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Review article

Immunogenicity and safety of adjuvant-associated COVID-19 vaccines: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Background: The benefits and risks of adjuvant-associated COVID-19 vaccines (ACVs) are unclear. The study aimed to assess the immunogenicity and safety of ACVs compared with controls (placebo or the same vaccine without adjuvants [NACVs]).

Methods: Randomized controlled trials sourced from PubMed, EMBASE, Web of Science, and Cochrane Library were systematically reviewed. Evaluators extracted information independently. The evidence quality was assessed using random-effects models. The risk of bias was assessed using the Cochrane Risk of Bias tool.

Results: Of the 33 studies, 27 analyzed immunogenicity (n = 9069, ACVs group; n = 3757, control), and 26 analyzed safety (n = 58669, ACVs groups; n = 30733 control). Compared with controls, full vaccination with ACVs produced significant immune responses (relative risk [RR] of seroneutralization reaction, 12.3; 95 % confidence interval [95 % CI], 6.92–21.89; standardized mean deviation of geometric mean titer 3.96, 95 % CI, 3.35–4.58). Additionally, ACVs produced significant immunoreactivity compared with NACVs only ($P < 0.05$). Furthermore, full vaccination with ACVs significantly increased the risk of local and systemic adverse reactions (AEs) compared with controls. However, vaccination with ACVs did not significantly increase the risk of systemic and localized AEs compared with vaccination with NACVs only ($P > 0.05$). It was observed that ACVs had a lower risk of all-cause mortality than controls (RR, 0.51; 95 % CI 0.30–0.87). It was further found that ACVs produced nAb response against all sublines of the Omicron variant, but the antibody titers were lower than those for the SARS-CoV-2 original strain.

Conclusions: The findings of this meta-analysis demonstrate that ACVs may have a superior effect and an acceptable safety in preventing COVID-19. Although these results suggest the potential of ACVs, further studies are required.

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1. Introduction

The emergence of SARS-CoV-2 and the resulting coronavirus disease (COVID-19) pandemic has led to the development of various COVID-19 vaccines for the prevention and control of the disease [1–3]. Despite the effectiveness of current vaccines, the constant evolution of the virus poses a significant threat to public health [4,5]. Adjuvants have been identified as a promising strategy to improve vaccine efficacy by promoting, improving, and maintaining the immune response to the vaccine antigen [6–9]. Previous experiences with influenza and malaria vaccines have demonstrated the importance of adjuvants during pandemics and their potential to accelerate vaccine development [10,11].

Currently, several adjuvants, including AS03 [6,12], MF59 [13], CpG1018 [14–16], Matrix-M [17], and Alum, among others, are licensed or under clinical evaluation as potential SARS-CoV-2 vaccines. Nevertheless, a comprehensive systematic review or meta-analysis regarding the immunogenicity and safety of adjuvant COVID-19 vaccines (ACVs) is presently lacking.

Therefore, this study aimed to provide a comprehensive evaluation of the efficacy and safety of ACVs based on existing randomized controlled trials. The findings of this study may provide further insight into understanding the immunogenicity and safety of the

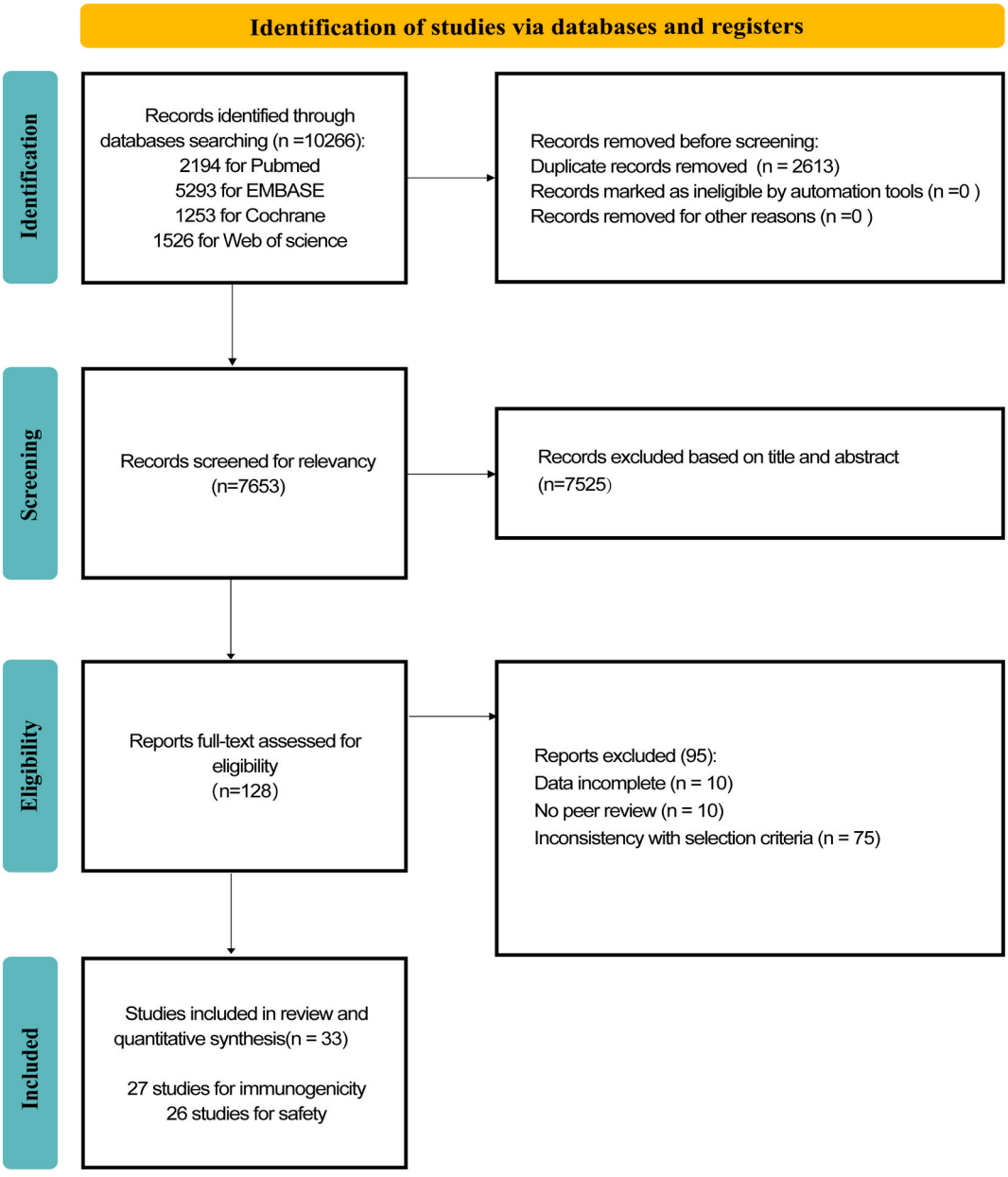

Fig. 1. Flow chart of the literature search.

various ACVs, offering reliable evidence for the development and optimization of COVID-19 vaccines.

2. Methods

2.1. The search strategy and selection criteria

This systematic review adhered to the guidelines established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [18]. As of August 14, 2023, a systematic search was performed in PubMed, Embase, Cochrane Library, and Web of Science databases, using MeSH terms and free words. Search terms included ("COVID-19" or "SARS-CoV-2"), ("adjuvanted vaccine" or "vaccination"), and ("immunogenicity" or "safety"). For more details on the search strategy, please refer to the supplementary material.

Two investigators (CMQ and LR) screened the literature independently, and discrepancies were resolved via discussion with a third investigator (SG, or WZY). Fig. 1 illustrates the process of research screening. The following inclusion criteria were established: (1) only RCTs were included to assess the immunogenicity or safety of full or boost vaccination using ACVs (2) all controls contained a placebo arm (e.g., saline, PBS, etc.); or the same vaccine as the intervention group without the adjuvants (non-adjuvanted COVID-19 vaccines [NACVs]); and (3) specific data for all results were available and confirmed by laboratory examinations. Unpublished, non-peer-reviewed, and non-English articles were excluded.

2.2. Data extraction

Using a pre-designed form, two investigators (CMQ and LR) independently extracted the data. Disagreements were resolved through discussions with the corresponding authors. If the doses of ACVs varied across multiple groups, only groups with the same dose as that of the NACVs groups were included. If two or more ACVs intervention groups in the same study met the inclusion criteria, the groups with more complete data were included. The graphic digitizing software GetData (version 2.20) is used to extract original data presented in graphic form.

2.3. Outcomes

The main objectives of the study were to 1) identify differences in neutralizing antibody responses (nAb) or geometric mean titers (GMT) after full or boost vaccination with ACVs compared with the control (or NACVs) group and 2) identify differences in local or systemic adverse events (AEs) after full or boost vaccination with ACVs compared with the control (or NACVs) group. We expressed dichotomous outcomes as relative risk (RR), with 95 % confidence intervals (CIs), whereas continuous data were expressed as standardized mean deviations (SMDs) after transformation by natural logarithms (Ln). AEs were evaluated as local and systemic adverse reactions and expressed as RR of dichotomous variables. In addition, serious AEs (grade $\geq$3) and all-cause mortality outcome indicators were included.

2.4. Risk of bias assessment

Two assessors (SG and CMQ) independently evaluated the risk of bias in the articles using the Cochrane Risk of Bias tool. Disagreements were resolved through discussions with the corresponding author (WZY). The following seven domains were addressed: random sequence generation, allocation concealment, participant and investigator blinding, outcome assessment blinding, incomplete outcome data, selective reporting, and other biases [19,20].

2.5. Data analysis and synthesis

Outcomes were combined using DerSimonian and Laird random effects model [21]. A continuity correction of 0.5 was used in case of zero events in one group. Missing standard deviations (SD) were calculated for each group based on the confidence interval and sample size. Heterogeneity was assessed using the Q-statistic and I^2 test [22]. Significant heterogeneity was indicated by $P_h < 0.1$ or I^2>50 %. Subgroup analyses that took into consideration adjuvant types, vaccine types, study design, number of centers, and control group types were performed. Possible sources of heterogeneity in eligible studies were investigated by subgroup analysis. Sensitivity analyses were performed on >10 included studies to determine the impact of individual studies on the pooled assessments. $P < 0.05$ was considered statistically significant, and statistical analyses were performed using Stata version 17.0.

3. Results

3.1. The search results and risk of bias

A total of 10,266 records were retrieved from the databases. After screening the titles and abstracts, we identified 128 studies that potentially met the eligibility criteria and obtained the full-text reports of these studies. Among them, 33 studies were included in the final analysis. Additionally, 27 studies quantified the immunogenicity [12–14,16,17,23–44] and 26 studies assessed the safety [12,14–17,24–26,28–35,37,38,40–42,45–49] of ACVs (Table 1). Furthermore, Fig. S1 presents the risk of bias assessment for individual

studies. Of the 33 trials, 6 had a high risk of bias, 16 had some concerns regarding bias, and 11 had a low risk of bias (Table S1).

3.2. Comparison of nAb response between ACVs and controls

In 23 studies [12–14,16,23–28,30–36,38–42] comprising 8568 ACVs and 3568 controls, nAb data were described for aluminum (n = 5), Complex (n = 5), Matrix-M (n = 3), squalene oil-in-water (n = 7), TLR-9 agonist (n = 1), and others adjuvants (n = 2) (Tables S2–S3). Of these, 6 studies had a control group receiving NACVs while the remaining 17 had a placebo group. A significantly increased risk of nAb after ACVs vaccination compared with controls (RR, 11.26; 95 % CI, 6.50–19.51) was observed. However, there was a high degree of heterogeneity (I^2 = 95.87 %) between studies (Table S3). Subgroup analysis showed significant differences between adjuvant types and control group types ($P < 0.05$). For adjuvant types, nAbs were relatively higher for Alum-adjuvants (RR, 41.55; 95 % CI, 5.68–303.66) and lower for TLR-9 agonist adjuvants (RR, 1.14; 95 % CI, 0.95–303.66). Regarding control group types, there was a significant nAb response to ACVs compared with the NACVs group (RR, 2.05; 95 % CI, 1.30–3.22) (Table 2). Subgroup analysis showed a significant elevation of nAb response to the squalene oil-in-water adjuvant (RR, 2.54; 95 % CI, 1.57–4.10) (Fig. 2 A).

3.3. Comparison of GMT of nAbs between ACVs and controls

In 23 studies [12–14,17,23–30,32–39,41–44] comprising 8731 ACVs and 3569 controls (Table 3), GMT data were described for aluminum (n = 5), Complex (n = 4), Matrix-M (n = 5), squalene oil-in-water (n = 7), TLR-9 agonist (n = 1), and others adjuvants (n = 1). Of these, 5 studies had a control group receiving NACVs while the remaining 13 had a placebo group. A significantly increased GMT after ACVs vaccination compared with controls (RR, 3.61; 95 % CI, 3.04–4.19) was observed. However, there was a high degree of heterogeneity (I^2 = 98.59 %) between studies. Subgroup analyses showed significant differences between adjuvant type, number of doses, and control type ($P < 0.05$). Regarding adjuvant type, all adjuvants except TLR-9 agonist (RR, 0.23; 95 % CI, −0.12–0.58) and other adjuvants (RR, 0.38; 95 % CI, −0.25–1.00) showed relatively high GMT of nAbs. Regarding the number of doses, vaccination with three doses produced higher GMT of nAbs (RR, 7.60; 95 % CI, 6.43–8.76). Regarding control group types, a significant GMT of nAbs to ACVs was observed compared with the NACVs group (RR, 2.53; 95 % CI, 1.38–3.67). A significant elevation of GMT of nAbs was observed for the squalene oil-in-water adjuvant (Fig. 2B).

3.4. nAb response to the SARS-CoV-2 original and Omicron variant

Herein, four studies [12,17,23,32] that investigated the Omicron variant were analyzed. However, none of the studies had a control group. The results showed that ACVs produced nAb response against all sublines of the Omicron variant, but the antibody titers were lower than those for the SARS-CoV-2 original strain (Table S4).

3.5. Comparison of risk of local AEs between ACVs and controls

In 21 studies [12,14–17,24,26,28–30,33,34,37,38,40–42,45–47,49] comprising 55531 ACVs and 28530 controls, local AEs data were described for aluminum (n = 2), Complex (n = 5), Matrix-M (n = 7), squalene oil-in-water (n = 5), and TLR-9 agonist (n = 2) (Tables S5–S6). Of these, 3 studies had a control group receiving NACVs, while the remaining 18 had a placebo group. A significantly

Table 1
Summary of the number of studies on the immunogenicity and safety of ACVs.

Adjuvant types	Adjuvant-Vaccine types	No. of doses	No. of studies for immunogenicity	No. of studies for safety
Total			27	26
Aluminum adjuvant				
	Alum-Inactivated Virus	2	4	3
	Alum-Protein subunit	2	1	1
Squalene-oil-in-water adjuvant				
	AS03-Virus like particle	2	2	3
	AS03-Protein subunit	2	3	1
	MF59-Protein subunit	2	1	0
	a-910823-Protein subunit	2	1	1
Matrix-M adjuvant				
	Matrix-M1-Protein subunit	2	5	7
TLR-9 agonist adjuvant				
	CpG1018-Inactivated Virus	2	2	2
Complex adjuvant				
	CpG 1018/Alum-Protein subunit	2	3	4
	CpG55.2™/Advax-Protein subunit	2/3	2	3
	CpG ODN/Alum-Protein subunit	3	1	0
Others adjuvants				
	OMV-Protein subunit	2	1	0
	corpuscular adjuvant-Protein subunit	2	1	1

Note : ACVs: adjuvant-associated COVID-19 vaccines; OMV, outer membrane vesicle.

Table 2
Subgroup analysis of neutralizing antibody response to ACVs inoculation compared with controls.

Subgroup	No. of studies	Reactions/total				RR (95 % CI)	Heterogeneity I^2 (%)	Test of group differences (p value)
		ACVs (n)	ACVs (N)	Control (n)	Control (N)			
Overall	23	8218	8568	376	3568	11.26 (6.50–19.51)	95.87 %	
Adjuvant types								< 0.001
Aluminum adjuvants	5	3616	3730	144	938	41.55 (5.68, 303.66)	87.54 %	
Complex adjuvant	5	1534	1670	26	310	23.77 (3.56, 158.73)	80.88 %	
Matrix-M adjuvant	3	2072	2127	118	1967	24.00 (8.79, 65.55)	35.90 %	
Squalene-oil-in-water adjuvant	7	944	964	57	276	6.09 (2.93, 12.64)	80.56 %	
TLR-9 agonist adjuvant	1	24	25	21	25	1.14 (0.95, 1.38)	NA	
Other adjuvants	2	28	52	10	52	2.74 (1.43, 5.25)	7.45 %	
Age								0.68
< 18	1	47	56	0	11	41.55 (5.68, 303.66)	NA	
≥18	22	8171	8512	376	3557	20.00 (1.32, 302.37)	96.05 %	
Vaccine types								0.66
Inactivated Virus	5	2811	2884	163	822	7.66 (2.55, 22.96)	96.98 %	
Protein subunit	16	4871	5141	185	2594	14.19 (6.70, 30.06)	93.83 %	
Virus like particle	2	536	543	28	152	12.40 (0.33, 470.12)	92.70 %	
Study design								0.72
single-blind	11	6325	6501	339	3079	12.86 (5.63, 29.37)	71.86 %	
double-blind	12	1893	2067	37	489	10.46 (4.87, 22.43)	97.97 %	
Days of immunoassay after the last vaccination								0.28
< 28	18	6235	6489	370	3208	2.24 (1.64, 2.84)	96.59 %	
≥28	5	1983	2079	6	360	3.47 (1.33, 5.61)	84.43 %	
no.of centers								0.63
Single-center	10	1077	1235	52	437	9.21 (3.93, 21.57)	88.37 %	
Multicenter	13	7141	7333	324	3131	12.04 (6.16, 23.54)	95.95 %	
Phase								0.47
< 3	19	5234	5428	233	2785	11.66 (5.83, 23.32)	96.51 %	
≥3	4	2984	3140	143	783	25.23 (3.51, 181.21)	80.11 %	
No. of doses								0.33
2	22	8067	8369	375	3529	10.83 (6.19, 18.94)	96.02 %	
3	1	151	199	1	39	29.59 (4.27, 205.16)	NA	
Control group types								< 0.001
NACVs	6	385	409	81	195	2.05 (1.30, 3.22)	83.56 %	
Placebo group	17	7833	8159	295	3373	20.99 (11.19, 39.39)	92.53 %	

Note: ACVs, adjuvant-associated COVID-19 vaccines; NACVs, Non-adjuvanted vaccine group; n, no. of neutralization reactions; N, Total number of vaccinations; RR, relative risk; CI, confidence interval; nAb, neutralizing antibody; NA, Not available.

increased risk of local AEs after two or three doses of ACVs compared with controls (RR, 3.26; 95 % CI, 2.76–3.84) was observed. However, a high degree of heterogeneity ($I^2 = 96.59$ %) was observed between studies (Table S6). Subgroup analyses showed significant differences in the adjuvant types ($P < 0.05$). Regarding adjuvant types, the risk of developing local AEs was relatively low for TLR-9 agonists (RR, 1.39; 95 % CI 1.03–1.88), whereas it was relatively high for the remaining ACVs. Notably, vaccination with ACVs did not result in significant local AEs compared with the NACVs group (RR, 2.88; 95 % CI, 0.99–8.38; $P > 0.05$) (Table S6, Fig. 3 A).

3.6. Comparison of risk of systemic AEs between ACVs and controls

An analysis of 24 studies [12,14–17,24–26,28–31,33,34,37,38,40–42,45–47,49] comprising 56833 ACVs and 29395 controls

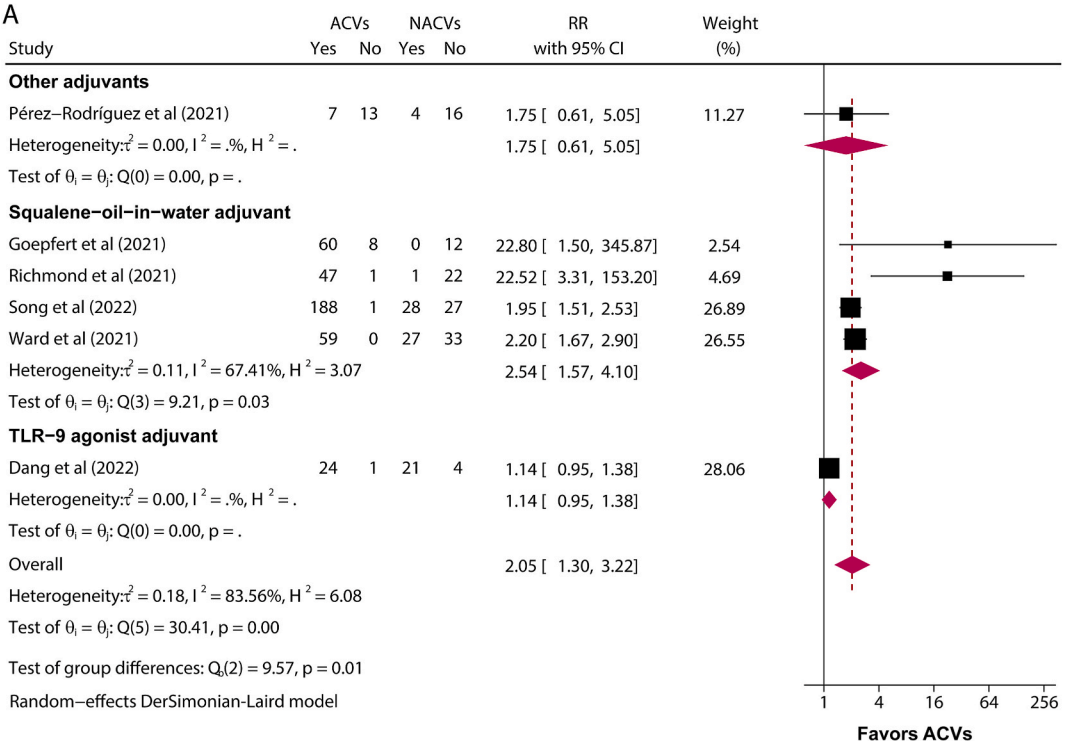

Fig. 2. Subgroup analysis of immunogenicity of ACVs compared to NACVs. A) Neutralizing antibody response. B) Geometric mean titers of neutralizing antibodies. ACVs, adjuvant-associated COVID-19 vaccines; NACVs, no adjuvant-associated COVID-19 vaccines; RR, relative risk; SMD, standardized mean difference; CI, confidence interval; SD, standard deviation; YES/N, Number of incidents; NO, Number of incidents not occurring.

showed that vaccination with ACVs was associated with an increased risk of systemic AEs compared with controls (RR, 2.68; 95 % CI 2.29–3.14). Notably, vaccination with ACVs did not result in significant systemic AEs compared with the NACVs group (RR, 2.33; 95 % CI, 0.66–8.28, $P > 0.05$) (Table S7, Fig. 3 B).

3.7. Comparison of risk of AEs ≥ grade 3 or mortality between ACVs and controls

Regarding severe AEs (grade ≥ 3), this study showed that ACVs vaccination did not result in a significantly increased rate of severe

Table 3
Subgroup analysis of geometric mean titers of neutralizing antibodies inoculated with ACVs compared with controls.

Subgroup	No. of studies	GMT-SMD (95%CI)	Heterogeneity I^2 (%)	Test of group differences (p value)
overall	23	3.61 (3.04, 4.19)	98.59 %	
adjuvant types				< 0.001
Aluminum adjuvants	5	3.75 (2.71, 4.78)	98.54 %	
Complex adjuvant	4	5.00 (2.03, 7.97)	99.40 %	
Matrix-M adjuvant	5	3.61 (2.37, 54.84)	98.13 %	
Squalene-oil-in-water adjuvant	7	3.62 (2.74, 4.50)	94.10 %	
TLR-9 agonist adjuvant	1	0.23 (-0.12, 0.58)	NA	
Other adjuvants	1	0.38 (-0.25, 1.00)	NA	
Age				0.23
< 18	2	2.20 (-0.24, 4.63)	96.27 %	
≥18	21	3.74 (3.15, 4.33)	98.57 %	
Vaccine types				0.96
Inactivated Virus	5	3.54 (1.86, 5.22)	99.31 %	
Protein subunit	16	3.73 (2.99, 4.47)	98.33 %	
Virus like particle	2	3.46 (1.37, 5.56)	98.07 %	
Study design				0.77
single-blind	13	3.48 (3.04, 4.19)	98.59 %	
double-blind	10	3.74 (2.07, 5.40)	98.75 %	
Days of immunoassay after the last vaccination				0.14
< 28	16	3.98 (3.47, 4.49)	97.24 %	
≥28	7	2.59 (0.81, 4.37)	99.37 %	
no.of centers				0.62
Single-center	9	3.92 (2.58, 5.25)	98.09 %	
Multicenter	14	3.54 (2.90, 4.19)	98.65 %	
Phase				0.1
< 3	19	3.88 (3.16, 4.60)	98.48 %	
≥3	4	2.55 (1.13, 3.98)	99.13 %	
No. of doses				< 0.001
2	22	3.45 (2.87, 4.03)	98.60 %	
3	1	7.60 (6.43, 8.76)	NA	
Control group types				0.04
NACVs	5	2.53 (1.38, 3.67)	94.91 %	
Placebo group	18	3.92 (3.26, 4.58)	98.82 %	

Note: ACVs: adjuvant-associated COVID-19 vaccines; NACVs, Non-adjuvanted vaccine group; SMD, standard mean difference; CI, confidence interval; GMT, Geometric mean titer of neutralizing antibody; NA, Not available.

systemic AEs compared with controls (RR, 1.56; 95 % CI, 0.83–2.95; $P = 0.17$) (Table 4). Regarding all-cause mortality, our analysis of four studies [45,46,48,49] showed that vaccination with ACVs reduced the risk of all-cause mortality compared with controls (RR, 0.51; 95 % CI, 0.30–0.87; $P = 0.01$) (Fig. 4).

3.8. Publication bias and sensitivity analyses

Inspection of the funnel plot and Egger's test indicated potential publication biases. The trim-and-fill method was employed to obtain adjusted summary estimates in the presence of publication bias, and the results demonstrated a close alignment between the adjusted RR and the original findings (Figure S1 A-D). Furthermore, the results of the sensitivity analysis served to reinforce the robustness and reliability of our findings (Fig. S2 A-D).

4. Discussion

This systematic review and meta-analysis of 33 RCTs provide important insights into the safety and immunogenicity of ACVs that can aid vaccine development and decision-making during the COVID-19 pandemic. The findings suggest that a significant increase in immune responses elicited by ACVs compared with controls and a further enhancement of the existing response compared to NACVs were observed. Although vaccination with ACVs increased local and systemic AEs compared with controls, their impact was significantly reduced in comparison with the NACVs group, especially with regard to systemic AEs. Notably, vaccination with ACVs reduced the risk of all-cause mortality, and these findings demonstrated that ACVs might have superior effect in preventing COVID-19.

4.1. Traditional adjuvant: alum

Aluminum hydroxide is a traditional adjuvant commonly used in vaccines; however, its mechanism of action remains unclear [50–52]. This meta-analysis found that aluminum ACVs produced relatively high immunogenicity (RR, 41.55; 95 % CI, 5.68–303.66; SMD, 3.61; 95 % CI, 3.04–4.19). However, it was also associated with an increased risk of local AEs (RR, 3.43; 95 % CI, 2.90–4.06). The use of aluminum adjuvants in other vaccines does not produce such a pronounced immune response. The possible reason for this may

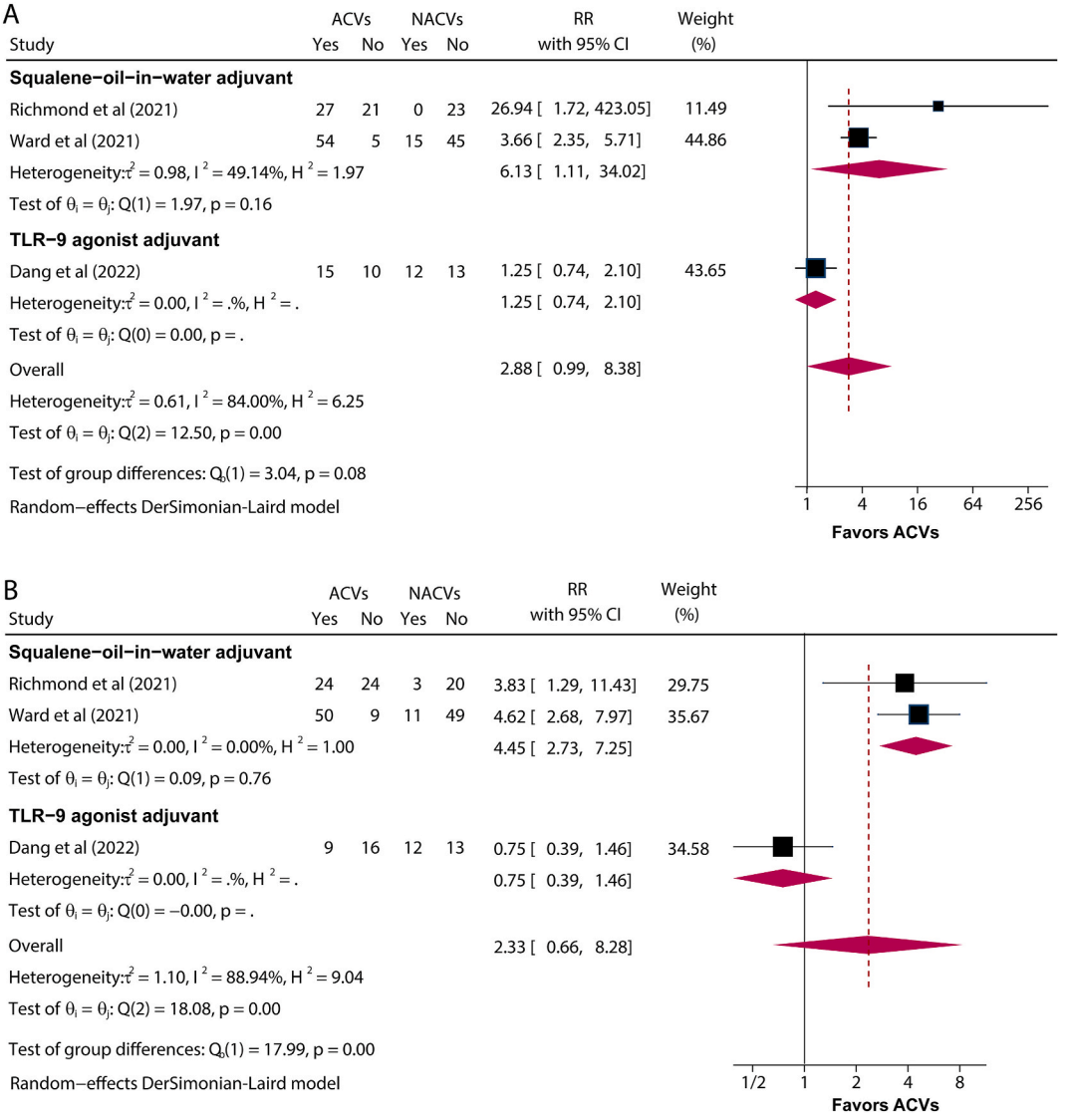

Fig. 3. Subgroup analysis of AEs inoculated with 2 doses of ACVs compared with NACVs. A) Local adverse reaction. B) Systemic adverse reaction. ACVs, adjuvant-associated COVID-19 vaccines; NACVs, no adjuvant-associated COVID-19 vaccines; RR, relative risk; CI, confidence interval; YES, Number of incidents; NO, Number of incidents not occurring.

Table 4
Risk of severe AEs (grade ≥3) for ACVs compared with controls.

AEs, ≥Grade 3	No. of studies	Reactions/total		RR (95 % CI)	Heterogeneity I^2 (%)	Test of heterogeneity (p value)	Test of effect size (p value)
		ACVs	Control				
Systemic AEs[#]	19	3090/47571	490/27394	1.56 (0.83, 2.95)	95.04	< 0.001	0.17
Local AEs[#]	16	1885/46269	45/26529	10.77 (5.23, 22.17)	66.54	< 0.001	< 0.001

Notes:ACVs:Adjuvant COVID-19 vaccines. Control: Non-adjuvanted COVID-19 vaccine group or Placebo group. [#]ACVs on second or third vaccination; RR, relative risk; CI, confidence interval; AEs, Adverse events.

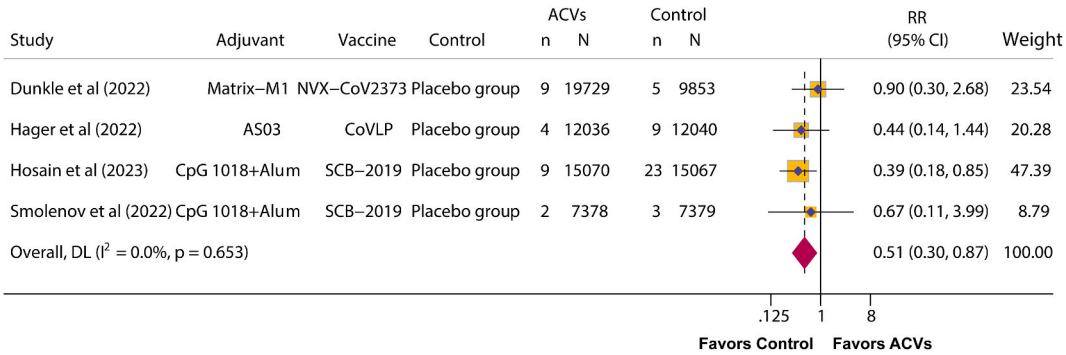

Fig. 4. Risk of all-cause death with ACVs vaccination compared with controls. ACVs, adjuvant-associated COVID-19 vaccines; NACVs, no adjuvant-associated COVID-19 vaccines; RR, relative risk; CI, confidence interval; n, number of all-cause mortality; N, total number of vaccinations.

be that the controls for aluminum ACVs in this study were all placebo and not active vaccines.

4.2. Novel adjuvants

4.2.1. Squalene oil-in-water adjuvant

Eight studies that used squalene-oil-in-water adjuvants, comprising a total of three adjuvants, AS03, MF59, and a-910823 were analyzed. Although MF59 and AS03 have been approved for use in influenza vaccines in Europe and have demonstrated safety in humans, their immunogenicity and safety in COVID-19 vaccines need to be further investigated [53,54]. This study demonstrated that vaccination with squalene oil-in-water adjuvants exhibited significantly enhanced immunogenicity compared with controls (RR, 6.09; 95 % CI, 2.93–12.64; SMD, 3.62; 95 % CI, 2.74–4.50); however, it was also associated with a further increase in the risk of systemic and localized AEs. Of note, four of these eight studies had an NACVs control group, all utilizing the AS03 adjuvant. This suggests that the amplification effect of the control groups being placebos may not be as pronounced. Similar to the present study, previous studies have shown that AS03 further enhances humoral and cellular immune responses and has protective effects against influenza compared with vaccines without adjuvants [54].

4.2.2. Matrix-M adjuvant

Matrix-M adjuvant is made from Quillaja saponin and has a dual role in immunomodulation and antigen delivery [55]. A study showed that vaccines based on nanoparticle/Matrix-M1 adjuvant technology have an acceptable safety profile in specific populations such as children, pregnant women, and older adults. During COVID-19, the saponin-based adjuvant (Matrix-M) was co-formulated with the SARS-CoV-2 vaccine NVX-CoV2373 (Novavax) as a nanoparticle vaccine. Similar to other ACVs, Matrix-M adjuvant significantly enhanced immunogenicity, albeit with some safety concerns. However, the controls for the Matrix-M adjuvant were all placebos. Further studies are needed to confirm the observations and eliminate the placebo amplification effect.

4.2.3. Complex and TLR-9 agonist adjuvants

Recently, combining two adjuvants has become a trend in adjuvant development [56,57]. The studies included in this review focused on the combination of CpG with alum or the Advax™ adjuvant. The results showed that the immunogenicity of the Complex AVC was significantly enhanced compared with the control group. Similarly, in terms of safety, the risk of AEs was significantly increased with the Complex adjuvant vaccine ($P < 0.05$). Of note, the TLR-9 receptor agonist CpG 1018 adjuvant had a favorable safety profile but elicited a weak nAb response. Due to the small sample size of the current study, concrete conclusions cannot be drawn. Further evidence is required to support the observations.

4.3. Limitations

This study had some limitations. First, it was limited by the relatively small number of studies with the NACVs group, which precluded direct one-to-one comparisons with ACVs. In addition, monitoring of AEs primarily assessed recruitment AEs, which may not capture rare and long-term AEs. Unfortunately, the number of studies with relevant variants was small and no control group was available, allowing only descriptive analysis. Future studies should aim to conduct large-scale clinical trials to better assess the immunogenicity and safety of ACVs. Toll-like receptor agonists, such as TLR-9 (CpG 1018), may be a safer class of vaccine adjuvants, and further studies are needed to confirm their immunogenicity. Despite some limitations of the current meta-analysis, it provided valuable insights into the immunogenicity and safety of ACVs.

5. Conclusion

The findings of this meta-analysis demonstrate that ACVs may have a superior effect and an acceptable safety in preventing COVID-

19. Although these results suggest the potential of ACVs, further studies are required.

6. Data availability statement

Data included in article/supplementary material/referenced in article.

Ethical statement

Though this article does not contain any studies with direct involvement of human participants or animals performed by any of the authors, all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e22858.

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