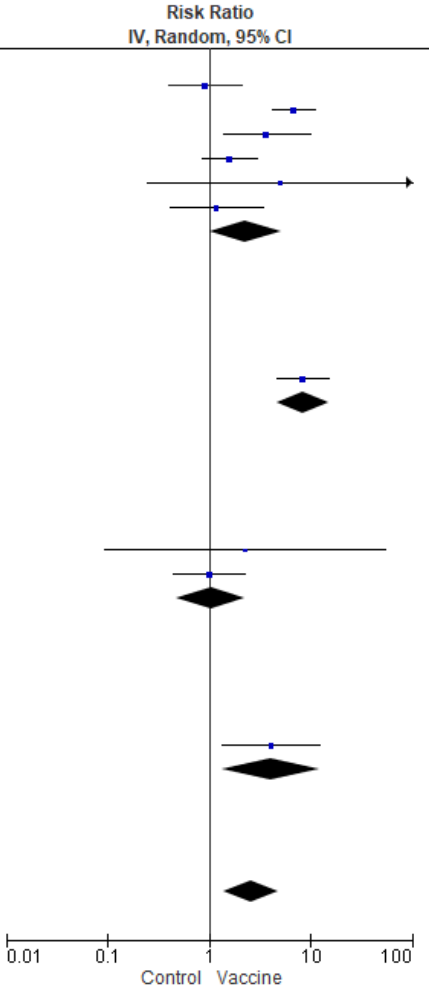
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
2.1.1 Protein subunit vaccines						
Dang 2022b	8	25	7	20	11.6%	0.91 [0.40, 2.09]
Formica 2021b	105	137	15	132	13.4%	6.74 [4.15, 10.96]
Iwata 2022	22	24	3	12	10.7%	3.67 [1.37, 9.84]
Pitisuttithum 2022 (3µg S)	16	35	10	35	12.7%	1.60 [0.85, 3.02]
Ryzhikov 2021	2	43	0	43	3.4%	5.00 [0.25, 101.18]
Shu 2021	14	119	4	40	10.4%	1.18 [0.41, 3.37]
Subtotal (95% CI)		**383**		**282**	**62.2%**	**2.29 [1.03, 5.12]**
Total events	167		39			
Heterogeneity: Tau² = 0.72; Chi² = 25.63, df = 5 (P = 0.0001); I² = 80%						
Test for overall effect: Z = 2.02 (P = 0.04)						
2.1.2 Nucleic acid vaccines						
Chu 2021	89	99	10	94	12.9%	8.45 [4.69, 15.24]
Subtotal (95% CI)		**99**		**94**	**12.9%**	**8.45 [4.69, 15.24]**
Total events	89		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 7.09 (P < 0.00001)						
2.1.3 Inactivated vaccines						
Ella 2021	1	100	0	75	3.1%	2.26 [0.09, 54.65]
Mohraz 2022	12	24	4	8	11.8%	1.00 [0.45, 2.23]
Subtotal (95% CI)		**124**		**83**	**14.9%**	**1.05 [0.48, 2.28]**
Total events	13		4			
Heterogeneity: Tau² = 0.00; Chi² = 0.24, df = 1 (P = 0.63); I² = 0%						
Test for overall effect: Z = 0.12 (P = 0.90)						
2.1.4 Viral vector vaccines						
Asano 2022	37	96	3	32	10.1%	4.11 [1.36, 12.43]
Subtotal (95% CI)		**96**		**32**	**10.1%**	**4.11 [1.36, 12.43]**
Total events	37		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.50 (P = 0.01)						
Total (95% CI)		**702**		**491**	**100.0%**	**2.61 [1.38, 4.90]**
Total events	306		56			
Heterogeneity: Tau² = 0.72; Chi² = 44.86, df = 9 (P < 0.00001); I² = 80%						
Test for overall effect: Z = 2.97 (P = 0.003)						
Test for subgroup differences: Chi² = 18.99, df = 3 (P = 0.0003), I² = 84.2%						



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b

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
2.2.1 Protein subunit vaccines						
Dang 2022b	7	25	5	20	9.0%	1.12 [0.42, 3.00]
Formica 2021b	88	137	42	132	36.6%	2.02 [1.53, 2.67]
Iwata 2022	19	24	2	12	5.8%	4.75 [1.32, 17.11]
Shu 2021	11	119	1	40	2.5%	3.70 [0.49, 27.75]
Subtotal (95% CI)		**305**		**204**	**53.9%**	**2.05 [1.39, 3.02]**
Total events	125		50			
Heterogeneity: Tau² = 0.03; Chi² = 3.43, df = 3 (P = 0.33); I² = 13%						
Test for overall effect: Z = 3.61 (P = 0.0003)						
2.2.2 Nucleic acid vaccines						
Chu 2021	78	99	23	94	30.5%	3.22 [2.23, 4.66]
Subtotal (95% CI)		**99**		**94**	**30.5%**	**3.22 [2.23, 4.66]**
Total events	78		23			
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.20 (P < 0.00001)						
2.2.3 Inactivated vaccines						
Ella 2021	1	100	0	75	1.0%	2.26 [0.09, 54.65]
Subtotal (95% CI)		**100**		**75**	**1.0%**	**2.26 [0.09, 54.65]**
Total events	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.50 (P = 0.62)						
2.2.4 Viral vector vaccines						
Asano 2022	30	96	7	32	14.6%	1.43 [0.70, 2.93]
Subtotal (95% CI)		**96**		**32**	**14.6%**	**1.43 [0.70, 2.93]**
Total events	30		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.97 (P = 0.33)						
Total (95% CI)		**600**		**405**	**100.0%**	**2.24 [1.61, 3.11]**
Total events	234		80			
Heterogeneity: Tau² = 0.06; Chi² = 9.18, df = 6 (P = 0.16); I² = 35%						
Test for overall effect: Z = 4.83 (P < 0.00001)						
Test for subgroup differences: Chi² = 5.08, df = 3 (P = 0.17), I² = 40.9%						

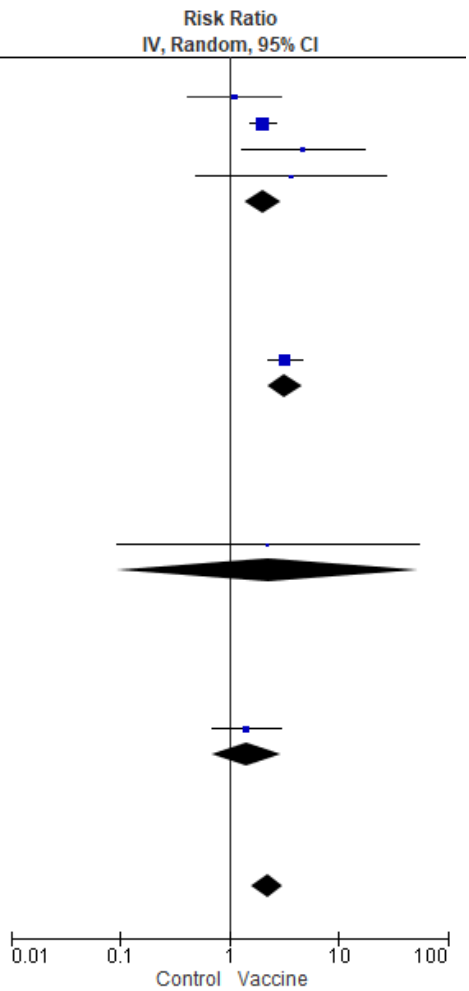

Fig. 6

a

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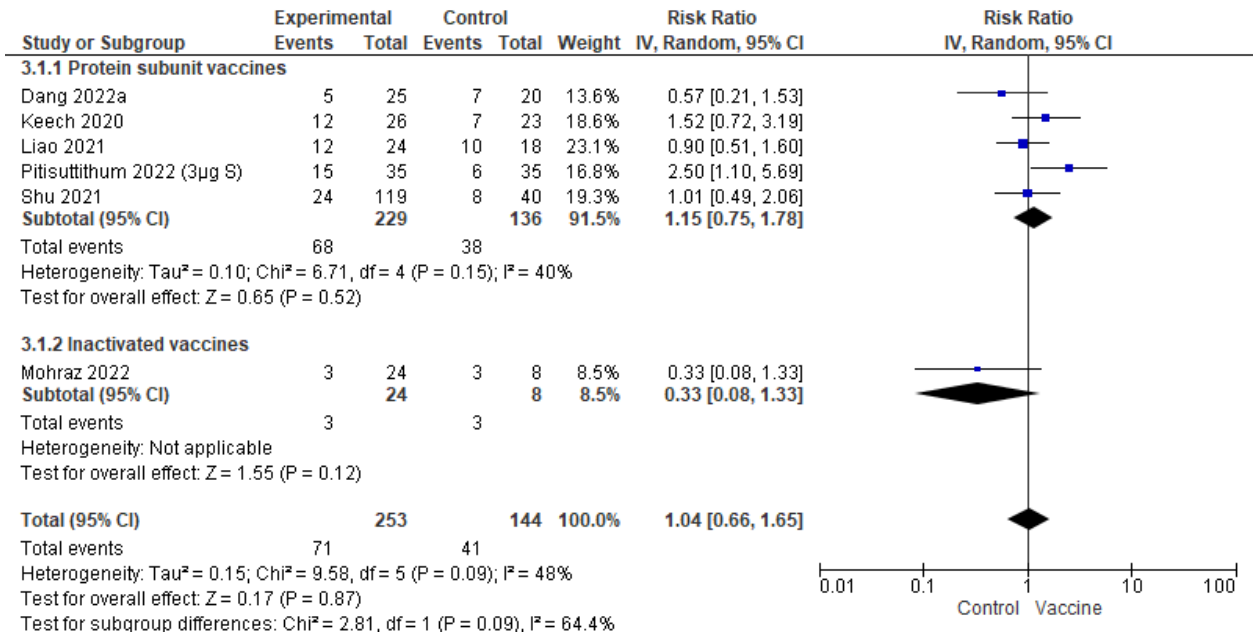

b

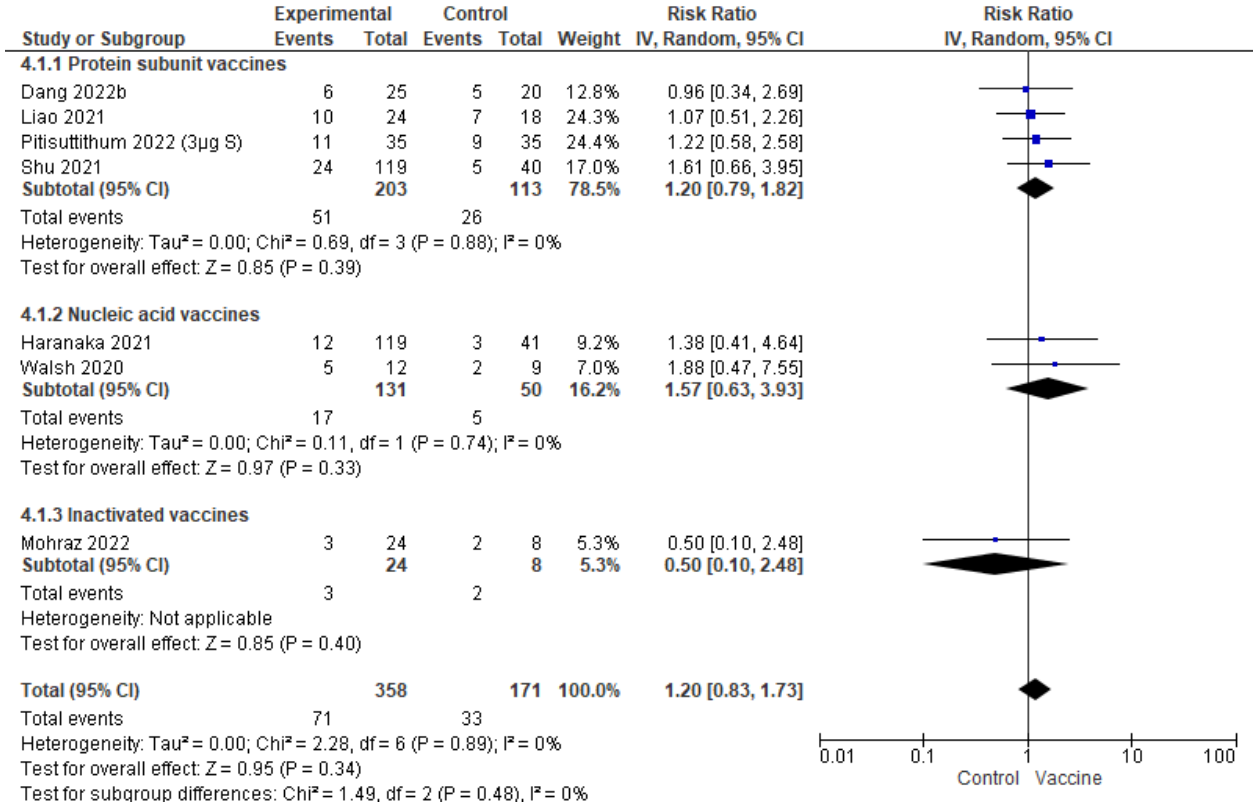

Fig. 7

a

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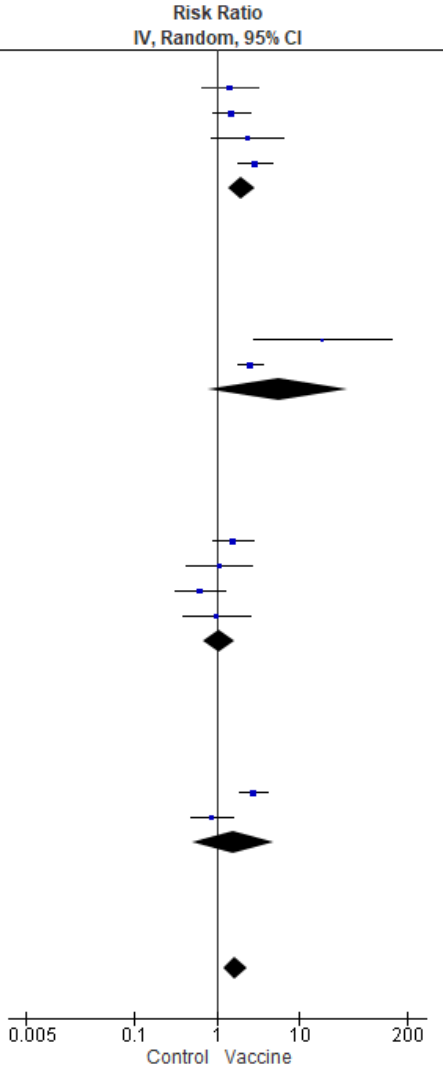
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
5.1.1 Protein subunit vaccines						
Meng 2021 (Phase 1)	10	24	7	24	7.6%	1.43 [0.65, 3.13]
Meng 2021 (Phase 2)	30	100	16	80	9.9%	1.50 [0.88, 2.55]
Yang 2021 (Phase 1)	14	20	3	10	6.1%	2.33 [0.87, 6.27]
Yang 2021 (Phase 2)	55	150	19	150	10.5%	2.89 [1.81, 4.63]
Subtotal (95% CI)		**294**		**264**	**34.1%**	**2.00 [1.37, 2.94]**
Total events	109		45			
Heterogeneity: Tau² = 0.05; Chi² = 4.29, df = 3 (P = 0.23); I² = 30%						
Test for overall effect: Z = 3.56 (P = 0.0004)						
5.1.2 Nucleic acid vaccines						
Chen 2022	19	20	1	20	2.4%	19.00 [2.81, 128.69]
Masuda 2022	144	150	19	50	11.6%	2.53 [1.77, 3.60]
Subtotal (95% CI)		**170**		**70**	**14.0%**	**5.52 [0.80, 37.86]**
Total events	163		20			
Heterogeneity: Tau² = 1.54; Chi² = 4.13, df = 1 (P = 0.04); I² = 76%						
Test for overall effect: Z = 1.74 (P = 0.08)						
5.1.3 Inactivated vaccines						
Che 2021	41	150	13	75	9.6%	1.58 [0.90, 2.76]
Guo 2021 (21 days apart)	16	84	5	28	6.6%	1.07 [0.43, 2.65]
Guo 2021 (28 days apart)	17	84	9	28	8.5%	0.63 [0.32, 1.25]
Xia 2021	15	84	5	28	6.6%	1.00 [0.40, 2.50]
Subtotal (95% CI)		**402**		**159**	**31.3%**	**1.05 [0.68, 1.62]**
Total events	89		32			
Heterogeneity: Tau² = 0.06; Chi² = 4.17, df = 3 (P = 0.24); I² = 28%						
Test for overall effect: Z = 0.21 (P = 0.83)						
5.1.4 Viral vector vaccines						
Sadoff 2021 (Cohort 1a)	115	152	21	77	11.4%	2.77 [1.91, 4.04]
Sadoff 2021 (Cohort 1b)	7	10	4	5	9.3%	0.88 [0.48, 1.59]
Subtotal (95% CI)		**162**		**82**	**20.7%**	**1.60 [0.52, 4.94]**
Total events	122		25			
Heterogeneity: Tau² = 0.60; Chi² = 10.27, df = 1 (P = 0.001); I² = 90%						
Test for overall effect: Z = 0.81 (P = 0.42)						
Total (95% CI)		**1028**		**575**	**100.0%**	**1.68 [1.21, 2.34]**
Total events	483		122			
Heterogeneity: Tau² = 0.21; Chi² = 36.75, df = 11 (P = 0.0001); I² = 70%						
Test for overall effect: Z = 3.10 (P = 0.002)						
Test for subgroup differences: Chi² = 6.48, df = 3 (P = 0.09), I² = 53.7%						



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b

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
5.2.1 Protein subunit vaccines						
Meng 2021 (Phase 1)	15	24	15	24	10.8%	1.00 [0.65, 1.55]
Meng 2021 (Phase 2)	41	100	23	80	11.4%	1.43 [0.94, 2.16]
Yang 2021 (Phase 1)	14	20	6	10	7.3%	1.17 [0.65, 2.09]
Yang 2021 (Phase 2)	72	150	47	150	16.7%	1.53 [1.15, 2.05]
Subtotal (95% CI)		**294**		**264**	**46.2%**	**1.34 [1.10, 1.63]**
Total events	142		91			
Heterogeneity: Tau² = 0.00; Chi² = 2.84, df = 3 (P = 0.42); I² = 0%						
Test for overall effect: Z = 2.92 (P = 0.003)						
5.2.2 Inactivated vaccines						
Che 2021	41	150	14	75	8.1%	1.46 [0.85, 2.51]
Guo 2021 (21 days apart)	21	84	8	28	5.5%	0.88 [0.44, 1.75]
Guo 2021 (28 days apart)	25	84	12	28	8.1%	0.69 [0.40, 1.19]
Pan 2021	25	100	11	50	6.6%	1.14 [0.61, 2.12]
Xia 2021	15	84	6	28	4.0%	0.83 [0.36, 1.94]
Zhang 2021 (14 days apart)	47	144	15	84	8.7%	1.83 [1.09, 3.06]
Zhang 2021 (28 days apart)	26	144	14	83	7.1%	1.07 [0.59, 1.93]
Subtotal (95% CI)		**790**		**376**	**48.2%**	**1.11 [0.85, 1.46]**
Total events	200		80			
Heterogeneity: Tau² = 0.04; Chi² = 8.42, df = 6 (P = 0.21); I² = 29%						
Test for overall effect: Z = 0.77 (P = 0.44)						
5.2.3 Viral vector vaccines						
Asano 2022	27	96	3	32	2.4%	3.00 [0.98, 9.23]
Zhu 2022	11	51	4	12	3.2%	0.65 [0.25, 1.68]
Subtotal (95% CI)		**147**		**44**	**5.6%**	**1.35 [0.30, 6.07]**
Total events	38		7			
Heterogeneity: Tau² = 0.89; Chi² = 4.15, df = 1 (P = 0.04); I² = 76%						
Test for overall effect: Z = 0.39 (P = 0.69)						
Total (95% CI)		**1231**		**684**	**100.0%**	**1.21 [1.01, 1.45]**
Total events	380		178			
Heterogeneity: Tau² = 0.03; Chi² = 16.72, df = 12 (P = 0.16); I² = 28%						
Test for overall effect: Z = 2.03 (P = 0.04)						
Test for subgroup differences: Chi² = 1.21, df = 2 (P = 0.55), I² = 0%						

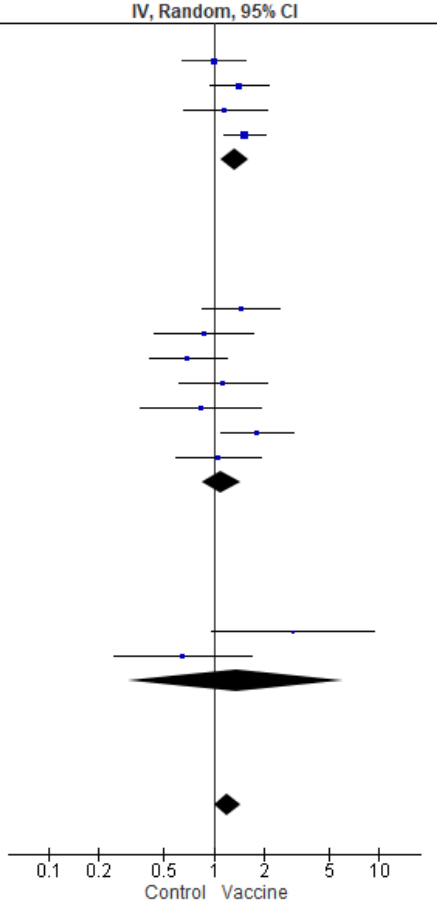

Fig. 8

Figure captions

Fig 1. PRISMA diagram showing study selection process.

Fig 2. (a) Risk of bias rating for each study and (b) risk of bias rating for each domain across all studies.

Fig. 3 (a) Forest plot for meta-analysis of log-transformed neutralising antibody levels 7 days after COVID-19 vaccination (measured using live virus neutralisation assays). (b) Forest plot for meta-analysis of log-transformed neutralising antibody levels 14 days after COVID-19 vaccination (measured using live virus neutralisation assays). (c) Forest plot for meta-analysis of log-transformed neutralising antibody levels 28 days after COVID-19 vaccination (measured

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using live virus neutralisation assays). (d) Forest plot for meta-analysis of log-transformed neutralising antibody levels 28 days after COVID-19 vaccination (measured using pseudo-neutralising antibody assays)

Fig. 4 (a) Forest plot for meta-analysis of log-transformed anti-RBD IgG levels 14 days after COVID-19 vaccination. (b) Forest plot for meta-analysis of log-transformed anti-S IgG levels 14 days after COVID-19 vaccination. (c) Forest plot for meta-analysis of log-transformed anti-S IgG levels 7 days after COVID-19 vaccination. (d) Forest plot for meta-analysis of log-transformed anti-RBD IgG levels 28 days after COVID-19 vaccination

Fig. 5 (a) Forest plot for meta-analysis of local adverse events after 7 days of the first COVID-19 vaccine dose. (b) Forest plot for meta-analysis of systemic adverse events after 7 days of first COVID-19 vaccine dose.

Fig. 6 (a) Forest plot for meta-analysis of local adverse events after 7 days of the second COVID-19 vaccine dose. (b) Forest plot for meta-analysis of systemic adverse events after 7 days of the second COVID-19 vaccine dose.

Fig. 7 (a) Forest plot for meta-analysis of any adverse events after 1 month of the first COVID-19 vaccine dose. (b) Forest plot for meta-analysis of any adverse events after 1 month of the second COVID-19 vaccine dose.

Fig. 8 (a) Forest plot for meta-analysis for overall adverse events within 7 days post COVID-19 vaccination. (b) Forest plot for meta-analysis for overall adverse events within 1 month post COVID-19 vaccination