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UNITED STATES DISTRICT COURT
DISTRICT OF ARIZONA

Mark Brnovich, in his official capacity as Attorney General of Arizona; and the State of Arizona,

Plaintiffs,

v.

Joseph R. Biden in his official capacity as President of the United States; Alejandro Mayorkas in his official capacity as Secretary of Homeland Security; United States Department of Homeland Security; Troy Miller in his official capacity as Senior Official Performing the Duties of the Commissioner of U.S. Customs and Border Protection; and Tae Johnson in his official capacity as Senior Official Performing the Duties of Director of U.S. Immigration and Customs Enforcement; United States Office of Personnel Management; Kiran Ahuja in her official capacity as director of the Office of Personnel Management and as co-chair of the Safer Federal Workforce Task Force; General Services

No. 2:21-cv-01568-MTL

DECLARATION OF JAMES K. ROGERS

Administration; Robin Carnahan in her official capacity as administrator of the General Services Administration and as co-chair of the Safer Federal Workforce Task Force; Office of Management and Budget; Shalanda Young in her official capacity as Acting Director of the Office of Management and Budget and as a member of the Safer Federal Workforce Task Force; Safer Federal Workforce Task Force; Jeffrey Zients is his official capacity as co-chair of the Safer Federal Workforce Task Force and COVID-19 Response Coordinator.

Defendants.

I, James K. Rogers, declare as follows:

1. I am an attorney licensed to practice law in Arizona. I am a Senior Litigation Counsel with the Arizona Office of the Attorney General.

2. Attached hereto as **Exhibit A** is a true and correct copy of an article titled "Psaki on Why Migrants Can Enter U.S. But Unvaccinated Foreign Nationals Can't: 'Not the Same Thing,'" written by Brittany Bernstein for *National Review*. The article was published on September 20, 2021, and is publicly available at https://tinyurl.com/vntj4d8d.

3. Attached hereto as **Exhibit B** is a true and correct copy of the Application of the United States filed in *United States v. Texas*, No. 21A85 (U.S. Oct. 18, 2021) which is publicly available at https://tinyurl.com/psevc77d.

4. Attached hereto as **Exhibit C** is a true and correct copy of the "Remarks by President Biden on Fighting the COVID-19 Pandemic." The remarks were delivered on September 9, 2021 and are publicly available at https://tinyurl.com/32hhppvv.

5. Attached hereto as **Exhibit D** is a true and correct copy of "Path out of the Pandemic President Biden's COVID-19 Action Plan." The plan was last accessed October 21, 2021 and is publicly available at https://tinyurl.com/2astufah.

6. Attached hereto as **Exhibit E** is a true and correct copy of Sivan Gazit, et al., "Comparing SARS-CoV-2 natural immunity to vaccine-induced immunity: reinfections versus breakthrough infections." The paper was published August 25, 2021 by *medRxiv*, https://doi.org/10.1101/2021.08.24.21262415.

7. Attached hereto as **Exhibit F** is a true and correct copy of Kristen W. Cohen, et al., "Longitudinal analysis shows durable and broad immune memory after SARS-CoV-2 infection with persisting antibody responses and memory B and T cells." The paper was published July 14, 2021 by *Cell Reports Medicine*, https://doi.org/10.1016/j.xcrm.2021.100354.

8. Attached hereto as **Exhibit G** is a true and correct copy of the article titled "Outdoor and Indoor Activities" updated by the Centers for Disease Control and Prevention on August 19, 2021. The article is publicly available at https://tinyurl.com/3244spju.

9. Attached hereto as **Exhibit H** is a true and correct copy of the guidance titled "COVID-19 Workplace Safety: Guidance for Federal Contractors and Subcontractors" The guidance was issued September 24, 2021 by SFWTF and is publicly available at https://tinyurl.com/n7nfuubn.

10. Attached hereto as **Exhibit I** is a true and correct copy of the fact sheet titled "FACT SHEET FOR HEALTHCARE PROVIDERS ADMINISTERING VACCINE (VACCINATION PROVIDERS) EMERGENCY USE AUTHORIZATION (EUA) OF THE MODERNA COVID-19 VACCINE TO PREVENT CORONAVIRUS DISEASE 2019 (COVID-19)." The fact sheet was revised by FDA on October 20, 2021 and is publicly available at https://tinyurl.com/4ax3r4yw.

11. Attached hereto as **Exhibit J** is a true and correct copy of the fact sheet titled "FACT SHEET FOR HEALTHCARE PROVIDERS ADMINISTERING

VACCINE (VACCINATION PROVIDERS) EMERGENCY USE AUTHORIZATION (EUA) OF THE JANSSEN COVID-19 VACCINE TO PREVENT CORONAVIRUS DISEASE 2019 (COVID-19)." The fact sheet was revised by FDA on October 20, 2021 and is publicly available at https://tinyurl.com/4w9p4y4y.

12. Attached hereto as **Exhibit K** is a true and correct copy of the BLA approval letter sent regarding the Comirnaty vaccine. The letter was sent by FDA on August 23, 2021 and is publicly available at https://tinyurl.com/s554fb7r.

13. Attached hereto as **Exhibit L** is a true and correct copy of the September 22, 2021 EUA letter sent by FDA regarding the Pfizer-BioNTech COVID-19 Vaccine. The letter is archived at https://tinyurl.com/2rerrv8s.

14. Attached hereto as **Exhibit M** is a true and correct copy of the "Summary Basis for Regulatory Action" regarding the Comirnaty vaccine. The document was issued by FDA on August 23, 2021 and is publicly available at https://tinyurl.com/n32vnkc5.

15. Attached hereto as **Exhibit N** is a true and correct copy of an article titled "Southwest Airlines cancels 1,800 flights days after pilot union sued over Covid-19 vaccine mandate," written by Graeme Massie for *The Independent*. The article was published on October 11, 2021, and is available at https://tinyurl.com/y73y7r7y.

16. Attached hereto as **Exhibit O** is a true and correct copy of an article titled "Southwest Airlines debacle is symptomatic of bigger pandemic problems," written by Sheldon H. Jacobson, PhD for *The Hill*. The article was published on October 18, 2021, and is publicly available at https://tinyurl.com/znj9vjt6.

17. Attached hereto as **Exhibit P** is a true and correct copy of an article titled "Southwest CEO says he's against vaccine mandates, blames Biden," written by Emily Crane for *The New York Post*. The article was published on October 12, 2021, and is publicly available at https://tinyurl.com/4adte998.

18. Attached hereto as **Exhibit Q** is a true and correct copy of an article titled "Southwest drops plan to put unvaccinated staff on unpaid leave starting in December,"

written by Leslie Josephs for *CNBC*. The article was published on October 19, 2021, and is publicly available at https://tinyurl.com/y4sxv8md.

19. Attached hereto as **Exhibit R** is a true and correct copy of an article titled "Biden's vaccine mandate is making America's most serious economic problem worse," written by Liz Peek for *The Hill*. The article was published on September 29, 2021, and is publicly available at https://tinyurl.com/3vmk27yw.

20. Attached hereto as **Exhibit S** is a true and correct copy of an article titled "Border arrests have soared to all-time high, new CBP data shows," written by Nick Miroff for *The Washington Post*. The article was published on October 20, 2021, and is publicly available at https://tinyurl.com/hd923tx4.

21. Attached hereto as **Exhibit T** is a true and correct copy of a page titled "What is Smallpox?" issued by the Centers for Disease Control and Prevention. The page was last reviewed by CDC on June 7, 2016 and is publicly available at https://tinyurl.com/2exc44x2.

22. Attached hereto as **Exhibit U** is a true and correct copy of John P. A. Ioannidis, "Reconciling estimates of global spread and infection fatality rates of COVID-19: An overview of systematic evaluations," Eur J Clin Invest, May 2021, available at https://tinyurl.com/ywnkf8sr.

23. Attached hereto as **Exhibit V** is a true and correct copy of a notice titled "Pfizer received FDA BLA license for its COVID-19 vaccine." The notice was issued by the National Institutes of Health on September 13, 2021 and is publicly available at https://tinyurl.com/36zmjwsy.

24. Attached hereto as **Exhibit W** is a true and correct copy of an article titled "Why The Big Quit Is Happening And Why Every Boss Should Embrace It," written by Lisa Curtis for *Forbes*. The article was published on June 30, 2021, and is publicly available at https://tinyurl.com/336xk6zf.

25. Attached hereto as **Exhibit X** is a true and correct copy of an article titled "How to Quit Your Job in the Great Post-Pandemic Resignation Boom," written by

Arianne Cohen for *Bloomberg*. The article was published on May 10, 2021, and is publicly available at https://tinyurl.com/4yuus6b9.

26. Attached hereto as **Exhibit Y** is a true and correct copy of an article titled "Survey: Vaccine-or-Testing Mandate Will Be Difficult to Implement," written by Allen Smith, J.D. for the *Society for Human Resource Management*. The article was published on October 15, 2021, and is publicly available at https://tinyurl.com/45e3ub2m.

27. Attached hereto as **Exhibit Z** is a true and correct copy of an article titled "Poll: President Biden's Vaccine Workplace Mandate," published by *Engineering News-Record*. The article was published on September 23, 2021, and is publicly available at https://tinyurl.com/2kzh9tka.

I declare under penalty of perjury that the foregoing is true and correct to the best of my knowledge, and that this declaration was issued on October 21, 2021, in Phoenix, Arizona.

s/ James K. Rogers
James K. Rogers

Exhibit A

NATIONAL REVIEW

Psaki on Why Migrants Can Enter U.S. But Unvaccinated Foreign Nationals Can't: 'Not the Same Thing'

Brittany Bernstein
September 20, 2021 · 2 min read

White House press secretary Jen Psaki on Monday dismissed a question about why migrants are not required to be vaccinated against COVID-19 before entering the U.S. but foreign nationals who arrive by plane are, arguing that "it is not the same thing."

"As individuals come across the border, they are both assessed for whether they have any symptoms, if they have symptoms, the intention is for them to have to be quarantined," Psaki said of migrants entering the U.S. "That is our process."

"They are not intending to stay here for a lengthy period of time," Psaki said of foreign nationals when pressed for further explanation. "I don't think it's the same thing. It is not the same thing."

The press briefing exchange came after the White House announced on Monday that the U.S. will require all foreign nationals to show proof of vaccination against COVID-19 to enter the country.

"With science and public health as our guide, we have developed a new international air travel system that both enhances the safety of Americans here at home and enhances the safety of international air travel," White House COVID-19 Response Coordinator Jeff Zients told reporters. "Foreign nationals flying to the U.S. will be required to be fully vaccinated."

Foreign travelers will be required to provide proof of vaccination and a negative COVID-19 test within three days prior to departure to the U.S.

Meanwhile, thousands of migrants with unknown vaccination statuses are entering the country through the southern border each day. In Del Rio, Texas, Border Patrol agents have been overwhelmed by thousands of mostly Haitian migrants who have illegally crossed the border and are camping out under the international bridge in squalid conditions. The number of migrants at the camp has exploded since Wednesday, when there were 4,000 migrants there. Since then, the number has topped 14,000 at times.

TRENDING

1. Laundrie family lawyer says 'prob is strong' that the apparent huma remains found are Brian's
2. In secret vaccine contracts with governments, Pfizer took hard lir push for profit, report says
3. Human remains found during sea Brian Laundrie in Florida
4. Washington newscast accidentall broadcasts pornographic clip dur weather report
5. Charges unlikely for riders who sa Philadelphia train rape

Representative August Pfluger (R., Texas) who visited the area described it as "worse than you could imagine" and said that Border Patrol agents are worried "the worst is yet to come."

"We are expelling individuals based on Title 42, specifically because of COVID," Psaki said Monday, referring to the public health order. "Because we want to prevent a scenario where large numbers of people are gathering, posing a threat to the community, and also to the migrants themselves."

Exhibit B

No. 21A-_____

IN THE SUPREME COURT OF THE UNITED STATES

UNITED STATES OF AMERICA, APPLICANT

v.

STATE OF TEXAS

APPLICATION TO VACATE STAY OF PRELIMINARY INJUNCTION ISSUED BY THE UNITED STATES COURT OF APPEALS FOR THE FIFTH CIRCUIT

BRIAN H. FLETCHER
Acting Solicitor General
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PARTIES TO THE PROCEEDING

Applicant, the United States of America, was the plaintiff-appellee below.

Respondents were the defendant-appellant and intervenor defendants-appellants below. They are the State of Texas (the defendant-appellant) and Erick Graham, Jeff Tuley, and Mistie Sharp (the intervenor defendants-appellants).

Oscar Stilley was an intervenor defendant in the district court, but did not appeal.

IN THE SUPREME COURT OF THE UNITED STATES

_____

No. 21A-_____

UNITED STATES OF AMERICA, APPLICANT

v.

STATE OF TEXAS

_____

APPLICATION TO VACATE STAY OF PRELIMINARY INJUNCTION ISSUED BY THE UNITED STATES COURT OF APPEALS FOR THE FIFTH CIRCUIT

_____

On October 14, 2021, the United States Court of Appeals for the Fifth Circuit stayed a preliminary injunction barring enforcement of Texas Senate Bill 8 (S.B. 8). Pursuant to Rule 23 of the Rules of this Court and the All Writs Act, 28 U.S.C. 1651, the Acting Solicitor General, on behalf of the United States of America, respectfully applies for an order vacating the stay.

For half a century, this Court has held that "a State may not prohibit any woman from making the ultimate decision to terminate her pregnancy before viability." Planned Parenthood of Se. Pa. v. Casey, 505 U.S. 833, 879 (1992) (plurality opinion); accord Roe v. Wade, 410 U.S. 113, 163-164 (1973). S.B. 8 defies those precedents by banning abortion long before viability -- indeed, before many women even realize they are pregnant. Texas is not the first State

to question Roe and Casey. But rather than forthrightly defending its law and asking this Court to revisit its decisions, Texas took matters into its own hands by crafting an "unprecedented" structure to thwart judicial review. Whole Woman's Health v. Jackson, 141 S. Ct. 2494, 2496 (2021) (Roberts, C.J., dissenting).

To avoid pre-enforcement suits against state officials, Texas "delegated enforcement" of the law "to the populace at large" in a system of private bounties. Whole Woman's Health, 141 S. Ct. at 2496 (Roberts, C.J., dissenting). And to frustrate constitutional defenses in those private suits, Texas designed them to be so procedurally lopsided -- and to threaten such crushing liability -- that they deter the provision of banned abortions altogether. Thus far, S.B. 8 has worked exactly as intended: Except for the few days the preliminary injunction was in place, S.B. 8's in terrorem effect has made abortion effectively unavailable in Texas after roughly six weeks of pregnancy. Texas has, in short, successfully nullified this Court's decisions within its borders.

All of this is essentially undisputed. The Fifth Circuit did not deny any of it. Texas itself has not seriously tried to reconcile S.B. 8's ban with this Court's precedents -- indeed, it said not a word about the law's constitutionality in the Fifth Circuit. The intervenors, for their part, boast that "Texas has boxed out the judiciary" and assert that States "have every

prerogative to adopt interpretations of the Constitution that differ from the Supreme Court's." Intervenors C.A. Reply Br. 3-4.

The question now is whether Texas's nullification of this Court's precedents should be allowed to continue while the courts consider the United States' suit. As the district court recognized, it should not: The United States is likely to succeed on the merits because S.B. 8 is clearly unconstitutional and because the United States has authority to seek equitable relief to protect its sovereign interests -- including its interest in the supremacy of federal law and the availability of the mechanisms for judicial review that Congress and this Court have long deemed essential to protect constitutional rights. Allowing S.B. 8 to remain in force would irreparably harm those interests and perpetuate the ongoing irreparable injury to the thousands of Texas women who are being denied their constitutional rights. Texas, in contrast, would suffer no cognizable injury from a preliminary injunction barring enforcement of a plainly unconstitutional law.

Again, the Fifth Circuit disputed none of this. Instead, the divided panel's one-paragraph order stayed the preliminary injunction solely for "the reasons stated in" two decisions addressing a prior challenge to S.B. 8, Whole Woman's Health v. Jackson, 13 F.4th 434 (5th Cir. 2021), and Whole Woman's Health, 141 S. Ct. at 2495. App., infra, 1a. But those reasons do not apply to this very different suit. Sovereign immunity forced the

private plaintiffs in Whole Woman's Health to sue individual state officers, and this Court and the Fifth Circuit questioned whether those officers were proper defendants. This suit does not raise those questions because it was brought against the State of Texas itself, and the State has no immunity from suits by the United States. The Fifth Circuit ignored that distinction, which refutes the court's only justification for the stay.

Because the United States has made all showings required for a preliminary injunction -- and because the Fifth Circuit's unjustified stay enables Texas's ongoing nullification of this Court's precedents and its citizens' constitutional rights -- the Court should vacate the stay. In addition, given the importance and urgency of the issues, the Court may construe this application as a petition for a writ of certiorari before judgment, grant the petition, and set this case for briefing and argument this Term. Cf. Nken v. Mukasey, 555 U.S. 1042 (2008).

STATEMENT

A. Texas's Enactment of S.B. 8

1. S.B. 8 provides that "a physician may not knowingly perform or induce an abortion on a pregnant woman" after cardiac activity is detected in the embryo. Tex. Health & Safety Code §§ 171.203(b), 171.204(a).[1] Cardiac activity begins at roughly

[1] All references in this application to the Texas Code and Rules of Procedure are to the versions in effect as of September 1, 2021.

six weeks of pregnancy, as measured from a woman's last menstrual period -- that is, just two weeks after a woman's first missed period, and roughly four months before viability. See App., infra, 3a-4a, 6a-7a. S.B. 8 contains no exception for pregnancies resulting from rape or incest. And it provides only a limited exception for "medical emergenc[ies] * * * that prevent[] compliance with" the law. Tex. Health & Safety Code § 171.205(a).

Because this Court has long held that a State may not prohibit any woman from choosing to terminate a pregnancy before viability, federal courts have uniformly enjoined similar "heartbeat laws" in traditional suits against the state officials charged with enforcing them. See, e.g., Jackson Women's Health Org. v. Dobbs, 951 F.3d 246, 248 (5th Cir. 2020) (per curiam). Seeking to avoid that result, Texas designed S.B. 8 to thwart judicial review. The law provides that it "shall be enforced exclusively through * * * private civil actions" rather than by the State's executive branch. Tex. Health & Safety Code § 171.207(a). Those suits may be brought against anyone who performs or aids, or intends to perform or aid, a prohibited abortion. Id. § 171.208(a). And they may be brought by "[a]ny person" other than a state or local official -- the plaintiff need not have any connection to the abortion, or even reside in Texas. Ibid.

Texas has thus "delegated enforcement of [S.B. 8's] prohibition to the populace at large" to "insulate the State from

responsibility for implementing and enforcing the regulatory regime." Whole Woman's Health, 141 S. Ct. at 2496 (Roberts, C.J, dissenting). The evident purpose of that "unprecedented" scheme, ibid., is to avoid pre-enforcement suits against state officers under 42 U.S.C. 1983 and Ex parte Young, 209 U.S. 123 (1908).

In theory, providers could perform prohibited abortions and then assert S.B. 8's unconstitutionality as a defense in the resulting enforcement actions. But that avenue of review is not even theoretically available to pregnant women -- whose rights S.B. 8 directly violates -- because they cannot be sued under the law. Tex. Health & Safety Code § 171.206(b)(1). And Texas crafted S.B. 8 to ensure that the threat of crippling liability would deter providers from taking their chances in court.

If an enforcement suit succeeds, S.B. 8 requires the court to award a bounty of "not less than" $10,000 in statutory damages for each abortion, plus costs, attorney's fees, and mandatory injunctive relief. Tex. Health & Safety Code § 171.208(b). The law raises the specter of retroactive liability by purporting to bar defendants from asserting reliance on precedent that was later "overruled." Id. § 171.208(e)(3). Its special venue rules encourage forum-shopping and suits in inconvenient locations. Id. § 171.210. And even if a provider defeats a suit on constitutional grounds, S.B. 8 limits the relief that success affords by barring "non-mutual issue preclusion or non-mutual claim preclusion." Id.

§ 171.208(e)(5). That means that even if a provider repeatedly prevails, she can be sued again and again by other plaintiffs -- even for the same abortion.

2. S.B. 8's architects have candidly acknowledged that the law was designed to deter constitutionally protected abortions while evading judicial review. App., infra, 51a. One of S.B. 8's principal proponents in the Texas Senate lauded the statute's "elegant use of the judicial system" and explained that its structure was intended to avoid the fate of other "heartbeat" bills that federal courts have held unconstitutional. Id. at 51a & n.34 (citations omitted); see C.A. App. 107, 111. And an attorney who helped draft the law described it as an effort to "counter the judiciary's constitutional pronouncements" on abortion. App., infra, 51a n.34 (citation omitted); see C.A. App. 116.

B. S.B. 8's Impact

S.B. 8 took effect on September 1, 2021. As the district court found, it virtually eliminated access to abortion in Texas after six weeks of pregnancy. App., infra, 77a. Indeed, the court observed that Texas could cite -- and the record revealed -- "only one case" of a post-cardiac-activity abortion being performed "in post-S.B. 8 Texas." Id. at 86a. And by banning abortions after roughly six weeks of pregnancy, S.B. 8 has blocked the vast majority of all abortions that would otherwise have been performed in the State. See id. at 85a (citing providers' statements that

S.B. 8 prohibits between 80% and 95% of all abortions previously provided in Texas).

Texans with sufficient means have traveled hundreds of miles to obtain abortions in other States -- often making multiple trips to comply with those States' abortion laws. App, infra, 94a; see id. at 87a-97a. As the district court found, the influx of patients from Texas has overwhelmed providers in Oklahoma, Kansas, Colorado, New Mexico, and as far away as Nevada. See id. at 91a-97a. Clinics in Oklahoma, for example, have been "forced to delay patients' abortions" for weeks "because of the volume of appointments needed." Id. at 91a (citation omitted); see id. at 91a n.72; see also id. at 97a. "And with the overlapping state regulation regimes, a delayed abortion can mean the difference between a medication abortion" and "a procedural abortion, if a patient is able to obtain an abortion at all." Id. at 94a; see id. at 94a n.79.

In addition, many Texans seeking abortions cannot travel to other States "for any number of reasons," including financial constraints; childcare, job, and school responsibilities; and "dangerous family situations." App., infra, 88a; see id. at 87a n.64, 88a n.66. As the district court found, women who cannot leave the State are being forced to "make a decision" about whether to have an abortion "before they are truly ready to do so." Id. at 84a (citation omitted). And if they do not learn they are

pregnant until after six weeks, women who cannot travel "are being forced to carry their pregnancy to term against their will or to seek ways to end their pregnancies on their own." Id. at 88a (citation omitted); see id. at 93a n.76.

C. The Whole Woman's Health Litigation

Before S.B. 8 took effect, abortion providers and patient advocates sued several state officials and an individual who had expressed an intent to bring S.B. 8 suits. The district court denied the state defendants' motion to dismiss. Whole Woman's Health v. Jackson, No. 21-cv-616, 2021 WL 3821062 (W.D. Tex. Aug. 25, 2021). After the defendants appealed, the Fifth Circuit stayed the district court's proceedings and rejected the plaintiffs' request for an injunction pending appeal. Whole Woman's Health v. Jackson, No. 21-5079, 2021 WL 3919252 (Aug. 29, 2021) (per curiam). The Fifth Circuit later explained that, in its view, the claims against state officials were barred by Texas's "Eleventh Amendment immunity." Whole Woman's Health v. Jackson, 13 F.4th 434, 438 (2021) (per curiam). The court acknowledged that state officials may be sued under Ex parte Young's exception to sovereign immunity, but it found that exception inapplicable because it concluded that the executive defendants had no role in enforcing S.B. 8 and that state judges and clerks are not proper defendants under Ex parte Young. Id. at 441-445.

Over the dissent of four Justices, this Court declined to grant an injunction or vacate the stay. Whole Woman's Health, 141 S. Ct. 2495. The Court explained that the private plaintiffs had "raised serious questions regarding the constitutionality of the Texas law," but it determined that they had not "carried their burden" as to "complex and novel antecedent procedural questions" resulting from the law's unprecedented design -- principally, whether the individual officials named in the lawsuit were proper defendants under Ex parte Young. Ibid.; see ibid. (noting that the sole private defendant had filed an affidavit disclaiming any present intent to enforce S.B. 8). The Court emphasized that its decision "in no way limit[ed] other procedurally proper challenges to the Texas law, including in Texas state courts." Id. at 2496. The plaintiffs in Whole Woman's Health have filed a petition for a writ of certiorari before judgment. Whole Woman's Health v. Jackson, No. 21-463 (filed Sept. 23, 2021).[2]

[2] To the government's knowledge, fourteen challenges to S.B. 8 have been filed in Texas courts. Although those cases were filed in August and early September, they were stayed pending a motion to transfer them to the State's multidistrict litigation court, which was recently granted. See Order, In re Texas Heartbeat Act Litigation, No. 21-782 (Tex. Multidistrict Litigation Panel Oct. 14, 2021). In addition, three individuals have filed S.B. 8 suits against a doctor who announced that he had performed a single prohibited abortion. See Stilley v. Braid, No. 2021CI19940 (Bexar County, 438th Judicial District); Gomez v. Braid, No. 2021CI19920 (Bexar County, 224th Judicial District); Texas Heartbeat Project v. Braid, No. 21-2276-C (Smith County, 241st Judicial District).

D. Proceedings Below

1. On September 9, 2021, the United States brought this suit against the State of Texas. On October 6, the district court granted the United States' motion for a preliminary injunction against S.B. 8's enforcement. App., infra, 2a-114a. The court explained that the United States has authority to bring this suit, id. at 25a-57a; that S.B. 8 plainly violates the Fourteenth Amendment and the doctrines of preemption and intergovernmental immunity, id. at 72a-105a; that a preliminary injunction was necessary to prevent irreparable harm, id. at 105a-108a; and that the balance of equities and the public interest favored an injunction, id. at 108a-109a. The preliminary injunction forbids "the State of Texas, including its officers, officials, agents, employees, and any other persons or entities acting on its behalf, * * * from enforcing [S.B. 8], including accepting or docketing, maintaining, hearing, resolving, awarding damages in, enforcing judgments in, enforcing any administrative penalties in, and administering any lawsuit brought pursuant to" the law. Id. at 110a. The district court declined to stay the injunction pending appeal. Id. at 113a.

2. Texas and the intervenor defendants-appellants (three individuals who seek to bring S.B. 8 enforcement suits) appealed and moved for a stay pending appeal. App., infra, 1a, 16a. On October 8 -- two days after the district court's order -- the Fifth

Circuit granted an administrative stay. Order 1. On October 14, a divided panel stayed the preliminary injunction pending an expedited appeal. App., infra, 1a. Although this suit is brought by the United States (rather than private plaintiffs) against the State of Texas (rather than individual state officials), the panel majority's single-sentence explanation for its decision simply invoked "the reasons stated in Whole Woman's Health v. Jackson, 13 F.4th 434 (5th Cir. 2021), and Whole Woman's Health v. Jackson, 141 S. Ct. 2494 (2021)." Ibid. Judge Stewart dissented. Ibid.

ARGUMENT

The United States respectfully requests that this Court vacate the Fifth Circuit's stay of the district court's preliminary injunction. "The well-established principles" that guide the determination whether "to stay a judgment entered below are equally applicable when considering an application to vacate a stay." Certain Named & Unnamed Non-Citizen Children & Their Parents v. Texas, 448 U.S. 1327, 1330 (1980) (Powell, J., in chambers); see Coleman v. Paccar Inc., 424 U.S. 1301, 1304 (1976) (Rehnquist, J., in chambers). In considering such an application, this Court has thus looked to the traditional "four-factor test" for a stay. Alabama Ass'n of Realtors v. HHS, 141 S. Ct. 2485, 2488 (2021) (per curiam). That test requires a court to consider: "(1) whether the stay applicant has made a strong showing that he is likely to succeed on the merits; (2) whether the applicant will be

irreparably injured absent a stay; (3) whether issuance of the stay will substantially injure the other parties interested in the proceeding; and (4) where the public interest lies." Nken v. Holder, 556 U.S. 418, 426 (2009) (citation omitted). Each of those factors strongly supports vacating the stay in this case.

I. The United States Is Likely To Succeed On The Merits

S.B. 8 is plainly unconstitutional under this Court's precedents. Texas has not seriously argued otherwise. Instead, the State has focused on purported procedural obstacles to judicial review. But this suit by the United States does not present the procedural questions at issue in the private plaintiffs' suit in Whole Woman's Health. And Texas's insistence that no party can bring a suit challenging S.B. 8 amounts to an assertion that the federal courts are powerless to halt the State's ongoing nullification of federal law. That proposition is as breathtaking as it is dangerous. S.B. 8 is "unprecedented," Whole Woman's Health v. Jackson, 141 S. Ct. 2494, 2496 (2021) (Roberts, C.J., dissenting), but other States are already regarding it as a model. App., infra, 112a. And if Texas is right, States are free to use similar schemes to nullify other precedents or suspend other constitutional rights. Our constitutional system does not permit States to so easily thwart the supremacy of federal law.

A. S.B. 8 Is Unconstitutional

The district court correctly held that the United States is likely to prevail on the merits of its two claims that S.B. 8 violates the Constitution.

1. In seeking a stay in the Fifth Circuit, Texas did not try to argue that S.B. 8 comports with this Court's precedents on abortion. With good reason: This Court has long recognized that the Constitution protects a pregnant woman's right "to have an abortion before viability and to obtain it without undue interference from the State," which until viability lacks "interests * * * strong enough to support a prohibition of abortion or the imposition of a substantial obstacle to the woman's effective right to elect the procedure." Planned Parenthood of Se. Pa. v. Casey, 505 U.S. 833, 846 (1992). Because S.B. 8 bans abortion several months before viability, it is unconstitutional without recourse to the undue-burden standard. Ibid.; see id. at 878-879 (plurality opinion); see also, e.g., Jackson Women's Health Org. v. Dobbs, 951 F.3d 246, 248 (5th Cir. 2020) (per curiam).

Even if the undue-burden test applied, S.B. 8 would fail it. By exposing abortion providers to crippling liability and thwarting pre-enforcement review, the law aims to deter them from providing constitutionally protected abortion care. See pp. 5-7, supra. And that is exactly what S.B. 8 has done. The resulting

near-total unavailability of abortion in Texas after six weeks of pregnancy -- before many women even realize they are pregnant -- is an undue burden by any measure. See Casey, 505 U.S. at 878 (plurality opinion).

That is true even though the statute purports to provide an "undue burden" defense. Tex. Health & Safety Code § 171.209(b); see Whole Woman's Health v. Jackson, 13 F.4th 434, 444 (5th Cir. 2021) (per curiam). That defense is a distorted shadow of the undue-burden standard mandated by this Court's precedents. Most obviously, it directly contradicts this Court's instruction that the undue-burden standard examines the cumulative real-world consequences of the challenged law. See, e.g., Whole Woman's Health v. Hellerstedt, 136 S. Ct. 2292, 2312-2318 (2016); Casey, 505 U.S. at 895; but see Texas Health & Safety Code § 171.209(b)(2) and (d)(2). And it is now indisputable that the theoretical availability of S.B. 8's "undue burden" defense has not actually prevented the law from achieving near-total deterrence of covered abortions. That result is manifestly an undue burden. And imposing that burden was the very purpose of S.B. 8 and its unprecedented scheme to thwart the traditional judicial mechanisms for ensuring the supremacy of federal law.

2. S.B. 8 also violates the doctrines of conflict preemption and intergovernmental immunity because it impairs the ability of federal agencies, contractors, and employees to carry

out their duties in a manner consistent with the Constitution and federal law. See, e.g., Arizona v. United States, 567 U.S. 387, 399 (2012) (conflict preemption); Trump v. Vance, 140 S. Ct. 2412, 2425 (2020) (intergovernmental immunity).

For example, the Bureau of Prisons must protect the rights of pregnant inmates by "arrang[ing] for an abortion to take place" if an inmate requests one. 28 C.F.R. 551.23(c). Other federal agencies have responsibilities that are also directly affected by S.B. 8. See App., infra, 26a-27a (discussing the United States Marshals Service, the Department of Defense, the Department of Health and Human Services, the Department of Labor, and the Office of Personnel Management). By imposing liability on anyone who aids or abets an abortion -- including in the case of a pregnancy resulting from rape or incest -- S.B. 8 threatens suits against federal employees and contractors for carrying out their duties under federal law. Id. at 26a; see id. at 101a-105a (rejecting the State's contrary arguments). It is thus preempted and contrary to principles of intergovernmental immunity, which apply even if a "federal function is carried out by a private contractor." Goodyear Atomic Corp. v. Miller, 486 U.S. 174, 181 (1988); see, e.g., United States v. California, 921 F.3d 865, 882 n.7 (9th Cir. 2019), cert. denied, 141 S. Ct. 124 (2020).

Texas has not denied that S.B. 8 suits against federal employees and contractors would violate intergovernmental

immunity. Instead, it has suggested that its courts might construe S.B. 8 not to apply to those federal actors. C.A. Stay Mot. 5. But S.B. 8's text contains no such exception. And even if state courts might construe it not to apply to the federal government or its contractors, S.B. 8 would still pose an obstacle to the federal government's operations: Because the law has essentially eliminated abortion in Texas after six weeks of pregnancy, federal employees and contractors who are required to facilitate abortion care cannot do so within the State. App., infra, 28a.

B. The Procedural Obstacles Identified In Whole Woman's Health Are Absent Here

The panel majority granted a stay solely "for the reasons stated in" the decisions of the Fifth Circuit and this Court in Whole Woman's Health, the private challenge to S.B. 8. App., infra, 1a. Those reasons have no application to this suit by the United States.

In Whole Woman's Health, the Fifth Circuit concluded that Texas executive officials, judges, and clerks were immune from suit under the Eleventh Amendment. 13 F.4th at 441-445. The court acknowledged that, under Ex parte Young, 209 U.S. 123 (1908), sovereign immunity does not prevent a court from ordering a state officer "not to enforce a state law that violates federal law." Id. at 442. But the Fifth Circuit concluded that Ex parte Young did not apply because the defendant executive officials did not enforce the law, and because the state judges and clerks were not subject to suit under Ex parte Young. Id. at 443. The court also determined that Section 1983 did

not authorize an injunction against state judges in these circumstances. Id. at 443-444.

This Court's decision rested on similar concerns about a suit against individual state officials. The Court explained that it was "unclear whether the named defendants in th[e] lawsuit can or will seek to enforce" S.B. 8, which created questions under Ex parte Young and Article III. 141 S. Ct. at 2495 (citing Clapper v. Amnesty Int'l USA, 568 U.S. 398, 409 (2013)). And the Court added that it was uncertain whether Ex parte Young authorizes "an injunction against state judges asked to decide a lawsuit" under S.B. 8. Ibid.

The concerns raised in Whole Woman's Health are wholly inapplicable in this suit by the United States against Texas itself. "In ratifying the Constitution, the States consented to suits brought by * * * the Federal Government." Alden v. Maine, 527 U.S. 706, 755 (1999). The district court thus correctly held that Texas's sovereign immunity poses no bar to this suit. Indeed, even Texas "d[id] not contend otherwise." App., infra, 59a. And because the United States can sue the State directly, this case likewise poses no question about which particular Texas officials would be proper defendants under Ex parte Young or Article III. Id. at 63a & n.40.

In short, the "reasons stated in Whole Woman's Health," App., infra, 1a, have no bearing on the validity of the preliminary injunction entered here. And the Fifth Circuit majority failed to

identify any other reasons justifying its stay of the injunction. That by itself provides sufficient reason to vacate the stay.

C. The District Court Properly Enjoined Enforcement of S.B. 8

Texas has argued that the United States lacks authority to bring this suit and that the scope of the preliminary injunction is improper. The Fifth Circuit did not rely on those contentions, and the district court correctly rejected them.

1. The United States Has Authority To Maintain This Suit

The United States has challenged S.B. 8 to vindicate two distinct sovereign interests. First, to the extent S.B. 8 interferes with the federal government's own activities, it is preempted and violates the doctrine of intergovernmental immunity. Second, S.B. 8 is an affront to the United States' sovereign interests in maintaining the supremacy of federal law and ensuring that the traditional mechanisms of judicial review endorsed by Congress and this Court remain available to challenge unconstitutional state laws. The United States has authority to seek equitable relief to vindicate both interests.

a. Courts have long recognized that even absent an express statutory cause of action, the United States may sue in equity to enjoin state statutes that interfere with the federal government's activities. See, e.g., Arizona, supra (preemption); California, 921 F.3d at 876-879 (intergovernmental immunity). The United

States' preemption and intergovernmental immunity claim falls squarely within that category.

b. The government also has authority to challenge S.B. 8 because the law's violation of the Fourteenth Amendment and the Supremacy Clause injures the United States' sovereign interests. In re Debs, 158 U.S. 564 (1895), is the canonical precedent recognizing that the federal government may, in appropriate circumstances, bring a suit in equity to vindicate such interests of the national government under the Constitution.

In Debs, the government sought an injunction against the Pullman rail strike. This Court explained that "[e]very government, entrusted, by the very terms of its being, with powers and duties to be exercised and discharged for the general welfare, has a right to apply to its own courts for any proper assistance in the exercise of the one and the discharge of the other." Id. at 584. The Court emphasized that "it is not the province of the government to interfere in any mere matter of private controversy between individuals." Id. at 586. But it explained that "whenever the wrongs complained of are such as affect the public at large, and are in respect of matters which by the Constitution are entrusted to the care of the Nation, and concerning which the Nation owes the duty to all the citizens of securing to them their common rights, then the mere fact that the government has no

pecuniary interest in the controversy is not sufficient to exclude it from the courts." Ibid.

In recognizing the United States' authority to sue in Debs, this Court noted the United States' proprietary interest in the mail carried by railroads, but expressly declined to "place [its] decision upon th[at] ground alone." 158 U.S. at 584. Nor did the Court rely solely upon the government's statutory authority over rail commerce. Rather, Debs reflects the "general rule that the United States may sue to protect its interests." Wyandotte Transp. Co. v. United States, 389 U.S. 191, 201 (1967). And this Court has recognized the government's authority -- even without an express statutory cause of action -- to seek equitable relief against threats to various sovereign interests. In addition to allowing challenges to state laws that conflict with federal law or otherwise hinder the federal government's activities (as discussed above), the Court has allowed federal suits to protect the public from fraudulent patents, United States v. American Bell Tel. Co., 128 U.S. 315 (1888); protect Indian tribes, Heckman v. United States, 224 U.S. 413, 438-439 (1912); and carry out the Nation's treaty obligations, Sanitary Dist. of Chicago v. United States, 266 U.S. 405, 426 (1925).[3]

[3] Texas has suggested (C.A. Reply Br. 4) that Sanitary District and Heckman "rested on statutory causes of action." That is incorrect. In Sanitary District, the Court explained that "[t]he Attorney General by virtue of his office may bring this proceeding and no statute is necessary to authorize the suit."

Here, too, the United States is suing to vindicate its distinct sovereign interests. Texas designed S.B. 8 to violate the Constitution, as interpreted by this Court, and to thwart judicial review -- both by forswearing enforcement by the State's executive officials, in an effort to avoid pre-enforcement review, and by designing S.B. 8 suits to frustrate post-enforcement review. The United States does not claim, and the district court did not recognize, authority to sue whenever a State enacts an unconstitutional law. App., infra, 49a-50a. If a state law is subject to judicial review through ordinary channels, there is no danger of constitutional nullification. But nullification is exactly what Texas intended and accomplished here. The United States has a sovereign interest in ensuring the supremacy of federal law by preventing a State from suspending a constitutional right within its borders.

The particular means by which Texas has accomplished that result also implicates the United States' sovereign interest in ensuring the effectiveness of the mechanisms for vindicating federal rights provided by Congress and recognized by this Court. In enacting Section 1983, Congress created "a uniquely federal remedy against incursions upon rights secured by the Constitution and laws of the Nation." Felder v. Casey, 487 U.S. 131, 139 (1988)

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266 U.S. at 426. And in Heckman, the Court merely noted the United States' statutory authority to sue in addition to its authority to sue in equity. See 224 U.S. at 439, 442.

(citation and ellipsis omitted). Section 1983 "interpose[s] the federal courts between the States and the people, as guardians of the people's federal rights." Mitchum v. Foster, 407 U.S. 225, 242 (1972). And by specifically authorizing a "suit in equity," 42 U.S.C. 1983, Congress sought to ensure that individuals "threatened" with a "deprivation of constitutional rights" would have "immediate access to the federal courts notwithstanding any provision of state law to the contrary." Patsy v. Board of Regents, 457 U.S. 496, 504 (1982) (citation omitted). S.B. 8 was designed to frustrate "[t]he 'general rule' * * * that plaintiffs may bring constitutional claims under § 1983" rather than being forced to assert their rights in state court. Knick v. Township of Scott, 139 S. Ct. 2162, 2172 (2019) (citation omitted); see id. at 2172-2173.

This Court has likewise recognized that the equitable cause of action recognized in Ex parte Young is "necessary to permit the federal courts to vindicate federal rights and hold state officials responsible to 'the supreme authority of the United States.'" Pennhurst State Sch. & Hosp. v. Halderman, 465 U.S. 89, 105 (1984) (citation omitted); accord Virginia Office for Protection and Advocacy v. Stewart, 563 U.S. 247, 254 (2011). Like Section 1983, Ex parte Young's cause of action ensures that individuals are "not * * * required to take" the risk of violating an unconstitutional

statute and "await[ing] proceedings" in state court. Ex parte Young, 209 U.S. at 165.

Texas has suggested that it has not frustrated judicial review because defendants in S.B. 8 suits could raise the statute's unconstitutionality as a defense. But that is no help for the women whose rights S.B. 8 most directly violates, because they cannot be defendants in S.B. 8 suits. And Texas designed S.B. 8 to ensure that such constitutional defenses will be infrequent (because S.B. 8 has so thoroughly chilled providers that few enforcement proceedings will be brought) and ineffective (because S.B. 8 limits the consequences of a successful constitutional defense to the particular plaintiff at issue).[4]

Indeed, S.B. 8's entire structure for its private enforcement suits manifests overt hostility to a defense based on this Court's decisions recognizing a constitutional right to abortion. See pp. 5-7, supra. Far from an effective means of judicial review, therefore, S.B. 8 suits are themselves an improper attempt to undermine federal rights: "States retain substantial leeway to establish the contours of their judicial systems," but "they lack authority to nullify a federal right or cause of action they

[4] For the same reason, S.B. 8 bears no resemblance to prior state laws that have conferred limited private rights of action on parties with a direct connection to a prohibited abortion. See, e.g., Nova Health Sys. v. Gandy, 416 F.3d 1149, 1152 (10th Cir. 2005) (describing an Oklahoma statute making abortion providers liable for certain medical costs resulting from an abortion performed on a minor without parental consent).

believe is inconsistent with their local policies." Haywood v. Drown, 556 U.S. 729, 736 (2009).

Texas has thus effectively suspended a federal constitutional right by thwarting the mechanisms of judicial review long recognized by Congress and this Court -- and by depriving the direct rightsholders (pregnant women) of any effective means of judicial review. Just as the United States could sue in Debs to eliminate a grave threat to its sovereign interest in the free flow of interstate commerce, it may sue here to eliminate S.B. 8's grave threat to the supremacy of federal law and the traditional mechanisms of judicial review.

The consequences of Texas's actions, moreover, are not confined to its own borders. Pervasive interference with access to abortion in one State affects "the availability of abortion-related services in the national market" by forcing women to travel to clinics in other States, burdening "the availability of abortion services" in neighboring jurisdictions. United States v. Bird, 124 F.3d 667, 678, 681 (5th Cir. 1997), cert. denied, 523 U.S. 1006 (1998). The district court found that S.B. 8 has had exactly that effect. For example, the court credited a declaration from a provider at two clinics in Oklahoma who stated that "since S.B. 8 took effect, we have seen an overall staggering 646% increase of Texan patients per day compared to the first six months of the year," with patients from Texas "taking up at least 50% (and on

some days nearly 75%) of the appointments we have available at our Oklahoma health centers." App., infra, 92a (quoting C.A. App. 199); see generally id. at 93a-97a (describing effects on clinics in Kansas, Colorado, New Mexico, and Nevada).

c. The United States' authority to bring suit to protect the sovereign interests threatened by S.B. 8 is well-grounded in equity. As this Court has explained, "[t]he ability to sue to enjoin unconstitutional actions by state * * * officers is the creation of courts of equity, and reflects a long history of judicial review of illegal executive action, tracing back to England." Armstrong v. Exceptional Child Ctr., Inc., 575 U.S. 320, 327 (2015). "'[S]uits to enjoin official conduct that conflicts with the federal Constitution are common,'" and "a cause of action routinely exists for such claims" -- not because it is implied "under the Constitution itself," but "as 'the creation of courts of equity.'" D.C. Ass'n of Chartered Public Sch. v. District of Columbia, 930 F.3d 487, 493 (D.C. Cir. 2019) (citations omitted). Indeed, in the last decade alone, the United States has brought numerous suits for equitable relief against States and localities to protect its sovereign interests, notwithstanding the absence of express statutory authority.[5]

[5] See, e.g., Arizona, supra; United States v. State Water Res. Control Bd., 988 F.3d 1194 (9th Cir. 2021); United States v. Washington, 971 F.3d 856 (9th Cir. 2020), as amended, 994 F.3d 994 (9th Cir. 2020), petition for cert. pending, No. 21-404 (filed Sept. 8, 2021); United States v. California, 921 F.3d 865, 876

Texas has asserted (e.g., C.A. Reply Br. 4) that the government's suit is inconsistent with Grupo Mexicano de Desarrollo S. A. v. Alliance Bond Fund, Inc., 527 U.S. 308 (1999). But Grupo Mexicano simply stands for the proposition that the equity jurisdiction of the federal courts does not authorize them to grant "a remedy" that was "historically unavailable from a court of equity." Id. at 333. Unlike the novel form of preliminary relief sought in Grupo Mexicano, the remedy the United States seeks here -- an injunction against enforcement of an unconstitutional statute -- falls squarely within the history and tradition of courts of equity. See Armstrong, 575 U.S. at 327.

Texas has also invoked lower-court decisions holding that the mere fact that a State has violated its citizens' Fourteenth Amendment rights does not authorize the United States to sue for an injunction. See, e.g., United States v. City of Philadelphia, 644 F.2d 187 (3d Cir. 1980); United States v. Mattson, 600 F.2d 1295 (9th Cir. 1979); United States v. Solomon, 563 F.2d 1121 (4th Cir. 1977). But again, this suit does not simply seek to enforce such rights; rather, it seeks to protect a distinct interest of the United States in preventing a State from nullifying federal law and evading Congress's direction in Section 1983, and this

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(9th Cir. 2019), cert. denied, 141 S. Ct. 124 (2020); United States v. Board of Cnty. Comm'rs, 843 F.3d 1208 (10th Cir. 2016), cert. denied, 138 S. Ct. 84 (2017); United States v. South Carolina, 720 F.3d 518, 524 (4th Cir. 2013); United States v. Alabama, 691 F.3d 1269, 1279 (11th Cir. 2012), cert. denied, 569 U.S. 968 (2013); United States v. City of Arcata, 629 F.3d 986, 988 (9th Cir. 2010).

Court's recognition in Ex parte Young, that injured individuals should be able to vindicate their federal constitutional rights in federal court. Texas's attempt to evade those traditional mechanisms of judicial review distinctly undermines the constitutional structure and distinctly harms the United States' sovereign interests. The district court's decision in this case was expressly limited to these "exceptional" circumstances. App., infra, 111a; see id. at 49a-50a. And because City of Philadelphia, Mattson, and Solomon involved no effort to frustrate other mechanisms for judicial review, the district court's reasoning in this case would not have authorized the suits in those cases.

For much the same reason, there is no merit to Texas's prior assertion (e.g., C.A. Stay Mot. 11-13) that Congress has displaced the United States' equitable cause of action by enacting Section 1983 and other express statutory mechanisms for vindicating constitutional rights. Whatever the force of that argument in other contexts, it is no help to Texas here. After all, the whole point of S.B. 8's unprecedented enforcement scheme is to thwart the express cause of action Congress provided in Section 1983. See Intervenors C.A. Reply Br. 3-4. In bringing this suit, the United States thus seeks to vindicate, not circumvent, Congress's judgment that state laws that prohibit the exercise of federal constitutional rights should be subject to suits for injunctive relief in federal court.

d. Finally, Texas has invoked Muskrat v. United States, 219 U.S. 346 (1911), to assert that there is no justiciable controversy here. Muskrat concerned a statute authorizing four individuals to sue the United States "to determine the validity" of an earlier statute broadening the class of Native Americans entitled to participate in an allotment of property. Id. at 350. This Court explained that the suit authorized by the statute amounted to an impermissible request for an advisory opinion, because the Court's judgment would have been "no more than an expression of opinion upon the validity of the acts in question." Id. at 362.

This case is entirely different. The United States seeks not an advisory opinion but an injunction barring enforcement of S.B. 8. And both the United States and Texas have genuine, adverse stakes in this controversy. As discussed above, S.B. 8 injures the United States' sovereign interests: Among other things, the statute nullifies federal law and frustrates Congress's enactment of Section 1983 for the enforcement of federal constitutional rights. And while Texas has attempted to delegate its enforcement powers to the citizenry at large, S.B. 8 plaintiffs do not seek to vindicate private rights through the courts; indeed, they need have no connection to the abortion at issue. Rather, S.B. 8 suits address an alleged public harm -- the provision of constitutionally

protected abortions that are inconsistent with Texas's preferred public policy.

2. The Relief Ordered By The District Court Was Proper

The district court properly enjoined "the State of Texas, including its officers, officials, agents, employees, and any other persons or entities acting on its behalf" from "maintaining, hearing, resolving, awarding damages in, enforcing judgments in, enforcing any administrative penalties in, and administering any lawsuit brought pursuant to" S.B. 8. App., infra, 110a.

a. S.B. 8 is a statute enacted by the Texas legislature, signed by the Texas governor, and enforceable in Texas courts. If Texas had not enacted S.B. 8, no private plaintiff could maintain the cause of action that it creates. And no plaintiff could maintain an S.B. 8 cause of action or recover the statutory damages it authorizes without action by the Texas courts. It is, in short, plain that Texas is responsible for the constitutional violations caused by S.B. 8. It should be equally plain that where, as here, the State's sovereign immunity does not apply, Texas can be enjoined to prevent those violations.

Everything after that is just a question of how best to craft the injunction -- that is, which state actors should be covered by an injunction against the State, and what specific conduct the injunction should prohibit or require. Those remedial questions should not distract from the core point: It was proper for the

district court to enjoin the State to halt its ongoing constitutional violations. And having chosen a supremely unusual means of enforcing its unconstitutional law, Texas should bear the obligation to identify an alternative form of injunctive relief if it is dissatisfied with the particular mechanism adopted by the district court.

Texas has steadfastly refused to propose such an alternative. That refusal gives the game away. Texas's objection is, at bottom, not to the particular structure of the district court's preliminary injunction, but to any injunction that would halt S.B. 8's ongoing nullification of the Constitution as interpreted by this Court. Indeed, that is why the State structured its statute in this unique manner to begin with. The implications of Texas's position are startling: If, as Texas insists, courts cannot enjoin the State itself, or individual state officers, or private parties who actually bring S.B. 8 suits, then a State could effectively nullify any constitutional decision of this Court with which it disagreed by enacting a sufficiently punitive statutory scheme and delegating its enforcement to the public at large.

A State might, for example, ban the possession of handguns in the home, contra District of Columbia v. Heller, 554 U.S. 570 (2008), or prohibit independent corporate campaign advertising, contra Citizens United v. FEC, 558 U.S. 310 (2010), and deputize its citizens to seek large bounties for each firearm or

advertisement. Those statutes, too, would violate the Constitution as interpreted by this Court. But under Texas's theory, they could be enforced without prior judicial review, chilling the protected activity -- and the effect of any successful constitutional defense in an enforcement proceeding could be limited to that proceeding alone. The district court correctly determined that the State's ingenuity does not permit it to nullify constitutional rights in that manner.

b. In any event, each aspect of the district court's injunction was an appropriate response to S.B. 8's unprecedented enforcement scheme.

First, the district court properly specified that the injunction against the State prevents state judges and court clerks from accepting or deciding S.B. 8 suits. This Court has held that "judicial immunity is not a bar to prospective injunctive relief against a judicial officer acting in her judicial capacity." Pulliam v. Allen, 466 U.S. 522, 541-542 (1984). And although Section 1983 permits injunctions against judicial officers only in specific circumstances, see Whole Woman's Health, 13 F.4th at 444, this suit by the United States is not based on Section 1983.

To be sure, injunctions that run to state judges are unusual. But that is because other forms of relief are typically more appropriate -- most obviously, a plaintiff can ordinarily secure an injunction binding "the enforcement official authorized to

bring suit under the statute." In re Justices of the Supreme Court of Puerto Rico, 695 F.2d 17, 21 (1st Cir. 1982) (Breyer, J.); see Ex parte Young, 209 U.S. at 163. Here, Texas has deliberately sought to thwart that ordinary remedy. Especially where other remedies are not available, injunctions that bind state judicial officials have long been permitted. The Anti-Injunction Act, for example, expressly contemplates that federal courts may "grant an injunction to stay proceedings in a State court." 28 U.S.C. 2283. And the Act's limits on those injunctions do not apply where, as here, the suit is brought by the United States. See Leiter Minerals, Inc. v. United States, 352 U.S. 220, 226 (1957).

Second, the district court properly barred state executive officials from "enforcing judgments in" S.B. 8 suits. App., infra, 110a. While S.B. 8 relies on private citizens to bring enforcement actions, state executive officials (including "sheriff[s]," "constable[s]," and "county clerk[s]") may enforce the resulting state-court judgments. Tex. R. Civ. P. 622; Tex. Prop. Code Ann. § 52.004. And although the Fifth Circuit concluded in Whole Woman's Health that other state executive officials do not enforce S.B. 8, that suit did not involve the officials who would enforce the judgments in S.B. 8 suits. See 13 F.4th at 439 n.2, 443-444.

Third, the district court correctly determined that an injunction against Texas could bind private plaintiffs who maintain S.B. 8 suits, because by filing suit those individuals

both "act on behalf of the State" and "act in active concert with the State." App., infra, 110a; see id. at 67a-72a. Under Federal Rule of Civil Procedure 65, an injunction binds not only the parties, but also their "officers, agents, servants, employees, and attorneys" and "other persons who are in active concert or participation with" them. Fed. R. Civ. P. 65(d)(2)(B) and (C). Here, the court stated that it "need not craft an injunction that runs to the future actions of private individuals per se." App., infra, 110a. But the court explained that "those private individuals' actions are proscribed to the extent their attempts to bring a civil action under [S.B. 8] would necessitate state action that [the injunction] prohibited." Ibid.

II. The Balance Of Equities Favors Vacating The Stay

The court of appeals did not address the balance of harms to the parties or whether the public interest favored staying the district court's injunction. See App., infra, 1a. To the contrary, it relied exclusively on the Whole Woman's Health decisions, which in turn relied solely on procedural issues related to the private plaintiffs' "likelihood of success" on the merits. 13 F.4th at 441; see 141 S. Ct. at 2495-2496. But the balance of the equities strongly supports vacating the stay and restoring "the status quo ante -- before the law went into effect -- so that the courts may consider whether a state can avoid responsibility

for its laws" in the manner Texas has attempted here. Whole Woman's Health, 141 S. Ct. at 2496 (Roberts, C.J., dissenting).

1. To begin, Texas is poorly positioned to assert irreparable injury from an injunction against the enforcement of S.B. 8. Throughout this case (and all other S.B. 8 litigation), the State has labored to distance itself from the law. If Texas is to believed, the State has no responsibility for S.B. 8 or its operation. And because Texas disclaims accountability for S.B. 8, it likewise has no basis for complaint if the law's enforcement is preliminarily enjoined.

Even more fundamentally, a State suffers no cognizable injury -- much less irreparable harm -- from an injunction against enforcement of a plainly unconstitutional statute. Put simply, there is "no harm" from the "nonenforcement of invalid legislation." United States v. Alabama, 691 F.3d 1269, 1301 (11th Cir. 2012), cert. denied, 569 U.S. 968 (2013).

2. By contrast, the Fifth Circuit's stay gravely injures the United States and the public interest. See Nken, 556 U.S. at 435 (recognizing that these interests "merge" in a case involving the federal government). Both the United States and the public have a manifest interest in "preventing a violation of the Supremacy Clause." United States v. California, 921 F.3d 865, 893 (9th Cir. 2019), cert. denied, 141 S. Ct. 124 (2020). And the stay prolongs not only S.B. 8's affront to the supremacy of federal

law, but also its disruption of judicial review through the channels this Court and Congress have identified as essential for the vindication of federal constitutional rights. Vacating the stay would serve the United States' overriding sovereign interest and the public interest in ensuring that all States honor the federal Constitution and the controlling precedent of this Court -- and that they do not seek to insulate unconstitutional laws from the framework of judicial review established by Section 1983 and Ex parte Young.

S.B. 8's practical consequences likewise overwhelmingly favor a preliminary injunction. The district court's findings document those consequences in detail. App., infra, 75a-98a & nn.44-87. Women with sufficient means are being forced to travel to other States to obtain pre-viability abortion care -- causing chaos and backlogs at clinics in other States, and delaying abortions by weeks. Id. at 87a-97a. Women who lack the ability to leave the State are forced to "make a decision" about whether to have an abortion "before they are truly ready to do so"; to carry unwanted pregnancies to term; or to "seek to terminate their pregnancies outside the medical system," "with potentially devastating consequences." Id. at 84a, 93a n.76, 106a (citations omitted). And "[i]f the law remains in effect for an extended period," providers in Texas may be forced to "shutter [their] doors" altogether and may be unable to reopen even if S.B. 8 is ultimately

struck down. Id. at 108a; see id. at 8a. These consequences confirm the district court's determination that the balance of equities strongly favors a preliminary injunction.

III. The Court May Treat This Application As A Petition For A Writ Of Certiorari Before Judgment

For the foregoing reasons, this Court should vacate the Fifth Circuit's stay, put a stop to Texas's ongoing nullification of the Court's precedents, and restore the status quo while this litigation proceeds. In addition, the Court may construe this application as a petition for a writ of certiorari before judgment, grant the petition, and set the case for briefing and argument this Term. Cf. Nken v. Mukasey, 555 U.S. 1042 (2008) (treating a stay application as a petition for a writ of certiorari before judgment).[6]

A petition for a writ of certiorari before judgment under 28 U.S.C. 2101(e) is an extraordinary remedy, but the issues presented by Texas's extraordinary law are "of such imperative public importance as to justify deviation from normal appellate practice and to require immediate determination in this Court."

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[6] See, e.g., Purcell v. Gonzalez, 549 U.S. 1, 2 (2006) (per curiam) (same); see also High Plains Harvest Church v. Polis, 141 S. Ct. 527 (2020) (same for an application for an injunction); Trump v. Mazars USA, LLP, 140 S. Ct. 660 (2019) (treating an application as a petition for a writ of certiorari). A petition for a writ of certiorari before judgment "may be initiated by any party, aggrieved or not by the district court decree." Stephen M. Shapiro et al., Supreme Court Practice § 2.2, at 2-12 (11th ed. 2019).

Sup. Ct. R. 11. The fundamental question presented in this case is whether States may nullify disfavored constitutional rights by purporting to disclaim their own enforcement authority and delegating enforcement of unconstitutional laws to private bounty hunters. S.B. 8's use of that scheme has already allowed Texas to nullify this Court's precedents for six weeks. That state of affairs should not be allowed to persist -- or spread to other States or other rights -- without this Court's review.

Absent certiorari before judgment, however, this Court likely could not hear the case this Term: The Fifth Circuit will not hear oral argument in this case and in Whole Woman's Health until early December, see C.A. Order (Oct. 15, 2021), and there is no guarantee when it will rule. The private plaintiffs in Whole Woman's Health have already sought certiorari before judgment. Whole Woman's Health v. Jackson, No. 21-463 (filed Sept. 23, 2021). And certiorari before judgment would allow this Court to "promptly" consider the constitutionality of S.B. 8's abortion ban and the propriety of its novel procedural scheme "after full briefing and oral argument." Whole Woman's Health, 141 S. Ct. at 2496 (Roberts, C.J., dissenting).

CONCLUSION

The stay of the district court's preliminary injunction should be vacated and the injunction restored pending disposition of the appeal in the Fifth Circuit and, if that court reverses the

injunction, pending the filing and disposition of a petition for a writ of certiorari and any further proceedings in this Court. In addition, the Court may construe this application as a petition for a writ of certiorari before judgment, grant the petition, and set the case for briefing and argument this Term.

Respectfully submitted.

BRIAN H. FLETCHER
Acting Solicitor General

OCTOBER 2021

Exhibit C

Remarks by President Biden on Fighting the COVID-19 Pandemic

SEPTEMBER 09, 2021 • SPEECHES AND REMARKS

5:02 P.M. EDT

THE PRESIDENT: Good evening, my fellow Americans. I want to talk to you about where we are in the battle against COVID-19, the progress we've made, and the work we have left to do.

And it starts with understanding this: Even as the Delta variant 19 [sic] has — COVID-19 — has been hitting this country hard, we have the tools to combat the virus, if we can come together as a country and use those tools.

If we raise our vaccination rate, protect ourselves and others with masking and expanded testing, and identify people who are infected, we can and we will turn the tide on COVID-19.

It will take a lot of hard work, and it's going to take some time. Many of us are frustrated with the nearly 80 million Americans who are still not vaccinated, even though the vaccine is safe, effective, and free.

You might be confused about what is true and what is false about COVID-19. So before I outline the new steps to fight COVID-19 that I'm going to be announcing tonight, let me give you some clear information about where we stand.

First, we have cons- — we have made considerable progress in battling COVID-19. When I became President, about 2 million Americans were fully vaccinated. Today, over 175 million Americans have that protection.

Before I took office, we hadn't ordered enough vaccine for every American. Just weeks in office, we did. The week before I took office, on January 20th of this year, over 25,000 Americans died that week from COVID-19. Last week, that grim weekly toll was down 70 percent.

And in the three months before I took office, our economy was faltering, creating just 50,000 jobs a month. We're now averaging 700,000 new jobs a month in the past three months.

This progress is real. But while America is in much better shape than it was seven months ago when I took office, I need to tell you a second fact.

We're in a tough stretch, and it could last for a while. The highly contagious Delta variant that I began to warn America about back in July spread in late summer like it did in other countries before us.

While the vaccines provide strong protections for the vaccinated, we read about, we hear about, and we see the stories of hospitalized people, people on their death beds, among the unvaccinated over these past few weeks.

This is a pandemic of the unvaccinated. And it's caused by the fact that despite America having an unprecedented and 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.

And to make matters worse, there are elected officials actively working to undermine the fight against COVID-19. Instead of encouraging people to get vaccinated and mask up, they're ordering mobile morgues for the unvaccinated dying from COVID in their communities. This is totally unacceptable.

Third, if you wonder how all this adds up, here's the math: The vast majority of Americans are doing the right thing. Nearly three quarters of the eligible have gotten at least one shot, but one quarter has not gotten any. That's nearly 80 million Americans not vaccinated. And in a country as large as ours, that's 25 percent minority. That 25 percent can cause a lot of damage — and they are.

The unvaccinated overcrowd our hospitals, are overrunning the emergency rooms and intensive care units, leaving no room for someone with a heart attack, or ~~pancreitis~~ [pancreatitis], or cancer.

And fourth, I want to emphasize that the vaccines provide very strong protection from severe illness from COVID-19. I know there's a lot of confusion and misinformation. But the world's leading scientists confirm that if you are fully vaccinated, your risk of severe illness from COVID-19 is very low.

In fact, based on available data from the summer, only one of out of every 160,000 fully vaccinated Americans was hospitalized for COVID per day.

These are the facts.

So here's where we stand: The path ahead, even with the Delta variant, is not nearly as bad as last winter. But what makes it incredibly more frustrating is that we have the tools to combat COVID-19, and a distinct minority of Americans –supported by a distinct minority of elected officials — are keeping us from turning the corner. These pandemic politics, as I refer to, are making people sick, causing unvaccinated people to die.

We cannot allow these actions to stand in the way of protecting the large majority of Americans who have done their part and want to get back to life as normal.

As your President, I'm announcing tonight a new plan to require more Americans to be vaccinated, to combat those blocking public health.

My plan also increases testing, protects our economy, and will make our kids safer in schools. It consists of six broad areas of action and many specific measures in each that — and each of those actions that you can read more about at WhiteHouse.gov. WhiteHouse.gov.

The measures — these are going to take time to have full impact. But if we implement them, I believe and the scientists indicate, that in the months ahead we can reduce the number of unvaccinated Americans, decrease hospitalizations and deaths, and allow our children to go to school safely and keep our economy strong by keeping businesses open.

First, we must increase vaccinations among the unvaccinated with new vaccination requirements. Of the nearly 80 million eligible Americans who have not gotten vaccinated, many said they were waiting for approval from the Food and Drug Administration — the FDA. Well, last month, the FDA granted that approval.

So, the time for waiting is over. This summer, we made progress through the combination of vaccine requirements and incentives, as well as the FDA approval. Four million more people got their first shot in August than they did in July.

But we need to do more. This is not about freedom or personal choice. It's about protecting yourself and those around you — the people you work with, the people you care about, the people you love.

My job as President is to protect all Americans.

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.

Some of the biggest companies are already requiring this. United Airlines

Some of the biggest companies are already requiring this: United Airlines, Disney, Tysons Food, and even Fox News.

The bottom line: We're going to protect vaccinated workers from unvaccinated co-workers. We're going to reduce the spread of COVID-19 by increasing the share of the workforce that is vaccinated in businesses all across America.

My plan will extend the vaccination requirements that I previously issued in the healthcare field. Already, I've announced, we'll be requiring vaccinations that all nursing home workers who treat patients on Medicare and Medicaid, because I have that federal authority.

Tonight, I'm using that same authority to expand that to cover those who work in hospitals, home healthcare facilities, or other medical facilities -- a total of 17 million healthcare workers.

If you're seeking care at a health facility, you should be able to know that the people treating you are vaccinated. Simple. Straightforward. Period.

Next, I will sign an executive order that will now require all executive branch federal employees to be vaccinated — all. And I've signed another executive order that will require federal contractors to do the same.

If you want to work with the federal government and do business with us, get vaccinated. If you want to do business with the federal government, vaccinate your workforce.

And tonight, I'm removing one of the last remaining obstacles that make it difficult for you to get vaccinated.

The Department of Labor will require employers with 100 or more workers to give those workers paid time off to get vaccinated. No one should lose pay in order to get vaccinated or take a loved one to get vaccinated.

Today, in total, the vaccine requirements in my plan will affect about 100 million Americans -- two thirds of all workers.

And for other sectors, I issue this appeal: To those of you running large entertainment venues — from sports arenas to concert venues to movie theaters — please require folks to get vaccinated or show a negative test as a condition of entry.

And to the nation's family physicians, pediatricians, GPs — general practitioners -- you're the most trusted medical voice to your patients. You may be the one person who can get someone to change their mind about being vaccinated.

Tonight, I'm asking each of you to reach out to your unvaccinated patients over the next two weeks and make a personal appeal to them to get the shot. America needs your personal involvement in this critical effort.

And my message to unvaccinated Americans is this: What more is there to wait for? What more do you need to see? 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. But just don't take it from me; listen to the voices of unvaccinated Americans who are lying in hospital beds, taking their final breaths, saying, "If only I had gotten vaccinated." "If only."

It's a tragedy. Please don't let it become yours.

The second piece of my plan is continuing to protect the vaccinated.

For the vast majority of you who have gotten vaccinated, I understand your anger at those who haven't gotten vaccinated. I understand the anxiety about

anger at those who haven't gotten vaccinated. I understand the anxiety about getting a "breakthrough" case.

But as the science makes clear, if you're fully vaccinated, you're highly protected from severe illness, even if you get COVID-19.

In fact, recent data indicates there is only one confirmed positive case per 5,000 fully vaccinated Americans per day.

You're as safe as possible, and we're doing everything we can to keep it that way — keep it that way, keep you safe.

That's where boosters come in — the shots that give you even more protection than after your second shot.

Now, I know there's been some confusion about boosters. So, let me be clear: Last month, our top government doctors announced an initial plan for booster shots for vaccinated Americans. They believe that a booster is likely to provide the highest level of protection yet.

Of course, the decision of which booster shots to give, when to start them, and who will give them, will be left completely to the scientists at the FDA and the Centers for Disease Control.

But while we wait, we've done our part. We've bought enough boosters — enough booster shots — and the distribution system is ready to administer them.

As soon as they are authorized, those eligible will be able to get a booster right away in tens of thousands of site across the — sites across the country for most Americans, at your nearby drug store, and for free.

The third piece of my plan is keeping — and maybe the most important — is keeping our children safe and our schools open. For any parent, it doesn't matter how low the risk of any illness or accident is when it comes to your

child or grandchild. Trust me, I know.

So, let me speak to you directly. Let me speak to you directly to help ease some of your worries.

It comes down to two separate categories: children ages 12 and older who are eligible for a vaccine now, and children ages 11 and under who are not are yet eligible.

The safest thing for your child 12 and older is to get them vaccinated. They get vaccinated for a lot of things. That's it. Get them vaccinated.

As with adults, almost all the serious COVID-19 cases we're seeing among adolescents are in unvaccinated 12- to 17-year-olds — an age group that lags behind in vaccination rates.

So, parents, please get your teenager vaccinated.

What about children under the age of 12 who can't get vaccinated yet? Well, the best way for a parent to protect their child under the age of 12 starts at home. Every parent, every teen sibling, every caregiver around them should be vaccinated.

Children have four times higher chance of getting hospitalized if they live in a state with low vaccination rates rather than the states with high vaccination rates.

Now, if you're a parent of a young child, you're wondering when will it be — when will it be — the vaccine available for them. I strongly support an independent scientific review for vaccine uses for children under 12. We can't take shortcuts with that scientific work.

But I've made it clear I will do everything within my power to support the FDA with any resource it needs to continue to do this as safely and as quickly as possible, and our nation's top doctors are committed to keeping the public

at large updated on the process so parents can plan.

Now to the schools. We know that if schools follow the science and implement the safety measures — like testing, masking, adequate ventilation systems that we provided the money for, social distancing, and vaccinations — then children can be safe from COVID-19 in schools.

Today, about 90 percent of school staff and teachers are vaccinated. We should get that to 100 percent. My administration has already acquired teachers at the schools run by the Defense Department — because I have the authority as President in the federal system — the Defense Department and the Interior Department — to get vaccinated. That's authority I possess.

Tonight, I'm announcing that we'll require all of nearly 300,000 educators in the federal paid program, Head Start program, must be vaccinated as well to protect your youngest — our youngest — most precious Americans and give parents the comfort.

And tonight, I'm calling on all governors to require vaccination for all teachers and staff. Some already have done so, but we need more to step up.

Vaccination requirements in schools are nothing new. They work. They're overwhelmingly supported by educators and their unions. And to all school officials trying to do the right thing by our children: I'll always be on your side.

Let me be blunt. My plan also takes on elected officials and states that are undermining you and these lifesaving actions. Right now, local school officials are trying to keep children safe in a pandemic while their governor picks a fight with them and even threatens their salaries or their jobs. Talk about bullying in schools. If they'll not help — if these governors won't help us beat the pandemic, I'll use my power as President to get them out of the way.

The Department of Education has already begun to take legal action against

states undermining protection that local school officials have ordered. Any teacher or school official whose pay is withheld for doing the right thing, we will have that pay restored by the federal government 100 percent. I promise you I will have your back.

The fourth piece of my plan is increasing testing and masking. From the start, America has failed to do enough COVID-19 testing. In order to better detect and control the Delta variant, I'm taking steps tonight to make testing more available, more affordable, and more convenient. I'll use the Defense Production Act to increase production of rapid tests, including those that you can use at home.

While that production is ramping up, my administration has worked with top retailers, like Walmart, Amazon, and Kroger's, and tonight we're announcing that, no later than next week, each of these outlets will start to sell at-home rapid test kits at cost for the next three months. This is an immediate price reduction for at-home test kits for up to 35 percent reduction.

We'll also expand — expand free testing at 10,000 pharmacies around the country. And we'll commit — we're committing $2 billion to purchase nearly 300 million rapid tests for distribution to community health centers, food banks, schools, so that every American, no matter their income, can access free and convenient tests. This is important to everyone, particularly for a parent or a child — with a child not old enough to be vaccinated. You'll be able to test them at home and test those around them.

In addition to testing, we know masking helps stop the spread of COVID-19. That's why when I came into office, I required masks for all federal buildings and on federal lands, on airlines, and other modes of transportation.

Today — tonight, I'm announcing that the Transportation Safety Administration — the TSA — will double the fines on travelers that refuse to mask. If you break the rules, be prepared to pay.

And, by the way, show some respect. The anger you see on television toward

flight attendants and others doing their job is wrong; it's ugly.

The fifth piece of my plan is protecting our economic recovery. Because of our vaccination program and the American Rescue Plan, which we passed early in my administration, we've had record job creation for a new administration, economic growth unmatched in 40 years. We cannot let unvaccinated do this progress — undo it, turn it back.

So tonight, I'm announcing additional steps to strengthen our economic recovery. We'll be expanding COVID-19 Economic Injury Disaster Loan programs. That's a program that's going to allow small businesses to borrow up to $2 million from the current $500,000 to keep going if COVID-19 impacts on their sales.

These low-interest, long-term loans require no repayment for two years and be can used to hire and retain workers, purchase inventory, or even pay down higher cost debt racked up since the pandemic began. I'll also be taking additional steps to help small businesses stay afloat during the pandemic.

Sixth, we're going to continue to improve the care of those who do get COVID-19. In early July, I announced the deployment of surge response teams. These are teams comprised of experts from the Department of Health and Human Services, the CDC, the Defense Department, and the Federal Emergency Management Agency — FEMA — to areas in the country that need help to stem the spread of COVID-19.

Since then, the federal government has deployed nearly 1,000 staff, including doctors, nurses, paramedics, into 18 states. Today, I'm announcing that the Defense Department will double the number of military health teams that they'll deploy to help their fellow Americans in hospitals around the country.

Additionally, we're increasing the availability of new medicines recommended by real doctors, not conspir- — conspiracy theorists. The monoclonal antibody treatments have been shown to reduce the risk of hospitalization by up to 70 percent for unvaccinated people at risk of developing safe — severe

up to 70 percent for unvaccinated people at risk of developing sele- — severe disease.

We've already distributed 1.4 million courses of these treatments to save lives and reduce the strain on hospitals. Tonight, I'm announcing we will increase the average pace of shipment across the country of free monoclonal antibody treatments by another 50 percent.

Before I close, let me say this: Communities of color are disproportionately impacted by this virus. And as we continue to battle COVID-19, we will ensure that equity continues to be at the center of our response. We'll ensure that everyone is reached. My first responsibility as President is to protect the American people and make sure we have enough vaccine for every American, including enough boosters for every American who's approved to get one.

We also know this virus transcends borders. That's why, even as we execute this plan at home, we need to continue fighting the virus overseas, continue to be the arsenal of vaccines.

We're proud to have donated nearly 140 million vaccines over 90 countries, more than all other countries combined, including Europe, China, and Russia combined. That's American leadership on a global stage, and that's just the beginning.

We've also now started to ship another 500 million COVID vaccines — Pfizer vaccines — purchased to donate to 100 lower-income countries in need of vaccines. And I'll be announcing additional steps to help the rest of the world later this month.

As I recently released the key parts of my pandemic preparedness plan so that America isn't caught flat-footed when a new pandemic comes again — as it will — next month, I'm also going to release the plan in greater detail.

So let me close with this: We have so- — we've made so much progress during the past seven months of this pandemic. The recent increases in vaccinations

in August already are having an impact in some states where case counts are dropping in recent days. Even so, we remain at a critical moment, a critical time. We have the tools. Now we just have to finish the job with truth, with science, with confidence, and together as one nation.

Look, we're the United States of America. There's nothing — not a single thing — we're unable to do if we do it together. So let's stay together.

God bless you all and all those who continue to serve on the frontlines of this pandemic. And may God protect our troops.

Get vaccinated.

5:28 P.M. EDT

Exhibit D

PATH OUT OF THE PANDEMIC

PRESIDENT BIDEN'S COVID-19 ACTION PLAN

President Biden is implementing a six-pronged, comprehensive national strategy that employs the same science-based approach that was used to successfully combat previous variants of COVID-19 earlier this year. This plan will ensure that we are using every available tool to combat COVID-19 and save even more lives in the months ahead, while also keeping schools open and safe, and protecting our economy from lockdowns and damage.

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inated

Keeping Schools Safely Open

Increasing Testing & Requiring Masking

Protect
Economic

Vaccinating the Unvaccinated

Since January, the Administration has taken actions to make vaccination conveniently available to all. COVID vaccines have been available to every

individual age 16 and older since April 19th and to those age 12 and older since May. The Administration took steps to make vaccines available at over 80,000 locations nationwide, worked with pharmacies to offer walk-in appointments, and put out a call to action to businesses and organizations across the nation.

The President announced vaccination requirements for the federal government in July and called on the private sector to do more to encourage vaccination as well. Since that time, employers, schools, nursing homes, restaurants, hospitals, and cities in all 50 states have announced new vaccination requirements. Since July, the share of job postings that require vaccination are up 90%. And we know these requirements work. At the beginning of August, when Tyson Foods announced its requirement—only 45% of its workforce had gotten a shot. Today, it stands at 72%, meaning half of Tyson's unvaccinated workers have now gotten a shot—well ahead of the company's November 1st deadline. After United Airlines announced its vaccination requirement, more than half of its unvaccinated employees went out and got vaccinated with weeks left to go before the deadline. In Washington State, the weekly vaccination rate jumped 34% after the Governor announced requirements for state workers.

All told, these efforts—and countless other Administration initiatives and policies—have resulted in over 175 million fully vaccinated Americans. But there are still nearly 80 million Americans eligible to be vaccinated who have not yet gotten their first shot.

The President's plan will reduce the number of unvaccinated Americans by using regulatory powers and other actions to substantially increase the number of Americans covered by vaccination requirements—these requirements will become dominant in the workplace. In addition, the plan will provide paid time off for vaccination for most workers in the country.

Requiring All Employers with 100+ Employees to Ensure their Workers are Vaccinated or Tested Weekly

Requiring Vaccinations for all Federal Workers and for Millions of Contractors that Do Business with the Federal Government

Requiring COVID-19 Vaccinations for Over 17 Million Health Care Workers at Medicare and Medicaid Participating Hospitals and Other Health Care Settings

Calling on Large Entertainment Venues to Require Proof of Vaccination or Testing for Entry

Requiring Employers to Provide Paid Time Off to Get Vaccinated

Further Protecting the Vaccinated

There are over 175 million fully vaccinated Americans who are largely protected from severe illness from COVID-19. While so-called "breakthrough infections" among this group do happen, they remain the exception: In fact, recent data indicates there is only 1 confirmed positive case per 5,000 fully vaccinated Americans per week.

But COVID-19 vaccination protection can be made even stronger. In August, the nation's top health officials—Dr. Rochelle Walensky, CDC Director; Dr. Janet Woodcock, Acting FDA Commissioner; Dr. Francis Collins, NIH Director; Dr. Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases; Surgeon General Dr. Vivek Murthy; Dr. David Kessler, COVID-19 Chief Science Officer; Dr. Rachel Levine, HHS Assistant Secretary for Health; and Dr. Marcella Nunez-Smith, Chair of the COVID-19 Health Equity Task Force—released an initial plan for booster shots aimed at staying ahead of the virus. The plan released by our nation's doctors allows for states,

pharmacies, doctors' offices, health insurers and others to prepare for the administration of boosters. In the beginning weeks of the initial vaccination program in December 2020, the country lost precious time because we were unprepared to administer shots. By planning now, we will be able to quickly get booster shots into the arms of eligible Americans once approved.

A booster promises to give Americans their highest level of protection yet. Three-shot vaccines are common (Hepatitis B, Tetanus) and offer some of the most durable and robust protection.

Implementation of this plan depends on authorization of boosters by the Food and Drug Administration (FDA) and recommendations by the CDC's independent Advisory Committee on Immunization Practices (ACIP). As soon as authorizations are given, the Administration will be prepared to offer booster shots, starting the week of September 20th.

Providing Easy Access to Booster Shots for All Eligible Americans

Ensuring Americans Know Where to Get a Booster

Keeping Schools Safely Open

A top priority for the Biden Administration since Day One has been to reopen schools safely and keep them open. The Administration has taken significant actions to get our kids back in the classroom, including providing $130 billion in American Rescue Plan (ARP) funds to help schools reopen, accelerate students' academic growth, address inequities exacerbated by the pandemic, allow local school districts to implement CDC-recommended COVID-19 prevention strategies, and support student and educators' social, emotional,

and mental health needs. We know how to keep students safe in schools by taking the right steps to prevent transmission—including getting all staff and eligible students vaccinated, implementing universal indoor masking, maintaining physical distancing, improving ventilation, and performing regular screening testing for students and school staff. The President's plan calls for additional actions to ensure all schools consistently implement these science-based prevention strategies recommended by the CDC so that they can remain open for in-person learning and maintain the health and safety of all students, staff, and families.

As we work to ensure our children are protected, we know that vaccination remains the best line of defense against COVID-19. For those adolescents aged 12 and above who are eligible for vaccination, the most important step parents can take is to get them vaccinated. To date, over half of the nation's adolescents have been vaccinated. For those too young to be vaccinated, it is especially critical that they are surrounded by vaccinated people and mask in public indoor spaces, including schools. Studies released by the CDC found that the rate of hospitalization for children was nearly four times higher in states with the lowest vaccination rates compared to states with high vaccination rates.

The FDA is undergoing a process now to evaluate a vaccine for children under the age of 12, and under the President's plan, the Administration will do whatever it takes to support those efforts, while continuing to respect and defer to the scientific decision-making of the agency.

Requiring Staff in Head Start Programs, Department of Defense Schools, and Bureau of Indian Education-Operated Schools to be Vaccinated

Calling on All States to Adopt Vaccine Requirements for All School Employees

Providing Additional Funding to School Districts for Safe School Reopening, Including Backfilling Salaries and Other Funding Withheld by States for Implementing COVID Safety Measures

Using the Department of Education's Full Legal Authority to Protect Students' Access to In-Person Instruction

Getting Students and School Staff Tested Regularly

Providing Every Resource to the FDA to Support Timely Review of Vaccines for Individuals Under the Age of 12

Increasing Testing & Requiring Masking

It will take time for the newly vaccinated to get protection from the virus. As we continue to combat COVID-19, testing is a key tool to identify infected individuals and prevent spread to others. Likewise, masking can also help slow and contain the spread of the virus—and the combination of increased vaccinations and masking will have a major impact on COVID-19 transmission. President Biden's plan takes new actions to increase the amount of testing—in your own home, at pharmacies, and in your doctor's office—and ensures that strong mask requirements remain in place.

Mobilizing Industry to Expand Easy-to-Use Testing Production

Making At-Home Tests More Affordable

Sending Free Rapid, At-Home Tests to Food Banks and Community Health Centers

Expanding Free, Pharmacy Testing

Continuing to Require Masking for Interstate Travel and Double Fines

Continue to Require Masking on Federal Property

Protecting Our Economic Recovery

President Biden's economic plan is working. Since Day One in office, the President has focused on jumpstarting the economy and rebuilding it from the bottom up and the middle out. America is getting back to work, and workers and small businesses are seeing the results. Since President Biden took office, there has been historic job growth—more than 4 million jobs created– the most in any President's first six months, with 750,000 jobs created on average per month over the last three months. Despite the challenges posed by the Delta variant, the economy created 235,000 jobs last month, and the unemployment rate fell to its lowest level since before the pandemic. The average number of new unemployment insurance claims has been cut by more than half since President Biden took office, and more than 70 percent of Americans say that now is a good time to find a quality job, up from less than 30 percent this time last year. The U.S. is the only major economy that has now exceeded its pre-pandemic growth projections, and independent forecasters believe America will this year reach the highest levels of growth in decades

decades.

COVID-19 impacts our economy, no doubt. But, the President's plan will limit the damage and ensure that the Delta variant cannot undo this progress. The policies outlined throughout this plan will ensure that we do not return to lockdowns and shutdowns. Additionally, we will offer new support to small businesses as they continue to weather the surge caused by the Delta variant. Supporting small businesses is critical to our economic growth, since they create two-thirds of net new jobs and employ nearly half of America's private workforce. These reforms include:

New Support for Small Businesses Impacted by COVID-19

Streamlining the Paycheck Protection Program (PPP) Loan Forgiveness Process

Launching the Community Navigator Program to Connect Small Businesses to the Help They Need

Improving Care for those with COVID-19

As we work to reduce cases, hospitalizations, and deaths, we will maintain our focus on treating people infected with COVID-19—and helping hard-hit health care systems in the most impacted areas. In early July, the Administration launched Surge Response Teams to help states experiencing case increases. Since then, the Administration has worked with 18 states, deploying nearly 1,000 personnel, including hundreds of EMTs, nurses and doctors on the ground providing emergency medical care; surged hundreds of ventilators,

ambulances and other critical assets to support strained health care systems; stood up dozens of new, free testing sites; and assisted with local outbreak investigations.

As we continue to battle the Delta surge, the President's plan will continue to send response teams to states that request them and take additional actions to accelerate this work.

Increasing Support for COVID-Burdened Hospitals

Getting Life-Saving Monoclonal Antibody Treatment to Those Who Need It

Expanding the Pool of Health Care Professionals Providing Treatment by Deploying Federal Monoclonal Antibody Strike Teams

President Biden's plan to continue to combat COVID-19 this fall is comprehensive, science-based and relies on the power of the federal government working hand-in-hand with states, local communities, the private sector, and all Americans to put this pandemic behind us. The strategy outlined here is domestic focused. **In the weeks ahead, the President will announce additional steps to build on the progress the Administration has made to combat this pandemic globally.** President Biden and his Administration will continue to use every tool necessary to protect the American people from COVID-19.

Exhibit E

Title page

Comparing SARS-CoV-2 natural immunity to vaccine-induced immunity: reinfections versus breakthrough infections

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Abstract

Background:

Reports of waning vaccine-induced immunity against COVID-19 have begun to surface. With that, the comparable long-term protection conferred by previous infection with SARS-CoV-2 remains unclear.

Methods:

We conducted a retrospective observational study comparing three groups: (1)SARS-CoV-2-naïve individuals who received a two-dose regimen of the BioNTech/Pfizer mRNA BNT162b2 vaccine, (2)previously infected individuals who have not been vaccinated, and (3)previously infected *and* single dose vaccinated individuals. Three multivariate logistic regression models were applied. In all models we evaluated four outcomes: SARS-CoV-2 infection, symptomatic disease, COVID-19-related hospitalization and death. The follow-up period of June 1 to August 14, 2021, when the Delta variant was dominant in Israel.

Results:

SARS-CoV-2-naïve vaccinees had a 13.06-fold (95% CI, 8.08 to 21.11) increased risk for breakthrough infection with the Delta variant compared to those previously infected, when the first event (infection or vaccination) occurred during January and February of 2021. The increased risk was significant (P<0.001) for symptomatic disease as well. When allowing the infection to occur at any time before vaccination (from March 2020 to February 2021), evidence of waning natural immunity was demonstrated, though SARS-CoV-2 naïve vaccinees had a 5.96-fold (95% CI, 4.85 to

7.33) increased risk for breakthrough infection and a 7.13-fold (95% CI, 5.51 to 9.21) increased risk for symptomatic disease. SARS-CoV-2-naïve vaccinees were also at a greater risk for COVID-19-related-hospitalizations compared to those that were previously infected.

Conclusions:

This study demonstrated that natural immunity confers longer lasting and stronger protection against infection, symptomatic disease and hospitalization caused by the Delta variant of SARS-CoV-2, compared to the BNT162b2 two-dose vaccine-induced immunity. Individuals who were both previously infected with SARS-CoV-2 and given a single dose of the vaccine gained additional protection against the Delta variant.

Introduction

The heavy toll that SARS-CoV-2 infection has been taking on global health and healthcare resources has created an urgent need to estimate which part of the population is protected against COVID-19 at a given time in order to set healthcare policies such as lockdowns and to assess the possibility of herd immunity.

To date, there is still no evidence-based, long-term correlate of protection[1]. This lack of correlate of protection has led to different approaches in terms of vaccine resource allocation, namely the need for vaccine administration in recovered patients, the need for booster shots in previously vaccinated individuals or the need to vaccinate low-risk populations, potentially previously exposed.

The short-term effectiveness of a two-dose regimen of the BioNTech/Pfizer BNT162b2 mRNA COVID-19 vaccine was demonstrated in clinical trials[2] and in observational settings[3,4]. However, long term effectiveness across different variants is still unknown, though reports of waning immunity are beginning to surface, not merely in terms of antibody dynamics over time[5–7], but in real-world settings as well[8].

Alongside the question of long-term protection provided by the vaccine, the degree and duration to which previous infection with SARS-CoV-2 affords protection against repeated infection also remains unclear. Apart from the paucity of studies examining long-term protection against reinfection[9], there is a challenge in defining reinfection as opposed to prolonged viral shedding[10]. While clear-cut cases exist, namely two separate clinical events with two distinct sequenced viruses, relying solely on these cases will likely result in an under-estimation of the incidence of reinfection. Different criteria based on more widely-available information have been suggested[11], the Centers for Disease Control and Prevention's (CDC) guidelines refer to two positive SARS-CoV-2 polymerase chain reaction (PCR) test results at least 90 days

apart.[12] Using similar criteria, population-based studies demonstrated natural immunity[13,14] with no signs of waning immunity for at least 7 months, though protection was lower for those aged 65 or older[9].

The Delta (B.1.617.2) Variant of Concern (VOC), initially identified in India and today globally prevalent, has been the dominant strain in Israel since June 2021. The recent surge of cases in Israel[15], one of the first countries to embark on a nationwide vaccination campaign (mostly with the BioNTech/Pfizer BNT162b2 vaccine), has raised concerns about vaccine effectiveness against the Delta variant, including official reports of decreased protection[16]. Concomitantly, studies have demonstrated only mild differences in short-term vaccine effectiveness[17] against the Delta variant, as well as substantial antibody response[18]. Apart from the variant, the new surge was also explained by the correlation found between time-from-vaccine and breakthrough infection rates, as early vaccinees were demonstrated to be significantly more at risk than late vaccinees[8]. Now, when sufficient time has passed since both the beginning of the pandemic and the deployment of the vaccine, we can examine the long-term protection of natural immunity compared to vaccine-induced immunity.

To this end, we compared the incidence rates of breakthrough infections to the incidence rates of reinfection, leveraging the centralized computerized database of Maccabi Healthcare Services (MHS), Israel's second largest Health Maintenance Organization.

Methods

Study design and population

A retrospective cohort study was conducted, leveraging data from MHS' centralized computerized database. The study population included MHS members aged 16 or older who were vaccinated prior to February 28, 2021, who had a documented SARS-CoV-2 infection by February 28, 2021, or who had both a documented SARS-CoV-2 infection by February 28, 2021 *and* received one dose of the vaccine by May 25, 2021, at least 7 days before the study period. On March 2, 2021, The Israeli Ministry of Health revised its guidelines and allowed previously SARS-CoV-2 infected individuals to receive one dose of the vaccine, after a minimum 3-month-interval from the date of infection

Data Sources

Anonymized Electronic Medical Records (EMRs) were retrieved from MHS' centralized computerized database for the study period of March 1, 2020 to August 14, 2021.

MHS is a 2.5-million-member, state-mandated, non-for-profit, second largest health fund in Israel, which covers 26% of the population and provides a representative sample of the Israeli population. Membership in one of the four national health funds is mandatory, whereas all citizens must freely choose one of four funds, which are prohibited by law from denying membership to any resident. MHS has maintained a centralized database of EMRs for three decades, with less than 1% disengagement rate among its members, allowing for a comprehensive longitudinal medical follow-up. The centralized dataset includes extensive demographic data, clinical measurements, outpatient and hospital diagnoses and procedures, medications

dispensed, imaging performed and comprehensive laboratory data from a single central laboratory.

Data extraction and definition of the study variables

COVID-19-related data

COVID-19-related information was captured as well, including dates of the first and second dose of the vaccine and results of any polymerase chain reaction (PCR) tests for SARS-CoV-2, given that all such tests are recorded centrally. Records of COVID-19-related hospitalizations were retrieved as well, and COVID-19-related mortality was screened for. Additionally, information about COVID-19-related symptoms was extracted from EMRs, where they were recorded by the primary care physician or a certified nurse who conducted in-person or phone visits with each infected individual.

Exposure variable: study groups

The eligible study population was divided into three groups: (1)fully vaccinated and SARS-CoV-2-naïve individuals, namely MHS members who received two doses of the BioNTech/Pfizer mRNA BNT162b2 vaccine by February 28, 2021, did not receive the third dose by the end of the study period and did not have a positive PCR test result by June 1, 2021; (2) unvaccinated previously infected individuals, namely MHS members who had a positive SARS-CoV-2 PCR test recorded by February 28, 2021 and who had not been vaccinated by the end of the study period; (3) previously infected *and* vaccinated individuals, including individuals who had a positive SARS-CoV-2 PCR test by February 28, 2021 and received one dose of the vaccine by May 25, 2021, at least 7 days before the study period. The fully vaccinated group was the comparison (reference) group in our study. Groups 2 and 3, were matched to the

comparison group 1 in a 1:1 ratio based on age, sex and residential socioeconomic status.

Dependent variables

We evaluated four SARS-CoV-2-related outcomes, or second events: documented RT-PCR confirmed SARS-CoV-2 infection, COVID-19, COVID-19-related hospitalization and death. Outcomes were evaluated during the follow-up period of June 1 to August 14, 2021, the date of analysis, corresponding to the time in which the Delta variant became dominant in Israel.

Covariates

Individual-level data of the study population included patient demographics, namely age, sex, socioeconomic status (SES) and a coded geographical statistical area (GSA, assigned by Israel's National Bureau of Statistics, corresponds to neighborhoods and is the smallest geostatistical unit of the Israeli census). The SES is measured on a scale from 1 (lowest) to 10, and the index is based on several parameters, including household income, educational qualifications, household crowding and car ownership. Data were also collected on last documented body mass index (BMI) and information about chronic diseases from MHS' automated registries, including cardiovascular diseases[19], hypertension[20], diabetes[21], chronic kidney disease[22], chronic obstructive pulmonary disease, immunocompromised conditions, and cancer from the National Cancer Registry[23].

Statistical analysis

Two multivariate logistic regression models were applied that evaluated the four aforementioned SARS-CoV-2-related outcomes as dependent variables, while the study groups were the main independent variables.

Model 1– previously infected vs. vaccinated individuals, with matching for time of first event

In model 1, we examined natural immunity and vaccine-induced immunity by comparing the likelihood of SARS-CoV-2-related outcomes between previously infected individuals who have never been vaccinated and fully vaccinated SARS-CoV-2-naïve individuals. These groups were matched in a 1:1 ratio by age, sex, GSA and time of first event. The first event (the preliminary exposure) was either the time of administration of the second dose of the vaccine *or* the time of documented infection with SARS-CoV-2 (a positive RT-PCR test result), both occurring between January 1, 2021 and February 28, 2021. Thereby, we matched the "immune activation" time of both groups, examining the long-term protection conferred when vaccination or infection occurred within the same time period. The three-month interval between the first event and the second event was implemented in order to capture reinfections (as opposed to prolonged viral shedding) by following the 90-day guideline of the CDC.

Model 2

In model 2, we compared the SARS-CoV-2 naïve vaccinees to unvaccinated previously infected individuals while intentionally *not* matching the time of the first event (i.e., either vaccination or infection), in order to compare vaccine-induced immunity to natural immunity, regardless of time of infection. Therefore, matching

was done in a 1:1 ratio based on age, sex and GSA alone. Similar to the model 1, either event (vaccination or infection) had to occur by February 28, to allow for the 90-day interval. The four SARS-CoV-2 study outcomes were the same for this model, evaluated during the same follow-up period.

Model 3

Model 3 examined previously infected individuals vs. previously-infected-and-once-vaccinated individuals, using "natural immunity" as the baseline group. We matched the groups in a 1:1 ratio based on age, sex and GSA. SARS-CoV-2 outcomes were the same, evaluated during the same follow-up period.

In all three models, we estimated natural immunity vs. vaccine-induced immunity for each SARS-CoV-2-related outcome, by applying logistic regression to calculate the odds ratio (OR) between the two groups in each model, with associated 95% confidence intervals (CIs). Results were then adjusted for underlying comorbidities, including obesity, cardiovascular diseases, diabetes, hypertension, chronic kidney disease, cancer and immunosuppression conditions.

Analyses were performed using Python version 3.73 with the stats model package. $P < 0.05$ was considered statistically significant.

Ethics declaration

This study was approved by the MHS (Maccabi Healthcare Services) Institutional Review Board (IRB). Due to the retrospective design of the study, informed consent was waived by the IRB, and all identifying details of the participants were removed before computational analysis.

Data availability statement

According to the Israel Ministry of Health regulations, individual-level data cannot be shared openly. Specific requests for remote access to de-identified community-level data should be directed to KSM, Maccabi Healthcare Services Research and Innovation Center.

Code availability

Specific requests for remote access to the code used for data analysis should be referred to KSM, Maccabi Healthcare Services Research and Innovation Center.

Results

Overall, 673,676 MHS members 16 years and older were eligible for the study group of fully vaccinated SARS-CoV-2-naïve individuals; 62,883 were eligible for the study group of unvaccinated previously infected individuals and 42,099 individuals were eligible for the study group of previously infected and single-dose vaccinees.

Model 1 – previously infected vs. vaccinated individuals, with matching for time of first event

In model 1, we matched 16,215 persons in each group. Overall, demographic characteristics were similar between the groups, with some differences in their comorbidity profile (Table 1a).

During the follow-up period, 257 cases of SARS-CoV-2 infection were recorded, of which 238 occurred in the vaccinated group (breakthrough infections) and 19 in the previously infected group (reinfections). After adjusting for comorbidities, we found a statistically significant 13.06-fold (95% CI, 8.08 to 21.11) increased risk for breakthrough infection as opposed to reinfection ($P<0.001$). Apart from age ≥60 years, there was no statistical evidence that any of the assessed comorbidities significantly affected the risk of an infection during the follow-up period (Table 2a).

As for symptomatic SARS-COV-2 infections during the follow-up period, 199 cases were recorded, 191 of which were in the vaccinated group and 8 in the previously infected group. Symptoms for all analyses were recorded in the central database within 5 days of the positive RT-PCR test for 90% of the patients, and included chiefly fever, cough, breathing difficulties, diarrhea, loss of taste or smell, myalgia, weakness, headache and sore throat. After adjusting for comorbidities, we found a 27.02-fold risk (95% CI, 12.7 to 57.5) for symptomatic breakthrough infection as

opposed to symptomatic reinfection (P<0.001) (Table 2b). None of the covariates were significant, except for age ≥60 years.

Nine cases of COVID-19-related hospitalizations were recorded, 8 of which were in the vaccinated group and 1 in the previously infected group (Table S1). No COVID-19-related deaths were recorded in our cohorts.

Model 2 –previously infected vs. vaccinated individuals, without matching for time of first event

In model 2, we matched 46,035 persons in each of the groups (previously infected vs. vaccinated). Baseline characteristics of the groups are presented in Table 1a. Figure 1 demonstrates the timely distribution of the first infection in reinfected individuals.

When comparing the vaccinated individuals to those previously infected at any time (including during 2020), we found that throughout the follow-up period, 748 cases of SARS-CoV-2 infection were recorded, 640 of which were in the vaccinated group (breakthrough infections) and 108 in the previously infected group (reinfections). After adjusting for comorbidities, a 5.96-fold increased risk (95% CI, 4.85 to 7.33) increased risk for breakthrough infection as opposed to reinfection could be observed (P<0.001) (Table 3a). Apart from SES level and age ≥60, that remained significant in this model as well, there was no statistical evidence that any of the comorbidities significantly affected the risk of an infection.

Overall, 552 symptomatic cases of SARS-CoV-2 were recorded, 484 in the vaccinated group and 68 in the previously infected group. There was a 7.13-fold (95% CI, 5.51 to 9.21) increased risk for symptomatic breakthrough infection than symptomatic reinfection (Table 3b). COVID-19 related hospitalizations occurred in 4 and 21 of the reinfection and breakthrough infection groups, respectively. Vaccinated

individuals had a 6.7-fold (95% CI, 1.99 to 22.56) increased to be admitted compared to recovered individuals. Being 60 years of age or older significantly increased the risk of COVID-19-related hospitalizations (Table S2). No COVID-19-related deaths were recorded.

Model 3 - previously infected vs. vaccinated and previously infected individuals

In model 3, we matched 14,029 persons. Baseline characteristics of the groups are presented in Table 1b. Examining previously infected individuals to those who were both previously infected and received a single dose of the vaccine, we found that the latter group had a significant 0.53-fold (95% CI, 0.3 to 0.92) (Table 4a) decreased risk for reinfection, as 20 had a positive RT-PCR test, compared to 37 in the previously infected and unvaccinated group. Symptomatic disease was present in 16 single dose vaccinees and in 23 of their unvaccinated counterparts. One COVID-19-related hospitalization occurred in the unvaccinated previously infected group. No COVID-19-related mortality was recorded.

We conducted a further sub-analysis, compelling the single-dose vaccine to be administered *after* the positive RT-PCR test. This subset represented 81% of the previously-infected-and-vaccinated study group. When performing this analysis, we found a similar, though not significant, trend of decreased risk of reinfection, with an OR of 0.68 (95% CI, 0.38 to 1.21, *P*-value=0.188).

Discussion

This is the largest real-world observational study comparing natural immunity, gained through previous SARS-CoV-2 infection, to vaccine-induced immunity, afforded by the BNT162b2 mRNA vaccine. Our large cohort, enabled by Israel's rapid rollout of the mass-vaccination campaign, allowed us to investigate the risk for additional infection – either a breakthrough infection in vaccinated individuals or reinfection in previously infected ones – over a longer period than thus far described.

Our analysis demonstrates that SARS-CoV-2-naïve vaccinees had a 13.06-fold increased risk for breakthrough infection with the Delta variant compared to those previously infected, when the first event (infection or vaccination) occurred during January and February of 2021. The increased risk was significant for a symptomatic disease as well.

Broadening the research question to examine the extent of the phenomenon, we allowed the infection to occur at any time between March 2020 to February 2021 (when different variants were dominant in Israel), compared to vaccination only in January and February 2021. Although the results could suggest waning natural immunity against the Delta variant, those vaccinated are still at a 5.96-fold increased risk for breakthrough infection and at a 7.13-fold increased risk for symptomatic disease compared to those previously infected. SARS-CoV-2-naïve vaccinees were also at a greater risk for COVID-19-related-hospitalization compared to those who were previously infected.

Individuals who were previously infected with SARS-CoV-2 seem to gain additional protection from a subsequent single-dose vaccine regimen. Though this finding corresponds to previous reports[24,25], we could not demonstrate significance in our cohort.

The advantageous protection afforded by natural immunity that this analysis demonstrates could be explained by the more extensive immune response to the SARS-CoV-2 proteins than that generated by the anti-spike protein immune activation conferred by the vaccine[26,27]. However, as a correlate of protection is yet to be proven[1,28], including the role of B-Cell[29] and T-cell immunity[30,31], this remains a hypothesis.

Our study has several limitations. First, as the Delta variant was the dominant strain in Israel during the outcome period, the decreased long-term protection of the vaccine compared to that afforded by previous infection cannot be ascertained against other strains. Second, our analysis addressed protection afforded solely by the BioNTech/Pfizer mRNA BNT162b2 vaccine, and therefore does not address other vaccines or long-term protection following a third dose, of which the deployment is underway in Israel. Additionally, as this is an observational real-world study, where PCR screening was not performed by protocol, we might be underestimating asymptomatic infections, as these individuals often do not get tested.

Lastly, although we controlled for age, sex, and region of residence, our results might be affected by differences between the groups in terms of health behaviors (such as social distancing and mask wearing), a possible confounder that was not assessed. As individuals with chronic illness were primarily vaccinated between December and February, confounding by indication needs to be considered; however, adjusting for obesity, cardiovascular disease, diabetes, hypertension, chronic kidney disease, chronic obstructive pulmonary disease, cancer and immunosuppression had only a small impact on the estimate of effect as compared to the unadjusted OR. Therefore, residual confounding by unmeasured factors is unlikely.

This analysis demonstrated that natural immunity affords longer lasting and stronger protection against infection, symptomatic disease and hospitalization due to the Delta variant of SARS-CoV-2, compared to the BNT162b2 two-dose vaccine-induced immunity. Notably, individuals who were previously infected with SARS-CoV-2 and given a single dose of the BNT162b2 vaccine gained additional protection against the Delta variant. The long-term protection provided by a third dose, recently administered in Israel, is still unknown.

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Tables and figures

Table 1a. Characteristics of study population, model 1 and 2.

	Model 1 – with matching of time of first event		**Model 2 – without matching of time of first event**	
Characteristics	Previously infected (n=16,215)	Vaccinated individuals (n=16,215)	Previously infected (n=46,035)	Previously infected *and* vaccinated (n =46,035)
Age years, mean (SD)	36.1 (13.9)	36.1 (13.9)	36.1 (14.7)	36.1 (14.7)
Age group – no. (%)				
16 to 39 yr	9,889 (61.0)	9,889 (61.0)	28,157 (61.2)	28,157 (61.2)
40 to 59 yr	5,536 (34.1)	5,536 (34.1)	14,973 (32.5)	14,973 (32.5)
≥60 yr	790 (4.9)	790 (4.9)	2,905 (6.3)	2,905 (6.3)
Sex – no. (%)				
Female	7,428 (45.8)	7,428 (45.8)	22,661 (49.2)	22,661 (49.2)
Male	8,787 (54.2)	8,787 (54.2)	23,374 (50.8)	23,374 (50.8)
SES, mean (SD)	5.5 (1.9)	5.5 (1.9)	5.3 (1.9)	5.3 (1.9)
Comorbidities – no. (%)				
Hypertension	1,276 (7.9)	1,569 (9.7)	4,009 (8.7)	4,301 (9.3)
CVD	551 (3.4)	647 (4.0)	1,875 (4.1)	1830 (4.0)
DM	635 (3.9)	877 (5.4)	2207 (4.8)	2300 (5.0)
Immunocompromised	164 (1.0)	420 (2.6)	527 (1.1)	849 (1.8)
Obesity (BMI ≥30)	3,076 (19.0)	3,073 (19.0)	9,117 (19.8)	8,610 (18.7)
CKD	196 (1.2)	271 (1.7)	659 (1.4)	814 (1.8)
COPD	65 (0.4)	97 (0.6)	218 (0.5)	292 (0.6)
Cancer	324 (2.0)	636 (3.9)	1,044 (2.3)	1,364 (3.0)

SD – Standard Deviation; SES – Socioeconomic status on a scale from 1 (lowest) to 10; CVD – Cardiovascular Diseases; DM – Diabetes Mellitus; CKD – Chronic Kidney Disease; COPD – Chronic Obstructive Pulmonary Disease.

Table 1b. Characteristics of study population, model 3.

Characteristics	Previously infected (n=14,029)	Previously infected and single dose vaccinated (n=14,029)
Age years, mean (SD)	33.2 (14.0)	33.2 (14.0)
Age group – no. (%)		
16 to 39 yr	9543 (68.0)	9543 (68.0)
40 to 59 yr	3919 (27.9)	3919 (27.9)
≥60 yr	567 (4.0)	567 (4.0)
Sex – no. (%)		
Female	7467 (53.2)	7467 (53.2)
Male	6562 (46.8)	6562 (46.8)
SES, mean (SD)	4.7 (1.9)	4.7 (1.9)
Comorbidities		
Hypertension	892 (6.4)	1004 (7.2)
CVD	437 (3.1)	386 (2.8)
DM	529 (3.8)	600 (4.3)
Immunocompromised	127 (0.9)	145 (1.0)
Obesity (BMI ≥30)	2599 (18.5)	2772 (19.8)
CKD	137 (1.0)	162 (1.2)
COPD	30 (0.2)	53 (0.4)
Cancer	241 (1.7)	267 (1.9)

SD – Standard Deviation; SES – Socioeconomic status on a scale from 1 (lowest) to 10; CVD – Cardiovascular Diseases; DM – Diabetes Mellitus; CKD – Chronic Kidney Disease; COPD – Chronic Obstructive Pulmonary Disease.

Table 2a. OR for SARS-CoV-2 infection, model 1, previously infected vs. vaccinated

Variable	Category	ß	OR	95%CI	P-value
Induced Immunity					
	Previously infected	Ref			
	Vaccinated	2.57	13.06	8.08 – 21.11	<0.001
SES		0.04	1.04	0.97 – 1.11	0.251
Age group, yr.					
	16-39	Ref			
	40-59	0.05	1.05	0.78 - 1.4	0.751
	≥60	0.99	2.7	1.68 – 4.34	<0.001
Sex					
	Female	Ref			
	Male	-0.03	0.97	0.76 – 1.25	0.841
Comorbidities					
	Obesity (BMI≥30)	0.01	1.01	0.73 – 1.39	0.967
	Diabetes mellitus	-0.36	0.7	0.39 – 1.25	0.229
	Hypertension	0.1	1.11	0.72 – 1.72	0.641
	Cancer	0.37	1.44	0.85 – 2.44	0.171
	CKD	0.53	1.7	0.83 – 3.46	0.146
	COPD	-0.46	0.63	0.15 – 2.66	0.529
	Immunosuppression	-0.1	0.91	0.42 – 1.97	0.803
	Cardiovascular diseases	0.26	1.3	0.75 – 2.25	0.343

OR – Odds Ratio; SES – Socioeconomic status on a scale from 1 (lowest) to 10; CVD – Cardiovascular Diseases; CKD – Chronic Kidney Disease; COPD – Chronic Obstructive Pulmonary Disease.

Table 2b. OR for Symptomatic SARS-CoV-2 infection, model 1, previously infected vs. vaccinated

Variable	Category	ß	OR	95%CI	P-value
Induced Immunity					
	Previously infected	Ref			
	Vaccinated	3.3	27.02	12.7 – 57.5	<0.001
SES		0.04	1.04	0.96 – 1.12	0.312
Age group, yr.					
	16-39	Ref			
	40-59	0.19	1.21	0.88 – 1.67	0.25
	≥60	1.06	2.89	1.68 – 4.99	<0.001
Sex					
	Female	Ref			
	Male	-0.19	0.82	0.62 – 1.1	0.185
Comorbidities					
	Obesity (BMI≥30)	0.02	1.02	0.71 – 1.48	0.899
	Diabetes mellitus	-0.31	0.73	0.37 – 1.43	0.361
	Hypertension	0.12	1.13	0.69 – 1.85	0.623
	Cancer	0.37	1.45	0.8 – 2.62	0.217
	CKD	0.1	1.1	0.42 – 2.87	0.846
	COPD	-0.78	0.46	0.06 – 3.41	0.445
	Immunosuppression	-0.37	0.69	0.25 – 1.89	0.468
	Cardiovascular diseases	0.03	1.03	0.52 – 2.03	0.941

OR – Odds Ratio; SES – Socioeconomic status on a scale from 1 (lowest) to 10; CVD – Cardiovascular Diseases; CKD – Chronic Kidney Disease; COPD – Chronic Obstructive Pulmonary Disease.

Table 3a. OR for SARS-CoV-2 infection, model 2, previously infected vs. vaccinated

Variable	Category	ß	OR	95%CI	P-value
Induced Immunity					
	Previously infected	Ref			
	Vaccinated	1.78	5.96	4.85 – 7.33	<0.001
SES		0.07	1.07	1.03 – 1.11	<0.001
Age group, yr.					
	16-39	Ref			
	40-59	0.06	1.06	0.9 – 1.26	0.481
	≥60	0.79	2.2	1.66 – 2.92	<0.001
Sex					
	Female	Ref			
	Male	-0.01	0.99	0.85 - 1.14	0.842
Comorbidities					
	Obesity (BMI≥30)	0.12	1.13	0.94 – 1.36	0.202
	Diabetes mellitus	-0.15	0.86	0.61 – 1.22	0.4
	Hypertension	-0.12	0.89	0.67 – 1.17	0.402
	Cancer	0.2	1.22	0.85 – 1.76	0.283
	CKD	0.3	1.35	0.85 – 2.14	0.207
	COPD	0.48	1.62	0.88 – 2.97	0.121
	Immunosuppression	-0.03	0.98	0.57 – 1.66	0.925
	Cardiovascular diseases	0.08	1.09	0.77 – 1.53	0.638

OR – Odds Ratio; SES – Socioeconomic status on a scale from 1 (lowest) to 10; CVD – Cardiovascular Diseases; CKD – Chronic Kidney Disease; COPD – Chronic Obstructive Pulmonary Disease.

Table 3b. OR for Symptomatic SARS-CoV-2 infection, model 2, previously infected vs. vaccinated

Variable	Category	ß	OR	95%CI	P-value
Induced Immunity					
	Previously infected	Ref			
	Vaccinated	1.96	7.13	5.51 – 9.21	<0.001
SES		0.07	1.07	1.02 – 1.12	0.003
Age group, yr.					
	16-39	Ref			
	40-59	0.09	1.1	0.9 – 1.33	0.35
	≥60	0.8	2.23	1.61 – 3.09	<0.001
Sex					
	Female	Ref			
	Male	-0.02	0.98	0.82 – 1.16	0.785
Comorbidities					
	Obesity (BMI≥30)	0.16	1.18	0.95 – 1.46	0.133
	Diabetes mellitus	-0.11	0.89	0.61 – 1.32	0.571
	Hypertension	-0.01	0.99	0.72 – 1.35	0.943
	Cancer	0.08	1.09	0.7 – 1.69	0.71
	CKD	0.13	1.14	0.65 – 1.98	0.654
	COPD	0.5	1.65	0.82 – 3.31	0.162
	Immunosuppression	0	1	0.54 – 1.85	0.999
	Cardiovascular diseases	0	1	0.67 – 1.5	0.99

OR – Odds Ratio; SES – Socioeconomic status on a scale from 1 (lowest) to 10; CVD – Cardiovascular Diseases; CKD – Chronic Kidney Disease; COPD – Chronic Obstructive Pulmonary Disease.

Table 4a. OR for SARS-CoV-2 infection, model 3, previously infected vs. previously infected and single-dose-vaccinated

Variable	Category	ß	OR	95%CI	P-value
Induced Immunity					
	Previously infected	Ref			
	Previously infected and vaccinated	-0.64	0.53	0.3 – 0.92	0.024
SES		0.11	1.12	0.98 – 1.28	0.096
Age group, yr.					
	16-59	Ref			
	≥60	-0.81	0.44	0.06 – 3.22	0.422
Comorbidities					
	Immunosuppression	0.72	2.06	0.28 – 15.01	0.475

SES – Socioeconomic status on a scale from 1 (lowest) to 10

Table 4b. OR for Symptomatic SARS-CoV-2 infection, model 2, previously infected vs. previously infected and vaccinated

Variable	Category	ß	OR	95%CI	P-value
Induced Immunity					
	Previously infected	Ref			
	Previously infected and vaccinated	-0.43	0.65	0.34 – 1.25	0.194
SES		0.06	1.06	0.9 – 1.24	0.508
Age group, yr.					
	16-59	Ref			
	≥60	-16.9	0	0.0 – inf	0.996
Comorbidities					
	Immunosuppression	1.15	3.14	0.43 – 23.01	0.26

OR – Odds Ratio; SES – Socioeconomic status on a scale from 1 (lowest) to 10.

Table S1. OR for COVID-19-related hospitalizations, model 1, previously infected vs. vaccinated

Variable	Category	ß	OR hospitalized	95%CI	*P*-value
Induced Immunity					
	Previously infected	Ref			
	Vaccinated	2.09	8.06	1.01 – 64.55	0.049
SES		0.05	1.05	0.72 – 1.53	0.81
Age ≥60 yrs (16-39, ref)		5.08	160.9	19.91 – 1300.44	<0.001

OR – Odds Ratio; SES – Socioeconomic status on a scale from 1 (lowest) to 10

Table S2. OR for COVID-19-related hospitalizations, model 2, previously infected vs. vaccinated

Variable	Category	ß	OR hospitalized	95%CI	*P*-value
Induced Immunity					
	Previously infected	Ref			
	Vaccinated	1.95	7.03	2.1 – 23.59	0.002
SES		-0.07	0.93	0.74 – 1.17	0.547
Age ≥60 yrs (16-39, ref)		4.3	73.5	25.09 – 215.29	<0.001

OR – Odds Ratio; SES – Socioeconomic status on a scale from 1 (lowest) to 10

Figure 1. Time of first infection in those reinfected between June and August 2021, model 2.

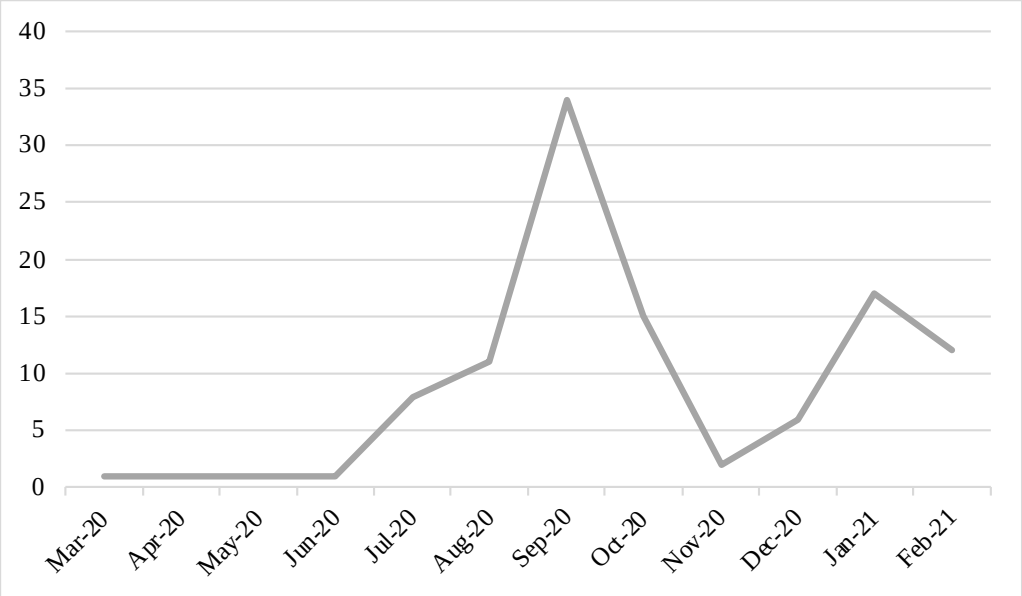

Exhibit F

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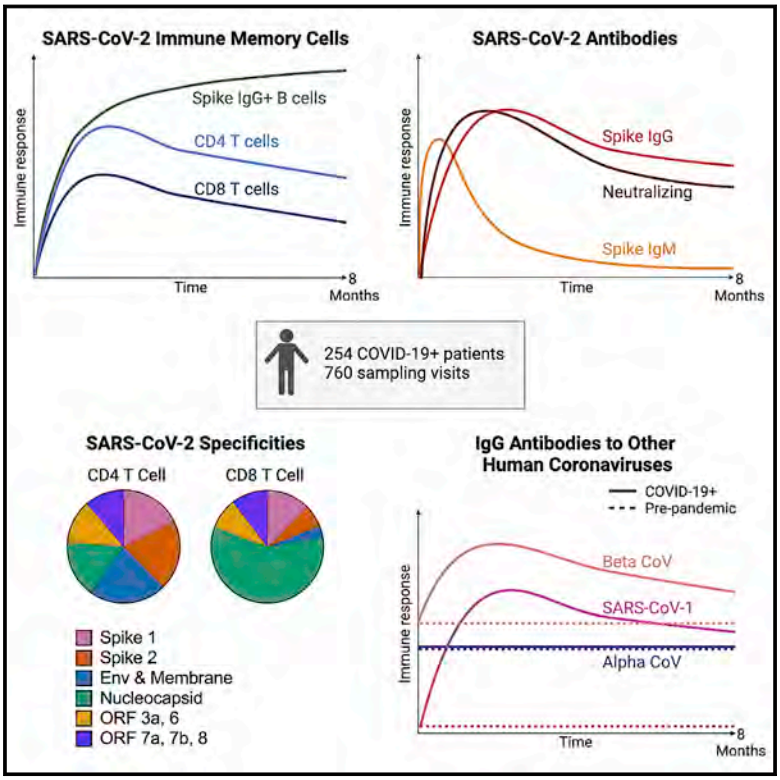
Longitudinal analysis shows durable and broad immune memory after SARS-CoV-2 infection with persisting antibody responses and memory B and T cells

Graphical abstract



Highlights

- Most recovered COVID-19 patients mount broad, durable immunity after infection
- Neutralizing antibodies show a bi-phasic decay with half-lives >200 days
- Spike IgG+ memory B cells increase and persist post-infection
- Durable polyfunctional CD4 and CD8 T cells recognize distinct viral epitope regions

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In brief

Cohen et al. evaluate immune responses longitudinally in 254 COVID-19 patients over 8 months. SARS-CoV-2-specific binding and neutralizing antibodies exhibit biphasic decay, suggesting long-lived plasma cell generation. Memory B cells remain stable; CD4 and CD8 memory T cells are polyfunctional. Thus, broad and effective immunity may persist long-term following COVID-19.

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Longitudinal analysis shows durable and broad immune memory after SARS-CoV-2 infection with persisting antibody responses and memory B and T cells

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SUMMARY

Ending the COVID-19 pandemic will require long-lived immunity to SARS-CoV-2. Here, we evaluate 254 COVID-19 patients longitudinally up to 8 months and find durable broad-based immune responses. SARS-CoV-2 spike binding and neutralizing antibodies exhibit a bi-phasic decay with an extended half-life of >200 days suggesting the generation of longer-lived plasma cells. SARS-CoV-2 infection also boosts antibody titers to SARS-CoV-1 and common betacoronaviruses. In addition, spike-specific IgG+ memory B cells persist, which bodes well for a rapid antibody response upon virus re-exposure or vaccination. Virus-specific CD4+ and CD8+ T cells are polyfunctional and maintained with an estimated half-life of 200 days. Interestingly, CD4+ T cell responses equally target several SARS-CoV-2 proteins, whereas the CD8+ T cell responses preferentially target the nucleoprotein, highlighting the potential importance of including the nucleoprotein in future vaccines. Taken together, these results suggest that broad and effective immunity may persist long-term in recovered COVID-19 patients.

INTRODUCTION

The COVID-19 pandemic caused by the rapid spread of SARS-CoV-2, a novel betacoronavirus, continues to cause significant morbidity and mortality. The induction of effective early immune control of SARS-CoV-2 and durable immune memory is critical to prevent severe disease and to protect upon re-exposure. SARS-CoV-2 infection induces polyclonal humoral and cellular responses targeting multiple viral proteins described in cross-sectional and longitudinal studies.[1] More comprehensive, quantitative analyses with extensive serial sampling in larger numbers of COVID-19 patients are limited and could resolve some conflicting views about the durability of humoral immunity. Importantly, defining the frequency, immune function, and specificity of the antibodies; memory B and T cell responses among COVID-19 patients; and identifying when they appear and how long they persist can provide understanding of the integral components for long-lived immunity to SARS-CoV-2 and potentially other human coronaviruses that emerge in the future.[2]

We initiated two prospective COVID-19 patient cohorts in Seattle and Atlanta during the first surge of the pandemic to investigate long-term immunity to SARS-CoV-2. Among 254 COVID-19 patients enrolled and frequently sampled, we identify binding and neutralizing antibodies to SARS-CoV-2 as well as antigen-specific B and T cells elicited early after infection, define their specificities, quantify the extent of antibody boosting of cross-reactive

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responses to other coronaviruses, and further characterize the decay rate and durability of these immune parameters over 250 days. We employ highly standardized or validated assays that are also being used to evaluate immunity in recent and ongoing clinical vaccine trials.[3-5] This in-depth longitudinal study demonstrates that durable immune memory persists in most COVID-19 patients, including those with mild disease, and serves as a framework to define and predict long-lived immunity to SARS-CoV-2 after natural infection. This investigation will also serve as a benchmark for immune memory induced in humans by SARS-CoV-2 vaccines.

RESULTS

COVID-19 study population

COVID-19-confirmed patients were recruited into our longitudinal study of SARS-CoV-2 specific B and T cell memory after infection. A total of 254 patients were enrolled at two sites, Atlanta and Seattle, starting in April 2020 and returned for follow up visits over a period of 250 days. We were able to collect blood samples at 2–3 time points from 165 patients and at 4–7 time points from another 80 patients, which allowed us to perform a longitudinal analysis of SARS-CoV-2-specific B and T cell responses on a large number of infected patients. The demographics and baseline characteristics of this cohort are described in Table S1. The study group was 55% female and 45% male and between 18 and 82 years old (median, 48.5 years). Based on World Health Organization (WHO) guidelines of disease severity, 71% of study participants exhibited mild disease, 24% had moderate disease, and 5% experienced severe disease.

Antibody responses to SARS-CoV-2 spike protein show a bi-phasic decay with an extended half-life

Binding antibodies to the SARS-CoV-2 full-length spike protein, to the receptor binding domain (RBD), and to the N-terminal domain (NTD) of the spike protein were assessed in COVID-19 patients (n = 222) over a period of 8 months post symptom onset. We included healthy individuals age 18–42 years as negative controls whose longitudinal blood samples were collected before the emergence of the COVID-19 pandemic. These pre-pandemic samples (n = 51) were from recipients of either the seasonal inactivated influenza vaccine (n = 27, collected from 2014-2018) or the live yellow fever virus (YFV-17D) vaccine (n = 24, collected from 2005–2007). The Mesoscale multiplex assay was used to measure IgG, IgA, and IgM antibody responses to SARS-CoV-2 proteins in the COVID-19 patients and in the pre-pandemic healthy controls.

The magnitude of serum IgG antibodies binding to the SARS-CoV-2 spike protein increased in 92% of COVID-19 convalescent participants (n = 222) relative to pre-pandemic controls (Figure 1A). The IgG responses to SARS-CoV-2 spike, RBD, and NTD declined over time with half-lives of 126 (95% confidence interval [95% CI] [107, 154]), 116 (95% CI [97, 144]), and 130 (95% CI [110, 158]) days, respectively, as estimated by an exponential decay model (Figures 1A–1C and S1A). We also estimated antibody waning using a power law model, which models a scenario in which the rate of antibody decay slows over time. The power law model produced a better fit for the decay of the SARS-CoV-2 spike, RBD, and NTD binding IgG antibodies (DAICs > 10), suggesting that spike-specific antibodies plateau over time. Because the decay rate changes over time, the half-life is predicted to change over time as well; therefore, we used the power law model to estimate the half-lives at 120 days after symptom onset. The power law estimated half-lives for the IgG antibody responses to spike ($t_{1/2}$ = 238 days), RBD ($t_{1/2}$ = 209 days), and NTD ($t_{1/2}$ = 244 days) were longer than those estimated by the exponential decay model (Figures S1A and S1C), indicating that the concentration of these IgG antibodies may be starting to stabilize. IgA (Figures 1D–1F) and IgM (Figures 1G–1I) antibodies reactive to the SARS-CoV-2 spike also increased after SARS-CoV-2 infection but were detected at lower levels and declined faster than the SARS-CoV-2-reactive IgG antibodies. As expected, spike-binding IgM decayed more rapidly than spike-binding IgA and IgG. Taken together, these results show that antibody responses, especially IgG antibody, were not only durable in the vast majority of patients in the 250 day period, but also that the bi-phasic decay curve suggests the generation of longer lived plasma cells producing antibody to the SARS-CoV-2 spike protein.

We also examined the antibody response to the SARS-CoV-2 nucleocapsid protein in these infected patients. As expected, the COVID-19 patients showed higher levels of antibody to the nucleocapsid protein compared to the pre-pandemic healthy controls (Figure S2). However, the nucleocapsid-specific antibodies declined with a much shorter half-life of 63 days (95% CI [58, 70]) compared to the spike protein antibodies (Figures S1A–S1C). Also, the nucleocapsid reactive IgG decay rate was best fit by the exponential model and not the power law model in contrast to what we observed with the spike IgG antibody decay rate (Figure S1A). Thus, the nucleocapsid reactive IgG not only declined much faster but also showed less evidence of stabilizing antibody levels, consistent with a response driven disproportionately by short-lived antibody secreting cells – at least at this stage of the immune response.

Stable and long-lived antibody responses to common human alpha- and betacoronaviruses in pre-pandemic healthy controls

We were interested in determining if SARS-CoV-2 infection had any effect on the levels of antibody to the circulating human alpha- and betacoronaviruses. As a prelude to this question, we first examined antibody levels to the spike protein of the two circulating alphacoronaviruses (229E and NL63) and the two betacoronaviruses (HKU1 and OC43) in our pre-pandemic samples. As shown in Figure 2, all 51 pre-pandemic samples had clearly detectable levels of IgG and IgA antibodies to the spike proteins of the four human coronaviruses. This is the expected result since seropositivity to these coronaviruses is very high in the adult population, but what was quite interesting was the remarkable stability of these antibody responses over a 200-day period in the pre-pandemic serum samples (shown as red lines in Figure 2). These were essentially flat lines with no decline in the antibody levels and question the prevailing belief that antibody responses to the endemic coronaviruses are short-lived.[6-8] While some occasional boosting of these childhood-acquired coronavirus infections cannot be ruled out, these data showing such stable antibody titers are best explained by

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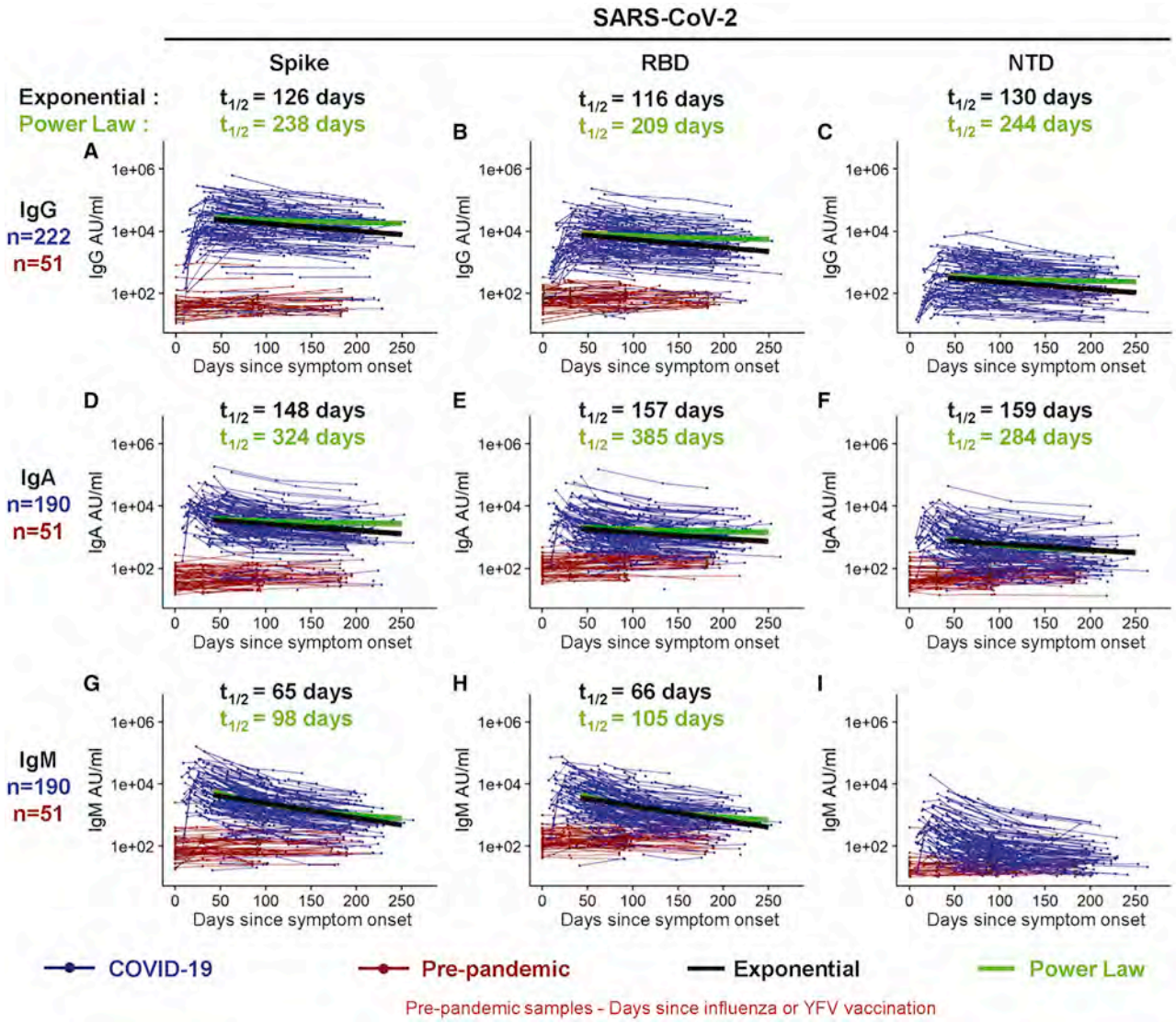

Figure 1. Longitudinal SARS-CoV-2 spike-binding antibody responses

IgG (A–C), IgA (D–F), and IgM (G–I) antibodies reactive to SARS-CoV-2 spike (A, D, G); spike receptor binding domain (RBD, [B, E, and H]), and the spike N-terminal domain (NTD, [C, F, and I]) were measured in triplicate by an electrochemiluminescent multiplex immunoassay and reported as arbitrary units per ml (AU/mL) as normalized by a standard curve. Longitudinal antibody titers of COVID-19 patients (in blue, n = 222 COVID-19+ for IgG; n = 190 COVID-19+ for IgA and for IgM) are plotted over days since symptom onset, whereas longitudinal pre-pandemic donor samples (in red, n = 51 for IgG, IgA, and IgM) were collected in the course of a non-SARS-CoV-2 vaccine study before 2019 and plotted over days since immunization. IgG decay curves and half-lives estimated by an exponential decay model are shown in black, and the decay curves and half-lives at day 120 post symptom onset estimated by a power law model are shown in green.

the persistence of long-lived plasma cells in the bone marrow many years after infection.[9-13]

COVID-19 infection results in increased levels of antibodies to two common human betacoronaviruses (HKU1 and OC43) and to SARS-CoV-1

We next examined if SARS-CoV-2 infection had any impact on the levels of antibodies to the other human coronaviruses. We measured IgG, IgA, and IgM antibody binding to the spike proteins of other known human coronaviruses in the COVID-19 patients (n = 222 for IgG and n = 190 for IgA and IgM) and compared these data to the 51 pre-pandemic healthy donor samples. In the COVID-19 patients, IgG and IgA antibodies to the alphacoronaviruses 229E and NL63 did not show any significant changes compared to the antibody levels in the pre-pandemic healthy controls (Figures 2A, 2B, 2F, and 2G; Figures S1C and S1D). In contrast, the IgG and IgA antibodies to betacoronaviruses HKU1 and OC43 were substantially elevated in COVID-19 patients relative to pre-pandemic controls (Figures 2C, 2D, 2H, and 2I; Figures S1C and S1D; $p < 0.0001$). After this boost, HKU1 and OC43 IgG antibody levels declined with estimated half-lives of 288 (95% CI [235, 372]) and 212 (95% CI [176, 268]) days, respectively (exponential decay

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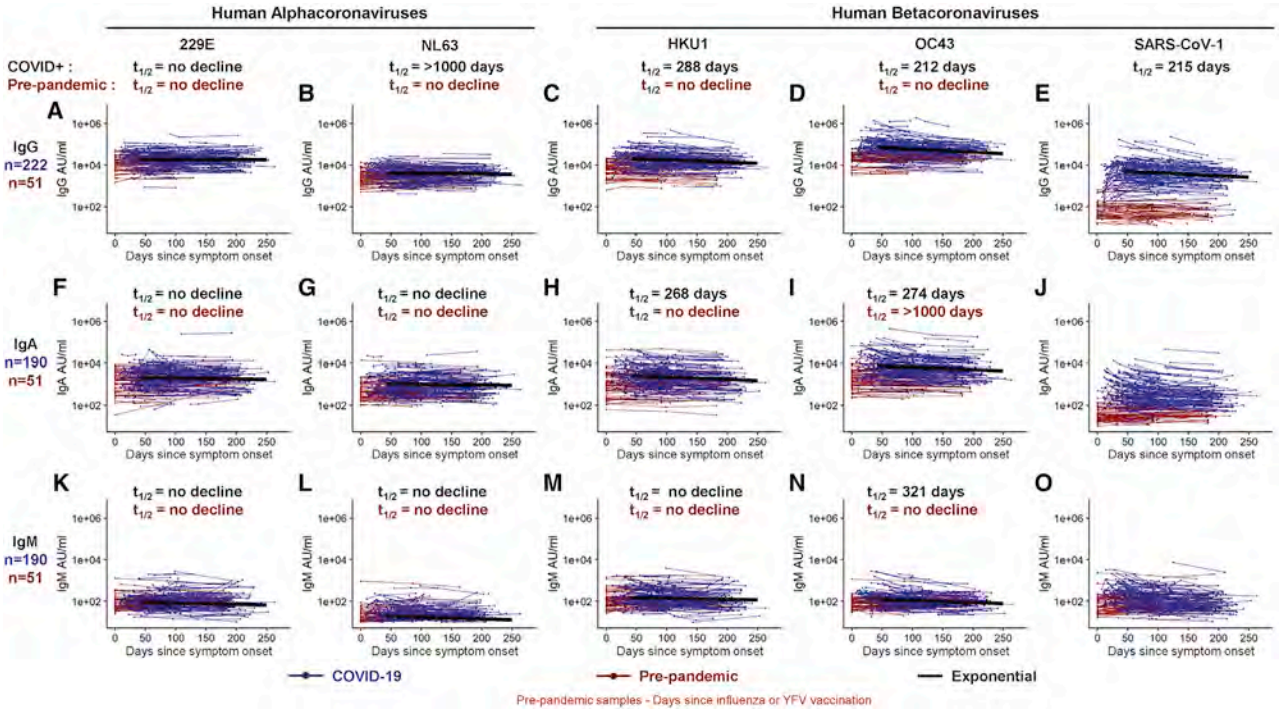

Figure 2. Longitudinal binding antibody responses to other coronavirus spike proteins

IgG (A–E), IgA (F–J), and IgM (K–O) antibody responses in sera collected from COVID-19+ patients (in blue, n = 222 for IgG; n = 190 for IgA and IgM) and pre-pandemic donors (in red, n = 51 for IgG, IgA and IgM) that were measured to 229E spike (A, F, and K), NL63 spike (B, G, and L), HKU1 spike (C, H, and M), OC43 spike (D, I, and N), and the SARS-CoV-1 spike protein (E, J, and O) in triplicate. Longitudinal antibody titers of COVID-19 patients are plotted over days since symptom onset, whereas longitudinal pre-pandemic donor samples were collected in the course of a non-SARS-CoV-2 vaccine study before 2019 and plotted over days since immunization. Antibody responses were measured by an electrochemiluminescent multiplex immunoassay and reported as arbitrary units per ml (AU/mL) as normalized by a standard curve. IgG decay curves and half-lives estimated by an exponential decay model are shown in black. There was no significant decline in IgG reactive to endemic alpha and betacoronaviruses in longitudinal samples collected in healthy donors before the pandemic (red, [A–D]).

model). IgM levels to common betacoronaviruses HKU1 and OC43 were low in both pre-pandemic controls and COVID-19 patients (Figures 2M and 2N). While pre-existing exposure and antibodies against HKU1 and OC43 betacoronaviruses are common in adults, pre-existing SARS-CoV-1 exposure is rare and antibody levels to SARS-CoV-1 spike protein were very low (essentially negative) in the pre-pandemic healthy controls. However, SARS-CoV-1 spike-reactive antibodies increased significantly after SARS-CoV-2 infection. These increases were quite striking for IgG ($p = 0.0038$) and also IgA ($p = 0.0084$) and most likely represent cross-reactive antibodies directed to SARS-CoV-2 spike epitopes that are conserved between SARS-CoV-2 and SARS CoV-1[14]. These newly induced cross-reactive IgG antibodies generated after COVID-19 infection declined with an estimated half-life of 215 days (95% CI [168, 298]) (exponential decay model) (Figure 2). Taken together, these results show that people infected with SARS-CoV-2 may have also have some heightened immunity against the common human betacoronaviruses and more importantly against SARS-CoV-1.

Durable neutralizing antibody responses to SARS-CoV-2 in infected patients

Neutralizing antibodies were measured with a live virus focus reduction neutralization test that uses a recombinant SARS-CoV-2 virus expressing the fluorescent reporter gene mNeonGreen (FRNT-mNG) (Figure 3A). During the first 250 days post-symptom onset, $FRNT_{50}$ titers varied considerably between individuals and ranged from < 20 to 3726 (Figure 3A). Of the 183 individuals for whom longitudinal neutralization titers were assayed, 140 (77%) had at least one time point with neutralization titers above the limit of detection (> 20). Seventy-five percent (43/57) of COVID-19 patients generated serum neutralizing antibodies between 30–50 days after symptom onset and similarly 72% (48/67) had measurable titers between 180–263 days after symptom onset. Using an exponential decay model, we evaluated the kinetics of neutralizing antibody titers after day 42 and estimated a half-life of 150 days (95% CI [124, 226]). However, similar to the spike-reactive IgG binding antibodies, we hypothesized that the neutralizing antibody rate of decay may actually slow over time during the recovery period. To address this, we fit a power law to the data. The power law model fit significantly better than the exponential decay model (DAIC = 9) and estimated the half-life of neutralizing antibody responses at 120 days post-symptom onset to be 254 days (95% CI [183, 400]).

Next, we assessed the relationship between the levels of spike and RBD binding antibodies and SARS-CoV-2 neutralization. Figures 3B and C show the SARS-CoV-2 spike and RBD binding antibody response kinetics of the 183 participants for whom

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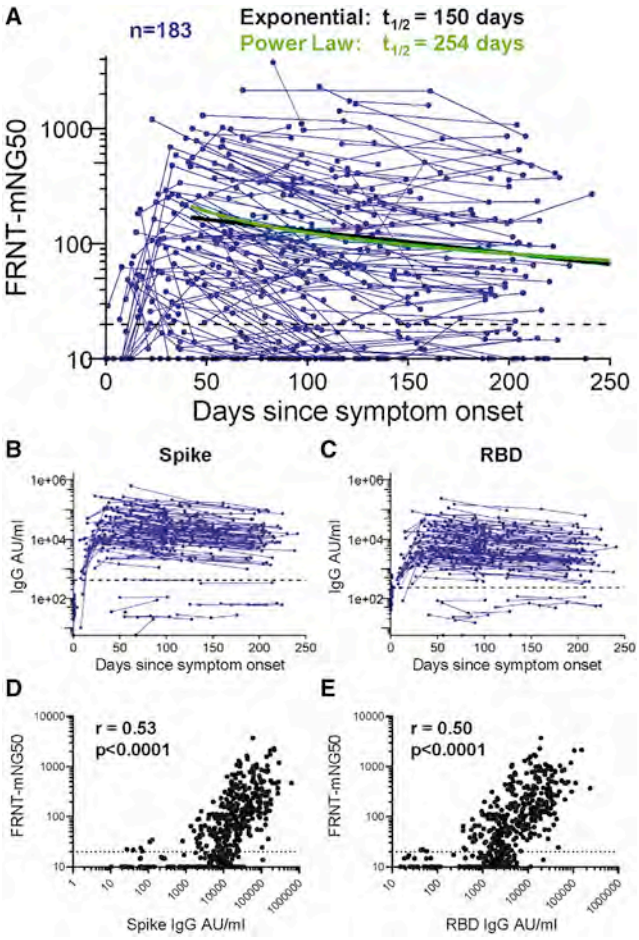

Figure 3. Neutralizing antibody responses to SARS-CoV-2

(A) *In vitro* serum neutralization antibody titers to SAR-CoV-2 were measured in duplicate by focus-reduction neutralization assay COVID-19 patients (n = 183). The limit of detection is indicated with a dashed line at FRNT-mNG$_{50}$ = 20. The half-life estimated by the exponential decay model (black) is 150 days, whereas the half-life estimated at day 120 using the power law model (green) is 254 days. (B and C) IgG antibody titers reactive to SARS-CoV-2 spike (B) and RBD (C) of the matched 183 COVID-19 for whom neutralization titers were assessed. The geometric mean titer plus 3 standard deviations of pre-pandemic samples is indicated by a dashed line.

(D and E) SARS-CoV-2 spike (D) and RBD (E) reactive IgG levels correlated with neutralization titers at the matched time point (repeated-measures correlation, $p < 0.0001$). The limit of detection is indicated with a dashed line at FRNT-mNG$_{50}$ = 20.

neutralization titers were assessed. These exhibited a wide range of antibody binding levels ranging from non-responders (n = 11) who did not elicit antibody titers above those of pre-pandemic controls (defined as a COVID-19 patient titer below the mean pre-pandemic antibody titer plus three standard deviations, see dashed line on Figures 3B and 3C) to those with IgG levels > 200,000 AU/mL. Spike and RBD binding IgG levels correlated significantly with the neutralization titers (Figure 3D, E; $p < 0.0001$).

Taken together, our findings show that induction of neutralizing antibodies occurs in the majority of COVID-19 patients. These neutralizing antibodies can persist over the 8–9 month period following infection, and show a correlation with spike and RBD binding IgG.

SARS-CoV-2 spike and RBD-specific memory B cells increase for several months after infection and then plateau over 8 months

Memory B cells (MBC) are an important component of humoral immunity and contribute to viral control by generating antibody responses upon re-exposure to the pathogen. We used full-length spike and RBD antigen probes to quantify the frequencies of SARS-CoV-2 spike- and RBD-specific MBC in longitudinal PBMC samples from 111 COVID-19 patients (Figure 4) and from 29 pre-pandemic controls (Figures S3A and S3B). Our flow cytometric gating strategy to identify SARS-CoV-2-specific MBC and classify them as IgG, IgM, and IgA MBC isotypes is shown in Figure 4A.

Among the total MBC, the spike IgG+ MBCs were significantly increased in COVID-19 patients (n = 111; Figure 4B) in comparison to pre-pandemic controls (n = 29; Figure S3A) (median increase, 0.73% versus 0.02%; $p < 0.0001$). After a steep early expansion over the first 2-3 months, the spike IgG+ MBC persisted in COVID-19 patients with no decline out to 250 days post symptom onset. These findings (Figure 4B) are supported by a positive slope (0.004) from the model of the longitudinal spike IgG+ MBC responses after day 30 (95% CI [0.002, 0.006], $p < 0.001$; Figures S4A and S4B).

The spike IgM+ MBC appeared within the first 2 weeks post-symptom onset and quickly declined (Figures 4C and 4D). The decay continued after day 30 (slope = −0.007, 95% CI [-0.010, −0.005], $p < 0.001$). One month after symptom onset, 56% of spike MBC were IgG+, which increased to a peak of 80% at 5–6 months (Figure 4D). Circulating spike IgA+ MBC were also detectable in many subjects at low frequencies and without significant change over time (day 30–250: slope = 0.000, 95% CI [-0.002, 0.002], $p = 0.91$, Figure 4D).

Since the RBD contains the primary neutralizing epitopes on the spike, we also used an RBD-specific probe to characterize this subset of spike-specific memory B cells. Overall, approximately 20% of the spike IgG+ memory B cells targeted the RBD, which was consistent across subjects and time (Figures 4E and 4F). As expected, RBD+ IgM+ MBC emerged early in infection and subsequently switched to RBD+ IgG+ MBCs, which gradually increased during follow-up (day 30–250: slope = 0.004, 95% CI [0.002, 0.005], $p < 0.001$, Figure 4E). Thus, the maintenance of circulating spike- and RBD-specific IgG memory B cells suggests that these cells could be recruited for a rapid secondary response following re-exposure or vaccination.

Induction of durable and polyfunctional virus specific memory CD4+ and CD8+ T cells in infected patients

CD4+ T cells are critical for generation of high affinity antibody responses and can also have anti-viral effects. In addition, they provide help for CD8+ T cell responses, which are vital for killing infected cells and mediating viral clearance. Thus, we next examined virus-specific CD4+ and CD8+ T cell responses longitudinally in COVID-19 patients and uninfected controls using a high-dimensional, multi-parameter *ex vivo* intracellular cytokine staining (ICS)

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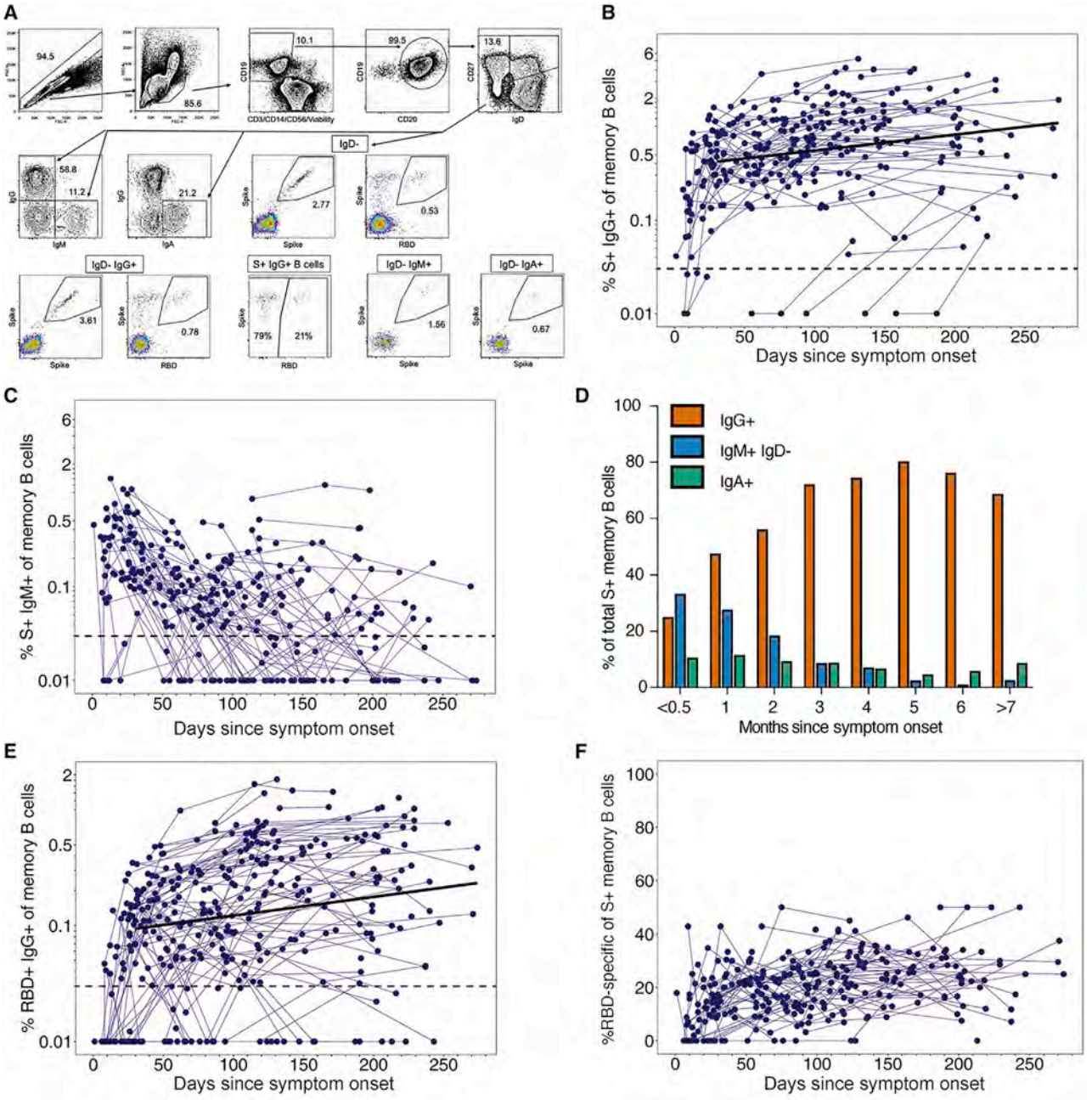

Figure 4. SARS-CoV-2 spike and RBD-specific memory B cells

(A) Representative memory B cell gating strategy is shown for identification of SARS-CoV-2 spike and RBD-specific IgD- IgG+, IgD- IgM+, and IgD- IgA+ memory B cells in PBMCs from a SARS-CoV-2 convalescent participant.

(B and C) The frequency of spike+ (B) IgG+ and (C) IgM+ memory B cells out of memory B cells (IgD- CD19+ CD20+) is displayed over time from initial symptom onset among SARS-CoV-2-infected subjects (n = 105 subjects; measured in singlet replicates). The dashed line indicates the limit of detection. The bold line represents the median fitted curve from a linear mixed effects model of post-day 30 responses.

(D) The median percent of spike+ memory B cells expressing IgG, IgM or IgA isotypes was assessed at monthly intervals post-symptom onset.

(E) The frequency of RBD+ IgG+ of memory B cells over time (n = 141).

(F) The proportion of S+ IgG+ memory B cells that are specific for the receptor binding domain are depicted over time.

assay. The assay is sensitive, precise, and specific for detection of antigen-specific T cells expressing multiple cytokines and effector molecules following a short-term (6 h) stimulation with peptide pools. Our lab developed and validated the assay, and we are currently using the method to quantitate Th1/Th2 CD4+ and CD8+ T cell responses in SARS-CoV-2 vaccine trials. Here,

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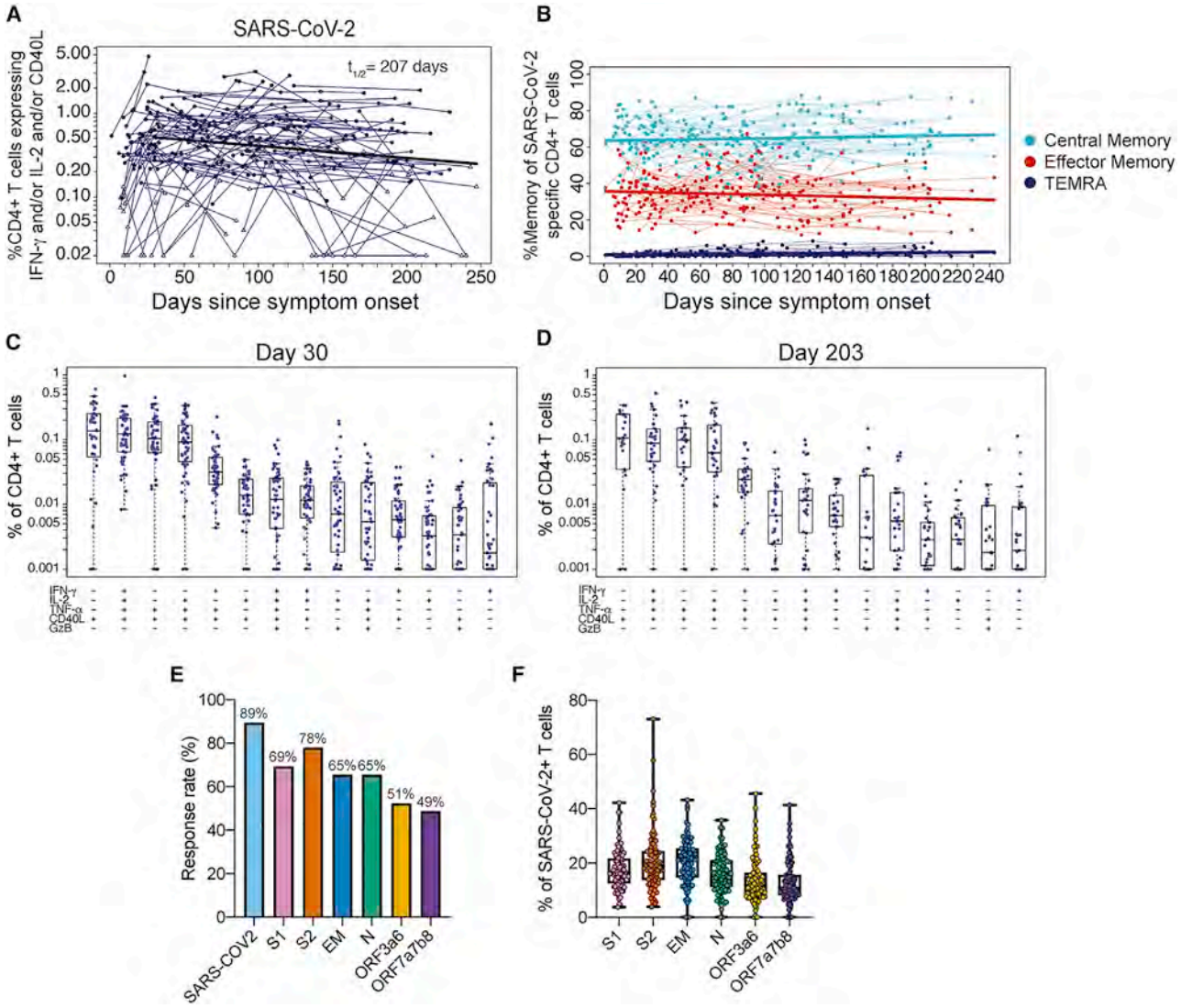

Figure 5. CD4+ T cell responses to SARS-CoV-2 antigens

(A) The sum of background-subtracted CD4+ T cells expressing *ex vivo* IFN-g, IL-2 and/or CD40L to peptide pools spanning SARS-CoV-2 structural proteins: S1, S2, envelope (E), membrane (M), nucleocapsid (N), and the following ORFs: 3a, 3b, 6, 7a, 7b, and 8 (n = 114; tested in singlets) for each individual/time point. Each sample that is "positive" (by MIMOSA) for at least one SARS-CoV-2 antigen is indicated by a solid circle, whereas samples that are "negative" for all of the SARS-CoV-2 antigens at that time point are indicated by open triangles. The bold line represents the median fitted curve from a nonlinear mixed effects model of post-day 30 responses among those with a positive response at $\geq$1 time point; $t_{1/2}$ is the median half-life estimated from the median slope, with 95% CI [104, 411].

(B) The proportion of SARS-CoV-2-specific CD4+ T cells expressing a specific memory phenotype over time: central memory (CCR7+ CD45RA-), effector memory (CCR7- CD45RA-), or T_{EMRA} (CCR7- CD45RA+); restricted to positive responders.

(C and D) Polyfunctionality of SARS-CoV-2-specific CD4+ T cells are shown at (C) 21-60 days since symptom onset (median, 30 days) and (D) > 180 days median post symptom onset (median, 203 days). Percentages of cytokine-expressing CD4+ T cells are background subtracted and only subsets with detectable T cells are displayed. Data shown were restricted to positive responders and a single data point per individual per time frame. All subsets were also evaluated for expression of IL-4, IL-5, IL-13, IL-17, and perforin and were found to be negative.

(E) Bar graphs indicate the proportion of COVID-19 convalescent patients who had a positive CD4+ T cell response to the individual SARS-CoV-2. peptide pool *ex vivo* stimulations. Some antigens were combined for stimulation as indicated.

(F) For each subject with positive SARS-CoV-2-specific CD4+ T cells, the proportion of the total SARS-CoV-2 responding CD4+ T cells that are specific for each stimulation.

we assessed T cell responses to the SARS-CoV-2 structural (S, E, M, and N) and accessory proteins (ORF 3a, 6, 7a, 7b, and 8) using overlapping peptide pools that span the sequences of these proteins.

Among COVID-19 patients, 89% (102/113) mounted CD4+ T cell responses (Figure 5A) recognizing at least one SARS-CoV-2 structural protein that was detectable at one or more visits. By contrast, SARS-CoV-2 specific CD4+ T cells were

rarely detected in the uninfected control group using this assay (Figure S3C). Antigen-specific CD4+ T cells expanded over the first month after infection and then gradually declined over subsequent months. Their estimated half-life was 207 days (95% CI [104, 211]) as shown in Figure 5A, and these findings are supported by the individual CD4+ T cell response levels and slopes after day 30 (slope = −0.0033, 95% CI [-0.0017, −0.0066], $p < 0.0001$) (Figures S4C and S4D). Of note, we observed a wide range in the total magnitude of responses, some reaching >1% of circulating CD4+ T cells, and an overall median frequency of 0.51% (Figures 5A and S5).

To better characterize the development of T cell memory in SARS-CoV-2 infection, we examined the differentiation profiles of virus-specific T cells longitudinally in COVID-19 patients. Based on CD45RA and CCR7 expression, SARS-CoV-2-specific CD4+ T cells were primarily central memory phenotype (CD 45RA- CCR7+) and to a lesser extent effector memory (CCRA-CCR7-); this profile of the memory T cell subsets was very consistent between subjects and stable over time (Figure 5B). The antigen-specific CD4+ T cells were Th1-biased with a predominant CXCR3+CCR6- phenotype, and highly polyfunctional, with simultaneous detection of antigen-specific CD154, IFN-γ, IL-2, TNF-α and less frequently granzyme B in the early expansion phase (21–60 days post symptom onset; median, 30 days) (Figure 5C). Interestingly, many of the virus-specific CD4+ T cells also exhibited this polyfunctionality at the memory time point (>180 days post symptom onset; median, 203 days) (Figure 5D). Circulating SARS-CoV-2-specific Th2 (IL-4, IL-5, and IL-13), Th17 (IL-17), or perforin-expressing subsets were not detected (Figures 5C and 5D).

Next, we examined the CD8+ T cell responses in COVID-19 patients and found that 69% generated CD8+ T cells recognizing at least one SARS-CoV-2 structural protein that were detectable at one or more visits (Figure 6A), in contrast to infrequent to rare, low-level antigen-specific responses in the uninfected control donors (Figure S3D). Expansion of CD8+ T cells occurred over the first month and then frequencies gradually declined, with a half-life of 196 days (95% CI [92, 417]) and a negative estimated slope after 30 days of symptom onset (slope = −0.004, 95% CI [-0.002, −0.008], $p < 0.0001$) (Figure 6A). The median frequency of SARS-CoV-2-specific CD8+ T cells was 0.2%, indicating a lower overall response magnitude than observed for CD4+ T cells. However, like the CD4+ T cells, a wide range in magnitudes was observed with many SARS-CoV-2-specific CD8+ T cell frequencies above 1% and even up to 12% (Figure 6A).

A very different pattern of phenotypic changes were observed with virus-specific CD8+ T cells compared to what we saw with the CD4+ T cells (Figure 6B versus Figure 5B). In contrast to the dominance of the central memory subset with SARS-CoV-2-specific CD4+ T cells, the vast majority of the virus-specific CD8+ T cells showed an effector memory phenotype during the early phase of the response. However, this population of SARS-CoV-2-specific effector memory (CD45RA-CCR7-) contracted over time (slope = −0.904, $p < 0.0001$; Figure 6B) and simultaneously there was an increase in the proportion of the TEMRA (CD45RA+CCR7-) subset of virus-specific CD8+ T cells (slope = 0.075, $p < 0.0001$; Figure 6B). A small but stable fraction of SARS-CoV-2-specific CD8+ T cells expressed a central memory phenotype (slope = 0.024, p = ns; Figure 6B).

The SARS-CoV-2-specific CD8+ T cells were highly polyfunctional with the highest magnitude populations secreting IFN-γ, TNF-α, and granzyme B; other dominant subsets also expressed IL-2 or perforin (Figures 6C and 6D). This polyfunctional profile was seen in the expansion phase (median 30 days; Figure 6C) and also at the later time points (>180 days post symptom onset; median 203 days; Figure 6D). It is important to note that this pattern of CD8+ T cell differentiation has been described in detail after vaccination in humans with the live attenuated yellow fever virus vaccine (YFV-17D).[15] This YFV-17D vaccine generates long-lived and functional virus-specific memory CD8+ T cells that persist in humans for decades.[15,16] That the CD8+ T cell differentiation program after COVID-19 infection resembles what is seen after YFV infection of human suggests that COVID-19 patients may also generate long-lived CD8+ T cell memory.

CD4+ and CD8+ cells target different SARS-CoV-2 antigen specificities

The majority of COVID-19 patients generated CD4+ T cells that recognized most SARS-CoV-2 viral structural and accessory proteins, with the highest percentage responding to S2 (78%) and S1 (69%) (Figures 5E and 5F). Among the COVID-19 subjects with positive responses, the proportion of SARS-CoV-2-specific CD4+ T cells reacting to each peptide pool was evenly distributed (Figure 5F). Thus, CD4+ T cells equally targeted multiple SARS-CoV-2 proteins.

In contrast to the results seen with CD4+ T cells, SARS-CoV-2-specific CD8+ T cells showed preferential recognition of the nucleocapsid protein. The dominant CD8+ T cell response rate was directed to the nucleocapsid (57%); followed by ORFs 7a, 7b, and/or 8 (25%); S1 (25%); ORFs 3a and/or 6 (16%); S2 (12%); and E and/or M (9%) (Figure 6E). Also, among the COVID-19 patients with CD8+ T cell responses, there was a bias with the largest percentage (median, 43%) reacting to the nucleoprocapsid protein (Figure 6F). While SARS-CoV-2 CD8+ T cell responses rates were much lower in uninfected controls, when present in a few control donors with lower frequencies, these were also targeted to the nucleocapsid protein (Figure S3D). A likely explanation for these findings is that in SARS-CoV-2 infection, antigen-presenting cells *in vivo* may display a higher proportion of peptides derived from the nucleocapsid protein and hence more nucleocapsid-specific CD8+ T cells are generated during infection. This has interesting implications suggesting that nucleocapsid-specific CD8+ T cells might be more efficient in recognizing virally infected cells.

Age and disease severity are significantly associated with magnitude of SARS-CoV-2 immune responses

We evaluated whether COVID-19 patient age, disease severity, or gender could account in part for the heterogeneity observed among the SARS-CoV-2-specific immune responses as estimated from the individual models (post day 30 for cellular and post day 42 for antibody responses). We observed that age was significantly associated with higher immune responses to SARS-CoV-2, independently of any covariation with disease

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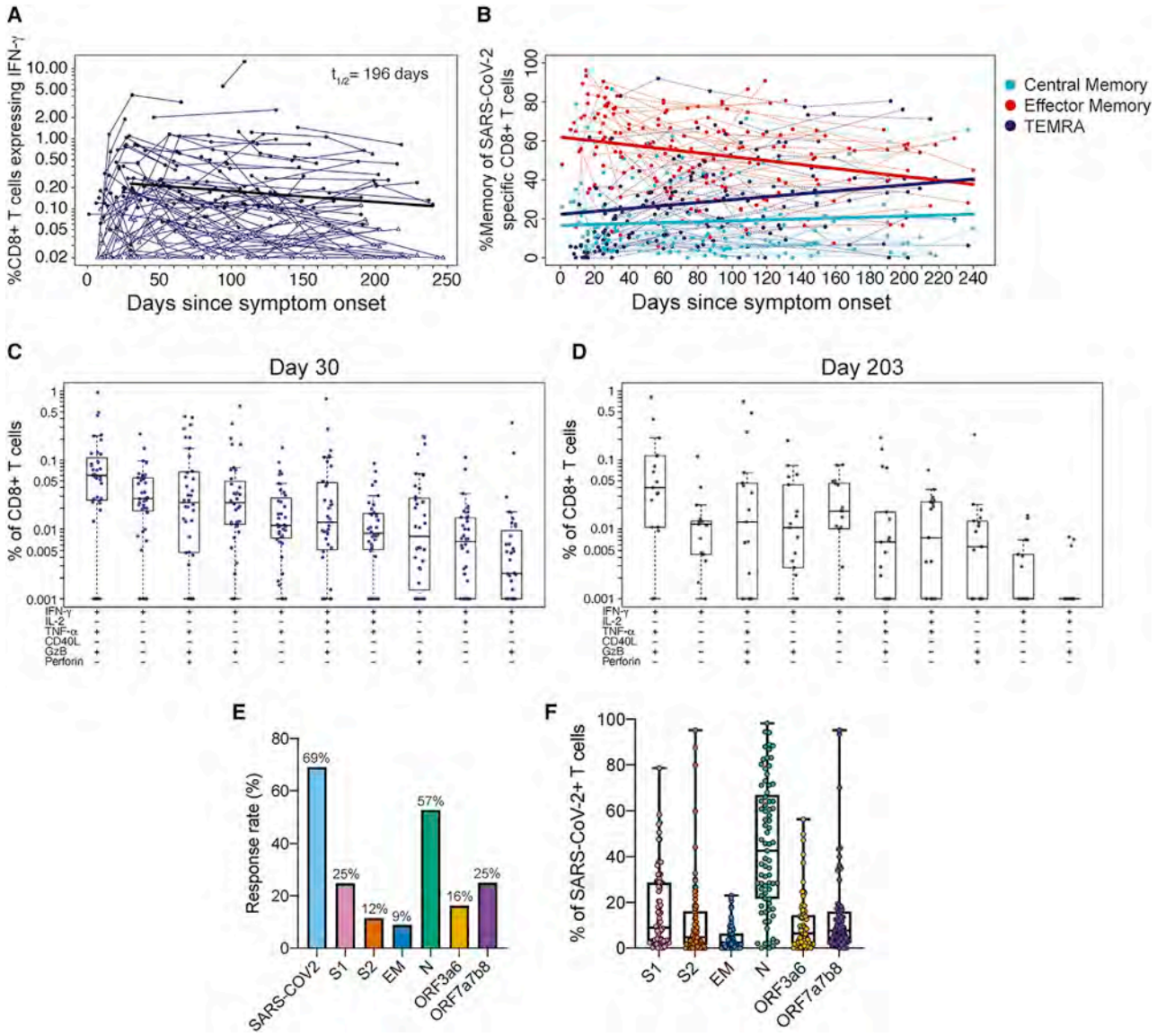

Figure 6. CD8+ T cell responses to SARS-COV-2 antigens

(A) The sum of background-subtracted CD8+ T cells expressing IFN-γ (with or without other cytokines), in response to peptide pools covering SARS-CoV-2 structural proteins: S1, S2, envelope (E), membrane (M), nucleocapsid (N), and the following ORFs: 3a, 3b, 6, 7a, 7b, and 8 (n = 114; tested in singlets) for each individual/time point. Each sample that is positive (MIMOSA) for at least 1 SARS-CoV-2 antigen is indicated by a solid circle, whereas samples that are negative for all of the SARS-CoV-2 antigens at that time point are indicated by open triangles. The bold black line represents the median fitted curve from a nonlinear mixed effects model of post-day 30 responses among those with a positive response to the antigen(s) under consideration at [3]1 time point; $t_{1/2}$ shown is the median half-life estimated from the median slope, with 95% CI [92, 417].

(B) The proportion of SARS-CoV-2-specific CD8+ T cells by memory phenotype over time: effector memory (EM; CCR7- CD45RA-), T_{EMRA} (CCR7- CD45RA+), and central memory (CM; CCR7+ CD45RA-). Analyses were restricted to positive responders.

(C and D) Polyfunctionality of SARS-CoV-2-specific CD8 T cells at (C) 21–60 days post symptom onset (median, 30 days) and (D) >180 days median post symptom onset (median, 203 days). Percentages of cytokine expressing CD8+ T cells are background subtracted and only subsets with detectable T cells are displayed. Data shown were restricted to positive responders and a single data point per individual per time frame. All CD8+ T cell subsets were also evaluated for expression of IL-4, IL-5, IL-13, and IL-17 and were found to be negative.

(E) The bar graphs indicate the proportion of COVID-19 convalescent patients who had a positive CD8+ T cell response to the individual SARS-CoV-2 stimulations.

(F) The fraction of the total SARS-CoV-2 responding CD8+ T cells per subject that are specific for each peptide pool.

severity (Figure 7A). Neutralizing antibody titers and IgG antibody responses to nucleocapsid increased 1.35-fold and 1.25-fold, respectively, with each decade of age and the same disease severity (95% *Cis* [1.19, 1.54] and [1.08, 1.43], p values < 0.003). Similarly, increased age positively correlated with increased frequencies of spike and RBD-specific IgG+ memory

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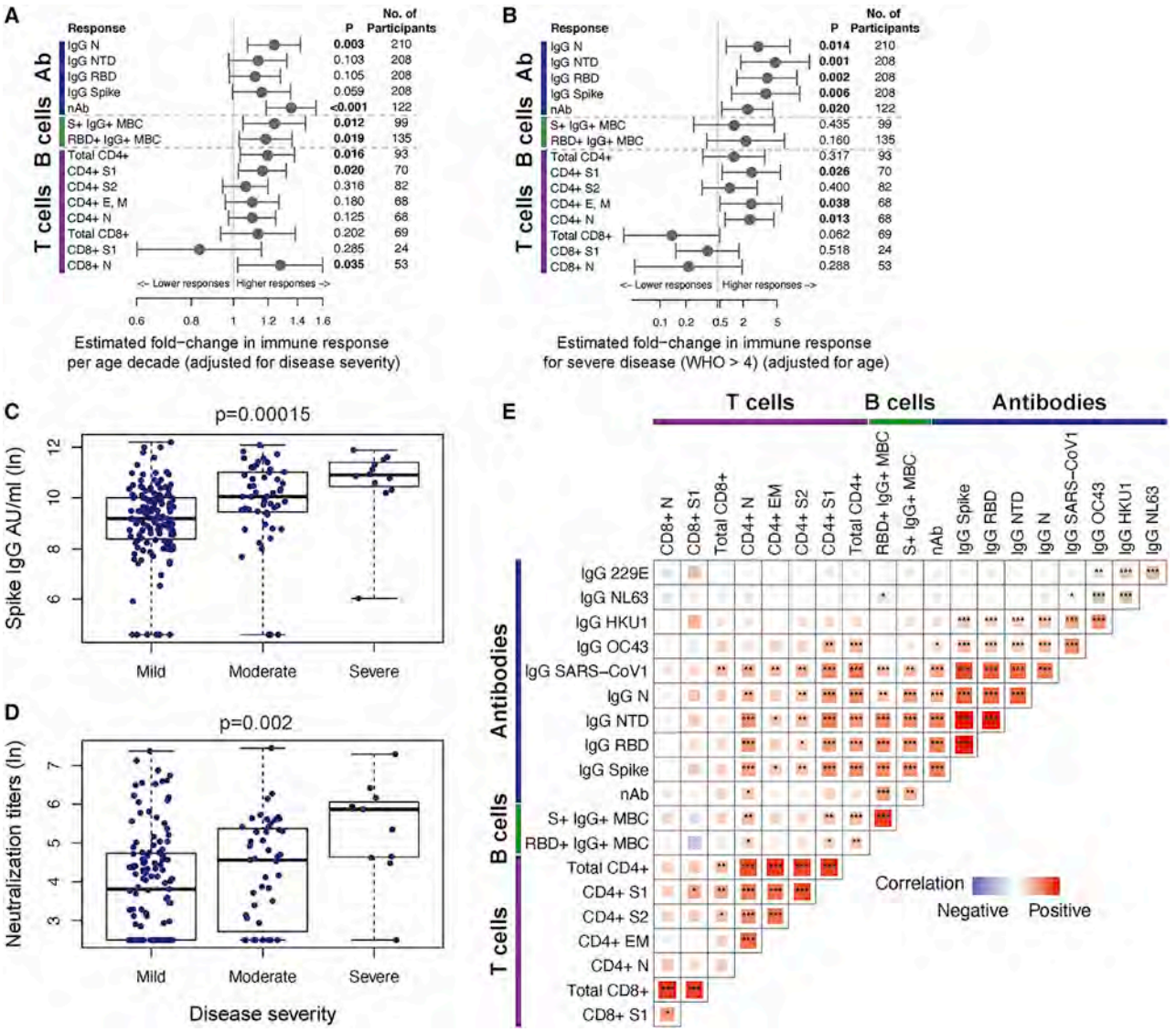

Figure 7. Correlations between SARS-CoV-2-specific immune responses and assessment of covariates

(A) The forest plot depicts the estimated fold-change in the level of each immune response per decade of age, with 95% Wald-based CIs and p values.

(B) The forest plot shows the estimated fold-change in the level of each immune response for severe (WHO score >4) versus non-severe (WHO score £4) disease, with 95% Wald-based CIs and p values. S1 CD8+ T cell responses compared moderate-severe (WHO score >2) to mild (WHO score £2) disease as there were no participants with severe disease with at least one positive S1 CD8+ T cell response post-day 30. Estimates in (A) and (B) are from mixed effects models of post-day 30 (B and T cell responses) or post-day 42 (antibody responses) among responders that account for fixed effects of age and disease severity on the level of immune response.

(C and D) Univariate assessment of disease severity on the magnitude of (C) spike IgG antibodies and (D) SARS-CoV-2 neutralizing antibodies at day 120 is shown for mild (WHO score: 0-2), moderate (WHO score: 3-4), and severe disease (WHO score: 5+); p values from one-way ANOVA.

(E) The heatmap shows Spearman correlations between critical SARS-CoV-2 memory immune responses (day 30 B and T cell responses and day 180 antibody responses) with significance levels: *p < 0.05, **p < 0.01, and ***p < 0.001. The tile size and color intensity correspond to the absolute value of the Spearman rank correlation coefficient, with red or blue indicating a positive or negative correlation, respectively. Day 30, 42, and 180 immune responses were estimated from mixed effects models of the longitudinal SARS-CoV-2 binding antibodies, SARS-CoV-2 neutralizing antibodies, CD4+ and CD8+ T cell responses, and B cell responses.

B cells, with 1.19- to 1.24-fold higher responses per decade of age (p values < 0.02; Figure 7A), accounting for disease severity. Increased age also correlated with higher SARS-CoV-2 and S1-specific CD4+ T cell responses (1.16- to 1.20-fold increase by decade of age, p values < 0.02) and N-specific CD8+ T cell responses (1.24-fold increase by decade of age, p = 0.039) accounting for disease severity (Figure 7A).

Since the cohort included primarily persons with mild-to-moderate COVID-19, we had limited ability to assess the relationship of severe disease and SARS-CoV-2 immune responses,

especially among the cellular responses. However, we found that after accounting for age, severe disease (WHO score >4) was associated with higher IgG antibodies to nucleocapsid, spike, RBD, and NTD (Figures 7B and 7C), and SARS-CoV-2 neutralization titers (Figure 7D). Severe disease was also associated with 2.30- to 2.46-fold higher S1, E and/or M, and nucleocapsid-specific CD4+ T cells (all p values < 0.05; Figure 7B). We found no significant relationships between gender and the immune responses evaluated, apart from 1.66-fold higher IgG NTD responses antibodies among males compared to females, after accounting for age and disease severity (95% CI [1.08, 2.55], p = 0.022). In all, our analyses suggest that there are synergistic but also independent mechanisms driving higher adaptive immune responses in COVID-19 patients who are older and/or who experienced more severe disease.

Early SARS-CoV-2 B and T cell responses correlated with durable spike and RBD IgG antibody binding and neutralization titers

We assessed correlations between SARS-CoV-2-specific immune responses using the individual-level models to interpolate the magnitude of responses for each COVID-19 patient at early (day 30) or later (day 180) convalescent time points (Figure 7E). We found that durable serum neutralization titers correlated with the magnitude of IgG+ binding antibodies to spike, NTD and RBD at day 180 each (day 180; Spearman R = 0.62, 0.61, and 0.61, respectively; all p values < 0.0001). Similarly, the frequency of RBD+ IgG+ memory B cells at day 30 correlated with the maintenance of RBD+ IgG antibodies (day 180; Spearman R = 0.53, p < 0.0001) and neutralization antibody titers (day 180; Spearman R = 0.48, p < 0.0001). We also observed that the magnitude of S1-specific CD4+ T cells at day 30 correlated with durable IgG antibodies against spike (day 180; Spearman R = 0.56, p < 0.0001), NTD (Spearman R = 0.62, p < 0.0001), and RBD (Spearman R = 0.47, p = 0.0002) (Figure 7E). These findings are consistent with early SARS-CoV-2 memory B cells and CD4+ T cells supporting the generation of durable antibody responses.

DISCUSSION

Establishing immune memory is essential in the defense against SARS-CoV-2 infection. To end the COVID-19 pandemic, it is critical to know how long immunity against SARS-CoV-2 will persist after infection and whether it will be sufficient to prevent new infections and severe disease in years to come. Identifying, in-depth, the adaptive immune components leading to recovery and modeling the trends of each response was enabled by the longitudinal sampling of a large number of COVID-19 patients. Here, we show that most convalescent COVID-19 patients mount durable antibodies, B cells, and T cells specific for SARS-CoV-2 up to 250 days, and the kinetics of these responses provide an early indication for a favorable course ahead to achieve long-lived immunity. Because the cohort will be followed for 2–3 more years, we can build on these results to define the progression to long-lived immunity against this novel human coronavirus, which can guide rational responses when future outbreaks occur.

The hallmark of the initial immune defense against SARS-CoV-2 is the emergence of antibodies recognizing the SARS-CoV-2 spike protein, including the RBD and NTD components of the S1 subunit, during the early phase of viral replication. These antibodies are likely secreted from plasmablasts rapidly generated from B cells that are activated upon their first encounter with the pathogen spike antigen. The brisk rise over the first month of infection, followed by a fast decline of the circulating spike IgG and IgA antibodies, is a consistent finding and likely explained by the disappearance of the short-lived plasmablasts. These events occur even sooner for the spike IgM and nucleocapsid antibodies.

Some antibodies that bind to specific epitopes on the spike RBD and NTD can block SARS-CoV-2 infection of respiratory epithelial cells by inhibiting the interactions of the viral spike with the ACE2 receptor.[17-20] Thus, as expected, the early rise and decline of antibodies neutralizing live SARS-CoV-2 were similar to the kinetics of antibodies binding the spike and RBD protein. The striking finding is the bi-phasic curve of the spike-specific binding and neutralizing antibody responses when analyzed with the power law model, which provides a better fit for the antibody kinetics after the peak response.[21] This bi-phasic decline accords with other recently published observations on SARS-CoV-2 serological kinetics.[22,23] With sampling data extended to 250 days, we were able to detect a slowing of the decay of these functional antibodies toward a plateau level, suggestive of the generation of longer-lived plasma cells, and durable antibody responses. The importance of these observations is that following recovery, neutralizing antibodies may persist, albeit at low levels, and may act as the first line of defense against future encounters of SARS-CoV-2 and possibly related human coronaviruses.

Another interesting finding of this investigation is the remarkably stable antibody responses among the pre-pandemic and COVID-19 patients to the common human coronaviruses that are acquired in children and adults. These data are most consistent with the generation of long-lived plasma cells and refute the current notion that these antibody responses to human coronaviruses are short lived. Moreover, the COVID-19 patients mounted increased IgG antibody responses to SARS-CoV-1, a related pathogen that none likely had experienced previous exposure to. This finding is consistent with the booster response of SARS-CoV-1 neutralizing antibodies that we recently observed following SARS-CoV-2 mRNA vaccination.[3,24] Taken together, these results may have implications for a broader strategy for vaccines targeting multiple betacoronaviruses.

The durable antibody responses in the COVID-19 recovery period are further substantiated by the ongoing rise in both the spike and RBD memory B cell responses after over 3–5 months before entering a plateau phase over 6–8 months. Persistence of RBD memory B cells has been noted.[25-27] We presume this may be explained by sustained production of memory B cells in germinal centers of lymph nodes draining the respiratory tract in the early months, followed by the memory B cell redistribution into the circulation as the germinal centers begin to recede. Thus, the induction and maintenance of memory B cells and, over time, long-lived plasma cells, will continue to furnish higher affinity antibodies if re-exposures occur.

In contrast to spike memory B cell kinetics, SARS-CoV-2-specific CD4+ and CD8+ memory T cells each peak early, within the first month, but then slowly decline over the next 6–7 months. Central memory Th1-type CD4+ T cells dominate throughout the early infection and recovery period. However, the CD8+ T cells exhibit a predominant effector memory phenotype early that transitions to those effector memory cells re-expressing CD45RA, maintaining expression of antiviral cytokines and effector functions that have been shown to provide protective immunity against other viral pathogens. We also provide clear evidence that the CD4+ T cells mount a broader antigen-specific response across the structural and accessory gene products, whereas the CD8+ T cells are predominantly nucleocapsid specific and spike-specific responses are substantially lower in frequency.

Our study demonstrates the considerable immune heterogeneity in the generation of potentially protective response against SARS-CoV-2, and by focusing on the dynamics and maintenance of B and T cell memory responses, we were able to identify features of these early cellular responses that can forecast the durability of a potentially effective antibody response. The ability to mount higher frequencies of RBD-specific memory IgG+ B cells early in infection was the best indicator for a durable RBD-specific IgG antibody and neutralizing antibody response. In addition, higher frequency CD4+ T cells were associated with stronger spike IgG and neutralizing antibody responses. However, the induction and peak response of SARS-CoV-2-specific CD8+ T cells occurs independently to these antibody responses. Interestingly, while it has been widely reported that age correlates with COVID-19 disease severity, we found that age and disease severity were independent co-variates associated with the magnitude of both SARS-CoV-2-specific CD4+ T cell and humoral SARS-CoV-2 immunity, but not with the magnitude of CD8+ T cell responses. In the case of T cells, whether the T cell differences are related to the frequencies or specificities of pre-existing coronavirus CD4+ and CD8+ T cell immunity will require additional future analysis.

The COVID-19 pandemic remains a global public health threat after 1 year of overwhelming disruption and loss. Overcoming the challenges to end the pandemic is accentuated by the recognition that SARS-CoV-2 can undergo rapid antigenic variation that may lower vaccine effectiveness in preventing new cases and progression to severe disease.[24,28,29] Our findings show that most COVID-19 patients induce a wide-ranging immune defense against SARS-CoV-2 infection, encompassing antibodies and memory B cells recognizing both the RBD and other regions of the spike, broadly-specific and polyfunctional CD4+ T cells, and polyfunctional CD8+ T cells. The immune response to natural infection is likely to provide some degree of protective immunity even against SARS-CoV-2 variants because the CD4+ and CD8+ T cell epitopes will likely be conserved. Thus, vaccine induction of CD8+ T cells to more conserved antigens such as the nucleocapsid, rather than just to SARS-CoV-2 spike antigens, may add benefit to more rapid containment of infection as SARS-CoV-2 variants overtake the prevailing strains.

Limitations of the study

Our study evaluates COVID-19 patients only up to 8 months and requires models to estimate immune response half-lives thereafter. Because our longitudinal study will extend beyond 2 years, we can corroborate our models with subsequent experimental data on the persistence of immune memory. Our study population was primarily outpatients with mild-to-moderate COVID-19 and thus we were unable to evaluate immune memory in those with the extreme presentations, both asymptomatic and severe COVID-19. However, mild-moderate illness accounts for >80% of COVID-19 cases[30], highlighting the relevance of our findings over time.

STAR★METHODS

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SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.xcrm.2021.100354.

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AUTHOR CONTRIBUTIONS

M.J.M and R. Ahmed conceived the study. M.J.M., S.E., J.C., E.J.A., A.K.M, N.R., and J.O.K. established the cohort and recruited the participants. S.L.L., M.P.L., C.W.D., M.P.G., S.G., K.A.S., G.M., C.N., V.V.E., L.L., and D.S.S. conducted serological assays and related analyses. H.A., V.I.Z., B.P., and Z.M. conducted formal statistical analyses and modeling. K.W.C., R.W., and L.E.N. planned, performed, and analyzed antigen-specific B cell flow cytometry. S.C.D., K.W.C., and S.F. conceived, supervised, performed, and analyzed T cell experiments. V.E.E, K.F., and L.L. performed FRNT assays. K.W.C., S.L.L., and Z.M. drafted the original manuscript; M.J.M., M.S.S., and R. Ahmed edited the manuscript. All authors read and approved the manuscript. M.J.M., R.A, J.W., and M.S.S. secured funds and supervised the project.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Antibodies		
Mouse Anti-Human CD3/BV510	BD Biosciences	564713; RRID:AB_2738909
Mouse Anti-Human CD14/BV510	BD Biosciences	563079; RRID:AB_2737993
Mouse Anti-Human CD56/BV510	BD Biosciences	563041; RRID:AB_2732786
Mouse Anti-Human CD19/BUV395	BD Biosciences	563549; RRID:AB_2738272
Mouse Anti-Human CD20/BUV737	BD Biosciences	612849; RRID:AB_2870169
Mouse Anti-Human CD21/PE-Cy7	BD Biosciences	561374; RRID:AB_10681717
Mouse Anti-Human CD27/BV605	BD Biosciences	302830; RRID: AB_2561450
Mouse Anti-Human CD38/BB700	BioLegend	566445; RRID:AB_2744375
Mouse Anti-Human IgA/VioBlue	Miltenyi Biotec	130-114-005; RRID:AB_2733958
Mouse Anti-Human IgD/BV650	BD Biosciences	740594; RRID:AB_2740295
Mouse Anti-Human IgG/BV786	BD Biosciences	564230; RRID:AB_2738684
Mouse Anti-Human IgM/PE-Dazzle 594	BioLegend	314530; RRID:AB_2566483
Streptavidin (PE)	Invitrogen	S21388; RRID:AB_2892541
Streptavidin (AF488)	Invitrogen	S32354; RRID:AB_2315383
Streptavidin (AF647)	Invitrogen	S32357; RRID:AB_2892542
Live/Dead Fixable Aqua Stain	Invitrogen	L34957
Fixable Viability Dye/eFluor 450	Invitrogen	65-0863
Mouse Anti-Human CD14/BUV661	BD Biosciences	741684; RRID:AB_2868407
Mouse Anti-Human CD19/BUV563	BD Biosciences	612916; RRID:AB_2870201
Mouse Anti-Human CD16/BV570	BioLegend	302036; RRID:AB_2632790
Mouse Anti-Human CD56/BV750	BioLegend	362556; RRID:AB_2801001
Mouse Anti-Human CD3/APC-Fire750	BioLegend	300470; RRID:AB_2629689
Mouse Anti-Human CD4/BV480	BD Biosciences	566104; RRID:AB_2739506
Mouse Anti-Human CD8/BUV805	BD Biosciences	612889; RRID:AB_2833078
Mouse Anti-Human CD197(CCR7)/BV605	BioLegend	353224; RRID:AB_2561753
Mouse Anti-Human CD45RA/BUV496	BD Biosciences	750258; RRID:AB_2874456
Mouse Anti-Human CD25/BV650	BD Biosciences	563719; RRID: AB2744337
Rat Anti-Human FOXP3/PE-Cy5.5	Invitrogen	35-4776-42; RRID:AB_11218682
Mouse Anti-Human CD32/PE-Dazzle	BioLegend	303218; RRID:AB_2716072
Mouse Anti-Human CD65/BV711	BioLegend	305042; RRID:AB_2800778
Mouse Anti-Human CD183/PE-Cy5	BD Biosciences	551128; RRID:AB_394061
Mouse Anti-Human CD196 (CCR6)/BV786	BD Biosciences	563704; RRID:AB_2738381
Rat Anti-Human CD294 (CRTH2)/PE	BioLegend	350106; RRID:AB_10900060
Mouse Anti-Human IFN-g/V450	BD Biosciences	560371; RRID:AB_1645594
Rat Anti-Human IL-2/APC	BioLegend	500310; RRID:AB_315097
Mouse Anti-Human TNF/BUV395	BD Biosciences	563996; RRID:AB_2738533
Mouse Anti-Human IL-17A/PE-Cy7	BioLegend	512315; RRID:AB_2295923
Rat Anti-Human IL-4/BB700	BD Biosciences	Custom
Rat Anti-Human/Anti-Mouse IL-5/BB630	BD Biosciences	Custom
Rat Anti-Human IL-13/BV421	BD Biosciences	Custom
Mouse Anti-Human CD154 (BUV737)	BD Biosciences	748983; RRID:AB_2873383
Mouse Anti-Human Granzyme B/AF700	BD Biosciences	560213; RRID:AB_1645453
Mouse Anti-Human Perforin/FITC	BD Biosciences	353310; RRID:AB_2571967
Mouse Anti-Human Ki-67/BB660	BD Biosciences	Custom

(*Continued on next page*)

Continued

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Bacterial and virus strains		
icSARS-CoV-2-mNG	Xie et a.	N/A
Chemicals, peptides, and recombinant proteins		
SARS-CoV-2 Spike peptides	Biosynthesis	Custom
SARS-CoV-2 E, M, N and ORF peptides	Genscript	Custom
SARS-CoV-2 Spike protein (S6P)	Fred Hutchinson Cancer Research Center	Custom
SARS-CoV-2 RBD protein	Fred Hutchinson Cancer Research Center	Custom
Methylcellulose	Sigma-Aldrich	M0512-250G
TrueBlue Peroxidase Substrate	KPL	5510-0050
Critical commercial assays		
V-PLEX COVID-19 Coronavirus Panel 2 (IgG) Kit	Meso Scale Discovery	K15369U
V-PLEX COVID-19 Coronavirus Panel 2 (IgA) Kit	Meso Scale Discovery	K15371U
V-PLEX COVID-19 Coronavirus Panel 2 (IgM) Kit	Meso Scale Discovery	K15370U
Experimental models: Cell lines		
VeroE6 C1008 cells	ATCC	Cat# CRL-1586; RRID:CVCL_0574
Software and algorithms		
FlowJo	BD Biosciences	V9.9.4
R	R Foundation for Statistical Computing	V3.6.1
GraphPad Prism	GraphPad	V7, 8 and 9
Viridot	Katzelnick et al.	https://github.com/leahkatzelnick/Viridot
Monolix	Lixoft	MonolixSuite2019R1
Other		
ELISPOT reader	Immunospot	CTL ImmunoSpot S6 Universal Analyzer

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources and reagents should be directed to and will be fulfilled by the lead contact, M. Juliana McElrath (jmcelrat@fredhutch.org).

Materials availability

This study did not generate new unique reagents.

Data and code availability

The underlying data for this paper will be shared by the lead contact upon request without restriction.

EXPERIMENTAL MODEL AND SUBJECT DETAILS

Study populations

Two longitudinal COVID-19 cohort studies at Fred Hutchinson Cancer Research Center (Seattle, Washington) and Emory University (Atlanta, Georgia) began after receiving institutional review board approvals (IRB 10440, IRB 00001080 and IRB00022371). Adults ^{3}18 years were enrolled who met eligibility criteria for SARS-CoV-2 infection and provided informed consent. Study participants provided medical history of co-morbidities, presentation of SARS-CoV-2 infection onset and disease course, and peripheral blood at initial and follow up visits for analysis of serum antibody and cellular immune responses. Additional longitudinal archived sera and PBMC from pre-pandemic study populations from Emory and Seattle served as controls for the immune assays.

The Atlanta study population included adult volunteers over the age of 18 who were diagnosed with COVID-19 by a commercially available SARS CoV-2 PCR assay, rapid antigen test, or clinical syndrome only (later confirmed with serology) due to limited SARS-CoV-2 testing during the early period of the pandemic. Ambulatory participants were recruited through local advertisements,

internet-based avenues (such as social media, listserves), COVID-19 testing sites, and primary care clinics. Hospitalized patients were identified through SARS-CoV-2 testing. Informed consent was obtained from all participants prior to conduct of study procedures. Initial acute peripheral blood samples were collected from hospitalized patients at the time of enrollment. Convalescent samples from hospitalized patients were collected when the patients were able to return for a visit to the clinical research site at the next study visit. Serial peripheral blood samples were collected starting at about 30 days after the onset of COVID-19 symptoms and/or after PCR positivity for SARS-CoV-2. Thereafter, samples were collected at 3, 6, and 9 months. The study is ongoing with expected completion of sample collection from participants in February 2023. Participants were excluded if they were immunocompromised, HIV positive, had active hepatitis B or C virus infection, used immunosuppressive drugs for 2 weeks or more in the preceding 3 months, received blood products or immune globulin 42 days prior to enrollment, received convalescent COVID-19 plasma, or were pregnant or breast feeding. We report on 110 participants to date, of which 73% were diagnosed by SARS-CoV-2 PCR, the remaining were diagnosed by rapid antigen test or serology. Demographic features of the participants are as follows: median age was 48; 45% were male; the majority (80%) were white, 11% Black/African American, 6% Asian, and 8% were Hispanic/Latinx ethnicity. The most frequent co-morbid conditions were hypertension, obesity, heart disease and diabetes mellitus. The most frequent COVID-19 symptoms were myalgia/fatigue, fever, cough, headache, loss of smell and taste (Table S1). Hospitalized patients were older, with a median age of 56; a higher percentage were Black/African American (27%); and 100% had fever.

Longitudinal pre-pandemic sera samples from Emory were collected from individuals participating in a yellow fever vaccine study from 2014-2016 or an influenza vaccine study from 2015-2018[15,31]. Data were included for analysis of binding antibody responses and are presented as days post-irrelevant (yellow fever) vaccination. The study was approved by the Emory University IRB and donors were enrolled after providing written informed consent.

The Seattle COVID-19 Cohort study participants were recruited from the Seattle metropolitan area by social media advertisements, partnership with the local emergency medical service and by word of mouth. Study participants were screened and enrolled by the Seattle Vaccine Trials Unit staff. Eligibility criteria included adults at risk for SARS-CoV-2 infection or those diagnosed with COVID-19 by a commercially available SARS-CoV-2 PCR assay or blood antibody test and willing to have at least four blood draws collected over one year. Exclusion criteria included pregnancy and inability to donate blood.

Informed electronic consent was obtained from all Seattle participants during a screening phone call with study clinical staff. Interested participants were screened, consented and medical history and COVID-19 illness onset date and symptoms collected. Participants undiagnosed with COVID-19 had a nasopharyngeal (NP) swab collected and tested for SARS-CoV-2 via an FDA-approved PCR test and blood was collected for SARS-CoV-2 antibody (Abbott) and study assays. Those with either a positive PCR or antibody test were asked to return for future blood draws. Those who tested negative were asked to return as controls for the positive cohort and in case they tested positive in the future. Participants with a positive test prior to study enrollment or those diagnosed in study were asked to provide blood donation at approximately 7 days, 2 weeks, 1, 2, 3, 4, 6, 9- and 12-months post symptom onset. After completing one year of study, participants will be given the option of continuing the longitudinal study for up to two or more years. At each study visit, participant symptoms and medical history is updated. Those with COVID-19 symptoms after enrollment in all groups are offered a nasopharyngeal swab PCR SARS-CoV-2 test.

As of October 2020, 805 individuals have contacted the Seattle COVID-19 cohort study and 425 have enrolled. This includes 281 negative and 144 SARS-CoV-2 positive participants. Reasons for not enrolling include lack of interest, not meeting the eligibility criteria, inability to travel to blood draw location and inability to collect study blood. No participants have terminated from the study. Study enrollment and follow-up remains ongoing. Samples from SARS-CoV-2 negative subjects were included in B and T cell assays as 'contemporaneous' negative controls.

Peripheral blood mononuclear cells (PBMC) were obtained from HIV-1 seronegative donors who were recruited at the Seattle Vaccine Trials Unit before 2019 as part of the study "Establishing Immunologic Assays for Determining HIV-1 Prevention and Control." All participants signed informed consent, and the Fred Hutchinson Cancer Research Center IRB (Seattle, WA, USA) institutional human subjects review committee approved the protocol prior to study initiation. Pre-pandemic samples from this cohort were used as assay controls in B and T cell assays.

METHOD DETAILS

PBMC processing

PBMC for cellular assays were isolated by density centrifugation and cryopreserved from ACD-anticoagulated whole blood within eight h of venipuncture, as described previously [32]. Sera were also processed and cryopreserved within 4 h after collection.

Antibody binding assay

Antibody binding titers were measured using a multiplex plate coated with the SARS-CoV-2 spike, SARS-CoV-2 spike receptor binding domain, SARS-CoV-2 spike N-terminal domain, SARS-CoV-2 nucleocapsid, SARS-CoV-1 spike, 229E spike, NL63 spike, HKU1 spike, and OC43 spike proteins (Mesoscale Discovery). Plates were blocked with 150ml/well with 5% bovine serum albumin in phosphate buffered saline (PBS) and shaken at 700 RPM at room temperature for at least 30 min. Plates were washed 3 times with 150ml/well 0.05% Tween-20 in PBS. Serum and plasma samples were added to the plate at dilutions between 1:500 and 1:50,000 and shaken at 700 RPM at room temperature for 2 h. Following a wash, plates were incubated with 50ul/well of Sulfo-Tag anti-human

IgG, IgA, or IgM detection antibody and shaken at 700RPM at room temperature for 1 h. After a subsequent wash, 150ml/well of MSD GOLD read buffer was added to the plate and plates were immediately read on the MSD instrument to measure light intensity. Antibody levels are reported as arbitrary units/mL (AU/mL) based on normalization to a standard curve.

Viruses and cell lines

VeroE6 cells were obtained from ATCC (clone E6, ATCC, #CRL-1586) and cultured in complete DMEM medium consisting of 1 × DMEM (VWR, #45000-304), 10% FBS, 25mM HEPES Buffer (Corning Cellgro), 2mM L-glutamine, 1mM sodium pyruvate, 1 × Non-essential Amino Acids, and 1 × antibiotics. The infectious clone SARS-CoV-2 (icSARS-CoV-2-mNG), derived from the 2019-nCoV/USA_WA1/2020 strain, was propagated in VeroE6 cells and sequenced [33,34].

Focus reduction neutralization test

Neutralization assays with SARS-CoV-2 virus were performed as previously described [33-35]. Plasma/serum were serially diluted (three-fold) in serum-free Dulbecco's modified Eagle's medium (DMEM) in duplicate wells and incubated with 100–200 FFU infectious clone derived SARS-CoV-2-mNG virus at 37°C for 1 h [33]. The antibody-virus mixture was added to VeroE6 cell (C1008, ATCC, #CRL-1586) monolayers seeded in 96-well blackout plates and incubated at 37°C for 1 h. Post-incubation, the inoculum was removed and replaced with pre-warmed complete DMEM containing 0.85% methylcellulose. Plates were incubated at 37°C for 24 h. After 24 h, methylcellulose overlay was removed, cells were washed twice with PBS and fixed with 2% paraformaldehyde in PBS for 30 min at room temperature. Following fixation, plates were washed twice with PBS and foci were visualized on a fluorescence ELISPOT reader (CTL ImmunoSpot S6 Universal Analyzer) and enumerated using Viridot [36]. The neutralization titers were calculated as follows: 1 - (ratio of the mean number of foci in the presence of sera and foci at the highest dilution of respective sera sample). Each specimen was tested in two independent assays performed at different times. The FRNT-mNG$_{50}$ titers were interpolated using a 4-parameter nonlinear regression in GraphPad Prism 8.4.3. Samples with an FRNT-mNG$_{50}$ value that was below the limit of detection were plotted at 20.

Spike and RBD memory B cell flow cytometry assays

Fluorescent SARS-CoV-2-specific S6P[37] (provided by Roland Strong, Fred Hutchinson Cancer Research Center, Seattle, WA) and RBD (provided by Leonidas Stamatatos, Fred Hutchinson Cancer Research Center, Seattle, WA) probes were made by combining biotinylated protein with fluorescently labeled streptavidin (SA). The S6P probes were made at a ratio of 1:1 molar ratio of trimer to SA. Two S6P probes, one labeled with AlexaFluor488 (Invitrogen), one labeled with AlexaFluor647 (Invitrogen), were used in this panel in order to increase specificity of the detection of SARS-CoV-2-specific B cells. The RBD probe was prepared at a 4:1 molar ratio of RBD monomers to SA, labeled with R-phycoerythrin (Invitrogen). Cryopreserved PBMCs from SARS-CoV-2-convalescent participants and a pre-pandemic SARS-CoV-2-naive donor were thawed at 37°C and stained for SARS-CoV-2-specific memory B cells as described previously[19] with a panel of fluorescently-labeled antibodies (see Key Resource Table). Cells were stained first with the viability stain (Invitrogen) in PBS for 15 min at 4°C. Cells were then washed with 2% FBS/PBS and stained with a cocktail of the three probes for 30 min at 4°C. The probe cocktail was washed off with 2% FBS/PBS and the samples were stained with the remaining antibody panel and incubated for 25 min at 4°C. The cells were washed two times and resuspended in 1% paraformaldehyde/1 × PBS for collection on a LSR II or FACSymphony flow cytometer (BD Biosciences). Data was analyzed in Flow Jo version 9.9.4.

Intracellular cytokine staining (ICS) assay

Flow cytometry was used to examine SARS-CoV-2-specific CD4+ and CD8+ T cell responses using a validated ICS assay. The assay was similar to a published report [5,38,39] and the details of the staining panel are included in the Key Resource Table. Peptide pools covering the structural proteins of SARS-CoV-2 were used for the six-h stimulation. Peptides matching the SARS-CoV-2 spike sequence (316 peptides, plus 4 peptides covering the G614 variant) were synthesized as 15 amino acids long with 11 amino acids overlap and pooled in 2 pools (S1 and S2) for testing (BioSynthesis). All other peptides were 13 amino acids overlapping by 11 amino acids and were synthesized by GenScript. The peptides covering the envelope (E), membrane (M) and nucleocapsid (N) were initially combined into one peptide pool, but the majority of the assays were performed using a separate pool for N and one that combined only E and M. Several of the open reading frame (ORF) peptides were combined into two pools: ORF 3a and 6, and ORF 7a, 7b and 8. All peptide pools were used at a final concentration of 1 mg/mL for each peptide. As a negative control, cells were not stimulated, only the peptide diluent (DMSO) was included. As a positive control, cells were stimulated with a polyclonal stimulant, staphylococcal enterotoxin B (SEB). Cells expressing IFN-g and/or IL-2 and/or CD154 was the primary immunogenicity endpoint for CD4+ T cells and cells expressing IFN-g was the primary immunogenicity endpoint for CD8+ T cells. The overall response to SARS-CoV-2 was defined as the sum of the background-subtracted responses to each of the individual pools. A sample was considered positive for CD4+ or CD8+ T cell responses to SARS-CoV-2 if any of the CD4+ or CD8+ T cell responses to the individual peptide pool stimulations was positive. Positivity was determined using MIMOSA [40]. The total number of CD4+ T cells must have exceeded 10,000 and the total number of CD8+ T cells must have exceeded 5,000 for the assay data to be included in the analysis.

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QUANTIFICATION AND STATISTICAL ANALYSIS

Binding and neutralizing antibody responses

Mixed effects exponential and power law models were used to analyze waning of antibody (day 42 to day 263 post symptom onset). For binding antibody analyses, antibody (Ab) was natural log transformed, yielding linear equations of the form ln(Ab) = a+b*(day-42) and ln(Ab) = a+b*ln(day/42) for the exponential and power law models, respectively, and fit using the lmer function (lme4 package) in R. Models included population level fixed effects and individual level random effects for intercept and slope and covariance between the random effects. Simplified models – with random effects only for intercept – were also fit. Neutralization antibody data were analyzed in Monolix (Lixoft). For analysis in Monolix, the exponential and power law models were formulated as ordinary differential equations, dAb/dt = k*Ab and dAb/dt = k*Ab/t, respectively, with antibody at day 42 lognormally distributed and lognormal multiplicative error. Neutralization titers < 20 were treated as left censored. For comparison of models, difference in Akaike information criterion (DAIC) > 4 was considered statistically significant. Models (in R and Monolix) were fit using maximum likelihood. To account for repeated-measures, correlations between antibody binding levels and neutralization titers were calculated using a repeated-measures correlation (rmcorr package) in R [41].

B cell responses

We considered linear mixed effects models for B cell response, y_{ij}, as a function of t_{ij}, the j^{th} time since symptom onset for the i^{th} individual, with random effects for intercept and slope and $t_{ij} > 30$ days for all i, j:

$$\log_e y_{ij} = \beta_{0i} + \beta_{1i} t_{ij} + \varepsilon_{ij}$$

where $\beta_{0i} = \beta_0 + b_i$ and $\beta_{1i} = \beta_1 + c_i$ with (b_i, c_i) iid $\sim N_2(0, \Sigma)$, with

$$\Sigma = \begin{bmatrix} \sigma_b^2 & Cov(b,c) \\ Cov(b,c) & \sigma_c^2 \end{bmatrix}$$

and σ_b^2 and σ_c^2 are the between-person variation in the intercept and slope of log B cell responses respectively, *Cov(b, c)* is the covariance between the intercept and slope, and ε_{ij} iid $\sim N(0, \sigma^2)$. The random effects, b_i and c_i, are each assumed to be independent for different individuals and the within-individual errors ε_{ij} are assumed to be independent for different *i, j* and to be independent of the random effects. The function lme from the R package nlme was used to fit the models.

T cell responses

Longitudinal analyses of CD4+ and CD8+ T cell responses were performed for individuals with a positive response for at least one time point 30 days after symptom onset. The MIMOSA (Mixture Models for Single-Cell Assays) [40] model incorporated cell count and cell proportion information to define a positive CD4+/CD8+ T cell response by ICS by comparing peptide pools stimulated cells and unstimulated negative controls. This method assumed a common distribution for cytokine positive CD4+/CD8+ T cells in stimulated and unstimulated samples in non-responders, resulting in paired differences that were zero on average. In contrast, for responders, the distribution of the proportion of cytokine positive cells for stimulated samples was assumed to be greater than for unstimulated samples, resulting in paired differences that were greater than zero on average. The MIMOSA method modeled this structure through a Bayesian hierarchical mixture model framework. One component (or distribution) of the model represented the responders, and the other component modeled the non-responders. The parameters defining these distributions, as well as the probabilities that each ICS response was either a responder or non-responder, were estimated from the observed data. This sharing of information across SARS-CoV-2 responders and non-responders increased the sensitivity and specificity to make positivity calls [42]. Responses with probability of response > 0.999 were considered positive responders.

We considered nonlinear mixed effects models for T cell response, y_{ij}, as a function of t_{ij}, the j^{th} time since symptom onset for the i^{th} individual, with random effects for intercept and slope and $t_{ij} > 30$ days for all i, j:

$$\log_e y_{ij} = \beta_{0i} - \exp(\beta_{1i}) t_{ij} + \varepsilon_{ij}$$

where $\beta_{0i} = \beta_0 + b_i$ and $exp(\beta_{1i}) = exp(\beta_1 + c_i)$ with (b_i, c_i) iid $\sim N_2(0, \Sigma)$, with

$$\Sigma = \begin{bmatrix} \sigma_b^2 & 0 \\ 0 & \sigma_c^2 \end{bmatrix}$$

and σ_b^2 and σ_c^2 are the between-person variation in the intercept and slope of log T cell responses respectively, and ε_{ij} iid $\sim logNormal(0, \sigma^2)$. The random effects, b_i and c_i, are each assumed to be independent for different individuals and the within-individual errors ε_{ij} are assumed to be independent for different *i, j* and to be independent of the random effects. The function nlme from the R package nlme was used to fit the models.

Diagnostic plots of residuals were examined to assess validity of the model assumptions.

Age at enrollment, gender, and disease severity (WHO score > 4) were included as covariates in the mixed effects models to assess their association with each immune response.

Individual-level estimates at days 30 (T and B cell responses), day 42 (binding and neutralizing antibody responses) and day 180 (all responses) were obtained from the mixed effects models described above. Spearman rank correlations, Wald-based two-sided 95% confidence intervals and p values were reported.

Generalized estimating equations (GEE), with an independence working covariance matrix, were used to confirm the results of the covariate assessments for B and T cell responses from the mixed effects models. Two-tailed P values based on the robust standard error estimates for the covariate coefficients were consistent with the corresponding two-tailed P values for the covariate associations from the mixed effects models.

All tests were two-sided and P values < 0.05 were considered statistically significant unless otherwise noted. Details of specific statistical analyses can be found in the Results section and in the Figure legends.

Exhibit G

Centers for Disease Control and Prevention

COVID-19

Participate in Outdoor and Indoor Activities

Updated Aug. 19, 2021 Print

If you want to spend time with people who don't live with you, outdoors is the safer choice! You are less likely to be exposed to COVID-19 during outdoor activities, even without the use of masks.

Why Outside is a Safer Choice

COVID-19 spreads more easily indoors than outdoors. Studies show that people are more likely to be exposed to COVID-19 when they are closer than 6 feet apart from others for longer periods of time.

You are **more likely to be exposed** to COVID-19 when you

- Attend crowded, poorly ventilated indoor events
- Have close contact with infected people at home

You are **less likely to be exposed** to COVID-19 when you

- Attend outdoor activities
- Stay at least 6 feet apart
- Limit the amount of time spent with people who don't live with you

Outdoor and Indoor Activities

Safer – Outdoor Activities

- Outside, at least 6 feet apart
- If you can't stay at least 6 feet apart from people who don't live with you, wear your mask.

Less Safe – Indoor Activities

- Inside, at least 6 feet apart
- Well ventilated room
- Wearing mask

Exercise

Safer

Outdoor Activities

- Run, walk, or bike at your neighborhood park
- Hike on local trails
- Take your dog for a walk around the neighborhood

Less Safe

Indoor Activities

- Exercise at a fitness center
- Walk around the mall during off hours
- Attend a class at a yoga studio
- Swim at your local pool

- Participate in an outdoor yoga class
- Work in the garden

Restaurants

Safer

Outdoor Activities

- Pick up curbside meals
- Get food delivered
- Eat outside at a restaurant where the tables are at least 6 feet apart

Less Safe

Indoor Activities

- Eat inside at a restaurant

Visiting or hosting people who don’t live with you

Safer

Outdoor Activities

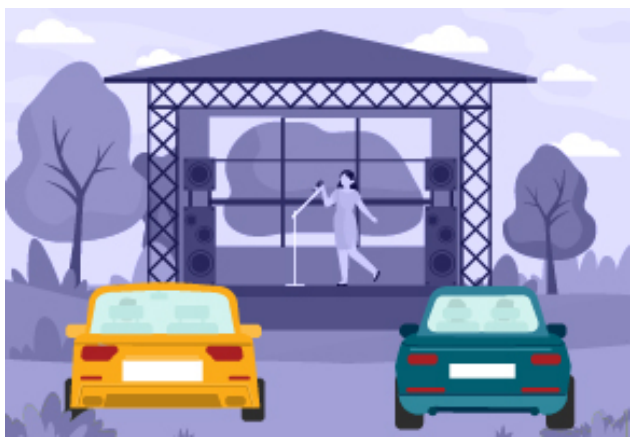
- Have a picnic at a park
- Play kickball in a friend’s backyard
- Roast marshmallows by a firepit
- Have an outdoor barbeque

Less Safe

Indoor Activities

- Watch movies
- Play games
- Chat with your friends

Entertainment



Safer

Outdoor Activities

- Go to a drive-in
- Listen to an outdoor concert from your car
- Create your own outdoor movie party

Less Safe

Indoor Activities

- Watch a movie at a theater
- Watch a musical performance
- Watch a play

Things you can do to be safer

- Wear a mask consistently and correctly over your nose and mouth
  - If you are not fully vaccinated and aged 2 or older, you should wear a mask in indoor public places.
  - If you are fully vaccinated, to maximize protection from the Delta variant and prevent possibly spreading it to others, wear a mask indoors in public if you are in an area of substantial or high transmission.
  - In general, you do not need to wear a mask in outdoor settings. In areas with high numbers of COVID-19 cases, consider wearing a mask in crowded outdoor settings and for activities with close contact with others who are not fully vaccinated.
  - People who have a condition or are taking medications that weaken their immune system may not be fully protected even if they are fully vaccinated. They should continue to take all precautions recommended for unvaccinated people, including wearing a well-fitted mask until advised otherwise by their healthcare provider.
- Stay at least 6 feet apart from people who don’t live with you
- Avoid crowds and places that are poorly ventilated or crowded
- Wash your hands

More Information

Small and Large Gatherings

Families with Vaccinated and Unvaccinated Members

Last Updated Aug. 19, 2021

Exhibit H

Safer Federal Workforce Task Force
COVID-19 Workplace Safety: Guidance for Federal Contractors and Subcontractors
Issued September 24, 2021

Introduction

On September 9, President Biden announced his Path Out of the Pandemic: COVID-19 Action Plan. One of the main goals of this science-based plan is to get more people vaccinated. As part of that plan, the President signed Executive Order 14042, Ensuring Adequate COVID Safety Protocols for Federal Contractors, ("the order") which directs executive departments and agencies, including independent establishments subject to the Federal Property and Administrative Services Act, 40 U.S.C. § 102(4)(A), to ensure that covered contracts and contract-like instruments include a clause ("the clause") that the contractor and any subcontractors (at any tier) shall incorporate into lower-tier subcontracts. This clause shall specify that the contractor or subcontractor shall, for the duration of the contract, comply with all guidance for contractor or subcontractor workplace locations published by the Safer Federal Workforce Task Force ("Task Force"), provided that the Director of the Office of Management and Budget ("OMB") approves the Task Force Guidance (the or this "Guidance") and determines that the Guidance, if adhered to by covered contractors, will promote economy and efficiency in Federal contracting.

The actions directed by the order will ensure that parties who contract with the Federal Government provide COVID-19 safeguards in workplaces with individuals working on or in connection with a Federal Government contract or contract-like instrument. These workplace safety protocols will apply to all covered contractor employees, including contractor or subcontractor employees in covered contractor workplaces who are not working on a Federal Government contract or contract-like instrument. These safeguards will decrease the spread of SARS-CoV-2, the virus that causes COVID-19, which will decrease worker absence, reduce labor costs, and improve the efficiency of contractors and subcontractors performing work for the Federal Government.

Pursuant to this Guidance, and in addition to any requirements or workplace safety protocols that are applicable because a contractor or subcontractor employee is present at a Federal workplace, Federal contractors and subcontractors with a covered contract will be required to conform to the following workplace safety protocols:

1. COVID-19 vaccination of covered contractor employees, except in limited circumstances where an employee is legally entitled to an accommodation;
2. Compliance by individuals, including covered contractor employees and visitors, with the Guidance related to masking and physical distancing while in covered contractor workplaces; and
3. Designation by covered contractors of a person or persons to coordinate COVID-19 workplace safety efforts at covered contractor workplaces.

The order also sets out a process for OMB and the Safer Federal Workforce Task Force to update the Guidance for covered contractors, which the Task Force will consider doing based on future changes to Centers for Disease Control and Prevention ("CDC") COVID-19 guidance and as warranted by the circumstances of the pandemic and public health conditions. It also sets out a process for the Federal Acquisition Regulatory Council ("FAR Council") to implement such protocols and guidance for covered Federal procurement solicitations and contracts subject to the Federal Acquisition Regulation ("FAR") and for agencies that are responsible for covered contracts and contract-like instruments not subject to the FAR to take prompt action to ensure that those covered contracts and contract-like instruments include the clause, consistent with the order.

Covered contractors shall adhere to the requirements of this Guidance. The Director of OMB has, as authorized by Executive Order 14042, approved this Guidance and has, an exercise of the delegation of authority (see 3 U.S.C. § 301) under the Federal Property and Administrative Services Act determined that this Guidance will promote economy and efficiency in Federal contracting if adhered to by Government contractors and subcontractors. The Director has published such determination in the Federal Register.

Definitions

Community transmission – means the level of community transmission as set forth in the CDC COVID-19 Data Tracker County View.

Contract and contract-like instrument – has the meaning set forth in the Department of Labor's proposed rule, "Increasing the Minimum Wage for Federal Contractors," 86 Fed. Reg. 38,816, 38,887 (July 22, 2021). If the Department of Labor issues a final rule relating to that proposed rule, this term shall have the meaning set forth in that final rule.

That proposed rule defines a contract or contract-like instrument as an agreement between two or more parties creating obligations that are enforceable or otherwise recognizable at law. This definition includes, but is not limited to, a mutually binding legal relationship obligating one party to furnish services (including construction) and another party to pay for them. The term contract includes all contracts and any subcontracts of any tier thereunder, whether negotiated or advertised, including any procurement actions, lease agreements, cooperative agreements, provider agreements, intergovernmental service agreements, service agreements, licenses, permits, or any other type of agreement, regardless of nomenclature, type, or particular form, and whether entered into verbally or in writing. The term contract shall be interpreted broadly as to include, but not be limited to, any contract within the definition provided in the FAR at 48 CFR chapter 1 or applicable Federal statutes. This definition includes, but is not limited to, any contract that may be covered under any Federal procurement statute. Contracts may be the result of competitive bidding or awarded to a single source under applicable authority to do so. In addition to bilateral instruments, contracts include, but are not limited to, awards and notices of awards; job orders or task letters issued under basic ordering agreements; letter contracts; orders, such as purchase orders, under which the contract becomes effective by written acceptance or performance; exercised contract options; and bilateral contract modifications. The term contract includes contracts covered by the Service Contract Act, contracts covered by the Davis-Bacon Act, concessions contracts not otherwise subject to the Service Contract Act, and contracts in connection with Federal property or land and related to offering services for Federal employees, their dependents, or the general public.

Contractor or subcontractor workplace location – means a location where covered contract employees work, including a covered contractor workplace or Federal workplace.

Covered contract – means any contract or contract-like instrument that includes the clause described in Section 2(a) of the order.

Covered contractor – means a prime contractor or subcontractor at any tier who is party to a covered contract.

Covered contractor employee – means any full-time or part-time employee of a covered contractor working on or in connection with a covered contract or working at a covered

contractor workplace. This includes employees of covered contractors who are not themselves working on or in connection with a covered contract.

Covered contractor workplace – means a location controlled by a covered contractor at which any employee of a covered contractor working on or in connection with a covered contract is likely to be present during the period of performance for a covered contract. A covered contractor workplace does not include a covered contractor employee's residence.

Federal workplace – means any place, site, installation, building, room, or facility in which any Federal executive department or agency conducts official business, or is within an executive department or agency's jurisdiction, custody, or control.

Fully vaccinated – People are considered fully vaccinated for COVID-19 two weeks after they have received the second dose in a two-dose series, or two weeks after they have received a single-dose vaccine. There is currently no post-vaccination time limit on fully vaccinated status; should such a limit be determined by the Centers for Disease Control and Prevention, that limit will be considered by the Task Force and OMB for possible updating of this Guidance.

For purposes of this Guidance, people are considered fully vaccinated if they have received COVID-19 vaccines currently approved or authorized for emergency use by the U.S. Food and Drug Administration (Pfizer-BioNTech, Moderna, and Johnson & Johnson [J&J]/Janssen COVID-19 vaccines) or COVID-19 vaccines that have been listed for emergency use by the World Health Organization (e.g., AstraZeneca/Oxford). More information is available at Interim Clinical Considerations for Use of COVID-19 Vaccines | CDC.

Clinical trial participants from a U.S. site who are documented to have received the full series of an "active" (not placebo) COVID-19 vaccine candidate, for which vaccine efficacy has been independently confirmed (e.g., by a data and safety monitoring board), can be considered fully vaccinated two weeks after they have completed the vaccine series. Currently, the Novavax COVID-19 vaccine meets these criteria. More information is available at the CDC website here.

Mask – means any mask that is consistent with CDC recommendations as set forth in Types of Masks and Respirators | CDC. This may include the following: disposable masks, masks that fit properly (snugly around the nose and chin with no large gaps around the sides of the face), masks made with breathable fabric (such as cotton), masks made with tightly woven fabric (i.e., fabrics that do not let light pass through when held up to a light source), masks with two or three layers, masks with inner filter pockets, and filtering facepiece respirators that are approved by the National Institute for Occupational Safety and Health or consistent with international standards. The following do not constitute masks for purposes of this Guidance: masks with exhalation valves, vents, or other openings; face shields only (without mask); or masks with single-layer fabric or thin fabric that does not block light.

Guidance

Covered contractors are responsible for ensuring that covered contractor employees comply with the workplace safety protocols detailed below. Covered contractor employees must also comply with agency COVID-19 workplace safety requirements while in Federal workplaces.

Consistent with applicable law, agencies are strongly encouraged to incorporate a clause requiring compliance with this Guidance into contracts that are not covered or directly addressed by the order because the contract is under the Simplified Acquisition Threshold as defined in section 2.101 of the FAR or is a contract or subcontract for the manufacturing of products. Agencies are also strongly encouraged to incorporate a clause requiring compliance with this Guidance into existing contracts and contract-like instruments prior to the date upon which the order requires inclusion of the clause.

1. *Vaccination of covered contractor employees, except in limited circumstances where an employee is legally entitled to an accommodation*

Covered contractors must ensure that all covered contractor employees are fully vaccinated for COVID-19, unless the employee is legally entitled to an accommodation. Covered contractor employees must be fully vaccinated no later than December 8, 2021. After that date, all covered contractor employees must be fully vaccinated by the first day of the period of performance on a newly awarded covered contract, and by the first day of the period of performance on an exercised option or extended or renewed contract when the clause has been incorporated into the covered contract.

A covered contractor may be required to provide an accommodation to covered contractor employees who communicate to the covered contractor that they are not vaccinated against COVID-19 because of a disability (which would include medical conditions) or because of a sincerely held religious belief, practice, or observance. A covered contractor should review and consider what, if any, accommodation it must offer. Requests for "medical accommodation" or "medical exceptions" should be treated as requests for a disability accommodation.

Should a Federal agency have an urgent, mission-critical need for a covered contractor to have covered contractor employees begin work on a covered contract or at a covered workplace before becoming fully vaccinated, the agency head may approve an exception for the covered contractor —in the case of such limited exceptions, the covered contractor must ensure these covered contractor employees are fully vaccinated within 60 days of beginning work on a covered contract or at a covered workplace. The covered contractor must further ensure that such employees comply with masking and physical distancing requirements for not fully vaccinated individuals in covered workplaces prior to being fully vaccinated.

The covered contractor must review its covered employees' documentation to prove vaccination status. Covered contractors must require covered contractor employees to show or provide their

employer with one of the following documents: a copy of the record of immunization from a health care provider or pharmacy, a copy of the COVID-19 Vaccination Record Card (CDC Form MLS-319813_r, published on September 3, 2020), a copy of medical records documenting the vaccination, a copy of immunization records from a public health or State immunization information system, or a copy of any other official documentation verifying vaccination with information on the vaccine name, date(s) of administration, and the name of health care professional or clinic site administering vaccine. Covered contractors may allow covered contractor employees to show or provide to their employer a digital copy of such records, including, for example, a digital photograph, scanned image, or PDF of such a record.

The covered contractor shall ensure compliance with the requirements in this Guidance related to the showing or provision of proper vaccination documentation.

Covered contractors are strongly encouraged to incorporate similar vaccination requirements into their non-covered contracts and agreements with non-covered contractors whose employees perform work at covered contractor workplaces but who do not work on or in connection with a Federal contract, such as those contracts and agreements related to the provision of food services, onsite security, or groundskeeping services at covered contractor workplaces.

2. *Requirements related to masking and physical distancing while in covered contractor workplaces*

Covered contractors must ensure that all individuals, including covered contractor employees and visitors, comply with published CDC guidance for masking and physical distancing at a covered contractor workplace, as discussed further in this Guidance.

In addition to the guidance set forth below, CDC's guidance for mask wearing and physical distancing in specific settings, including healthcare, transportation, correctional and detention facilities, and schools, must be followed, as applicable.

In areas of high or substantial community transmission, fully vaccinated people must wear a mask in indoor settings, except for limited exceptions discussed in this Guidance. In areas of low or moderate community transmission, fully vaccinated people do not need to wear a mask. Fully vaccinated individuals do not need to physically distance regardless of the level of transmission in the area.

Individuals who are not fully vaccinated must wear a mask indoors and in certain outdoor settings (see below) regardless of the level of community transmission in the area. To the extent practicable, individuals who are not fully vaccinated should maintain a distance of at least six feet from others at all times, including in offices, conference rooms, and all other communal and work spaces.

Covered contractors must require individuals in covered contractor workplaces who are required to wear a mask to:

- Wear appropriate masks consistently and correctly (over mouth and nose).
- Wear appropriate masks in any common areas or shared workspaces (including open floorplan office space, cubicle embankments, and conference rooms).
- For individuals who are not fully vaccinated, wear a mask in crowded outdoor settings or during outdoor activities that involve sustained close contact with other people who are not fully vaccinated, consistent with CDC guidance.

A covered contractor may be required to provide an accommodation to covered contractor employees who communicate to the covered contractor that they cannot wear a mask because of a disability (which would include medical conditions) or because of a sincerely held religious belief, practice, or observance. A covered contractor should review and consider what, if any, accommodation it must offer.

Covered contractors may provide for exceptions to mask wearing and/or physical distancing requirements consistent with CDC guidelines, for example, when an individual is alone in an office with floor to ceiling walls and a closed door, or for a limited time when eating or drinking and maintaining appropriate distancing. Covered contractors may also provide exceptions for covered contractor employees engaging in activities in which a mask may get wet; high intensity activities where covered contractor employees are unable to wear a mask because of difficulty breathing; or activities for which wearing a mask would create a risk to workplace health, safety, or job duty as determined by a workplace risk assessment. Any such exceptions must be approved in writing by a duly authorized representative of the covered contractor to ensure compliance with this Guidance at covered contractor workplaces, as discussed further below.

Masked individuals may be asked to lower their masks briefly for identification purposes in compliance with safety and security requirements.

Covered contractors must check the CDC COVID-19 Data Tracker County View website for community transmission information in all areas where they have a covered contractor workplace at least weekly to determine proper workplace safety protocols. When the level of community transmission in the area of a covered contractor workplace increases from low or moderate to substantial or high, contractors and subcontractors should put in place more protective workplace safety protocols consistent with published guidelines. However, when the level of community transmission in the area of a covered contractor workplace is reduced from high or substantial to moderate or low, the level of community transmission must remain at that lower level for at least two consecutive weeks before the covered contractor utilizes those protocols recommended for areas of moderate or low community transmission.

3. *Designation by covered contractors of a person or persons to coordinate COVID-19 workplace safety efforts at covered contractor workplaces.*

Covered contractors shall designate a person or persons to coordinate implementation of and compliance with this Guidance and the workplace safety protocols detailed herein at covered contractor workplaces. The designated person or persons may be the same individual(s) responsible for implementing any additional COVID-19 workplace safety protocols required by local, State, or Federal law, and their responsibilities to coordinate COVID-19 workplace safety protocols may comprise some or all of their regular duties.

The designated individual (or individuals) must ensure that information on required COVID-19 workplace safety protocols is provided to covered contractor employees and all other individuals likely to be present at covered contractor workplaces, including by communicating the required workplace safety protocols and related policies by email, websites, memoranda, flyers, or other means and posting signage at covered contractor workplaces that sets forth the requirements and workplace safety protocols in this Guidance in a readily understandable manner. This includes communicating the COVID-19 workplace safety protocols and requirements related to masking and physical distancing to visitors and all other individuals present at covered contractor workplaces. The designated individual (or individuals) must also ensure that covered contractor employees comply with the requirements in this guidance related to the showing or provision of proper vaccination documentation.

Frequently Asked Questions

Vaccination and Safety Protocols

Q1: How do covered contractors determine vaccination status of visitors to covered contractor workplaces?

A: Covered contractors should post signage at entrances to covered contractor workplaces providing information on safety protocols for fully vaccinated and not fully vaccinated individuals, including the protocols defined in the masking and physical distancing section above, and instruct individuals to follow the appropriate workplace safety protocols while at the covered contractor workplace. Covered contractors may take other reasonable steps, such as by communicating workplace safety protocols to visitors prior to their arrival at a covered contractor workplace or requiring all visitors to follow masking and physical distancing protocols for not fully vaccinated individuals.

Q2: Do covered contractors need to provide onsite vaccinations to their employees?

A: Covered contractors should ensure their employees are aware of convenient opportunities to be vaccinated. Although covered contractors may choose to provide vaccinations at their facilities or workplaces, given the widespread availability of vaccinations, covered contractors are not required to do so.

Q3: What should a contractor employee do if a covered contractor employee has lost or does not have a copy of required vaccination documentation?

A: If covered contractor employees need new vaccination cards or copies of other documentation proof of vaccination, they should contact the vaccination provider site where they received their vaccine. Their provider should be able to provide them with new cards or documentation with up-to-date information about the vaccinations they have received. If the location where the covered contractor employees received their COVID-19 vaccine is no longer operating, the covered contractor employees should contact their State or local health department's immunization information system (IIS) for assistance. Covered contractor employees should contact their State or local health department if they have additional questions about vaccination cards or vaccination records.

An attestation of vaccination by the covered contractor employee is not an acceptable substitute for documentation of proof of vaccination.

Q4: Who is responsible for determining if a covered contractor employee must be provided an accommodation because of a disability or because of a sincerely held religious belief, practice, or observance?

A: A covered contractor may be required to provide an accommodation to contractor employees who communicate to the covered contractor that they are not vaccinated for COVID-19, or that they cannot wear a mask, because of a disability (which would include medical conditions) or because of a sincerely held religious belief, practice, or observance. A covered contractor should review and consider what, if any, accommodation it must offer. The contractor is responsible for considering, and dispositioning, such requests for accommodations regardless of the covered contractor employee's place of performance. If the agency that is the party to the covered contract is a "joint employer" for purposes of compliance with the Rehabilitation Act and Title VII of the Civil Rights Act, both the agency and the covered contractor should review and consider what, if any, accommodation they must offer.

Q5: Are covered contractor employees who have a prior COVID-19 infection required to be vaccinated?

A: Yes, covered contractor employees who have had a prior COVID-19 infection are required to be vaccinated. More information from CDC can be found here.

Q6: Can a covered contractor accept a recent antibody test from a covered contractor employee to prove vaccination status?

A: No. A covered contractor cannot accept a recent antibody test from a covered contractor employee to prove vaccination status.

Workplaces

Q7: Does this Guidance apply to outdoor contractor or subcontractor workplace locations?

A: Yes, this Guidance applies to contractor or subcontractor workplace locations that are outdoors.

Q8: If a covered contractor employee is likely to be present during the period of performance for a covered contract on only one floor or a separate area of a building, site, or facility controlled by a covered contractor, do other areas of the building, site, or facility controlled by a covered contractor constitute a covered contractor workplace?

A: Yes, unless a covered contractor can affirmatively determine that none of its employees on another floor or in separate areas of the building will come into contact with a covered contractor employee during the period of performance of a covered contract. This would include affirmatively determining that there will be no interactions between covered contractor employees and non-covered contractor employees in those locations during the period of performance on a covered contract, including interactions through use of common areas such as lobbies, security clearance areas, elevators, stairwells, meeting rooms, kitchens, dining areas, and parking garages.

Q9: If a covered contractor employee performs their duties in or at only one building, site, or facility on a campus controlled by a covered contractor with multiple buildings, sites, or facilities, are the other buildings, sites, or facility controlled by a covered contractor considered a covered contractor workplace?

A: Yes, unless a covered contractor can affirmatively determine that none of its employees in or at one building, site, or facility will come into contact with a covered contractor employee during the period of performance of a covered contract. This would include affirmatively determining that there will be no interactions between covered contractor employees and non-covered contractor employees in those locations during the period of performance on a covered contract, including interactions through use of common areas such as lobbies, security clearance areas, elevators, stairwells, meeting rooms, kitchens, dining areas, and parking garages.

Q10: Are the workplace safety protocols enumerated above the same irrespective of whether the work is performed at a covered contractor workplace or at a Federal workplace?

A: Yes. The Guidance applies to all covered contractor employees and to all contractor or subcontractor workplace locations. While at a Federal workplace, covered contractor employees must also comply with any additional agency workplace safety requirements for that workplace. Because covered contractor employees working on a covered contract need to be fully vaccinated after December 8, 2021, covered contractor employees who work only at a Federal workplace need to be fully vaccinated by that date as well, unless legally entitled to an accommodation.

Q11: How does this Guidance apply to covered contractor employees who are authorized under the covered contract to perform work remotely from their residence?

A: An individual working on a covered contract from their residence is a covered contractor employee, and must comply with the vaccination requirement for covered contractor employees, even if the employee never works at either a covered contractor workplace or Federal workplace during the performance of the contract. A covered contractor employee's residence is not a covered contractor workplace, so while in the residence the individual need not comply with requirements for covered contractor workplaces, including those related to masking and physical distancing, even while working on a covered contract.

Scope and Applicability

Q12: By when must the requirements of the order be reflected in contracts?

A: Section 6 of the order lays out a phase-in of the requirements for covered contracts as follows:

- *Contracts awarded prior to October 15 where performance is ongoing* – the requirements must be incorporated at the point at which an option is exercised or an extension is made.
- *New contracts* – the requirements must be incorporated into contracts awarded on or after November 14. Between October 15 and November 14, agencies must include the clause in the solicitation and are encouraged to include the clause in contracts awarded during this time period but are not required to do so unless the solicitation for such contract was issued on or after October 15.

Q13: Must the order's requirements be flowed down to all lower-tier subcontractors and, if so, who is responsible for flowing the clause down?

A: Yes. The requirements in the order apply to subcontractors at all tiers, except for subcontracts solely for the provision of products. The prime contractor must flow the clause down to first-tier subcontractors; higher-tier subcontractors must flow the clause down to the next lower-tier subcontractor, to the point at which subcontract requirements are solely for the provision of products.

Q14: Does the Guidance apply to small businesses?

A: Yes, the requirement to comply with this Guidance applies equally to covered contractors regardless of whether they are a small business. This broad application of COVID-19 guidance will more effectively decrease the spread of COVID-19, which, in turn, will decrease worker absence, reduce labor costs, and improve the efficiency of contractors and subcontractors at workplaces where they are performing work for the Federal Government.

Q15: What steps are being taken to promote consistent application of the order's requirements across agencies?

A: The FAR Council will conduct a rulemaking to amend the FAR to include a clause that requires covered contractors performing under FAR-based contracts to comply with this Guidance for contractor and subcontractor workplace locations. Prior to rulemaking, by October 8, 2021, the FAR Council will develop a clause and recommend that agencies exercise their authority to deviate from the FAR using the procedures set forth in subpart 1.4. Agencies responsible for contracts and contract-like instruments that are not subject to the FAR, such as concession contracts, will be responsible for developing appropriate guidance by October 8, 2021 to incorporate requirements into their covered instruments entered into on or after October 15, 2021.

Q16: If the Safer Federal Workforce Task Force updates this Guidance to add new requirements, do those requirements apply to existing contracts?

A: Yes. Covered contractors are required to, for the duration of the contract, comply with all Task Force Guidance for contractor or subcontractor workplace locations, including any new

Guidance where the OMB Director approves the Guidance and determines that adherence to the Guidance will promote economy and efficiency in Federal contracting. The Task Force and OMB plan to ensure any workplace safety protocols reflect what is necessary to decrease the spread of COVID-19.

Q17: What constitutes work performed "in connection with" a covered contract?

A: Employees who perform duties necessary to the performance of the covered contract, but who are not directly engaged in performing the specific work called for by the covered contract, such as human resources, billing, and legal review, perform work in connection with a Federal Government contract.

Q18: Do the workplace safety protocols in the Guidance apply to covered contractor employees who perform work outside the United States?

A: No. The workplace safety protocols in the Guidance do not apply to covered contractor employees who only perform work outside the United States or its outlying areas, as those terms are defined in section 2.101 of the FAR.

Compliance

Q19: Does this clause apply in States or localities that seek to prohibit compliance with any of the workplace safety protocols set forth in this Guidance?

A: Yes. These requirements are promulgated pursuant to Federal law and supersede any contrary State or local law or ordinance. Additionally, nothing in this Guidance shall excuse noncompliance with any applicable State law or municipal ordinance establishing more protective workplace safety protocols than those established under this Guidance.

Q20: Can a covered contractor comply with workplace safety requirements from the Occupational Safety and Health Administration, including pursuant to any current or forthcoming Emergency Temporary Standard related to COVID-19, instead of the requirements of this Guidance?

A: No. Covered contractors must comply with the requirements set forth in this Guidance regardless of whether they are subject to other workplace safety standards.

Q21: What is the prime contractor's responsibility for verifying that subcontractors are adhering to the mandate?

A: The prime contractor is responsible for ensuring that the required clause is incorporated into its first-tier subcontracts in accordance with the implementation schedule set forth in section 6 of the order. When the clause is incorporated into a subcontract, a subcontractor is required to

comply with this Guidance and the workplace safety protocols detailed herein. Additionally, first-tier subcontractors are expected to flow the clause down to their lower-tier subcontractors in similar fashion so that accountability for compliance is fully established throughout the Federal contract supply chain for covered subcontractor employees and workplaces at all tiers through application of the clause.