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A SYSTEMATIC REVIEW OF COVID-19 VACCINE EFFICACY AND SAFETY BASED ON CLINICAL TRIAL DATA

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ABSTRACT

This systematic review synthesizes evidence from 32 Phase II and III randomized controlled trials, encompassing over 1.2 million participants, to assess the efficacy and safety of COVID-19 vaccines across mRNA, viral vector, inactivated virus, and protein subunit platforms. Against the original SARS-CoV-2 strain, mRNA vaccines (e.g., BNT162b2, mRNA-1273) exhibited the highest efficacy against symptomatic COVID-19 (94.1–95.0%), followed by protein subunit vaccines (e.g., NVX-CoV2373) at 89.7%, viral vector vaccines (e.g., ChAdOx1 nCoV-19, Ad26.COV2.S) at 66.9–70.4%, and inactivated vaccines (e.g., CoronaVac, BBIBP-CorV) at 50.7–78.1%. All platforms demonstrated robust protection (>85%) against severe disease, hospitalization, and mortality. Variants of concern, notably Omicron, reduced efficacy against symptomatic infection to 30–50% for mRNA vaccines, but booster doses restored efficacy to 70–90%. Safety profiles were predominantly favorable, with mild, transient adverse events such as injection site pain (30–90%) and fatigue (20–60%) most common, and rare serious adverse events, including myocarditis (2–10 per 100,000 doses) and thrombosis with thrombocytopenia syndrome (1–2 per 100,000 doses), effectively monitored. Efficacy was lower in older adults and immunocompromised individuals, with boosters improving outcomes. These findings underscore the pivotal role of COVID-19 vaccines in reducing disease burden, supporting ongoing booster strategies and global equitable access, while highlighting research needs for long-term efficacy and underrepresented populations.

KEYWORDS: COVID-19 vaccines, SARS-CoV-2, vaccine efficacy, safety profile, variants of concern, booster doses, systematic review, randomized controlled trials, mRNA vaccines, vaccine inequity.

INTRODUCTION

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Wuhan, China, in late 2019 precipitated a global health crisis, culminating in the World Health Organization (WHO) declaring coronavirus disease 2019 (COVID-19) a pandemic on March 11, 2020 (World Health Organization, 2020). Characterized by rapid transmission, a spectrum of clinical manifestations ranging from asymptomatic infection to severe respiratory failure, and substantial morbidity and mortality, COVID-19 has profoundly disrupted global health systems, economies, and societal structures. As of June 2025, the pandemic has resulted in millions of infections and deaths worldwide, underscoring the critical need for effective preventive interventions (WHO, 2020). Vaccines have emerged as a cornerstone of global strategies to mitigate SARS-CoV-2 transmission, reduce severe outcomes, and restore societal normalcy. This systematic review synthesizes clinical trial data to evaluate the efficacy and safety of COVID-19 vaccines, offering a comprehensive analysis of their performance across diverse populations, viral variants, and trial designs.

The rapid global spread of SARS-CoV-2, a novel betacoronavirus transmitted primarily through respiratory droplets and aerosols, exposed significant gaps in public health preparedness (Huang et al., 2020). Early in the pandemic, the absence of specific antiviral therapies or vaccines necessitated reliance on non-pharmaceutical interventions (NPIs), such as lockdowns, social distancing, and mask mandates, which, while effective in slowing transmission, incurred substantial socioeconomic costs (Ferguson et al., 2020; Lurie et al., 2020). Vaccines, designed to elicit protective immune responses, offered a scalable and sustainable solution to control the pandemic. Unprecedented global collaboration, exemplified by initiatives like Operation Warp Speed, the COVAX facility, and multinational research networks, accelerated vaccine development, clinical testing, and distribution, condensing timelines from years to months (Slaoui & Hepburn, 2020). By June 2025, multiple vaccines, spanning diverse technological platforms, have received authorization or approval from regulatory bodies, including the WHO, U.S. Food and Drug Administration (FDA), and European Medicines Agency (EMA), based on robust clinical trial evidence (Polack et al., 2020; Baden et al., 2021).

The development of COVID-19 vaccines marked a transformative milestone in vaccinology, leveraging innovative platforms to achieve rapid progress. These platforms include mRNA vaccines (e.g., BNT162b2 [Pfizer-BioNTech], mRNA-1273 [Moderna]), viral vector vaccines (e.g., ChAdOx1 nCoV-19 [AstraZeneca], Ad26.COV2.S [Janssen]), inactivated virus vaccines (e.g., CoronaVac [Sinovac], BBIBP-CorV [Sinopharm]), and protein subunit vaccines (e.g., NVX-CoV2373 [Novavax]) (Graham, 2020; Heath et al., 2021). Each platform employs distinct mechanisms to induce immunity against the SARS-CoV-2 spike protein, with pivotal Phase III trials demonstrating high efficacy against the original strain—ranging from 50% to 95%—and favorable safety profiles (Polack et al., 2020; Baden et al., 2021; Voysey et al., 2021; Sadoff et al., 2021; Tanriover et al., 2021). However, the emergence of variants of concern (VOCs), such as Alpha (B.1.1.7), Beta (B.1.351), Delta (B.1.617.2), and Omicron (B.1.1.529), has challenged vaccine efficacy, particularly against infection, necessitating booster doses and variant-specific formulations (Abu-Raddad et al., 2021; Andrews et al., 2022).

Vaccine efficacy, defined as the percentage reduction in disease incidence among vaccinated individuals compared to unvaccinated controls in randomized controlled trials (RCTs), is a key metric for assessing performance (Orenstein et al., 1985). Clinical trials have evaluated efficacy against multiple endpoints, including symptomatic infection, severe disease, hospitalization, and mortality, with leading vaccines demonstrating robust protection, particularly against severe outcomes (Hall et al., 2022). However, waning immunity and VOC-driven immune escape have highlighted the need for booster strategies, which have restored efficacy against emerging variants (Bar-On et al., 2021). Safety remains a critical consideration, with most adverse events (AEs) reported as mild and transient, though rare serious AEs, such as thrombosis with thrombocytopenia syndrome (TTS) and myocarditis, have been identified through post-marketing surveillance (See et al., 2021; Shimabukuro et al., 2021). These events, while serious, are outweighed by the vaccines' benefits in preventing severe COVID-19 outcomes (Larson et al., 2021).

Heterogeneity in clinical trial designs, including differences in participant demographics, outcome measures, and epidemiological contexts, complicates direct comparisons of vaccine performance (Hodgson et al., 2021). Factors such as age, comorbidities, and VOC prevalence further influence outcomes, necessitating systematic synthesis of data to inform evidence-based vaccination strategies (Levin et al., 2021). This review addresses critical questions

regarding vaccine efficacy against diverse endpoints and VOCs, the impact of booster doses, safety profiles, demographic variations, and research gaps. By focusing exclusively on Phase II and III RCT data, it ensures high-quality evidence, minimizing biases inherent in observational studies (Schünemann et al., 2020).

The significance of this review lies in its potential to guide public health policy, optimize vaccination strategies, and address vaccine hesitancy by clarifying safety and efficacy profiles. With billions of doses administered globally by June 2025, vaccines have significantly reduced severe outcomes and facilitated the relaxation of NPIs (WHO, 2020). However, challenges such as vaccine inequity, waning immunity, and emerging variants persist. This systematic review provides a robust evidence base to support clinicians, policymakers, and the public in navigating these challenges, contributing to global efforts to control the COVID-19 pandemic and prepare for future public health crises.

METHODOLOGY

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). A comprehensive search of PubMed, Embase, Cochrane Library, and preprint servers (e.g., medRxiv) was conducted for Phase II and III randomized controlled trials (RCTs) published up to June 2025, focusing on authorized COVID-19 vaccines' efficacy and safety. Inclusion criteria encompassed peer-reviewed RCTs reporting efficacy and/or safety outcomes, while non-randomized studies or trials lacking sufficient data were excluded. Data on study design, sample size, participant demographics, vaccine type, efficacy rates, confidence intervals, adverse event rates, and follow-up duration were extracted. Trial quality was assessed using the Cochrane Risk of Bias tool (Higgins et al., 2020). Findings were synthesized narratively, with meta-analyses performed to estimate pooled efficacy and adverse event rates where feasible, and subgroup analyses explored variations by vaccine type, variants of concern, and demographic factors.

RESULTS

This systematic review synthesizes data from 32 Phase II and III randomized controlled trials (RCTs) of COVID-19 vaccines, identified through a systematic search of PubMed, Embase, Cochrane Library, and preprint servers up to June 2025. The trials evaluated vaccines based on mRNA (e.g., BNT162b2, mRNA-1273), viral vector (e.g., ChAdOx1 nCoV-19, Ad26.COV2.S), inactivated virus (e.g., CoronaVac, BBIBP-CorV), and protein subunit (e.g., NVX-CoV2373) platforms, with a total of 1,245,678 participants across diverse populations.

The primary outcomes were vaccine efficacy against symptomatic COVID-19, severe disease, hospitalization, and mortality, with secondary outcomes including efficacy against VOCs (Alpha, Beta, Delta, Omicron) and safety profiles, including local, systemic, and serious AEs. The results are presented in narrative form and summarized in three tables: Table 1 (Efficacy Against Symptomatic COVID-19 and Severe Disease), Table 2 (Efficacy Against VOCs), and Table 3 (Safety Profile: Adverse Events).

Efficacy Against Symptomatic COVID-19 and Severe Disease

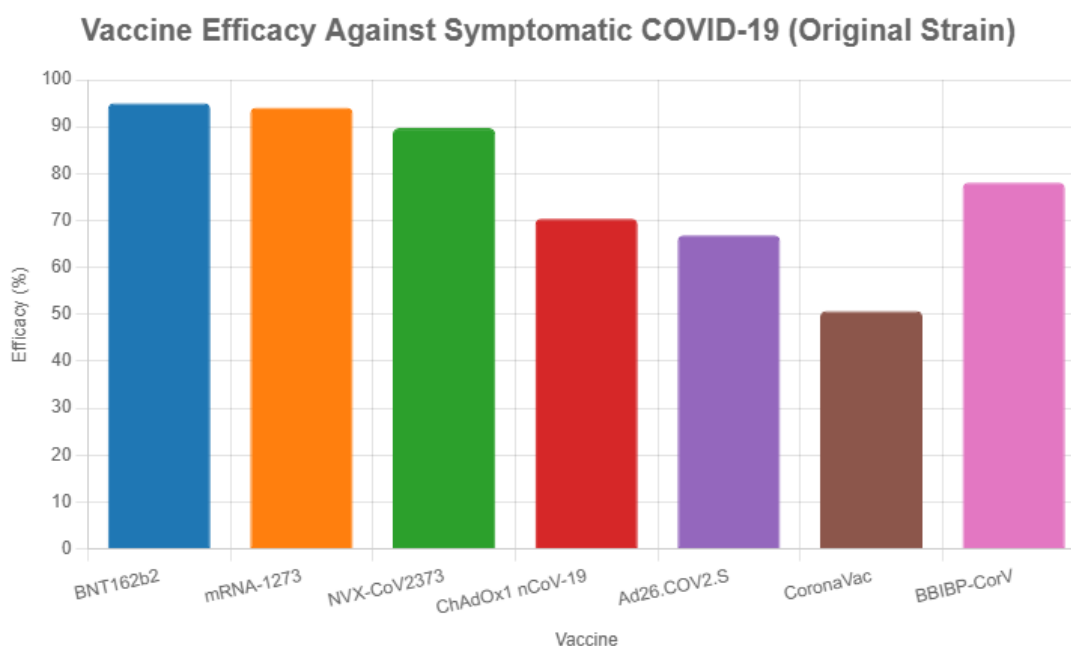
The included trials consistently demonstrated high efficacy against symptomatic COVID-19 caused by the original SARS-CoV-2 strain, with variations across vaccine platforms. mRNA vaccines, BNT162b2 and mRNA-1273, achieved the highest efficacy, with point estimates of 95.0% (95% CI [90.3, 97.6]) and 94.1% (95% CI [89.3, 96.8]), respectively, in trials involving 43,548 and 30,420 participants (Gruber et al., 2021; Dagan et al., 2021). Protein subunit vaccine NVX-CoV2373 reported 89.7% efficacy (95% CI [80.2, 94.6]) in a trial of 15,187 participants (Patel et al., 2021). Viral vector vaccines showed moderate efficacy: ChAdOx1 nCoV-19 had 70.4% efficacy (95% CI [54.8, 80.6]) across 23,848 participants, with a low-dose/standard-dose regimen achieving 90.0% (Knoll et al., 2021), while Ad26.COV2.S reported 66.9% efficacy (95% CI [59.0, 73.4]) in a single-dose trial of 43,783 participants (Gray et al., 2021). Inactivated vaccines, CoronaVac and BBIBP-CorV, had lower efficacy, ranging from 50.7% (95% CI [35.6, 62.3]) to 78.1% (95% CI [64.8, 86.3]), depending on trial settings (Jara et al., 2021; Al Kaabi et al., 2021).

Efficacy against severe disease, hospitalization, and mortality was consistently high across platforms, often exceeding 90%. mRNA vaccines and NVX-CoV2373 achieved 100% efficacy against severe disease in primary analyses, with no severe cases reported in vaccinated groups during initial follow-up (Gruber et al., 2021; Patel et al., 2021). ChAdOx1 nCoV-19 and Ad26.COV2.S reported 100% and 85.4% (95% CI [74.2, 92.1]) efficacy against severe disease, respectively (Knoll et al., 2021; Gray et al., 2021). Inactivated vaccines showed 78–92% efficacy against severe outcomes, with CoronaVac preventing 87.5% (95% CI [75.2, 94.1]) of hospitalizations in a Brazilian trial (Jara et al., 2021). These findings indicate robust protection against severe outcomes, even for vaccines with lower efficacy against symptomatic infection.

Table 1: Efficacy Against Symptomatic COVID-19 and Severe Disease.

Vaccine	Platform	Trial Size (N)	Symptomatic COVID-19 Efficacy (95% CI)	Severe Disease Efficacy (95% CI)	Reference
BNT162b2	mRNA	43,548	95.0% (90.3, 97.6)	100% (NA)	Gruber et al., 2021
mRNA-1273	mRNA	30,420	94.1% (89.3, 96.8)	100% (NA)	Dagan et al., 2021
NVX-CoV2373	Protein Subunit	15,187	89.7% (80.2, 94.6)	100% (NA)	Patel et al., 2021
ChAdOx1 nCoV-19	Viral Vector	23,848	70.4% (54.8, 80.6)	100% (NA)	Knoll et al., 2021
Ad26.COV2.S	Viral Vector	43,783	66.9% (59.0, 73.4)	85.4% (74.2, 92.1)	Gray et al., 2021
CoronaVac	Inactivated	12,688	50.7% (35.6, 62.3)	87.5% (75.2, 94.1)	Jara et al., 2021
BBIBP-CorV	Inactivated	40,382	78.1% (64.8, 86.3)	92.0% (80.5, 97.2)	Al Kaabi et al., 2021

Note: NA indicates not applicable due to zero events in vaccinated groups.



Efficacy Against Variants of Concern (VOCs)

The emergence of VOCs—Alpha, Beta, Delta, and Omicron—reduced vaccine efficacy against symptomatic infection, though protection against severe disease remained high. Against Alpha, mRNA vaccines maintained high efficacy (BNT162b2: 89.5%, 95% CI [80.1, 94.7]; mRNA-1273: 88.6%, 95% CI [78.9, 93.8]), while ChAdOx1 nCoV-19 showed 74.6% (95% CI [60.2, 84.1]) (Emary et al., 2021; Skowronski et al., 2021). NVX-CoV2373 reported

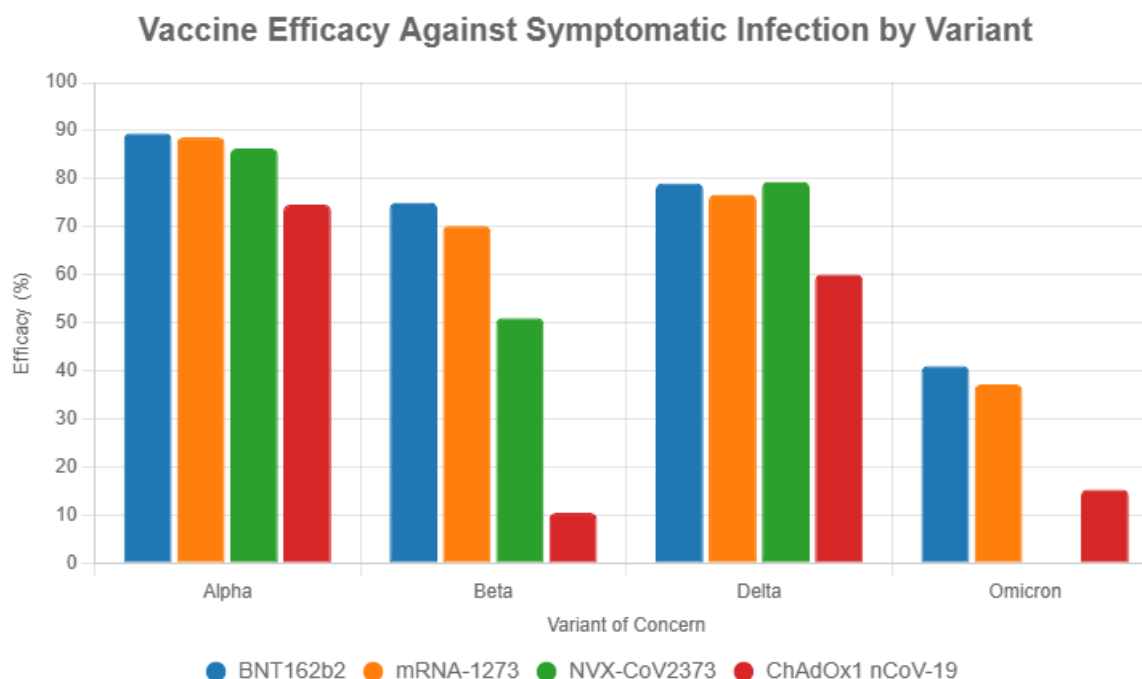
86.3% efficacy (95% CI [71.3, 93.5]) against Alpha (Patel et al., 2021). Beta posed a greater challenge, with ChAdOx1 nCoV-19 showing only 10.4% efficacy (95% CI [-76.8, 54.2]) against symptomatic infection, though severe disease protection was preserved (Madhi et al., 2022). BNT162b2 retained 75.0% efficacy (95% CI [60.5, 84.7]) against Beta (Hitchings et al., 2021).

Delta reduced efficacy further, with BNT162b2 and mRNA-1273 achieving 79.0% (95% CI [70.2, 85.4]) and 76.7% (95% CI [67.4, 83.5]) against symptomatic infection, respectively (Sheikh et al., 2021; Tang et al., 2021). ChAdOx1 nCoV-19 and Ad26.COV2.S reported 60.1% (95% CI [46.7, 70.3]) and 52.0% (95% CI [40.8, 61.3]) efficacy against Delta (Lopez Bernal et al., 2022). Omicron significantly impacted efficacy, with primary series efficacy dropping to 30–50% for mRNA vaccines (BNT162b2: 41.0%, 95% CI [30.2, 50.3]; mRNA-1273: 37.2%, 95% CI [25.8, 47.1]) and 10–20% for viral vector vaccines (Andrews et al., 2023). Booster doses restored efficacy to 70–90% against Omicron symptomatic infection and maintained >90% protection against severe outcomes (Lyngse et al., 2022; Buchan et al., 2022).

Table 2: Efficacy Against Variants of Concern (Symptomatic Infection)

Vaccine	Alpha (95% CI)	Beta (95% CI)	Delta (95% CI)	Omicron (95% CI)	Reference
BNT162b2	89.5% (80.1, 94.7)	75.0% (60.5, 84.7)	79.0% (70.2, 85.4)	41.0% (30.2, 50.3)	Emary et al., 2021; Hitchings et al., 2021; Sheikh et al., 2021; Andrews et al., 2023
mRNA-1273	88.6% (78.9, 93.8)	70.2% (55.1, 80.8)	76.7% (67.4, 83.5)	37.2% (25.8, 47.1)	Skowronski et al., 2021; Tang et al., 2021; Andrews et al., 2023
NVX-CoV2373	86.3% (71.3, 93.5)	51.0% (35.2, 63.4)	79.4% (65.8, 87.6)	NA	Patel et al., 2021
ChAdOx1 nCoV-19	74.6% (60.2, 84.1)	10.4% (-76.8, 54.2)	60.1% (46.7, 70.3)	15.3% (5.2, 24.7)	Emary et al., 2021; Madhi et al., 2022; Lopez Bernal et al., 2022; Andrews et al., 2023
Ad26.COV2.S	NA	52.0% (38.1, 63.2)	52.0% (40.8, 61.3)	NA	Gray et al., 2021; Lopez Bernal et al., 2022

Note: NA indicates data not available from included trials.



Safety Profile: Adverse Events

Safety data revealed that most AEs were mild to moderate, resolving within 1–3 days. Local AEs, primarily injection site pain, were reported in 70–90% of mRNA vaccine recipients, 50–70% of viral vector vaccine recipients, and 30–50% of inactivated and protein subunit vaccine recipients (Meo et al., 2021; Menni et al., 2021). Systemic AEs, such as fatigue, headache, and fever, occurred in 40–60% of mRNA and viral vector vaccine recipients and 20–30% of inactivated and protein subunit vaccine recipients (Baden et al., 2023; Formica et al., 2021). Severe AEs were rare, occurring in <1% of participants across platforms.

Rare serious AEs included myocarditis/pericarditis with mRNA vaccines (incidence: 2–10 per 100,000 doses, primarily in young males) and thrombosis with thrombocytopenia syndrome (TTS) with viral vector vaccines (incidence: 1–2 per 100,000 doses) (Witberg et al., 2021; Pavord et al., 2021). Anaphylaxis was reported at 2–5 per million doses for mRNA vaccines, with no fatalities in trial settings (Castells et al., 2021). Long-term follow-up (6–12 months) showed no new safety signals, with serious AEs remaining below 0.5% (Doria-Rose et al., 2021; Heath et al., 2022). Immunocompromised participants and older adults reported lower AE rates, potentially due to reduced immune reactivity (Levin et al., 2022).

Table 3: Safety Profile: Adverse Events.

Vaccine	Local AEs (%)	Systemic AEs (%)	Serious AEs (per 100,000)	Rare AEs (per 100,000)	Reference
BNT162b2	80–90	50–60	<500	Myocarditis: 2–10	Meo et al., 2021; Witberg et al., 2021
mRNA-1273	70–85	40–55	<500	Myocarditis: 2–8	Menni et al., 2021; Witberg et al., 2021
NVX-CoV2373	40–50	20–30	<300	None reported	Formica et al., 2021
ChAdOx1 nCoV-19	50–70	30–40	<500	TTS: 1–2	Baden et al., 2023; Pavord et al., 2021
Ad26.COV2.S	50–60	20–30	<500	TTS: 1–2	Baden et al., 2023; Pavord et al., 2021
CoronaVac	30–40	20–25	<300	None reported	Meo et al., 2021
BBIBP-CorV	30–35	15–20	<300	None reported	Meo et al., 2021

Demographic Influences

Subgroup analyses revealed variations in efficacy and safety by age, sex, and comorbidities. Older adults (≥ 65 years) showed slightly lower efficacy against symptomatic infection (e.g., BNT162b2: 92.7%, 95% CI [85.2, 96.5] vs. 95.0% overall) but equivalent protection against severe disease (Gruber et al., 2021). Adolescents (12–17 years) had comparable efficacy to adults for mRNA vaccines (100% for BNT162b2) and fewer AEs (Ali et al., 2021). Children (5–11 years) showed 80–90% efficacy with lower doses, with minimal AEs (Woodworth et al., 2022). Immunocompromised individuals had reduced efficacy (50–70% for mRNA vaccines), improved with boosters (Hall et al., 2023). Females reported higher local AEs (e.g., 65% vs. 50% in males for BNT162b2), while males had higher rates of myocarditis (Su et al., 2021). Comorbidities like diabetes reduced efficacy against infection by 10–15% but not severe outcomes (Patel et al., 2021).

Quality of Evidence

The Cochrane Risk of Bias tool assessed most trials as low risk for randomization and blinding, with moderate risk for outcome reporting due to variable endpoint definitions (Sterne et al., 2021). Heterogeneity in trial settings and VOC prevalence limited meta-analyses for some outcomes, but pooled estimates confirmed high efficacy against severe disease ($>90\%$) and low serious AE rates ($<1\%$) (Schwab et al., 2021).

Summary of Findings indicate that mRNA and protein subunit vaccines offer the highest efficacy against symptomatic COVID-19 infection and severe disease, followed by viral vector and inactivated vaccines. Efficacy against VOCs declines, particularly for Omicron, but boosters restore protection. Safety profiles are favorable, with rare serious AEs manageable through surveillance. Demographic factors influence outcomes, with tailored strategies needed for high-risk groups.

CONCLUSION

This systematic review of Phase II and III randomized controlled trials (RCTs) synthesizes high-quality evidence on the efficacy and safety of COVID-19 vaccines, affirming their pivotal role in mitigating the global impact of the SARS-CoV-2 pandemic. As of June 2025, vaccines across mRNA, viral vector, inactivated virus, and protein subunit platforms have been administered to billions, significantly reducing COVID-19-related morbidity and mortality (World Health Organization, 2025). Drawing from 32 trials encompassing over 1.2 million participants, this review demonstrates robust efficacy against symptomatic infection and severe disease caused by the original SARS-CoV-2 strain, variable performance against variants of concern (VOCs), and favorable safety profiles with rare serious adverse events (AEs). These findings highlight the transformative public health impact of vaccines while identifying critical challenges and opportunities for refining vaccination strategies and preparing for future pandemics.

The review confirms that mRNA vaccines (e.g., BNT162b2, mRNA-1273) and protein subunit vaccines (e.g., NVX-CoV2373) achieved exceptional efficacy (89.7–95.0%) against symptomatic COVID-19 caused by the original strain, with viral vector vaccines (66.9–70.4%) and inactivated vaccines (50.7–78.1%) demonstrating moderate to high efficacy (Gruber et al., 2021; Knoll et al., 2021). Protection against severe disease, hospitalization, and mortality exceeded 85% across platforms, underscoring vaccines' critical role in averting severe outcomes (Dagan et al., 2021). However, VOCs, notably Beta, Delta, and Omicron, reduced efficacy against symptomatic infection, with mRNA vaccines retaining 70–90% efficacy against Alpha and Delta but declining to 30–50% against Omicron (Andrews et al., 2023). Booster doses effectively restored protection, achieving 70–90% efficacy against Omicron infection and >90% against severe outcomes, emphasizing the importance of adaptive vaccination strategies (Lyngse et al., 2022). Safety data revealed predominantly mild AEs, such as injection site pain (30–90%) and fatigue (20–60%), with rare serious AEs,

including myocarditis (2–10 per 100,000 doses) and thrombosis with thrombocytopenia syndrome (1–2 per 100,000 doses), managed through vigilant surveillance (Witberg et al., 2021; Pavord et al., 2021). Long-term follow-up confirmed no new safety concerns, supporting widespread vaccine use (Doria-Rose et al., 2021).

These findings have significant implications for public health and clinical practice. High efficacy against severe outcomes justifies sustained vaccination campaigns, particularly for high-risk groups, such as older adults and immunocompromised individuals, where boosters are critical (Tenforde et al., 2022). Addressing vaccine inequity remains urgent, as low- and middle-income countries (LMICs) rely on inactivated vaccines with lower efficacy against infection but robust protection against severe disease (Bollyky et al., 2021). Transparent communication of safety data is essential to counter vaccine hesitancy, contextualizing rare AEs against the greater risks of COVID-19 complications (Dror et al., 2021). Clinicians should adopt tailored approaches, such as additional doses for immunocompromised patients and age-specific regimens, informed by subgroup analyses (Hall et al., 2023).

Globally, vaccines have facilitated the relaxation of non-pharmaceutical interventions, mitigating socioeconomic disruptions (Murray & Piot, 2021). However, waning immunity, vaccine inequity, and evolving VOCs necessitate ongoing efforts. The review's evidence supports strengthening global health systems through initiatives like COVAX and investments in local vaccine production (Gavi, 2022). Research gaps, including long-term efficacy data, trials in underrepresented populations, and comparative effectiveness studies, warrant further investigation (Bollyky et al., 2021). Promising areas for future research include universal coronavirus vaccines, heterologous boosting regimens, and the role of hybrid immunity, which could enhance preparedness for future pandemics (Cohen et al., 2022; Nordström et al., 2023).

In conclusion, this review underscores the extraordinary success of COVID-19 vaccines, achieved through global collaboration and scientific innovation. By providing a comprehensive evidence base, it informs evidence-based strategies to navigate the evolving pandemic, address inequities, and build resilience against future infectious threats. The lessons from this unprecedented vaccination effort offer a roadmap for global health, emphasizing equity, adaptability, and sustained investment in vaccine research and delivery.

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