



IMMUNOGENICITY, SAFETY, AND EFFICACY OF COVID-19 VACCINES: A SYSTEMATIC REVIEW OF THE LITERATURE

**Tarik Chmitah^{*1}, Sofia Fellah², Mohamed El Arbi Tahiri Alaoui³, Mohamed Amine Sehhar¹,
Salaheddine Soltani¹, Jalal Kasouati¹, Larbi El Bouaiti¹, Karim Sbai Idrissi¹**

¹Educational and Research Unit of Social and Preventive Medicine, Legal Medicine and Occupational Medicine -
Faculty of Medicine and Pharmacy of Rabat, Mohammed V, Morocco.

²Faculty of Medicine and Pharmacy, Mohammed V University, Rabat, Morocco.

³Department of Maxillofacial Surgery and Stomatology, Mohammed V Military Hospital of Instruction, hay Riad,
RABAT, MOROCCO.



***Corresponding Author: Tarik Chmitah**

Educational and Research Unit of Social and Preventive Medicine, Legal Medicine and Occupational Medicine -
Faculty of Medicine and Pharmacy of Rabat, Mohammed V, Morocco.

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ABSTRACT

Objective: To systematically evaluate the safety, immunogenicity, and protective efficacy of COVID-19 vaccines in the general population. **Methods:** PubMed and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched to identify phase I/II/III randomized controlled trials of COVID-19 vaccines published up to November 2021. **Results:** Thirty-eight studies met the inclusion criteria, comprising 35 randomized clinical trials, 2 non-randomized clinical trials, and 1 observational study. The descending order of vaccines according to the ratio of neutralizing-antibody titers in vaccinated versus convalescent sera was: mRNA-1273, NVX-CoV2373, BNT162b2, AZD1222, Ad26.COV2.S, Sputnik V, BBV152, BBIBP-CorV, and CoronaVac. Production of neutralizing antibodies against the SARS-CoV-2 receptor-binding domain in more than 90% of vaccinees was reported within 30 days of the first or second vaccine dose. BNT162b2, mRNA-1273, Sputnik V, and CoronaVac, after two doses, showed the best efficacy (>80%) in preventing symptomatic cases in Phase III trials. mRNA vaccines, AZD1222, and CoronaVac were effective in preventing symptomatic COVID-19 infection and severe disease against the Alpha, Beta, and Gamma variants. Most adverse events were mild to moderate and transient; injection-site pain was the most common local event across vaccine types, while fever, fatigue, and headache were the most common systemic events. Rare serious adverse events were observed with the AZD1222 and Ad26.COV2.S vaccines. **Conclusion:** Most COVID-19 vaccines appear to be effective and safe. Clinical trial data on long-term protection and protection against multiple variants remain limited. Further research is needed to investigate the long-term efficacy and safety of these vaccines, and the influence of dose, age, and manufacturing process on protective efficacy.

KEYWORDS: COVID-19; SARS-CoV-2; Vaccines; Immunogenicity; Efficacy; Safety; Systematic review.

INTRODUCTION

The novel coronavirus SARS-CoV-2 was identified in Wuhan, China, and spread rapidly from December 2019 onward, first across China and then worldwide. On 31 January 2020, the World Health Organization (WHO) declared a global public health emergency, and on 11 March 2020 the outbreak was characterized as a pandemic. At the time the underlying thesis work was

conducted, the virus had infected more than 200 million people and caused more than 4 million deaths worldwide.^[1]

The COVID-19 crisis placed considerable strain on already fragile health systems and economies, increasing demand for intensive care capacity, hospital beds, and healthcare personnel, while heightening dependence on

imported medicines and medical supplies.^[2] To contain transmission, countries worldwide implemented strict measures, including mandatory lockdowns and border closures, which disrupted major pillars of economic activity, production, and supply chains.^[3] In Morocco, national economic activity contracted in 2020 for the first time in over two decades, with GDP falling by 5.5% under the combined effect of drought and the pandemic.^[4] Globally, the economic contraction associated with COVID-19 has been projected to push several hundred million people into poverty, marking the first rise in global poverty in three decades.^[5] The pandemic's economic and psychosocial toll has also been linked to adverse mental health outcomes, including elevated symptoms of post-traumatic stress and depression, particularly among healthcare workers.^[6,7]

Coronaviruses are enveloped, positive-sense single-stranded RNA viruses belonging to the family Coronaviridae, subdivided into four genera, of which only the alpha- and beta-coronaviruses infect mammals.^[8] SARS-CoV-2 belongs to the beta-coronavirus genus, alongside SARS-CoV and MERS-CoV, the two other coronaviruses known to cause severe respiratory disease in humans.^[9] Whole-genome sequencing indicates that SARS-CoV-2 shares approximately 96% identity with a bat coronavirus, suggesting a zoonotic origin, although the intermediate host or hosts remain incompletely characterized.^[11]

Ending the pandemic and curbing its evolving impact requires reaching a threshold of population immunity, generally attainable only through high vaccination coverage. However, many epidemiologists have questioned whether such a threshold remains realistically attainable, given the continued emergence of new variants, delayed vaccine availability for children, and vaccine hesitancy.^[1] Vaccine hesitancy poses a direct threat to pandemic control, since the achievement of population immunity depends not only on vaccine efficacy itself but also on the willingness of populations to accept vaccination — a willingness shaped chiefly by perceptions of vaccine efficacy and safety. A comprehensive evaluation of vaccine efficacy and safety is therefore essential to inform effective health communication strategies and support successful population-level vaccination campaigns.

Origin, transmission, and spread of SARS-CoV-2

As with previous invasive coronaviruses such as SARS and MERS-CoV, SARS-CoV-2 is thought to be of zoonotic origin, resulting from cross-species transmission; bats have been proposed as a likely natural reservoir, while pangolins and other species have been proposed as possible intermediate hosts.^[11,32] The epidemiological link common to the initial human cluster in Wuhan was a live-animal market, though bats themselves were apparently not sold there, prompting continued research into alternative reservoirs and intermediate hosts.^[34,35] Human-to-mink and mink-to-

human transmission has also been documented in several countries, raising concern about the potential formation of non-human viral reservoirs.^[37]

SARS-CoV-2 spreads between infected and susceptible individuals through direct and indirect routes. Direct transmission occurs mainly via respiratory droplets and aerosols expelled during coughing, sneezing, speaking, or singing, as well as via close contact with infected secretions.^[40,41] Prolonged fecal viral shedding has also been documented in some patients, raising the possibility of a fecal-oral transmission route, although its clinical significance remains uncertain.^[42,43]

Public health control measures and the rationale for vaccination

Beyond individual protective measures such as masking and hand hygiene, countries have relied on a range of collective public health interventions to curb transmission, including social distancing orders, closure of schools and non-essential businesses, restrictions on gatherings and travel, case isolation, and contact tracing.^[140,156] Serial and pre-event screening strategies, using nucleic-acid amplification or antigen-based tests, have also been used in high-risk congregate settings, though their real-world impact depends heavily on testing frequency, turnaround time, and concurrent adherence to other preventive measures.^[150]

Among available interventions, vaccination is widely regarded as the most promising approach for controlling the pandemic, aiming to reduce mortality and the broader societal and economic impact of COVID-19.^[156] Vaccine development conventionally proceeds through preclinical evaluation and four clinical phases — dose-finding and initial safety (Phase I), expanded safety and immunogenicity assessment (Phase II), pivotal efficacy evaluation against a predefined clinical endpoint (Phase III), and post-marketing surveillance (Phase IV) — a process that, for established vaccines, typically spans many years but was markedly accelerated for COVID-19 vaccines without relaxing safety oversight.^[157,158,159]

COVID-19 vaccines have been developed on several distinct platforms: traditional approaches such as inactivated whole-virus vaccines, alongside newer platforms including messenger RNA (mRNA) vaccines, non-replicating adenovirus-vector vaccines, and recombinant protein-subunit vaccines — the latter two building on technology previously used for other diseases, while mRNA platforms had never before been deployed in a licensed human vaccine.^[159] As of the most recent WHO Emergency Use Listing data available at the time of this review, eight vaccines spanning these platforms had received WHO emergency authorization: Comirnaty (Pfizer/BioNTech), Covishield/AZD1222 (AstraZeneca/SII), Ad26.COV2.S (Janssen), the Moderna mRNA-1273 vaccine, the Sinopharm and Sinovac-CoronaVac inactivated vaccines,

Covaxin/BBV152 (Bharat Biotech), and NVX-CoV2373/Nuvaxovid (Novavax).^[160,161]

This systematic review aimed to evaluate and compare the immunogenicity, clinical efficacy, and safety of COVID-19 vaccines authorized for use in the general population.

Table 1: PICOS framework underlying the research question.

Component	Description
Population	General adult population (healthy adults)
Intervention	COVID-19 vaccines authorized by the WHO (all platforms)
Comparison	Placebo, convalescent sera, or comparator vaccine platforms
Outcome	Immunogenicity, protective efficacy, and safety of COVID-19 vaccines
Study design	Randomized and non-randomized phase I/II/III clinical trials; observational studies

MATERIALS AND METHODS

Search strategy

This is a systematic literature review conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) methodology. All published clinical trials relating to SARS-CoV-2 vaccines were retrieved from PubMed and the Cochrane Central Register of Controlled Trials (CENTRAL), to identify articles addressing the immunogenicity, efficacy, and safety of COVID-19 vaccines published between 2020 and 2021.

Databases were searched using the following MeSH terms: "COVID-19 vaccine" or "SARS-CoV-2 vaccine", "immunogenicity", "efficacy" or "efficiency", and "safety", together with all relevant synonyms. A supplementary search by individual vaccine name was conducted for completeness. The PubMed search string used was: (("covid 19 vaccines"[MeSH Terms] OR ("covid 19"[MeSH Terms] AND "vaccines"[MeSH Terms]) OR ("covid 19"[All Fields] AND "vaccines"[All Fields]) OR "covid 19 vaccines"[All Fields] OR "sars cov 2 vaccines"[All Fields]) AND ("immunogenicity"[All Fields] OR "immunogenicity, vaccine"[MeSH Terms]) AND ("effectiveness"[All Fields] OR "efficiency/drug effects"[MeSH Terms] OR "efficacy"[All Fields]) AND ("safety"[All Fields] OR "safety"[MeSH Terms]) AND ("harm"[All Fields] OR "damage"[All Fields] OR "side effects"[All Fields] OR "adverse events"[All Fields])) AND (clinicaltrial[Filter] OR randomizedcontrolledtrial[Filter]).

Study selection

Selected studies underwent independent qualitative evaluation to identify articles relevant to the review question.

Eligibility criteria

Inclusion criteria: articles published in English, peer-reviewed; target population: general population (healthy adults); phase I/II/III clinical trials, randomized or non-randomized, as well as observational studies on COVID-19 vaccines authorized by the WHO.

Exclusion criteria: articles addressing vaccines still under trial (phase 1 or 2); vaccines not used in the

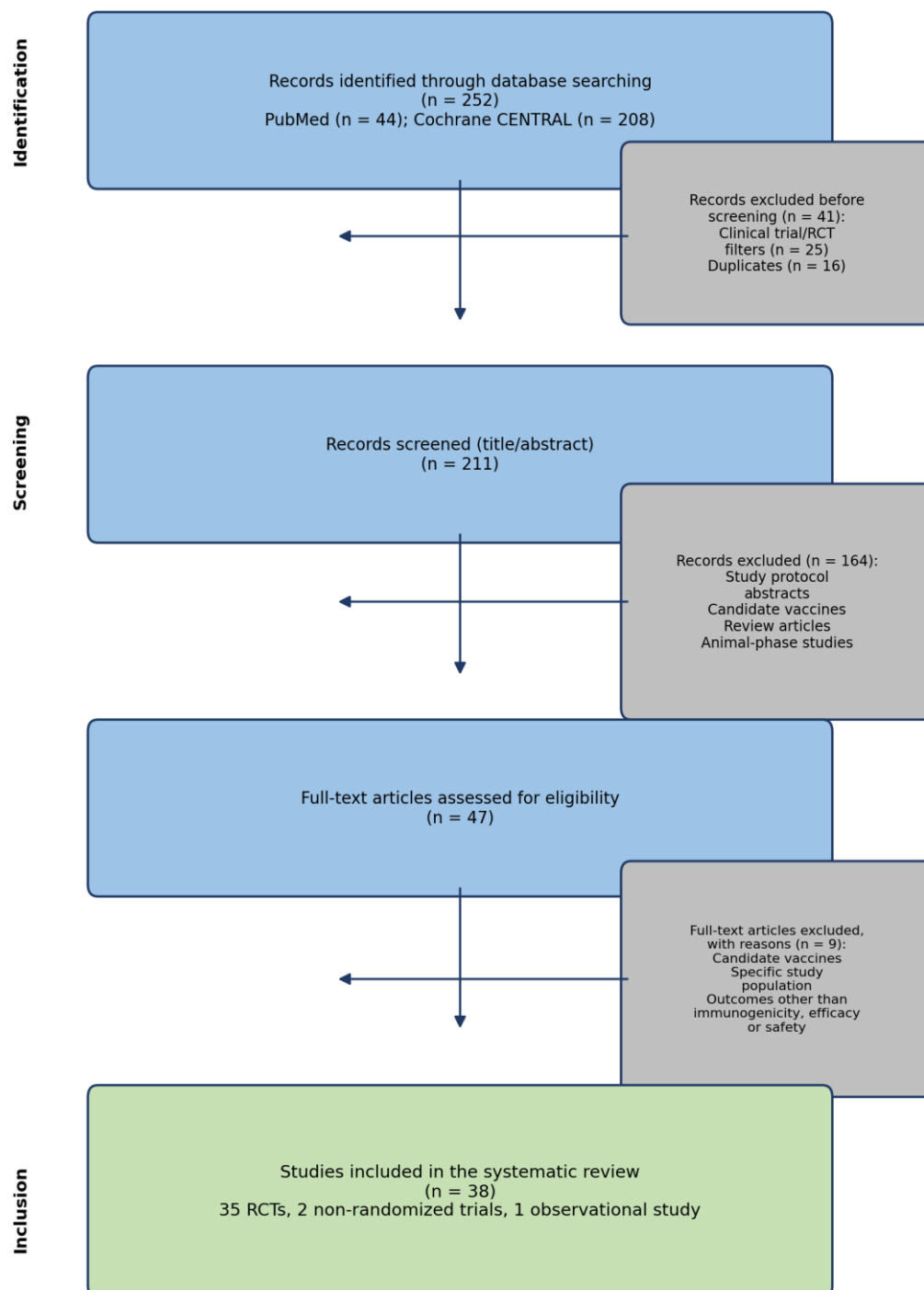
general population, or used exclusively in a specific population subgroup.

Data analysis

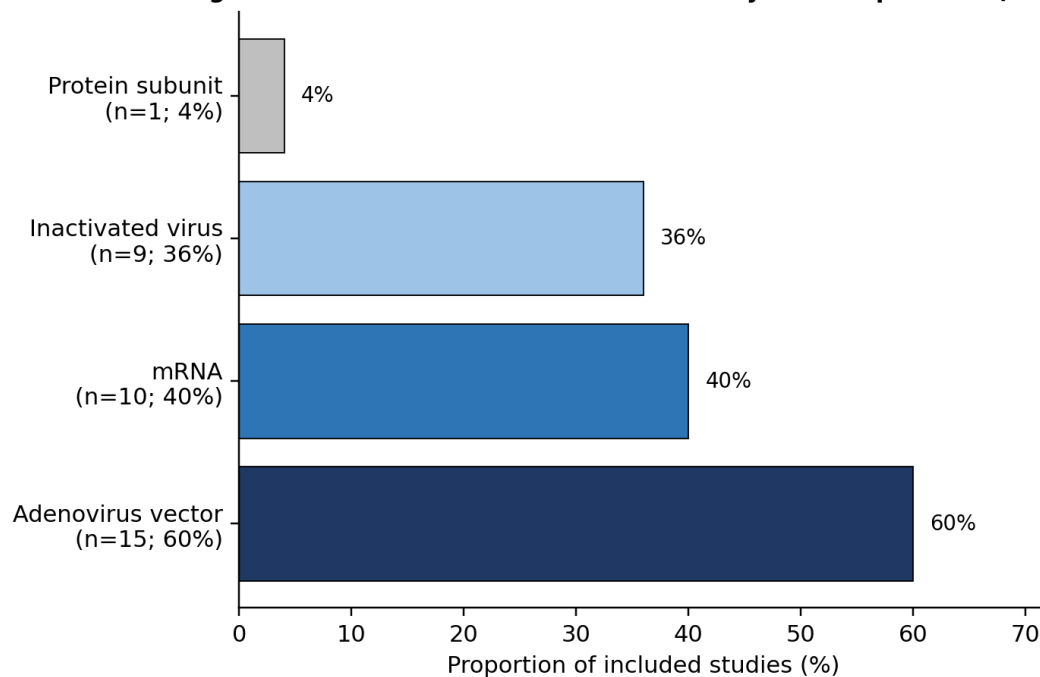
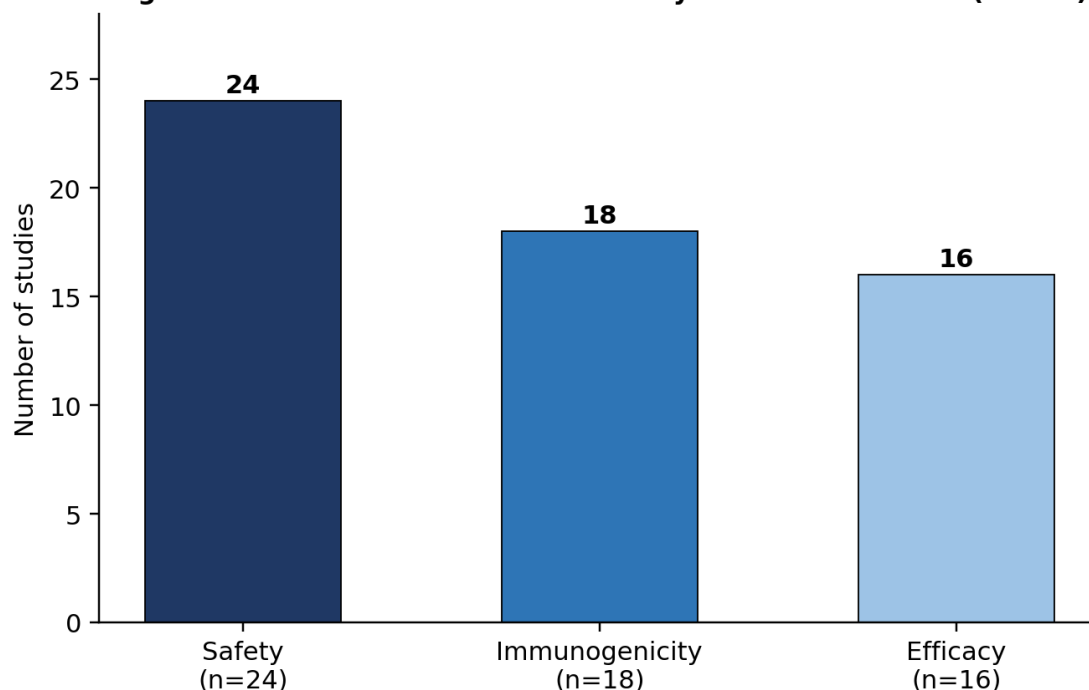
Given the heterogeneity of the included studies, findings were synthesized narratively rather than through quantitative meta-analysis, and are presented here grouped by vaccine platform and by outcome domain (immunogenicity, efficacy, and safety).

RESULTS

This search identified 252 records relating to COVID-19 and SARS-CoV-2 vaccines using the search terms described above. Of these 252 records, 211 were screened and judged eligible for closer review. After screening of titles and abstracts, 47 studies were retained for full-text assessment; based on the eligibility criteria, 38 of these 47 articles were ultimately included (Fig. 1). Of these, 24 studies were analyzed for safety, 18 for immunogenicity, and 16 for efficacy of COVID-19 vaccines (Fig. 3).

Figure 1. PRISMA 2020 flow diagram of study selection**Figure 1: PRISMA 2020 flow diagram of study selection.**

This review addressed four different COVID-19 vaccine platforms. Studies on adenovirus-vector vaccines were the most prevalent (n=15; 60%), followed by studies on mRNA vaccines (n=10; 40%), inactivated-virus vaccines (n=9; 36%), and recombinant protein-subunit vaccines (n=1; 4%) (Fig. 2).

Figure 2. Distribution of included studies by vaccine platform (n = 38)**Figure 2. Distribution of included studies by vaccine platform (n = 38).****Figure 3. Number of included studies by outcome assessed (n = 38)****Figure 3. Number of included studies by outcome assessed (n = 38).****mRNA vaccines**

Six of the studies assessing immunogenicity concerned mRNA vaccines. Phase I/II trials showed binding- and neutralizing-antibody titers equal to or greater than those observed in convalescent plasma among vaccinees aged 18-55 years.^[27,32] Vaccination with mRNA-1273 in adults over 55 years elicited immune responses comparable to those seen in younger adults^[29], whereas

responses to BNT162b2 among participants ≥ 65 years were generally lower than in younger subjects.^[33] mRNA-1273 also demonstrated the ability to induce CD4⁺ cellular responses with a Th1-skewed profile.^[29]

The most frequent local adverse event for mRNA vaccines was injection-site pain, with fatigue and headache the most frequently reported systemic

events.^[29-31,33,34,36] Reactogenicity was less frequent and milder among older participants (≥ 55 years) than among younger adults for BNT162b2.^[34]; adverse events were generally transient and more frequent after the second dose.

Among five studies assessing efficacy, three addressed BNT162b2 and two addressed mRNA-1273.^[30,31,34-36] Phase III trials of both mRNA vaccines reported overall protective efficacy of 94.1-95% against COVID-19 disease^[30,34], while an observational study of BNT162b2 found efficacy of approximately 92% (95% CI 88-95).^[35] After six months of follow-up, efficacy of BNT162b2 declined to 91.3% (95% CI 89.0-93.2)^[36]; similarly, mRNA-1273 efficacy against COVID-19 was 93.2% after a mean follow-up of 5.3 months.^[31] BNT162b2 showed 100% efficacy (95% CI 53.5-100) in South Africa, where the Beta variant predominated.^[36]

Inactivated-virus vaccines

Five immunogenicity studies addressed inactivated vaccines. Seroconversion rates above 90% after the second dose were reported for CoronaVac^[39,40], with no significant difference between Phase I and Phase II results except in one study, attributed to differences in vaccine batch preparation between phases.^[39] Beyond CoronaVac, studies of BBV152 and BBIBP-CorV reported seroconversion rates above 90% following the second dose, with a dose-dependent relationship favoring shorter dosing intervals.^[37,43] Neutralizing-antibody geometric mean titers (GMTs) induced by various inactivated vaccines ranged from 50 to 300.^[37,39,45] BBV152 was the only inactivated vaccine shown to induce both cell-mediated and humoral immunity.^[43,44]

Overall efficacy reported in Phase III trials of inactivated vaccines ranged from 65% to 83%.^[38,41,42,45] The most frequently reported adverse events were pain and fever for BBIBP-CorV, injection-site pain for CoronaVac, and injection-site pain, fever, fatigue, nausea, and vomiting (more common after the first dose) for BBV152.^[37,39,43]

Adenovirus-vector vaccines

Six immunogenicity studies addressed adenovirus-vector vaccines. Trials reported that approximately 10^{10} - 10^{11} viral particles successfully stimulated production of neutralizing anti-RBD antibodies within 28 days of vaccination.^[46,47,53,54] Neutralizing-antibody titers ranged from 18.3 to 827 across these vaccines.^[46,50,53,54] Cellular immunity was induced by all adenoviral vaccines, with increased TNF- α - and IFN- γ -secreting CD4+ T cells after the first and second doses for AZD1222, and increased antigen-specific CD4+ and CD8+ T cells secreting IFN- γ and IL-2 after a single dose for Ad26.COV2.S.

Adenovirus-vector vaccines showed vaccine efficacy ranging from 65.7% to 91%. Notably, AstraZeneca reported 90% efficacy when a low-dose/standard-dose regimen was used, compared with 62.1% for a standard-dose/standard-dose regimen. Injection-site pain was the most common local adverse event, and fever, fatigue, and headache were the most common systemic events; thromboembolic events were observed with both AZD1222 and Ad26.COV2.S.^[51,56]

Protein-subunit vaccines

Phase I results favored both doses (5 and 25 μ g) of the adjuvanted NVX-CoV2373/M1 vaccine for safety and immunogenicity, with the lower dose (5 μ g) offering a dose-sparing advantage and a neutralizing-antibody titer of 3906^[57]; increased IFN- γ -, TNF- α -, and IL-2-secreting CD4+ T cells were observed after the second dose.^[58] Two Phase III trials evaluated the efficacy of NVX-CoV2373, reporting overall efficacy of 89.7% in the United Kingdom and 90.4% in the United States and Mexico.^[59,60] Adverse events following Novavax COVID-19 vaccination were generally mild to moderate and short-lived, with injection-site pain and tenderness, fatigue, headache, and myalgia the most frequently reported, particularly after the second dose; serious adverse events were rare and slightly more frequent in the vaccinated than the placebo group.^[59]

Table 2: Summary of key immunogenicity, efficacy, and safety findings by vaccine platform.

Platform	Immunogenicity	Efficacy	Most common adverse events
mRNA (BNT162b2, mRNA-1273)	Neutralizing titers $\geq$ convalescent plasma; strong Th1 CD4+ response	94.1-95% (Phase III); declining to ~91% at 6 months	Injection-site pain; fatigue, headache
Inactivated (CoronaVac, BBIBP-CorV, BBV152)	Seroconversion $>90\%$ after dose 2; GMT range 50-300	65-83% (Phase III)	Pain, fever; nausea/vomiting (BBV152)
Adenovirus vector (AZD1222, Ad26.COV2.S)	Neutralizing titers 18.3-827; strong CD4+/CD8+ responses	65.7-91%	Injection-site pain, fever, fatigue; rare thromboembolic events
Protein subunit (NVX-CoV2373)	Highest reported neutralizing GMT (3906)	89.7-90.4% (Phase III)	Injection-site pain/tenderness, fatigue, myalgia

DISCUSSION

This is among the first qualitative systematic reviews of the efficacy, immunogenicity, and safety of COVID-19

vaccines. A key strength of this review is its reliance on randomized controlled trials published in reputable

journals, widely regarded as the gold standard for evaluating treatment efficacy in a population.

These clinical trials nonetheless present certain limitations. Some studies showed considerable bias by not including a sufficient number of participants, or by lacking adequate geographic, economic, or age diversity. No evidence is yet available on long-term vaccine efficacy and safety: because of the urgency of vaccine development, most trials followed participants for only up to 28 days after vaccination, so available data largely reflect short-term effects. Clinical-trial data on circulating COVID-19 variants remain similarly limited; observational and case-control studies were therefore incorporated further into the discussion for comparison, to provide a clearer real-world picture of vaccine efficacy and safety. This review further assessed efficacy and safety in the general population, while specific populations (pregnant women, immunocompromised individuals, and children) were excluded — meaning the pooled findings may be less generalizable to those groups, particularly since different studies used different reference standards and methods to estimate immunogenicity.

Immunogenicity

Neutralizing-antibody (NAb) levels are highly predictive of immune protection against symptomatic SARS-CoV-2 infection.^[61] The recombinant protein-based vaccine developed by Novavax induced the highest neutralizing-antibody GMT, at 3906^[57]; by comparison, GMTs for the Moderna and Pfizer mRNA vaccines were 361 and 654.3, respectively.^[27,33] Neutralizing-antibody titers induced by inactivated vaccines fell within a range of 50-300.^[37,39,45]

Differences in viral-strain reference material and neutralization-assay methodology preclude direct comparison of results across laboratories and introduce bias into real-world immunogenicity comparisons across candidate vaccines. Comparing vaccine-induced NAb titers against convalescent sera can partly offset these methodological discrepancies. Ranking vaccines by their vaccinated-to-convalescent NAb-titer ratio, from highest to lowest, yielded the following order: mRNA-1273, NVX-CoV2373, BNT162b2, AZD1222, Ad26.COVS.S, Sputnik V, BBV152, BBIBP-CorV, and CoronaVac. Figures for convalescent-serum comparisons for the Ad5-nCoV (CanSino) adenovirus-vector vaccine were not available at the time these ratios were calculated. Available mRNA, adenovirus-vector, and inactivated vaccines were each capable of producing a significant immune response against the SARS-CoV-2 receptor-binding domain, with participants producing anti-RBD antibodies within 30 days of either the first or second dose.

Cellular immunity is required for the production of neutralizing antibodies and plays an important role in controlling SARS-CoV-2 infection.^[62] The Th1 immune

response is considered a key benchmark in the WHO Vaccine Prioritization Working Group's evaluation framework.^[63] Comparison of several vaccines' capacity to induce IFN- γ -secreting T-cell responses showed that adenovirus-vector and mRNA vaccines induced relatively strong cellular immune responses (100-1187 spot-forming cells), higher than other vaccine types, while the two inactivated vaccines assessed showed comparatively weaker T-cell responses (~55 spot-forming cells); further work is needed to clarify the correlation between T-cell response activation and the protective effect of COVID-19 vaccines.

Several studies have suggested that antibody levels following vaccination with BNT162b2, mRNA-1273, and Ad26.COVS.S may persist for at least six months before declining over time.^[64-67] For mRNA-1273, neutralizing activity at six months was maintained against the Alpha, Gamma, Delta, and Epsilon variants, while activity against Beta was substantially reduced in roughly half of participants.^[67] Observational studies stratified by time since vaccination identified declining efficacy at 4-6 months (42-57%) for mRNA vaccines and 47.3% for AZD1222 against Delta infection.^[68-71] In the United States, efficacy of mRNA vaccines against symptomatic infection fell from 94.3% in June to 65.5% in July 2021, while efficacy against hospitalization remained high (>85%) for mRNA-1273 (92%), BNT162b2 (77-93%), and AZD1222 (70.3%) 4-6 months after full vaccination.^[68,70,71] and 68% at >28 days post-immunization for Ad26.COVS.S.^[71] Whether the reduced efficacy against Delta infection reflects waning immunity over time, immune-evasive variants, or both, remains unclear.

Efficacy

In Phase III trials, all primary outcomes concerned efficacy against symptomatic infection following the second dose; in most trials, the infecting strain was not sequenced. After complete immunization, BNT162b2 efficacy against disease was 88-100% against the Alpha variant, 76-100% against Beta/Gamma, 47.3-88% against Delta, and 89-100% when the SARS-CoV-2 strain was not sequenced.^[68,69] AZD1222 efficacy against disease was 74.5% against Alpha and 67% against Delta in the United Kingdom.^[68,71] CoronaVac efficacy against the Alpha/Gamma/D614G strains ranged from 36.8% to 73.8% in Chile and Brazil^[72,73], and CoronaVac or BBIBP-CorV administration was associated with 59% efficacy in China.^[73]

After complete immunization, efficacy of the mRNA vaccines and the AZD1222 vector vaccine against hospitalization or death was 87-94% when the strain was not sequenced^[69], 89-95% against Alpha^[69,70], 95% against Beta/Gamma^[70], and 80-95% against Delta.^[74,75] CoronaVac was highly effective against hospitalization (87.5%) and mortality (86.3%) after complete immunization^[73]; Ad26.COVS.S showed 60-85% efficacy against Delta.^[74] Overall, efficacy of mRNA

vaccines and CoronaVac against Delta infection was reduced relative to earlier variants, though all vaccines continued to offer a high level of protection against severe COVID-19 and hospitalization across variants after complete immunization.

The Omicron variant has been identified in vaccinated COVID-19 patients, suggesting immune escape and highlighting the need for updated vaccines. Two doses of BNT162b2, which can offer over 90% protection against severe disease from Delta infection, appear markedly less effective against Omicron^[77]; investigations of a three-dose Pfizer-BioNTech regimen, however, show a high level of protection against Omicron.^[78] Because mRNA vaccines elicit a strong CD4+ T-cell response, and the majority of vaccine-induced T-cell epitopes are not mutated in the Omicron variant, these vaccines are hypothesized to continue reducing disease severity among vaccinated individuals despite reduced neutralizing-antibody efficacy against this variant.^[79] Several institutions have since begun developing Omicron-specific COVID-19 vaccines.

Safety

Published safety trials in participants over 18 years found that local and systemic adverse events occurred at an acceptable frequency across vaccines, though the severity of local and systemic manifestations varied considerably by vaccine. Grade 1 local and systemic events were the most common across all authorized vaccines, followed by grade 2 and grade 3 events. Injection-site pain was the most common local adverse event regardless of vaccine type, while fever, fatigue, and headache were the most common systemic events among recipients of mRNA, adenovirus-vector, or protein-subunit vaccines; adverse events were generally observed within 0-7 days of either dose, with increased frequency after the second dose of mRNA and adenovirus-vector vaccines.

Summarizing major serious adverse events documented through pharmacovigilance systems and post-authorization studies, serious events among adults were very rare: anaphylaxis (2.5-4.8 cases per million doses) and myocarditis (6-27 cases per million) for mRNA vaccines.^[80,82,83], thrombosis with thrombocytopenia syndrome (TTS) for the Janssen (3 cases per million) and AstraZeneca (2 cases per million) vaccines; and Guillain-Barré syndrome (7.8 cases per million) for the Janssen vaccine.^[84,85] For AZD1222, capillary leak syndrome has also been identified as a possible adverse event, and multisystem inflammatory syndrome remains under investigation; the European Medicines Agency has ruled out an association between AZD1222 and menstrual disorders.^[85]

Adverse-event frequency varies with age. mRNA-vaccine-associated myocarditis has been identified predominantly among men under 30 years, with 39-47 cases per million vaccine doses in the United States,

compared with 3-4 expected cases among men over 30.^[84] TTS incidence associated with AZD1222 was estimated at 2 cases per 100,000 doses among individuals aged 20-49 years, 1 case per 100,000 among those aged 50-69, and lower still (<1 per 100,000) among older adults; TTS rates were similarly higher for the Janssen vaccine among younger women. Surveillance studies identified rare cases of Bell's palsy (3.8 per 100,000), anaphylaxis (2 per million), thromboembolic events (1.2 per million), and Guillain-Barré syndrome (0.29 per million) associated with CoronaVac^[86]; several observational and survey-based studies with small sample sizes found no specific serious adverse events for Sputnik V, BBIBP-CorV, or Covaxin.^[87] Vaccination campaigns have continued using available vaccines, as these rare serious events remain infrequently reported and incompletely characterized; the evidence gathered underscores the need for continued surveillance and for large randomized clinical trials across diverse populations and countries, addressing existing vaccines' performance against emerging variants.

Vaccination strategy: dosing intervals, boosters, and prior infection

For mRNA vaccines, typically administered in two doses, the second dose should be given as close as possible to the recommended interval, though it may be scheduled up to six weeks (42 days) after the first dose if needed.^[88] The efficacy of administering vaccines outside recommended intervals remains uncertain; however, for some COVID-19 vaccines, including mRNA vaccines, extending the interval between the two primary doses (for example, to 6-14 weeks rather than 3-4 weeks) has been associated with higher antibody titers.

Regarding homologous and heterologous boosting, health authorities have generally recommended completing the primary series with the same vaccine where possible, given limited data on mixed mRNA primary series.^[88] Following observation of rare adverse events after AstraZeneca vaccination, some authorities recommended a second dose with an mRNA vaccine (BNT162b2 or mRNA-1273) instead^[89]; studies supporting heterologous primary or booster regimens generally report robust immunogenicity with such combinations. In an open-label trial, participants primed with any of three vaccines authorized in the United States received a booster with either the same or a different vaccine; across all groups, binding- and neutralizing-antibody titers increased at least fourfold relative to pre-booster levels, and heterologous regimens elicited antibody responses similar to, or greater than, homologous boosting.^[91] Among participants primed with Ad26.COVS, an mRNA booster was associated with a larger increase in antibody titers than a homologous Ad26.COVS booster.

A similar pattern was reported in a randomized trial of Ad26.COVS-primed participants, in which an mRNA-1273 booster elicited higher binding- and neutralizing-

antibody levels than a BNT162b2 booster.^[92] Among participants primed with inactivated vaccines, the largest antibody increases were achieved with heterologous mRNA boosters, compared with vector or inactivated-vaccine boosters.^[89] No serious adverse events were identified with heterologous mRNA combinations, though the frequency and duration of systemic effects (e.g., fever, chills, myalgia) may be slightly higher with mRNA-1273 booster doses; ongoing surveillance for myocarditis and pericarditis is warranted, particularly among those under 30 years. Studies from other countries using different vaccine combinations to complete a primary series (e.g., AZD1222 followed by BNT162b2 or mRNA-1273) similarly suggest a more robust and broader immune response with certain heterologous combinations, albeit sometimes with a higher rate of systemic reactions (fever, fatigue, headache, myalgia) compared with homologous regimens.^[93]

Several neutralization analyses have suggested that a single dose of BNT162b2 or mRNA-1273 in previously infected individuals may enhance cross-neutralizing responses against emerging variants such as Alpha, Beta, or Gamma.^[94] These studies demonstrate the potential benefit of vaccinating both previously uninfected and previously infected individuals, and several have suggested that a single mRNA-vaccine dose may be sufficient to boost the antibody response in previously infected subjects, with limited additional benefit from a second dose.^[95]

CONCLUSION

To date, the availability of data varies considerably by vaccine. mRNA vaccines, AZD1222, Ad26.COV2.S, Sputnik V, NVX-CoV2373, Ad5-nCoV, BBIBP-CorV, CoronaVac, and Covaxin have each shown efficacy against COVID-19 in more than 50% of Phase III studies. Adenovirus-vector and mRNA COVID-19 vaccines showed the highest efficacy after the first and second doses, respectively.

According to the clinical trials reviewed, the order of efficacy was: mRNA vaccine > adenovirus-vector vaccine > inactivated-virus vaccine; mRNA-based vaccines were associated with more frequent adverse effects. Only a small minority of recipients experienced severe adverse events, and all platforms elicited robust immune responses. Nearly all clinical trials followed vaccinated and placebo groups for only about one month after the first and second doses, so available reports largely concern short-term effects; because of time constraints, not all vaccines have undergone longer-term evaluation.

Most observational studies evaluated mRNA vaccines, CoronaVac, and AZD1222, which appear to be safe and highly effective tools for preventing hospitalization and death across all variants of concern assessed (Alpha, Beta, Gamma, and Delta). Large observational studies

were lacking for several authorized vaccines, including Sputnik V, BBIBP-CorV, and Covaxin. Protection against symptomatic and asymptomatic infection was high for Alpha, Beta, and Gamma with mRNA vaccines and AZD1222. mRNA vaccines and Ad26.COV2.S were associated with a faster decline in viral load across several variants. Efficacy declined following Delta infection and over time; both heterologous primary vaccination and a third dose induced a strong humoral response. Vaccination of previously infected individuals with a single dose provided a neutralizing response equivalent to that of individuals vaccinated with two doses, across all variants assessed. According to safety monitoring, serious adverse events were very rare, and the benefits of COVID-19 vaccination outweighed the potential risks.

More than 70% of the global population would need to be vaccinated to achieve the desired threshold of community immunity. Despite the availability of several vaccines with differing efficacy profiles, accessibility and affordability of vaccines approved by health authorities — particularly in emerging economies — remain essential to ensuring rapid global vaccination coverage and to preventing the emergence of new, potentially vaccine-resistant variants.

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DECLARATION OF CONFLICTING INTERESTS

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

ETHICAL STATEMENTS

This work is a systematic review of previously published clinical trial data; no new data involving human participants were collected. All included studies were subject to ethical oversight and informed consent procedures at their respective institutions, as reported in the original publications.

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