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| 07/31/2025 | 103 | | FILED OPINION (MARY H. MURGUIA, KIM MCLANE WARDLAW, CONSUELO M. CALLAHAN, JOHN B. OWENS, MARK J. BENNETT, BRIDGET S. BADE, DANIEL P. COLLINS, KENNETH K. LEE, DANIELLE J. FORREST, SALVADOR MENDOZA, JR. and ROOPALI H. DESAI) AFFIRMED. Opinion by Judge Bennett; Dissent by Judge Owens; Partial Dissent by Judge Lee. FILED AND ENTERED JUDGMENT. [12935203] −−[Edited: Forward dated entry to reflect correct filing date. 07/31/2025 by TYL] (MM) |
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**FOR PUBLICATION**

# UNITED STATES COURT OF APPEALS
# FOR THE NINTH CIRCUIT

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| HEALTH FREEDOM DEFENSE FUND, INC., a Wyoming Not-for-Profit Corporation; JEFFREY FUENTES; SANDRA GARCIA; HOVHANNES SAPONGHIAN; NORMA BRAMBILA; CALIFORNIA EDUCATORS FOR MEDICAL FREEDOM,<br><br>*Plaintiffs-Appellants*,<br><br>v.<br><br>ALBERTO CARVALHO, in his official capacity as Superintendent of the Los Angeles Unified School District; ILEANA DAVALOS, in her official capacity as Chief Human Resources Officer for the Los Angeles School District; GEORGE MCKENNA; MONICA GARCIA; SCOTT SCHMERELSON; NICK MELVOIN; JACKIE GOLDBERG; KELLY GONEZ; TANYA ORTIZ FRANKLIN, in their official capacities as members of the Los Angeles Unified School District governing board, | No. 22-55908<br><br>D.C. No. 2:21-cv-08688-DSF-PVC<br><br>OPINION |

*Defendants-Appellees*.

Appeal from the United States District Court
for the Central District of California
Dale S. Fischer, District Judge, Presiding

Argued and Submitted En Banc March 18, 2025
San Francisco, California

Filed July 31, 2025

Before: Mary H. Murguia, Chief Judge, and Kim McLane Wardlaw, Consuelo M. Callahan, John B. Owens, Mark J. Bennett, Bridget S. Bade, Daniel P. Collins, Kenneth K. Lee, Danielle J. Forrest, Salvador Mendoza, Jr. and Roopali H. Desai, Circuit Judges.

Opinion by Judge Bennett;
Dissent by Judge Owens;
Partial Dissent by Judge Lee

## SUMMARY*

### COVID-19 Vaccination Policy

The en banc court affirmed the district court's judgment on the pleadings in favor of the Los Angeles Unified School

* This summary constitutes no part of the opinion of the court. It has been prepared by court staff for the convenience of the reader.

District (LAUSD) in an action brought pursuant to 42 U.S.C. § 1983 alleging that LAUSD's COVID-19 vaccination policy (the Policy), which required all employees to be fully vaccinated, violated plaintiffs' substantive due process and equal protection rights.

Plaintiffs alleged that the Policy violated their fundamental right to bodily integrity in refusing medical treatment because COVID-19 vaccines are therapeutic treatments that reduce symptoms but do not prevent infection or transmission and additionally pose significant health risks to the recipients. Plaintiffs also alleged that the Policy violated their right to equal protection because it arbitrarily classifies employees based on their vaccination status.

As a threshold issue, the en banc court held that this case was not moot. Although LAUSD rescinded the Policy shortly after oral argument before the three-judge panel, the court could still grant effective relief by ordering reinstatement of the individual plaintiffs who remain terminated from their original positions under the Policy.

On the merits, the en banc court, joining all the sister circuits that have considered substantive due process challenges to COVID-19 vaccine mandates, held that the Policy was subject to rational basis review because *Jacobson v. Massachusetts*, 197 U.S. 11 (1905), which upheld a smallpox vaccine mandate, remains binding. *Jacobson* holds that the constitutionality of a vaccine mandate, like the Policy here, turns on what reasonable legislative and executive decisionmakers could have rationally concluded about whether a vaccine protects the public's health and safety, not whether a vaccine actually provides immunity to or prevents transmission of a disease.

The Policy survives such review, as the LAUSD could have reasonably concluded that COVID-19 vaccines would protect the health and safety of its employees and students. For this reason, plaintiffs' equal protection claim also failed under rational basis review. The en banc court therefore affirmed the district court's order granting LAUSD's motion for judgment on the pleadings.

Dissenting, Judge Owens wrote that the court lacks jurisdiction because the case is moot, given that there is no longer any policy for the court to enjoin or declare unlawful. Nothing in the record (or the world) even hints at the possibility that LAUSD would resurrect its COVID-19 vaccine mandate. The majority's assertion that the complaint's boilerplate language fairly encompassed a request for employment reinstatement did not survive close inspection.

Dissenting in part, Judge Lee, joined by Judge Collins, wrote that although he agrees that the case is not moot, he believes that the court should not affirm the dismissal of this lawsuit without permitting the plaintiffs to offer evidence to rebut government officials' far-reaching claims. Contrary to the majority, he read the Supreme Court's decision in *Jacobson* as applying only if a vaccine prevents the transmission and contraction of a disease. The plaintiffs here plausibly claimed—at least at the pleading stage—that the COVID-19 vaccine mitigates serious symptoms but does not "prevent transmission or contraction of COVID-19." And if that is true, then *Jacobson*'s rational basis review does not apply, and the court must examine the vaccine mandate under a more stringent standard of review. Ultimately, the plaintiffs may be wrong about the COVID-19 vaccine, but they should be given a chance to challenge the government's assertions about it.

## COUNSEL

Scott J. Street (argued) and John W. Howard, JW Howard Attorneys Ltd., San Diego, California; George R. Wentz Jr., The Davillier Law Group LLC, New Orleans, Louisiana; for Plaintiffs-Appellants.

Keith A. Jacoby (argued) and Connie L. Michaels, Littler Mendelson PC, Los Angeles, California; Carrie A. Stringham, Littler Mendelson PC, San Diego, California; for Defendants-Appellees.

Leigh A. Salmon, Senior Assistant Attorney General; Benjamin Gutman, Solicitor General; Dan Rayfield, Attorney General; State of Oregon, Salem, Oregon; Rob Bonta, Attorney General, State of California, San Francisco, California; Kathleen Jennings, Attorney General, State of Delaware, Wilmington, Delaware; Kwame Raoul, Attorney General, State of Illinois, Chicago, Illinois; William Tong, Attorney General, State of Connecticut, Hartford, Connecticut; Anne E. Lopez, Attorney General, State of Hawai‘i, Honolulu, Hawai‘i; Anthony G. Brown, Attorney General, State of Maryland, Baltimore, Maryland; Andrea J. Campbell, Attorney General, Commonwealth of Massachusetts, Boston, Massachusetts; Keith Ellison, Attorney General, State of Minnesota, St. Paul, Minnesota; Raul Torrez, Attorney General, State of New Mexico, Santa Fe, New Mexico; Charity R. Clark, Attorney General, Office of the Vermont Attorney General, Montpelier, Vermont; Brian L. Schwalb, Attorney General, District of Columbia, Washington, D.C.; Peter F. Neronha, Attorney General, State of Rhode Island, Providence, Rhode Island; Dana Nessel, Attorney General, State of Michigan; Lansing, Michigan; Matthew J. Platkin, Attorney General, State of New Jersey, Trenton, New Jersey; Letitia James, Attorney

General, Office of the New York State Attorney General, Albany, New York; Nicholas W. Brown, Attorney General, State of Washington, Olympia, Washington; Edward E. Manibusan, Attorney General, Commonwealth of the Northern Mariana Islands, Saipan, Northern Mariana Islands; for Amici Curiae States of Oregon, California, Connecticut, Delaware, Hawai'i, Illinois, Maryland, Massachusetts, Michigan, Minnesota, New Jersey, New Mexico, New York, Rhode Island, Vermont, and Washington, and the District of Columbia, and the Commonwealth of the Northern Mariana Islands.

Sloan R. Simmons, Alyssa R. Bivins, and Ryan I. Ichinaga, Lozano Smith LLP, Sacramento, California; Kristin Lindgren-Bruzzone, California School Boards Association's Education Legal Alliance, West Sacramento, California; for Amicus Curiae California School Boards Association's Education Legal Alliance.

Gregory Dolin, Mark Chenoweth, and Jenin Younes, New Civil Liberties Alliance, Arlington, Virginia, for Amicus Curiae New Civil Liberties Alliance.

## OPINION

BENNETT, Circuit Judge:

This case concerns the Los Angeles Unified School District's ("LAUSD") COVID-19 vaccination policy ("Policy"), which essentially required all of its employees to be fully vaccinated. As relevant here, Plaintiffs[1] filed suit under 42 U.S.C. § 1983, claiming that the Policy violated their Fourteenth Amendment substantive due process and equal protection rights. The district court granted judgment on the pleadings to the LAUSD.[2] Plaintiffs appeal. We have jurisdiction under 28 U.S.C. § 1291 and affirm.

As a threshold issue, this case is not moot. Although the LAUSD rescinded the Policy shortly after oral argument before the three-judge panel, a court could still grant effective relief by ordering reinstatement of the individual Plaintiffs who remain terminated from their original positions under the Policy.

On the merits, we hold that the Policy is subject to rational basis review because *Jacobson v. Massachusetts*, 197 U.S. 11 (1905), is binding and controls. The Policy survives such review, as the LAUSD could have reasonably concluded that COVID-19 vaccines would protect the health and safety of its employees and students. For this reason, Plaintiffs' equal protection claim also fails under rational

[1] "Plaintiffs" are the Health Freedom Defense Fund, California Educators for Medical Freedom, and certain individuals who are or were employed by the LAUSD.

[2] Defendants are LAUSD employees and board members, named in their official capacities. For simplicity, we refer to defendants collectively as the "LAUSD."

basis review. We therefore affirm the district court's order granting the LAUSD's motion for judgment on the pleadings.

## BACKGROUND AND PROCEDURAL HISTORY[3]

On January 30, 2020, the World Health Organization declared COVID-19 a public health emergency. The next day, President Trump and the Secretary of Health and Human Services ("Secretary") declared COVID-19 a public health emergency. These emergency declarations were renewed and extended into at least 2021. In February 2021, President Biden extended the emergency declaration because more than "500,000 people in th[e] Nation ha[d] perished from the disease." The Secretary renewed his emergency declaration in January, April, and July 2021.

On August 13, 2021, the LAUSD issued the Policy challenged here. The Policy established a mandatory vaccination requirement for all LAUSD employees. Under the Policy, employees had to be fully vaccinated[4] against COVID-19 by October 15, 2021. The Policy allowed employees to apply for religious or medical exemptions. But even "exempt" employees were excludable from the

[3] These facts are based on the allegations in the operative second amended complaint, which we accept as true and construe in Plaintiffs' favor. *See Fleming v. Pickard*, 581 F.3d 922, 925 (9th Cir. 2009). We also consider documents incorporated into the complaint by reference. *See Webb v. Trader Joe's Co.*, 999 F.3d 1196, 1201 (9th Cir. 2021). We GRANT Plaintiffs' motion to take judicial notice that the LAUSD voted to withdraw the Policy on September 26, 2023. Dkt. No. 46.

[4] The Policy defines "fully-vaccinated" as having "received the first and second doses of the vaccine (or, in the case of Johnson & Johnson, the single required dose) and [having] completed the two-week period that follows to ensure maximum immunity."

workplace "[i]f a risk to the health and safety of others [could not] be reduced to an acceptable level through a workplace accommodation." The Policy explained that its purpose was to "provide the safest possible environment in which to learn and work."

At the time the LAUSD issued the Policy, health experts had been recommending that individuals get COVID-19 vaccinations and had been reporting that such vaccinations are effective in preventing and spreading the disease. For example, the U.S. Centers for Disease Control and Prevention ("CDC") reported that COVID-19 vaccines "are highly effective at protecting vaccinated people against symptomatic and severe COVID-19," and "[f]ully vaccinated people are less likely to become infected" and "less likely to get and spread SARS-CoV-2." *Interim Public Health Recommendations for Fully Vaccinated People*, CDC (July 28, 2021), https://stacks.cdc.gov/view/cdc/108355 [https://perma.cc/AMW8-KH3Z]. The director of the CDC reiterated that COVID-19 vaccines prevent "severe illness and death." Madeline Holcombe & Christina Maxouris, *Fully Vaccinated People Who Get a Covid-19 Breakthrough Infection Can Transmit the Virus, CDC Chief Says*, CNN Health (Aug. 6, 2021), https://edition.cnn.com/2021/08/05/health/us-coronavirus-thursday/index.html [https://perma.cc/Z5RV-UPLR]. Other experts urged that "[g]etting more people vaccinated . . . w[ould] help prevent other—potentially even more aggressive—variants from arising in the future." *Id.* A former CDC director explained that "outbreaks . . . w[ould] not be as explosive in areas with higher vaccination coverage." *Id.* And a children's hospital

president characterized "adult vaccination" as a "simple solution" to protect children from COVID-19. *Id.*

After the LAUSD issued the Policy, health experts continued to urge the public to get vaccinated. Indeed, the CDC reported that "[v]accines remain the best public health measure to protect people from COVID-19, slow transmission, and reduce the likelihood of new variants emerging." *Omicron Variant: What You Need to Know*, CDC (Dec. 9, 2021), https://stacks.cdc.gov/view/cdc/112430 [https://perma.cc/B4EG-5QMR]. The CDC recommended that "everyone 5 years and older protect themselves from COVID-19 by getting fully vaccinated." *Id.*

In November 2021, Plaintiffs filed this suit challenging the Policy. The operative second amended complaint ("SAC") alleges that, under the Policy, the LAUSD threatened to terminate employees who failed to get the COVID-19 vaccination. According to the SAC, the LAUSD terminated at least two of the individual Plaintiffs based on their refusal to get vaccinated.

Although the SAC asserts several state and federal law claims, the only claims before us are Plaintiffs' Fourteenth Amendment substantive due process and equal protection claims brought under 42 U.S.C. § 1983. As to their due process claim, Plaintiffs allege that the Policy violates their fundamental right to bodily integrity in refusing medical treatment, as the vaccines are "therapeutic treatments for COVID and not vaccines at all." According to Plaintiffs, COVID-19 vaccines do not prevent infection or transmission of COVID-19. Instead, the vaccines "only reduce symptoms of those who are infected by COVID," and thus they are medical "treatments" and not traditional vaccines. The SAC

also alleges that the COVID-19 vaccines "cause a significantly higher incidence of injuries, adverse reactions, and deaths than any prior vaccines that have been allowed to remain on the market, and, therefore, pose a significant health risk to recipients."

Plaintiffs also claim that the Policy violates their right to equal protection because it arbitrarily classifies employees based on their vaccination status. The SAC alleges that vaccinated and unvaccinated employees are similarly situated because both groups can be infected with and transmit COVID-19. Thus, in Plaintiffs' view, the Policy arbitrarily treats the unvaccinated differently.

In terms of relief, the SAC seeks "[t]emporary, preliminary, and permanent injunctive relief restraining [the LAUSD] from enforcing" the Policy. It also contains a general prayer for relief for "such other and further relief as the Court may deem just and proper."

The LAUSD moved for judgment on the pleadings under Federal Rule of Civil Procedure 12(c), and the district court granted the motion in September 2022. The court determined that, under *Jacobson*, the substantive due process claim failed because the Policy did not violate any fundamental right and survived rational basis review. The district court also decided that the equal protection claim failed under rational basis review. The district court's order permitted Plaintiffs to amend their equal protection and ADA claims. Plaintiffs declined to do so and instead timely appealed.

A divided three-judge panel of our court vacated the district court's order and remanded. *Health Freedom Def. Fund, Inc. v. Carvalho*, 104 F.4th 715, 718 (9th Cir. 2024), *vacated and reh'g en banc granted*, 127 F.4th 750 (9th Cir.

2025). Before addressing the merits, the panel considered whether the case had become moot in light of the LAUSD's recent recission of the Policy (twelve days after oral argument). *Id.* at 721–22. Applying the voluntary cessation exception to mootness, the panel majority determined that the case was not moot because the LAUSD had failed to show it was reasonably clear that the Policy would not be reinstated.[5] *Id.* at 722–24. Judge Hawkins dissented from the majority's mootness determination. *Id.* at 728–32 (Hawkins, J., dissenting). In his view, the case was moot "[b]ecause there [wa]s no longer any policy for the court to enjoin or declare unlawful." *Id.* at 732 (Hawkins, J., dissenting).

On the merits, the panel majority held that the district court erred in applying *Jacobson*. *Id.* at 724–25. The majority reasoned that *Jacobson* did not apply, much less control, because it addressed only those vaccines that provide immunity and prevent transmission. *Id.* Because Plaintiffs alleged that COVID-19 vaccines, unlike traditional vaccines, do not provide immunity and prevent transmission (and the court must accept those allegations as true at the judgment-on-the-pleadings stage), the panel majority held that *Jacobson* did not apply. *Id.* Therefore, the panel vacated the district court's order and remanded for further proceedings. *Id.* at 725.

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[5] *See Rosemere Neighborhood Ass'n v. EPA*, 581 F.3d 1169, 1173 (9th Cir. 2009) ("Under [the voluntary cessation exception to mootness], the mere cessation of illegal activity in response to pending litigation does not moot a case, unless the party alleging mootness can show that the 'allegedly wrongful behavior could not reasonably be expected to recur.'" (quoting *Friends of the Earth, Inc. v. Laidlaw Env't Servs. (TOC), Inc.*, 528 U.S. 167, 189 (2000))).

The LAUSD petitioned for rehearing en banc. Dkt. No. 56. While it continued to urge that the case was moot, the LAUSD also argued that the three-judge panel had misapplied *Jacobson*, creating a conflict with our sister circuits. *Id.* at 13–17. A majority of our active judges voted to rehear this case en banc, and we vacated the three-judge panel opinion. *Health Freedom*, 127 F.4th 750.

## STANDARD OF REVIEW

"We review de novo an order granting a Rule 12(c) motion for judgment on the pleadings. We must accept all factual allegations in the complaint as true and construe them in the light most favorable to the non-moving party." *Fleming v. Pickard*, 581 F.3d 922, 925 (9th Cir. 2009) (citation omitted). Along with the complaint, we may also consider documents incorporated into the complaint by reference and matters of which we may take judicial notice. *Webb v. Trader Joe's Co.*, 999 F.3d 1196, 1201 (9th Cir. 2021). "Judgment on the pleadings is properly granted when there is no issue of material fact in dispute, and the moving party is entitled to judgment as a matter of law." *Fleming*, 581 F.3d at 925.

## DISCUSSION

### I.

We first explain why this case is not moot even though the Policy has been rescinded. "The test for mootness of an appeal is whether the appellate court can give the [plaintiff] *any* effective relief in the event that it decides the matter on the merits in his favor. If it can grant such relief, the matter is not moot." *Garcia v. Lawn*, 805 F.2d 1400, 1402 (9th Cir. 1986) (emphasis added). In the context of injunctive relief, a case is not moot if the court is able to "undo" the effects of

the alleged illegal action. *Id.*; *see, e.g.*, *id.* ("The question [of mootness] thus becomes whether we can now give [plaintiff] effective relief which would 'undo' the effects of the alleged retaliatory action . . . .").

The SAC seeks "injunctive relief restraining [the LAUSD] from enforcing the [Policy]" and "other and further relief as the Court may deem just and proper." The SAC also alleges that one of the individual Plaintiffs was terminated from employment by the LAUSD for refusing to be vaccinated and another was "separated from his employment with LAUSD" after objecting to being vaccinated. There is no suggestion that these individuals have been reinstated,[6] and so construing these allegations in Plaintiffs' favor, *see Fleming*, 581 F.3d at 925, we accept that these individuals remain terminated from their original positions.

Given the SAC's broad request for *any* proper injunctive relief, along with the allegations that individual Plaintiffs have been terminated under the Policy and have not been reinstated to their prior positions, the SAC fairly encompasses a request for reinstatement. *See Garcia*, 805 F.2d at 1402–04 (noting that reinstatement to a prior position can be a proper injunctive remedy). Because reinstatement would undo some effects of the alleged illegal action—the LAUSD's enforcement of the Policy—a court could grant effective relief despite the Policy's rescission.[7] Thus, this

[6] Indeed, during en banc oral argument, Plaintiffs' counsel represented that at least one individual remains terminated from his original full-time position. Oral Arg. at 1:47–2:12.

[7] During en banc oral argument, Plaintiffs' counsel confirmed that if the case were remanded, Plaintiffs would explicitly seek reinstatement for all the individual Plaintiffs who have not been reinstated to their former positions. Oral Arg. at 52:14–52:25.

case is not moot.[8] *See id.* at 1402–03 (holding, in an action seeking an injunction, that the case was not moot because the court could order reinstatement of the plaintiff to his prior position); *see also Norris v. Stanley*, 73 F.4th 431, 433 n.1 (6th Cir. 2023) (holding, in similar circumstances, that the case was not moot despite rescission of the vaccine policy at issue because, among other reasons, there was no "indication that [the university] ha[d] undone any of the negative employment actions faced by [some of the plaintiffs], so the harm plaintiffs faced ha[d] not been removed"), *cert. denied*, 144 S. Ct. 1353 (2024).

Our precedent supports that this case is not moot. In *Neighbors of Cuddy Mountain v. Alexander*, 303 F.3d 1059 (9th Cir. 2002), the plaintiffs sought an injunction to stop a timber sale on national forest land. *Id.* at 1064–65. Although the timber sale had been completed, we held that the case was not moot because the alleged "harm to old growth species may yet be remedied by any number of mitigation strategies." *Id.* at 1066. Significantly, we held that such mitigation measures were fairly requested in the complaint because "[i]n addition to an injunction, [the plaintiffs'] complaint request[ed] 'such further relief as may

[8] For this reason, the LAUSD's motion to dismiss is DENIED, Dkt. No. 49, and we need not (and do not) decide whether the voluntary cessation exception to mootness applies. We also need not address whether our recent decision in *Kohn v. State Bar of California*, 87 F.4th 1021 (9th Cir. 2023) (en banc), *cert. denied*, 144 S. Ct. 1465 (2024), would permit Plaintiffs to seek damages against the LAUSD. *See Health Freedom*, 104 F.4th at 726–27 (R. Nelson, J., concurring) (opining that *Kohn* may conflict with our precedent holding that California school districts have sovereign immunity under the Eleventh Amendment); *id.* at 727 n.2 (R. Nelson, J., concurring) ("If LAUSD does not have sovereign immunity, Plaintiffs may be able to amend to raise a monetary claim, which would be another reason this case is not moot.").

be necessary and appropriate to avoid further irreparable harm.'" *Id.* In so holding, we noted that our prior case law had recognized that we "may construe such requests for [other appropriate] relief 'broadly to avoid mootness.'" *Id.* (quoting *Headwaters, Inc. v. Bureau of Land Mgmt.*, 893 F.2d 1012, 1015 n.6 (9th Cir. 1989)); *see also Oregon Nat. Desert Ass'n v. U.S. Forest Serv.*, 957 F.3d 1024, 1032 n.7 (9th Cir. 2020) (explaining that, even though the complaint "ask[ed] for injunctive relief only with respect to claims that [were] not on appeal," "we c[ould] consider further injunctive relief in deciding whether th[e] appeal [wa]s moot" because the complaint "also request[ed] 'any such further relief as requested by the Plaintiffs or as this Court deems just and proper'" (citing *Neighbors of Cuddy Mountain*, 303 F.3d at 1066)).[9]

[9] Judge Owens's dissent argues that *Neighbors of Cuddy Mountain*'s mootness rationale should be limited to "the narrow context of [National Forest Management Act] and [National Environmental Policy Act] violations." Owens Dissent at 33. But we do not read *Neighbors of Cuddy Mountain* as suggesting such a limitation. *See* 303 F.3d at 1065–66. Indeed, in *Neighbors of Cuddy Mountain*, our mootness analysis derived from the generally applicable and longstanding principle that "a case is moot only where no effective relief for the alleged violation can be given." *Id.* at 1065; *see also Garcia*, 805 F.2d at 1402 (noting that "[t]he test for mootness of an appeal"—"whether the appellate court can give the appellant any effective relief in the event that it decides the matter on the merits in his favor"—"goes back at least to" the Supreme Court's decision in *Mills v. Green*, 159 U.S. 651 (1895)).

We also note that our conclusion that this case is not moot is consistent with *Z Channel Limited Partnership v. Home Box Office, Inc.*, 931 F.2d 1338 (9th Cir. 1991). Federal Rule of Civil Procedure 54(c) provides that a final judgment "should grant the relief to which each party is entitled, even if the party has not demanded that relief in its pleadings." In *Z Channel*, "[t]he only relief expressly requested [in the

Contrary to Judge Owens's suggestion in his dissent, *Arizonans for Official English v. Arizona*, 520 U.S. 43 (1997), does not undermine our conclusion that this case is not moot. In *Arizonans for Official English*, the Supreme Court noted that we had held that the case was not moot because the plaintiff's broad request for "other relief" could encompass a request for nominal damages. *Id.* at 60 (quoting *Yniguez v. Arizona*, 975 F.2d 646, 647 n.1 (9th Cir. 1992) (per curiam)). The Supreme Court reversed that holding—but not because we relied on the broad request for other relief. Rather, the Supreme Court reversed because it would have been *impossible* for the plaintiff there to seek nominal damages against the state under 42 U.S.C. § 1983. *Id.* at 69 ("[T]he claim for relief the Ninth Circuit found sufficient to overcome mootness was *nonexistent* [because] . . . § 1983 creates no remedy against a State." (emphasis added)). But here, reinstatement of the individual Plaintiffs to their original positions is not impossible. *See Doe v. Lawrence Livermore Nat'l Lab'y*, 131 F.3d 836, 839–42 (9th Cir. 1997) (holding that a request for reinstatement of employment is a request for prospective injunctive relief that

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complaint] . . . was declaratory and injunctive relief," and such relief had become "clearly moot" on appeal. 931 F.2d at 1340. Applying Rule 54(c), we held that the unavailability of declaratory and injunctive relief did not moot the case because, even though the plaintiff had not expressly requested relief in the form of damages in its complaint, a court could nonetheless award damages as a form of relief. *Id.* at 1340–41; *see also Walden v. Bodley*, 39 U.S. (14 Pet.) 156, 164 (1840) ("Under [a] general prayer for relief, the [c]ourt [in equity] will often extend relief beyond the specific prayer, and not exactly in accordance with it.").

falls within the *Ex parte Young* exception to Eleventh Amendment immunity).[10]

## II.

### A.

The Due Process Clause of the Fourteenth Amendment includes "a substantive component that protects certain individual liberties from state interference." *Mullins v. Oregon*, 57 F.3d 789, 793 (9th Cir. 1995). "Only those

[10] Respectfully, we also disagree with Judge Owens's dissent because it is based on the incorrect premise that our holding rests only on the SAC's broad request for relief. Owens Dissent at 30–31. We also see no violation of the party presentation rule. *See United States v. Sineneng-Smith*, 590 U.S. 371, 375 (2020) ("In our adversarial system of adjudication, we follow the principle of party presentation."). As previously explained, Plaintiffs themselves fairly raised a request for reinstatement in the SAC.

"We have noted in cases involving questions of mootness that ordinary discretionary principles of waiver and forfeiture can affect whether certain relief is available." *United States v. Yepez*, 108 F.4th 1093, 1099 n.1 (9th Cir. 2024); *see Bain v. Cal. Tchrs. Ass'n*, 891 F.3d 1206, 1212 (9th Cir. 2018) (holding that the plaintiffs' "eleventh hour" request for damages was an attempt "to transform their lawsuit from a request for prospective equitable relief into a plea for money damages to remedy past wrongs"); *Seven Words LLC v. Network Sols.*, 260 F.3d 1089, 1095 (9th Cir. 2001) (holding that the plaintiff's belated request for damages had been "effectively disavowed . . . for tactical reasons"). But Plaintiffs here have neither waived nor forfeited their request for reinstatement to their prior positions. Throughout this case (which was dismissed at the pleadings stage), the gravamen of the relief sought by Plaintiffs has been prospective injunctive relief to permit them to continue to work for the LAUSD without also having to comply with the Policy. For this reason, we also believe that the out-of-circuit and rescinded-COVID-19-policy cases relied upon by Judge Owens are inapt. *See* Owens Dissent at 31–32, 31 n.1. In none of those cases did the courts find that they could still grant effective injunctive relief consistent with the gravamen of the injunctive relief sought by the respective plaintiffs all along.

aspects of liberty that we as a society traditionally have protected as fundamental are included within the substantive protection of the Due Process Clause." *Id.* When no fundamental liberty interest is implicated, a legislative act "must satisfy only the deferential rational basis standard of review." *Erotic Serv. Provider Legal Educ. & Rsch. Project v. Gascon*, 880 F.3d 450, 455 (9th Cir.), *amended by* 881 F.3d 792 (9th Cir. 2018). Under that standard, we "merely look to see whether the government *could* have had a legitimate reason for acting as it did." *Dittman v. California*, 191 F.3d 1020, 1031 (9th Cir. 1999) (quoting *Halverson v. Skagit County*, 42 F.3d 1257, 1262 (9th Cir. 1994), *amended on denial of reh'g* (9th Cir. Feb. 9, 1995)). "Rational basis review is highly deferential to the government, allowing any conceivable rational basis to suffice." *Erotic Serv. Provider*, 880 F.3d at 457.

Like all our sister circuits that have considered substantive due process challenges to COVID-19 vaccine mandates, we hold that *Jacobson* controls our analysis. *See We The Patriots USA, Inc. v. Hochul*, 17 F.4th 266, 293–94 (2d Cir.) (per curiam) (applying *Jacobson* to plaintiffs' claim that a COVID-19 vaccine mandate "violate[d] their fundamental rights to privacy, medical freedom, and bodily autonomy under the Fourteenth Amendment"), *clarified*, 17 F.4th 368 (2d Cir. 2021); *Child.'s Health Def., Inc. v. Rutgers, The State Univ. of N.J.*, 93 F.4th 66 (3d Cir.) (holding that "*Jacobson* control[led]," *id.* at 80, plaintiffs' claim that a COVID-19 vaccine mandate "violated their substantive due process rights under the Fourteenth Amendment," *id.* at 78), *cert. denied*, 144 S. Ct. 2688 (2024); *Norris*, 73 F.4th at 435 (applying *Jacobson* to plaintiffs' substantive due process challenge to a COVID-19 vaccine mandate); *Klaassen v. Trs. of Ind. Univ.*, 7 F.4th

592, 593 (7th Cir. 2021) (holding that, because the court "must apply the law established by the Supreme Court," *Jacobson* applied to plaintiffs' substantive due process claim challenging a COVID-19 vaccine mandate); *see also Antunes v. Becerra*, No. 22-2190, 2024 WL 511038, at *1 (4th Cir. Feb. 9, 2024) (per curiam) (adopting the district court's decision in *Antunes v. Rector & Visitors of Univ. of Va.*, 627 F. Supp. 3d 553 (W.D. Va. 2022), which applied *Jacobson* in rejecting plaintiff's claim that a COVID-19 vaccine mandate violated her due process right to refuse unwanted medical treatment, *id.* at 564–65), *cert. denied*, 145 S. Ct. 159 (2024); *Brox v. Hole*, 83 F.4th 87, 100–01 (1st Cir. 2023) (applying *Jacobson*'s rational basis test to a due process challenge to a COVID-19 vaccination mandate (based on plaintiffs' failure to challenge the application of the rational basis test) and holding that the mandate easily satisfied rational basis review).

In *Jacobson*, the Supreme Court considered a substantive due process challenge to a smallpox vaccination requirement for all adult residents of Cambridge, Massachusetts, with criminal penalties. 197 U.S. at 12–14. The Massachusetts legislature provided that certain municipalities could require vaccinations, if the board of health of a municipality determined that "in its opinion, it [wa]s necessary for the public health or safety . . . [to] require and enforce the vaccination and revaccination of all [its] inhabitants." *Id.* at 12. The Board of Health of the City of Cambridge adopted the following regulation in the face of a health emergency:

> Whereas, smallpox has been prevalent to some extent in the city of Cambridge, and still continues to increase; and whereas, it is

> necessary for the speedy extermination of the disease that all persons not protected by vaccination should be vaccinated; and whereas, in the opinion of the board, the public health and safety require the vaccination or revaccination of all the inhabitants of Cambridge; be it ordered, that all the inhabitants of the city who have not been successfully vaccinated since March 1st, 1897, be vaccinated or revaccinated.

*Id.* at 12–13.

Jacobson, who had been convicted for refusing to get vaccinated for smallpox in violation of the Cambridge regulation, *id.* at 14, argued that the statute was "hostile to the inherent right of every freeman to care for his own body and health in such way as to him seems best," *id.* at 26. He claimed, among other things, that the vaccine resulted in "injurious or dangerous effects." *Id.* at 23.

The Court first explained that state legislatures and other policymakers have the authority to enforce "reasonable [laws] . . . as will protect the public health and the public safety," like vaccination requirements. *Id.* at 25. But because such laws remain subject to the Constitution of the United States, the Court next considered whether the statute violated a right to bodily integrity secured by the Constitution. *Id.* at 25–26; *see also Roman Cath. Diocese of Brooklyn v. Cuomo*, 592 U.S. 14, 24 (2020) (per curiam) (Gorsuch, J., concurring) ("Mr. Jacobson claimed that he possessed an implied 'substantive due process' right to 'bodily integrity' that emanated from the Fourteenth Amendment . . . ."). The Court determined that the Constitution secured no fundamental right to be free from

vaccine requirements imposed to protect the safety and health of the community. *Jacobson*, 197 U.S. at 26–27. And the Court stressed that whether a vaccine requirement would protect the safety and health of the community is a matter for the legislature or policymakers, not a question for a court or jury. *Id.* at 30 ("It is no part of the function of a court or a jury to determine which one of two modes was likely to be the most effective for the protection of the public against disease. That was for the legislative department to determine in the light of all the information it had or could obtain.").

Having determined that Jacobson had no fundamental right to refuse the vaccination, the Court essentially applied rational basis review to his due process challenge. *Id.* at 31 ("[But] if a statute purporting to have been enacted to protect the public health, the public morals, or the public safety, has no real or substantial relation to those objects, or is, beyond all question, a plain, palpable invasion of rights secured by the fundamental law, it is the duty of the courts to so adjudge, and thereby give effect to the Constitution."); *see also Roman Cath. Diocese*, 592 U.S. at 23 (Gorsuch, J., concurring) ("Although *Jacobson* pre-dated the modern tiers of scrutiny, this Court essentially applied rational basis review to Henning Jacobson's challenge . . . ."). Because the state legislature and the Cambridge Board of Health could have reasonably concluded that requiring adults to get the smallpox vaccine would protect the public's health and safety, the Court held that it survived rational basis review. *Jacobson*, 197 U.S. at 30–31 (explaining that the legislature could have found that the vaccine requirement "was likely to be the most effective for the protection of the public against disease," *id.* at 30); *id.* at 38 ("[The Court] do[es] not perceive that this [regulation] has invaded any right secured by the Federal Constitution.").

*Jacobson* holds that the constitutionality of a vaccine mandate, like the Policy here, turns on what reasonable legislative and executive decisionmakers *could* have rationally concluded about whether a vaccine protects the public's health and safety, not whether a vaccine actually provides immunity to or prevents transmission of a disease. Whether a vaccine protects the public's health and safety is committed to policymakers, not a court or a jury. Further, alleged scientific uncertainty over a vaccine's efficacy is irrelevant under *Jacobson*. *Jacobson* simply does not allow debate *in the courts* over whether a mandated vaccine prevents the spread of disease. *Jacobson* makes clear that it is up to the political branches, within the parameters of rational basis review, to decide whether a vaccine effectively protects public health and safety.

*Jacobson* is materially indistinguishable from this case. Here, as in *Jacobson*, we are presented with a bodily integrity substantive due process challenge to a vaccine mandate imposed to protect the public's health and safety in response to a health emergency. Thus, under *Jacobson*, we must apply rational basis review.

The Policy easily survives such review because (even assuming the truth of Plaintiffs' allegations) it was more than reasonable for the LAUSD to conclude that COVID-19 vaccines would protect the health and safety of its employees and students. The SAC concedes that COVID-19 vaccines "lessen the severity of symptoms for individuals who receive them." From this, the LAUSD could have reasonably determined that the vaccines would protect the health of its employees. And as discussed above, the LAUSD could have reasonably concluded, based on information in the documents incorporated by reference into the SAC, that COVID-19 vaccines would protect the health and safety of

its students and employees. In fact, the CDC reported that COVID-19 vaccines "are highly effective at protecting vaccinated people against symptomatic and severe COVID-19," and "[f]ully vaccinated people are less likely to become infected" and "less likely to get and spread SARS-CoV-2." *Interim Public Health Recommendations for Fully Vaccinated People*, CDC (July 28, 2021), https://stacks.cdc.gov/view/cdc/108355 [https://perma.cc/AMW8-KH3Z]. The CDC also recommended that "everyone 5 years and older protect themselves from COVID-19 by getting fully vaccinated." *Omicron Variant: What You Need to Know*, CDC (Dec. 9, 2021), https://stacks.cdc.gov/view/cdc/112430 [https://perma.cc/B4EG-5QMR].

**B.**

We reject Plaintiffs' attempt to limit *Jacobson* to only those vaccines that prevent the spread of a disease and provide immunity. *Jacobson* required no such findings. The Court dealt with arguments very similar to Plaintiffs' about the nature of vaccines, including through offers of proof made by Jacobson on which he sought to introduce expert testimony:

> Looking at the propositions embodied in the defendant's rejected offers of proof, it is clear that they are more formidable by their number than by their inherent value. Those offers in the main seem to have had no purpose except to state the general theory of those of the medical profession who attach little or no value to vaccination as a means of preventing the spread of smallpox, or who think that vaccination causes other diseases

of the body. What everybody knows the court must know, and therefore the state court judicially knew, as this court knows, that an opposite theory accords with the common belief, and is maintained by high medical authority. We must assume that, when the statute in question was passed, the legislature of Massachusetts was not unaware of these opposing theories, and was compelled, of necessity, to choose between them. It was not compelled to commit a matter involving the public health and safety to the final decision of a court or jury. It is no part of the function of a court or a jury to determine which one of two modes was likely to be the most effective for the protection of the public against disease. That was for the legislative department to determine in the light of all the information it had or could obtain. It could not properly abdicate its function to guard the public health and safety. The state legislature proceeded upon the theory which recognized vaccination as at least an effective, if not the best-known, way in which to meet and suppress the evils of a smallpox epidemic that imperiled an entire population. Upon what sound principles as to the relations existing between the different departments of government can the court review this action of the legislature? If there is any such power in the judiciary to review legislative action in respect of a matter affecting the general welfare, it can only be when that which the

> legislature has done comes within the rule that, if a statute purporting to have been enacted to protect the public health, the public morals, or the public safety, has no real or substantial relation to those objects, or is, beyond all question, a plain, palpable invasion of rights secured by the fundamental law, it is the duty of the courts to so adjudge, and thereby give effect to the Constitution.
>
> Whatever may be thought of the expediency of this statute, it cannot be affirmed to be, beyond question, in palpable conflict with the Constitution. Nor, in view of the methods employed to stamp out the disease of smallpox, can anyone confidently assert that the means prescribed by the state to that end has no real or substantial relation to the protection of the public health and the public safety.

197 U.S. at 30–31 (citations omitted).

As this discussion demonstrates, the Court determined that Jacobson's claims about the smallpox vaccine—very similar to Plaintiffs' claims—were immaterial, given the other evidence from which the legislature could have reasonably concluded that the vaccine would likely protect the health and safety of the public.[11] *Jacobson* thus applies

[11] For this reason, we respectfully disagree with Judge Lee's attempt to limit *Jacobson* "to apply only if a vaccine prevents transmission and contraction of a disease." Lee Partial Dissent at 35. By rejecting Jacobson's argument—supported by offers of proof—that the smallpox

to vaccination requirements regardless of whether such vaccines actually provide immunity and prevent the spread of disease or whether they provide no immunity and merely render COVID-19 less dangerous to those who contract it, so long as policymakers could reasonably conclude that the vaccines would protect the public's health and safety.[12]

We also reject Plaintiffs' argument that a heightened standard of review applies based on a more recent line of cases that, according to Plaintiffs, recognize a fundamental right to refuse unwanted medical treatment. Plaintiffs primarily rely on *Cruzan ex rel. Cruzan v. Director, Missouri Department of Health*, 497 U.S. 261 (1990) (stating that "a competent person has a constitutionally protected liberty interest in refusing unwanted medical treatment," *id.* at 278), and *Washington v. Glucksberg*, 521 U.S. 702 (1997) (noting that the Court "ha[s] also assumed, and strongly suggested, that the Due Process Clause protects the traditional right to refuse unwanted lifesaving medical treatment," *id*. at 720 (citing *Cruzan*, 497 U.S. at 278–79)).

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vaccine did not prevent the spread of the disease, the Court necessarily held that whether the vaccine actually prevented the spread of smallpox did not matter, given the contrary evidence from which policymakers could reasonably conclude that the vaccine would protect the public's health and safety. *See Jacobson*, 197 U.S. at 30–31; *see also Child.'s Health Def.*, 93 F.4th at 79 ("*Jacobson* did not turn on the longevity of the vaccine or consensus regarding its efficacy."). *Jacobson* cannot be cabined to circumstances that the Court found immaterial.

[12] Even if the SAC plausibly alleged that COVID-19 vaccines do not effectively provide immunity or prevent the spread of COVID-19 and that they only reduce symptoms for the recipient, that would be irrelevant. What matters is whether policymakers could reasonably conclude that vaccination requirements are necessary to protect public health and safety. *Jacobson*, 197 U.S. at 30–31.

Whatever the reach of these cases, they did not overrule *Jacobson*.[13] *See We The Patriots USA*, 17 F.4th at 293 n.35 ("*Jacobson* remains binding precedent."); *Norris*, 73 F.4th at 436 ("[A]bsent any indication from the [Supreme] Court that *Jacobson* is to be overruled or limited, [the court is] bound to apply that decision to reject plaintiffs' arguments here."). Indeed, even Plaintiffs do not go so far as to claim that *Jacobson* is no longer good law. As *Jacobson* remains binding and squarely governs this case, we must apply it.

## III.

Plaintiffs concede, and we agree, that their equal protection claim is subject to rational basis review. *See Hooks v. Clark Cnty. Sch. Dist.*, 228 F.3d 1036, 1041 (9th Cir. 2000) ("To withstand [a due process or equal protection challenge under the] Fourteenth Amendment . . . , a regulation must bear only a rational relation to a legitimate

[13] Moreover, these cases do not address the circumstances addressed in *Jacobson*: a due process challenge to a vaccine policy imposed to protect the public's health and safety. So we do not read these cases as undermining *Jacobson*. But even if we did, we would still need to apply *Jacobson*. *See In re Twelve Grand Jury Subpoenas*, 908 F.3d 525, 529 (9th Cir. 2018) (per curiam) ("Where Supreme Court precedent 'has direct application in a case,' the Supreme Court has instructed 'the Court of Appeals [to] follow the case which directly controls,' even if it 'appears to rest on reasons rejected in some other line of decisions,' and thereby to 'leav[e] to th[e] Court the prerogative of overruling its own decisions.'" (alterations in original) (quoting *Agostini v. Felton*, 521 U.S. 203, 237 (1997))). We thus agree with our sister circuits that, despite *Cruzan* and its progeny, *Jacobson* continues to control in cases challenging COVID-19 vaccination policies. *See We The Patriots USA*, 17 F.4th at 293–94 (rejecting plaintiffs' argument that *Jacobson* did not apply because *Cruzan* and its progeny recognized a fundamental right to refuse medical treatment); *Child.'s Health Def.*, 93 F.4th at 79–80 (same); *Norris*, 73 F.4th at 437 (same).

governmental purpose, unless the regulation implicates a fundamental right or an inherently suspect classification."). Because we hold above that the Policy is rationally related to the LAUSD's legitimate interest in protecting the health and safety of its employees and students, Plaintiffs' equal protection claim fails.

## CONCLUSION

Although the LAUSD has rescinded the Policy, this case is not moot. Given the SAC's broad request for any proper injunctive relief along with its allegations that individual Plaintiffs were terminated under the Policy, the SAC fairly encompasses a request for reinstatement of the individual Plaintiffs who have not been restored to their prior positions.

On the merits, *Jacobson* is binding and controls, and thus rational basis review applies to Plaintiffs' substantive due process claim. Even construing Plaintiffs' allegations in their favor, the Policy survives such review, as the LAUSD could have reasonably concluded that COVID-19 vaccines would protect the health and safety of its employees and students. For this same reason, Plaintiffs' equal protection claim fails under rational basis review. We therefore affirm the district court's order granting the LAUSD's motion for judgment on the pleadings.

**AFFIRMED.**

OWENS, Circuit Judge, dissenting.

Plaintiffs brought this suit to obtain "injunctive relief restraining Defendants from enforcing" their vaccine policy. As Judge Hawkins correctly concluded in his dissent from the panel decision, this case is moot, as "there is no longer any policy for the court to enjoin or declare unlawful." *Health Freedom Def. Fund, Inc. v. Carvalho*, 104 F.4th 715, 732 (9th Cir. 2024) (Hawkins, J., dissenting), *vacated and reh'g en banc granted*, 127 F.4th 750 (9th Cir. 2025). Nothing in the record (or the world) even hints at the possibility that the Los Angeles Unified School District would resurrect its COVID-19 vaccine mandate, which has been dead for nearly two years. The majority does not dispute this reality. We lack Article III jurisdiction and must dismiss this case. *See Brach v. Newsom*, 38 F.4th 6, 12 (9th Cir. 2022) (en banc) (dismissing a challenge to a pandemic-related restriction as moot in line with "the numerous other circuit courts across the country" that have done the same).

The majority first attempts to skirt the mootness problem by asserting that the complaint "fairly encompasses a request for reinstatement," leaning on a boilerplate catchall request for "other and further relief as the Court may deem just and proper." Maj. Op. at 14. Yet when unanimously reversing our court on mootness grounds, the Supreme Court warned that new forms of relief, "extracted late in the day from [a] general prayer for relief and asserted solely to avoid otherwise certain mootness, bore close inspection." *Arizonans for Off. Eng. v. Arizona*, 520 U.S. 43, 71 (1997) (rejecting this court's theory that a live controversy existed where the "complaint did not expressly request nominal damages" but "it did request 'all other relief that the Court deems just and proper'" (citation omitted)). Indeed, the

Court has distinguished cases where a plaintiff "has presented a claim" for the type of relief that "ensure[s] a live controversy," *Mission Prod. Holdings v. Tempnology, LLC*, 587 U.S. 370, 377 (2019), from those where a plaintiff "ha[s] not prayed for" such relief and thus "no longer ha[s] a legally cognizable interest in the result of th[e] case," *Murphy v. Hunt*, 455 U.S. 478, 491 (1982); *cf. United States v. Sineneng-Smith*, 590 U.S. 371, 380 (2020) (unanimously reversing this court and applying the party presentation principle to require that cases be "shaped by the parties," not the court).

Not surprisingly, our sister circuits routinely reject attempts to grow a magic Article III jurisdiction beanstalk from boilerplate language. For example, the First Circuit, in a nearly identical rescinded COVID-19 mandate case, cited *Arizonans for Official English* to hold that "the students' request for 'any other relief [the] Court deems proper' cannot operate to save their otherwise moot action." *Harris v. Univ. of Mass.*, 43 F.4th 187, 193 (1st Cir. 2022).[1] The

[1] *See, e.g.*, *Thomas R.W. v. Mass. Dep't of Educ.*, 130 F.3d 477, 480 (1st Cir. 1997) (holding that a "general prayer for relief" cannot preserve a request for damages to avoid mootness, citing *Arizonans for Official English*); *Fox v. Bd. of Trs. of State Univ. of N.Y.*, 42 F.3d 135, 141 (2d Cir. 1994) (declining to "read a damages claim into the Complaint's boilerplate prayer" for relief when there was "absolutely no specific mention in [the Complaint] of nominal damages" (citation omitted)); *Lillbask ex rel. Mauclaire v. Conn. Dep't of Educ.*, 397 F.3d 77, 90 (2d Cir. 2005) (applying *Arizonans for Official English* to reject that a "general claim for 'other such relief as the Court deems appropriate' is sufficiently expansive to include" the only relief that would render the case not moot); *WildEarth Guardians v. Pub. Serv. Co.*, 690 F.3d 1174, 1191 (10th Cir. 2012) (holding that "[a] broad request for 'other' relief cannot save [a] complaint" from mootness); *Harris v. City of Houston*,

majority attempts to distinguish the many contrary precedents from other circuits by asserting that, unlike in those cases, relief consistent with the "gravamen" of Plaintiffs' requested injunction—even if not expressly sought—can still be granted. Maj. Op. at 18 n.10. But the mootness inquiry hinges on the relief "specific[ally] mention[ed]" by the parties, not on the court's post hoc characterization of the case's supposed essence. *Fox v. Bd. of Trs. of State Univ. of N.Y.*, 42 F.3d 135, 141 (2d Cir. 1994). Blindly embracing a never briefed or argued theory that the Supreme Court and our sister circuits have explicitly rejected is more Inspector Clouseau than "close inspection."

To side shuffle this constitutional black hole, the majority departs from the many analogous challenges to rescinded COVID-19 policies that have been dismissed as moot, *see Brach*, 38 F.4th at 12 n.3 (collecting cases), and instead relies on *Neighbors of Cuddy Mountain v. Alexander*, 303 F.3d 1059 (9th Cir. 2002), which concerned alleged violations of the National Forest Management Act (NFMA) and the National Environmental Policy Act (NEPA). Maj. Op. at 15-16.[2] In that case, plaintiffs sought to enjoin a timber sale on national forest land or any other relief that "may be necessary and appropriate to avoid further irreparable harm" from the sale. *Id*. at 1066. Even after

151 F.3d 186, 191 (5th Cir. 1998) (declining to "conjure up relief" by "'read[ing] into' [the] complaint additional requests" that would manufacture a live controversy).

[2] The majority also cites *Norris v. Stanley*, 73 F.4th 431 (6th Cir. 2023), *cert. denied*, 144 S. Ct. 1353 (2024)—another pandemic-related case that it claims involves "similar circumstances" and was not moot. Maj. Op. at 15. Unlike here, however, the plaintiffs in *Norris* specifically "sought nominal damages for the alleged violations of their constitutional rights." *Id*. at 433 n.1.

logging of the timber concluded, we held over a dissent that the case was not moot because further environmental harm from the sale "may yet be remedied by any number of mitigation strategies," which were fairly encompassed in the requested relief. *Id*.

The parties never cited *Neighbors of Cuddy Mountain* nor its underlying theory in their many briefs submitted to this court, nor did the original panel or dissent. And despite the majority's claim that *Neighbors of Cuddy Mountain* derived from longstanding mootness principles, Maj. Op. at 16 n.9, no published decision in this circuit—or any other—has ever relied on *Neighbors of Cuddy Mountain*'s mootness rationale outside the narrow context of NFMA and NEPA violations. That collective silence speaks for itself: There is simply no basis to extend *Neighbors of Cuddy Mountain*'s mootness holding beyond its specific environmental context to the claims presented here. *Compare Feldman v. Bomar*, 518 F.3d 637, 642 (9th Cir. 2008) (citing *Neighbors of Cuddy Mountain* and similar cases to illustrate this court's recognition of "'live' controversies *in environmental cases* even after the contested government projects were complete" (emphasis added)), *with Brach*, 38 F.4th at 11 (holding that, where plaintiffs sue to enjoin a pandemic policy but the policy no longer remains, the plaintiffs "have gotten everything they asked for" and the "actual controversy has evaporated," presenting a "classic case" of mootness).[3]

[3] The majority's tepid reliance on *Z Channel Limited Partnership v. Home Box Office, Inc.*, 931 F.2d 1338 (9th Cir. 1991)—a nearly thirty-five-year-old case that was also never cited by the parties nor the original panel—is even less persuasive. Maj. Op. at 16 n.9. No published

Because neither of the majority's last-minute mootness rationales survive "close inspection," *Arizonans for Off. Eng.*, 520 U.S. at 71, I respectfully dissent for the reasons stated by Judge Hawkins.

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LEE, Circuit Judge, joined by COLLINS, Circuit Judge, dissenting in part.

The majority's opinion comes perilously close to giving the government carte blanche to require a vaccine or even medical treatment against people's will so long as it asserts—even if incorrectly—that it would promote "public health and safety." But the many mistakes and missteps by our government and the scientific establishment over the past five years counsel caution: Their errors underscore the importance of carefully evaluating the sort of sweeping claims of public-health authority asserted by the Los Angeles Unified School District ("LAUSD") here. Faithful adherence to Supreme Court precedent confirms that we

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decision from this circuit in nearly three decades has relied on *Z Channel* to overcome a mootness challenge based on hypothetical relief that no party specifically sought. And for good reason: *Z Channel* is a textbook example of overreach, with the majority "[d]efying a clear rule of procedure, creating an inter-circuit conflict and resurrecting a legal theory long ago abandoned by the parties" to bring the case "back from the dead." 931 F.2d at 1346, 1349 (Kozinski, J., dissenting); *see also Sineneng-Smith*, 590 U.S. at 380 (cautioning against appellate courts "interject[ing]" themselves into cases); *NAACP v. U.S. Sugar Corp.*, 84 F.3d 1432, 1438 (D.C. Cir. 1996) (citing the *Z Channel* dissent); *Seven Words LLC v. Network Sols.*, 260 F.3d 1089, 1095–97 (9th Cir. 2001) (declining to apply *Z Channel* to overcome a mootness challenge); *Bain v. Cal. Tchrs. Ass'n*, 891 F.3d 1206, 1212 (9th Cir. 2018) (declining to "transform" the requested relief "at the eleventh hour" to avoid mootness, citing *Seven Words* and *Arizonans for Official English*).

should not blindly accept the mere say-so of the government. We thus should not affirm the dismissal of this lawsuit challenging LAUSD's COVID-19 vaccine mandate—without permitting the plaintiffs to offer evidence to rebut the government officials' far-reaching claims.[1]

Contrary to the majority, I read the Supreme Court's decision in *Jacobson v. Massachusetts*—which upheld a smallpox vaccine mandate—to apply only if a vaccine prevents transmission and contraction of a disease. 197 U.S. 11 (1905). The plaintiffs here have plausibly claimed—at least at the pleading stage where we must accept the truth of the allegations—that the COVID-19 vaccine mitigates serious symptoms but does not "prevent transmission or contraction of COVID-19." And if that is true, then *Jacobson*'s rational basis review does not apply, and we must examine the vaccine mandate under a more stringent standard. Ultimately, the plaintiffs may be wrong about the COVID-19 vaccine, but they should be given a chance to challenge the government's assertions about it.

I respectfully dissent in part.

* * * *

When the mRNA-based COVID-19 vaccines were first announced in late 2020, pharmaceutical companies touted clinical trials that they claimed showed an efficacy rate of over 90 percent.[2] As scientists contended then, these

[1] I agree with the majority that this appeal is not moot.

[2] *Pfizer and BioNTech Announce Vaccine Candidate Against COVID-19 Achieved Success in First Interim Analysis from Phase 3 Study*, Pfizer, https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-announce-vaccine-candidate-against (Nov. 9,

vaccines would "protect individuals from infection and transmission."[3]

Based in part on these trial results, federal, state and local governments acted swiftly to impose vaccine mandates. The United States government required federal employees, government contractors, and millions of private sector employees to be vaccinated.[4] Over 8,000 men and women in uniform were discharged and severed from service for their refusal to be vaccinated.[5] States also imposed their own mandates. Even 18 months into the pandemic, California Governor Gavin Newsom announced that he planned to require schoolchildren to be vaccinated, despite scientific evidence that showed young children face extremely low

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2020); *Moderna's COVID-19 Vaccine Candidate Meets its Primary Efficacy Endpoint in the First Interim Analysis of the Phase 3 COVE Study*, Moderna, https://investors.modernatx.com/news/news-details/2020/Modernas-COVID-19-Vaccine-Candidate-Meets-its-Primary-Efficacy-Endpoint-in-the-First-Interim-Analysis-of-the-Phase-3-COVE-Study/default.aspx (Nov. 16, 2020).

[3] Ali Pormohammad et al., *Efficacy and Safety of COVID-19 Vaccines: A Systematic Review and Meta-Analysis of Randomized Clinical Trials*, 9 Vaccines 1, 15 (2021), https://pmc.ncbi.nlm.nih.gov/articles/PMC8148145/.

[4] *See, e.g.*, Kathryn Watson et al., *Biden announces COVID-19 vaccine mandates that will affect 100 million Americans*, CBS News (Sept. 10, 2021), https://www.cbsnews.com/live-updates/biden-covid-19-vaccine-mandates-announcement/.

[5] *Fact Sheet: President Donald J. Trump Reinstates Service Members Discharged for Refusing the COVID Vaccine*, The White House, https://www.whitehouse.gov/fact-sheets/2025/01/fact-sheet-president-donald-j-trump-reinstates-service-members-discharged-for-refusing-the-covid-vaccine/ (Jan. 27, 2025).

health risks from COVID-19.[6] That proposed mandate would have banned unvaccinated children from the classroom and relegated them to online learning. And relevant here, LAUSD issued a memorandum requiring all employees to get vaccinated—or lose their jobs.

But it turned out that the government—and the scientific establishment—were wrong about a lot of things. The COVID-19 vaccines did not end up having an efficacy rate of over 90 percent in real-life. People repeatedly caught COVID-19, despite being vaccinated and "boosted." Indeed, repeat infections among the vaccinated became so common that the phrase "breakthrough infection" entered common parlance. Given this reality, the government shifted its emphasis on why people should get vaccinated: It was less about preventing transmission and contraction of COVID-19 and more about mitigating serious symptoms.[7] Even LAUSD in its brief before the three-judge panel focused largely on the vaccine's effect in lessening symptoms, stating that "[t]he overwhelming consensus amongst the nation's leading health experts is that COVID-

[6] California Becomes First State in Nation to Announce COVID-19 Vaccine Requirements for Schools, *Governor Gavin Newsom*, https://www.gov.ca.gov/2021/10/01/california-becomes-first-state-in-nation-to-announce-covid-19-vaccine-requirements-for-schools/ (last visited May 28, 2025). California ultimately walked away from this announced policy.

[7] *See Benefits of Getting Vaccinated*, CDC, https://www.cdc.gov/covid/vaccines/benefits.html#:~:text=Vaccination%20is%20more%20reliable%20way,associated%20with%20COVID%2D19%20infection., (Jan 13, 2025) (emphasizing that "Getting vaccinated against COVID-19 has many benefits that are supported by scientific studies. The COVID-19 vaccine helps protect you from severe illness, hospitalization, and death.").

19 vaccines are safe and effective in preventing serious illness and death from this highly contagious virus."

The plaintiffs here go further and contend that the COVID-19 vaccine is not even a "traditional" vaccine that prevents transmission or provides immunity. Rather, the COVID-19 vaccines merely mitigate symptoms in a manner more akin to a medical treatment than a vaccine. Thus, according to the plaintiffs, the Supreme Court's *Jacobson v. Massachusetts* decision does not apply here. The district court, for its part, held that the plaintiffs' "distinction" between "lessen[ing] the severity of the disease" and "prevent[ing] contraction or transmission" was "misplaced" and that *Jacobson* applies even if requiring the COVID-19 vaccines constitutes forced medical treatment. *Health Freedom Def. Fund v. Reilly*, 2022 WL 5442479, at *5 (C.D. Cal. Sept. 2, 2022).

The majority reads *Jacobson* broadly to empower the government to impose any vaccine mandate so long as it believes the mandate would "protect public health and safety." Maj. Op. 23. Under the majority's reading, "alleged scientific uncertainty over a vaccine's efficacy is irrelevant under *Jacobson*." *Id.* In other words, if the government believes a vaccine will protect "public health and safety," that is the end of the story. The majority adopts a sweeping definition of "public health and safety" such that the government can mandate a vaccine—and potentially any medical treatment—if the required measure just "lessen[s] the severity of symptoms," whether or not it prevents transmission and contraction of the disease. *Id.*

I disagree with the majority's overly broad reading of *Jacobson*. The Supreme Court upheld Massachusetts' vaccine requirement against smallpox precisely because the

vaccine prevented the transmission and contraction of smallpox. It emphasized this point repeatedly:

- The "principle of vaccination as a means to *prevent the spread* of smallpox has been enforced in many [S]tates." 197 U.S. at 31–32 (emphasis added).
- "[V]accination strongly tends to *prevent the transmission or spread* of this disease." *Id.* at 34 (quoting *Viemeister v. White,* 179 N.Y. 235, 72 N.E. 97, 98–99 (1904) (emphasis added)).
- It is "common belief" that a vaccine has a "decided tendency to *prevent the spread* of this fearful disease." *Id.* at 34 (emphasis added).
- Quarantine requirements were justified because of "the danger of the *spread of the disease*." *Id.* at 29 (emphasis added).

To be sure, the Court in *Jacobson* noted that the defendant had challenged the effectiveness of the smallpox vaccine in limiting the spread of the disease. *Id.* at 23–24. The majority opinion latches onto that language to argue that it does not matter whether a vaccine limits transmission and contraction of a disease; we must just defer to a state's belief that a vaccine will protect "public health and safety." Maj. Op. 23. But the Court did not hold that vaccines can be required even if they do not prevent the transmission and contraction of the disease.

Admittedly, it is somewhat difficult to parse this 120-year-old case because it predates our tiers-of-scrutiny

analysis. But I read the Court's opinion much more narrowly than the majority does: If "everybody knows . . . and therefore the [trial] court judicially knew, as th[e] [C]ourt knows, that an opposite theory [about the public-health efficacy of the smallpox vaccine] accords with the common belief, and is maintained by high medical authority," Jacobson's argument that this overwhelming consensus was not unanimous does not amount to a viable constitutional claim. *Jacobson*, 197 U.S. at 30. While it acknowledged that some people shared Jacobson's distinctly unorthodox belief, the Court noted that it is "common belief" that is "accepted by the mass of the people, as well as by most members of the medical profession" that the smallpox vaccine has the "decided tendency to prevent the spread" of disease. *Id.* at 34 (quoting *Viemeister*'s upholding of a smallpox vaccine mandate in New York); *see also id.* at 35 ("vaccination, as a means of protecting a community against smallpox, finds strong support in the experience of this and other countries"); *id*. at 37 (suggesting that there is "deep and universal" belief in the "community" and "medical advisers" about the vaccine's efficacy). *Jacobson* then recited the number of states—and countries ranging from Britain to Denmark to Germany to Sweden—that have adopted compulsory smallpox vaccination, underscoring the common and almost universal belief that smallpox vaccines prevent the spread of that disease. *Id.* at 31 n.1.

Our case is factually different from *Jacobson*. At the pleading stage, we must accept as true the plaintiffs' well-pleaded allegation that the newly developed mRNA COVID-19 vaccines do not effectively prevent the transmission and contraction of COVID-19 and thus more resemble medical treatments than the sort of robustly validated smallpox vaccine at issue in *Jacobson*. *Ashcroft v.*

*Iqbal*, 556 U.S. 662, 678 (2009). That allegation may ultimately not bear out once the parties offer evidence, but the plaintiffs' theory appears plausible at this stage, especially given the federal government's focus on mitigation of symptoms over prevention of transmission and LAUSD's failure in its brief to try to factually rebut that claim. This means that *Jacobson* does not bar this suit—at least for now.

The majority opinion suggests that *Jacobson*'s reference to "public health and public safety" is so capacious that merely "lessen[ing] the severity of symptoms" is enough to justify a vaccine mandate. Maj. Op. 23. But nothing in *Jacobson* hints that just mitigating symptoms alone can count as "public health and public safety." The entire thrust of *Jacobson* is that "*public* health and *public* safety" means protecting the mass public from the spread of smallpox. Aside from the repeated references to "preventing the spread" of smallpox, the opinion makes many allusions to the dangers of widespread transmission of the disease among the public. *See, e.g.*, 197 U.S. at 26 (mentioning the "injury that may be done to others" if a person has the liberty to refuse vaccines); *id*. at 27 ("a community has the right to protect itself against an epidemic of disease which threatens the safety of its members"); *id*. at 28 (noting smallpox was "prevalent and increasing at Cambridge"); *id*. at 30–31 (vaccination is the "best known[] way in which to meet and suppress the evils of a smallpox epidemic that imperiled an entire population"); *id.* at 31 (discussing the need to "stamp out the disease of smallpox" for the "protection of the public health and the public safety").

If we accept the majority's holding that a state can impose a vaccine mandate just to "lessen the severity of symptoms" of sick persons—without considering whether it

lessens transmission and contraction of this disease—then we are opening the door for compulsory medical treatment against people's wishes. Vaccines, by definition, build immunity and prevent transmission and contraction of an infectious disease, but we risk blurring the line between vaccines and medical treatment if vaccines are defined as anything that lessens symptoms.

None of this is to deny that the COVID-19 vaccines may well have saved millions of lives of the elderly, people with comorbidities, and others with weakened immune systems. But we have held that the government cannot compel people to involuntarily receive even life-saving medical treatment. If lessening the severity of symptoms alone justifies vaccine mandates, then it may well implicate the fundamental right to "refus[e] unwanted medical treatment," as explained by Judge Collins in his panel concurrence. *Health Freedom Def. Fund v. Carvalho*, 104 F.4th 715, 728 (9th Cir. 2024) (Collins, J., concurring), *vacated*, 127 F.4th 750 (9th Cir. 2025); *see also Cruzan ex rel. Cruzan v. Director, Mo. Dep't of Health*, 497 U.S. 261, 278–79 (1990); *Washington v. Glucksberg*, 521 U.S. 702, 724–25 (1997) (holding that the "right of a competent individual to refuse medical treatment" is "entirely consistent with this Nation's history and constitutional traditions" (citation omitted)). Indeed, under the majority's reasoning, we are only a step or two from allowing the government to require COVID-19 patients to take, say, Ivermectin if the government in its judgment believes that it would "lessen the severity of symptoms."

As a practical matter, I fear we are giving the government a blank check to foist health treatment mandates on the people—despite its checkered track record—when we should be imposing a check against the government's incursion into our liberties.

I respectfully dissent in part.

# Pfizer and BioNTech Announce Vaccine Candidate Against COVID-19 Achieved Success in First Interim Analysis from Phase 3 Study

Monday, November 09, 2020 - 06:45am

- *Vaccine candidate was found to be more than 90% effective in preventing COVID-19 in participants without evidence of prior SARS-CoV-2 infection in the first interim efficacy analysis*
- *Analysis evaluated 94 confirmed cases of COVID-19 in trial participants*
- *Study enrolled 43,538 participants, with 42% having diverse backgrounds, and no serious safety concerns have been observed; Safety and additional efficacy data continue to be collected*
- *Submission for Emergency Use Authorization (EUA) to the U.S. Food and Drug Administration (FDA) planned for soon after the required safety milestone is achieved, which is currently expected to occur in the third week of November*
- *Clinical trial to continue through to final analysis at 164 confirmed cases in order to collect further data and characterize the vaccine candidate's performance against other study endpoints*



This press release features multimedia. View the full release here: https://www.businesswire.com/news/home/20201109005539/en/

NEW YORK & MAINZ, GERMANY--(BUSINESS WIRE)-- Pfizer Inc. (NYSE: PFE) and BioNTech SE (Nasdaq: BNTX) today announced their mRNA-based vaccine candidate, BNT162b2, against SARS-CoV-2 has demonstrated evidence of efficacy against COVID-19 in participants without prior evidence of SARS-CoV-2 infection, based on the first interim efficacy analysis conducted on November 8, 2020 by an external, independent Data Monitoring Committee (DMC) from the Phase 3 clinical study.

After discussion with the FDA, the companies recently elected to drop the 32-case interim analysis and conduct the first interim analysis at a minimum of 62 cases. Upon the conclusion of those discussions, the evaluable case count reached 94 and the DMC performed its first analysis on all cases. The case split between vaccinated individuals and those who received the placebo indicates a vaccine efficacy rate above 90%, at 7 days after the second dose. This means that protection is achieved 28 days after the initiation of the vaccination, which consists of a 2-dose schedule. As the study continues, the final vaccine efficacy percentage may vary. The DMC has not reported any serious safety concerns and recommends that the study continue to collect additional safety and efficacy data as planned. The data will be discussed with regulatory authorities worldwide.

“Today is a great day for science and humanity. The first set of results from our Phase 3 COVID-19 vaccine trial provides the initial evidence of our vaccine’s ability to prevent COVID-19,” said Dr. Albert Bourla, Pfizer Chairman and CEO. “We are reaching this critical milestone in our vaccine development program at a time when the world needs it most with infection rates setting new records, hospitals nearing over-capacity and economies struggling to reopen. With today’s news, we are a significant step closer to providing people around the world with a much-needed breakthrough to help bring an end to this global health crisis. We look forward to sharing additional efficacy and safety data generated from thousands of participants in the coming weeks.”After discussion with the FDA, the companies recently elected to drop the 32-case interim analysis and conduct the first interim analysis at a minimum of 62 cases. Upon the conclusion of those discussions, the evaluable case count reached 94 and the DMC performed its first analysis on all cases. The case split between vaccinated individuals and those who received the placebo indicates a vaccine efficacy rate above 90%, at 7 days after the second dose. This means that protection is achieved 28 days after the initiation of the vaccination, which consists of a 2-dose schedule. As the study continues, the final vaccine efficacy percentage may vary. The DMC has not reported any serious safety concerns and recommends that the study continue to collect additional safety and efficacy data as planned. The data will be discussed with regulatory authorities worldwide.



“I want to thank the thousands of people who volunteered to participate in the clinical trial, our academic collaborators and investigators at the study sites, and our colleagues and collaborators around the world who are dedicating their time to this crucial endeavor,” added Bourla. “We could not have come this far without the tremendous commitment of everyone involved.”

“The first interim analysis of our global Phase 3 study provides evidence that a vaccine may effectively prevent COVID-19. This is a victory for innovation, science and a global collaborative effort,” said Prof. Ugur Sahin, BioNTech co-founder and CEO. “When we embarked on this journey 10 months ago this is what we aspired to achieve. Especially today, while we are all in the midst of a second wave and many of us in lockdown, we appreciate even more how important this milestone is on our path towards ending this pandemic and for all of us to regain a sense of normality. We will continue to collect further data as the trial continues to enroll for a final analysis planned when a total of 164 confirmed COVID-19 cases have accrued. I would like to thank everyone who has contributed to make this important achievement possible.”

The Phase 3 clinical trial of BNT162b2 began on July 27 and has enrolled 43,538 participants to date, 38,955 of whom have received a second dose of the vaccine candidate as of November 8, 2020. Approximately 42% of global participants and 30% of U.S. participants have racially and ethnically diverse backgrounds. The trial is continuing to enroll and is expected to continue through the final analysis when a total of 164 confirmed COVID-19 cases have accrued. The study also will evaluate the potential for the vaccine candidate to provide protection against COVID-19 in those who have had prior exposure to SARS-CoV-2, as well as vaccine prevention against severe COVID-19 disease. In addition to the primary efficacy endpoints evaluating confirmed COVID-19 cases accruing from 7 days after the second dose, the final analysis now will include, with the approval of the FDA, new secondary endpoints evaluating efficacy based on cases accruing 14 days after the second dose as well. The companies believe that the addition of these secondary endpoints will help align data across all COVID-19 vaccine studies and allow for cross-trial learnings and comparisons between these novel vaccine platforms. The companies have posted an updated version of the study protocol at https://www.pfizer.com/science/coronavirus.



Pfizer and BioNTech are continuing to accumulate safety data and currently estimate that a median of two months of safety data following the second (and final) dose of the vaccine candidate – the amount of safety data specified by the FDA in its guidance for potential Emergency Use Authorization – will be available by the third week of November. Additionally, participants will continue to be monitored for long-term protection and safety for an additional two years after their second dose.

Along with the efficacy data generated from the clinical trial, Pfizer and BioNTech are working to prepare the necessary safety and manufacturing data to submit to the FDA to demonstrate the safety and quality of the vaccine product produced.

Based on current projections we expect to produce globally up to 50 million vaccine doses in 2020 and up to 1.3 billion doses in 2021.

Pfizer and BioNTech plan to submit data from the full Phase 3 trial for scientific peer-review publication.

**About Pfizer: Breakthroughs That Change Patients' Lives**

At Pfizer, we apply science and our global resources to bring therapies to people that extend and significantly improve their lives. We strive to set the standard for quality, safety and value in the discovery, development and manufacture of health care products, including innovative medicines and vaccines. Every day, Pfizer colleagues work across developed and emerging markets to advance wellness, prevention, treatments and cures that challenge the most feared diseases of our time. Consistent with our responsibility as one of the world's premier innovative biopharmaceutical companies, we collaborate with health care providers, governments and local communities to support and expand access to reliable, affordable health care around the world. For more than 150 years, we have worked to make a difference for all who rely on us. We routinely post information that may be important to investors on our website at www.Pfizer.com. In addition, to learn more, please visit us on www.Pfizer.com and follow us on Twitter at @Pfizer and @Pfizer News, LinkedIn, YouTube and like us on Facebook at Facebook.com/Pfizer.



**Pfizer Disclosure Notice**

The information contained in this release is as of November 9, 2020. Pfizer assumes no obligation to update forward-looking statements contained in this release as the result of new information or future events or developments.

This release contains forward-looking information about Pfizer's efforts to combat COVID-19, the collaboration between BioNTech and Pfizer to develop a potential COVID-19 vaccine, the BNT162 mRNA vaccine program, and modRNA candidate BNT162b2 (including qualitative assessments of available data, potential benefits, expectations for clinical trials, anticipated timing of clinical trial readouts and regulatory submissions and anticipated manufacturing, distribution and supply), that involves substantial risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such statements. Risks and uncertainties include, among other things, the uncertainties inherent in research and development, including the ability to meet anticipated clinical endpoints, commencement and/or completion dates for clinical trials, regulatory submission dates, regulatory approval dates and/or launch dates, as well as risks associated with preliminary and interim data, (including the Phase 3 interim data

that is the subject of this release), including the possibility of unfavorable new preclinical or clinical trial data and further analyses of existing preclinical or clinical trial data; the risk that clinical trial data are subject to differing interpretations and assessments, including during the peer review/publication process, in the scientific community generally, and by regulatory authorities; whether and when data from the BNT162 mRNA vaccine program will be published in scientific journal publications and, if so, when and with what modifications; whether regulatory authorities will be satisfied with the design of and results from these and future preclinical and clinical studies; whether and when any biologics license and/or emergency use authorization applications may be filed in any jurisdictions for BNT162b2 or any other potential vaccine candidates; whether and when any such applications may be approved by regulatory authorities, which will depend on myriad factors, including making a determination as to whether the vaccine candidate's benefits outweigh its known risks and determination of the vaccine candidate's efficacy and, if approved, whether it will be commercially successful; decisions by regulatory authorities impacting labeling, manufacturing processes, safety and/or other matters that could affect the availability or commercial potential of a vaccine, including development of products or therapies by other companies; disruptions in the relationships between us and our collaboration partners or third-party suppliers; risks related to the availability of raw materials to manufacture a vaccine; challenges related to our vaccine candidate's ultra-low temperature formulation and attendant storage, distribution and administration requirements, including risks related to handling after delivery by Pfizer; the risk that we may not be able to successfully develop non-frozen formulations; the risk that we may not be able to create or scale up manufacturing capacity on a timely basis or have access to logistics or supply channels commensurate with global demand for any potential approved vaccine, which would negatively impact our ability to supply the estimated numbers of doses of our vaccine candidate within the projected time periods indicated; whether and when additional supply agreements will be reached; uncertainties regarding the ability to obtain recommendations from vaccine technical committees and other public health authorities and uncertainties regarding the commercial impact of any such recommendations; and competitive developments.



A further description of risks and uncertainties can be found in Pfizer's Annual Report on Form 10-K for the fiscal year ended December 31, 2019 and in its subsequent reports on Form 10-Q, including in the sections thereof captioned "Risk Factors" and "Forward-Looking Information and Factors That May Affect Future Results", as well as in its subsequent reports on Form 8-K, all of which are filed with the U.S. Securities and Exchange Commission and available at www.sec.gov and www.pfizer.com.

**About BioNTech**

Biopharmaceutical New Technologies is a next generation immunotherapy company pioneering novel therapies for cancer and other serious diseases. The Company exploits a wide array of computational discovery and therapeutic drug platforms for the rapid development of novel biopharmaceuticals. Its broad portfolio of oncology product candidates includes individualized and off-the-shelf mRNA-based therapies, innovative chimeric antigen receptor T cells, bi-specific checkpoint immuno-modulators, targeted cancer antibodies and small molecules. Based on its deep expertise in mRNA vaccine development and in-house manufacturing capabilities, BioNTech and its collaborators are developing multiple mRNA vaccine candidates for a range of infectious diseases alongside its diverse oncology pipeline. BioNTech has established a broad set of relationships with multiple global pharmaceutical collaborators, including Genmab, Sanofi, Bayer Animal Health, Genentech, a member of the Roche Group, Genevant, Fosun Pharma, and Pfizer. For more information, please visit www.BioNTech.de.

**BioNTech Forward-looking statements**

This press release contains “forward-looking statements” of BioNTech within the meaning of the Private Securities Litigation Reform Act of 1995. These forward-looking statements may include, but may not be limited to, statements concerning: BioNTech’s efforts to combat COVID-19; the collaboration between BioNTech and Pfizer to develop a potential COVID-19 vaccine; our expectations regarding the potential characteristics of BNT162b2 in our Phase 2/3 trial and/or in commercial use based on data observations to date; the expected timepoint for additional readouts on efficacy data of BNT162b2 in our Phase 2/3 trial; the nature of the clinical data, which is subject to ongoing peer review, regulatory review and market interpretation; the timing for submission of data for, or receipt of, any potential Emergency Use Authorization; the timing for submission of manufacturing data to the FDA; and the ability of BioNTech to supply the quantities of BNT162 to support clinical development and, if approved, market demand, including our production estimates for 2020 and 2021. Any forward-looking statements in this press release are based on BioNTech current expectations and beliefs of future events, and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. These risks and uncertainties include, but are not limited to: the ability to meet the pre-defined endpoints in clinical trials; competition to create a vaccine for COVID-19; the ability to produce comparable clinical or other results, including our stated rate of vaccine effectiveness and safety and tolerability profile observed to date, in the remainder of the trial or in larger, more diverse populations upon commercialization; the ability to

effectively scale our productions capabilities; and other potential difficulties. For a discussion of these and other risks and uncertainties, see BioNTech's Annual Report on Form 20-F filed with the SEC on March 31, 2020, which is available on the SEC's website at www.sec.gov. All information in this press release is as of the date of the release, and BioNTech undertakes no duty to update this information unless required by law.

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Source: Pfizer Inc.

moderna

# Moderna's COVID-19 Vaccine Candidate Meets its Primary Efficacy Endpoint in the First Interim Analysis of the Phase 3 COVE Study

November 16, 2020

*First interim analysis included 95 participants with confirmed cases of COVID-19*

*Phase 3 study met statistical criteria with a vaccine efficacy of 94.5% (p <0.0001)*

*Moderna intends to submit for an Emergency Use Authorization (EUA) with U.S. FDA in the coming weeks and expects the EUA to be based on the final analysis of 151 cases and a median follow-up of more than 2 months*

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Nov. 16, 2020-- Moderna, Inc. (Nasdaq: MRNA), a biotechnology company pioneering messenger RNA (mRNA) therapeutics and vaccines to create a new generation of transformative medicines for patients, today announced that the independent, NIH-appointed Data Safety Monitoring Board (DSMB) for the Phase 3 study of mRNA-1273, its vaccine candidate against COVID-19, has informed Moderna that the trial has met the statistical criteria pre-specified in the study protocol for efficacy, with a vaccine efficacy of 94.5%. This study, known as the COVE study, enrolled more than 30,000 participants in the U.S. and is being conducted in collaboration with the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), and the Biomedical Advanced Research and Development Authority (BARDA), part of the Office of the Assistant Secretary for Preparedness and Response at the U.S. Department of Health and Human Services.

The primary endpoint of the Phase 3 COVE study is based on the analysis of COVID-19 cases confirmed and adjudicated starting two weeks following the second dose of vaccine. This first interim analysis was based on 95 cases, of which 90 cases of COVID-19 were observed in the placebo group versus 5 cases observed in the mRNA-1273 group, resulting in a point estimate of vaccine efficacy of 94.5% (p <0.0001).

A secondary endpoint analyzed severe cases of COVID-19 and included 11 severe cases (as defined in the study protocol) in this first interim analysis. All 11 cases occurred in the placebo group and none in the mRNA-1273 vaccinated group.

The 95 COVID-19 cases included 15 older adults (ages 65+) and 20 participants identifying as being from diverse communities (including 12 Hispanic or LatinX, 4 Black or African Americans, 3 Asian Americans and 1 multiracial).

The interim analysis included a concurrent review of the available Phase 3 COVE study safety data by the DSMB, which did not report any significant safety concerns. A review of solicited adverse events indicated that the vaccine was generally well tolerated. The majority of adverse events were mild or moderate in severity. Grade 3 (severe) events greater than or equal to 2% in frequency after the first dose included injection site pain (2.7%), and after the second dose included fatigue (9.7%), myalgia (8.9%), arthralgia (5.2%), headache (4.5%), pain (4.1%) and erythema/redness at the injection site (2.0%). These solicited adverse events were generally short-lived. These data are subject to change based on ongoing analysis of further Phase 3 COVE study data and final analysis.



Preliminary analysis suggests a broadly consistent safety and efficacy profile across all evaluated subgroups.

As more cases accrue leading up to the final analysis, the Company expects the point estimate for vaccine efficacy may change. The Company plans to submit data from the full Phase 3 COVE study to a peer-reviewed publication.

"This is a pivotal moment in the development of our COVID-19 vaccine candidate. Since early January, we have chased this virus with the intent to protect as many people around the world as possible. All along, we have known that each day matters. This positive interim analysis from our Phase 3 study has given us the first clinical validation that our vaccine can prevent COVID-19 disease, including severe disease," said Stéphane Bancel, Chief Executive Officer of Moderna. "This milestone is only possible because of the hard work and sacrifices of so many. I want to thank the thousands of participants in our Phase 1, Phase 2 and Phase 3 studies, and the staff at our clinical trial sites who have been on the front lines of the fight against the virus. They are an inspiration to us all. I want to thank the NIH, particularly NIAID, for their scientific leadership including through years of foundational research on potential pandemic threats at the Vaccine Research Center that led to the discovery of the best way to make Spike protein antigens that are being used in our vaccine and others'. I want to thank our partners at BARDA and Operation Warp Speed who have been instrumental to accelerating our progress to this point. Finally, I want to thank the Moderna team, our suppliers and our partners, for their tireless work across research, development and manufacturing of the vaccine. We look forward to the next milestones of submitting for an EUA in the U.S., and regulatory filings in countries around the world, while we continue to collect data on the safety and efficacy of the vaccine in the COVE study. We remain committed to and focused on doing our part to help end the COVID-19 pandemic."

Based on these interim safety and efficacy data, Moderna intends to submit for an Emergency Use Authorization (EUA) with the U.S. Food and Drug Administration (FDA) in the coming weeks and anticipates having the EUA informed by the final safety and efficacy data (with a median duration of at least 2 months). Moderna also plans to submit applications for authorizations to global regulatory agencies.

Moderna is working with the U.S. Centers for Disease Control and Prevention (CDC), Operation Warp Speed and McKesson (NYSE: MCK), a COVID-19 vaccine distributor contracted by the U.S. government, as well as global stakeholders to be prepared for distribution of mRNA-1273, in the event that it receives an EUA and similar global authorizations. By the end of 2020, the Company expects to have approximately 20 million doses of mRNA-1273 ready to ship in the U.S. The Company remains on track to manufacture 500 million to 1 billion doses globally in 2021. On November 10, the American Medical Association (AMA) issued a Current Procedural Terminology (CPT) code to report vaccination with mRNA-1273 (code: 91301). Moderna recently announced further progress towards ensuring the distribution, storage and handling of the vaccine can be done using existing infrastructure.

To learn more about Moderna's work on mRNA-1273, visit www.modernatx.com/COVID19.

**About the Phase 3 COVE Study**

The Phase 3 COVE trial is a randomized, 1:1 placebo-controlled study testing mRNA-1273 at the 100 µg dose level in 30,000 participants in the U.S., ages 18 and older. The primary endpoint is the prevention of symptomatic COVID-19 disease. Key secondary endpoints include prevention of severe COVID-19 disease and prevention of infection by SARS-CoV-2. The trial will continue to accrue additional data relevant to safety and efficacy even after an EUA is submitted. The final estimates of vaccine efficacy for both primary and secondary endpoints will depend on the totality of data that will accumulate to inform the final analysis. Moderna worked closely with BARDA and the NIH, including NIAID's COVID-19 Prevention Network (CoVPN), to conduct the Phase 3 COVE study under Operation Warp Speed. Moderna's partner PPD (Nasdaq: PPD), a leading global contract research organization providing comprehensive, integrated drug development, laboratory and lifecycle management services, has also been essential to the successful execution of the COVE study.

The Phase 3 COVE study was designed in collaboration with the FDA and NIH to evaluate Americans at risk of severe COVID-19 disease and completed enrollment of 30,000 participants ages 18 and older in the U.S. on October 22, including those at high risk of the severe complications of COVID-19 disease. The COVE study includes more than 7,000 Americans over the age of 65. It also includes more than 5,000 Americans who are under the age of 65 but have high-risk chronic diseases that put them at increased risk of severe COVID-19, such as diabetes, severe obesity and cardiac disease. These medically high-risk groups represent 42% of the total participants in the Phase 3 COVE study. The study also included communities that have historically been under-represented in clinical research and have been disproportionately impacted by COVID-19. The study includes more than 11,000 participants from communities of color, representing 37% of the study population, which is similar to the diversity of the U.S. at large. This includes more than 6,000 participants who identify as Hispanic or LatinX, and more than 3,000 participants who identify as Black or African American.

**About mRNA-1273**

mRNA-1273 is an mRNA vaccine against COVID-19 encoding for a prefusion stabilized form of the Spike (S) protein, which was co-developed by Moderna and investigators from NIAID's Vaccine Research Center. The first clinical batch, which was funded by the Coalition for Epidemic Preparedness Innovations, was completed on February 7, 2020 and underwent analytical testing; it was shipped to the NIH on February 24, 42 days from sequence selection. The first participant in the NIAID-led Phase 1 study of mRNA-1273 was dosed on March 16, 63 days from sequence selection to Phase 1 study dosing. On May 12, the FDA granted mRNA-1273 Fast Track designation. On May 29, the first participants in each age cohort: adults ages 18-55 years (n=300) and older adults ages 55 years and above (n=300) were dosed in the Phase 2 study of mRNA-1273. On July 8, the Phase 2 study completed enrollment.

Results from the second interim analysis of the NIH-led Phase 1 study of mRNA-1273 in the 56-70 and 71+ age groups were published on September 29 in *The New England Journal of Medicine*. On July 28, results from a non-human primate preclinical viral challenge study evaluating mRNA-1273 were published in *The New England Journal of Medicine.* On July 14, an interim analysis of the original cohorts in the NIH-led Phase 1 study of mRNA-1273 was published in *The New England Journal of Medicine*. mRNA-1273 currently is not approved for use by any regulatory body.

BARDA is supporting the continued research and development of mRNA-1273 with $955 million in federal funding under Contract no. 75A50120C00034. BARDA is reimbursing Moderna for 100 percent of the allowable costs incurred by the Company for conducting the program described in the BARDA contract. The U.S. government has agreed to provide up to $1.525 billion to purchase supply of mRNA-1273 under U.S. Department of Defense Contract No. W911QY-20-C-0100.



**Forward Looking Statements**

This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including regarding the Company's development of a potential vaccine (mRNA-1273) against the novel coronavirus, mRNA-1273's efficacy and its ability to prevent infection or mitigate symptoms of COVID-19, the safety profile for mRNA-1273, further changes to mRNA-1273's efficacy as the study continues, the Company's plans to seek regulatory approval for the use of mRNA-1273 in the U.S. and other jurisdictions, and the Company's anticipated production of mRNA-1273. In some cases, forward-looking statements can be identified by terminology such as "will," "may," "should," "could", "expects," "intends," "plans," "aims," "anticipates," "believes," "estimates," "predicts," "potential," "continue," or the negative of these terms or other comparable terminology, although not all forward-looking statements contain these words. The forward-looking statements in this press release are neither promises nor guarantees, and you should not place undue reliance on these forward-looking statements because they involve known and unknown risks, uncertainties, and other factors, many of which are beyond Moderna's control and which could cause actual results to differ materially from those expressed or implied by these forward-looking statements. These risks, uncertainties, and other factors include, among others: the fact that there has never been a commercial product utilizing mRNA technology approved for use; the fact that the rapid response technology in use by Moderna is still being developed and implemented; the fact that the safety and efficacy of mRNA-1273 has not yet been established; despite having ongoing interactions with the FDA or other regulatory agencies, the FDA or such other regulatory agencies may not agree with the Company's regulatory approval strategies, components of our filings, such as clinical trial designs, conduct and methodologies, or the sufficiency of data submitted; potential adverse impacts due to the global COVID-19 pandemic such as delays in regulatory review, manufacturing and clinical trials, supply chain interruptions, adverse effects on healthcare systems and disruption of the global economy; and those other risks and uncertainties described under the heading "Risk Factors" in Moderna's most recent Quarterly Report on Form 10-Q filed with the U.S. Securities and Exchange Commission (SEC) and in subsequent filings made by Moderna with the SEC, which are available on the SEC's website at www.sec.gov. Except as required by law, Moderna disclaims any intention or responsibility for updating or revising any forward-looking statements contained in this press release in the event of new information, future developments or otherwise. These forward-looking statements are based on Moderna's current expectations and speak only as of the date hereof.

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vaccines

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*Review*

# Efficacy and Safety of COVID-19 Vaccines: A Systematic Review and Meta-Analysis of Randomized Clinical Trials

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**Abstract:** The current study systematically reviewed, summarized and meta-analyzed the clinical features of the vaccines in clinical trials to provide a better estimate of their efficacy, side effects and immunogenicity. All relevant publications were systematically searched and collected from major databases up to 12 March 2021. A total of 25 RCTs (123 datasets), 58,889 cases that received the COVID-19 vaccine and 46,638 controls who received placebo were included in the meta-analysis. In total, mRNA-based and adenovirus-vectored COVID-19 vaccines had 94.6% (95% CI 0.936–0.954) and 80.2% (95% CI 0.56–0.93) efficacy in phase II/III RCTs, respectively. Efficacy of the adenovirus-vectored vaccine after the first (97.6%; 95% CI 0.939–0.997) and second (98.2%; 95% CI 0.980–0.984) doses was the highest against receptor-binding domain (RBD) antigen after 3 weeks of injections. The mRNA-based vaccines had the highest level of side effects reported except for diarrhea and arthralgia. Aluminum-adjuvanted vaccines had the lowest systemic and local side effects between vaccines' adjuvant or without adjuvant, except for injection site redness. The adenovirus-vectored and mRNA-based vaccines for COVID-19 showed the highest efficacy after first and second doses, respectively. The mRNA-based vaccines had higher side effects. Remarkably few experienced extreme adverse effects and all stimulated robust immune responses.



**Keywords:** COVID-19; SARS-CoV-2; vaccines; efficacy; side effect; randomized clinical trial; meta-analysis



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## 1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a non-segmented positive-sense, single-stranded ribonucleic acid (RNA) beta coronavirus [1] that was first reported in Wuhan, China. The SARS-CoV-2 infection causes the coronavirus disease 2019 (COVID-19) that became a global pandemic and public health crisis. Over 140 million infected and 3 million deaths are reported from COVID-19 by April 2021, with the death rate accelerating; according to WHO, the case fatality ratio (CFR) of SARS-CoV-2 ranges from less than 0.1% to over 25% depending on the country [2].

To overcome this pandemic, vaccination is the hope for a safe and effective way to help build protection and reduce disease spread [3]. More than 200 COVID-19 vaccine candidates presented in different stages of development and over 50 candidates have reached clinical trials to date [4], including: Oxford-AstraZeneca's ChAdOx1/AZD1222, Moderna's mRNA-1273, Pfizer-BioNTech's mRNA BNT162b2, Gamaleya's Sputnik V, Johnson & Johnson's INJ-7843735/Ad26.COV2.s, CoronaVac, Sinopharm's BBIBP-CorV, Novavax's NVX-CoV2373, EpiVacCorona, CanSino's Convidicea (Ad5-nCoV), SinoVac's

CoronaVac, Anhui Zhifei Longcom's ZF2001, GlaxoSmithKline and Medicago's CoVLP, and Bharat Biotech's BBV152/Covaxin.

Different strategies have been considered for the development of vaccines against SARS-CoV-2 based on the following vaccine platforms: (I) Nucleic acid mRNA-based vaccines are the newest generation of vaccine production approach [5]. The mRNA vaccine technology is a single-stranded RNA molecule that carries a portion of the coding sequence for the peptide or protein from the virus that can be synthesized in the cytoplasm (ribosomes). The resulting antigen triggers an immune response, including the production of antibodies [5]. For instance, the current vaccines developed by the companies Pfizer and Moderna utilize synthetic mRNA encoding the sequence of the coronavirus's signature spike protein (S-protein) that is then encapsulated within a lipid vesicle nanoparticle. (II) Viral vector vaccines that are developed with new biotechnology [6]. A modified existing virus, able to infect human cells, is introduced carrying the genetic code of the target virus antigen in order to stimulate an immune response. Oxford-AstraZeneca, Gamaleya, CanSio and Johnson & Johnson developed their vaccines based on a DNA sequence encoding the S-protein inserted into the genome of a modified safe adenovirus. (III) Whole-Pathogen Inactivated virus vaccines consisting of killed/inactivated whole viruses or virus fragments. Here the pathogen's genetic material is destroyed by heat, chemicals, or radiation, so that they cannot replicate but their presence can still stimulate immunogenicity [7]. Sinopharm, SinoVac, and Bharat Biotech's vaccines were produced by inactivating the SARS-CoV-2 with B-propiolactone, but all the viral protein remains intact. (IV) Subunit vaccines that contain a fragment of the pathogen, either a protein (Pro-subunit), a polysaccharide, or a combination of both, without introducing viable pathogen particles [8]. Lack of genetic material makes them safe and non-infectious/non-viable. Novavax and Anhui Zhifei Longcom applied this technology for the development of their vaccine, using nanoparticles coated with synthetic S-protein and an adjuvant for boosting the immune response. Virus-like particle (VLP) vaccines, also a subunit vaccine, mimic the native virus structure, but contain no viral genetic material [9]. A VLP presents the antigen inserted on a nanoparticle surface. GlaxoSmithKline and Medicago used a plant-derived platform to produce a particle that elicits neutralizing antibody and immune cell (e.g., TH1 T cell) responses against COVID-19.



The structural proteins of SARS-CoV-2 include four major proteins: spike (S), membrane (M), and envelope (E) part of the viral surface envelope, and the nucleocapsid (N) protein in the ribonucleoprotien core. Among viral surface elements, the S-protein is a primary target for vaccines and therapeutic development against COVID-19 due to its role in the receptor recognition for cell entry and cell membrane fusion process. The trimeric S-protein contains two subunits, S1 and S2. The S1 contains a receptor-binding domain (RBD), which is responsible for recognizing and binding to the host receptor angiotensin-converting enzyme 2 (ACE2), while the S2 mediates the membrane fusion process by forming a six-helical bundle (6-HB) via the two-heptad repeat (HR) regions [10]. However, S1 is the immunodominant antigen during CoV infections and induces long-lasting and broad-spectrum neutralizing antibodies (NAbs) and T-cell immune responses against the RBD. Thus, the S-protein and the RBD serve as the promising targets of SARS-CoV-2 vaccines and the predominant antigenic target for developing a vaccine [11]. Other antigenic targets, such as non-structural proteins (nsp) 3, nsp8-10 [12], papain-like proteases (PLpro), and cysteine-like protease (3CLpro) [13] can be considered an alternative for vaccine development, but these are expected to elicit less of an immune response.

Efficacy and safety, thus side effect profiles, are core vaccine competencies required by medical care systems and public health. To the best of our knowledge, there is still no comprehensive comparative study around the efficacy and safety of COVID-19-related vaccines. In this regard, we provide here a meta-analysis on available randomized clinical trial (RCT) publications providing information on the efficacy and side effects of COVID-19 vaccines.

## 2. Methods

### *2.1. Search Strategy*

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (PRISMA) recommendations were followed in this analysis [14]. We searched all clinical trial publications related to SARS-CoV-2 vaccines from the following databases: Scopus, EMBASE, Medline (via PubMed), and Web of Science. All studies published up to 12 March 2021 were searched without language restriction by three independent reviewers. Search medical subject headings (MeSH) terms used were "Covid-19 Vaccine", "SARS-CoV-2 Vaccine", "clinical trial" or "phase trial", and "randomized", as well as all synonyms. We used the Center for Disease Control (CDC), World Health Organization (WHO), and Google Scholar databases/academic search engines to look for unpublished and grey literature. References and citation lists of selected articles and reviews were also reviewed for any other relevant literature (forward and backward citation, recommended by Cochrane). Additional search strategy details are provided in Table S1.

### *2.2. Study Selection*

The records were first reviewed by three independent authors based on the title and abstract (MHR, AP, and SG), all unrelated publications were removed and the full texts of the remaining articles were reviewed. Then, two independent reviewers (AP and SG) judged potentially eligible articles and disagreements were resolved by discussion and for each article a consensus was reached.

### *2.3. Eligibility and Inclusion Criteria*

The following predetermined conditions had to be met for studies to be considered for inclusion in this meta-analysis. For initial screening, all clinical studies were included in the systematic review, while RCT studies in phase I/II/III of COVID-19 vaccines were included in the meta-analysis.



### *2.4. Exclusion Criteria*

Non-randomized studies, studies without a placebo group, preclinical studies, studies on animal phase, meta-analyses, letters to the editor, review articles, studies with no extractable data, and news reports were excluded for the meta-analysis. However, non-randomized studies were included only in the systematic review. Additionally, 11 vaccine studies (43 datasets) with no report in the type of adjuvants were excluded from the adjuvant side effect sub-group meta-analysis.

### *2.5. Data Extraction*

Four independent reviewers extracted data from the studies that were chosen. The following data were obtained from each article: first authors, trial initiation date, published year, vaccine name, company, study type, vaccine type, adjuvant, store temperature, trial phase, doses, injection interval (days), concentration, volume, trial country, all side effects, and efficacy-related data. Three of the authors (S.G, M.H.R, and A.P) extracted data independently, and another author (M.Z) reviewed extracted data at random; discrepancies were resolved by consensus.

### *2.6. Quality Assessment*

The JADAD scale (Oxford quality scoring system) for reporting quality of RCTs was used to evaluate the included articles' quality. The JADAD scale included the three quality parameters of randomization, blinding, and account of all patients. Two questions are asked for the first two parameters, and one question is asked for the third parameter. Each query is given a score of one or zero. The highest acceptable score on the prepared checklist was five, with the lowest acceptable score being three. Data were derived from papers with a ranking of at least three (Table S2).

### *2.7. Analysis*

Initially, cleaning data and preparing them for analysis was done in Microsoft Office 365 and analysis was performed by Comprehensive Meta-Analysis Software Version 2.0 software. The point estimates of the effect size, odds ratios (ORs), and 95% confidence interval (95% CI) were calculated for estimating vaccine efficacy and side effects. Random effects models were used to estimate pooled effects. Additionally, to search for heterogeneity between studies, the I2 statistic was used [15] and high heterogeneity was characterized as an I2 > 50%, with sources of heterogeneity established through meta-regression and subgroup analyses. Subgroup analysis based on the vaccine phases significantly decreased the heterogeneity in the high heterogeneity cases. The presence and effect of publication bias were examined using funnel plots, Begg's test, and Egger weighted regression methods [16,17]. For all analyses, two-tailed statistics and a significance level of less than 0.05 were considered.

## 3. Result

### *3.1. Characteristics of Included Studies*

A total of 32,790 publications were screened for the COVID-19 vaccines' side effects and efficacies. Out of these studies, 27 met the systematic review's inclusion criteria (non-randomized and randomized), while 25 randomized studies were included in the meta-analysis (Figure 1). Characteristics of the selected articles are summarized in Table 1. A total of 25 studies (123 datasets) were included in the meta-analysis. Studies with different vaccine phase reports, number of doses, injection concentration, different case, and control group numbers are considered a separate dataset for the meta-analysis. All included studies were written in English. Out of 25 randomized studies, 12 were double-blind, 2 participant-blind, 6 observer-blind, 3 single-blind, and 2 partially blind. The number of studies by vaccine platforms were 7 mRNA-based, 4 pro-subunit, 8 adenovirus-vector, 5 inactivated, and 1 VLP's.



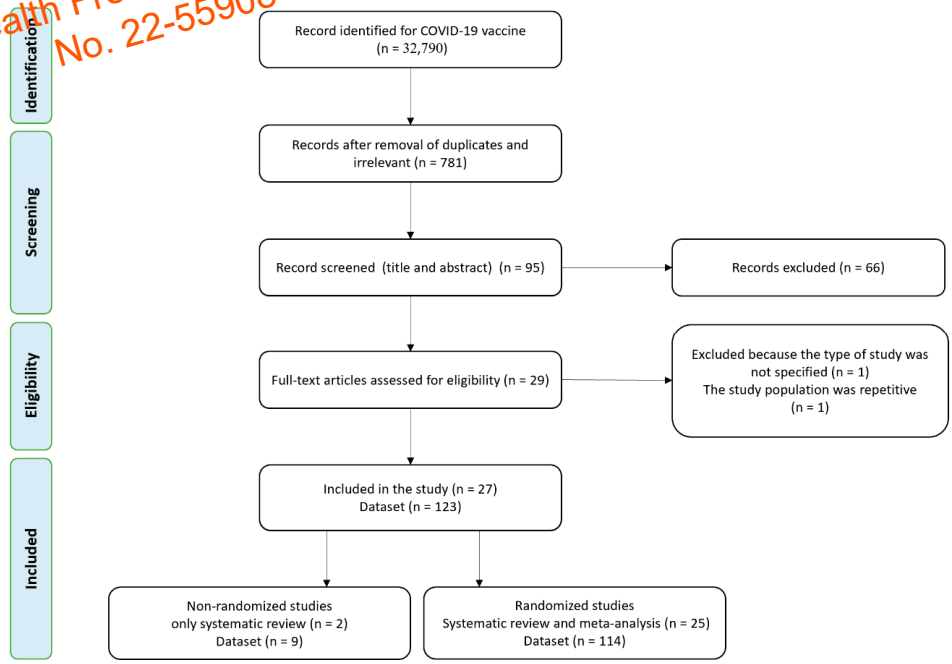


**Figure 1.** Flow diagram of literature search and study selection for meta-analysis (PRISMA flow chart).

**Table 1.** Characterization of included studies.

| Study | Trial Initiation Date | Pub. Year | Vaccine Name | Company | Study Type | Vaccine Type | Adjuvant | Store Temp (°C) | RCT Phase | Dose (s) | Age Range (Year) | Injection Interval (Days) | Concentration | Trial Country | Ref |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Yang et al. | 22 June and 3 July 2020 | 2020 | ZF2001 | Anhui Zhifei Longcom | Randomized, double-blind, placebo-controlled | Pro-Subunit | Aluminum hydroxide | 2–8 | I | 3 | 22.9–54.7 | 30 | 25 μg * | China | [18] |
| Yang et al. | 22 June and 3 July 2020 | 2020 | ZF2001 | Anhui Zhifei Longcom | Randomized, double-blind, placebo-controlled | Pro-Subunit | Aluminum hydroxide | 2–8 | I | 3 | 20.9–49.4 | 30 | 50 μg * | China | [18] |
| Ella et al. | 13 and 30 July 2020 | 2021 | BBV152 (Covaxin) | Bharat Biotech | Randomized, double-blind, placebo-controlled | Inactivated | Algel-IMDG | 2–8 | I | 2 | 18–55 | 14 | 3 μg * | India | [19] |
| Ella et al. | 13 and 30 July 2020 | 2021 | BBV152 (Covaxin) | Bharat Biotech | Randomized, double-blind, placebo-controlled | Inactivated | Algel-IMDG | 2–8 | I | 2 | 18–55 | 14 | 6 μg * | India | [19] |
| Ella et al. | 13 and 30 July 2020 | 2021 | BBV152 (Covaxin) | Bharat Biotech | Randomized, double-blind, placebo-controlled | Inactivated | Algel | 2–8 | I | 2 | 18–55 | 14 | 6 μg* | India | [19] |
| Zhu et al. | 16 and 27 March 2020 | 2020 | Ad5-nCoV | CanSino | Non-randomized | Adenovirus-based | No adjuvant | UN | I | 1 | 18–60 | No | $5 \times 10^{10}$ VP * | China | [20] |
| Zhu et al. | 16 and 27 March 2020 | 2020 | Ad5-nCoV | CanSino | Non-randomized | Adenovirus-based | No adjuvant | UN | I | 1 | 18–60 | No | $1 \times 10^{11}$ VP * | China | [20] |
| Zhu et al. | 16 and 27 March 2020 | 2020 | Ad5-nCoV | CanSino | Non-randomized | Adenovirus-based | No adjuvant | UN | I | 1 | 18–60 | No | $1.5 \times 10^{11}$ VP * | China | [20] |
| Richmond et al. | 19 June and 23 September 2020 | 2021 | SCB-2019 | Clover | Randomized, double-blind, placebo-controlled | Pro-Subunit | No adjuvant | 2–8 | I | 2 | 20–50 | 21 | 3 μg * | Australia | [21] |
| Richmond et al. | 19 June and 23 September 2020 | 2021 | SCB-2019 | Clover | Randomized, double-blind, placebo-controlled | Pro-Subunit | AS03 | 2–8 | I | 2 | 20–53 | 21 | 3 μg * | Australia | [21] |
| Richmond et al. | 19 June and 23 September 2020 | 2021 | SCB-2019 | Clover | Randomized, double-blind, placebo-controlled | Pro-Subunit | AS03 | 2–8 | I | 2 | 55–70 | 21 | 3 μg * | Australia | [21] |
| Richmond et al. | 19 June and 23 September 2020 | 2021 | SCB-2019 | Clover | Randomized, double-blind, placebo-controlled | Pro-Subunit | CpG/Alum | 2–8 | I | 2 | 20–53 | 21 | 3 μg * | Australia | [21] |
| Richmond et al. | 19 June and 23 September 2020 | 2021 | SCB-2019 | Clover | Randomized, double-blind, placebo-controlled | Pro-Subunit | CpG/Alum | 2–8 | I | 2 | 55–71 | 21 | 3 μg * | Australia | [21] |
| Richmond et al. | 19 June and 23 September 2020 | 2021 | SCB-2019 | Clover | Randomized, double-blind, placebo-controlled | Pro-Subunit | No adjuvant | 2–8 | I | 2 | 20–54 | 21 | 9 μg * | Australia | [21] |
| Richmond et al. | 19 June and 23 September 2020 | 2021 | SCB-2019 | Clover | Randomized, double-blind, placebo-controlled | Pro-Subunit | AS03 | 2–8 | I | 2 | 21–53 | 21 | 9 μg * | Australia | [21] |
| Richmond et al. | 19 June and 23 September 2020 | 2021 | SCB-2019 | Clover | Randomized, double-blind, placebo-controlled | Pro-Subunit | AS03 | 2–8 | I | 2 | 55–64 | 21 | 9 μg * | Australia | [21] |
| Richmond et al. | 19 June and 23 September 2020 | 2021 | SCB-2019 | Clover | Randomized, double-blind, placebo-controlled | Pro-Subunit | CpG/Alum | 2–8 | I | 2 | 19–55 | 21 | 9 μg * | Australia | [21] |
| Richmond et al. | 19 June and 23 September 2020 | 2021 | SCB-2019 | Clover | Randomized, double-blind, placebo-controlled | Pro-Subunit | CpG/Alum | 2–8 | I | 2 | 55–67 | 21 | 9 μg * | Australia | [21] |
| Richmond et al. | 19 June and 23 September 2020 | 2021 | SCB-2019 | Clover | Randomized, double-blind, placebo-controlled | Pro-Subunit | No adjuvant | 2–8 | I | 2 | 18–49 | 21 | 30 μg * | Australia | [21] |
| Richmond et al. | 19 June and 23 September 2020 | 2021 | SCB-2019 | Clover | Randomized, double-blind, placebo-controlled | Pro-Subunit | AS03 | 2–8 | I | 2 | 19–47 | 21 | 30 μg * | Australia | [21] |
| Richmond et al. | 19 June and 23 September 2020 | 2021 | SCB-2019 | Clover | Randomized, double-blind, placebo-controlled | Pro-Subunit | AS03 | 2–8 | I | 2 | 55–63 | 21 | 30 μg * | Australia | [21] |
| Richmond et al. | 19 June and 23 September 2020 | 2021 | SCB-2019 | Clover | Randomized, double-blind, placebo-controlled | Pro-Subunit | CpG/Alum | 2–8 | I | 2 | 21–50 | 21 | 30 μg * | Australia | [21] |
| Richmond et al. | 19 June and 23 September 2020 | 2021 | SCB-2019 | Clover | Randomized, double-blind, placebo-controlled | Pro-Subunit | CpG/Alum | 2–8 | I | 2 | 55–74 | 21 | 30 μg * | Australia | [21] |
| Kremsner et al. | June, 2020 | 2020 | CVnCoV | Curevac | Randomized, partially blind, placebo-controlled | mRNA-based | No adjuvant | 5 | I | 2 | 18–60 | 28 | 2 μg * | Germany | [22] |
| Kremsner et al. | June, 2020 | 2020 | CVnCoV | Curevac | Randomized, partially blind, placebo-controlled | mRNA-based | No adjuvant | 5 | I | 2 | 19–59 | 28 | 4 μg * | Germany | [22] |
| Kremsner et al. | June, 2020 | 2020 | CVnCoV | Curevac | Randomized, partially blind, placebo-controlled | mRNA-based | No adjuvant | 5 | I | 2 | 20–59 | 28 | 6 μg * | Germany | [22] |
| Kremsner et al. | June, 2020 | 2020 | CVnCoV | Curevac | Randomized, partially blind, placebo-controlled | mRNA-based | No adjuvant | 5 | I | 2 | 20–59 | 28 | 8 μg * | Germany | [22] |
| Kremsner et al. | June, 2020 | 2020 | CVnCoV | Curevac | Randomized, partially blind, placebo-controlled | mRNA-based | No adjuvant | 5 | I | 2 | 19–59 | 28 | 12 μg * | Germany | [22] |
| Ward et al. | July, 2020 | 2020 | CoVLP | Medicago | Randomized, partially blind | VLP | No adjuvant | 2–8 | I | 2 | 18–55 | 21 | 3.75 μg * | Canada | [23] |
| Ward et al. | July, 2020 | 2020 | CoVLP | Medicago | Randomized, partially blind | VLP | CpG 1018 | 2–8 | I | 2 | 18–55 | 21 | 3.75 μg * | Canada | [23] |
| Ward et al. | July, 2020 | 2020 | CoVLP | Medicago | Randomized, partially blind | VLP | AS03 | 2–8 | I | 2 | 18–55 | 21 | 3.75 μg * | Canada | [23] |
| Ward et al. | July, 2020 | 2020 | CoVLP | Medicago | Randomized, partially blind | VLP | No adjuvant | 2–8 | I | 2 | 18–55 | 21 | 7.5 μg * | Canada | [23] |
| Ward et al. | July, 2020 | 2020 | CoVLP | Medicago | Randomized, partially blind | VLP | CpG 1018 | 2–8 | I | 2 | 18–55 | 21 | 7.5 μg * | Canada | [23] |
| Ward et al. | July, 2020 | 2020 | CoVLP | Medicago | Randomized, partially blind | VLP | AS03 | 2–8 | I | 2 | 18–55 | 21 | 7.5 μg * | Canada | [23] |
| Ward et al. | July, 2020 | 2020 | CoVLP | Medicago | Randomized, partially blind | VLP | No adjuvant | 2–8 | I | 2 | 18–55 | 21 | 15 μg * | Canada | [23] |
| Ward et al. | July, 2020 | 2020 | CoVLP | Medicago | Randomized, partially blind | VLP | CpG 1018 | 2–8 | I | 2 | 18–55 | 21 | 15 μg * | Canada | [23] |
| Ward et al. | July, 2020 | 2020 | CoVLP | Medicago | Randomized, partially blind | VLP | AS03 | 2–8 | I | 2 | 18–55 | 21 | 15 μg | Canada | [23] |
| Jackson et al. | 16 March and 14 April 2020 | 2020 | mRNA-1273 | Moderna | Open-label | mRNA-based | No adjuvant | −20 | I | 2 | 18–55 | 28 | 25 μg * | United States | [24] |
| Jackson et al. | 16 March and 14 April 2020 | 2020 | mRNA-1273 | Moderna | Open-label | mRNA-based | No adjuvant | −20 | I | 2 | 18–55 | 28 | 100 mg * | United States | [24] |
| Jackson et al. | 16 March and 14 April 2020 | 2020 | mRNA-1273 | Moderna | Open-label | mRNA-based | No adjuvant | −20 | I | 2 | 18–55 | 28 | 250 mg * | United States | [24] |
| Anderson et al. | 16 April and 12 May 2020 | 2020 | mRNA-1273 | Moderna | Open-label | mRNA-based | No adjuvant | −20 | I | 2 | 56–70 | 28 | 25 mg * | United States | [25] |
| Anderson et al. | 16 April and 12 May 2020 | 2020 | mRNA-1273 | Moderna | Open-label | mRNA-based | No adjuvant | −20 | I | 2 | 71≤ | 28 | 25 mg * | United States | [25] |
| Anderson et al. | 16 April and 12 May 2020 | 2020 | mRNA-1273 | Moderna | Open-label | mRNA-based | No adjuvant | −20 | I | 2 | 56–70 | 28 | 100 mg * | United States | [25] |
| Anderson et al. | 16 April and 12 May 2020 | 2020 | mRNA-1273 | Moderna | Open-label | mRNA-based | No adjuvant | −20 | I | 2 | 71≤ | 28 | 100 mg * | United States | [25] |
| Keech et al. | 26 May and 6 June 2020 | 2020 | NVX-CoV2373 | Novavax | Randomized, observer-blind, placebo-controlled | Pro-Subunit | No adjuvant | 2–8 | I | 2 | 18–59 | 21 | 25 μg/0.6 ml | Australia, United States | [26] |
| Keech et al. | 26 May and 6 June 2020 | 2020 | NVX-CoV2373 | Novavax | Randomized, observer-blind, placebo-controlled | Pro-Subunit | Matrix-M1 | 2–8 | I | 2 | 18–59 | 21 | 5 μg/0.6 ml | Australia, United States | [26] |
| Keech et al. | 26 May and 6 June 2020 | 2020 | NVX-CoV2373 | Novavax | Randomized, observer-blind, placebo-controlled | Pro-Subunit | Matrix-M1 | 2–8 | I | 2 | 18–59 | 21 | 25 μg/0.6 ml | Australia, United States | [26] |
| Keech et al. | 26 May and 6 June 2020 | 2020 | NVX-CoV2373 | Novavax | Randomized, observer-blind, placebo-controlled | Pro-Subunit | Matrix-M1 | 2–8 | I | 1 | 18–59 | 21 | 25 μg/0.6 ml | Australia, United States | [26] |

**Table 1.** *Cont.*

| Study | Trial Initiation Date | Pub. Year | Vaccine Name | Company | Study Type | Vaccine Type | Adjuvant | Store Temp (°C) | RCT Phase | Dose (s) | Age Range (Year) | Injection Interval (Days) | Concentration | Trial Country | Ref |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sahin et al. | 23 April and 22 May 2020 | 2020 | BNT162b1 | Pfizer/BioNTech | Randomized, single-blind | mRNA-based | No adjuvant | (−60)–(−80) | I | 2 | 18–55 | 21 | 1 µg * | Germany | [27] |
| Sahin et al. | 23 April and 22 May 2020 | 2020 | BNT162b1 | Pfizer/BioNTech | Randomized, single-blind | mRNA-based | No adjuvant | (−60)–(−80) | I | 2 | 21.4–55.8 | 21 | 10 µg * | Germany | [27] |
| Sahin et al. | 23 April and 22 May 2020 | 2020 | BNT162b1 | Pfizer/BioNTech | Randomized, single-blind | mRNA-based | No adjuvant | (−60)–(−80) | I | 2 | 25.1–55 | 21 | 30 µg * | Germany | [27] |
| Sahin et al. | 23 April and 22 May 2020 | 2020 | BNT162b1 | Pfizer/BioNTech | Randomized, single-blind | mRNA-based | No adjuvant | (−60)–(−80) | I | 2 | 23.9–54 | 21 | 50 µg * | Germany | [27] |
| Sahin et al. | 23 April and 22 May 2020 | 2020 | BNT162b1 | Pfizer/BioNTech | Randomized, single-blind | mRNA-based | No adjuvant | (−60)–(−80) | I | 1 | 19.9–47.8 | No | 60 µg * | Germany | [27] |
| Walsh et al. | 4 May and 22 June 2020 | 2020 | BNT162b1 | Pfizer/BioNTech | Randomized, observer-blind, placebo-controlled | mRNA-based | No adjuvant | (−60)–(−80) | I | 2 | 20.9–53.2 | 21 | 10 µg * | United States, Germany | [28] |
| Walsh et al. | 4 May and 22 June 2020 | 2020 | BNT162b1 | Pfizer/BioNTech | Randomized, observer-blind, placebo-controlled | mRNA-based | No adjuvant | (−60)–(−80) | I | 2 | 18–55 | 21 | 10 µg * | United States, Germany | [28] |
| Walsh et al. | 4 May and 22 June 2020 | 2020 | BNT162b1 | Pfizer/BioNTech | Randomized, observer-blind, placebo-controlled | mRNA-based | No adjuvant | (−60)–(−80) | I | 2 | 65–85 | 21 | 20 µg * | United States, Germany | [28] |
| Walsh et al. | 4 May and 22 June 2020 | 2020 | BNT162b1 | Pfizer/BioNTech | Randomized, observer-blind, placebo-controlled | mRNA-based | No adjuvant | (−60)–(−80) | I | 2 | 18–55 | 21 | 20 µg * | United States, Germany | [28] |
| Walsh et al. | 4 May and 22 June 2020 | 2020 | BNT162b1 | Pfizer/BioNTech | Randomized, observer-blind, placebo-controlled | mRNA-based | No adjuvant | (−60)–(−80) | I | 2 | 65–85 | 21 | 30 µg * | United States, Germany | [28] |
| Walsh et al. | 4 May and 22 June 2020 | 2020 | BNT162b1 | Pfizer/BioNTech | Randomized, observer-blind, placebo-controlled | mRNA-based | No adjuvant | (−60)–(−80) | 1 | 2 | 18–55 | 21 | 30 µg * | United States, Germany | [28] |
| Walsh et al. | 4 May and 22 June 2020 | 2020 | BNT162b2 | Pfizer/BioNTech | Randomized, observer-blind, placebo-controlled | mRNA-based | No adjuvant | (−60)–(−80) | I | 2 | 65–85 | 21 | 10 µg * | United States, Germany | [28] |
| Walsh et al. | 4 May and 22 June 2020 | 2020 | BNT162b2 | Pfizer/BioNTech | Randomized, observer-blind, placebo-controlled | mRNA-based | No adjuvant | (−60)–(−80) | I | 2 | 18–55 | 21 | 10 µg * | United States, Germany | [28] |
| Walsh et al. | 4 May and 22 June 2020 | 2020 | BNT162b2 | Pfizer/BioNTech | Randomized, observer-blind, placebo-controlled | mRNA-based | No adjuvant | (−60)–(−80) | I | 2 | 65–85 | 21 | 20 µg * | United States, Germany | [28] |
| Walsh et al. | 4 May and 22 June 2020 | 2020 | BNT162b2 | Pfizer/BioNTech | Randomized, observer-blind, placebo-controlled | mRNA-based | No adjuvant | (−60)–(−80) | I | 2 | 18–55 | 21 | 20 µg * | United States, Germany | [28] |
| Walsh et al. | 4 May and 22 June 2020 | 2020 | BNT162b2 | Pfizer/BioNTech | Randomized, observer-blind, placebo-controlled | mRNA-based | No adjuvant | (−60)–(−80) | I | 2 | 65–85 | 21 | 30 µg * | United States, Germany | [28] |
| Walsh et al. | 4 May and 22 June 2020 | 2020 | BNT162b2 | Pfizer/BioNTech | Randomized, observer-blind, placebo-controlled | mRNA-based | No adjuvant | (−60)–(−80) | I | 2 | 18–55 | 21 | 30 µg * | United States, Germany | [28] |
| Xia et al. | 12 April and 2 May 2020 | 2020 | BBIBP-CorV | Sinopharm | Randomized, double-blind, placebo controlled | Inactivated | Aluminum hydroxide | 2–8 | I | 3 | 65–85 | 28 | 2.5 µg * | China | [29] |
| Xia et al. | 12 April and 2 May 2020 | 2020 | BBIBP-CorV | Sinopharm | Randomized, double-blind, placebo controlled | Inactivated | Aluminum hydroxide | 2–8 | I | 3 | 18–59 | 28 | 5 µg * | China | [29] |
| Xia et al. | 12 April and 2 May 2020 | 2020 | BBIBP-CorV | Sinopharm | Randomized, double-blind, placebo controlled | Inactivated | Aluminum hydroxide | 2–8 | I | 3 | 18–59 | 28 | 10 µg * | China | [29] |
| Xia et al. | 29 April and 28 June 2020 | 2020 | BBIBP-CorV | Sinopharm | Randomized, double-blind, placebo controlled | Inactivated | Aluminum hydroxide | 2–8 | I | 2 | 18–59 | 28 | 2 µg * | China | [30] |
| Xia et al. | 29 April and 28 June 2020 | 2020 | BBIBP-CorV | Sinopharm | Randomized, double-blind, placebo controlled | Inactivated | Aluminum hydroxide | 2–8 | I | 2 | 18–59 | 28 | 2 µg * | China | [30] |
| Xia et al. | 29 April and 28 June 2020 | 2020 | BBIBP-CorV | Sinopharm | Randomized, double-blind, placebo controlled | Inactivated | Aluminum hydroxide | 2–8 | I | 2 | 60 ≤ | 28 | 4 µg * | China | [30] |
| Xia et al. | 29 April and 28 June 2020 | 2020 | BBIBP-CorV | Sinopharm | Randomized, double-blind, placebo controlled | Inactivated | Aluminum hydroxide | 2–8 | I | 2 | 18–59 | 28 | 4 µg * | China | [30] |
| Xia et al. | 29 April and 28 June 2020 | 2020 | BBIBP-CorV | Sinopharm | Randomized, double-blind, placebo controlled | Inactivated | Aluminum hydroxide | 2–8 | I | 2 | 60 ≤ | 28 | 8 µg * | China | [30] |
| Xia et al. | 29 April and 28 June 2020 | 2020 | BBIBP-CorV | Sinopharm | Randomized, double-blind, placebo controlled | Inactivated | Aluminum hydroxide | 2–8 | I | 2 | 18–59 | 28 | 8 µg * | China | [30] |
| Zhang et al. | 16 and 25 April 2020 | 2020 | CoronaVac | Sinovac | Randomized, double-blind, placebo controlled | Inactivated | Aluminum hydroxide | 2–8 | I | 2 | 60≤ | 14 | 3 µg * | China | [31] |
| Zhang et al. | 16 and 25 April 2020 | 2020 | CoronaVac | Sinovac | Randomized, double-blind, placebo controlled | Inactivated | Aluminum hydroxide | 2–8 | I | 2 | 18–59 | 28 | 3 µg * | China | [31] |
| Zhang et al. | 16 and 25 April 2020 | 2020 | CoronaVac | Sinovac | Randomized, double-blind, placebo controlled | Inactivated | Aluminum hydroxide | 2–8 | I | 2 | 18–59 | 14 | 6 µg * | China | [31] |
| Zhang et al. | 16 and 25 April 2020 | 2020 | CoronaVac | Sinovac | Randomized, double-blind, placebo controlled | Inactivated | Aluminum hydroxide | 2–8 | I | 2 | 18–59 | 28 | 6 µg * | China | [31] |
| Logunov et al. | 18 June and 3 August 2020 | 2020 | Sputnik V | Gamaleya | Non-randomized | Adenovirus-based | No adjuvant | 2–8 | I | 1 | 18–59 | No | $10^{11}$ VP * | Russia | [32] |
| Logunov et al. | 18 June and 3 August 2020 | 2020 | Sputnik V | Gamaleya | Non-randomized | Adenovirus-based | No adjuvant | 2–8 | I | 1 | 18–60 | No | $10^{11}$ * | Russia | [32] |

**Table 1.** *Cont.*

| Study | Trial Initiation Date | Pub. Year | Vaccine Name | Company | Study Type | Vaccine Type | Adjuvant | Store Temp (°C) | RCT Phase | Dose (s) | Age Range (Year) | Injection Interval (Days) | Concentration | Trial Country | Ref |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Logunov et al. | 18 June and 3 August 2020 | 2020 | Sputnik V (Lyo) | Gamaleya | Non-randomized | Adenovirus-based | No adjuvant | 2–8 | I | 1 | 18–60 | No | $10^{11}$ * | Russia | [32] |
| Logunov et al. | 18 June and 3 August 2020 | 2020 | Sputnik V (Lyo) | Gamaleya | Non-randomized | Adenovirus-based | No adjuvant | 2–8 | I | 1 | 18–60 | No | $10^{11}$ * | Russia | [32] |
| Folegatti et al. | 23 April and 21 May 2020 | 2020 | AZD1222 | Oxford/AstraZeneca | Randomized, participant-blind, placebo-controlled | Adenovirus-based | No adjuvant | 2–8 | I/II | 2 | 18–60 | 28 | $5 \times 10^{10}$ VP * | United Kingdom | [33] |
| Mulligan et al. | 4 May and 19 June 2020 | 2020 | BNT162b1 | Pfizer/BioNTech | Randomized, observer-blind, placebo-controlled | mRNA-based | No adjuvant | (−60)–(−80) | I/II | 2 | 18–55 | 21 | 10 µg * | Multicenter [1] | [34] |
| Mulligan et al. | 4 May and 19 June,2020 | 2020 | BNT162b1 | Pfizer/BioNTech | Randomized, observer-blind, placebo-controlled | mRNA-based | No adjuvant | (−60)–(−80) | I/II | 2 | 24–42 | 21 | 30 µg * | Multicenter [1] | [34] |
| Mulligan et al. | 4 May and 19 June 2020 | 2020 | BNT162b1 | Pfizer/BioNTech | Randomized, observer-blind, placebo-controlled | mRNA-based | No adjuvant | (−60)–(−80) | I/II | 1 | 23–52 | No | 100 µg * | Multicenter [1] | [34] |
| Yang et al. | 12 and 17 July 2020 | 2020 | ZF2001 | Anhui Zhifei Longcom | Randomized, double-blind, placebo-controlled | Pro-Subunit | Aluminum hydroxide | 2–8 | II | 2 | 25–53 | 30 | 25 µg * | China | [18] |
| Yang et al. | 12 and 17 July 2021 | 2020 | ZF2001 | Anhui Zhifei Longcom | Randomized, double-blind, placebo-controlled | Pro-Subunit | Aluminum hydroxide | 2–8 | II | 2 | 18.8–58.4 | 30 | 50 µg * | China | [18] |
| Yang et al. | 12 and 17 July 2022 | 2020 | ZF2001 | Anhui Zhifei Longcom | Randomized, double-blind, placebo-controlled | Pro-Subunit | Aluminum hydroxide | 2–8 | II | 3 | 19.9–59.1 | 30 | 25 µg * | China | [18] |
| Yang et al. | 12 and 17 July 2023 | 2020 | ZF2001 | Anhui Zhifei Longcom | Randomized, double-blind, placebo-controlled | Pro-Subunit | Aluminum hydroxide | 2–8 | II | 3 | 20–59.7 | 30 | 50 µg * | China | [18] |
| Zhu et al. | 11 and 16 April 2020 | 2020 | Ad5-nCoV | CanSino | Randomized, double-blind, placebo-controlled | Adenovirus-based | No adjuvant | UN | II | 1 | 9.3–59.6 | No | $1 \times 10^{11}$ * | China | [35] |
| Zhu et al. | 11 and 16 April 2020 | 2020 | Ad5-nCoV | CanSino | Randomized, double-blind, placebo-controlled | Adenovirus-based | No adjuvant | UN | II | 1 | 18≤ | No | $5 \times 10^{10}$ * | China | [35] |
| Chu et al. | 29 May and 8 July 2020 | 2020 | mRNA-1273 | Moderna | Randomized, observer-blind, placebo-controlled | mRNA-based | No adjuvant | −20 | II | 2 | 18≤ | 28 | 50 mg * | United States | [36] |
| Chu et al. | 29 May and 8 July 2020 | 2020 | mRNA-1273 | Moderna | Randomized, observer-blind, placebo-controlled | mRNA-based | No adjuvant | −20 | II | 2 | 18–54.99 | 28 | 50 mg * | United States | [36] |
| Chu et al. | 29 May and 8 July 2020 | 2020 | mRNA-1273 | Moderna | Randomized, observer-blind, placebo-controlled | mRNA-based | No adjuvant | −20 | II | 2 | 55≤ | 28 | 100 mg * | United States | [36] |
| Chu et al. | 29 May and 8 July 2020 | 2020 | mRNA-1273 | Moderna | Randomized, observer-blind, placebo-controlled | mRNA-based | No adjuvant | −20 | II | 2 | 18–54.99 | 28 | 100 mg * | United States | [36] |
| Ramasamy et al. | 30 May and 8 August 2020 | 2020 | AZD1222 | Oxford/AstraZeneca | Randomized, participant-blind, placebo-controlled | Adenovirus-based | No adjuvant | 2–8 | II | 2 | 55≤ | 28 | $2.2 \times 10^{10}$ VP * | United Kingdom | [37] |
| Ramasamy et al. | 30 May and 8 August 2020 | 2020 | AZD1222 | Oxford/AstraZeneca | Randomized, participant-blind, placebo-controlled | Adenovirus-based | No adjuvant | 2–8 | II | 1 | 18–55 | No | $2.2 \times 10^{10}$ VP * | United Kingdom | [37] |
| Ramasamy et al. | 30 May and 8 August 2020 | 2020 | AZD1222 | Oxford/AstraZeneca | Randomized, participant-blind, placebo-controlled | Adenovirus-based | No adjuvant | 2–8 | II | 2 | 56–69 | 28 | $2.2 \times 10^{10}$ VP * | United Kingdom | [37] |
| Ramasamy et al. | 30 May and 8 August 2020 | 2020 | AZD1222 | Oxford/AstraZeneca | Randomized, participant-blind, placebo-controlled | Adenovirus-based | No adjuvant | 2–8 | II | 1 | 56–69 | No | $2.2 \times 10^{10}$ VP * | United Kingdom | [37] |
| Ramasamy et al. | 30 May and 8 August 2020 | 2020 | AZD1222 | Oxford/AstraZeneca | Randomized, participant-blind, placebo-controlled | Adenovirus-based | No adjuvant | 2–8 | II | 2 | 70≤ | 28 | $2.2 \times 10^{10}$ VP * | United Kingdom | [37] |
| Ramasamy et al. | 30 May and 8 August 2020 | 2020 | AZD1222 | Oxford/AstraZeneca | Randomized, participant-blind, placebo-controlled | Adenovirus-based | No adjuvant | 2–8 | II | 2 | 70≤ | 28 | $3.5–6.5 \times 10^{10}$ VP * | United Kingdom | [37] |
| Ramasamy et al. | 30 May and 8 August 2020 | 2020 | AZD1222 | Oxford/AstraZeneca | Randomized, participant-blind, placebo-controlled | Adenovirus-based | No adjuvant | 2–8 | II | 1 | 18–55 | No | $3.5–6.5 \times 10^{10}$ VP * | United Kingdom | [37] |
| Ramasamy et al. | 30 May and 8 August 2020 | 2020 | AZD1222 | Oxford/AstraZeneca | Randomized, participant-blind, placebo-controlled | Adenovirus-based | No adjuvant | 2–8 | II | 2 | 56–69 | 28 | $3.5–6.5 \times 10^{10}$ VP * | United Kingdom | [37] |
| Ramasamy et al. | 30 May and 8 August 2020 | 2020 | AZD1222 | Oxford/AstraZeneca | Randomized, participant-blind, placebo-controlled | Adenovirus-based | No adjuvant | 2–8 | II | 1 | 56–69 | No | $3.5–6.5 \times 10^{10}$ VP * | United Kingdom | [37] |
| Ramasamy et al. | 30 May and 8 August 2020 | 2020 | AZD1222 | Oxford/AstraZeneca | Randomized, participant-blind, placebo-controlled | Adenovirus-based | No adjuvant | 2–8 | II | 2 | 70≤ | 28 | $3.5–6.5 \times 10^{10}$ VP * | United Kingdom | [37] |
| Xia et al. | 12 April and 2 May 2020 | 2020 | BBIBP-CorV | Sinopharm | Randomized, double-blind, placebo controlled | Inactivated | Aluminum hydroxide | 2–8 | II | 3 | 70≤ | 28 | 5 µg * | China | [29] |
| Xia et al. | 12 April and 2 May 2020 | 2020 | BBIBP-CorV | Sinopharm | Randomized, double-blind, placebo controlled | Inactivated | Aluminum hydroxide | 2–8 | II | 3 | 18–59 | 28 | 5 µg * | China | [29] |
| Xia et al. | 18 May and 30 July 2020 | 2020 | BBIBP-CorV | Sinopharm | Randomized, double-blind, placebo controlled | Inactivated | Aluminum hydroxide | 2–8 | II | 1 | 18–59 | No | 8 µg * | China | [30] |
| Xia et al. | 18 May and 30 July 2020 | 2020 | BBIBP-CorV | Sinopharm | Randomized, double-blind, placebo controlled | Inactivated | Aluminum hydroxide | 2–8 | II | 2 | 18–59 | 14 | 4 µg * | China | [30] |
| Xia et al. | 18 May and 30 July 2020 | 2020 | BBIBP-CorV | Sinopharm | Randomized, double-blind, placebo controlled | Inactivated | Aluminum hydroxide | 2–8 | II | 2 | 18–59 | 21 | 4 µg * | China | [30] |
| Xia et al. | 18 May and 30 July 2020 | 2020 | BBIBP-CorV | Sinopharm | Randomized, double-blind, placebo controlled | Inactivated | Aluminum hydroxide | 2–8 | II | 2 | 18–59 | 28 | 4 µg * | China | [30] |
| Zhang et al. | 3 and 5 May 2020 | 2020 | CoronaVac | Sinovac | Randomized, double-blind, placebo controlled | Inactivated | Aluminum hydroxide | 2–8 | II | 2 | 18–59 | 14 | 3 µg * | China | [31] |

**Table 1.** *Cont.*

| Study | Trial Initiation Date | Pub. Year | Vaccine Name | Company | Study Type | Vaccine Type | Adjuvant | Store Temp (°C) | RCT Phase | Dose (s) | Age Range (Year) | Injection Interval (Days) | Concentration | Trial Country | Ref |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Zhang et al. | 3 and 5 May 2020 | 2020 | CoronaVac | Sinovac | Randomized, double-blind, placebo controlled | Inactivated | Aluminum hydroxide | 2–8 | II | 2 | 18–59 | 28 | 3 μg * | China | [31] |
| Zhang et al. | 3 and 5 May 2020 | 2020 | CoronaVac | Sinovac | Randomized, double-blind, placebo controlled | Inactivated | Aluminum hydroxide | 2–8 | II | 2 | 18–59 | 14 | 6 μg * | China | [31] |
| Zhang et al. | 3 and 5 May 2020 | 2020 | CoronaVac | Sinovac | Randomized, double-blind, placebo controlled | Inactivated | Aluminum hydroxide | 2–8 | II | 2 | 18–59 | 28 | 6 μg * | China | [31] |
| Logunov et al. | 18 June and 3 August 2020 | 2020 | Sputnik V | Gamaleya | Non-randomized | Adenovirus-based | No adjuvant | 2–8 | II | 2 | 18–59 | 21 | $10^{11}$ VP * | Russia | [32] |
| Logunov et al. | 18 June and 3 August 2020 | 2020 | Sputnik V (lyophilised) | Gamaleya | Non-randomized | Adenovirus-based | No adjuvant | 2–8 | II | 2 | 18–60 | 21 | $10^{11}$ VP * | Russia | [32] |
| Voysey et al. | 23 April and 4 November 2020 | 2021 | AZD1222 | Oxford/AstraZeneca | Randomized, single-blind, placebo-controlled | Adenovirus-based | No adjuvant | 2–8 | II/III | 2 | 18–60 | 28 | $2.2 \times 10^{10}$ VP * (1st)/$5 \times 10^{10}$ VP * (2nd) | United Kingdom | [38] |
| Voysey et al. | 23 April and 4 November 2020 | 2021 | AZD1222 | Oxford/AstraZeneca | Randomized, single-blind, placebo-controlled | Adenovirus-based | No adjuvant | 2–8 | II/III | 2 | 18≤ | 28 | $5 \times 10^{10}$ VP * | United Kingdom | [38] |
| Pollack et al. | 27 July and 14 November 2020 | 2020 | BNT162b2 | Pfizer/BioNTech | Randomized, observer-blind, placebo-controlled | mRNA-based | No adjuvant | (−60)–(−80) | II/III | 2 | 18≤ | 21 | 30 μg/0.3 ml | Multinational [1] | [39] |
| Baden et al. | 27 July and 23 October | 2020 | mRNA-1273 | Moderna | Randomized, observer-blind, placebo-controlled | mRNA-based | No adjuvant | −20 | III | 2 | 16–89 | 28 | 100 μg * | United States | [40] |
| Voysey et al. | 23 April and 4 November 2020 | 2021 | AZD1222 | Oxford/AstraZeneca | Randomized, single-blind, placebo-controlled | Adenovirus-based | No adjuvant | 2–8 | III | 2 | 18–55 | 28 | $5 \times 10^{10}$ VP * | Brazil | [38] |
| Logunov et al. | 7 September and 24 November 2020 | 2021 | Sputnik V | Gamaleya | Randomized, double-blind, placebo controlled | Adenovirus-based | No adjuvant | 2–8 | III | 2 | 18≤ | 21 | $10^{11}$ VP * | Russia | [41] |
| Sadoff et al. | 20 July 2020 | 2021 | Ad26.COV2.S | Johnson & Johnson | Randomized, double-blind, placebo-controlled | Adenoviral vector | No adjuvant | UN | I/II | 2 | 18–55 | No | $5 \times 10^{10}$ | Belgium, US | [42] |
| Sadoff et al. | 20 July 2020 | 2021 | Ad26.COV2.S | Johnson & Johnson | Randomized, double-blind, placebo-controlled | Adenoviral vector | No adjuvant | UN | I/II | 2 | 19–55 | No | $1 \times 10^{11}$ | Belgium, US | [42] |
| Sadoff et al. | November 2020 | 2021 | Ad26.COV2.S | Johnson & Johnson | Randomized, double-blind, placebo-controlled | Adenoviral vector | No adjuvant | UN | I/II | 2 | 65–83 | No | $5 \times 10^{10}$ | Belgium, US | [42] |
| Sadoff et al. | November 2020 | 2021 | Ad26.COV2.S | Johnson & Johnson | Randomized, double-blind, placebo-controlled | Adenoviral vector | No adjuvant | UN | I/II | 2 | 65–88 | No | $1 \times 10^{11}$ | Belgium, US | [42] |

[1] From 152 sites worldwide (United States, 130 sites; Argentina, 1; Brazil, 2; South Africa, 4; Germany, 6; and Turkey, 9). UN = unavailable. VP = virus particle; Pro-Subunit = protein subunit; VLP = virus-like particle; Alum = aluminium; Adv= adenovirus; CpG = cytosine-guanine oligodeoxynucleotide; AS03 = squalene-based immunologic adjuvant; Algel-IMDG (an imidazoquinoline molecule chemisorbed on alum [Algel]); RCT = randomized control trial. * per 0.5 m. Studies with different reports for the vaccine phase, the vaccine dose, injection concentration, different case, and control group numbers are considered as a separate dataset. More detailed information is provided in Table S3.

### *3.2. Characteristics of Participants*

A total of 58,889 cases that received the COVID-19 vaccine and 46,638 controls who received placebo were included in this study. Out of 58,889 vaccine cases, 31,070 were male and 27,819 female. Out of 46,638 individuals in the placebo group, 33,354 were male and 13,284 female. All vaccines and placebos were intramuscularly (IM) injected. Detailed information of age ranges of either vaccine or placebo groups is shown in Table 1.

### *3.3. Efficacy of Different COVID-19 Vaccines*

#### 3.3.1. Efficacy of mRNA-Based COVID-19 Vaccines

The mRNA-based COVID-19 vaccines had 94.6% (95% CI 0.936–0.954) efficacy in a total of 34,041 cases in phase II/III RCTs (Table 2). Figure 2 shows the efficacy of COVID-19 vaccines after the first and second doses. Efficacy four weeks after first dose was reported for only one antibody (NAb 70.2% (95% CI 0.655–0.746)). Efficacy after a second dose of mRNA-based COVID-19 vaccines was reported for RBD, S-protein, and NAbs, with the highest efficacy for NAbs at 99.5% (95% CI 0.980–0.999) (Table 3).

**Table 2.** Efficacy of adenovirus-based and mRNA-based COVID-19 vaccines.

| Vaccine Type | RCT Phase | Number Studies | Efficacy (%) | 95% CI (%) | | Included Case N | Heterogeneity Test, *p*-Value |
|---|---|---|---|---|---|---|---|
| | | | | Lower Limit | Upper Limit | | |
| Adenovirus-based | 2/3 | 4 | 80.2 | 0.564 | 0.927 | 20771 | <0.001 |
| mRNA-based | 2/3 | 2 | 94.6 | 0.936 | 0.954 | 34041 | <0.001 |

RCT = randomized control trial.



#### 3.3.2. Efficacy of Adenovirus-Vectored COVID-19 Vaccines

The pooling of four RCTs (in phases II/III) results (a total of 20,771 cases included) showed adenovirus-vectored COVID-19 vaccines had 80.2% (95% CI 0.56–0.93) efficacy (Table 2). After the first dose, the efficacy of the adenovirus-vectored COVID-19 vaccine was the highest at 97.6% (95% CI 0.939–0.997) against RBD three weeks after injection. Whereas, adenovirus-vectored COVID-19 vaccine had the highest efficacy by producing NAbs 99.9% (95% CI 0.985–1.000) after 4 and 2 weeks of the second injection (Table 3).

#### 3.3.3. Efficacy of Inactivated COVID-19 Vaccines

After the first vaccine dose, the inactivated COVID-19 vaccine's efficacy was the highest against RBD at 91.3% (95% CI 00.564–0.96) four weeks after injection. Whereas, the highest efficacy against S-protein was 94% (95% CI 0.941 0.877–0.973) two weeks after the second injection (Table 3).

#### 3.3.4. Efficacy of Pro-Subunit COVID-19 Vaccines

Pro-subunit vaccine efficacy was the highest against RBD at 87.3% (95% CI 0.671–0.892) four weeks after the first dose. Similarly, it had the highest efficacy against RBD protein at 95.6% (95% CI 0.937–0.970) four weeks after the second dose (Table 3).

#### 3.3.5. Efficacy of VLP COVID-19 Vaccines

Efficacy of VLP vaccines was reported only against RBD three weeks after the first dose at 23.8% (95% CI 0.091–0.375) and three weeks after the second dose at 78.7% (95% CI 0.581–0.908) (Table 3).

### *3.4. Side Effects of Different COVID-19 Vaccines*

Adjusted pooled odds ratio (OR) between vaccine and placebo groups were assessed for estimating the association of side effects by the administration of different COVID-19 vaccines. mRNA-based vaccines had the highest number of associated side effects, except for diarrhea and arthralgia, for which the adenovirus-vectored vaccine had the highest OR (Figure 3).

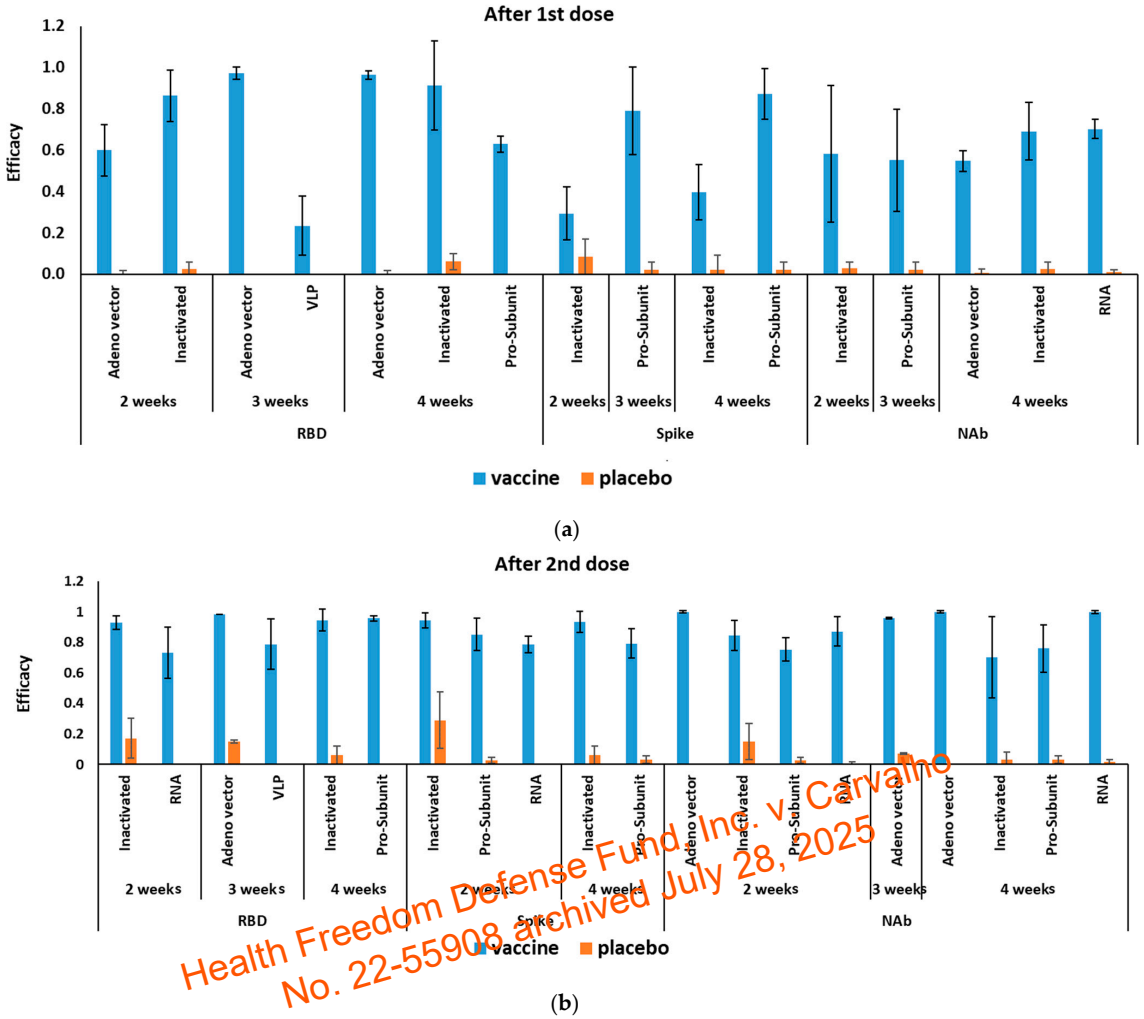




**Figure 2.** Efficacy of different COVID-19 vaccines (**a**) after the first and (**b**) second doses.

The administration of mRNA-based vaccine was associated with a greater number of side effects, such as injection site pain, fever, redness, swelling, induration, pruritus, chills, myalgia, arthralgia, vomiting, fatigue, and headache, by yielding a summary OR of 83.06 (95% CI 37.05–186.1) (in phase II/III RCTs), 36.90 (95% CI 12.34–105.21) (in phase I/II/III RCTs), 24.40 (95% CI 18.73–31.77) (in phase I/II/III RCTs), 18.79 (95% CI 4.87–72.40) (in phase I/II/III RCTs), 17.5 (95% CI 1.96–155.58) (in phase I/II RCTs), 17.50 (95% CI 1.98–155.58) (in phase II/III RCTs), 13.11 (95% CI 7.19–23.89) (in phase II/III RCTs), 10.71 (95% CI 6.51–17.60) (in phase I/II RCTs), 9.67 (95% CI 1.27–76.90) (in phase III/II RCTs), 8.71 (95% CI 4.38–17.34) (in phase I/II RCTs), 6.16 (95% CI 5.86–6.48) (in phase III RCTs), and 5.13 (95% CI 2.32–11.31) (in phase I/II RCTs), respectively, compared to other types of vaccines. Nevertheless, the adenovirus-vectored vaccine was associated with higher rates of diarrhea with OR of 4.59 (95% CI 3.58–5.89), and arthralgia OR of 10.61 (95% CI 7.60–14.83) compared to others (Table 4). It should be considered that heterogeneity (I-squared test) of the pooled meta-analysis for most of the side effects was low (I2 < 50%), which indicates that variation in study outcomes between the included studies was low, even though different companies and different research groups across the world have been included. More detailed information such as Forest plot, Funnel plot, heterogeneity test, and sub-group analysis of each side effects are shown in Figures S1–S21 (in the Supplementary Materials).

**Table 3.** Efficacy of different COVID-19 vaccines after the first and second doses.

| | | | | Vaccine | | | | | Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Shot** | **Antigen/ Antibody** | **After Injection (Week)** | **Vaccine Type** | **Studies N** | **Efficacy** | **Lower Limit** | **Upper Limit** | **I-Squared** | **Studies N** | **Efficacy** | **Lower Limit** | **Upper Limit** | **I-Squared** |
| **After 1st dose** | RBD | 2 | Adenovirus-based | 4 | 0.603 | 0.471 | 0.722 | 73.8 | 2 | 0.004 | 0.001 | 0.027 | 0 |
| | | | Inactivated | 4 | 0.870 | 0.734 | 0.983 | 93.8 | 4 | 0.024 | 0.008 | 0.072 | 0 |
| | | 3 | Adenovirus-based | 2 | 0.976 | 0.939 | 0.997 | 0.0 | NA | NA | NA | NA | NA |
| | | | VLP | 8 | 0.238 | 0.091 | 0.375 | 84.3 | NA | NA | NA | NA | NA |
| | | 4 | Adenovirus-based | 2 | 0.966 | 0.942 | 0.980 | 0.0 | 2 | 0.004 | 0.001 | 0.027 | 0 |
| | | | Inactivated | 4 | 0.913 | 0.564 | 0.958 | 90.7 | 4 | 0.061 | 0.033 | 0.110 | 0 |
| | | | Pro-Subunit | 6 | 0.628 | 0.590 | 0.665 | 0.0 | NA | NA | NA | NA | NA |
| | S-protein | 2 | Inactivated | 2 | 0.293 | 0.182 | 0.437 | 0.0 | 2 | 0.083 | 0.032 | 0.202 | 0 |
| | | 3 | Pro-Subunit | 4 | 0.790 | 0.474 | 0.874 | 91.0 | 4 | 0.021 | 0.005 | 0.079 | 0 |
| | | 4 | Inactivated | 2 | 0.396 | 0.269 | 0.539 | 0.0 | 2 | 0.021 | 0.003 | 0.134 | 0 |
| | | | Pro-Subunit | 4 | 0.873 | 0.671 | 0.892 | 91.9 | 4 | 0.021 | 0.005 | 0.079 | 0 |
| | NAb | 2 | Inactivated | 4 | 0.583 | 0.210 | 0.868 | 95.0 | 4 | 0.030 | 0.013 | 0.070 | 0 |
| | | 3 | Pro-Subunit | 4 | 0.551 | 0.291 | 0.786 | 85.0 | 4 | 0.021 | 0.005 | 0.079 | 0 |
| | | 4 | Adenovirus-based | 2 | 0.547 | 0.496 | 0.596 | 76.8 | 2 | 0.008 | 0.002 | 0.031 | 0 |
| | | | Inactivated | 4 | 0.691 | 0.537 | 0.812 | 91.0 | 4 | 0.025 | 0.008 | 0.074 | 0 |
| | | | mRNA-based | 4 | 0.702 | 0.656 | 0.746 | 79.9 | 4 | 0.010 | 0.004 | 0.026 | 0 |
| **After 2nd dose** | RBD | 2 | Inactivated | 9 | 0.929 | 0.876 | 0.960 | 61.8 | 9 | 0.171 | 0.077 | 0.336 | 85 |
| | | | mRNA-based | 5 | 0.731 | 0.532 | 0.866 | 86.0 | NA | NA | NA | NA | NA |
| | | 3 | Adenovirus-based | 3 | 0.982 | 0.980 | 0.984 | 0.0 | 1 | 0.149 | 0.139 | 0.159 | 0 |
| | | | VLP | 9 | 0.737 | 0.581 | 0.908 | 78.1 | NA | NA | NA | NA | NA |
| | | 4 | Inactivated | 4 | 0.944 | 0.842 | 0.982 | 15.9 | 4 | 0.063 | 0.026 | 0.143 | 0 |
| | | | Pro-Subunit | 6 | 0.956 | 0.937 | 0.970 | 0.0 | NA | NA | NA | NA | NA |
| | S-protein | 2 | Inactivated | 7 | 0.941 | 0.877 | 0.973 | 61.4 | 7 | 0.290 | 0.139 | 0.507 | 87 |
| | | | Pro-Subunit | 18 | 0.852 | 0.719 | 0.928 | 62.4 | 18 | 0.028 | 0.014 | 0.052 | 0 |
| | | | mRNA-based | 5 | 0.786 | 0.725 | 0.836 | 0.0 | NA | NA | NA | NA | NA |
| | | 4 | Inactivated | 4 | 0.934 | 0.842 | 0.974 | 15.9 | 4 | 0.063 | 0.026 | 0.143 | 0 |
| | | | Pro-Subunit | 14 | 0.792 | 0.679 | 0.873 | 50.7 | 15 | 0.031 | 0.015 | 0.061 | 0 |
| | NAbs | 2 | Adenovirus-based | 1 | 0.999 | 0.985 | 1.000 | 0.0 | NA | NA | NA | NA | NA |
| | | | Inactivated | 9 | 0.845 | 0.724 | 0.919 | 86.5 | 9 | 0.151 | 0.068 | 0.303 | 85 |
| | | | Pro-Subunit | 23 | 0.753 | 0.667 | 0.823 | 68.2 | 19 | 0.028 | 0.015 | 0.052 | 0 |
| | | | mRNA-based | 9 | 0.870 | 0.747 | 0.938 | 82.4 | 4 | 0.008 | 0.003 | 0.024 | 0 |
| | | 3 | Adenovirus-based | 1 | 0.958 | 0.955 | 0.961 | 0.0 | 1 | 0.071 | 0.065 | 0.079 | 0 |
| | | 4 | Adenovirus-based | 1 | 0.999 | 0.985 | 1.000 | 0.0 | NA | NA | NA | NA | NA |
| | | | Inactivated | 4 | 0.700 | 0.375 | 0.901 | 86.1 | 4 | 0.033 | 0.011 | 0.099 | 0 |
| | | | Pro-Subunit | 17 | 0.759 | 0.574 | 0.881 | 62.9 | 15 | 0.031 | 0.015 | 0.061 | 0 |
| | | | mRNA-based | 4 | 0.995 | 0.980 | 0.999 | 0.0 | 4 | 0.016 | 0.007 | 0.035 | 0 |

S-protein = spike protein, Alum = aluminium, CpG = cytosine-guanine oligodeoxynucleotide, AS03 = squalene-based immunologic adjuvant, RBD = receptor-binding domain, NAb = neutralizing antibody, Pro-Subunit = protein subunit, NA = not available.

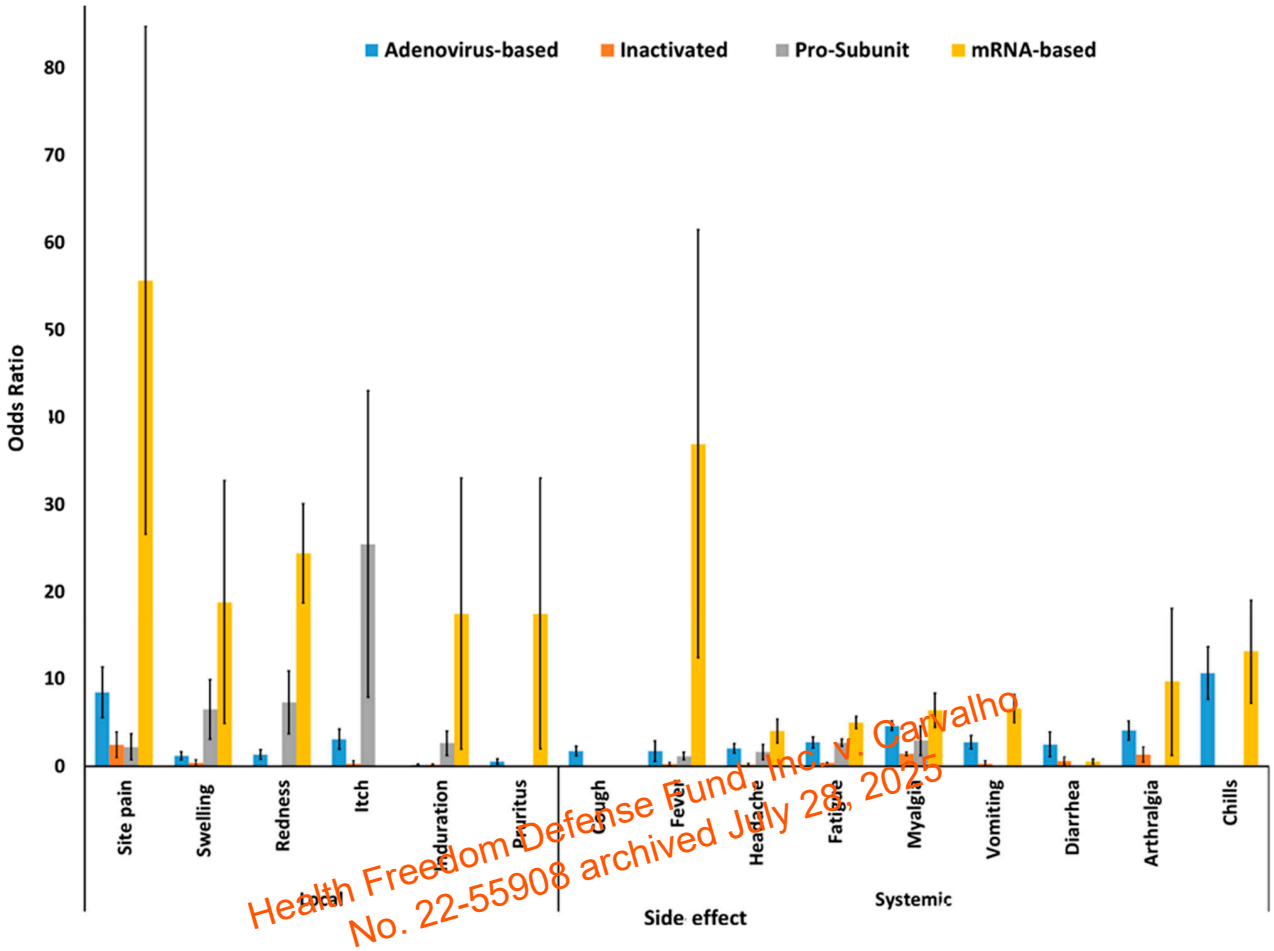




**Figure 3.** Local and systemic side effects of different COVID-19 vaccines.

**Table 4.** Association of side effects with different COVID-19 vaccines.

| Side Effect | Vaccine Type | Phase | Odds Ratio (95% CI) | Included Study | Heterogeneity Test, I-Squared |
|---|---|---|---|---|---|
| Site pain | mRNA-based | 2/3 | 83.06 (37.05–186.1) | 5 | 81.33 |
| | | 1/2 | 28.26 (16.18–49.35) | 17 | 0 |
| | Adenovirus-based | 2/3 | 13.64 (8.39–22.17) | 2 | 0 |
| | | 1/2 | 3.2 (2.7–4) | 2 | 0 |
| | Inactivated | 2/3 | 1.73 (0.667–4.5) | 6 | 46.64 |
| | | 1/2 | 3.19 (1.3–7.6) | 10 | 52.14 |
| | Pro-Subunit | 2/3 | 2.14 (1.01–4.5) | 4 | 48.55 |
| | | 1/2 | 2.29 (0.48–10.8) | 2 | 29.93 |
| Swelling | Adenovirus-based | 1/2/3 | 1.21 (0.77–1.89) | 2 | 0 |
| | Inactivated | 1/2/3 | 0.402 (0.056–2.90) | 2 | 0 |
| | Pro-Subunit | 1/2/3 | 6.48 (3.09–13.67) | 5 | 0 |
| | mRNA-based | 1/2/3 | 18.79 (4.87–72.40) | 3 | 59.08 |
| Redness | Adenovirus-based | 1/2/3 | 1.35 (0.815–2.25) | 4 | 0 |
| | Pro-Subunit | 1/2/3 | 7.29 (3.70–14.38) | 6 | 0 |
| | mRNA-based | 1/2/3 | 24.40 (18.73–31.77) | 1 | 0 |
| Itch | Adenovirus-based | 1/2 | 3.10 (1.96–4.89) | 1 | 0 |
| | Inactivated | 1/2 | 0.32 (0.02–5.3) | 1 | 0 |
| | Pro-Subunit | 1/2 | 25.44 (7.85–82.40) | 6 | 0 |

**Table 4.** *Cont.*

| Side Effect | Vaccine Type | Phase | Odds Ratio (95% CI) | Included Study | Heterogeneity Test, I-Squared |
|---|---|---|---|---|---|
| Cough | Adenovirus-based | 1/2/3 | 1.76 (1.20–2.58) | 3 | 0 |
| Fever | Adenovirus-based | 1/2/3 | 1.73 (0.57–5.66) | 3 | 90.5 |
| | Inactivated | 1/2/3 | 0.27 (0.09–0.76) | 5 | 0 |
| | Pro-Subunit | 1/2/3 | 1.17 (0.73–1.86) | 4 | 0 |
| | mRNA-based | 1/2/3 | 36.90 (12.34–105.21) | 3 | 43.31 |
| Headache | mRNA-based | 3 | 4.63 (4.4–4.86) | 1 | 0 |
| | | 2 | 2.32 (1.28–4.19) | 4 | 69.20 |
| | | 1/2 | 5.13 (2.32–11.31) | 5 | 63.02 |
| | Adenovirus-based | 2 | 2.54 (1.65–3.91) | 2 | 0 |
| | | 1/2 | 3.01 (2.35–3.87) | 1 | 0 |
| | | 3 | 0.58 (0.49–0.68) | 1 | 0 |
| | Inactivated | 2 | 0.18 (0.02–1.14) | 2 | 0 |
| | Pro-Subunit | 2 | 1.25 (0.33–4.7) | 2 | 0 |
| | | 1/2 | 1.99 (1.21–3.26) | 14 | 0 |
| Fatigue | Adenovirus-based | 1/2 | 2.72 (2.2–3.37) | 3 | 0 |
| | Inactivated | 1/2 | 0.39 (0.18–0.82) | 7 | 0 |
| | Pro-Subunit | 1/2 | 2.7 (1.01–7.16) | 4 | 37.2 |
| | mRNA-based | 1/2 | 5.0 (3.42–7.33) | 24 | 48.23 |
| | | 2–3 | 4.87 (4.65–5.09) | 1 | 0 |
| | | 3 | 6.16 (5.86–6.48) | 1 | 0 |
| Induration | Adenovirus-based | 1/2 | 0.16 (0.08–0.49) | 2 | 46.44 |
| | Inactivated | 1/2 | 0.18 (0.06–0.58) | 4 | 0 |
| | Pro-Subunit | 1/2 | 2.62 (1.23–5.58) | 2 | 0 |
| | mRNA-based | 1/2 | 17.5 (1.96–155.58) | 1 | 0 |
| Vomiting | Adenovirus-based | 1/2 | 2.75 (1.99–3.82) | 3 | 0 |
| | Inactivated | 1/2 | 0.32 (0.02–5.38) | 1 | 0 |
| | mRNA-based | 1/2 | 8.71 (4.38–17.34) | 8 | 0 |
| | | 2–3 | 4.87 (4.65–5.09) | 1 | 0 |
| | | 3 | 6.16 (5.86–6.48) | 1 | 0 |
| Diarrhea | Adenovirus-based | 1/2 | 2.51 (1.12–5.63) | 2 | 0 |
| | Inactivated | 1/2 | 0.60 (0.13–2.83) | 3 | 0 |
| | mRNA-based | 1/2 | 0.54 (0.27–1.10) | 5 | 0 |
| Myalgia | Adenovirus-based | 1/2 | 4.59 (3.58–5.89) | 3 | 0 |
| | Inactivated | 1/2 | 1.43 (0.25–8.08) | 2 | 0 |
| | Pro-Subunit | | 2.92 (0.57–8.75) | 8 | 53.30 |
| | mRNA-based | 1/2 | 10.71 (6.51–17.60) | 10 | 33.74 |
| | | 2/3 | 7.0 (6.57–7.47) | 1 | 0 |
| | | 3 | 1.43 (0.25–8.08) | 1 | 0 |
| Arthralgia | Adenovirus-based | 2/3 | 4.06 (2.99–5.57) | 3 | 0 |
| | Pro-Subunit | 2/3 | 1.34 (0.47–3.83) | 4 | 4.833 |
| | mRNA-based | 2/3 | 9.67 (1.27–76.90) | 3 | 67.97 |
| Chills | Adenovirus-based | 2/3 | 10.61 (7.60–14.83) | 1 | 0 |
| | mRNA-based | 2/3 | 13.11 (7.19–23.89) | 8 | 3.82 |
| Pruritus | Adenovirus-based | 2/3 | 0.54 (0.23–1.25) | 2 | 0 |
| | mRNA-based | 2/3 | 17.50 (1.98–155.58) | 1 | 0 |

Serious Adverse Side Effects of COVID-19 Vaccines

Only three studies reported anaphylactic shock as an adverse effect of COVID-19 vaccines—(1) 1 out of 84 vaccine cases for the inactivated vaccine [30]; (2) 1 case out of 2063 vaccinated for the adenovirus-based vaccine [38], (3) 1 case out of 15,181 in the vaccine group, and 1 case out of 15,170 in the placebo group, for the mRNA-based vaccine [40]. A total of 37 blot clots, including 22 pulmonary embolus cases (PE) and 5 deep vein thrombosis (DVT), have been reported for the Oxford-AstraZeneca vaccine among 17 million people in the EU and Britain [43]; see discussion for recent contributions. The number of clotting events is not greater than what is seen in the general population, with no indication that there is a causal effect.

### *3.5. Side Effects of COVID-19 Vaccines Based on Different Adjuvants*

The sub-group analysis was assessed to estimate the potential side effects of COVID-19 vaccines based on the different types of administrated adjuvants. Interestingly, in all cases, potassium aluminum sulfate (alum) had the smallest number of systemic and local side effects compared to other adjuvants or vaccines without adjuvant, except injection site redness, of which vaccines without adjuvant had higher rates of site redness (Figure 4). Accordingly, vaccines with alum adjuvant had lower systemic side effects of fatigue OR 0.392 (95% 0.18–0.82), vomiting 0.325 (95% 0.02–5.30), fever 0.85 (95% 0.51–1.43), myalgia 1.43 (95% 0.25–8.0), diarrhea 0.608 (95% 0.13–2.87), and injection site pain 2.40 (95% 1.51–3.83) between different adjuvants and vaccines with no adjuvant (Table 5). The vaccine with no adjuvant was associated with higher redness OR 0.923 (95% 0.23–3.6). Itch OR 13.20 (95% 3.23–53.90) and swelling OR of 3.83 (95% 1.52–9.64) was only reported for vaccines with alum adjuvant. For more detailed information see Figures S22–S30.



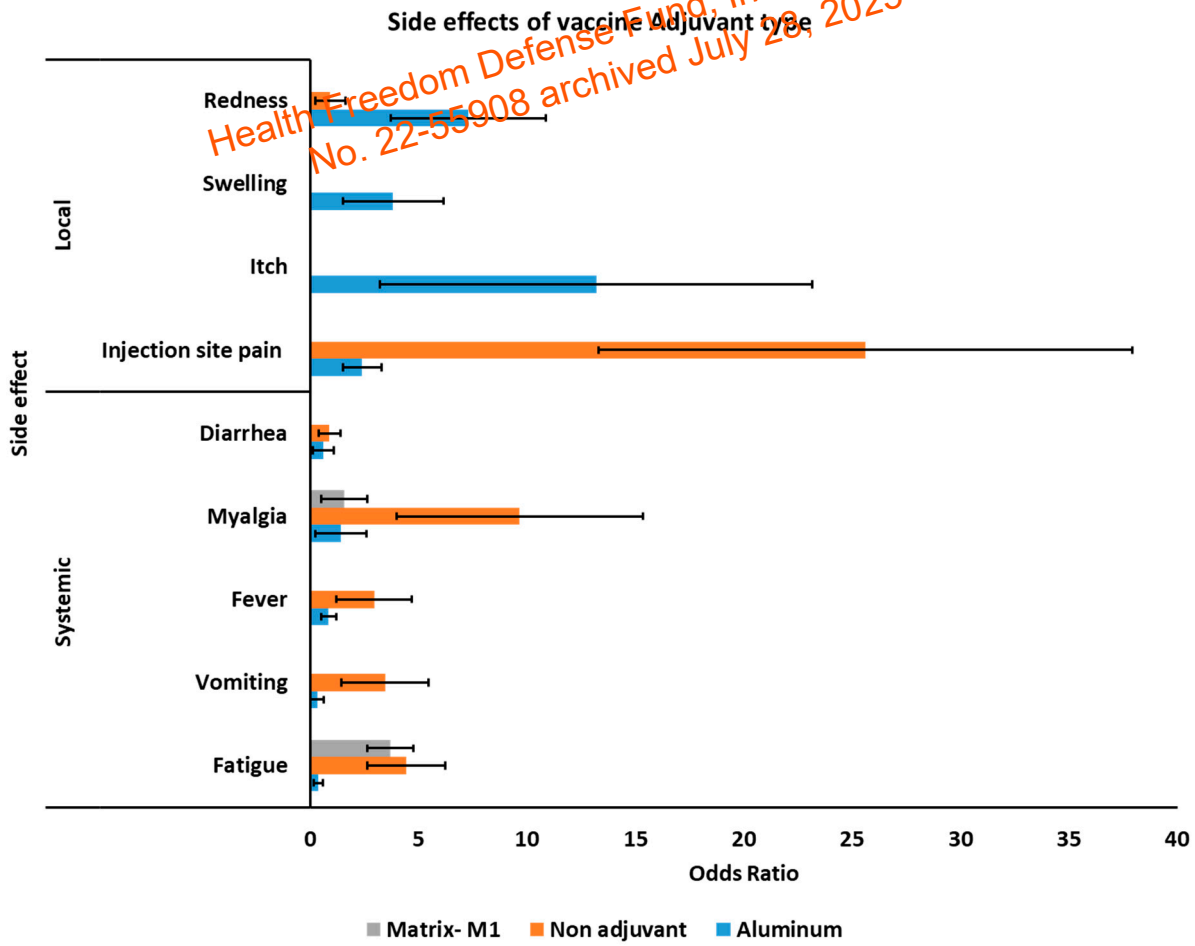


**Figure 4.** Association of adjuvant side effects of different COVID-19 vaccines.

**Table 5.** Side effects of COVID-19 vaccines based on different adjuvant types.

| Side Effect | | Adjuvant Type | Phase | Odds Ratio (95% CI) | Included Study | Heterogeneity Test, I-Squared |
|---|---|---|---|---|---|---|
| Systemic | Fatigue | Alum | 2/3 | 0.392 (0.18–0.82) | 7 | 0 |
| | | Matrix-M1 | 2/3 | 3.70 (1.36–10.02) | 3 | 24.81 |
| | | No adjuvant | 2/3 | 4.43 (2.62–7.49) | 6 | 54.08 |
| | Vomiting | Alum | 2/3 | 0.325 (0.02–5.30) | 1 | 0 |
| | | No adjuvant | 2/3 | 3.46 (1.45–8.26) | 7 | 0 |
| | Fever | Alum | 2/3 | 0.85 (0.51–1.43) | 9 | 20.78 |
| | | No adjuvant | 2/3 | 2.96 (1.22–7.17) | 2 | 68.19 |
| | Myalgia | Alum | 2/3 | 1.43 (0.25–8.0) | 2 | 0 |
| | | AS03 | 2/3 | 14.331 (3.39–60.56) | 3 | 0 |
| | | CpG/Alum | 2/3 | 2.42 (0.13–44.50) | 1 | 0 |
| | | Matrix-M1 | 2/3 | 1.57 (0.26–9.4) | 3 | 67.96 |
| | | No adjuvant | 2/3 | 9.66 (3.97–23.47) | 8 | 49.99 |
| | Diarrhea | Alum | 2/3 | 0.608 (0.13–2.87) | 3 | 0 |
| | | No adjuvant | 2/3 | 0.89 (0.40–1.97) | 6 | 50.47 |
| Local | Injection site pain | Alum | 2/3 | 2.40 (1.51–3.83) | 22 | 44.55 |
| | | No adjuvant | 2/3 | 25.61 (13.31–49.30) | 7 | 36.60 |
| | Itch | Alum | 2/3 | 13.20 (3.23–53.90) | 7 | 40.58 |
| | Swelling | Alum | 2/3 | 3.83 (1.52–9.64) | 7 | 37.52 |
| | Redness | Alum | 2/3 | 7.29 (3.7–14.39) | 6 | 0 |
| | | No adjuvant | 2/3 | 0.923 (0.23–3.6) | 2 | 0 |

Alum = aluminum, CpG = cytosine-guanine oligodeoxynucleotide, AS03 = squalene-based immunologic adjuvant.



## 4. Discussion

The purpose of vaccination is to protect individuals from infection and transmission. Although the emergency use authorization for some of the COVID-19 vaccines has been approved by the Food and Drug Administration in the US and the Department of Health and Human Services of each country, the vaccines' efficacy and side effects have not yet been comprehensively discussed, although popular media and politicians have made many unsubstantiated claims. Therefore, in the current meta-analysis, we provide systematic and comprehensive data regarding the vaccines' safety, efficacy, and immunogenicity against SARS-CoV-2. Here, we mainly focused on available RCTs publications on the safety, efficacy, and immunogenicity of COVID-19 vaccines.

The present study was carefully surveyed for the general and specific target antigen efficacy of each vaccine group. Our analysis showed that variation in the efficacy of vaccines after the first doses are remarkable in comparison with the efficacies after the second doses. Therefore, enrollment of the second dose should produce a more reliable outcome and efficacy compared to a single dose. In total, mRNA-based COVID-19 vaccines had 94.6% efficacy. The RNA-based vaccine elicited high levels of NAbs after one month of the first (70%) and second (99.5%) doses. Unfortunately, data for the RNA-based vaccines against RBD antigen were not available after the first dose. Protection against variants has been shown with the mRNA-based vaccine against the United Kingdom (B.1.1.7, also called 20I/501Y.V1) variant [44,45], but they may be less effective against the variant first detected in South Africa (B.1.351, known as 20H/501Y.V2) [46]. A week after the second dose of mRNA-based vaccine, induction of neutralizing antibody titers in the serum sample was 6-fold lower for participants bearing B.1.351 variant compared to original Wuhan-Hu-1 spike protein [47]. The B.1.351 variant carries two substitutions within the S-protein, which can escape three classes of therapeutically relevant antibodies. These data indicate reinfection with antigenically distinct variants and mitigates the full efficacy of spike-based COVID-19 vaccines [48].

From our summary analysis, the total efficacy of the adenovirus-vectored COVID-19 vaccines was 80.2%. The highest efficacy after a single dose is reported with the adenovirus-vectored COVID-19 vaccines, with very low variation and CI against RBD at 3 weeks (96.7%) and 4 weeks (96.6%) after vaccination compared to placebo controls. Some of the adenovirus-vectored COVID-19 vaccines, such as Johnson & Johnson, need just one dose, with the efficacy against RBD being a possible reason. However, based on the rollout timeline, long-term (more than four weeks) efficacy of adenovirus-vectored COVID-19 vaccines was not reported by any of the RCTs. For the other vaccine types, total efficacy has not been reported, only the antigen-specific efficacy was reported in these RCTs. The pro-subunit vaccine had the highest efficacy against spike antigen at 1 month after the first injection. The efficacy of the VLP vaccines was lower than other COVID-19 vaccines and reported only against RBD after the first (23.8%) and second dose (78.7%). All reports for VLP vaccines are from RCT phase I trials, and the lower efficacy of these vaccines may be the most probable reason.

Any vaccine is expected to cause temporary side effects caused by activation of an immune response and injection site tissue trauma. Uptake of vaccines is related to perceived and real adverse side effects, both short-term and long-term. In this study, adjusted pooled odds ratios between vaccine and placebo groups indicated that RNA-based vaccines had higher rates of side effects in reactogenicity, including site pain, swelling, redness, fever, headache, fatigue, induration, vomiting, myalgia, chills, and pruritus (Table 2). No sign of cough or itch was found in RNA-based vaccines, and lower rates of diarrhea and arthralgia were observed for this vaccine. By avoiding negativity bias, this might provide strong evidence of RNA-based vaccines' effectiveness, by eliciting a more robust immune response than other vaccine groups. Additionally, the rate of serious adverse side effects such as anaphylactic shock, an allergic reaction, was not remarkable with this vaccine, with only one case reported in both the vaccine and placebo groups [40].

In the context of side effects, the adenovirus-vectored vaccines are associated with increased diarrhea and arthralgia in comparison with other vaccines, see Table 2. A recent systematic review and meta-analysis by Yuan et al. [49] showed no significant difference in systemic reactions, with only local side effects, including pain, itching, and redness, being reported [49]. One case of anaphylactic shock was reported for this vaccine [38].



Several pulmonary emboli (PE) and deep vein thrombosis (DVT) cases have been reported as rare events for the Oxford-AstraZeneca vaccine, causing a temporary suspension of this vaccine's use in many countries and age-specific rollout in others. However, to date, the data are too weak and anecdotal to provide clear evidence of cause and effect [50]. Similarly, the Johnson & Johnson vaccine was also temporarily suspended in April 2021 by the FDA, as several people developed rare blood-related problems of thrombosis with thrombocytopenia syndrome leading to cerebral venous sinus thrombosis (CVST) [51]. A DVT has also been reported shortly after the second dose of an mRNA-based vaccine as well [52]. Anaphylaxis as an acute allergic reaction has also been reported as a rare event for some vaccines, such as mRNA COVID-19 vaccines [53] and adenovector vaccines against COVID-19 [54]. Overall, these severe life-threatening adverse events are occurring rarely, thus supporting the ongoing rollout of global vaccination programs.

Data are currently emerging on Vaccine-induced Immune Thrombotic Thrombocytopenia (VITT) following vaccination with COVID-19 vaccines [55]. VITT presents with symptoms of thromboembolism and especially signs of thrombocytopenia, cerebral blood clots, or abdominal or arterial clots, such as easy bruising, bleeding or new and/or severe headaches, and pain in the abdomen or a painful, cold numb extremity, particularly with onset 4 to 28 days after immunization. This is due to thrombosis (blood clots) involving the cerebral venous sinuses, or CVST (large blood vessels in the brain), and other sites in the body (including but not limited to the large blood vessels of the abdomen and the veins of the legs) along with thrombocytopenia, or low blood platelet counts. These events are rare, but to date have been documented for the mRNA vaccines BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) and the adenoviral vector vaccines ChAdOx1 nCoV-19 vaccine

(Astra Zeneca) and Ad26. COV2-S vaccine (Janssen; Johnson & Johnson). Given the very recent emergence, our meta study does not include an analysis of VITT.

Co-administration of vaccine with adjuvants is being used in VLP subunit vaccines and certain inactivated vaccines [55]. Adjuvants have an essential role owning to inducing specific immune responses, $IgG_1$, and NAbs titers. It also considers potential dose-sparing of CoV vaccine [56]. Multiple adjuvants, such as alum salts, emulsions, and TLR agonists have been formulated for SARS-CoV, SARS-CoV-2, and MERS-CoV [55]. The potential side effects of COVID-19 vaccines based on the different types of adjuvants investigated showed that alum-adjuvanted CoV vaccines had the lowest systemic side effects among other adjuvants or non-adjuvant in Table 3. The non-adjuvanted vaccines revealed immunopathologic reactions including high fatigue, vomiting, fever, myalgia, and diarrhea and redness, while alum-adjuvanted CoV vaccines showed itch and swelling. Overall, the metadata obtained in this study demonstrated that the alum-adjuvanted CoV vaccines had the smallest number of issues compared with other adjuvants and the non-adjuvant formulations.

The limitations of this study are: 1. The overall effectiveness and antigen-specific efficacy of some vaccines have not been reported after the first or second dose. 2. Some trials had considerable bias by not including a sufficient number of samples or a broad enough geographical, economic, and age diversity. 3. Timing of vaccine trials in relation to overall prevalence through the COVID-19 pandemic impacts direct comparison. 4. The IgG and IgM antibodies in serum levels had a wide range of variation across the different vaccines after the first or second dose, thus, these data were not included in the meta-analysis. 5. The lack of data on specific categories of patients such as pregnant patients and lifestyles. 6. All RCTs followed up the vaccine and placebo groups one month after both first and second doses, therefore, all reports are related to short-term impacts of the vaccine. 7. For the prevention of database bias, we searched various databases and websites for finding all relevant and gray publications and a proper test for publication bias using Egger's regression test conducted. We did not find remarkable publication bias in this study by Egger's regression test. However, publication bias and heterogeneity for some of the pooled results, as well as all the above limitations, must be considered when interpreting the outcomes.



## 5. Conclusions

The adenovirus-vectored and mRNA-based vaccines for COVID-19 showed the highest efficacy after first and second doses, respectively. The mRNA-based vaccines had higher side effects. Only a rare few recipients have experienced extreme adverse effects and all stimulated robust immune responses. All RCTs followed up the vaccine and placebo groups after one month after both first and second doses, therefore, all reports are related to short-term impacts. Due to the timeline, all the vaccines are missing longer-term assessments. This meta-analysis allows us to incorporate relevant new evidence for summarizing and analyzing the clinical features of current vaccines for COVID-19 in phase I, II, and III RCTs. The results support the overall efficacy and safety of all available COVID-19 vaccines, providing clear data-driven evidence to support the ongoing global public health effort to vaccinate the entire population.

**Supplementary Materials:** The following are available online at https://www.mdpi.com/article/10.3390/vaccines9050467/s1, Figure S1. Meta-analysis A. Forest plot, B. Funnel plot for the injection site pain as a side effect of different COVID 19 vaccine in phase 2/3 RCT, Figure S2. Meta-analysis A. Forest plot, B. Funnel plot for the injection site pain as a side effect of different COVID 19 vaccine in phase 1/2 RCT, Figure S3. Meta-analysis A. Forest plot, B. Funnel plot for the Swelling as a side effect of different COVID 19 vaccine in phase 1/2/3 RCT, Figure S4. Meta-analysis A. Forest plot, B. Funnel plot for the Redness as a side effect of different COVID 19 vaccine in phase 1/2/3 RCT, Figure S5. Meta-analysis A. Forest plot, B. Funnel plot for the Itch as a side effect of different COVID 19 vaccine in phase 1/2 RCT, Figure S6. Meta-analysis A. Forest plot, B. Funnel plot for the Cough as a side effect of different COVID 19 vaccine in phase 1/2/3 RCT, Figure S7. Meta-analysis A. Forest

plot, B. Funnel plot for the Fever as a side effect of different COVID 19 vaccine in phase 1/2/3 RCT, Figure S8. Meta-analysis A. Forest plot, B. Funnel plot for the Headache as a side effect of different COVID 19 vaccine in phase 1/2 RCT, Figure S9. Meta-analysis A. Forest plot, B. Funnel plot for the Headache as a side effect of different COVID 19 vaccine in phase 2 RCT, Figure S10. Meta-analysis A. Forest plot, B. Funnel plot for the Headache as a side effect of different COVID 19 vaccine in phase 3 RCT, Figure S11. Meta-analysis A. Forest plot, B. Funnel plot for the Fatigue as a side effect of different COVID 19 vaccine in phase 1/2 RCT, Figure S12. Meta-analysis A. Forest plot, B. Funnel plot for the Fatigue as a side effect of different COVID 19 vaccine in both mRNA-based vaccine, in RCT 2/3, and 3, Figure S13. Meta-analysis A. Forest plot, B. Funnel plot for the Induration as a side effect of different COVID 19 vaccine in RCT $\frac{1}{2}$, Figure S14. Meta-analysis A. Forest plot, B. Funnel plot for the Vomiting as a side effect of different COVID 19 vaccine in RCT $\frac{1}{2}$, Figure S15. Meta-analysis A. Forest plot, B. Funnel plot for the Vomiting as a side effect of different COVID 19 vaccine in both mRNA-based vaccine, in RCT 2/3, and 3, Figure S16. Meta-analysis A. Forest plot, B. Funnel plot for the Diarrhea as a side effect of different COVID 19 vaccine in RCT $\frac{1}{2}$, Figure S17. Meta-analysis A. Forest plot, B. Funnel plot for the Myalgia as a side effect of different COVID 19 vaccine in RCT $\frac{1}{2}$, Figure S18. Meta-analysis A. Forest plot, B. Funnel plot for the Myalgia as a side effect of different COVID 19 vaccine in RCT 3, Figure S19. Meta-analysis A. Forest plot, B. Funnel plot for the Arthralgia as a side effect of different COVID 19 vaccine in RCT 2/3, Figure S20. Meta-analysis A. Forest plot, B. Funnel plot for the Chills as a side effect of different COVID 19 vaccine in RCT 2/3, Figure S21. Meta-analysis A. Forest plot, B. Funnel plot for the Pruritus as a side effect of different COVID 19 vaccine in RCT 2/3, Figure S22. Meta-analysis A. Forest plot, B. Funnel plot for the Fatigue as a side effect based on the adjuvant type in phase 2/3 RCT, Figure S23. Meta-analysis A. Forest plot, B. Funnel plot for the Diarrhea as a side effect based on the adjuvant type in phase 2/3 RCT, Figure S24. Meta-analysis A. Forest plot, B. Funnel plot for the Injection site pain as a side effect based on the adjuvant type in phase 2/3 RCT, Figure S25. Meta-analysis A. Forest plot, B. Funnel plot for the Itch as a side effect based on the adjuvant type in phase 2/3 RCT, Figure S26. Meta-analysis A. Forest plot, B. Funnel plot for the Myalgia as a side effect based on the adjuvant type in phase 2/3 RCT, Figure S27. Meta-analysis A. Forest plot, B. Funnel plot for the Swelling as a side effect based on the adjuvant type in phase 2/3 RCT, Figure S28. Meta-analysis A. Forest plot, B. Funnel plot for the Redness as a side effect based on the adjuvant type in phase 2/3 RCT, Figure S29. Meta-analysis A. Forest plot, B. Funnel plot for the Vomiting as a side effect based on the adjuvant type in phase 2/3 RCT, Figure S30. Meta-analysis A. Forest plot, B. Funnel plot for the Fever as a side effect based on the adjuvant type in phase 2/3 RCT, Table S1. Search strategy, Table S2. Quality assessment of included studies.



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## Abbreviations

| | |
|---|---|
| PRISMA | The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement |
| MeSH | Medical subject headings |
| WHO | World Health Organization |
| CDC | Center for Disease Control |
| RCT | Randomized clinical trial |
| COVID-19 | Coronavirus disease 2019 |
| alum | Potassium aluminum sulfate |
| VLPs | Virus-like particles |
| ORs | Odds ratios |
| 6-HB | six-helical bundle |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |
| 95% CI | 95% confidence interval |
| GMT | Geometric mean titer |
| RBD | Receptor-binding domain |
| PLpro | Papain-like proteases |
| 3CLpro | Cysteine-like protease |
| NAb | Neutralizing antibody |
| Pro-subunit | Protein subunit |
| VLP | Virus-like particle |
| BMI | Body mass index |
| CFR | Case fatality ratio |
| RNA | Ribonucleic acid |
| messenger RNA | mRNA |
| S-protein | Spike protein |
| ACE2 | Angiotensin-converting enzyme 2 |
| nsp | Non-structural proteins |
| IM | Intramuscular |



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Biden announces COVID-19 vaccine mandates that will affect 100 million Americans



*Washington* – President Biden announced the most sweeping COVID-19 vaccine requirements yet on Thursday, which will affect roughly 100 million Americans. The new measures include a vaccine mandate for all federal workers and contractors, and a requirement that large companies must mandate vaccines or regular testing for employees.

"My job as president is to protect all Americans," Mr. Biden said Thursday. "So tonight, I'm announcing that the Department of Labor is developing an emergency rule to require all employers with 100 or more employees that together employ over 80 million workers to ensure their workforces are fully vaccinated or show a negative test at least once a week."

Mr. Biden noted that many large companies already require vaccinations. "The bottom line – we're going to protect vaccinated workers from unvaccinated coworkers," he said.

The Department of Labor's Occupational Safety and Health Administration is developing a rule requiring all employers with at least 100 employees to make sure their workforce is fully vaccinated or require unvaccinated workers to get a negative test at least once a week. OSHA will issue an Emergency Temporary Standard to introduce the vaccine requirement. Companies that fail to comply could face fines of $14,000 per violation, Mr. Biden said.

That was just one of the mandates and changes the president announced in a speech on boosting vaccinations and battling the COVID-19 pandemic. The president also announced vaccination requirements for health care providers that accept Medicare and Medicaid, for all federal employees and contractors and for the staffs of Head Start programs, Department of Defense Schools and Bureau of Indian Education-operated schools. Mr. Biden had announced in July the federal workforce would need to provide evidence that they had been vaccinated or submit to regular testing and practice social distancing measures in the workplace.

Within hours of his speech, the Republican National Committee announced that it plans to file a lawsuit against the Biden administration.



"Joe Biden told Americans when he was elected that he would not impose vaccine mandates," RNC chairwoman Ronna McDaniel said in a statement Thursday. "He lied. Now small businesses, workers, and families across the country will pay the price. Like many Americans, I am pro-vaccine and anti-mandate. Many small businesses and workers do not have the money or legal resources to fight Biden's unconstitutional actions and authoritarian decrees, but when his decree goes into effect, the RNC will sue the administration to protect Americans and their liberties."

President Joe Biden pauses as he speaks in the State Dining Room at the White House, Thursday, Sept. 9, 2021, in Washington.

ANDREW HARNIK / AP



The new mandates are part of a six-pronged White House strategy to battle the COVID-19 Delta variant and boost vaccinations as cases, hospitalizations and deaths continue to climb. The six pillars are: vaccinating the unvaccinated; furthering protection for the unvaccinated; keeping schools safely open; increasing testing and requiring masking; protecting economic recovery; and improving care for those with COVID-19.

The president started out his speech by saying he knows many are frustrated with the 25% of adults in the U.S. who have yet to get a single COVID-19 shot. That 25% "can do a lot of damage," he said. He made an appeal directly to unvaccinated Americans.

"What more is there to wait for? What more do you need to see?" he said. "We've made vaccinations free, safe and convenient. The vaccine has FDA approval. Over 200 million Americans have gotten at least one shot. We've been patient. But our patience is wearing thin. And your refusal has cost all of us. So please, do the right

thing."

White House press secretary Jen Psaki said earlier Thursday there will be limited disability and religious exceptions to the federal employee vaccine requirement. Those who are not exempt and do not comply will be subject to disciplinary action, including possible termination, she said.

"There are limited exceptions, but yeah, the expectation is that if you want to work in the federal government or be a contractor, you need to be vaccinated, unless you are eligible for one of the exemptions," Psaki told reporters.



The American Federation of Government Employees, the largest federal employee union, is taking issue with the mandatory vaccine requirement, even though it has encouraged workers to get vaccinated. AFGE president Everett Kelley said that "changes like this should be negotiated with our bargaining units where appropriate," and he said the union expects to bargain over this rule before it's implemented.

Still, Psaki said the president "has every intention of signing this executive order, getting the clock running on the timeline for these requirements, and his view and our view is this will serve as a model to the rest of the country on the need to get more people vaccinated in order to save more lives."

The president also announced measures to ensure kids are adequately protected in classrooms, as he aims to make more testing available. He's also urging states to require vaccinations for all school teachers and staffs.

Mr. Biden also said he's using the Defense Production Act to ramp up the production of rapid COVID-19 tests, and at-home rapid tests will be available at major pharmacies over the next several months at cost.

CBS News has learned the president will raise the issue of COVID vaccination effort on a global scale with other world leaders when they meet at the United Nations General Assembly later this month. A senior administration official told CBS News that while they are "still planning the president's schedule around UN General Assembly High Level week, it is safe to assume we are actively looking at COVID-19 and public-health centered options."

The official stopped short of calling it a summit, but added that the administration anticipates "that there will be an opportunity for the president to engage with his counterparts on this issue during UNGA week." One topic expected to be discussed among Mr. Biden and his counterparts, according to a second administration official will be about advancing and improving international cooperation on research and development on the COVID-19 front.



According to the Centers for Disease Control and Prevention, 75.2% of American adults have at least one COVID-19 vaccine shot. But community transmission across most of the country remains high, as the Delta variant makes up nearly all of the country's cases. Nearly 650,000 people have died in the U.S. from COVID-19 since the beginning of the pandemic last year.

## Here are the major measures announced Thursday:

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6:17 PM / SEPTEMBER 9, 2021

## How many people are affected?

The new vaccine mandates the president announced Thursday will affect roughly

100 million Americans, although many of that group are already vaccinated. The White House estimates there are roughly 80 million people working at companies with at least 100 employees. The White House also estimates the mandate will affect more than 17 million health care workers, as well as federal employees, and teachers and staff at specific Head Start programs and Department of Defense schools.

"This is a pandemic of the unvaccinated, and it's caused by the fact that despite America having unprecedented and a successful vaccination program, despite the fact that for almost five months, free vaccines have been available in 80,000 different locations, we still have nearly 80 million Americans who have failed to get the shot," the president said, making his case for the need for more aggressive action.

BY KATHRYN WATSON

6:17 PM / SEPTEMBER 9, 2021



## Companies with 100 or more employees will have to require shots or testing

The Department of Labor's Occupational Safety and Health Administration, better known as OSHA, is developing an emergency rule requiring employers with at least 100 employees to require all employees to be vaccinated or get tested at least once a week. Failure to comply with the yet-to-be-released rule could result in a $14,000 fine.

The announcement marks the most authoritative step involving private businesses the administration has taken yet to curb the pandemic, and it's one that's sure to be challenged in court.

"The bottom line – we're going to protect vaccinated workers from unvaccinated coworkers,." he said.

BY KATHRYN WATSON

6:18 PM / SEPTEMBER 9, 2021

## Federal employees must be vaccinated

Mr. Biden issued an executive order on Thursday requiring all federal employees be vaccinated, with no option to undergo tests. "If you want to work for the federal government, get vaccinated," Mr. Biden said. "If you want to do business with the federal government, get vaccinated."

Mr. Biden also issued an executive order on Thursday requiring all contractors who do business with the government be vaccinated.

The executive orders both refer to the national emergency declared on January 31, 2020 and the National Emergency Concerning the Coronavirus Disease 2019 (COVID-19) declared pursuant to the National Emergencies Act in Proclamation 9994 of March 13, 2020, both of which remain in effect.



"The health and safety of the Federal workforce, and the health and safety of members of the public with whom they interact, are foundational to the efficiency of the civil service," both executive orders say. "I have determined that ensuring the health and safety of the Federal workforce and the efficiency of the civil service requires immediate action to protect the Federal workforce and individuals interacting with the Federal workforce. It is essential that Federal employees take all available steps to protect themselves and avoid spreading COVID-19 to their co-workers and members of the public. The CDC has found that the best way to do so is to be vaccinated."

BY CAROLINE LINTON

6:18 PM / SEPTEMBER 9, 2021

## Workers at health care facilities accepting federal funds will need to be vaccinated

The Centers for Medicare and Medicaid Services will require vaccinations for workers in most health care settings that receive Medicare or Medicaid reimbursement. That covers hospitals, home health agencies and many other types of health care facilities, and roughly 17 million workers.

"If you're seeking care at a health facility, you should be able to know that the people treating you are vaccinated," he said.

BY KATHRYN WATSON

6:19 PM / SEPTEMBER 9, 2021

## Air travelers refusing to wear masks could face up to $3,000 fines

Air travelers who refuse to wear masks could be fined up to $3,000, starting Friday.



The Transportation Security Administration (TSA) announced Thursday it will double fines for those who flout federal mask mandates for air travel.

First-time offenders will be fined $500 to $1,000, while repeat offenders will be forced to shell out $1,000 to $3,000.

BY NICOLE SGANGA

6:18 PM / SEPTEMBER 9, 2021

## Biden acknowledges "confusion" on booster shots

Several weeks after the Biden administration announced a plan to roll out booster shots, Mr. Biden acknowledged Thursday there is "confusion" around whether or when Americans should get them. Mr. Biden said that while the administration stands ready, the decision of which shots to give, to whom, and when "will be left

completely to the scientists."

BY CAROLINE LINTON

**Coronavirus Pandemic** More ›


COVID-19 cases are rising in these states amid summer wave

COVID cases likely rising in half of states, CDC estimates

CDC official overseeing COVID hospitalization data resigns in protest

New COVID variant NB.1.8.1 could be more than 1 in 3 cases, CDC says

In: **Vaccine Mandate** **COVID-19 Vaccine** **Joe Biden** **COVID-19** **Delta Variant**



CBS NEWS

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# Fact Sheet: President Donald J. Trump Reinstates Service Members Discharged for Refusing the COVID Vaccine

The White House

January 27, 2025

**REINSTATING THE UNJUSTLY DISCHARGED:** Today, President Donald J. Trump signed an Executive Order to reinstate service members who were dismissed for refusing the COVID vaccine, with full back pay and benefits.

- The Executive Order directs the Secretary of Defense to reinstate all members of the military (active and reserve) who were discharged for refusing the COVID vaccine and who request to be reinstated.
    - Those who are reinstated will receive their former rank and full back pay with benefits.



**CORRECTING AN INJUSTICE:** In spite of the scientific evidence, the Biden Administration discharged healthy service members—many of whom had natural immunity and dedicated their entire lives to serving our country—for refusing the COVID vaccine. Government redress of these wrongful dismissals is overdue.

- From 2021 to 2023, the Biden Administration and former Secretary of Defense Lloyd Austin discharged over 8,000 troops solely due to their COVID-19 vaccination status.
    - Such dismissals likely had a chilling effect on recruitment, with the Department of Defense missing its collective recruiting targets by around 41,000 recruits in FY2023.
    - After the vaccine mandate was repealed in 2023, only 43 of the more than the 8,000 troops dismissed elected to return to service under the Biden Administration and Secretary Austin.

**CHARTING A NEW COURSE FORWARD:** In 2024, President Trump declared that “there should have never been a [COVID vaccine] mandate. That should have never happened.”

- President Trump went on to lament that, due to the mandate, “we’ve lost some of our best people in the military too.”
- President Trump duly promised in 2024 that he “will rehire every patriot who was fired from the military with…backpay. They will get their backpay…”

THE WHITE HOUSE

1600 Pennsylvania Ave NW
Washington, DC 20500

# California Becomes First State in Nation to Announce COVID-19 Vaccine Requirements for Schools

*After implementing first-in-the-nation school masking and staff vaccination measures, California becomes the first state to announce plans to require student vaccinations – adding the COVID-19 vaccine to list of vaccinations required for school, such as the vaccines for measles, mumps, and rubella*

*Students will be required to be vaccinated for in person learning starting the term following FDA full approval of the vaccine for their grade span (7-12 and K-6).*



SAN FRANCISCO – At a school in San Francisco, Governor Newsom announced plans to add the COVID-19 vaccine to the list of vaccinations required to attend school in-person when the vaccine receives full approval from the Food and Drug Administration (FDA) for middle and high school grades, making California the first state in the nation to announce such a measure. Following the other **first-in-the-nation school masking and staff vaccination measures**, Governor Newsom announced the COVID-19 vaccine will be required for in-person school attendance—just like vaccines for measles, mumps, rubella and more.

“The state already requires that students are vaccinated against viruses that cause measles, mumps, and rubella – there’s no reason why we wouldn’t do the same for COVID-19. Today’s measure, just like our first-in-the-nation school masking and staff vaccination requirements, is about protecting our children and school staff, and keeping them in the classroom,” said Governor Newsom. “Vaccines

work. It's why California leads the country in preventing school closures and has the lowest case rates. We encourage other states to follow our lead to keep our kids safe and prevent the spread of COVID-19."

Thanks to the state's bold public health measures, California continues to maintain the **lowest case rate in the entire country** and is one of only two states to have **advanced out of the CDC's 'high' COVID transmission** category. More information about the announcement can be found **here**.

The vast majority of school districts have reported that over 95% of students have returned to in-person instruction this school year, as can be seen on the state's **Student Supports & In-Person Dashboard**. Thanks to unprecedented resources and public health measures (**measures shown to be highly effective**), California is **leading national trends in preventing school closures** and keeping kids in classrooms, accounting for only 14 out of over 2,000 school closures nationwide, or roughly 0.7% – despite the fact that California educates an estimated 12% of the nation's public school students. If California's rates had aligned with national trends, the state would have seen upwards of 240 school closures.



In order to further protect students and staff and continue supporting a safe return to in-person instruction for all students, the Governor directed the California Department of Public Health (CDPH) to follow the procedures established by the Legislature to add the COVID-19 vaccine to other vaccinations required for in-person school attendance—such as measles, mumps, and rubella—pursuant to the Health and Safety Code. COVID-19 vaccine requirements will be phased-in by grade span, which will also promote smoother implementation.

Upon full FDA approval of age groups within a grade span, CDPH will consider the recommendations of the Advisory Committee on Immunization Practices of the United States Department of Health and Human Services, the American Academy of Pediatrics, and the American Academy of Family Physicians prior to implementing a requirement. Following existing statute, full approval of ages 12+ corresponds to grades 7-12, and full approval of ages 5-11

corresponds to grades K-6. Students who are under the age of full approval, but within the grade span, will be required to be vaccinated once they reach the age of full approval (with a reasonable period of time to receive both doses), consistent with existing procedures for other vaccines. The requirement will take effect at the start of the term following full approval of that grade span, to be defined as January 1st or July 1st, whichever comes first. Based on current information, the requirement is expected to apply to grades 7-12 starting on July 1, 2022. However, local health jurisdictions and local education agencies are encouraged to implement requirements ahead of a statewide requirement based on their local circumstances.

Governor Newsom's historic **$123.9 billion Pre-K and K-12 education package** is providing an unprecedented level of school and student funding to transform the state's public schools into gateways of equity and opportunity, supporting the potential of every California student by: achieving universal transitional kindergarten for four-year-olds by 2025, expanding afterschool and summer programs, providing universal free school nutrition, increasing the number of well-prepared staff per pupil, creating full-service community schools to support the mental and social-emotional well-being of students, and more.



###

COVID-19

# Benefits of Getting Vaccinated

For Everyone

JUNE 11, 2025 •

**WHAT TO KNOW**

- Getting vaccinated against COVID-19 has many benefits that are supported by scientific studies.
- The COVID-19 vaccine helps protect you from severe illness, hospitalization, and death.
- CDC recommends an updated COVID-19 vaccine for most adults ages 18 years and older.
- Parents of children ages 6 months to 17 years should discuss the benefits of vaccination with a healthcare provider.



## COVID-19 vaccines protect your health

COVID-19 continues to cause millions of illnesses, hundreds of thousands of hospitalizations, and tens of thousands of deaths each year in the United States.[1] [2] It was the 10th leading cause of death in 2023.[3]

COVID-19 vaccines can help keep you from getting sick from COVID-19. If you do get COVID-19, vaccines can make the illness shorter[4] [5] and less severe.

**Stay up to date**

Learn about the latest recommendations for the updated COVID-19 vaccine.

Stay Up to Date with COVID-19 Vaccines

The data below describe how well vaccines work to reduce your risk. This risk reduction is in addition to protection you may have from previous infections with COVID-19 or from receiving earlier versions of COVID-19 vaccines.

COVID-19 vaccines:

- **Reduce your risk for critical illness** (admission to intensive care unit or death)
  - For adults ages 18 and older, the 2023–2024 COVID-19 vaccines reduced the risk of critical illness from COVID-19 by almost 70% in the first 2 months after vaccination. Protection decreased over time. During the 10 months after vaccination, the vaccines reduced critical illness risk by about 50%.[6]
- **Reduce your risk of being hospitalized**
  - For adults ages 18 and older, the 2023–2024 COVID-19 vaccines reduced the risk of COVID-19 hospitalization by about 50% in the first 2 months after vaccination. Protection decreased over time. During the 10 months after vaccination, the vaccines reduced hospitalization risk by about 30%.[6] [7]
- **Reduce your risk of getting sick and needing to go to urgent care or the emergency department**
  - For adults ages 18 and older, the 2023–2024 COVID-19 vaccines reduced the risk of COVID-19 urgent care and emergency department visits by about 50% in the first 2 months after vaccination. Protection decreased over time, with little protection remaining at 4–6 months.[6] [7]
- **Reduce your risk for Long COVID**

- Studies show that people who got vaccinated against COVID-19 and later get COVID-19 are less likely to have Long COVID, compared to people who are unvaccinated or not up to date with their COVID-19 vaccines. [8] [9]

## Important for people at higher risk from COVID-19

- **If you are 65 years or older**
  - The 2023–2024 COVID-19 vaccines reduced the risk of critical illness (admission to intensive care unit or death) among older adults by about 67% in the first 2 months after vaccination. During the 4–6 months after vaccination, the vaccines reduced critical illness risk by about 40%. [6]
  - The 2023–2024 COVID-19 vaccines reduced the risk of COVID-19 hospitalization among older adults by about 50% in the first 2 months after vaccination. Protection from vaccination wanes by 4–6 months after vaccination. [6] [7] Because adults ages 65 years and older have a higher risk for severe COVID-19, they are recommended to receive a second dose of COVID-19 vaccine 6 months after their first dose.
- **If you have a weakened immune system**
  - The 2023–2024 COVID-19 vaccines reduced the risk of COVID-19 hospitalization for people with a weakened immune system by about 36% in the first 2 months after vaccination. Protection from vaccination wanes by 4–6 months after vaccination. [6] [10] Because people with a weakened immune system have a higher risk for severe COVID-19, they are recommended to receive a second dose of COVID-19 vaccine 6 months after their first dose.
- **If you are pregnant**
  - Getting a COVID-19 vaccine while you are pregnant helps protect you. It also helps protect your baby from severe health outcomes due to COVID-19 before they become eligible for COVID-19 vaccination when they are 6 months old. [11]
  - COVID-19–associated hospitalization rates among infants younger than 6 months remain higher than rates among any other age group except adults ages 75 years and older. [12]
  - Maternal vaccination during pregnancy reduced the risk of COVID-19-related hospitalization by around 54% among infants during the first 3 months of life. [11]

## Children

The 2023–2024 COVID-19 vaccines reduced the risk of COVID-19-associated emergency room and urgent care visits by

- Around 65% in children **ages 9 months to 4 years** in the first 2 months after vaccination. Protection decreased over time. [6]
- About 70% in children **ages 5–17 years** in the first 2 months after vaccination. Protection decreased over time. At 4–6 months after vaccination, the vaccines reduced risk by about 50%. [6]

KEEP READING
6 Things to Know about COVID-19 Vaccination for Children



## Vaccination is more reliable way to build protection than getting sick

COVID-19 vaccination helps protect people by creating an immune response without the potentially severe illness that can be associated with COVID-19 infection.

**What Can Happen If You Get Sick with COVID-19**

- COVID-19 can cause severe illness or death, even in children, but it is not always possible to determine who will experience mild or severe illness from COVID-19 infection.
- People may have long-term health issues after having COVID-19. Even people who do not have symptoms when they are first infected with COVID-19 can experience long-term health problems, also known as Long COVID or post-COVID conditions.
- Complications can appear after mild or severe COVID-19, or after multisystem inflammatory syndrome in children (MIS-C).

**Protection from having had COVID-19**

**Keep in mind**

While people can get some protection from having COVID-19, the level and length of that protection varies, especially as COVID-19 variants continue to emerge.

- Immunity (protection) from infection can vary depending on how mild or severe someone's illness was, their age, and whether they have a weakened immune system. Immunity also changes depending on what variant of SARS-CoV-2 someone had and how similar it is to the variants currently circulating.
- Immunity from infection decreases over time.

**A closer look at the safety data**

During the COVID-19 pandemic, COVID-19 vaccines underwent the most intensive safety analysis in U.S. history. COVID-19 vaccines continue to be monitored for safety, even after FDA approval, to make sure they continue to meet FDA's standards for safety and effectiveness.

To date, the systems in place to monitor the safety of COVID-19 vaccines currently used in the United States have identified anaphylaxis and myocarditis or pericarditis as serious types of adverse events following COVID-19 vaccination. Other rare events, such as Guillain-Barré syndrome (GBS), are also monitored for and studied.

Read more about COVID-19 vaccine safety

## After vaccination

Learn what you can do after vaccination to protect your family from COVID-19 in CDC's respiratory virus guidance.

SOURCES

**CONTENT SOURCE:**
National Center for Immunization and Respiratory Diseases; Coronavirus and Other Respiratory Viruses Division

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