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Review Article

Effect of Different Adjuvants on the Performance of SARS-CoV-2 Vaccines: A Narrative Review of Phase III Trials

Humna Farooqi[1], Meerab Tufail[1], Areeha Akbar[1], Syeda Zahra Shaharyar[1], Saba Iqbal[2], Fatima Azhar[1], Nishat[1], Misbah Shaukat[3]

1 Department of Life Sciences, University of Management and Technology, Lahore, Pakistan
2 School of Biochemistry and Biotechnology, University of the Punjab, Lahore, Pakistan
3 Department of Biosciences, COMSATS University, Islamabad, Pakistan

***Corresponding author: Fatima Azhar, kalsoom8292@gmail.com**

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ABSTRACT

Background: The rapid development of vaccines against severe acute respiratory syndrome coronavirus 2 introduced diverse technological platforms, antigen designs, dosing schedules, delivery routes, and adjuvant systems. Adjuvants are important components of several inactivated, recombinant protein, protein-subunit, and conjugated vaccines because they can strengthen innate and adaptive immune responses. However, the clinical performance of an adjuvanted vaccine is determined by the complete formulation and cannot be attributed to the adjuvant alone. Objective: To narratively review the characteristics and reported efficacy of late-phase SARS-CoV-2 vaccines, with particular emphasis on the biological role, clinical context, and apparent performance patterns of their adjuvant systems. Methods: A structured narrative review was undertaken using literature identified through PubMed, the Cochrane Library, ScienceDirect, Google Scholar, ClinicalTrials.gov, and CenterWatch. Phase III and combined Phase II/III vaccine trials, supporting immunological studies, and relevant publications on SARS-CoV-2 vaccine platforms and adjuvants were considered. Evidence was organized thematically according to vaccine platform, adjuvant system, dosing regimen, trial-level efficacy, infection outcomes, and implementation characteristics. Numerical findings were interpreted descriptively because the included trials differed substantially in populations, circulating variants, endpoints, follow-up periods, baseline risks, and trial settings. Results: The reviewed vaccines included inactivated whole-virus, adenoviral-vector, recombinant protein, protein-subunit, DNA, conjugated protein, and intranasal live-attenuated platforms. Reported adjuvants included alum, aluminium hydroxide, alumina, AS03, CpG-1018 combined with alum, Advax-SM, and a toll-like receptor 7/8 agonist combined with alum. Trial-reported efficacy ranged from 15.3% to 92.2%. Most vaccine–control comparisons demonstrated lower infection frequencies among vaccinated participants, although marked variation existed across formulations and trial contexts. The evidence did not permit separation of the independent contribution of an adjuvant from that of the antigen, platform, dosage, route, schedule, or epidemiological setting. Conclusion: Adjuvants contributed to the immunological architecture of several successful SARS-CoV-2 vaccines, but available cross-trial evidence did not establish the independent superiority of any individual adjuvant. Future research should directly compare alternative adjuvant formulations using standardized endpoints, comparable populations, and consistent follow-up periods. Keywords: SARS-CoV-2; COVID-19 Vaccines; Adjuvants, Immunologic; Vaccine Efficacy; Phase III Clinical Trials; Immunogenicity; Aluminium Compounds; Protein Subunit Vaccines.

INTRODUCTION

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) created an urgent need for safe, scalable, and effective vaccines capable of reducing symptomatic infection, severe disease, hospitalization, and mortality. The rapid global spread of coronavirus disease 2019 and the subsequent emergence of viral variants accelerated vaccine development across several technological platforms, including inactivated whole-virus vaccines, viral-vector vaccines, nucleic-acid vaccines, recombinant proteins, protein subunits, conjugated proteins, and mucosal formulations (1–5). These platforms

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differed substantially in antigen presentation, intrinsic immunostimulatory activity, production requirements, storage conditions, dosing schedules, and the extent to which an external adjuvant was required.

An adjuvant is a component incorporated into a vaccine formulation to enhance, direct, or prolong the immune response to the administered antigen. Adjuvants can improve antigen uptake, stimulate innate immune pathways, activate antigen-presenting cells, promote cytokine production, and strengthen humoral and cellular immunity. Their role is particularly important in vaccine platforms containing purified or recombinant antigens that may have limited intrinsic immunogenicity when administered alone (6,7). Aluminium-containing compounds have historically been among the most widely used adjuvants, while newer systems such as AS03, CpG oligodeoxynucleotides, Advax-based formulations, and toll-like receptor agonists have been developed to produce broader or more targeted immune activation.

The clinical performance of an adjuvanted vaccine cannot, however, be understood by examining the adjuvant in isolation. Vaccine efficacy is influenced by the interaction between the adjuvant and antigen, antigen dose, platform, route of administration, dosing interval, participant characteristics, prior exposure, circulating variants, endpoint definitions, follow-up duration, and background transmission. Safety findings and implementation requirements must also be considered because vaccine acceptability, storage, transport, and completion of multidose schedules affect real-world effectiveness (8–12).

Experimental studies demonstrated that different adjuvant mechanisms could alter the magnitude and quality of SARS-CoV-2-specific immune responses. Alum combined with CpG motifs, for example, was investigated to enhance both humoral and cellular responses, while oil-in-water emulsions such as AS03 were used in recombinant protein formulations to increase immunogenicity and permit antigen-sparing approaches (6,13). Nevertheless, laboratory immunogenicity does not automatically translate into equivalent clinical protection, and numerical efficacy estimates obtained from separate trials do not constitute direct comparisons.

Late-phase vaccine trials reported considerable variation in efficacy across products. Such variation generated interest in whether particular adjuvants were associated with superior vaccine performance. This interpretation is methodologically difficult because each adjuvant was integrated into a distinct product tested under a specific epidemiological and clinical context. A narrative synthesis is therefore useful for integrating biological mechanisms, vaccine-platform characteristics, trial-level findings, and implementation considerations without treating heterogeneous trials as if they were direct head-to-head comparisons.

This narrative review examined the reported performance of late-phase SARS-CoV-2 vaccines across different platforms and adjuvant systems. It aimed to describe the immunological functions of the principal adjuvants, compare trial-level performance patterns, identify factors that limited cross-vaccine interpretation, and clarify priorities for future comparative vaccine research.

MATERIALS AND METHODS

This article was structured as a narrative review with a transparent literature-identification and thematic-synthesis process. The narrative design was selected because the primary objective was to interpret the relationship between vaccine platforms, antigen formulations, adjuvant systems, dosing characteristics, and reported clinical performance rather than to generate a single summary estimate across clinically heterogeneous vaccines.

Relevant literature was identified through searches of PubMed, the Cochrane Library, ScienceDirect, Google Scholar, ClinicalTrials.gov, and CenterWatch. The literature search was undertaken in January 2024 and focused on SARS-CoV-2 vaccines evaluated in Phase III or combined Phase II/III trials. Search concepts included combinations of terms related to “SARS-CoV-2,” “COVID-19 vaccine,” “vaccine

efficacy," "Phase III trial," "adjuvant," "alum," "aluminium hydroxide," "AS03," "CpG-1018," "Advax," "TLR7/8 agonist," "protein-subunit vaccine," "inactivated vaccine," and "viral-vector vaccine." Reference lists of relevant publications were also reviewed to identify additional mechanistic, preclinical, and clinical evidence.

Publications were considered relevant when they described the efficacy, immunogenicity, safety, formulation, adjuvant system, dosing schedule, storage requirements, or infection outcomes of a SARS-CoV-2 vaccine. Priority was given to randomized late-phase clinical trials for clinical performance data. Earlier-phase, preclinical, mechanistic, and methodological publications were used where necessary to explain the biological role of adjuvants and the relationship between adjuvant selection and vaccine-platform characteristics. Publications that did not provide relevant information on vaccine formulation, immunological mechanisms, clinical performance, or implementation were not emphasized in the synthesis.

Information was extracted on vaccine name, technological platform, antigen formulation, adjuvant, trial location, clinical phase, dose regimen, dose interval, storage temperature, reported efficacy, and vaccine and control infection events where available. Because the trials differed in outcome definitions, circulating variants, follow-up periods, participant risk profiles, geographic settings, and background transmission, numerical findings were interpreted as descriptive trial-level observations rather than as direct comparative estimates.

The evidence was organized into thematic domains comprising vaccine-platform diversity, mechanisms and functions of adjuvants, performance of aluminium-containing systems, performance of newer adjuvant systems, apparent differences in trial-level efficacy, dosing and formulation considerations, cold-chain requirements, and limitations of cross-trial comparison. No formal pooled effect was used to rank vaccines or adjuvants. The possibility of selection bias was acknowledged because the review did not employ a prospectively registered systematic-review protocol, duplicate independent screening, or a formal domain-based risk-of-bias assessment of every included publication.

RESULTS

The reviewed evidence covered vaccines evaluated across Asia, Europe, Africa, North America, and South America. The technological platforms included inactivated whole-virus vaccines, adenoviral-vector vaccines, recombinant protein and protein-subunit vaccines, a DNA vaccine, conjugated protein vaccines, and an intranasal live-attenuated vaccine. Dose schedules ranged from a single dose to three doses, while multidose intervals generally ranged from 14 to 28 days.

The reviewed formulations contained alum, aluminium hydroxide, alumina, AS03, CpG-1018 combined with alum, Advax-SM, and a toll-like receptor 7/8 agonist combined with alum. Several adenoviral-vector, DNA, and intranasal formulations did not have an identified external adjuvant in the reviewed characteristics. This did not necessarily imply an absence of immunostimulatory activity because some platforms possess intrinsic properties capable of activating innate immunity.

Table 1. Characteristics of Late-Phase SARS-CoV-2 Vaccines Included in the Narrative Synthesis

Vaccine	Vaccine Platform	Adjuvant	Trial Country or Region	Phase	Dose Regimen	Dose Interval	Storage Temperature	Reported Efficacy (%)
BIV1-CovIran	Inactivated virus particle	Alum	Iran	III	2 doses	28 days	Not specified	50.2
CoronaVac	Inactivated whole virion	Aluminium hydroxide	Turkey	III	2 doses	14 days	2–8°C	83.5
BBV152	Whole-virion inactivated	TLR7/8 agonist plus alum	India	III	2 doses	28 days	Not specified	77.8
Ad5-nCoV	Adenoviral vector	No external adjuvant identified	Argentina, Chile, Mexico, Pakistan, and Russia	III	Single dose	Not applicable	2–8°C	57.5
AZD1222	Adenoviral vector	No external adjuvant identified	United States, Chile, and Peru	III	2 doses	28 days	Not specified	74.0

Vaccine	Vaccine Platform	Adjuvant	Trial Country or Region	Phase	Dose Regimen	Dose Interval	Storage Temperature	Reported Efficacy (%)
Gam-COVID-Vac	Recombinant adenoviral vector	No external adjuvant identified	Russia	III	2 doses	21 days	−18°C	91.6
ABDALA	Recombinant subunit protein	Alumina	Cuba	III	3 doses	14 days	2–8°C	92.2
CoV2 preS dTM	Recombinant protein, bivalent	AS03	Multinational	III	2 doses	21 days	Not specified	64.7
Monovalent D614	Recombinant protein	AS03	Multinational	III	2 doses	22 days	Not specified	15.3
ZyCoV-D	DNA vaccine	No external adjuvant identified	India	III	3 doses	28 days	2–8°C	66.6
SOBERANA-02	RBD-conjugated protein	Alumina	Cuba	III	2 doses	28 days	2–8°C	69.7
SOBERANA-02 plus SOBERANA-Plus	Conjugated protein with heterologous booster	Alumina	Cuba	III	3 doses	28 days	2–8°C	92.0
SCB-2019	Protein subunit	CpG-1018 plus alum	Belgium, Brazil, Colombia, the Philippines, and South Africa	II/III	2 doses	21 days	2–8°C	83.2
SpikoGen	Spike protein subunit	Advax-SM	Iran	III	2 doses	21 days	Not specified	59.69
dNS1-RBD	Live-attenuated intranasal vaccine	No external adjuvant identified	Colombia, the Philippines, South Africa, and Vietnam	III	2 doses	14 days	Not specified	28.2

RBD, receptor-binding domain; TLR, toll-like receptor.

Biological Functions of Vaccine Adjuvants

Adjuvants enhanced vaccine responses through several overlapping biological mechanisms. Aluminium-based adjuvants promoted antigen retention, local inflammatory signalling, recruitment of antigen-presenting cells, and antibody-dominant immune responses. Their established manufacturing history, relative stability, and extensive safety experience supported their use in several inactivated and protein-based SARS-CoV-2 vaccines.

Toll-like receptor agonists enhanced innate immune recognition by activating pattern-recognition pathways. BBV152 combined an inactivated whole-virion antigen with alum and a TLR7/8 agonist, thereby integrating the established antibody-enhancing properties of aluminium salts with additional innate immune stimulation. Experimental evidence involving alum and CpG combinations similarly indicated that pairing aluminium compounds with nucleic-acid-based innate immune agonists could enhance immunogenicity beyond that produced by alum alone (13).

AS03 is an oil-in-water emulsion containing squalene and immunostimulatory components. It was used in recombinant protein vaccine formulations to enhance antigen presentation and immune activation. The reviewed evidence demonstrated, however, that two formulations containing AS03 produced markedly different efficacy estimates. The bivalent CoV2 preS dTM formulation reported an efficacy of 64.7%, whereas the monovalent D614 formulation reported 15.3%. This difference illustrated that the presence of the same adjuvant did not ensure equivalent clinical performance because antigen composition, variant matching, dose, trial period, and epidemiological conditions remained influential.

CpG-1018, used with alum in SCB-2019, was intended to enhance immune responses through toll-like receptor 9 signalling. Advax-SM, used in SpikoGen, represented a polysaccharide-based adjuvant system designed to strengthen immune responses while maintaining tolerability. Alumina-containing formulations were used in ABDALA, SOBERANA-02, and the SOBERANA-02 plus SOBERANA-Plus schedule. Their reported efficacy values ranged from 69.7% to more than 92%, but the differences could not be attributed solely to alumina because antigen construction, booster strategy, dose number, and trial conditions differed.

Trial-Level Infection Outcomes

Fourteen vaccine–control comparisons contained usable infection-event data. Infection frequencies were numerically lower in the vaccine groups than in the control groups across all 14 comparisons. Vaccine-

group event proportions ranged from 0.04% for SOBERANA-02 plus SOBERANA-Plus to 4.74% for BIV1-CovIran. Control-group event proportions ranged from 0.24% to 7.80%.

The direction of the trial-level effect generally favoured vaccination. Thirteen comparisons had odds-ratio confidence intervals below the null value. The estimate for dNS1-RBD numerically favoured vaccination but had a confidence interval that included the null value. These observations supported the broad protective performance of the reviewed vaccines while also demonstrating substantial variation in the magnitude and precision of trial-level findings.

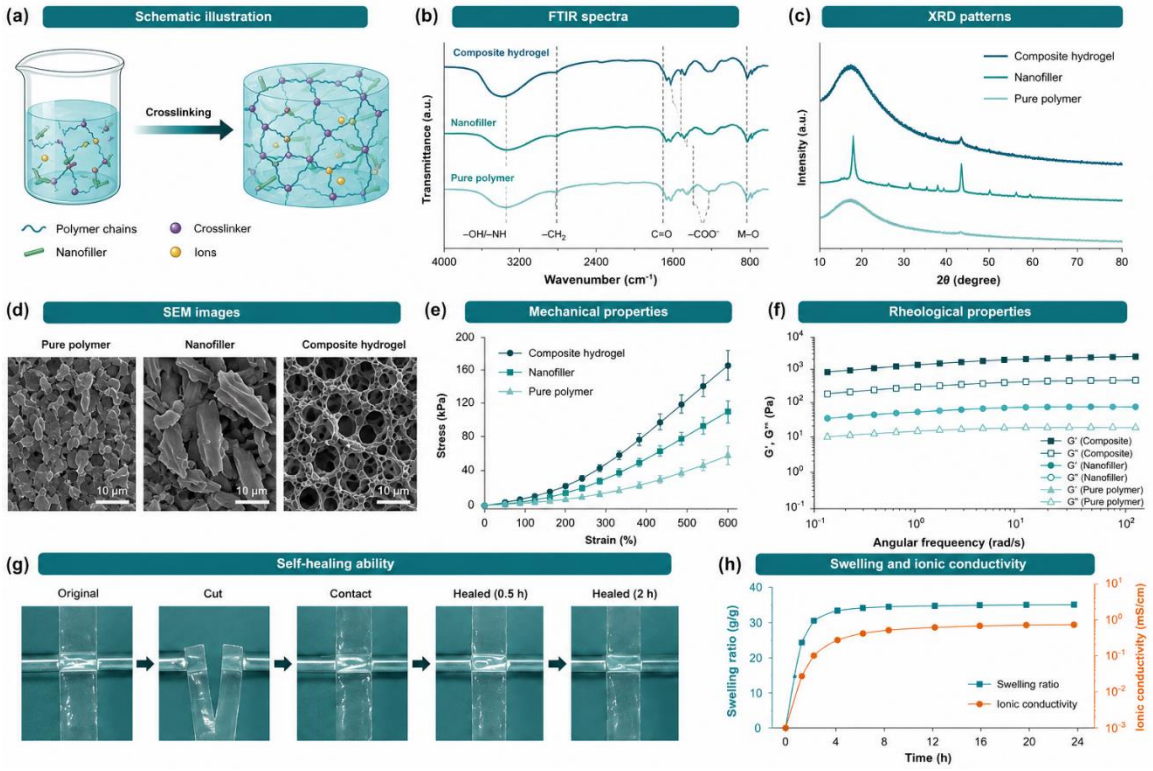

Figure 1 presents the composite hydrogel's preparation and characterization, including the crosslinking mechanism, FTIR and XRD profiles, SEM morphology, mechanical and rheological performance, self-healing progression, and time-dependent swelling and ionic conductivity, collectively demonstrating successful composite formation, improved structural and functional properties, and sustained recovery and transport behaviour.

Table 2. Descriptive Infection Outcomes in Late-Phase SARS-CoV-2 Vaccine Trials

Vaccine	Vaccine Events, n/N (%)	Control Events, n/N (%)	Descriptive Odds Ratio	95% CI
BIV1-CovIran	632/13,335 (4.74)	520/6,665 (7.80)	0.588	0.522–0.663
CoronaVac	12/6,646 (0.18)	38/3,568 (1.07)	0.168	0.088–0.322
Monovalent D614	126/4,702 (2.68)	182/4,675 (3.89)	0.680	0.539–0.857
BBV152	16/12,221 (0.13)	34/12,198 (0.28)	0.469	0.259–0.849
Ad5-nCoV	45/10,660 (0.42)	105/10,590 (0.99)	0.423	0.298–0.601
AZD1222	95/21,587 (0.44)	145/10,792 (1.34)	0.325	0.250–0.421
ABDALA	11/24,144 (0.05)	142/24,146 (0.59)	0.077	0.042–0.142
dNS1-RBD	47/15,496 (0.30)	62/15,494 (0.40)	0.757	0.518–1.108
Gam-COVID-Vac	16/16,427 (0.10)	62/1,029 (6.03)	0.015	0.009–0.026
CoV2 preS dTM	32/5,736 (0.56)	85/5,680 (1.50)	0.369	0.246–0.555
ZyCoV-D	20/13,849 (0.14)	61/13,852 (0.44)	0.327	0.197–0.542
SOBERANA-02	38/14,679 (0.26)	136/14,675 (0.93)	0.277	0.193–0.398
SOBERANA-02 plus SOBERANA-Plus	6/14,677 (0.04)	35/14,675 (0.24)	0.171	0.072–0.407
SpikoGen	50/12,657 (0.40)	37/4,219 (0.88)	0.448	0.293–0.687

CI, confidence interval. These estimates are presented descriptively and do not represent direct head-to-head comparisons between vaccines or adjuvants.

Reported efficacy varied from 15.3% for the monovalent D614 recombinant protein formulation to 92.2% for ABDALA. Values exceeding 90% were reported for ABDALA, SOBERANA-02 plus

SOBERANA-Plus, and Gam-COVID-Vac. Intermediate efficacy estimates were reported for CoronaVac, SCB-2019, BBV152, AZD1222, SOBERANA-02, ZyCoV-D, CoV2 preS dTM, SpikoGen, and Ad5-nCoV. Lower estimates were reported for dNS1-RBD and monovalent D614.

These differences did not constitute a valid hierarchy of vaccines or adjuvants. The trials were conducted in different countries and epidemic periods, involved different circulating variants, and used non-identical case definitions, follow-up periods, participant populations, and dosing schedules. A product evaluated during intense community transmission or against an immune-evasive variant could produce a lower observed efficacy than another product tested under more favourable epidemiological conditions, even when both generated clinically meaningful immunity.

Patterns in Reported Vaccine Efficacy

The apparent performance of multidose and heterologous schedules was notable. ABDALA used a three-dose recombinant protein schedule, while SOBERANA-02 plus SOBERANA-Plus incorporated a heterologous booster. Both reported efficacy values above 90%. Repeated antigen exposure and heterologous boosting may broaden or strengthen immune responses, but these cross-trial observations were not sufficient to establish that dose number or booster heterogeneity independently caused the higher estimates.

Storage and Implementation Considerations

Most vaccines with reported storage information could be maintained at 2–8°C. This temperature range is compatible with established vaccine-distribution systems and may facilitate deployment in regions without extensive frozen-storage capacity. Gam-COVID-Vac was reported to require storage at −18°C, creating greater logistical demands.

Storage requirements did not determine biological efficacy directly, but they could influence population-level effectiveness. Unreliable transport, temperature excursions, product wastage, delayed administration, and failure to complete multidose schedules may reduce the public-health impact of an otherwise efficacious vaccine. Selection of an adjuvant and formulation must therefore consider not only immunological performance but also stability, manufacturing scalability, cost, tolerability, and compatibility with available distribution systems.

DISCUSSION

This narrative review demonstrated that adjuvants formed an important component of several successful SARS-CoV-2 vaccine formulations, particularly inactivated, recombinant protein, protein-subunit, and conjugated protein vaccines. The reviewed products incorporated established aluminium compounds as well as newer systems such as AS03, CpG-1018 combined with alum, Advax-SM, and TLR7/8 agonist–alum combinations. Most late-phase vaccine–control comparisons showed fewer infection events among vaccinated participants, supporting the broad clinical value of SARS-CoV-2 vaccination across diverse technological approaches.

The findings were consistent with evidence showing that adjuvants enhanced antigen presentation and promoted stronger humoral and cellular responses. Recombinant spike-protein vaccines formulated with adjuvants having different mechanisms of action produced protective immune responses in experimental models, while clinical studies of adjuvanted trimeric spike-protein vaccines demonstrated substantial immunogenicity in both SARS-CoV-2-naïve and previously exposed populations (6,7). Alum-plus-CpG formulations and other pattern-recognition-receptor agonists were also developed to broaden immune activation beyond the predominantly antibody-oriented response traditionally associated with aluminium salts (13).

The reviewed clinical patterns nevertheless showed that adjuvant identity alone did not predict vaccine efficacy. AS03 was present in recombinant protein formulations with markedly different reported

efficacy values. Aluminium-containing systems were used in products whose efficacy estimates ranged from approximately 50% to more than 90%. These differences reinforced the principle that an adjuvant operates as part of an integrated formulation. Antigen sequence, structural conformation, dose, presentation, route, schedule, manufacturing quality, and antigen–adjuvant compatibility collectively influence the resulting immune response.

Vaccine-platform characteristics further complicated interpretation. Inactivated vaccines generally required external adjuvants because chemical or physical inactivation reduced viral replication and limited intrinsic immune stimulation. Protein and protein-subunit vaccines similarly benefited from adjuvants because purified antigens often generated insufficient immune activation when administered alone. In contrast, viral-vector, DNA, and live-attenuated platforms could activate innate immune pathways through their delivery systems or nucleic-acid components, reducing the need for a separately identified adjuvant.

Trial context was another major determinant of apparent vaccine performance. The reviewed trials differed in baseline infection risk, age distribution, comorbidity, prior SARS-CoV-2 exposure, circulating variants, endpoint definitions, surveillance intensity, and follow-up duration. These factors could substantially affect the number of detected infections and the calculated efficacy. Consequently, comparing percentages across separate trials as though they arose from a common randomized experiment would produce potentially misleading conclusions.

The observed differences between the monovalent D614 and bivalent recombinant protein formulations illustrated the importance of antigenic composition. Although both used AS03, their reported efficacy differed considerably. This pattern suggested that antigen–variant matching and formulation design may have been at least as influential as adjuvant selection. Similarly, the strong reported performance of some three-dose and heterologous schedules suggested a potential benefit from repeated or diversified antigen exposure, but direct comparative trials would be required to isolate the effect of schedule from other product characteristics.

The review also highlighted the importance of implementation. Vaccines stored at 2–8°C were more compatible with conventional immunization infrastructure than products requiring frozen storage. In settings with constrained logistics, formulation stability and ease of distribution may influence public-health effectiveness as strongly as modest differences in trial efficacy. Adjuvant development should therefore integrate immunogenicity with stability, dose sparing, manufacturing capacity, reactogenicity, affordability, and cold-chain feasibility.

This review had several strengths. It integrated late-phase randomized evidence with mechanistic and immunological literature, included geographically diverse vaccine trials, and examined a broad range of technological platforms and adjuvant systems. It also avoided interpreting cross-trial efficacy differences as proof of direct superiority and distinguished the contribution of the complete vaccine formulation from that of the adjuvant alone.

Several limitations should be considered. The review was narrative and did not use a prospectively registered protocol, duplicate independent screening, or a comprehensive domain-based risk-of-bias assessment. Study selection may therefore have been affected by reviewer judgment and publication availability. The included trials used heterogeneous infection endpoints, follow-up durations, participant populations, and epidemiological conditions. Several products were represented by a single trial, limiting confidence in platform- or adjuvant-specific patterns. Trial-level data did not permit adjustment for age, previous infection, comorbidities, geographic region, or circulating variants. Some formulations had incomplete publicly reported information on storage or adjuvant composition. In addition, an unusually extreme estimate associated with the reported Gam-COVID-Vac control denominator requires verification against the primary trial publication before the table is used for publication.

Future studies should directly compare alternative adjuvants using the same antigen, dose, route, population, endpoint definition, and follow-up period. Factorial or multi-arm randomized trials would be especially valuable for isolating antigen and adjuvant effects. Standardized reporting of symptomatic infection, severe disease, hospitalization, durability, neutralization breadth, cellular immunity, reactogenicity, and variant-specific performance would improve comparability. Individual-participant-data analyses could also clarify whether the effects of particular formulations vary according to age, previous infection, immune status, comorbidity, or geographic setting.

CONCLUSION

Adjuvants enhanced the immunological potential of several inactivated, recombinant protein, protein-subunit, and conjugated SARS-CoV-2 vaccines, but clinical performance reflected the interaction of the adjuvant with the antigen, platform, dose, route, schedule, population, and epidemiological context. Most reviewed late-phase trials reported lower infection frequencies among vaccinated participants, although efficacy estimates varied considerably across products. Cross-trial differences did not establish the independent superiority of alum, aluminium hydroxide, alumina, AS03, CpG-1018, Advax-SM, or TLR7/8 agonist–based formulations. Direct comparative trials using standardized clinical and immunological endpoints are required to determine which adjuvant–antigen combinations provide the best balance of protection, durability, safety, scalability, and implementation feasibility.

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