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Attorney for Plaintiff John Doe

UNITED STATES DISTRICT COURT
DISTRICT OF ARIZONA

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

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; Tae Johnson in his official capacity as Senior Official Performing the Duties of Director of U.S. Immigration and Customs Enforcement; Ur M. Jaddou in her official capacity as Director of U.S. Citizenship and Immigration Services; 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 Administration; Robin Carnahan in her

No. 2:21-cv-01568-MTL

PLAINTIFFS' MOTION FOR LEAVE TO FILE AN OVERLENGTH MOTION FOR A TEMPORARY RESTRAINING ORDER AND PRELIMINARY INJUNCTION

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; and Jeffrey Zients in his official capacity as co-chair of the Safer Federal Workforce Task Force and COVID-19 Response Coordinator

Defendants.

Pursuant to LRCiv 7.2(e), Plaintiffs Mark Brnovich, in his official capacity as Attorney General of Arizona, the State of Arizona, and John Doe (together, the "Plaintiffs") respectfully request leave to file the attached Motion for a Temporary Restraining Order and Preliminary Injunction, which exceeds the 17-page limit applicable to their Motion. Plaintiffs seek to file a motion that is seventeen (17) pages longer than the applicable limit, for a total of thirty-four (34) pages.

Plaintiffs' Motion is filed on behalf of a sovereign state in an important case raising novel and complex issues of national interest, and which have significant importance for the parties, as well as for the residents of Arizona. As such, fully apprising the Court of the issues and interests involved requires greater detail than most motions and justifies a reasonable extension of the typical page limit. The additional length will assist the State in presenting the issues to this Court and should aid this Court's resolution of the questions presented.[1]

To this end, Plaintiffs respectfully request leave to file a 34-page Motion for a Temporary Restraining Order and Preliminary Injunction.

RESPECTFULLY SUBMITTED this 22nd of October, 2021.

MARK BRNOVICH
ATTORNEY GENERAL

By: */s/ James K. Rogers*
Joseph A. Kanefield (No. 15838)
Brunn W. Roysden III (No. 28698)
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Attorneys for Plaintiffs

[1] For the same reasons as well as fairness considerations, the State will not oppose any commensurate increase for Defendants' response.

WILENCHIK & BARTNESS PC

By: */s/ Jack Wilenchik (with permission)*
Jack Wilenchik (No. 029353)

Attorney for Plaintiff John Doe

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Defendants.

No. 2:21-cv-01568-MTL

[PROPOSED] ORDER

Having considered the Plaintiffs' Motion for Leave to File an Overlength Motion for a Temporary Restraining Order and Preliminary Injunction, **IT IS HEREBY ORDERED** granting the motion. The proposed motion attached to the motion for leave is deemed **FILED.**

MARK BRNOVICH
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No. 2:21-cv-01568-MTL

MOTION FOR A TEMPORARY RESTRAINING ORDER AND PRELIMINARY INJUNCTION

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 in his official capacity as co-chair of the Safer Federal Workforce Task Force and COVID-19 Response Coordinator.

Defendants.

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INTRODUCTION

The State of Arizona, its Attorney General, and John Doe (collectively, the "State") seek a temporary restraining order ("TRO") and preliminary injunction against two unprecedented vaccination mandates. Those mandates—one relating to federal contractors and subcontractors ("Contractor Mandate") and another relating to all federal employees ("Employee Mandate")—transgress numerous constitutional and statutory requirements. They are, in other words, patently unlawful. But if they are permitted to go into effect, contractors and employees will rapidly be forced to comply with these illegal mandates and this Court's power to prevent harms resulting from those illegal mandates will rapidly diminish into near-nothingness. A TRO is thus appropriate to prevent irreversible harm while the State's request for a preliminary injunction is decided. And such a preliminary injunction is warranted here, since the mandates violate both constitutional and statutory provisions, will cause irreparable harm, and the balance of harms and public interest favor enjoining these illegal mandates.

The Contractor Mandate is unlawful both procedurally and substantively. The President's power over contractors is derived from the federal procurement statutes that only permit him to impose obligations through notice-and-comment procedures—which Defendants did not even *attempt* to comply with. Moreover, under the Major Questions Doctrine and related case law, Defendants lack statutory authority to enact the sweeping social changes they seek for which they have no explicit statutory mandate. Instead, Defendants' mandates essentially assert far-reaching authority based upon finding hidden "elephants in mouseholes." *Whitman v. Am. Trucking Associations*, 531 U.S. 457, 468 (2001). But that is precisely how Congress does *not* convey unheard-of powers. Defendants thus do not have delegated authority to impose these unprecedented mandates, the likes of which no prior Administration has ever attempted. Moreover, while the President has power to employ procurement authority to improve efficiency of federal contracting, there is every reason to believe that these mandates will lead to *in*efficiency: particularly as they are likely to provoke employee resignations that will increase expenses, particularly in the

current tight labor market already undergoing a "Great Resignation." *See, e.g.,* First Amended Complaint ("FAC") ¶¶83-84.

Both the Contractor and Employee Mandates also violate the Emergency Use Authorization ("EUA") statute, which expressly requires disclosure of "the option to accept *or refuse* administration" of a product approved only under an EUA. 21 U.S.C. § 360bbb-3(e)(1)(A)(ii)(III) (emphasis added). But the whole point of the Mandates is to deny any such "option" to those governed by them. Notably, only the Pfizer vaccine has received FDA approval, and none of the stock of it in the U.S. is actually the FDA-approved version (and instead is entirely under the EUA label subject to the EUA-mandated conference of choice). Defendants' mandates thus violate the EUA statute.

Both of these mandates also violate the Equal Protection Clause, because Defendants have issued them as part of a policy of unconstitutional favoritism towards non-citizens not lawfully present in the U.S. (hereinafter, "unauthorized aliens"). Defendants have expressly refused to impose any vaccination mandates on unauthorized aliens, instead offering them a completely uncoerced choice as to whether to accept vaccination or not. But they have no equivalent respect for the rights of U.S. citizens and lawful permanent residents, who are the target of numerous such mandates.

Defendants have been completely forthright about this favoritism and their inexplicable preference for those entering the U.S. illegally over lawful residents and entrants. Defendants have announced, for example, that "[f]oreign nationals flying to the U.S. will be required to be fully vaccinated." Rogers Decl. Ex. A. But for those illegally crossing the northern and southern borders, they will not be subject to any vaccination mandates even when *apprehended* by Defendants and set to be released into the United States. *Id.* In other words, the *only* individuals whose personal autonomy is respected by Defendants are those that have elected to break U.S. immigration laws. U.S. citizens, lawful permanent residents, and those lawfully entering the U.S. (including through international flights) enjoy no equivalent respect. That favoritism is unconstitutional.

The State, its citizens, and John Doe will also suffer irreparable harm absent a TRO

and preliminary injunction. The harms at issue here cannot be remedied by money damages, which are not available in any event against Federal Defendants due to sovereign immunity. *See East Bay Sanctuary Covenant v. Biden*, 993 F.3d 640, 677 (9th Cir. 2021) (irrecoverable harms are irreparable harms). Nor does this Court have the medical power to remedy any potential side effects caused by vaccines taken purely as a result of compliance with these illegal mandates. If such harms are permitted to occur, they will not be remediable from subsequent judicial actions. Nor are the violations of constitutional rights here remediable by monetary damages.

The balance of harms and public interest also favor issuance of a TRO and preliminary injunction. As the United States itself told the Supreme Court just this week, "there is 'no harm' from the 'nonenforcement of invalid legislation.'" Application of the United States, *United States v. Texas*, No. 21A85 (U.S. Oct. 18, 2021) (attached here to as Rogers Decl. Ex. B.) (quoting *United States v. Alabama*, 691 F.3d 1269, 1301 (11th Cir. 2012)). And the "public interest [is served] in having governmental agencies abide by the federal laws that govern their existence and operations." *Texas v. Biden*, 10 F.4th 538, 559 (5th Cir. 2021); *accord League of Women Voters of United States v. Newby*, 838 F.3d 1, 12 (D.C. Cir. 2016).

Because the Contractor and Employee Mandates will soon compel individuals to comply with those mandates or suffer grievous financial harm, this Court should immediately issue a TRO while awaiting Defendants' response (which should be expedited), so that it can decide Plaintiffs' request for a preliminary injunction without enormous harms occurring in the interim, which it would lack the power to remedy. Put simply, absent expeditious action by this Court, Defendants will be able to effectuate the vast majority of their aims—despite the unlawfulness of their Mandates—simply by default. This Court should grant the State's motion to prevent such harms from occurring.

FACTUAL BACKGROUND

On September 9, 2021, President Biden gave remarks at the White House announcing plans for COVID-19 vaccination mandates for federal workers and certain

businesses, including healthcare facilities receiving federal funding, and all businesses with more than 99 employees. Rogers Decl. Ex. C. In that announcement, President Biden announced several categories of vaccination requirements, including those for (1) federal contractors, (2) federal employees, (3) employers with 100 or more employees, and (4) health care providers. This suit challenges the first and second mandates because these are the two about to take effect.

Federal Contractor Mandate

On September 9, 2021, President Biden signed Executive Order ("EO") 14042, imposing on federal contractors "COVID [s]afety [p]rotocols" to be established and issued by the Safer Federal Workforce Task Force ("SFWTF")[1] by September 24, 2021. On September 24, 2021 the SFWTF released on its website guidance to federal agencies for implementing Defendants' vaccine mandate on contractors and subcontractors (the "Contractor Mandate"). This guidance was never published to the Federal Register for public comment. Attached to the First Amended Complaint as Exhibit 1 is a copy of that guidance. Among other things, the guidance included the following:

- A deadline of December 8, 2021 for "covered contractor employees" to be fully vaccinated.
- A deadline of November 24, 2021 for employees of contractors or subcontractors to receive their final vaccination (or only vaccination, in the case of the Johnson & Johnson vaccine), because the guidance defines "fully vaccinated" to mean two weeks after receiving the requisite number of doses of an approved COVID-19 vaccine. The guidance defines "fully vaccinated" to include vaccines approved only by Emergency Use Authorization ("EUA").

[1] President Biden established the SFWTF on January 20, 2021 through Executive Order 13,991 (86 Fed. Reg. 7045 (Jan. 25, 2021)). He tasked the SFWTF with "provid[ing] ongoing guidance to heads of agencies on the operation of the Federal Government, the safety of its employees, and the continuity of Government functions during the COVID–19 pandemic." The SFWTF is headed by three co-chairs: (1) the Director of OPM; (2) the Administrator of GSA; and (3) the COVID–19 Response Coordinator. The Director of OPM is also a member of the SFWTF. The EO also required that GSA "provide funding and administrative support for the" SFWTF. 85 Fed. Reg. at 7046.

- A definition of the term "covered contractor employee" to "include[] employees of covered contractors who are not themselves working on or in connection with a covered contract" if they are working at the same location, thus imposing vaccine requirements on employees of contractors and subcontractors who are not even working on federal contracts.
- A requirement that the Federal Acquisition Regulatory Council ("FAR Council") conduct rulemaking to amend the Federal Acquisition Regulation ("FAR") to impose the Contractor Mandate.
- A deadline of October 8, 2021 for the FAR Council to develop a contract clause to implement the Contractor Mandate for agencies to include in contracts. The guidance also instructs the FAR Council to "recommend that agencies exercise their authority to deviate from the FAR" and use the vaccination mandate clause in contracts even before the FAR is amended.
- A deadline of October 15, 2021 for agencies to include that contractual clause in solicitations.
- A deadline of November 14, 2021 after which awarded contracts must include that contractual clause. For contracts entered into between October 15 and November 14 and for which the solicitation was issued before October 15, the guidance states that agencies are encouraged to include the clause, but are not required to do so.
- A requirement that, for contracts awarded "prior to October 15 and where performance is ongoing," the vaccine mandate clause "must be incorporated at the point at which an option is exercised or an extension is made."
- Requirements that the Contractor Mandate must apply even to: 1) persons who have already been infected with COVID-19; 2) workplace locations that are outdoors; and 3) contractor employees who are working remotely full time.
- A statement asserting that the guidance supersedes legal requirements in States or localities that prohibit vaccine mandates.

On September 28, 2021, Shalanda Young, the Acting Director of the Office of

Management and Budget, published a notice in the Federal Register in which Ms. Young made the conclusory contention that "compliance with COVID–19-related safety protocols improves economy and efficiency by reducing absenteeism and decreasing labor costs for contractors and subcontractors working on or in connection with a Federal Government contract." 86 Fed. Reg. 53,691 (Sept. 28, 2021). She further stated that she had "determined that compliance by Federal contractors and subcontractors with the COVID–19-workplace safety protocols detailed in [the SFWTF] guidance will improve economy and efficiency by reducing absenteeism and decreasing labor costs for contractors and subcontractors working on or in connection with a Federal Government contract." *Id.*

Ms. Young did not cite to any information or evidence that would support the claims in her determination, nor did she explain how she reached her conclusion. Furthermore, Ms. Young's notice was not subject to public commenting. Ms. Young's determination did not claim there were any urgent and compelling circumstances that warranted foregoing notice-and-comment procedures, and her Federal Register notice did not include a 41 U.S.C. § 1707(d) waiver of the Procurement Policy Act requirement that a procurement policy may not take effect until 60 days after it is published for public comment in the Federal Register. Nor did Ms. Young's notice invoke the good cause exception (5 U.S.C. § 553(b)(3)(B)) to the APA's notice-and-comment requirements.

Federal authorities have already communicated with some Arizona State agencies, including public universities, claiming that the agency is subject to the Contractor Mandate and must impose vaccine mandates on their employees. This creates a significant conflict, as mandates are illegal under State law. *See* FAC ¶57.

Federal Employee Mandate.

Also on September 9, 2021, President Biden signed EO 14043, which required that "[e]ach agency shall implement ... a program to require COVID-19 vaccination for all of its Federal employees." The EO also required the SFWTF to issue guidance for agencies by September 16, 2021. Exec. Order No. 14043, 86 Fed. Reg. 50,989, "Requiring

Coronavirus Disease 2019 Vaccination for Federal Employees" (Sept. 14, 2021).

On September 16, 2021 the SFWTF updated the "Frequently Asked Questions" ("FAQ") section of its website, in an attempt to fulfill the EO's guidance requirement. Among other things, the updated FAQ included the following:

- A deadline of November 22, 2021 for federal employees to be "fully vaccinated" and also after which new federal employees would need to be fully vaccinated before starting work.
- A deadline of November 8, 2021 for employees to receive their final vaccination (or only vaccination, in the case of the Johnson & Johnson vaccine), because the FAQ defines "fully vaccinated" to mean "2 weeks after [employees] have received the requisite number of doses of a[n approved] COVID-19 vaccine." The FAQ defines "fully vaccinated" as including vaccines approved only by EUA.
- Imposition of the Employee Mandate 1) for federal employees who are working remotely full-time and thus do not pose any risk of exposing other federal employees to COVID-19 and 2) for federal employees who have already been infected with COVID-19 and thus already have natural immunity.
- A warning to agencies to allow exemptions from the Employee Mandate only "in limited circumstances where the law requires an exception." (emphasis added).

Attached to the First Amended Complaint as Exhibit 2 is a copy of the updated FAQ. The SFWTF has never issued official, formal guidance to agencies; has never published its guidance in the Federal Register; and has not followed any notice-and-comment procedures before issuing its guidance.

LEGAL STANDARD

Plaintiffs seek a preliminary injunction under Rule of Civil Procedure 65(a) for the purpose of "preserv[ing] the relative positions of the parties until a trial on the merits can be held." *Univ. of Tex. v. Camenisch*, 451 U.S. 390, 395 (1981). As the moving party, a plaintiff can obtain a preliminary injunction by showing that (1) it is likely to succeed on the merits, (2) it is likely to suffer irreparable harm in the absence of preliminary relief,

(3) the balance of equities tips in [its] favor, and (4) an injunction is in the public interest. *Winter v. NRDC*, 555 U.S. 7, 20 (2008); *Alliance for the Wild Rockies v. Cottrell*, 632 F.3d 1127, 1131 (9th Cir. 2011).

ARGUMENT

I. Plaintiffs Are Likely To Prevail On The Merits Of Their Claims Against the Contractor Mandate

The Contractor Mandate violates both the Constitution and federal statutory law. Specifically, it is unconstitutional because 1) it violates the Tenth Amendment and principles of federalism because it attempts to usurp the States' police powers and 2) it violates the Equal Protection Clause by conferring preferential treatment upon unauthorized aliens as a favored class. The mandate is also unlawful because it violates 1) the Federal Property and Administrative Services Act (the "Procurement Act"), 40 U.S.C. §§ 101 and 121; 2) the Office of Federal Procurement Policy Act ("Procurement Policy Act"), 41 U.S.C. § 1707; and 3) the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3 ("the EUA statute").

A. The Contactor Mandate Is Unconstitutional

The Contractor Mandate is unconstitutional, and the Plaintiffs are likely to succeed on the merits of their constitutional challenge to it.

In our federal republic, powers are divided between the States and the Federal government. The Federal government possesses only those powers specifically enumerated in the Constitution. And at all levels of government, powers are further limited by the natural rights retained by the people.

The Contractor Mandate is unconstitutional because it violates the Tenth Amendment and the Equal Protection Clause.

1. The Contractor Mandate Violates The Tenth Amendment

The Contractor Mandate violates the Tenth Amendment and principles of federalism. The Tenth Amendment states that "[t]he powers not delegated to the United States by the Constitution, nor prohibited by it to the States, are reserved to the States

respectively, or to the people." U.S. Const. amend. X.

Under principles of federalism, the federal government has only enumerated powers and not the sort of general police power reserved *solely* to the States under the Tenth Amendment. "Residual state sovereignty was also implicit, of course, in the Constitution's conferral upon Congress of not all governmental powers, but only discrete, enumerated ones, Art. I, § 8, which implication was rendered express by the Tenth Amendment's assertion that '[t]he powers not delegated to the United States by the Constitution, nor prohibited by it to the States, are reserved to the States respectively, or to the people.'" *Printz v. United States*, 521 U.S. 898, 919 (1997).

As James Madison explained, "[t]he powers reserved to the several States will extend to all the objects which, in the ordinary course of affairs, concern the lives, liberties, and properties of the people, and the internal order, improvement, and prosperity of the State." The Federalist No. 45 (James Madison). Thus, the "police power" is "inherent in the states" and is "reserved from the grant of powers to the federal government by the Constitution." *United States v. Constantine*, 296 U.S. 287, 295–96 (1935).

It is well-settled that the power to impose vaccine mandates, to the extent that such power exists at all, is part of the police powers reserved to the States. *See*, *e.g.*, *Zucht v. King*, 260 U.S. 174, 176 (1922) ("[I]t is within the police power of a *state* to provide for compulsory vaccination" (emphasis added)). Thus, Defendants' attempts to impose the Contractor Mandate on private companies is an unconstitutional usurpation of the States' police powers and Plaintiffs are likely to succeed on the merits of their federalism challenge to the mandate.

2. The Contractor Mandate Violates The Equal Protection Clause

Defendants' Contractor Mandate (and Employee Mandate as well) would require vaccination of U.S. citizens (and also lawful permanent residents and other aliens lawfully employed by qualifying employers), but not of unauthorized aliens. This violates the Equal Protection Clause because it confers preferential treatment upon unauthorized aliens as a favored class without a valid basis to do so.

The Supreme Court established in *Bolling v. Sharpe*, 347 U.S. 497, 498 (1954) that the Equal Protection Clause of the Fourteenth Amendment is incorporated against the federal government through the Fifth Amendment's Due Process Clause. *See also Sessions v. Morales-Santana*, 137 S. Ct. 1678, 1686 n.1 (2017) (the Supreme Court's "approach to Fifth Amendment equal protection claims has always been precisely the same as to equal protection claims under the Fourteenth Amendment").

Aliens and citizens are protected classes in equal protection jurisprudence, triggering strict scrutiny when the government has a differential policy based on such classifications. *See Graham v. Richardson*, 403 U.S. 365, 371, 375–376 (1971); *Application of Griffiths*, 413 U.S. 717, 721 (1973). Generally, prior case law in this area has involved discrimination *against* aliens as a class. But the reverse preference in *favor* of unauthorized aliens is just as constitutionally suspect.

This unlawful discrimination is occurring at the applicable decision-making level here. All of the decisions regarding the vaccination mandates and non-mandates have been made by the President himself and the Executive Office of the President ("EOP"), with individual agencies then given commands to implement their respective mandates/non-mandates. And the President/EOP have (1) expressly decided to impose a variety of vaccination mandates that will fall overwhelmingly or exclusively upon U.S. citizens, lawful permanent residents, and aliens otherwise lawfully present in the United States and (2) simultaneously decided to *decline* to impose any vaccination mandates upon migrants unlawfully entering the United States even when in U.S. custody. The EOP has been explicit about its refusal to impose mandates on unauthorized aliens and instead giving them a true choice about whether to accept the U.S. government's offer of vaccination. For example, during a September 10, 2021 press conference, White House Press Secretary Jen Psaki had the following exchange with a reporter:

> Q Okay. And then why is it that you're trying to require anybody with a job or anybody who goes to school to get the COVID-19 vaccine, but you're not requiring that of migrants that continue walking across the southern border into the country?
>
> MS. PSAKI: Well, look, our objective is to get as many people vaccinated

> across the country as humanly possible. And so the President's announcement yesterday was an effort to empower businesses, to give businesses the tools to protect their workforces. That's exactly what we did.
>
> But certainly we want everybody to get vaccinated. And more people who are vaccinated, whether they are migrants or whether they are workers, protects more people in the United States.
>
> Q But it's a requirement for people at a business with more than 100 people, but it's not a requirement for migrants at the southern border. Why?
>
> MS. PSAKI: That's correct.[2]

At a press briefing on September 20, the issue came up again. Psaki announced that "in early November, we'll be putting in place strict protocols to prevent the spread of COVID-19 from passengers flying internationally into the United States by requiring that adult foreign nationals traveling to the United States be fully vaccinated."[3] When Psaki was questioned about the different policy for unauthorized aliens crossing the border illegally, Psaki said "[a]s individuals come across the border and — they are both assessed for whether they have any symptoms. If they have symptoms, they are — the intention is for them to be quarantined; that is our process. They're not intending to stay here for a lengthy period of time. I don't think it's the same thing."[4] Psaki never explained that putative difference, particularly given that most international air travelers are temporary visitors who are also "not intending to stay here for a lengthy period of time."

U.S. citizens, lawful permanent residents, lawfully present migrants, and unauthorized aliens are all similarly situated for purposes of the relevant decisions here. Coronavirus is an equal opportunity infector that is completely indifferent to the nationality/citizenship status of any human being. It will happily infect them all. Unauthorized aliens do not spread coronavirus any better or worse than those lawfully present in the United States. But the Biden Administration has unlawfully exempted

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[2] Jen Psaki, White House Press Briefing (Sept. 10, 2021), https://www.whitehouse.gov/briefing-room/press-briefings/2021/09/10/press-briefing-by-press-secretary-jen-psaki-september-10-2021/ (accessed Oct. 20, 2021)

[3] Jen Psaki, White House Press Briefing (Sept. 20, 2021), https://www.whitehouse.gov/briefing-room/press-briefings/2021/09/20/press-briefing-by-press-secretary-jen-psaki-september-20-2021/ (accessed Oct. 20, 2021); *see also* Rogers Decl. Ex. A.

[4] *Id.*

authorized aliens from all of its vaccination mandates, while imposing an array of unprecedented, overlapping, and extensive mandates that fall almost exclusively upon U.S. citizens and lawful permanent residents. This preference for unauthorized aliens violates the Equal Protection Clause.

There is no justification under a strict scrutiny standard that could possibly justify vaccine mandates for citizens but not for aliens. And even if a rational basis standard applied, there still would be no valid justification for affording more favorable treatment to aliens than citizens. Plaintiffs are thus likely to succeed on the merits of their Equal Protection challenge to the Contractor and Employee Mandates.

B. The Contractor Mandate Violates The Procurement Act

EO 14042 cites the Procurement Act as the basis for its authority for the Contractor Mandate. But the Procurement Act confers no such authority. Congress adopted the Act in 1949 with the stated statutory purpose "to provide the Federal Government with an economical and efficient system for" procurement. 40 U.S.C. § 101. The Procurement Act states that "[t]he President may prescribe policies and directives that the President considers necessary to carry out" the Procurement Act, but requires that the President's "policies must be consistent with" the Act. 40 U.S.C. § 121(a).

Defendants' attempts to use the Procurement Act as justification for the Contractor Mandate is akin to the Federal government's recent attempt at using the Public Health Safety Act as justification for a far-reaching nationwide eviction moratorium. That attempt was swiftly struck down by the Supreme Court, which held that the text of the statute clearly did not grant such sweeping authority to the government and that "[e]ven if the text were ambiguous, the sheer scope of the CDC's claimed authority ... would counsel against the Government's interpretation. We expect Congress to speak clearly when authorizing an agency to exercise powers of 'vast economic and political significance.'" *Alabama Ass'n of Realtors v. HHS*, 141 S. Ct. 2485, 2489 (2021). (quoting *Utility Air Regulatory Group v. EPA*, 573 U.S. 302, 324 (2014)). Particularly relevant was that "[t]he moratorium intrude[d] into an area that is the particular domain of state law." *Id.* That is just so here,

intruding upon the State's traditional police powers over public health issues. The Supreme Court's "precedents require Congress to enact exceedingly clear language if it wishes to significantly alter the balance between federal and state power and the power of the Government over private property." *Id.* The Procurement Act has no such language.

Congress enacted the Procurement Act to ensure the efficient purchase of goods and services, not to empower the Executive Branch to engage in far-reaching public health programs that are either unrelated to—or outright contrary to—the explicit efficiency rationale. "The text of the Procurement Act and its legislative history indicate that Congress was troubled by the absence of central management that could coordinate the entire government's procurement activities in an efficient and economical manner. The legislative history is replete with references for the need to have an 'efficient, businesslike system of property management.'" *Chamber of Commerce of U.S. v. Reich*, 74 F.3d 1322, 1333 (D.C. Cir. 1996) (citation omitted)). The Procurement Act does not give the President "unlimited authority to make decisions he believes will likely result in savings to the government.... The procurement power must be exercised consistently with the structure and purposes of the statute that delegates that power." *Id*. at 1330–31 (citation omitted).

Federal government spending typically accounts for about a quarter of the U.S. economy. Since the COVID-19 pandemic, that share has likely increased substantially. *See* FAC ¶85. Congress did *not* enact the Procurement Act to give the President sweeping power to issue decrees over one-quarter of the economy, like a Politburo ordering citizens to obey or starve. Nowhere in the Procurement Act is there any mention of vaccination, or even of a disease prevention objective of any kind. The Contractor Mandate could only be held permissible under an extraordinarily expansive interpretation of the Procurement Act that would give the government "a breathtaking amount of authority" over the economy, thus making it "hard to see what measures this interpretation would place outside [Defendants'] reach." *Alabama Realtors*, 141 S. Ct. at 2489.

Just as in *Alabama Realtors*, the statute confers no such authority. The Procurement Act is "a wafer-thin reed on which to rest such sweeping power." *Id.* "[O]ur system does

not permit agencies to act unlawfully even in pursuit of desirable ends," even in the face of "a strong [public] interest in combating the spread of the COVID–19 Delta variant." *Id.*at 2490.

1. There Is No Nexus Between The Contractor Mandate And Procurement

The Supreme Court's test for whether Executive Branch procurement requirements are permissible under the Procurement Act is whether there is a "nexus" with "some delegation of the requisite legislative authority by Congress ... reasonably within the contemplation of that grant of authority." *Chrysler Corp. v. Brown*, 441 U.S. 281, 304, 306 (1979). In *Chrysler*, a corporation sued to prevent disclosure of information it had given to the government about its employment of women and minorities. The disclosures were required by regulations adopted by the Department of Labor pursuant to an EO that claimed to be authorized by civil rights statutes and by the Procurement Act. The Court struck down the regulations because there was no "nexus" between the regulations and statutes involved. The Court explained that "it is clear that when it enacted these statutes, Congress was not concerned with public disclosure of trade secrets or confidential business information, and, unless we were to hold that any federal statute that implies some authority to collect information must grant *legislative* authority to disclose that information to the public, it is simply not possible to find in these statutes a delegation of the disclosure authority asserted by the" government. *Id*. at 306 (emphasis in original).

The Court went on to explain that for there to be a valid "grant of legislative authority to a federal agency" to promulgate regulations, "the reviewing court [must] reasonably be able to conclude that the grant of authority contemplates the regulations issued." *Id*. at 308. Even when the D.C. Circuit upheld a broad Carter Administration mandate imposing wage and price controls under the Procurement Act, it emphasized "the importance to our ruling today of the nexus between the wage and price standards and likely savings to the Government. As is clear from the terms and history of the [Procurement Act] and from experience with its implementation, our decision today *does*

not write a blank check for the President to fill in at his will." *AFL-CIO v. Kahn*, 618 F.2d 784, 793 (D.C. Cir. 1979) (en banc) (emphasis added).

Particularly relevant to the *Chrysler* Court's determination that there was no "nexus" to the Procurement Act was that "nowhere in the Act is there a specific reference to employment discrimination." *Chrysler*, 441 U.S. at 306 n.34. So too here—nowhere in the Procurement Act is there a specific reference to vaccination or even to disease prevention more generally. There is thus no authority to impose far-reaching mandates on millions of individuals[5] in an attempt to achieve broad public health social objectives.

The Contractor Mandate is on even shakier ground in its extension to subcontractors, as subcontractors have "no direct connection to federal procurement." *Liberty Mut. Ins. Co. v. Friedman*, 639 F.2d 164, 171 (4th Cir. 1981). At issue in *Liberty Mutual* was EO 11246, which imposed affirmative action racial mandates on government contractors and subcontractors. The Social Security Administration claimed that Liberty Mutual Insurance Company was subject to the EO's requirements because it provided workers' compensation insurance to federal contractors and thus qualified as a subcontractor under Department of Labor regulations adopted pursuant to the EO. Applying the Supreme Court's holding in *Chrysler*, the Fourth Circuit rejected the government's argument that the Procurement Act conferred on the President the authority to impose affirmative action mandates on subcontractors, holding "that application of the Executive Order to plaintiffs is not reasonably within the contemplation of any statutory grant of authority." *Liberty Mut. Ins. Co.*, 639 F.2d at 168.

The Contractor Mandate as applied to direct contractors also has no nexus with any delegation of legislative authority by Congress. Defendants claim as their purported justification for the Contractor Mandates that COVID-19 vaccination of contractors and subcontractors will reduce "absenteeism and decreas[e] labor costs for contractors and subcontractors working on or in connection with a Federal Government contract." 86 Fed.

[5] Rogers Decl. Ex. D (characterizing EO 14042 as plan "[r]equiring [v]accinations for ... [m]illions of [c]ontractors")

Reg. 53,691, 53,692 (Sept. 28, 2021). Defendants, however, have made no administrative "findings that suggest what percentage of the total price of federal contracts may be attributed" to the effect of COVID-19 vaccination on reduced absenteeism and labor costs. *Liberty Mut. Ins. Co*., 639 F.2d at 171. Indeed, Defendants have not even made any specific administrative findings at all about how COVID-19 vaccination might affect absenteeism and labor costs, let alone whether any costs would translate into changed Federal government contract costs.

Apart from making a bare allegation unsupported by any facts, Defendants failed to even make specific administrative findings that establish whether COVID-19 vaccination would increase or decrease absenteeism and labor costs. When the Executive Branch tries to impose procurement requirements targeted at achieving "social objectives," yet fails to make specific quantitative factual findings that demonstrate a nexus with procurement, "the connection ... is simply too attenuated to allow a reviewing court to find the requisite connection between procurement costs and social objectives," and the procurement policy is unlawful under the Procurement Act. *Id*.

The heavy-handed and illogical requirements of the SFWTF contractor guidance illustrate just how attenuated the connection is between the Contractor Mandate and economy and efficiency in procurement. For example, the SFWTF contractor guidance requires contractors to impose vaccine mandates on employees who are not even working on federal contracts. Rogers Decl. Ex. H at 3-4 ("[t]his includes employees of covered contractors who are not themselves working on or in connection with a covered contract"). The SFWTF contractor guidance also explicitly states that its vaccine mandate applies in a number of situations where solid science,[6] basic logic,[7] and even the CDC's own guidance,[8]

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[6] Rogers Decl. Ex. E ("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."); Rogers Decl. Ex. F ("Here, we evaluate 254 COVID-19 patients longitudinally up to 8 months and find durable broad-based immune responses.").

[7] It is impossible for employees working 100% remotely to infect co-workers.

[8] *E.g.*, Rogers Decl. Ex. G ("COVID-19 spreads more easily indoors than outdoors.... You are less likely to be exposed to COVID-19 when you [a]ttend outdoor activities.");

has established that the risk of COVID-19 infection or transmission to other contractor employees is exceedingly low, or even impossible, such as to 1) persons who have already been infected with COVID-19 and thus have natural immunity, *id*. at 10; 2) workplace locations that are outdoors, i*d*.; and 3) contractor employees who are working remotely full time, *id*. at 11.

As in *Liberty Mutual*, so too here: the connection between COVID-19 vaccination rates "and any increase in the cost of federal contracts that could be attributed to" vaccination "is simply too attenuated," and there is thus no nexus with economic and efficient procurement. *Liberty Mut. Ins. Co*, 639 F.2d at 171. The Procurement Act is about ensuring the government's efficient and economic acquisition of goods and services, not about achieving broad social public health objectives. The Procurement Act does not confer on Defendants the power to impose COVID-19 vaccination mandates on contractors and subcontractors. Accordingly, the Contractor Mandate is unlawful.

2. Defendants Lack Authority To Impose The Contractor Mandate Under The Major Questions Doctrine

Courts will not assume that Congress has assigned to the Executive Branch questions of "deep economic and political significance" unless Congress has done so expressly. *King v. Burwell*, 576 U.S. 473, 486 (2015); *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 160 (2000). By Defendants' own estimates, the Contractor Mandate will affect "millions" of individuals.[9] Indeed, on average, federal government spending accounts for 20% to 25% of the U.S. economy, and has been even higher during the COVID-19 pandemic. Defendants' vaccine mandates will thus have deep economic and political significance on a significant portion of the economy.

Congress did not intend, nor does the Procurement Act allow, the President to exercise such sweeping authority under the pretext of efficient procurement. In the absence of clear and explicit congressional authorization, the Procurement Act's purpose of achieving economy and efficiency does not grant the federal government power to usurp

[9] Rogers Decl. Ex. D at 3 (characterizing EO 14042 as a plan "[r]equiring [v]accinations for ... [m]illions of [c]ontractors").

the States' traditional police power over public health and vaccination requirements (to the extent any such power exists).

3. The Contractor Mandate Is Unlawful Because It Conflicts With Anther Federal Statute

"The President's authority [under the Procurement Act] to pursue 'efficient and economic' procurement" does not extend to EOs that "conflict with another federal statute." *Chamber of Commerce*, 74 F.3d at 1333.

The Contractor Mandate accordingly fails because it conflicts with the EUA Statute, 21 U.S.C. § 360bbb-3, under which the vaccines at issue are available. Because the EUA statute mandates that individuals have the right to refuse EUA-approved product and the Contractor Mandate denies them that choice, it is unlawful.[10]

C. The Contractor Mandate Is Unlawful Under The Procurement Policy Act

The Office of Federal Procurement Policy Act ("Procurement Policy Act") requires that a procurement "policy, regulation, procedure, or form (including an amendment or modification thereto) may not take effect until 60 days after it is published for public comment in the Federal Register ... if it--(A) relates to the expenditure of appropriated funds; and (B)(i) has a significant effect beyond the internal operating procedures of the agency issuing the policy, regulation, procedure, or form; or (ii) has a significant cost or administrative impact on contractors or offerors." 41 U.S.C. § 1707(a). "[T]he language of [§ 1707] is broad" and applies not only to Federal Acquisition Regulations, but to all procurement policies, regulations, procedures, and forms "'on down to the lowest level.'" *Munitions Carriers Conf., Inc. v. United States*, 932 F. Supp. 334, 338 (D.D.C. 1996), *rev'd on other grounds*, 147 F.3d 1027 (D.C. Cir. 1998).

The notice-and-comment requirement of § 1707 may only be "waived by the officer authorized to issue a procurement policy, regulation, procedure, or form if urgent and compelling circumstances make compliance with the requirements impracticable." 41

[10] As explained below at 22-23, while the FDA has granted approval to the Pfizer Comirnaty vaccine, the FDA-approved version of the vaccine is not yet available, and the only version of the Pfizer vaccine available for administration to individuals is the version approved and labeled under the EUA and to which the EUA statute therefore still applies.

U.S.C. § 1707(d). And even when Section 1707 has been waived, the Procurement Policy Act implementing regulations require that revisions subject to a waiver "shall be issued on a temporary basis and shall provide for at least a 30 day public comment period." 48 C.F.R. § 1.501-3(b).

The SFWTF guidance qualifies both as a "policy" and a "procedure" under the Procurement Policy Act. The Act does not define the terms policy, regulation, procedure, or form, and "in the absence of a statutory definition [courts] 'start with the assumption that the legislative purpose is expressed by the ordinary meaning of the words used.'" *Mississippi Band of Choctaw Indians v. Holyfield*, 490 U.S. 30, 47 (1989) (quoting *Richards v. United States*, 369 U.S. 1, 9 (1962)). Black's Law Dictionary defines "policy" to mean "[a] standard course of action that has been officially established by an organization," and it defines "procedure" to mean "[a] specific method or course of action." *Policy* and *Procedure*, *Black's Law Dictionary* (11th ed. 2019). The SFWTF Contractor Mandate establishes an official standard course of action and specific methods for imposing COVID-19 vaccine mandates. The SFWTF guidance therefore qualifies as both a procurement "policy" and "procedure," under the ordinary meanings of those terms.

Furthermore, the requirements of Section 1707 apply to the SFWTF contractor guidance because it relates to the expenditure of appropriated funds, has a significant effect beyond internal operating procedures, and imposes significant costs and administrative impacts on contractors and offerors. As discussed above, by their own estimates, Defendants expect that the Contractor Mandate will affect "millions" of individuals. The Procurement Policy Act implementing regulations confirm that the SFWTF guidance is the type of procurement change to which Section 1707 applies. The regulations explain that the types of changes that do not require notice and comment are "editorial, stylistic, or other revisions that have no impact on the basic meaning of the coverage being revised." 48 C.F.R. § 1.501-1. But the SFWTF guidance is nothing of the sort.

Defendants never published the SFWTF contractor guidance "for public comment in the Federal Register," as required by Section 1707. Instead, they released the guidance

only on the SFWTF website.[11] The only Federal Register publication related to the SFWTF contractor guidance was a short notice published on September 28, 2021 in which Defendant Young made the conclusory contention that she had "determined that compliance by Federal contractors and subcontractors with the COVID–19-workplace safety protocols detailed in [the SFWTF] guidance will improve economy and efficiency by reducing absenteeism and decreasing labor costs for contractors and subcontractors working on or in connection with a Federal Government contract." 86 Fed. Reg. 53,691, 53,692 (Sept. 28, 2021). Ms. Young did not cite to any information or evidence that would support the claims in her determination, nor did she explain how she reached her conclusion. *See id.* Furthermore, Ms. Young's notice was not open to public comment. Nor did she claim there were any urgent and compelling circumstances preventing compliance with notice-and-comment requirements or justifying a 41 U.S.C. § 1707(d) waiver of the requirement that procurement policies not take effect for 60 days.

Because the SFWTF Contractor Guidance was never published for public comment in the Federal Register, and because Defendants never waived the application of Section 1707, the SFWTF is unlawful and "may not take effect." Plaintiffs are therefore likely to succeed on the merits of their Procurement Policy Act challenge.

D. The Contractor Mandate Is Unlawful Under The Emergency Use Authorization Statute

Under 21 U.S.C. § 360bbb-3, the Secretary of Health and Human Services "may authorize the introduction ... of a drug, device, or biological product intended for use in an actual or potential emergency" before such products receive full FDA approval. Such Emergency Use Authorizations ("EUAs") are subject to strict requirements, including that "individuals to whom the product is administered are informed ... of the *option to accept or refuse administration of the product*." 21 U.S.C. § 360bbb-3(e)(1)(A)(ii)(III) (emphasis added).

The SFWTF contractors guidance states that "people are considered fully

[11] *See* Rogers Decl. Ex. H.

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)." Rogers Decl. Ex. H at 4. The Moderna and Janssen vaccines are still only available under EUAs. *See* Rogers Decl. Exs. I, J. The part of the Contractor Mandate that requires administration of the Moderna or the Janssen vaccine is therefore unlawful under 21 U.S.C. § 360bbb-3 because it does not afford to contractors and subcontractors a meaningful opportunity to refuse them.

On August 23, 2021, the FDA approved the Biologics License Application ("BLA") for the Comirnaty vaccine jointly made by Pfizer and BioNTech. Rogers Decl. Ex. K. But there is no indication when the Comirnaty vaccine will become available, or indeed, when production of it would even begin. An NIH notice from September 13, 2021 states that "[a]t present, Pfizer does not plan to produce any [Comirnaty] product with these new NDCs and labels over the next few months while EUA authorized product is still available and being made available for U.S. distribution."[12] On September 22, 2021, the FDA issued an updated EUA letter for the prior Pfizer-BioNTech COVID-19 that explained that while "COMIRNATY (COVID-19 Vaccine, mRNA) is now licensed for individuals 16 years of age and older," "[t]here remains, however, a significant amount of Pfizer-BioNTech COVID-19 Vaccine that was manufactured and labeled in accordance with this emergency use authorization. The authorization remains in place with respect to the Pfizer-BioNTech COVID-19 Vaccine." Rogers Decl. Ex. L. The FDA-approved Comirnaty vaccine is not yet available in the United States. The only Pfizer-BioNTech vaccine currently available is of the prior EUA version of the vaccine.

The same FDA letter also acknowledges that the "licensed vaccine" and "the EUA-authorized vaccine ... are legally distinct...." *Id*. at 3 n.10.[13] The legal distinctions between

[12] Rogers Decl. Ex. V.

[13] And while the letter also claims that the Pfizer-BioNTech EUA vaccine and Comirnaty have "the same formulation," *id.*, the FDA released together with its Comirnaty approval a document titled "Summary Basis for Regulatory Action" that acknowledges that there is at least one compositional difference: as opposed to the EUA version of the vaccine, "COMIRNATY includes the presence of optimized codons to improve antigen

the two versions of the Pfizer-BioNTech vaccine are relevant here, because the requirements of 21 U.S.C. § 360bbb-3 still apply to the EUA version of the vaccine. Defendants are therefore required to afford to all individuals subject to the Contractor and Employee Mandates the "option to ... refuse administration of the product."

1. Legislative History And Agency Interpretation Establish That The EUA Statute Creates A Right To Refuse EUA Products

Beyond just the clear statutory language requiring that individuals have the "option to ... refuse," the legislative history and agency interpretation also establish that the EUA statute creates a right to refuse EUA products.

When Congress adopted the EUA statute, it interpreted the statute as conferring "the *right* ... to refuse administration of a product." H.R. Conf. Rep. No. 108-354, at 782 (2003) (emphasis added). The FDA's interpretation of the statute also agrees that the EUA statute means that "[r]ecipients *must have an opportunity to accept or refuse the EUA product*" and that this right to refuse can only be waived if the President makes a specific determination in writing, and only with respect to members of the armed forces.[14]

A specific statute, 10 U.S.C. § 1107a, gives the President the power to waive the right to refuse of members of the armed forces. He may waive their right, however, only if

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expression." Rogers Decl. Ex. M at 14.

[14] FDA, *Guidance Emergency Use Authorization of Medical Products*, 2007 WL 2319112, at *15 and n.16 (acknowledging that "Congress authorized the President to waive, under certain circumstances, the option for members of the armed forces to accept or refuse administration of an EUA product") (emphasis added); *see also*, FDA, *Emergency Use Authorization of Medical Products and Related Authorities: Guidance for Industry and Other Stakeholders*, OMB Control No. 0910-0595 at 24 n.46, 2017 WL 345587, at *31 n.46 (Jan. 2017) (characterizing the requirements of 21 U.S.C. § 360bbb-3(e)(1)(A)(ii)(III) as "the option ... to accept or refuse administration of an EUA product" and explaining that "[t]he President may under certain circumstances waive the option for members of the armed forces"); 10 U.S.C. § 1107a(a) (stating that the requirements of 21 U.S.C. § 360bbb-3(e)(1)(A)(ii)(III), as applied to the armed forces, "may be waived only by the President only if the President determines, in writing, that complying with such requirement is not in the interests of national security"); *Authorization of Emergency Use of Anthrax Vaccine Adsorbed for Prevention of Inhalation Anthrax by Individuals at Heightened Risk of Exposure Due to Attack With Anthrax; Availability*, 70 Fed. Reg. 5452-02, 5455 (Feb. 2, 2005) (creating EUA for anthrax vaccine for members of the armed forces, and stating that "[i]ndividuals who refuse anthrax vaccination will not be punished").

he makes a specific determination in writing "that complying with such requirement is not in the interests of national security." 10 U.S.C. § 1107a(a)(1). A parallel statute, 10 U.S.C. § 1107, imposes similar requirements for investigational drugs. That Congress adopted these statutes makes clear that Congress meant for the "option to ... refuse" to be just that. Otherwise, there would be no reason to enact statutes allowing the President to waive those requirements when national security so requires.

At least one District Court interpreting Section 1107 has held that its requirements meant that the military could not require that personnel receive an investigational vaccine "absent informed consent or a Presidential waiver." *Doe v. Rumsfeld*, 341 F. Supp. 2d 1, 16 (D.D.C. 2004), *modified sub nom. John Doe No. 1 v. Rumsfeld*, No. CIV.A. 03-707 (EGS), 2005 WL 774857 (D.D.C. Feb. 6, 2005), and *modified* 2005 WL 1124589 (D.D.C. Apr. 6, 2005); *see also John Doe No. 1 v. Rumsfeld*, No. 03-707, 2005 WL 774857, at *1 (D.D.C. Feb. 6, 2005) (ordering that administration to military personnel of experimental anthrax vaccine subject to an EUA was permitted, but only "on a *voluntary* basis, pursuant to the terms of a *lawful* emergency use authorization" (emphasis in original)). The FDA's own regulations specifically state that one of the elements of "informed consent" is that "participation [be] voluntary" and "that refusal to participate will involve *no penalty or loss of benefits* to which the subject is otherwise entitled." 21 C.F.R. § 50.25 (emphasis added).

The court's reasoning in *Doe* applies here. The only exception to the EUA statute's informed consent requirement is for members of the armed forces, and only when the President has issued a specific determination. Getting fired is a "penalty or loss of benefits to which the subject is otherwise entitled." 21 C.F.R. § 50.25. The mandates' coercive threat of "get the jab or get fired" means that individuals subject to the mandates do not have a meaningful "option to . . . refuse" the vaccine. The mandates are therefore unlawful under 21 U.S.C. § 360bbb-3.The Contractor (and Employee) Mandates thus violate the EUA statute.

2. Canons Of Construction Make Clear That The EUA Statute Creates A Right To Refuse EUA Products

The canons of construction confirm what Section 360bbb-3's text already makes plain. Two are critical here: avoidance of surplusage and *expressio unius*.

1) Avoidance Of Surplusage. "It is 'a cardinal principle of statutory construction' that 'a statute ought, upon the whole, to be so construed that, if it can be prevented, no clause, sentence, or word shall be superfluous, void, or insignificant.'" *TRW Inc. v. Andrews*, 534 U.S. 19, 31 (2001) (citation omitted). If Section 360bbb-3 were interpreted to allow Defendants to require that contractors fire employees who refuse to take EUA vaccines, it would render a nullity the statutory language providing for the "option to accept or refuse administration of the product."

2) Expressio Unius. Under the venerable *expressio unius* canon, "[t]he expression of one thing implies the exclusion of others." *Jennings v. Rodriguez*, 138 S.Ct. 830, 844 (2018). Thus, "[w]hen a statute limits a thing to be done in a particular mode, it includes a negative of any other mode." *Christensen v. Harris Cty.*, 529 U.S. 576, 583 (2000) (cleaned up) (citation omitted). As explained above, Congress provided for only one exception to the right to refuse: when the President makes a national security determination in writing and waives the requirement as it applies to members of the military. Application of the e*xpressio unius* canon is particularly appropriate here, as "[w]here Congress explicitly enumerates certain exceptions to a general prohibition, additional exceptions are not to be implied, in the absence of evidence of a contrary legislative intent." *TRW Inc.* 534 U.S. at 28 (quoting *Andrus v. Glover Constr. Co.*, 446 U.S. 608, 616–617 (1980)). And there is no "evidence of a contrary legislative intent" here.

II. Plaintiffs Are Likely To Prevail On The Merits Of Their Claims Against the Employee Mandate

A. The Employee Mandate Violates The Equal Protection Clause And The EUA Statute

For all the same reasons discussed above with respect to the Contractor Mandate, the Employee Mandate also violates the Equal Protection Clause and the EUA statute. The

State is therefore likely to prevail on its challenges to the Employee Mandate on those bases as well. *Supra* at 10-12, 21-25.

B. The Federal Employee Mandate Violates Employees' Constitutional Right To Bodily Integrity And To Refuse Medical Procedures

"[E]ven in a pandemic, the Constitution cannot be put away and forgotten." *Roman Cath. Diocese of Brooklyn v. Cuomo*, 141 S. Ct. 63, 68 (2020). And under Supreme Court precedent, Defendants' Employee Mandate is an unconstitutional violation of the Due Process Clause and the right to bodily integrity.

"[A] competent person has a constitutionally protected liberty interest in refusing unwanted medical treatment." *Cruzan by Cruzan v. Dir., Missouri Dep't of Health*, 497 U.S. 261, 278 (1990). This right is rooted in "the common-law rule that forced medication was a battery, and the long legal tradition protecting the decision to refuse unwanted medical treatment." *Washington v. Glucksberg*, 521 U.S. 702, 725 (1997).

Closely related to the right to refuse unwanted medical treatment is the right to bodily integrity. "[D]ue process ... substantively protects a person's rights to be free from unjustified intrusions to the body, to refuse unwanted medical treatment and to receive sufficient information to exercise these rights intelligently." *Benson v. Terhune*, 304 F.3d 874, 884 (9th Cir. 2002) (citations omitted). Individuals thus have a "constitutional right to be free from state-imposed violations of bodily integrity." *Plumeau v. Sch. Dist. No. 40 Cty. of Yamhill*, 130 F.3d 432, 438 (9th Cir. 1997).

Defendants may not evade these constitutional requirements by claiming to be acting merely as an employer or participant in the market economy. Under the unconstitutional conditions doctrine, the government may not condition employment "on a basis that infringes [an employee's] constitutionally protected interests." *Perry v. Sindermann*, 408 U.S. 593, 597 (1972); *see also*, *Koontz v. St. Johns River Water Mgmt. Dist.*, 570 U.S. 595, 606 (2013) ("[T]he unconstitutional conditions doctrine forbids burdening the Constitution's enumerated rights by coercively withholding benefits from those who exercise them...."); *Koontz*, 570 U.S. at 604 ("[A]n overarching principle, known

as the unconstitutional conditions doctrine, ... vindicates the Constitution's enumerated rights by preventing the government from coercing people into giving them up.") The unconstitutional conditions doctrine also applies to government contracts. *Bd. of Cty. Comm'rs, Wabaunsee Cty., Kan. v. Umbehr*, 518 U.S. 668, 678 (1996).

1. The Employee Mandate Is Subject To Strict Scrutiny

The "rights to determine one's own medical treatment[] and to refuse unwanted medical treatment" are fundamental rights, and individuals have "a fundamental liberty interest in medical autonomy." *Coons v. Lew*, 762 F.3d 891, 899 (9th Cir. 2014), *as amended* (Sept. 2, 2014) (cleaned up). Similarly, the right to "bodily integrity" is also "fundamental" and is "deeply rooted in this Nation's history and tradition." *Franceschi v. Yee*, 887 F.3d 927, 937 (9th Cir. 2018) (quoting *Moore v. East Cleveland*, 431 U.S. 494, 503 (1977)). "Every violation of a person's bodily integrity is an invasion of his or her liberty. The invasion is particularly intrusive if it creates a substantial risk of permanent injury and premature death. Moreover, any such action is degrading if it overrides a competent person's choice to reject a specific form of medical treatment." *Washington v. Harper*, 494 U.S. 210, 237 (1990) (Stevens, J., concurring in part).

"Governmental actions that infringe upon a fundamental right receive strict scrutiny." *Fields v. Palmdale Sch. Dist.*, 427 F.3d 1197, 1208 (9th Cir. 2005), *as amended by* 447 F.3d 1187 (9th Cir. 2006). Accordingly, the Employee Mandate is subject to strict scrutiny and must be struck down unless it "advance[s] a compelling state interest by the least restrictive means available." *Bernal v. Fainter*, 467 U.S. 216, 219 (1984).

In this case, the Employee Mandate fails the strict scrutiny test because it is both under- and over-inclusive. It is overinclusive because it applies to persons and situations where risk of infection is either extremely low or nonexistent such as to employees who are working remotely full-time and thus do not pose any risk of exposing other federal employees to COVID-19 and to federal employees who have already been infected with COVID-19 and thus already have natural immunity. *See supra* at 17. The Employee Mandate is under-inclusive because it does not apply to unauthorized aliens, even though

they can become infected with, and carriers of, COVID-19 just like U.S. citizens and lawful permanent residents. Indeed, the Employee Mandate's parameters are so irrational and arbitrary that they would fail even under a rational basis standard.

2. *Jacobson* Does Not Command A Different Result

Public debate about government vaccine mandates has often focused on the Supreme Court's decision in *Jacobson v. Commonwealth of Massachusetts*, 197 U.S. 11 (1905). That case, however, has little applicability here for four reasons.

First, it was addressing whether *States* have the power to impose vaccine mandates. The Court never considered the constitutionality of the Federal government imposing such mandates, which have always been considered as being part of the police power held exclusively by the States, to the extent that such power exists at all.

Second, *Jacobson* was decided 116 years ago, just months before the Court issued its decision in *Lochner v. New York*, 198 U.S. 45 (1905), which is now widely regarded as having been relegated to the ash heap of jurisprudential history. Needless to say, a lot has changed doctrinally since then. As one district court has explained:

> There is no question, therefore, that even under the plain language of *Jacobson*, a public health measure may violate the Constitution.
>
> *Jacobson* was decided over a century ago. Since that time, there has been substantial development of federal constitutional law in the area of civil liberties. As a general matter, this development has seen a jurisprudential shift whereby federal courts have given greater deference to considerations of individual liberties, as weighed against the exercise of state police powers. That century of development has seen the creation of tiered levels of scrutiny for constitutional claims. They did not exist when *Jacobson* was decided. While *Jacobson* has been cited by some modern courts as ongoing support for a broad, hands-off deference to state authorities in matters of health and safety, other courts and commentators have questioned whether it remains instructive in light of the intervening jurisprudential developments....
>
> The permissive *Jacobson* rule floats about in the air as a rubber stamp for all but the most absurd and egregious restrictions on constitutional liberties, free from the inconvenience of meaningful judicial review. This may help explain why the Supreme Court established the traditional tiers of scrutiny in the course of the 100 years since *Jacobson* was decided.

Cty. of Butler v. Wolf, 486 F. Supp. 3d 883, 897 (W.D. Pa. 2020) (cleaned up).

Third, as Justice Gorsuch recently explained, it is important to "consider the

different nature of the restriction" in *Jacobson* versus Defendants' mandate. *Roman Cath. Diocese of Brooklyn*, 141 S. Ct. at 70 (Gorsuch, J., concurring). "In *Jacobson*, individuals could accept the vaccine, pay the fine [$5, or about $140 today], or identify a basis for exemption. The imposition on Mr. Jacobson's claimed right to bodily integrity, thus, was avoidable and relatively modest. It easily survived rational basis review, and might even have survived strict scrutiny, given the opt-outs available to certain objectors." *Id*. at 70-71. There is nothing "avoidable" or "relatively modest" about Defendants' draconian "get the jab or get fired" mandate. Curiously, the modest penalties involved in *Jacobson* were aimed at fighting a significantly more deadly disease: the death rate for smallpox infection is about 30%,[15] whereas the death rate for COVID-19 is about 0.15%,[16] which is 200 times lower than the death rate for smallpox.

Fourth, while *Jacobson* has never been formally abrogated, its doctrinal underpinnings have been cut out from under it. *Jacobson* was the only citation that Justice Holmes provided to support his now-infamous statement that "[t]hree generations of imbeciles are enough," in his opinion in *Buck v. Bell* upholding compulsory eugenics-based sterilization laws as both constitutional and socially desirable. 274 U.S. 200, 207 (1927). The full quotation in context shows how essential *Jacobson* was to Justice Holmes's opinion:

> The principle that sustains compulsory vaccination is broad enough to cover cutting the Fallopian tubes. *Jacobson v. Massachusetts*, 197 U. S. 11, 25 S. Ct. 358, 49 L. Ed. 643, 3 Ann. Cas. 765. Three generations of imbeciles are enough.

Id. While *Buck v. Bell* has never been overruled, its inapplicability today is not seriously disputed. The same result should obtain for *Jacobson*.

III. All The Other Requirements For An Injunction Are Met

A. Plaintiffs Will Suffer Irreparable Harm If An Injunction Is Not Granted

Plaintiffs are likely to suffer irreparable harm in the absence of the requested preliminary injunction because the harms incurred from vaccination compelled by

[15] Rogers Decl. Ex. T.
[16] Rogers Decl. Ex. U.

Defendants' Mandates—including the potential for well-documented side-effects—cannot be remedied through monetary damages or other *post hoc* judicial relief. Irreparable harm exists where there is no adequate legal remedy to cure the harm. *See Arizona Recovery House Ass'n v. Arizona Dep't of Health Services*, 462 F. Supp. 3d 990, 997 (D. Ariz. 2020). "[A] regulation later held invalid almost *always* produces the irreparable harm of nonrecoverable compliance costs." *Thunder Basin Coal Co. v. Reich*, 510 U.S. 200, 220–21 (1994) (Scalia, J., concurring) (emphasis in original).

Moreover, "where parties cannot typically recover monetary damages flowing from their injury … economic harm can be considered irreparable" and "[i]ntangible injuries may also qualify as irreparable harm, because such injuries 'generally lack an adequate legal remedy.'" *East Bay*, 950 F.3d at 1280 (9th Cir. 2020) (quoting *California v. Azar*, 911 F.3d 558, 581 (9th Cir. 2018) and *Arizona Dream Act Coal. v. Brewer*, 757 F.3d 1053, 1068 (9th Cir. 2014)). "The mere fact that the damages are susceptible to quantification, however, does not necessarily mean that a preliminary injunction will not lie." *Arizona Recovery Hous. Ass'n*, 462 F. Supp. 3d at 997; *City & County of San Francisco v. United States Citizenship & Immigration Services*, 981 F.3d 742, 762 (9th Cir. 2020) ("There is no dispute that such economic harm is sufficient to constitute irreparable harm because of the unavailability of monetary damages.") (citing *Azar*, 911 F.3d at 581).

Defendants' Mandates will also cause substantial harm to Arizona's economy and to Arizona businesses that will either have to fire valuable employees, or give up lucrative government contracts. The Society for Human Resource Management conducted a survey of businesses subject to Defendants' Mandates and found that "85 percent said the anticipated requirement will make retaining employees more difficult. Eighty-nine percent said some of their employees will quit due to the new mandate." FAC ¶83. Similarly, a leading trade publication covering the construction industry has predicted that more than 40% of employees in the construction industry, "when faced with the choice between the vaccine and their job with a federal contractor, will quit and go to work for another

contractor that does not have such a mandate" *Id*. This is particularly true as the U.S. economy is currently undergoing the so-called "Great Resignation," where employee attrition is already at extraordinary high levels.[17] Furthermore, the confusion and dislocation caused by mass layoffs and possible labor actions by affected employees threaten to cause substantial economic loss. The recent chaos faced by Southwest Airlines (*see infra* at 32-34) is an example of the widespread harm that Arizona faces.

Additionally, the State of Arizona will suffer direct economic loss. Since some Arizona state agencies are federal contractors, they face the loss of federal funds and contracts. And if State agencies were able to impose the mandate, it would force many State employees to resign or get fired. In the current tight labor market, this will cause significant harm to the State's operations through the loss of institutional knowledge and human capital. It will also cause the State to incur significant recruitment, on-boarding, and training costs to replace lost employees.

Similarly, Plaintiff Doe faces the heavy economic harm of losing his job, and thus his income.

B. The Balance Of Harms And Public Interest Support A Preliminary Injunction

The third and fourth *Winter* factors, the balance of the equities and public interest factors, also weigh in favor of Plaintiffs, and are properly considered together here. "When the Government is a party to a case, the balance of the equities and public interest factors merge." *Doe #1 v. Trump*, 984 F.3d 848, 861–62 (9th Cir. 2020) (internal quotation marks omitted). The "purpose of a preliminary injunction is merely to preserve the relative positions of the parties until a trial on the merits can be held." *Univ. of Tex.*, 451 U.S. at 395; *Doe #1 v. Trump*, 957 F.3d 1050, 1068 (9th Cir. 2020). Here, as "often happens … this purpose is furthered by the status quo," *Doe #1*, 957 F.3d at 1068, which in this case is the regime prior to September 9, under which there were no federal vaccination mandates (with Defendants themselves having admitted that the federal government

[17] Rogers Decl. Exs. W, X.

lacked authority to impose them, FAC ¶74).

In *Doe #1*, plaintiffs challenged a presidential proclamation affecting immigration policy and obtained a preliminary injunction. In reviewing the federal government's request for a stay of the injunction, the Ninth Circuit held that "it was the Proclamation that altered the *status quo*," rejecting the federal government's argument that the status quo is the "Proclamation as implemented." *Id.* The same analysis controls here as the discriminatory vaccine mandate presents the anomaly in the normal course of business.

And enjoining an unconstitutional and discriminatory mandate poses no harm to Defendants. They have no legitimate interest in the implementation of an unlawful policy. *See N.Y. Progress & Prot. PAC v. Walsh*, 733 F.3d 483, 488 (2d Cir. 2013) (recognizing that government officials "do[] not have an interest in the enforcement of an unconstitutional law"). In contrast, the public interest is served by an injunction because maintaining the status quo will prevent further disruption in the delivery of goods and services dependent upon industries already experiencing a labor shortage that will be predictably exacerbated by additional conditions on employment.

This has been prominently displayed in the case of Southwest Airlines, which had to cancel over 2000 flights in the past ten days as pilots refused to work in the wake of the company's vaccine mandate and the pilot's union's suit to stop it.[18] "The key driver for such cancellations is likely the COVID-19 vaccine mandate for its employees. Southwest employees are expressing their concern in droves by simultaneously and strategically using their sick time benefits."[19] What's more, estimates indicate that such a massive impact can be felt by the action of "just over 2 percent of their employees being unavailable. This illustrates how vulnerable the airline is to organized worker shortages even among a small group of potentially disgruntled employees."[20] And the company would not have put a vaccine requirement in place but for the Biden administration's mandate, as Southwest's

[18] Rogers Decl. Exs. N, O.
[19] Rogers Decl. Ex. O.
[20] *Id.*

CEO Gary Kelly has "never been in favor of corporations imposing that kind of a mandate. I'm not in favor of that, never have been."[21] In addition to being consumer airlines, "Southwest Airlines and American Airlines are among the carriers that are federal contractors and subject to" the Contractor Mandate, so their employees may not utilize "regular Covid testing as an alternative to a vaccination" as other large, non-contractor business employees may.[22] And while the airline claims weather and air traffic control issues as its official justification for the unprecedented disruption in service, it is telling that in response, it has dropped one of its major enforcement mechanisms for the mandate: forced unpaid leave.[23]

As other industries lose workers to the mandate, similar to Southwest's experience, the already-ongoing labor shortage will only deepen, impacting multiple industries and disrupting the supply chain.[24] This is predicted to have a significant impact on the availability of goods, increase consumer prices, and cost billions of dollars in trade, as workers pull out of critical industries or switch to jobs without such mandates:

> Biden's vaccine mandates are one reason that our ports, clogged with stacked-up ships waiting to disgorge needed goods, may not be freed up any time soon. There are currently an unprecedented 62 cargo ships awaiting unloading at the Los Angeles and Long Beach, Calif., docks. The back-up, said likely to disrupt $90 billion in trade and possibly cause holiday-season goods shortages, is partly because of the sheer volume of goods being pushed through the supply chains as stores and manufacturers try to dig out from the COVID-related shut-downs.[25]

This is why the pre-mandate status quo of vaccine choice should be maintained: Entering a preliminary injunction will put these ill effects on hold until the illegality of the mandate orders can be properly reviewed. Thus, the public interest will be served as employees can continue working with job security regardless of vaccine choice, allowing the economy

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[21] Rogers Decl. Ex. P.
[22] Rogers Decl. Ex. Q.
[23] *Id.*; Massie, n. 10, *supra*.
[24] Rogers Decl. Ex. R.
[25] *Id.*

and supply chains to continue recovering without disruptions caused by the predictable protest actions some have already seen.

IV. Plaintiffs Request a Temporary Restraining Order

Plaintiffs request that this Court immediately issue a temporary restraining order ("TRO") while this Motion for Preliminary Injunction is pending for the purpose "of preserving the status quo and preventing [the] irreparable harm" that is occurring and will continue to occur if Defendants' Mandates are allowed to remain in effect, as the next vaccination deadline is just days away. *Granny Goose Foods, Inc. v. Brotherhood of Teamsters & Auto Truck Drivers Local No. 70 of Alameda Cnty.*, 415 U.S. 423, 439 (1974).

"The standard for issuing a TRO is the same as that for issuing a preliminary injunction." *Spears v. Arizona Bd. of Regents*, 372 F. Supp. 3d 893, 926 (D. Ariz. 2019). As demonstrated above, Plaintiffs are likely to succeed on the merits, are likely to suffer irreparable harm in the absence of a TRO, and the balance of equities and public interest favor a TRO.

What makes a TRO especially necessary here are the proximity of vaccination deadlines to the filing of the Motion, many of which are likely to come and go before the preliminary injunction will be fully briefed, and the irreversibility of receiving a vaccine. The Contractor and Employee Mandates seek to coerce certain categories of individuals into undergoing an invasive medical procedure, an experience that cannot be undone. The deadline for federal contractors to receive their first vaccine is approaching as early as October 27, 2021, so time is of the essence. The deadline for federal employees to receive their first Pfizer or Moderna vaccine has already passed, but the November 8 deadline for them to receive their second dose (or their first and only dose of the Johnson & Johnson vaccine) is just weeks away. As a consequence of the mandate's timeline, Plaintiffs are suffering, and will continue to suffer, irreparable harm in the absence of a TRO. These factors and the disruption in business and travel linked to the application of federal COVID-19 vaccine mandates emphasize that the public interest favors a TRO because it

will preserve the status quo until this Motion for Preliminary Injunction can be reached by this Court.

CONCLUSION

Plaintiffs respectfully request that the Court issue a temporary restraining order and preliminary injunction enjoining enforcement of the Contractor and Employee Mandates.

RESPECTFULLY SUBMITTED this 22nd day of October, 2021.

MARK BRNOVICH
ATTORNEY GENERAL

By: */s/ James K. Rogers*
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Attorneys for Plaintiffs Mark Brnovich and the State of Arizona

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By: /s/ Jack Wilenchik (with permission)
Jack Wilenchik (No. 029353)

Attorney for Plaintiff John Doe

CERTIFICATE OF SERVICE

I hereby certify that on this 22nd day of October, 2021, I electronically filed the foregoing with the Clerk of the Court for the United States District Court for the District of Arizona using the CM/ECF filing system. Counsel for all parties are registered CM/ECF users and will be served by the CM/ECF system pursuant to the notice of electronic filing.

/s/ James K. Rogers
Attorney for Plaintiff Mark Brnovich, in his official capacity as Attorney General of Arizona; and the State of Arizona

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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
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Counsel of Record
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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.

rotecting
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.

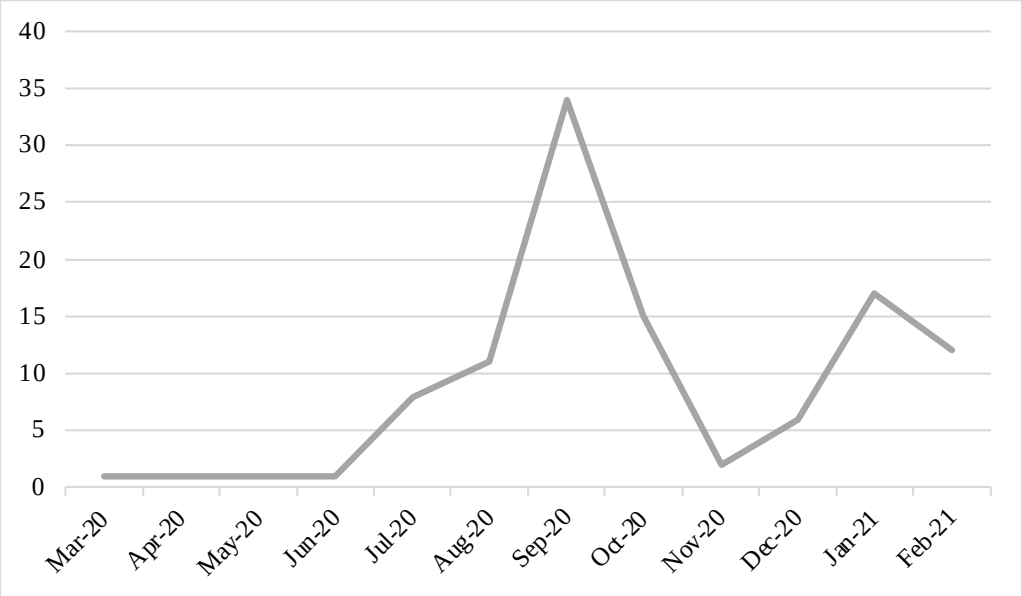


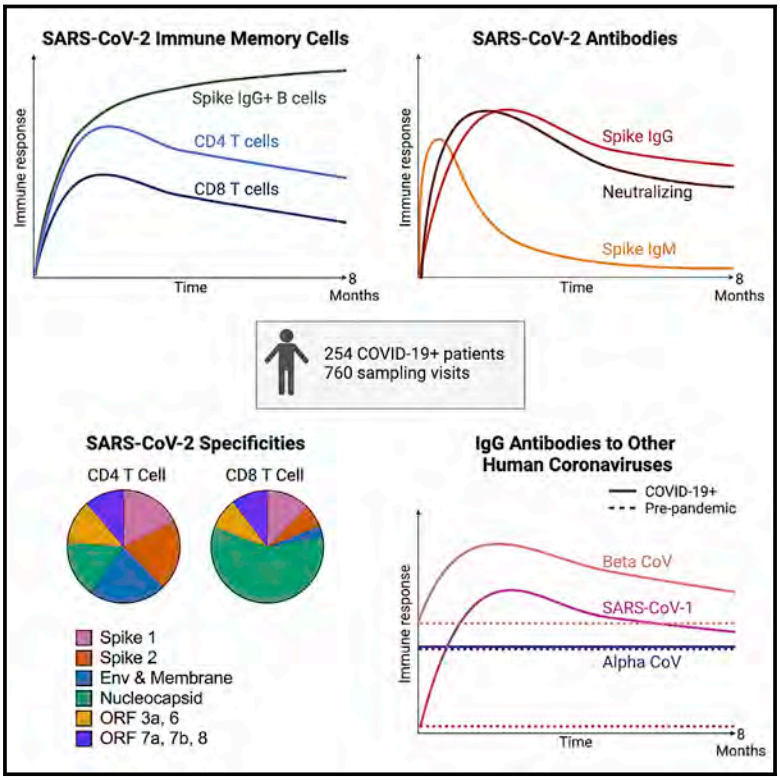
Exhibit F

Cell Reports Medicine

Article

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.

Cohen et al., 2021, Cell Reports Medicine 2, 100354
July 20, 2021
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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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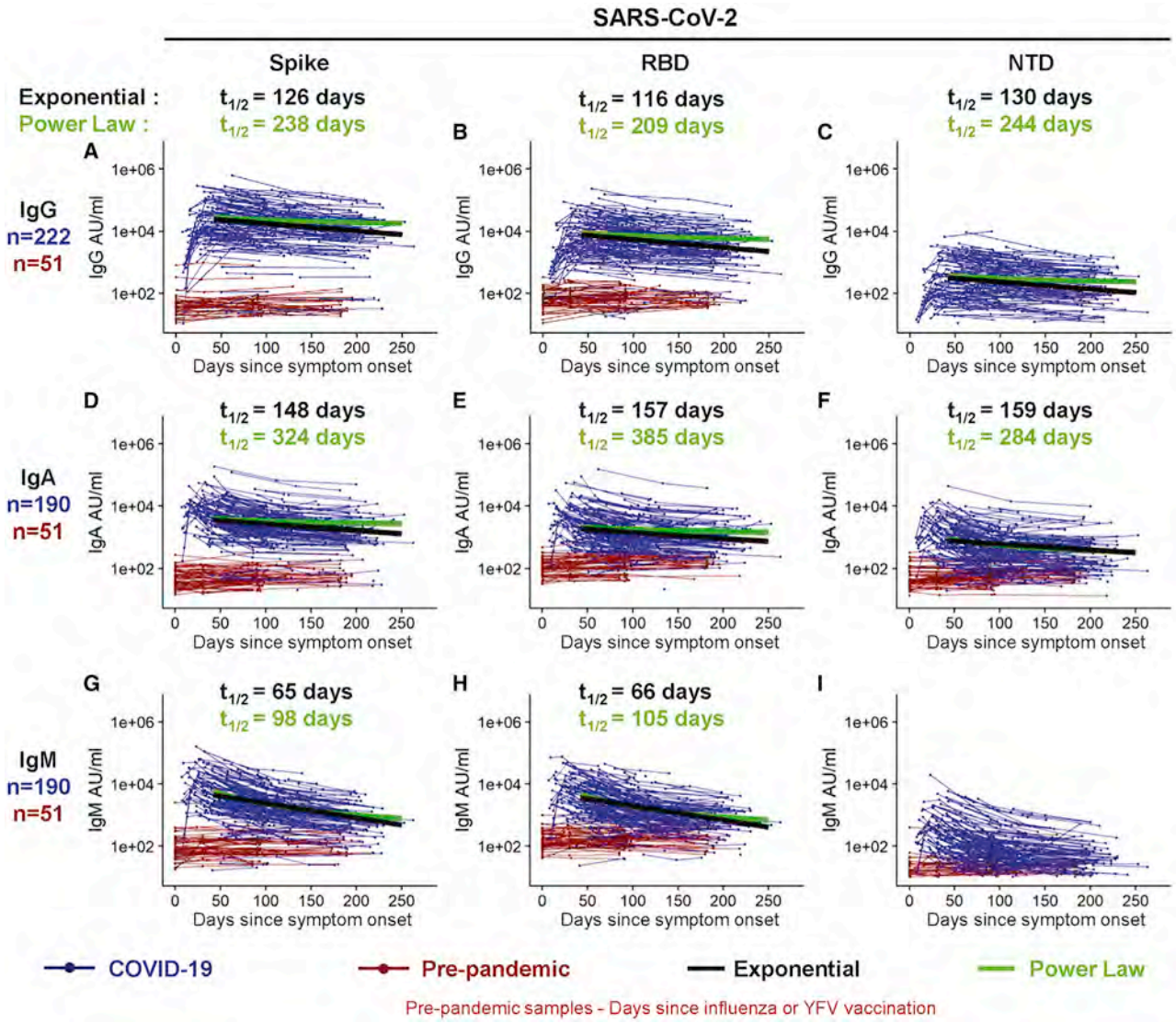

Figure 1. Longitudinal SARS-CoV-2 spike-binding antibody responses

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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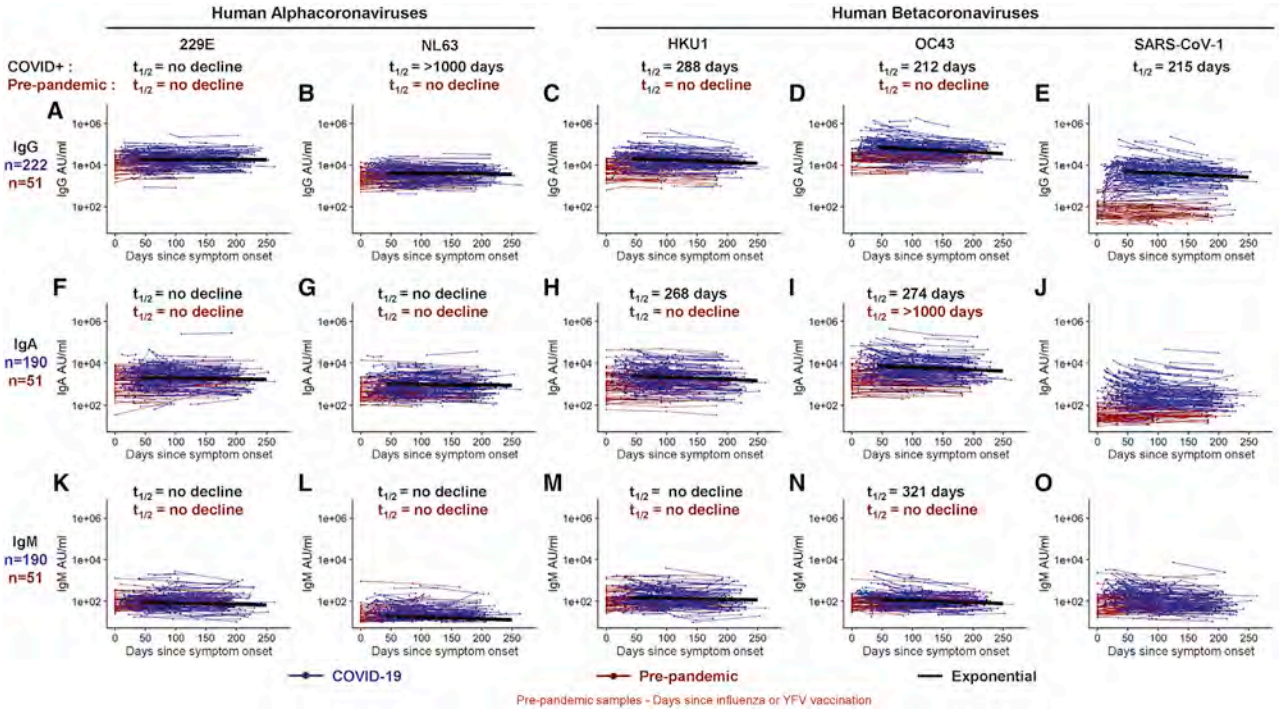

Figure 2. Longitudinal binding antibody responses to other coronavirus spike proteins

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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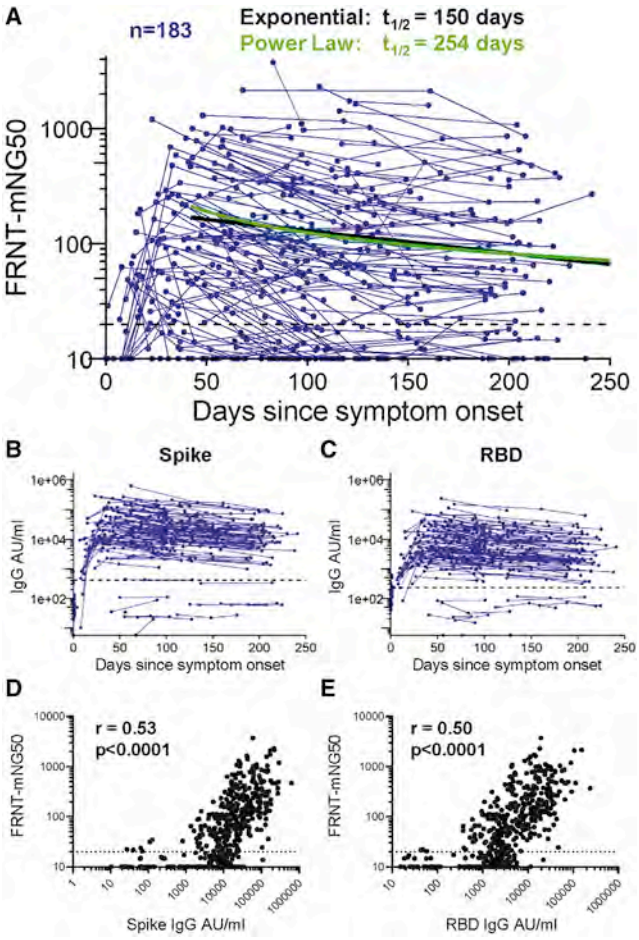

Figure 3. Neutralizing antibody responses to SARS-CoV-2

(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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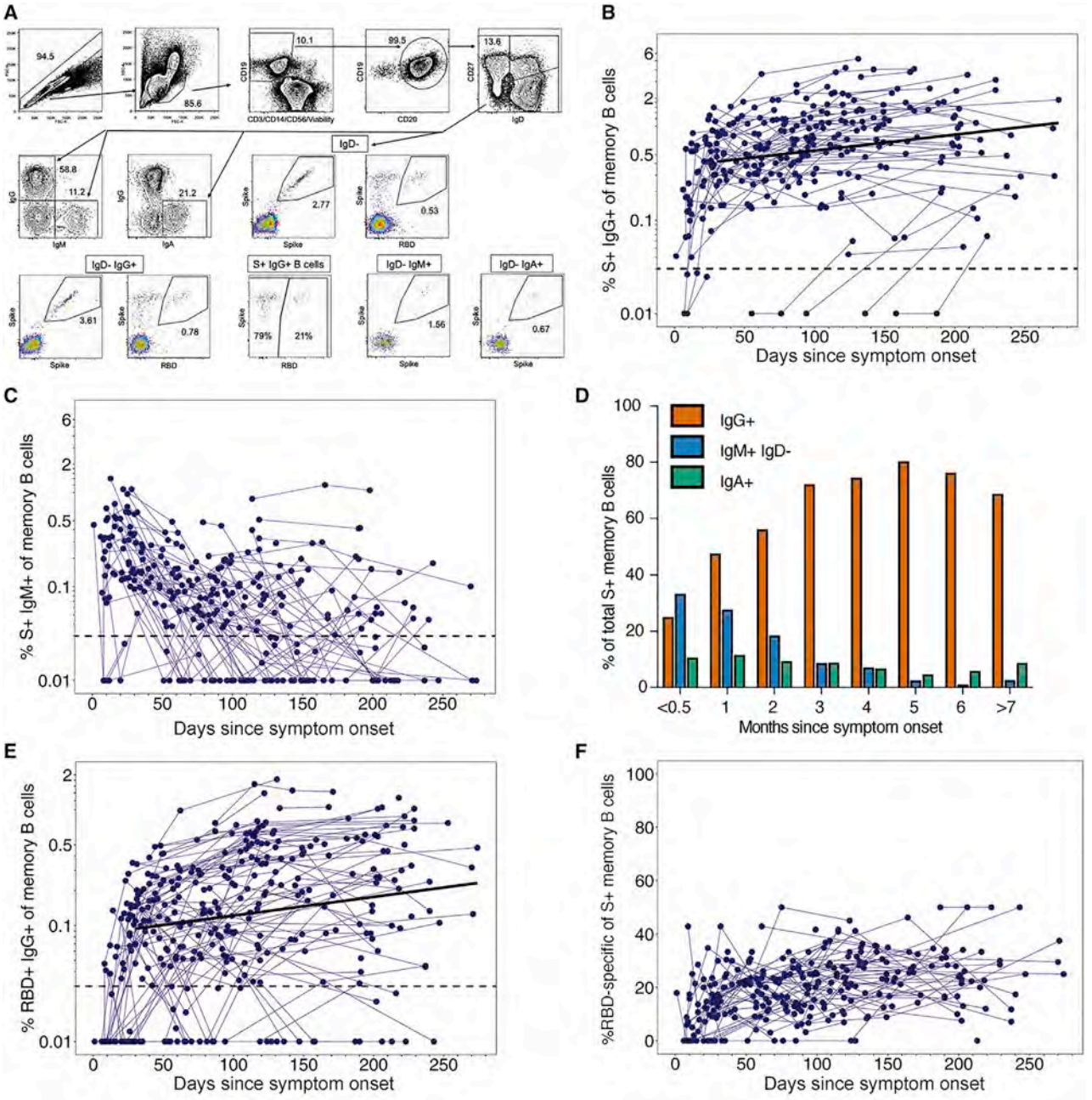

Figure 4. SARS-CoV-2 spike and RBD-specific memory B cells

(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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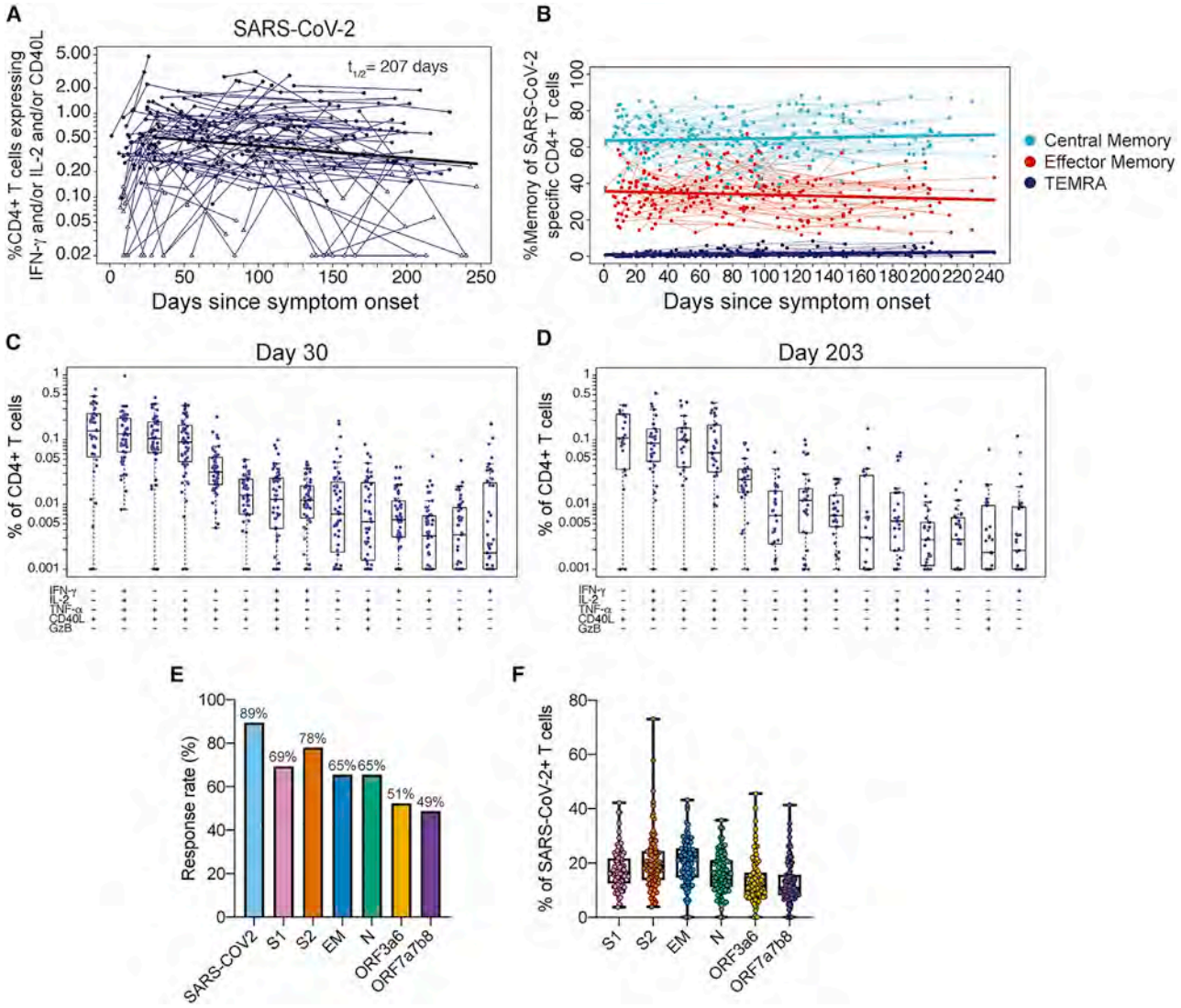

Figure 5. CD4+ T cell responses to SARS-CoV-2 antigens

(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

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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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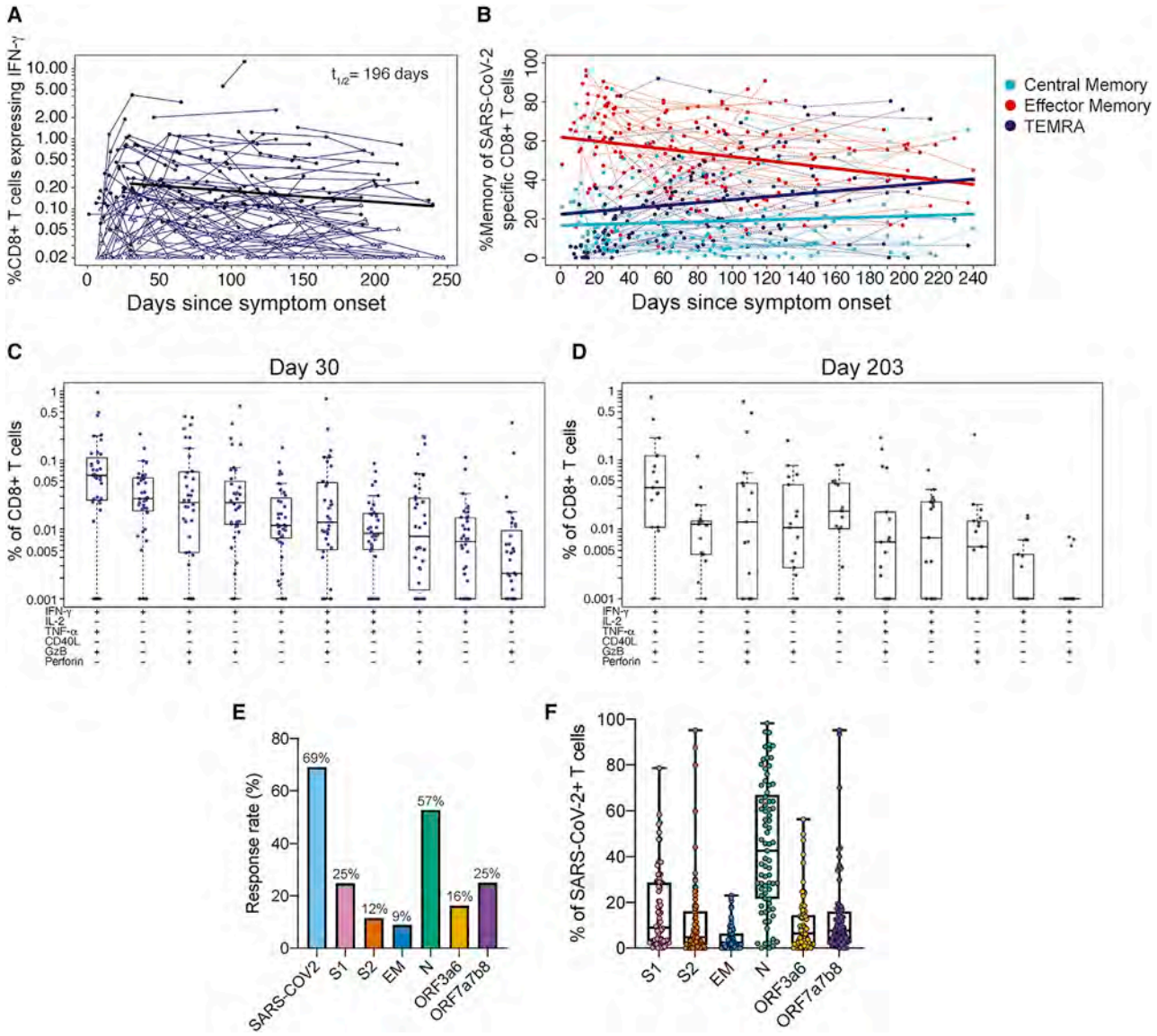

Figure 6. CD8+ T cell responses to SARS-COV-2 antigens

(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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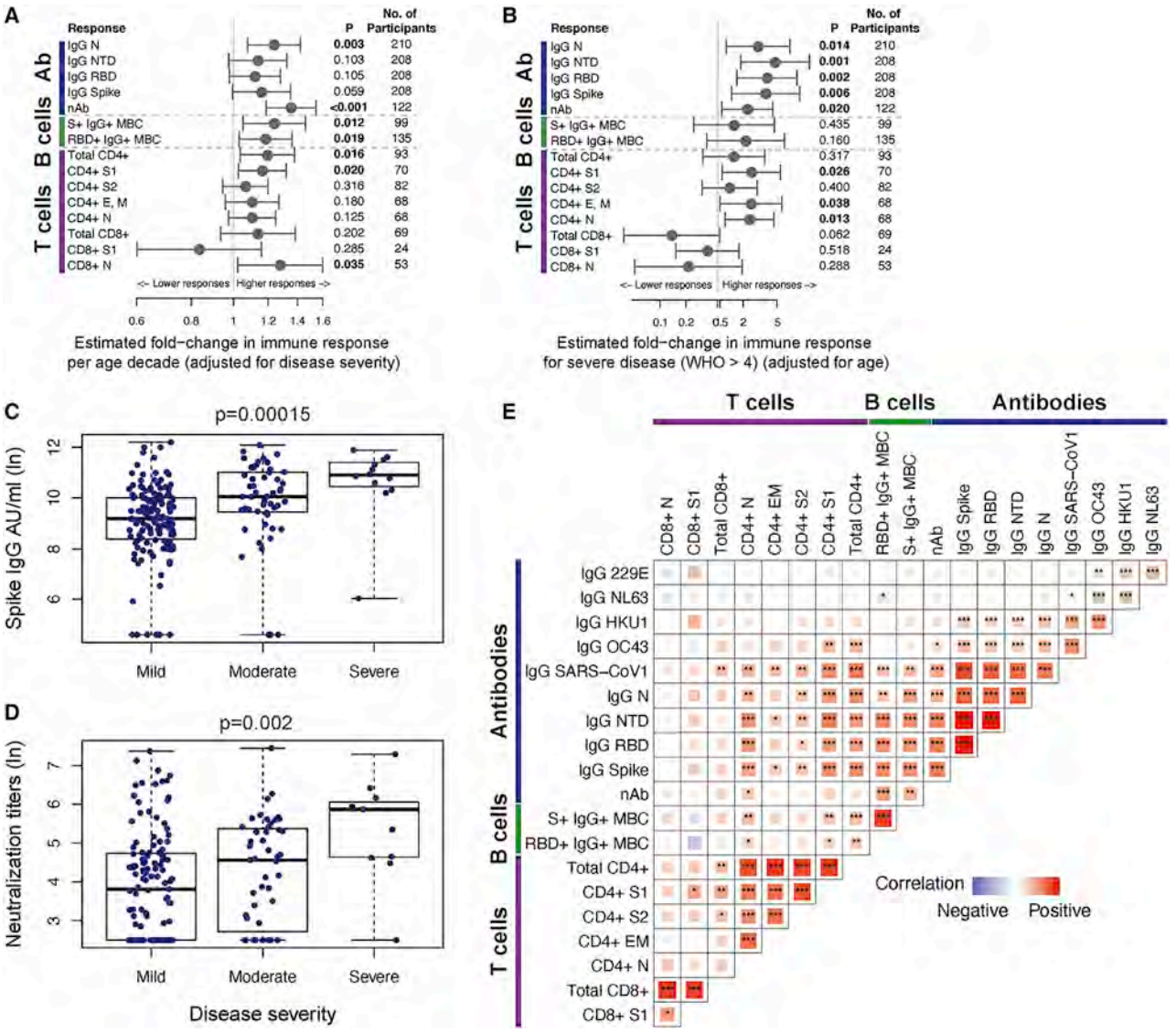

Figure 7. Correlations between SARS-CoV-2-specific immune responses and assessment of covariates

(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

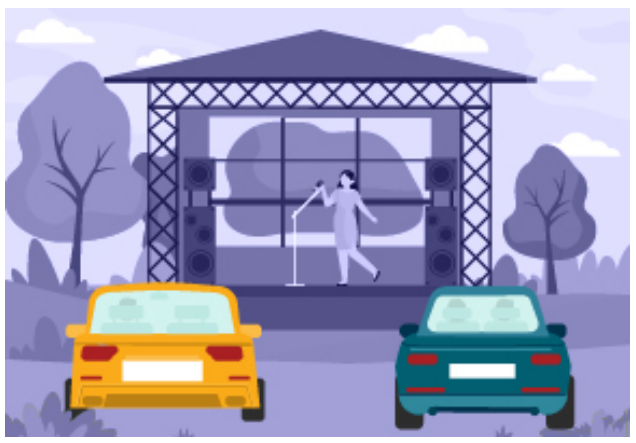
- Have a picnic at a park
- Play kickball in a friend’s backyard
- Roast marshmallows by a firepit
- Have an outdoor barbeque

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.

Exhibit I

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 U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product, **MODERNA COVID-19 VACCINE**, for active immunization to prevent COVID-19 in individuals 18 years of age and older.

SUMMARY OF INSTRUCTIONS FOR COVID-19 VACCINATION PROVIDERS
Vaccination providers enrolled in the federal COVID-19 Vaccination Program must report all vaccine administration errors, all serious adverse events, cases of Multisystem Inflammatory Syndrome (MIS) in adults, and cases of COVID-19 that result in hospitalization or death following administration of the Moderna COVID-19 Vaccine. See "MANDATORY REQUIREMENTS FOR MODERNA COVID-19 VACCINE ADMINISTRATION UNDER EMERGENCY USE AUTHORIZATION" for reporting requirements.

The Moderna COVID-19 Vaccine is a suspension for intramuscular injection.

Primary Series:
Each primary series dose of the Moderna COVID-19 Vaccine is **0.5 mL**.

The Moderna COVID-19 Vaccine is administered as a primary series of two doses (0.5 mL each) 1 month apart to individuals 18 years of age or older.

A third primary series dose of the Moderna COVID-19 Vaccine (0.5 mL) at least 1 month following the second dose is authorized for administration to individuals at least 18 years of age who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.

Booster Dose:
The booster dose of the Moderna COVID-19 Vaccine is **0.25 mL**.

A single Moderna COVID-19 Vaccine booster dose (0.25 mL) may be administered intramuscularly at least 6 months after completing a primary series of the Moderna COVID-19 Vaccine to individuals:

- 65 years of age and older
- 18 through 64 years of age at high risk of severe COVID-19
- 18 through 64 years of age with frequent institutional or occupational exposure to SARS-CoV-2

A single booster dose of the Moderna COVID-19 Vaccine (0.25 mL) may be administered as a heterologous booster dose following completion of primary vaccination with another authorized or approved COVID-19 vaccine. The eligible population(s) and dosing interval for the

heterologous booster dose are the same as those authorized for a booster dose of the vaccine used for primary vaccination.

See this Fact Sheet for instructions for preparation and administration. This Fact Sheet may have been updated. For the most recent Fact Sheet, please see www.modernatx.com/covid19vaccine-eua.

For information on clinical trials that are testing the use of the Moderna COVID-19 Vaccine for active immunization against COVID-19, please see www.clinicaltrials.gov.

DESCRIPTION OF COVID-19

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the novel coronavirus, SARS-CoV-2, that appeared in late 2019. It is predominantly a respiratory illness that can affect other organs. People with COVID-19 have reported a wide range of symptoms, ranging from mild symptoms to severe illness. Symptoms may appear 2 to 14 days after exposure to the virus. Symptoms may include: fever or chills; cough; shortness of breath; fatigue; muscle and body aches; headache; new loss of taste or smell; sore throat; congestion or runny nose; nausea or vomiting; diarrhea.

DOSAGE AND ADMINISTRATION

Storage and Handling

The information in this Fact Sheet supersedes the information on the vial and carton labels.

During storage, minimize exposure to room light.

The Moderna COVID-19 Vaccine multiple-dose vials are stored frozen between -50º to -15ºC (-58º to 5ºF). Store in the original carton to protect from light.

Do not store on dry ice or below -50ºC (-58ºF). Use of dry ice may subject vials to temperatures colder than -50°C (-58°F).

Vials may be stored refrigerated between 2° to 8°C (36° to 46°F) for up to 30 days prior to first use.

Vials may be stored between 8° to 25°C (46° to 77°F) for a total of 24 hours.

After the first dose has been withdrawn, the vial should be held between 2° to 25°C (36° to 77°F). Vials should be discarded 12 hours after the first puncture.

Thawed vials can be handled in room light conditions.

Do not refreeze once thawed.

Transportation of Thawed Vials at 2° to 8°C (36° to 46°F)

If transport at -50° to -15°C (-58° to 5°F) is not feasible, available data support transportation of one or more thawed vials for up to 12 hours at 2° to 8°C (36° to 46°F) when shipped using shipping containers which have been qualified to maintain 2° to 8°C (36° to 46°F) and under routine road and air transport conditions with shaking and vibration minimized. Once thawed and transported at 2° to 8°C (36° to 46°F), vials should not be refrozen and should be stored at 2° to 8°C (36° to 46°F) until use.

Dosing and Schedule

Primary Series:
Each primary series dose of the Moderna COVID-19 Vaccine is **0.5 mL**.

The Moderna COVID-19 Vaccine is administered as a primary series of two doses (0.5 mL each) 1 month apart to individuals 18 years of age or older.

A third primary series dose of the Moderna COVID-19 Vaccine (0.5 mL) at least 1 month following the second dose is authorized for administration to individuals at least 18 years of age who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.

Booster Dose:
The booster dose of the Moderna COVID-19 Vaccine is **0.25 mL**.

A single Moderna COVID-19 Vaccine booster dose (0.25 mL) may be administered intramuscularly at least 6 months after completing a primary series of the Moderna COVID-19 Vaccine to individuals:

- 65 years of age and older
- 18 through 64 years of age at high risk of severe COVID-19
- 18 through 64 years of age with frequent institutional or occupational exposure to SARS-CoV-2

A single booster dose of the Moderna COVID-19 Vaccine (0.25 mL) may be administered as a heterologous booster dose following completion of primary vaccination with another authorized or approved COVID-19 vaccine. The eligible population(s) and dosing interval for the heterologous booster dose are the same as those authorized for a booster dose of the vaccine used for primary vaccination.

Dose Preparation

- The Moderna COVID-19 Vaccine multiple-dose vials contain a frozen suspension that does not contain a preservative and must be thawed prior to administration.
- Remove the required number of vial(s) from storage and thaw each vial before use following the instructions below.

Multiple-dose Vials Containing	Thaw in Refrigerator	Thaw at Room Temperature
5.5 mL	Thaw in refrigerated conditions between 2° to 8°C (36° to 46°F) for 2 hours and 30 minutes. Let each vial stand at room temperature for 15 minutes before administering.	Alternatively, thaw at room temperature between 15° to 25°C (59° to 77°F) for 1 hour.
7.5 mL	Thaw in refrigerated conditions between 2° to 8°C (36° to 46°F) for 3 hours. Let each vial stand at room temperature for 15 minutes before administering.	Alternatively, thaw at room temperature between 15° to 25°C (59° to 77°F) for 1 hour and 30 minutes.

- After thawing, do not refreeze.
- Swirl vial gently after thawing and between each withdrawal. **Do not shake.** Do not dilute the vaccine.
- The Moderna COVID-19 Vaccine is a white to off-white suspension. It may contain white or translucent product-related particulates. Visually inspect the Moderna COVID-19 Vaccine vials for other particulate matter and/or discoloration prior to administration. If either of these conditions exists, the vaccine should not be administered.
- The Moderna COVID-19 Vaccine is supplied in two multiple-dose vial presentations:
    - A multiple-dose vial containing 5.5 mL
    - A multiple-dose vial containing 7.5 mL
- Primary series doses of 0.5 mL and booster doses of 0.25 mL may be extracted from either vial presentation, preferentially using low dead-volume syringes and/or needles.
- When extracting only primary series doses, depending on the syringes and needles used, a maximum of 11 doses (range: 10-11 doses) may be extracted from the vial containing 5.5 mL or a maximum of 15 doses (range: 13-15 doses) may be extracted from the vial containing 7.5 mL.
- When extracting only booster doses or a combination of primary series and booster doses, the maximum number of doses that may be extracted from either vial presentation should not exceed 20 doses. Do not puncture the vial stopper more than 20 times.
- Irrespective of the type of syringe and needle:
    - Each primary series dose must contain 0.5 mL of vaccine.
    - Each booster dose must contain 0.25 mL of vaccine.
    - If the vial stopper has been punctured 20 times, discard the vial and contents.
    - If the amount of vaccine remaining in the vial cannot provide a full dose of 0.5 mL or 0.25 mL, discard the vial and contents. Do not pool excess vaccine from multiple vials.
- After the first dose has been withdrawn, the vial should be held between 2° to 25°C (36° to 77°F). Record the date and time of first use on the Moderna COVID-19 Vaccine vial label. Discard vial after 12 hours. Do not refreeze.

Administration
Visually inspect each dose of the Moderna COVID-19 Vaccine in the dosing syringe prior to administration. The white to off-white suspension may contain white or translucent product-related particulates. During the visual inspection,

- verify the final dosing volume of 0.5 mL for a primary series dose or 0.25 mL for a booster dose.
- confirm there are no other particulates and that no discoloration is observed.
- do not administer if vaccine is discolored or contains other particulate matter.

Administer the Moderna COVID-19 Vaccine intramuscularly.

CONTRAINDICATION
Do not administer the Moderna COVID-19 Vaccine to individuals with a known history of a severe allergic reaction (e.g., anaphylaxis) to any component of the Moderna COVID-19 Vaccine *(see Full EUA Prescribing Information)*.

WARNINGS

Management of Acute Allergic Reactions
Appropriate medical treatment to manage immediate allergic reactions must be immediately available in the event an acute anaphylactic reaction occurs following administration of the Moderna COVID-19 Vaccine.

Monitor Moderna COVID-19 Vaccine recipients for the occurrence of immediate adverse reactions according to the Centers for Disease Control and Prevention (CDC) guidelines (https://www.cdc.gov/vaccines/covid-19/clinical-considerations/managing-anaphylaxis.html).

Myocarditis and Pericarditis
Postmarketing data demonstrate increased risks of myocarditis and pericarditis, particularly within 7 days following the second dose. The observed risk is higher among males under 40 years of age than among females and older males. The observed risk is highest in males 18 through 24 years of age. Although some cases required intensive care support, available data from short-term follow-up suggest that most individuals have had resolution of symptoms with conservative management. Information is not yet available about potential long-term sequelae. The CDC has published considerations related to myocarditis and pericarditis after vaccination, including for vaccination of individuals with a history of myocarditis or pericarditis (https://www.cdc.gov/vaccines/covid-19/clinical-considerations/myocarditis.html).

Syncope
Syncope (fainting) may occur in association with administration of injectable vaccines. Procedures should be in place to avoid injury from fainting.

Altered Immunocompetence
Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the Moderna COVID-19 Vaccine.

Limitations of Vaccine Effectiveness
The Moderna COVID-19 Vaccine may not protect all vaccine recipients.

ADVERSE REACTIONS

Adverse Reactions in Clinical Trials
Adverse reactions reported in clinical trials following administration of the Moderna COVID-19 Vaccine include pain at the injection site, fatigue, headache, myalgia, arthralgia, chills, nausea/vomiting, axillary swelling/tenderness, fever, swelling at the injection site, erythema at the injection site, and rash. *(See Full EUA Prescribing Information)*

Adverse Reactions in Post-Authorization Experience
Anaphylaxis and other severe allergic reactions, myocarditis, pericarditis, and syncope have been reported following administration of the Moderna COVID-19 Vaccine during mass vaccination outside of clinical trials.

Additional adverse reactions, some of which may be serious, may become apparent with more widespread use of the Moderna COVID-19 Vaccine.

USE WITH OTHER VACCINES
There is no information on the co-administration of the Moderna COVID-19 Vaccine with other vaccines.

INFORMATION TO PROVIDE TO VACCINE RECIPIENTS/CAREGIVERS
As the vaccination provider, you must communicate to the recipient or their caregiver, information consistent with the "Fact Sheet for Recipients and Caregivers" (and provide a copy or direct the individual to the website www.modernatx.com/covid19vaccine-eua to obtain the Fact Sheet) prior to the individual receiving each dose of the Moderna COVID-19 Vaccine, including:

- FDA has authorized the emergency use of the Moderna COVID-19 Vaccine, which is not an FDA-approved vaccine.
- The recipient or their caregiver has the option to accept or refuse the Moderna COVID-19 Vaccine.
- The significant known and potential risks and benefits of the Moderna COVID-19 Vaccine, and the extent to which such risks and benefits are unknown.
- Information about available alternative vaccines and the risks and benefits of those alternatives.

For information on clinical trials that are evaluating the use of the Moderna COVID-19 Vaccine to prevent COVID-19, please see www.clinicaltrials.gov.

Provide a vaccination card to the recipient or their caregiver with the date when the recipient needs to return for the second dose of Moderna COVID-19 Vaccine.

Provide the **v-safe** information sheet to vaccine recipients/caregivers and encourage vaccine

recipients to participate in **v-safe**. **V-safe** is a new voluntary smartphone-based tool that uses text messaging and web surveys to check in with people who have been vaccinated to identify potential side effects after COVID-19 vaccination. **V-safe** asks questions that help CDC monitor the safety of COVID-19 vaccines. **V-safe** also provides second-dose reminders if needed and live telephone follow-up by CDC if participants report a significant health impact following COVID-19 vaccination. For more information, visit: www.cdc.gov/vsafe.

MANDATORY REQUIREMENTS FOR MODERNA COVID-19 VACCINE ADMINISTRATION UNDER EMERGENCY USE AUTHORIZATION

In order to mitigate the risks of using this unapproved product under EUA and to optimize the potential benefit of the Moderna COVID-19 Vaccine, the following items are required. Use of unapproved Moderna COVID-19 Vaccine for active immunization to prevent COVID-19 under this EUA is limited to the following (all requirements **must** be met):

1. The Moderna COVID-19 Vaccine is authorized for use in individuals 18 years of age and older.

2. The vaccination provider must communicate to the individual receiving the Moderna COVID-19 Vaccine or their caregiver information consistent with the "Fact Sheet for Recipients and Caregivers" prior to the individual receiving the Moderna COVID-19 Vaccine.

3. The vaccination provider must include vaccination information in the state/local jurisdiction's Immunization Information System (IIS) or other designated system.

4. The vaccination provider is responsible for mandatory reporting of the following to the Vaccine Adverse Event Reporting System (VAERS):
   - vaccine administration errors whether or not associated with an adverse event,
   - serious adverse events* (irrespective of attribution to vaccination),
   - cases of Multisystem Inflammatory Syndrome (MIS) in adults, and
   - cases of COVID-19 that result in hospitalization or death.

   Complete and submit reports to VAERS online at https://vaers.hhs.gov/reportevent.html. For further assistance with reporting to VAERS, call 1-800-822-7967. The reports should include the words "Moderna COVID-19 Vaccine EUA" in the description section of the report.

5. The vaccination provider is responsible for responding to FDA requests for information about vaccine administration errors, adverse events, cases of MIS in adults, and cases of COVID-19 that result in hospitalization or death following administration of the Moderna COVID-19 Vaccine to recipients.

   *Serious adverse events are defined as:
   - Death;
   - A life-threatening adverse event;

- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect;
- An important medical event that based on appropriate medical judgement may jeopardize the individual and may require medical or surgical intervention to prevent one of the outcomes listed above.

OTHER ADVERSE EVENT REPORTING TO VAERS AND MODERNATX, INC.
Vaccination providers may report to VAERS other adverse events that are not required to be reported using the contact information above.

To the extent feasible, report adverse events to ModernaTX, Inc. using the contact information below or by providing a copy of the VAERS form to ModernaTX, Inc.

Email	Fax number	Telephone number
ModernaPV@modernatx.com	1-866-599-1342	1-866-MODERNA (1-866-663-3762)

ADDITIONAL INFORMATION
For general questions, visit the website or call the telephone number provided below.

To access the most recent Moderna COVID-19 Vaccine Fact Sheets, please scan the QR code or visit the website provided below.

Website	Telephone number
www.modernatx.com/covid19vaccine-eua	1-866-MODERNA (1-866-663-3762)

AVAILABLE ALTERNATIVES
Comirnaty (COVID-19 Vaccine, mRNA) is an FDA-approved vaccine to prevent COVID-19 caused by SARS-CoV-2. There may be clinical trials or availability under EUA of other COVID-19 vaccines.

FEDERAL COVID-19 VACCINATION PROGRAM
This vaccine is being made available for emergency use exclusively through the CDC COVID-19 Vaccination Program (the Vaccination Program). Healthcare providers must enroll as providers in the Vaccination Program and comply with the provider requirements. Vaccination providers may not charge any fee for the vaccine and may not charge the vaccine recipient any

out-of-pocket charge for administration. However, vaccination providers may seek appropriate reimbursement from a program or plan that covers COVID-19 vaccine administration fees for the vaccine recipient (private insurance, Medicare, Medicaid, HRSA COVID-19 Uninsured Program for non-insured recipients). For information regarding provider requirements and enrollment in the CDC COVID-19 Vaccination Program, see https://www.cdc.gov/vaccines/covid-19/provider-enrollment.html.

Individuals becoming aware of any potential violations of the CDC COVID-19 Vaccination Program requirements are encouraged to report them to the Office of the Inspector General, U.S. Department of Health and Human Services, at 1-800-HHS-TIPS or TIPS.HHS.GOV.

AUTHORITY FOR ISSUANCE OF THE EUA

The Secretary of the Department of Health and Human Services (HHS) has declared a public health emergency that justifies the emergency use of drugs and biological products during the COVID-19 Pandemic. In response, the FDA has issued an EUA for the unapproved product, Moderna COVID-19 Vaccine, for active immunization to prevent COVID-19 in individuals 18 years of age and older.

FDA issued this EUA, based on ModernaTX, Inc.'s request and submitted data.

Although limited scientific information is available, based on the totality of the scientific evidence available to date, it is reasonable to believe that the Moderna COVID-19 Vaccine may be effective for the prevention of COVID-19 in individuals as specified in the *Full EUA Prescribing Information*.

This EUA for the Moderna COVID-19 Vaccine will end when the Secretary of HHS determines that the circumstances justifying the EUA no longer exist or when there is a change in the approval status of the product such that an EUA is no longer needed.

For additional information about Emergency Use Authorization, visit FDA at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization.

COUNTERMEASURES INJURY COMPENSATION PROGRAM

The Countermeasures Injury Compensation Program (CICP) is a federal program that has been created to help pay for related costs of medical care and other specific expenses to compensate people injured after use of certain medical countermeasures. Medical countermeasures are specific vaccines, medications, devices, or other items used to prevent, diagnose, or treat the public during a public health emergency or a security threat. For more information about CICP regarding the vaccines to prevent COVID-19, visit http://www.hrsa.gov/cicp, email cicp@hrsa.gov, or call: 1-855-266-2427.

Moderna US, Inc.
Cambridge, MA 02139

Patent(s): www.modernatx.com/patents
Revised: Oct/20/2021

END SHORT VERSION FACT SHEET
Long Version (Full EUA Prescribing Information) Begins On Next Page

FULL EMERGENCY USE AUTHORIZATION (EUA) PRESCRIBING INFORMATION

MODERNA COVID-19 VACCINE

FULL EUA PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

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FULL EMERGENCY USE AUTHORIZATION (EUA) PRESCRIBING INFORMATION

1 AUTHORIZED USE

Moderna COVID-19 Vaccine is authorized for use under an Emergency Use Authorization (EUA) for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 18 years of age and older.

2 DOSAGE AND ADMINISTRATION

For intramuscular injection only.

2.1 Preparation for Administration

- The Moderna COVID-19 Vaccine multiple-dose vials contain a frozen suspension that does not contain a preservative and must be thawed prior to administration.
- Remove the required number of vial(s) from storage and thaw each vial before use following the instructions below.

Multiple-dose Vials Containing	Thaw in Refrigerator	Thaw at Room Temperature
5.5 mL	Thaw in refrigerated conditions between 2° to 8°C (36° to 46°F) for 2 hours and 30 minutes. Let each vial stand at room temperature for 15 minutes before administering.	Alternatively, thaw at room temperature between 15° to 25°C (59° to 77°F) for 1 hour.
7.5 mL	Thaw in refrigerated conditions between 2° to 8°C (36° to 46°F) for 3 hours. Let each vial stand at room temperature for 15 minutes before administering.	Alternatively, thaw at room temperature between 15° to 25°C (59° to 77°F) for 1 hour and 30 minutes.

- After thawing, do not refreeze.
- Swirl vial gently after thawing and between each withdrawal. **Do not shake.** Do not dilute the vaccine.
- The Moderna COVID-19 Vaccine is a white to off-white suspension. It may contain white or translucent product-related particulates. Visually inspect the Moderna COVID-19 Vaccine vials for other particulate matter and/or discoloration prior to administration. If either of these conditions exists, the vaccine should not be administered.
- The Moderna COVID-19 Vaccine is supplied in two multiple-dose vial presentations:
    - A multiple-dose vial containing 5.5 mL
    - A multiple-dose vial containing 7.5 mL
- Primary series doses of 0.5 mL and booster doses of 0.25 mL may be extracted from either vial presentation, preferentially using low dead-volume syringes and/or needles.
- When extracting only primary series doses, depending on the syringes and needles used, a maximum of 11 doses (range: 10-11 doses) may be extracted from the vial containing 5.5 mL or a maximum of 15 doses (range: 13-15 doses) may be extracted from the vial containing 7.5 mL.
- When extracting only booster doses or a combination of primary series and booster doses, the maximum number of doses that may be extracted from either vial presentation should not exceed 20 doses. Do not puncture the vial stopper more than 20 times.
- Irrespective of the type of syringe and needle:
    - Each primary series dose must contain 0.5 mL of vaccine.
    - Each booster dose must contain 0.25 mL of vaccine.
    - If the vial stopper has been punctured 20 times, discard the vial and contents.
    - If the amount of vaccine remaining in the vial cannot provide a full dose of 0.5 mL or 0.25 mL, discard the vial and contents. Do not pool excess vaccine from multiple vials.
- After the first dose has been withdrawn, the vial should be held between 2° to 25°C (36° to 77°F). Record the date and time of first use on the Moderna COVID-19 Vaccine vial label. Discard vial after 12 hours. Do not refreeze.

2.2 Administration

Visually inspect each dose of the Moderna COVID-19 Vaccine in the dosing syringe prior to administration. The white to off-white suspension may contain white or translucent product-related particulates. During the visual inspection,

- verify the final dosing volume of 0.5 mL for a primary series dose or 0.25 mL for a booster dose.
- confirm there are no other particulates and that no discoloration is observed.
- do not administer if vaccine is discolored or contains other particulate matter.

Administer the Moderna COVID-19 Vaccine intramuscularly.

2.3 Dosing and Schedule

Primary Series:
Each primary series dose of the Moderna COVID-19 Vaccine is **0.5 mL**.

The Moderna COVID-19 Vaccine is administered as a primary series of two doses (0.5 mL each) 1 month apart to individuals 18 years of age or older.

A third primary series dose of the Moderna COVID-19 Vaccine (0.5 mL) at least 1 month following the second dose is authorized for administration to individuals at least 18 years of age who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.

Booster Dose:
The booster dose of the Moderna COVID-19 Vaccine is **0.25 mL**.

A single Moderna COVID-19 Vaccine booster dose (0.25 mL) may be administered intramuscularly at least 6 months after completing a primary series of the Moderna COVID-19 Vaccine to individuals:

- 65 years of age and older
- 18 through 64 years of age at high risk of severe COVID-19
- 18 through 64 years of age with frequent institutional or occupational exposure to SARS-CoV-2

A single booster dose of the Moderna COVID-19 Vaccine (0.25 mL) may be administered as a heterologous booster dose following completion of primary vaccination with another authorized or approved COVID-19 vaccine. The eligible population(s) and dosing interval for the heterologous booster dose are the same as those authorized for a booster dose of the vaccine used for primary vaccination.

3 DOSAGE FORMS AND STRENGTHS

Moderna COVID-19 Vaccine is a suspension for intramuscular injection.

- Each primary series dose is 0.5 mL.
- The booster dose is 0.25 mL.

4 CONTRAINDICATIONS

Do not administer the Moderna COVID-19 Vaccine to individuals with a known history of severe allergic reaction (e.g., anaphylaxis) to any component of the Moderna COVID-19 Vaccine *[see Description (13)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Management of Acute Allergic Reactions

Appropriate medical treatment to manage immediate allergic reactions must be immediately available in the event an acute anaphylactic reaction occurs following administration of the Moderna COVID-19 Vaccine.

Monitor Moderna COVID-19 Vaccine recipients for the occurrence of immediate adverse reactions according to the Centers for Disease Control and Prevention (CDC) guidelines (https://www.cdc.gov/vaccines/covid-19/clinical-considerations/managing-anaphylaxis.html).

5.2 Myocarditis and Pericarditis

Postmarketing data demonstrate increased risks of myocarditis and pericarditis, particularly within 7 days following the second dose. The observed risk is higher among males under 40 years of age than among females and older males. The observed risk is highest in males 18 through 24 years of age. Although some cases required intensive care support, available data from short-term follow-up suggest that most individuals have had resolution of symptoms with conservative management. Information is not yet available about potential long-term sequelae. The CDC has published considerations related to myocarditis and pericarditis after vaccination, including for vaccination of individuals with a history of myocarditis or pericarditis (https://www.cdc.gov/vaccines/covid-19/clinical-considerations/myocarditis.html).

5.3 Syncope

Syncope (fainting) may occur in association with administration of injectable vaccines. Procedures should be in place to avoid injury from fainting.

5.4 Altered Immunocompetence

Immunocompromised persons, including individuals receiving immunosuppressive therapy, may have a diminished response to the Moderna COVID-19 Vaccine.

5.5 Limitations of Vaccine Effectiveness

The Moderna COVID-19 Vaccine may not protect all vaccine recipients.

6 OVERALL SAFETY SUMMARY

It is MANDATORY for vaccination providers to report to the Vaccine Adverse Event Reporting System (VAERS) all vaccine administration errors, all serious adverse events, cases of Multisystem Inflammatory Syndrome (MIS) in adults, and hospitalized or fatal cases of COVID-19 following vaccination with the Moderna COVID-19 Vaccine. To the extent feasible, provide a copy of the VAERS form to ModernaTX, Inc. Please see the REQUIREMENTS AND INSTRUCTIONS FOR REPORTING ADVERSE EVENTS AND VACCINE ADMINISTRATION ERRORS section for details on reporting to VAERS and ModernaTX, Inc.

In a clinical study, the adverse reactions in participants 18 years of age and older following administration of the primary series included pain at the injection site (92.0%), fatigue (70.0%), headache (64.7%), myalgia (61.5%), arthralgia (46.4%), chills (45.4%), nausea/vomiting (23.0%), axillary swelling/tenderness (19.8%), fever (15.5%), swelling at the injection site (14.7%), and erythema at the injection site (10.0%).

In a clinical study, the adverse reactions in participants 18 years of age and older following administration of a booster dose included pain at the injection site (83.8%), fatigue (58.7%), headache (55.1%), myalgia (49.1%), arthralgia (41.3%), chills (35.3%), axillary swelling/tenderness (20.4%), nausea/vomiting (11.4%), fever (6.6%), swelling at the injection site (5.4%), and erythema at the injection site (4.8%), rash (1.8%).

Anaphylaxis and other severe allergic reactions, myocarditis, pericarditis, and syncope have been reported following administration of the Moderna COVID-19 Vaccine outside of clinical trials.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared with rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

Overall, 15,419 participants aged 18 years and older received at least one dose of Moderna COVID-19 Vaccine in three clinical trials (NCT04283461, NCT04405076, and NCT04470427). In a fourth clinical trial (NCT04885907), 60 solid organ transplant recipients received a third dose of Moderna COVID-19 Vaccine.

Two-Dose Primary Series

The safety of Moderna COVID-19 Vaccine was evaluated in an ongoing Phase 3 randomized, placebo-controlled, observer-blind clinical trial conducted in the United States involving 30,351 participants 18 years of age and older who received at least one dose (0.5 mL) of Moderna COVID-19 Vaccine (n=15,185) or placebo (n=15,166) (Study 1, NCT04470427). At the time of

vaccination, the mean age of the population was 52 years (range 18-95); 22,831 (75.2%) of participants were 18 to 64 years of age and 7,520 (24.8%) of participants were 65 years of age and older. Overall, 52.7% were male, 47.3% were female, 20.5% were Hispanic or Latino, 79.2% were White, 10.2% were African American, 4.6% were Asian, 0.8% were American Indian or Alaska Native, 0.2% were Native Hawaiian or Pacific Islander, 2.1% were other races, and 2.1% were Multiracial. Demographic characteristics were similar among participants who received Moderna COVID-19 Vaccine and those who received placebo.

Solicited Adverse Reactions

Local and systemic adverse reactions and use of antipyretic medication were solicited in an electronic diary for 7 days following each injection (i.e., day of vaccination and the next 6 days) among participants receiving Moderna COVID-19 Vaccine (n=15,179) and participants receiving placebo (n=15,163) with at least 1 documented dose. Events that persisted for more than 7 days were followed until resolution. Solicited adverse reactions were reported more frequently among vaccine participants than placebo participants.

The reported number and percentage of the solicited local and systemic adverse reactions by age group and dose are presented in Table 1 and Table 2, respectively.

Table 1: Number and Percentage of Participants With Solicited Local and Systemic Adverse Reactions Starting Within 7 Days* After Each Dose in Participants 18-64 Years (Solicited Safety Set, Dose 1 and Dose 2)

	Moderna COVID-19 Vaccine		**Placebo[a]**	
	Dose 1 (N=11,406) n (%)	**Dose 2** (N=10,985) n (%)	**Dose 1** (N=11,407) n (%)	**Dose 2** (N=10,918) n (%)
Local Adverse Reactions				
Pain	9,908 (86.9)	9,873 (89.9)	2,177 (19.1)	2,040 (18.7)
Pain, Grade 3[b]	366 (3.2)	506 (4.6)	23 (0.2)	22 (0.2)
Axillary swelling/tenderness	1,322 (11.6)	1,775 (16.2)	567 (5.0)	470 (4.3)
Axillary swelling/tenderness, Grade 3[b]	37 (0.3)	46 (0.4)	13 (0.1)	11 (0.1)
Swelling (hardness) ≥25 mm	767 (6.7)	1,389 (12.6)	34 (0.3)	36 (0.3)
Swelling (hardness), Grade 3[c]	62 (0.5)	182 (1.7)	3 (<0.1)	4 (<0.1)
Erythema (redness) ≥25 mm	344 (3.0)	982 (8.9)	47 (0.4)	43 (0.4)
Erythema (redness), Grade 3[c]	34 (0.3)	210 (1.9)	11 (<0.1)	12 (0.1)

	Moderna COVID-19 Vaccine		Placebo[a]	
	Dose 1 (N=11,406) n (%)	**Dose 2** (N=10,985) n (%)	**Dose 1** (N=11,407) n (%)	**Dose 2** (N=10,918) n (%)
Systemic Adverse Reactions				
Fatigue	4,384 (38.4)	7,430 (67.6)	3,282 (28.8)	2,687 (24.6)
Fatigue, Grade 3[d]	120 (1.1)	1,174 (10.7)	83 (0.7)	86 (0.8)
Fatigue, Grade 4[e]	1 (<0.1)	0 (0)	0 (0)	0 (0)
Headache	4,030 (35.3)	6,898 (62.8)	3,304 (29.0)	2,760 (25.3)
Headache, Grade 3[f]	219 (1.9)	553 (5.0)	162 (1.4)	129 (1.2)
Myalgia	2,699 (23.7)	6,769 (61.6)	1,628 (14.3)	1,411 (12.9)
Myalgia, Grade 3[d]	73 (0.6)	1,113 (10.1)	38 (0.3)	42 (0.4)
Arthralgia	1,893 (16.6)	4,993 (45.5)	1,327 (11.6)	1,172 (10.7)
Arthralgia, Grade 3[d]	47 (0.4)	647 (5.9)	29 (0.3)	37 (0.3)
Arthralgia, Grade 4[e]	1 (<0.1)	0 (0)	0 (0)	0 (0)
Chills	1,051 (9.2)	5,341 (48.6)	730 (6.4)	658 (6.0)
Chills, Grade 3[g]	17 (0.1)	164 (1.5)	8 (<0.1)	15 (0.1)
Nausea/vomiting	1,068 (9.4)	2,348 (21.4)	908 (8.0)	801 (7.3)
Nausea/vomiting, Grade 3[h]	6 (<0.1)	10 (<0.1)	8 (<0.1)	8 (<0.1)
Fever	105 (0.9)	1,908 (17.4)	37 (0.3)	39 (0.4)
Fever, Grade 3[i]	10 (<0.1)	184 (1.7)	1 (<0.1)	2 (<0.1)
Fever, Grade 4[j]	4 (<0.1)	12 (0.1)	4 (<0.1)	2 (<0.1)
Use of antipyretic or pain medication	2,656 (23.3)	6,292 (57.3)	1,523 (13.4)	1,248 (11.4)

* 7 days included day of vaccination and the subsequent 6 days. Events and use of antipyretic or pain medication were collected in the electronic diary (e-diary).

[a] Placebo was a saline solution.

[b] Grade 3 pain and axillary swelling/tenderness: Defined as any use of prescription pain reliever; prevents daily activity.

[c] Grade 3 swelling and erythema: Defined as >100 mm / >10 cm.

[d] Grade 3 fatigue, myalgia, arthralgia: Defined as significant; prevents daily activity.

[e] Grade 4 fatigue, arthralgia: Defined as requires emergency room visit or hospitalization.

[f] Grade 3 headache: Defined as significant; any use of prescription pain reliever or prevents daily activity.

[g] Grade 3 chills: Defined as prevents daily activity and requires medical intervention.

[h] Grade 3 nausea/vomiting: Defined as prevents daily activity; requires outpatient intravenous hydration.
[i] Grade 3 fever: Defined as ≥39.0° – ≤40.0°C / ≥102.1° – ≤104.0°F.
[j] Grade 4 fever: Defined as >40.0°C / >104.0°F.

Table 2: Number and Percentage of Participants With Solicited Local and Systemic Adverse Reactions Starting Within 7 Days* After Each Dose in Participants 65 Years and Older (Solicited Safety Set, Dose 1 and Dose 2)

	Moderna COVID-19 Vaccine		Placebo[a]	
	Dose 1 (N=3,762) n (%)	**Dose 2** (N=3,692) n (%)	**Dose 1** (N=3,748) n (%)	**Dose 2** (N=3,648) n (%)
Local Adverse Reactions				
Pain	2,782 (74.0)	3,070 (83.2)	481 (12.8)	437 (12.0)
Pain, Grade 3[b]	50 (1.3)	98 (2.7)	32 (0.9)	18 (0.5)
Axillary swelling/tenderness	231 (6.1)	315 (8.5)	155 (4.1)	97 (2.7)
Axillary swelling/tenderness, Grade 3[b]	12 (0.3)	21 (0.6)	14 (0.4)	8 (0.2)
Swelling (hardness) ≥25 mm	165 (4.4)	400 (10.8)	18 (0.5)	13 (0.4)
Swelling (hardness), Grade 3[c]	20 (0.5)	72 (2.0)	3 (<0.1)	7 (0.2)
Erythema (redness) ≥25 mm	86 (2.3)	275 (7.5)	20 (0.5)	13 (0.4)
Erythema (redness), Grade 3[c]	8 (0.2)	77 (2.1)	2 (<0.1)	3 (<0.1)
Systemic Adverse Reactions				
Fatigue	1,251 (33.3)	2,152 (58.3)	851 (22.7)	716 (19.6)
Fatigue, Grade 3[d]	30 (0.8)	254 (6.9)	22 (0.6)	20 (0.5)
Headache	921 (24.5)	1,704 (46.2)	723 (19.3)	650 (17.8)
Headache, Grade 3[e]	52 (1.4)	106 (2.9)	34 (0.9)	33 (0.9)
Myalgia	742 (19.7)	1,739 (47.1)	443 (11.8)	398 (10.9)
Myalgia, Grade 3[d]	17 (0.5)	205 (5.6)	9 (0.2)	10 (0.3)
Arthralgia	618 (16.4)	1,291 (35.0)	456 (12.2)	397 (10.9)
Arthralgia, Grade 3[d]	13 (0.3)	123 (3.3)	8 (0.2)	7 (0.2)
Chills	202 (5.4)	1,141 (30.9)	148 (4.0)	151 (4.1)

	Moderna COVID-19 Vaccine		Placebo[a]	
	Dose 1 (N=3,762) n (%)	**Dose 2** (N=3,692) n (%)	**Dose 1** (N=3,748) n (%)	**Dose 2** (N=3,648) n (%)
Chills, Grade 3[f]	7 (0.2)	27 (0.7)	6 (0.2)	2 (<0.1)
Nausea/vomiting	194 (5.2)	437 (11.8)	166 (4.4)	133 (3.6)
Nausea/vomiting, Grade 3[g]	4 (0.1)	10 (0.3)	4 (0.1)	3 (<0.1)
Nausea/vomiting, Grade 4[h]	0 (0)	1 (<0.1)	0 (0)	0 (0)
Fever	10 (0.3)	370 (10.0)	7 (0.2)	4 (0.1)
Fever, Grade 3[i]	1 (<0.1)	18 (0.5)	1 (<0.1)	0 (0)
Fever, Grade 4[j]	0 (0)	1 (<0.1)	2 (<0.1)	1 (<0.1)
Use of antipyretic or pain medication	673 (17.9)	1,546 (41.9)	477 (12.7)	329 (9.0)

* 7 days included day of vaccination and the subsequent 6 days. Events and use of antipyretic or pain medication were collected in the electronic diary (e-diary).
[a] Placebo was a saline solution.
[b] Grade 3 pain and axillary swelling/tenderness: Defined as any use of prescription pain reliever; prevents daily activity.
[c] Grade 3 swelling and erythema: Defined as >100 mm / >10 cm.
[d] Grade 3 fatigue, myalgia, arthralgia: Defined as significant; prevents daily activity.
[e] Grade 3 headache: Defined as significant; any use of prescription pain reliever or prevents daily activity.
[f] Grade 3 chills: Defined as prevents daily activity and requires medical intervention.
[g] Grade 3 nausea/vomiting: Defined as prevents daily activity; requires outpatient intravenous hydration.
[h] Grade 4 nausea/vomiting: Defined as requires emergency room visit or hospitalization for hypotensive shock.
[i] Grade 3 fever: Defined as ≥39.0° – ≤40.0°C / ≥102.1° – ≤104.0°F.
[j] Grade 4 fever: Defined as >40.0°C / >104.0°F.

Solicited local and systemic adverse reactions reported following administration of Moderna COVID-19 Vaccine had a median duration of 1 to 3 days.

Grade 3 solicited local adverse reactions were more frequently reported after Dose 2 than after Dose 1. Solicited systemic adverse reactions were more frequently reported by vaccine recipients after Dose 2 than after Dose 1.

Unsolicited Adverse Events

Participants were monitored for unsolicited adverse events for up to 28 days following each dose and follow-up is ongoing. Serious adverse events and medically attended adverse events will be recorded for the entire study duration of 2 years. As of November 25, 2020, among participants who had received at least 1 dose of vaccine or placebo (vaccine=15,185, placebo=15,166), unsolicited adverse events that occurred within 28 days following each vaccination were reported by 23.9% of participants (n=3,632) who received Moderna COVID-19 Vaccine and 21.6% of

participants (n=3,277) who received placebo. In these analyses, 87.9% of study participants had at least 28 days of follow-up after Dose 2.

Lymphadenopathy-related events that were not necessarily captured in the 7-day e-diary were reported by 1.1% of vaccine recipients and 0.6% of placebo recipients. These events included lymphadenopathy, lymphadenitis, lymph node pain, vaccination-site lymphadenopathy, injection-site lymphadenopathy, and axillary mass, which were plausibly related to vaccination. This imbalance is consistent with the imbalance observed for solicited axillary swelling/tenderness in the injected arm.

Hypersensitivity adverse events were reported in 1.5% of vaccine recipients and 1.1% of placebo recipients. Hypersensitivity events in the vaccine group included injection site rash and injection site urticaria, which are likely related to vaccination. Delayed injection site reactions that began >7 days after vaccination were reported in 1.2% of vaccine recipients and 0.4% of placebo recipients. Delayed injection site reactions included pain, erythema, and swelling and are likely related to vaccination.

Throughout the same period, there were three reports of Bell's palsy in the Moderna COVID-19 Vaccine group (one of which was a serious adverse event), which occurred 22, 28, and 32 days after vaccination, and one in the placebo group which occurred 17 days after vaccination. Currently available information on Bell's palsy is insufficient to determine a causal relationship with the vaccine.

There were no other notable patterns or numerical imbalances between treatment groups for specific categories of adverse events (including other neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to Moderna COVID-19 Vaccine.

Serious Adverse Events

As of November 25, 2020, serious adverse events were reported by 1.0% (n=147) of participants who received Moderna COVID-19 Vaccine and 1.0% (n=153) of participants who received placebo, one of which was the case of Bell's palsy which occurred 32 days following receipt of vaccine.

In these analyses, 87.9% of study participants had at least 28 days of follow-up after Dose 2, and the median follow-up time for all participants was 9 weeks after Dose 2.

There were two serious adverse events of facial swelling in vaccine recipients with a history of injection of dermatological fillers. The onset of swelling was reported 1 and 2 days, respectively, after vaccination and was likely related to vaccination.

There was one serious adverse event of intractable nausea and vomiting in a participant with prior history of severe headache and nausea requiring hospitalization. This event occurred 1 day after vaccination and was likely related to vaccination.

There were no other notable patterns or imbalances between treatment groups for specific

categories of serious adverse events (including neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to Moderna COVID-19 Vaccine.

Solid Organ Transplant Recipients

From an independent study (NCT04885907), in 60 participants who had undergone various solid organ transplant procedures (heart, kidney, kidney-pancreas, liver, lung, pancreas) a median of 3.57 years previously (range 1.99-6.75 years) who received a third vaccine dose (0.5 mL), the adverse event profile was similar to that after the second dose and no Grade 3 or Grade 4 events were reported.

Booster Dose Following a Primary Series of Moderna COVID-19 Vaccine

Study 2 is an ongoing Phase 2, randomized, observer-blind, placebo-controlled, dose-confirmation study to evaluate the safety, reactogenicity, and immunogenicity of the Moderna COVID-19 Vaccine in participants 18 years of age and older (NCT04405076). In this study, 198 participants received two doses (0.5 mL 1 month apart) of the Moderna COVID-19 Vaccine primary series. In an open label-phase, 171 of those participants received a single booster dose (0.25 mL) at least 6 months (range of 5.8 to 8.5 months) after receiving the second dose of the primary series. Safety monitoring after the booster dose was the same as that described for Study 1 participants who received the primary series.

Among the 171 booster dose recipients, the median age was 55 years (range 18-87), 39.2% were male and 60.8% were female, 95.9% were White, 5.8% were Hispanic or Latino, 2.9% were Black or African American, 0.6% were Asian, and 0.6% were American Indian or Alaska Native. Following the booster dose, the median follow-up time was 5.7 months (range of 3.1 to 6.4 months).

Solicited Adverse Reactions

Tables 3 and 4 present the frequency and severity of reported solicited local and systemic adverse reactions among Study 2 Moderna COVID-19 Vaccine booster dose recipients 18 to <65 years of age and ≥65 years of age, respectively, within 7 days of a booster vaccination.

Table 3: Number and Percentage of Study 2 Participants 18-64 Years of Age With Solicited Local and Systemic Adverse Reactions Starting Within 7 Days* After the Booster Dose or After the Second Dose of Primary Series (Solicited Safety Set)

	Study 2 Second Dose of Primary Series (N=155) n (%)	**Study 2 Booster Dose** (N=129) n (%)
Local Adverse Reactions		
Pain	137 (88.4)	111 (86.0)
Pain, Grade 3[a]	1 (0.6)	4 (3.1)
Axillary swelling/tenderness	18 (11.6)	32 (24.8)

	Study 2 Second Dose of Primary Series (N=155) n (%)	**Study 2 Booster Dose** (N=129) n (%)
Axillary swelling/tenderness, Grade 3[a]	0 (0)	1 (0.8)
Swelling (hardness) ≥25 mm	16 (10.3)	8 (6.2)
Erythema (redness) ≥25 mm	12 (7.7)	7 (5.4)
Erythema (redness), Grade 3[b]	2 (1.3)	1 (0.8)
Systemic Adverse Reactions		
Fatigue	105 (67.7)	80 (62.0)
Fatigue, Grade 3[c]	16 (10.3)	4 (3.1)
Headache	87 (56.1)	76 (58.9)
Headache, Grade 3[d]	8 (5.2)	1 (0.8)
Myalgia	89 (57.4)	64 (49.6)
Myalgia, Grade 3[c]	15 (9.7)	4 (3.1)
Arthralgia	66 (42.6)	54 (41.9)
Arthralgia, Grade 3[c]	8 (5.2)	4 (3.1)
Chills	71 (45.8)	52 (40.3)
Chills, Grade 3[e]	1 (0.6)	0 (0)
Nausea/vomiting	36 (23.2)	16 (12.4)
Fever	24 (15.5)	9 (7.0)
Fever, Grade 3[f]	3 (1.9)	2 (1.6)
Rash	5 (3.2)	3 (2.3)
Use of antipyretic or pain medication	86 (55.5)	64 (49.6)

* 7 days included day of vaccination and the subsequent 6 days. Events and use of antipyretic or pain medication were collected in the electronic diary (e-diary).
[a] Grade 3 pain and axillary swelling/tenderness: Defined as any use of prescription pain reliever; prevents daily activity.
[b] Grade 3 erythema: Defined as >100 mm / >10 cm.
[c] Grade 3 fatigue, myalgia, arthralgia: Defined as significant; prevents daily activity.
[d] Grade 3 headache: Defined as significant; any use of prescription pain reliever or prevents daily activity.
[e] Grade 3 chills: Defined as prevents daily activity and requires medical intervention.
[f] Grade 3 fever: Defined as ≥39.0° – ≤40.0°C / ≥102.1° – ≤104.0°F.

Table 4: Number and Percentage of Study 2 Participants ≥65 Years of Age With Solicited Local and Systemic Adverse Reactions Starting Within 7 Days* After the Booster Dose or After the Second Dose of Primary Series (Solicited Safety Set)

	Study 2 Second Dose of Primary Series (N=43) n (%)	**Study 2 Booster Dose** (N=38) n (%)
Local Adverse Reactions		
Pain	32 (74.4)	29 (76.3)
Pain, Grade 3[a]	0 (0.0)	2 (5.3)
Axillary swelling/tenderness	2 (4.7)	2 (5.3)
Swelling (hardness) ≥25 mm	5 (11.6)	1 (2.6)
Swelling (hardness), Grade 3[b]	1 (2.3)	1 (2.6)
Erythema (redness) ≥25 mm	3 (7.0)	1 (2.6)
Erythema (redness), Grade 3[b]	3 (7.0)	0 (0.0)

	Study 2 Second Dose of Primary Series (N=43) n (%)	**Study 2 Booster Dose** (N=38) n (%)
Systemic Adverse Reactions		
Fatigue	23 (53.5)	18 (47.4)
Fatigue, Grade 3[c]	2 (4.7)	3 (7.9)
Myalgia	15 (34.9)	18 (47.4)
Myalgia, Grade 3[c]	0 (0)	1 (2.6)
Headache	17 (39.5)	16 (42.1)
Headache, Grade 3[d]	1 (2.3)	1 (2.6)
Arthralgia	11 (25.6)	15 (39.5)
Arthralgia, Grade 3[c]	0 (0)	1 (2.6)
Chills	7 (16.3)	7 (18.4)
Nausea/vomiting	5 (11.6)	3 (7.9)
Fever	2 (4.7)	2 (5.4)
Fever, Grade 3[e]	1 (2.3)	0 (0)
Rash	1 (2.3)	0 (0.0)
Use of antipyretic or pain medication	11 (25.6)	11 (28.9)

* 7 days included day of vaccination and the subsequent 6 days. Events and use of antipyretic or pain medication were collected in the electronic diary (e-diary).
a Grade 3 pain: Defined as any use of prescription pain reliever; prevents daily activity.
b Grade 3 swelling and erythema: Defined as >100 mm / >10 cm.
c Grade 3 fatigue, myalgia, arthralgia: Defined as significant; prevents daily activity.
d Grade 3 headache: Defined as significant; any use of prescription pain reliever or prevents daily activity.
e Grade 3 fever: Defined as ≥39.0° – ≤40.0°C / ≥102.1° – ≤104.0°F.

In participants who received a booster dose, the median duration of solicited local and systemic adverse reactions was 2 to 3 days.

Unsolicited Adverse Events

Overall, the 171 participants who received a booster dose, had a median follow-up time of 5.7 months after the booster dose to the cut-off date (August 16, 2021). Through the cut-off date, there were no unsolicited adverse events not already captured as solicited local and systemic reactions that were considered causally related to the Moderna COVID-19 Vaccine.

Serious Adverse Events

Of the 171 participants who received a booster dose of Moderna COVID-19 Vaccine, there were no serious adverse events reported from the booster dose through 28 days after the booster dose. Through the cut-off date of August 16, 2021, there were no serious adverse events following the booster dose considered causally related to the Moderna COVID-19 Vaccine.

Booster Dose Following Primary Vaccination with Another Authorized or Approved COVID-19 Vaccine

The safety of a Moderna COVID-19 Vaccine (0.25 mL) booster dose in individuals who

completed primary vaccination with another authorized or approved COVID-19 Vaccine (heterologous booster dose) is inferred from the safety of a Moderna COVID-19 Vaccine (0.25 mL) booster dose administered following completion of a Moderna COVID-19 Vaccine primary series (homologous booster dose) and from data from an independent Phase 1/2 open-label clinical trial (NCT04889209) conducted in the United States that evaluated a heterologous booster dose (0.5 mL) of the Moderna COVID-19 Vaccine. In this study, adults who had completed primary vaccination with a Moderna COVID-19 Vaccine 2-dose series (N=151), a Janssen COVID-19 Vaccine single dose (N=156), or a Pfizer-BioNTech COVID-19 Vaccine 2-dose series (N=151) at least 12 weeks prior to enrollment and who reported no history of SARS-CoV-2 infection were randomized 1:1:1 to receive a booster dose of one of three vaccines: Moderna COVID-19 Vaccine (0.5 mL), Janssen COVID-19 Vaccine, or Pfizer-BioNTech COVID-19 Vaccine. Adverse events were assessed through 28 days after the booster dose. An overall review of adverse reactions reported following the Moderna COVID-19 Vaccine heterologous booster dose (0.5 mL) did not identify any new safety concerns, as compared with adverse reactions reported following Moderna COVID-19 Vaccine primary series doses or homologous booster dose (0.25 mL).

6.2 Post-Authorization Experience

The following adverse reactions have been identified during post-authorization use of the Moderna COVID-19 Vaccine. Because these reactions are reported voluntarily, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.

Cardiac Disorders: myocarditis, pericarditis
Immune System Disorders: anaphylaxis
Nervous System Disorders: syncope

8 REQUIREMENTS AND INSTRUCTIONS FOR REPORTING ADVERSE EVENTS AND VACCINE ADMINISTRATION ERRORS

See Overall Safety Summary (Section 6) for additional information.

The vaccination provider enrolled in the federal COVID-19 Vaccination Program is responsible for the MANDATORY reporting of the listed events following Moderna COVID-19 Vaccine to the Vaccine Adverse Event Reporting System (VAERS)

- Vaccine administration errors whether or not associated with an adverse event
- Serious adverse events* (irrespective of attribution to vaccination)
- Cases of Multisystem Inflammatory Syndrome (MIS) in adults
- Cases of COVID-19 that results in hospitalization or death

*Serious Adverse Events are defined as:

- Death;
- A life-threatening adverse event;
- Inpatient hospitalization or prolongation of existing hospitalization;

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect;
- An important medical event that based on appropriate medical judgement may jeopardize the individual and may require medical or surgical intervention to prevent one of the outcomes listed above.

Instructions for Reporting to VAERS

The vaccination provider enrolled in the federal COVID-19 Vaccination Program should complete and submit a VAERS form to FDA using one of the following methods:

- Complete and submit the report online: https://vaers.hhs.gov/reportevent.html, or
- If you are unable to submit this form electronically, you may fax it to VAERS at 1-877-721-0366. If you need additional help submitting a report, you may call the VAERS toll-free information line at 1-800-822-7967 or send an email to info@vaers.org.

IMPORTANT: When reporting adverse events or vaccine administration errors to VAERS, please complete the entire form with detailed information. It is important that the information reported to FDA be as detailed and complete as possible. Information to include:

- Patient demographics (e.g., patient name, date of birth)
- Pertinent medical history
- Pertinent details regarding admission and course of illness
- Concomitant medications
- Timing of adverse event(s) in relationship to administration of Moderna COVID-19 Vaccine
- Pertinent laboratory and virology information
- Outcome of the event and any additional follow-up information if it is available at the time of the VAERS report. Subsequent reporting of follow-up information should be completed if additional details become available.

The following steps are highlighted to provide the necessary information for safety tracking:

1. In Box 17, provide information on Moderna COVID-19 Vaccine and any other vaccines administered on the same day; and in Box 22, provide information on any other vaccines received within one month prior.
2. In Box 18, description of the event:
    a. Write “Moderna COVID-19 Vaccine EUA” as the first line
    b. Provide a detailed report of vaccine administration error and/or adverse event. It is important to provide detailed information regarding the patient and adverse event/medication error for ongoing safety evaluation of this unapproved vaccine. Please see information to include listed above.
3. Contact information:
    a. In Box 13, provide the name and contact information of the prescribing healthcare provider or institutional designee who is responsible for the report.
    b. In Box 14, provide the name and contact information of the best doctor/healthcare

professional to contact about the adverse event.

c. In Box 15, provide the address of the facility where vaccine was given (NOT the healthcare provider's office address).

Other Reporting Instructions

Vaccination providers may report to VAERS other adverse events that are not required to be reported using the contact information above.

To the extent feasible, report adverse events to ModernaTX, Inc. using the contact information below or by providing a copy of the VAERS form to ModernaTX, Inc.

Email	Fax number	Telephone number
ModernaPV@modernatx.com	1-866-599-1342	1-866-MODERNA (1-866-663-3762)

10 DRUG INTERACTIONS

There are no data to assess the concomitant administration of the Moderna COVID-19 Vaccine with other vaccines.

11 USE IN SPECIFIC POPULATIONS

11.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Moderna COVID-19 Vaccine during pregnancy. Women who are vaccinated with Moderna COVID-19 Vaccine during pregnancy are encouraged to enroll in the registry by calling 1-866-MODERNA (1-866-663-3762).

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Available data on Moderna COVID-19 Vaccine administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

In a developmental toxicity study, 0.2 mL of a vaccine formulation containing the same quantity of nucleoside-modified messenger ribonucleic acid (mRNA) (100 mcg) and other ingredients included in a single human dose of Moderna COVID-19 Vaccine was administered to female rats by the intramuscular route on four occasions: 28 and 14 days prior to mating, and on gestation days 1 and 13. No vaccine-related adverse effects on female fertility, fetal development, or

postnatal development were reported in the study.

11.2 Lactation

Risk Summary

Data are not available to assess the effects of Moderna COVID-19 Vaccine on the breastfed infant or on milk production/excretion.

11.3 Pediatric Use

Safety and effectiveness have not been assessed in persons less than 18 years of age. Emergency Use Authorization of Moderna COVID-19 Vaccine does not include use in individuals younger than 18 years of age.

11.4 Geriatric Use

Clinical studies of Moderna COVID-19 Vaccine included participants 65 years of age and older receiving vaccine or placebo, and their data contribute to the overall assessment of safety and efficacy. In an ongoing Phase 3 clinical study (Study 1) of primary series dosing (0.5 mL), 24.8% (n=7,520) of participants were 65 years of age and older and 4.6% (n=1,399) of participants were 75 years of age and older. Vaccine efficacy in participants 65 years of age and older was 86.4% (95% CI 61.4, 95.2) compared to 95.6% (95% CI 90.6, 97.9) in participants 18 to <65 years of age *[see Clinical Trial Results and Supporting Data for EUA (18)]*. Overall, there were no notable differences in the safety profiles observed in participants 65 years of age and older and younger participants *[*see *Overall Safety Summary (6.1)]*.

In an ongoing Phase 2 clinical study (Study 2) of a single booster dose (0.25 mL), 22.2% (n=38) of participants were 65 years of age and older. This study did not include sufficient numbers of participants 65 years of age and older to determine whether they respond differently than younger participants. Some local and systemic adverse reactions were reported in a lower proportion of participants 65 years of age and older compared to participants 18 through 64 years of age *[see Overall Safety Summary (6.1)]*.

11.5 Use in Immunocompromised

In an independent study, safety and effectiveness of a third 0.5 mL primary series dose of the Moderna COVID-19 Vaccine have been evaluated in participants who received solid organ transplants *[see Overall Safety Summary (6.1) and Clinical Trial Results and Supporting Data for EUA (18.2)]*. The administration of a third primary series vaccine dose appears to be only moderately effective in increasing antibody titers. Patients should be counseled to maintain physical precautions to help prevent COVID-19. In addition, close contacts of immunocompromised persons should be vaccinated, as appropriate for their health status.

13 DESCRIPTION

Moderna COVID-19 Vaccine is provided as a white to off-white suspension for intramuscular injection.

Each 0.5 mL dose of Moderna COVID-19 Vaccine contains 100 mcg of nucleoside-modified messenger RNA (mRNA) encoding the pre-fusion stabilized Spike glycoprotein (S) of SARS-CoV-2 virus. Each 0.5 mL dose of the Moderna COVID-19 Vaccine contains the following ingredients: a total lipid content of 1.93 mg (SM-102, polyethylene glycol [PEG] 2000 dimyristoyl glycerol [DMG], cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC]), 0.31 mg tromethamine, 1.18 mg tromethamine hydrochloride, 0.043 mg acetic acid, 0.20 mg sodium acetate trihydrate, and 43.5 mg sucrose. Each 0.25 mL dose of Moderna COVID-19 Vaccine contains half of these ingredients.

Moderna COVID-19 Vaccine does not contain a preservative.

The vial stoppers are not made with natural rubber latex.

14 CLINICAL PHARMACOLOGY

14.1 Mechanism of Action

The nucleoside-modified mRNA in the Moderna COVID-19 Vaccine is formulated in lipid particles, which enable delivery of the nucleoside-modified mRNA into host cells to allow expression of the SARS-CoV-2 S antigen. The vaccine elicits an immune response to the S antigen, which protects against COVID-19.

18 CLINICAL TRIAL RESULTS AND SUPPORTING DATA FOR EUA

18.1 Efficacy of Two-Dose Primary Series

Study 1 is an ongoing Phase 3 randomized, placebo-controlled, observer-blind clinical trial to evaluate the efficacy, safety, and immunogenicity of the Moderna COVID-19 Vaccine in participants 18 years of age and older in the United States (NCT04470427). Randomization was stratified by age and health risk: 18 to <65 years of age without comorbidities (not at risk for progression to severe COVID-19), 18 to <65 years of age with comorbidities (at risk for progression to severe COVID-19), and 65 years of age and older with or without comorbidities. Participants who were immunocompromised and those with a known history of SARS-CoV-2 infection were excluded from the study. Participants with no known history of SARS-CoV-2 infection but with positive laboratory results indicative of infection at study entry were included. The study allowed for the inclusion of participants with stable pre-existing medical conditions, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 3 months before enrollment, as well as participants with stable human immunodeficiency virus (HIV) infection. A total of 30,420 participants were randomized equally to receive 2 doses of the Moderna COVID-19 Vaccine or saline placebo 1 month apart. Participants will be followed for efficacy and safety until 24 months after the second dose.

The primary efficacy analysis population (referred to as the Per-Protocol Set) included 28,207 participants who received two doses (0.5 mL at 0 and 1 month) of either Moderna COVID-19 Vaccine (n=14,134) or placebo (n=14,073), and had a negative baseline SARS-CoV-2 status. In the Per-Protocol Set, 47.4% were female, 19.7% were Hispanic or Latino; 79.5% were White, 9.7% were African American, 4.6% were Asian, and 2.1% other races. The median age of participants was 53 years (range 18-95) and 25.3% of participants were 65 years of age and older. Of the study participants in the Per-Protocol Set, 18.5% were at increased risk of severe COVID-19 due to at least one pre-existing medical condition (chronic lung disease, significant cardiac disease, severe obesity, diabetes, liver disease, or HIV infection) regardless of age. Between participants who received Moderna COVID-19 Vaccine and those who received placebo, there were no notable differences in demographics or pre-existing medical conditions.

Efficacy Against COVID-19

COVID-19 was defined based on the following criteria: The participant must have experienced at least two of the following systemic symptoms: fever (≥38ºC / ≥100.4°F), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s); or the participant must have experienced at least one of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, or clinical or radiographical evidence of pneumonia; and the participant must have at least one NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS- CoV-2 by RT-PCR. COVID-19 cases were adjudicated by a Clinical Adjudication Committee.

The median length of follow up for efficacy for participants in the study was 9 weeks post Dose 2. There were 11 COVID-19 cases in the Moderna COVID-19 Vaccine group and 185 cases in the placebo group, with a vaccine efficacy of 94.1% (95% confidence interval of 89.3% to 96.8%).

Table 5: Primary Efficacy Analysis: COVID-19* in Participants 18 Years of Age and Older Starting 14 Days After Dose 2 per Adjudication Committee Assessments – Per-Protocol Set

Moderna COVID-19 Vaccine			Placebo			% Vaccine Efficacy (95% CI)†
Participants (N)	COVID-19 Cases (n)	Incidence Rate of COVID-19 per 1,000 Person-Years	Participants (N)	COVID-19 Cases (n)	Incidence Rate of COVID-19 per 1,000 Person-Years	
14,134	11	3.328	14,073	185	56.510	94.1 (89.3, 96.8)

* COVID-19: symptomatic COVID-19 requiring positive RT-PCR result and at least two systemic symptoms or one respiratory symptom. Cases starting 14 days after Dose 2.
† VE and 95% CI from the stratified Cox proportional hazard model.

The subgroup analyses of vaccine efficacy are presented in Table 6.

Table 6: Subgroup Analyses of Vaccine Efficacy: COVID-19* Cases Starting 14 Days After Dose 2 per Adjudication Committee Assessments – Per-Protocol Set

Age Subgroup (Years)	Moderna COVID-19 Vaccine			Placebo			% Vaccine Efficacy (95% CI)†
	Participants (N)	COVID-19 Cases (n)	Incidence Rate of COVID-19 per 1,000 Person-Years	Participants (N)	COVID-19 Cases (n)	Incidence Rate of COVID-19 per 1,000 Person-Years	
18 to <65	10,551	7	2.875	10,521	156	64.625	95.6 (90.6, 97.9)
≥65	3,583	4	4.595	3,552	29	33.728	86.4 (61.4, 95.2)

* COVID-19: symptomatic COVID-19 requiring positive RT-PCR result and at least two systemic symptoms or one respiratory symptom. Cases starting 14 days after Dose 2.
† VE and 95% CI from the stratified Cox proportional hazard model.

Severe COVID-19 was defined based on confirmed COVID-19 as per the primary efficacy endpoint case definition, plus any of the following: Clinical signs indicative of severe systemic illness, respiratory rate ≥30 per minute, heart rate ≥125 beats per minute, SpO2 ≤93% on room air at sea level or PaO2/FIO2 <300 mm Hg; or respiratory failure or ARDS (defined as needing high-flow oxygen, non-invasive or mechanical ventilation, or ECMO), evidence of shock (systolic blood pressure <90 mmHg, diastolic BP <60 mmHg or requiring vasopressors); or significant acute renal, hepatic, or neurologic dysfunction; or admission to an intensive care unit or death.

Among all participants in the Per-Protocol Set analysis, which included COVID-19 cases confirmed by an adjudication committee, no cases of severe COVID-19 were reported in the Moderna COVID-19 Vaccine group compared with 30 cases reported in the placebo group (incidence rate 9.138 per 1,000 person-years). One PCR-positive case of severe COVID-19 in a vaccine recipient was awaiting adjudication at the time of the analysis.

18.2 Immunogenicity in Solid Organ Transplant Recipients

An independent randomized-controlled study has been conducted in 120 participants who had undergone various solid organ transplant procedures (heart, kidney, kidney-pancreas, liver, lung, pancreas) a median of 3.57 years previously (range 1.99-6.75 years). A third 0.5 mL primary series dose of the Moderna COVID-19 Vaccine was administered to 60 participants approximately 2 months after they had received a second dose; saline placebo was given to 60 individuals for comparison. Significant increases in levels of SARS-CoV-2 antibodies occurred four weeks after the third dose in 55.0% of participants in the Moderna COVID-19 Vaccine group (33 of 60) and 17.5% of participants in the placebo group (10 of 57).

18.3 Immunogenicity of a Booster Dose Following a Moderna COVID-19 Vaccine Primary Series

Effectiveness of a booster dose of the Moderna COVID-19 Vaccine was based on assessment of neutralizing antibody titers (ID50) against a pseudovirus expressing the SARS-CoV-2 Spike protein from a USA_WA1/2020 isolate carrying the D614G mutation. Immunogenicity analyses compared the ID50 following the booster dose to the ID50 following the primary series.

In an open-label phase of Study 2, participants 18 years of age and older received a single booster dose (0.25 mL) at least 6 months after completion of the primary series (two doses of 0.5 mL 1 month apart). The primary immunogenicity analysis population included 149 booster dose participants in Study 2 (including one individual who had only received a single dose of the primary series) and a random subset of 1055 participants from Study 1 who received two doses (0.5 mL 1 month apart) of Moderna COVID-19 Vaccine. Study 1 and 2 participants included in the analysis population had no serologic or virologic evidence of SARS-CoV-2 infection prior to the first primary series dose and prior to the booster dose, respectively. Among participants assessed for immunogenicity, 60.4% were female, 6.7% were Hispanic or Latino; 95.3% were White, 3.4% were Black or African American, 0.7% were Asian, and 0.7% were American Indian or Alaskan Native; 9.4% were obese (body mass index ≥30 kg/m^2). The median age of Study 2 participants was 56 years of age (range 18-82) and 24.8% of participants were 65 years of age and older. Study 2 participants included in the primary immunogenicity analysis population did not have pre-existing medical conditions that would place them at risk of severe COVID-19. Study 1 participants included in the primary immunogenicity analysis population were a stratified random sample which reflected the overall primary efficacy analysis population with regards to demographics and pre-existing medical conditions with a higher percentage of those ≥65 years of age (33.6%), with risk factors for severe COVID-19 (39.4%), and communities of color (53.5%).

Immunogenicity analyses included an assessment of ID50 geometric mean titer (GMT) ratio and difference in seroresponse rates. The analysis of the GMT ratio of ID50 following the booster dose compared to the primary series met the immunobridging criteria for a booster response. Seroresponse for a participant was defined as achieving a ≥4-fold rise in ID50 from baseline (before the booster dose in Study 2 and before the first dose of the primary series in Study 1). The lower limit of the 2-sided 95% CI for the difference in seroresponse rates between Study 1 and Study 2 was -16.7%, which did not meet the immunobridging criterion for a booster response (lower limit of 2-sided 95% CI for the percentage difference of ≥ -10%). These analyses are summarized in Tables 7 and 8.

Table 7: Neutralizing Antibody Geometric Mean Titers (ID50) Against a Pseudovirus Expressing the SARS-CoV-2 Spike Protein (USA_WA1/2020 isolate carrying the D614G mutation) at 28 Days After a Booster Dose in Study 2 vs 28 Days After Completion of the Primary Series in Study 1, Participants ≥18 Years of Age, Per-Protocol Immunogenicity Set*

Study 2 Booster Dose N[a]=149 GMT[b] (95% CI)	Study 1 Primary Series N[a]=1053 GMT[b] (95% CI)	GMT Ratio (Study 2/Study 1)	Met Success Criteria[c]
1802 (1548, 2099)	1027 (968, 1089)	1.8 (1.5, 2.1)	Lower limit of 95% CI ≥0.67 Criterion: Yes Point Estimate ≥1.0 Criterion: Yes

* Per-Protocol Immunogenicity Set included all subjects who had both baseline (or Study 2 Day 1 for Study 2) and post-vaccination immunogenicity samples, did not have SARS-CoV-2 infection at baseline (or Study 2 Day 1 for Study 2), did not have a major protocol deviation that impacted immune response, and had post-injection immunogenicity assessment at timepoint of primary interest (Day 29 for Study 2 and Day 57 for Study 1).

[a] Number of subjects with non-missing data at the corresponding timepoint.

[b] Given the lack of randomization in Study 2, the statistical analysis plan pre-specified an analysis of covariance model for estimating the geometric mean titer that adjusts for differences in age groups (<65 years, ≥65 years).

[c] Immunobridging is declared if the lower limit of the 2-sided 95% CI for the GMR is >0.67 and the point estimate of the GLSM ratio is ≥1.0.

Note: Antibody values < the lower limit of quantitation (LLOQ) are replaced by 0.5 × LLOQ. Values > the upper limit of quantitation (ULOQ) are replaced by the ULOQ if actual values are not available.

GLSM = Geometric least squares mean

GMR = Geometric mean ratio

Table 8: Seroresponse Rates Against A Pseudovirus Expressing the SARS-CoV-2 Spike Protein (USA_WA1/2020 isolate carrying the D614G mutation) at 28 Days Post-Booster Dose in Study 2 and 28 Days After Completion of the Primary Series in Study 1, Participants ≥18 Years of Age, Per-Protocol Immunogenicity Set*

Study 2 Booster Seroresponse[a] N[b]=149 n (%) (95% CI)[c]	Study 1 Primary Series Seroresponse[a] N[b]=1050 n (%) (95% CI)[c]	Difference in Seroresponse Rate (Study 2-Study 1) % (95% CI)[d]	Met Success Criterion[e]
131 (87.9) (81.6, 92.7)	1033 (98.4) (97.4, 99.1)	-10.5 (-16.7, -6.1)	Lower limit of 95% CI ≥-10% Criterion: No

* Per-Protocol Immunogenicity Set included all subjects who had both baseline (or Study 2 Day 1 for Study 2) and post-vaccination immunogenicity samples, did not have SARS-CoV-2 infection at baseline (or Study 2 Day 1 for Study 2), did not have a major protocol deviation that impacted immune response, and had post-injection immunogenicity assessment at timepoint of primary interest (Day 29 for Study 2 and Day 57 for Study 1).

[a] Seroresponse is defined as ≥4-fold rise of pseudovirus neutralizing antibody titers (ID50) from baseline (pre-booster dose in Study 2 and pre-dose 1 in Study 1), where baseline titers < LLOQ are set to LLOQ for the analysis.

[b] Number of subjects with non-missing data at both baseline and the post-baseline timepoint of interest.

[c] 95% CI is calculated using the Clopper-Pearson method.

[d] 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.

[e] Immunobridging is declared if the lower limit of the 2-sided 95% CI for the percentage difference is > -10%.

Study 2 participants who met the ≥4-fold increase in titer post-booster dose (87.9%) had a lower baseline GMT of 109 (range of individual titers 9, 4393), whereas Study 2 participants who did not meet the ≥4-fold increase in titers post-booster had a higher baseline GMT of 492 (range of individual titers 162, 2239).

An additional descriptive analysis evaluated seroresponse rates using baseline neutralizing antibody titers prior to dose 1 of the primary series. As shown in Table 9 below, the booster dose seroresponse rate, with seroresponse defined as at least a 4-fold rise relative to the pre-dose 1 titer, was 100%. The difference in seroresponse rates in this post-hoc analysis was 1.6% (95% CI -0.9, 2.6).

Table 9: Analysis of Seroresponse Rates Against a Pseudovirus Expressing the SARS-CoV-2 Spike Protein (USA_WA1/2020 isolate carrying the D614G mutation) at 28 Days Post-Booster Dose in Study 2 and 28 Days After Completion of the Primary Series in Study 1, Participants ≥18 Years of Age, Per-Protocol Immunogenicity Set*

Study 2 Booster Seroresponse[a] N[b]=148 n (%) (95% CI)[d]	Study 1 Primary Series Seroresponse[a] N[c]=1050 n (%) (95% CI)[d]	Difference in Seroresponse Rate (After Booster-After Primary Series) % (95% CI)[e]
148 (100) (97.5, 100)	1033 (98.4) (97.4, 99.1)	1.6 (-0.9, 2.6)

* Per-Protocol Immunogenicity Set included all subjects who had non-missing data at baseline (before dose 1) and 28 days post-booster in Study 2 or 28 days post-dose 2 in the primary series in Study 1, respectively, did not have SARS-CoV-2 infection at pre-booster in Study 2 or baseline in Study 1, did not have a major protocol deviation that impacted immune response, and had post-injection immunogenicity assessment at timepoint of primary interest.

[a] Seroresponse is defined as ≥4-fold rise of pseudovirus neutralizing antibody titers (ID50) from pre-dose 1, where baseline titers < LLOQ are set to LLOQ for the analysis.

[b] Number of subjects with non-missing data at baseline (before dose 1) and 28 days post-booster in Study 2.

[c] Number of subjects with non-missing data at baseline (before dose 1) and 28 days post-dose 2 in the primary series in Study 1.

[d] 95% CI is calculated using the Clopper-Pearson method.

[e] 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.

18.4 Immunogenicity of a Booster Dose Following Primary Vaccination with Another Authorized or Approved COVID-19 Vaccine

Effectiveness of a Moderna COVID-19 Vaccine (0.25 mL) booster dose in individuals who completed primary vaccination with another authorized or approved COVID-19 Vaccine (heterologous booster dose) is inferred from immunogenicity data supporting effectiveness of a Moderna COVID-19 Vaccine (0.25 mL) booster dose administered following completion of a Moderna COVID-19 Vaccine primary series and from immunogenicity data from an independent Phase 1/2 open-label clinical trial (NCT04889209) conducted in the United States that evaluated a heterologous booster dose (0.5 mL) of the Moderna COVID-19 Vaccine. In this study, adults who had completed primary vaccination with a Moderna COVID-19 Vaccine 2-dose series (N=151), a Janssen COVID-19 Vaccine single dose (N=156), or a Pfizer-BioNTech COVID-19 Vaccine 2-dose series (N=151) at least 12 weeks prior to

enrollment and who reported no history of SARS-CoV-2 infection were randomized 1:1:1 to receive a booster dose of one of three vaccines: Moderna COVID-19 Vaccine, Janssen COVID-19 Vaccine, or Pfizer-BioNTech COVID-19 Vaccine. Neutralizing antibody titers, as measured by a pseudovirus neutralization assay using a lentivirus expressing the SARS-CoV-2 Spike protein with D614G mutation, were assessed on Day 1 prior to administration of the booster dose and on Day 15 after the booster dose. A booster response to the Moderna COVID-19 Vaccine (0.5 mL) was demonstrated regardless of primary vaccination.

19 HOW SUPPLIED/STORAGE AND HANDLING

Moderna COVID-19 Vaccine Suspension for Intramuscular Injection Multiple-Dose Vials are supplied as follows:

NDC 80777-273-99 Carton of 10 multiple-dose vials, each vial containing 5.5 mL

NDC 80777-273-98 Carton of 10 multiple-dose vials, each vial containing 7.5 mL

During storage, minimize exposure to room light.

Store frozen between -50º to -15ºC (-58º to 5ºF). Store in the original carton to protect from light.

Do not store on dry ice or below -50ºC (-58ºF). Use of dry ice may subject vials to temperatures colder than -50°C (-58°F).

Vials may be stored refrigerated between 2° to 8°C (36° to 46°F) for up to 30 days prior to first use. Do not refreeze.

Vials may be stored between 8° to 25°C (46° to 77°F) for a total of 24 hours.

After the first dose has been withdrawn, the vial should be held between 2° to 25°C (36° to 77°F). Vials should be discarded 12 hours after the first puncture.

Thawed vials can be handled in room light conditions.

Do not refreeze once thawed.

Transportation of Thawed Vials at 2° to 8°C (36° to 46°F)

If transport at -50° to -15°C (-58° to 5°F) is not feasible, available data support transportation of one or more thawed vials for up to 12 hours at 2° to 8°C (36° to 46°F) when shipped using shipping containers which have been qualified to maintain 2° to 8°C (36° to 46°F) and under routine road and air transport conditions with shaking and vibration minimized. Once thawed and transported at 2° to 8°C (36° to 46°F), vials should not be refrozen and should be stored at 2° to 8°C (36° to 46°F) until use.

20 PATIENT COUNSELING INFORMATION

Advise the recipient or caregiver to read the Fact Sheet for Recipients and Caregivers.

The vaccination provider must include vaccination information in the state/local jurisdiction's Immunization Information System (IIS) or other designated system. Advise recipient or caregiver that more information about IISs can be found at:
https://www.cdc.gov/vaccines/programs/iis/about.html.

21 CONTACT INFORMATION

For general questions, send an email or call the telephone number provided below.

Email	Telephone number
medinfo@modernatx.com	1-866-MODERNA (1-866-663-3762)

This EUA Prescribing Information may have been updated. For the most recent Full EUA Prescribing Information, please visit www.modernatx.com/covid19vaccine-eua.

Moderna US, Inc.
Cambridge, MA 02139

Patent(s): www.modernatx.com/patents
Revised: Oct/20/2021

Exhibit J

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 U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product, Janssen COVID-19 Vaccine, for active immunization to prevent COVID-19 in individuals 18 years of age and older.

SUMMARY OF INSTRUCTIONS FOR COVID-19 VACCINATION PROVIDERS

Vaccination providers enrolled in the federal COVID-19 Vaccination Program must report all vaccine administration errors, all serious adverse events, cases of Multisystem Inflammatory Syndrome (MIS) in adults, and cases of COVID-19 that result in hospitalization or death following administration of the Janssen COVID-19 Vaccine. See "MANDATORY REQUIREMENTS FOR THE JANSSEN COVID-19 VACCINE ADMINISTRATION UNDER EMERGENCY USE AUTHORIZATION" for reporting requirements.

The Janssen COVID-19 Vaccine is a suspension for intramuscular injection.

Primary Vaccination

The primary vaccination regimen for the Janssen COVID-19 Vaccine is a **single-dose** (0.5 mL) administered to individuals 18 years of age and older.

Booster Dose

A single Janssen COVID-19 Vaccine booster dose (0.5 mL) may be administered at least 2 months after primary vaccination with the Janssen COVID-19 Vaccine, to individuals 18 years of age and older.

A single booster dose of the Janssen COVID-19 Vaccine (0.5 mL) may be administered as a heterologous booster dose following completion of primary vaccination with another authorized or approved COVID-19 vaccine. The eligible population(s) and dosing interval for the heterologous booster dose are the same as those authorized for a booster dose of the vaccine used for primary vaccination.

See this Fact Sheet for instructions for preparation and administration. This Fact Sheet may have been updated. For the most recent Fact Sheet, please see www.janssencovid19vaccine.com.

For information on clinical trials that are testing the use of the Janssen COVID-19 Vaccine for active immunization against COVID-19, please see www.clinicaltrials.gov.

DESCRIPTION OF COVID-19

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the novel coronavirus, SARS-CoV-2, that appeared in late 2019. It is predominantly a respiratory illness that can affect other organs. People with COVID-19 have reported a wide range of symptoms, ranging from mild

symptoms to severe illness. Symptoms may appear 2 to 14 days after exposure to the virus. Symptoms may include: fever or chills; cough; shortness of breath; fatigue; muscle or body aches; headache; new loss of taste or smell; sore throat; congestion or runny nose; nausea or vomiting; diarrhea.

DOSAGE AND ADMINISTRATION

The storage and handling information in this Fact Sheet supersedes the storage and handling information on the carton and vial labels.

Storage and Handling

Storage Prior to First Puncture of the Vaccine Vial

Store unpunctured multi-dose vials of the Janssen COVID-19 Vaccine at 2°C to 8°C (36°F to 46°F) and protect from light. Do not store frozen.

Unpunctured vials of Janssen COVID-19 Vaccine may be stored between 9°C to 25°C (47°F to 77°F) for up to 12 hours.

The Janssen COVID-19 Vaccine is initially stored frozen by the manufacturer, then shipped at 2°C to 8°C (36°F to 46°F). If vaccine is still frozen upon receipt, thaw at 2°C to 8°C (36°F to 46°F). If needed immediately, thaw at room temperature (maximally 25°C/77°F). At room temperature (maximally 25°C/77°F), a carton of 10 vials will take approximately 4 hours to thaw, and an individual vial will take approximately 1 hour to thaw. Do not refreeze once thawed.

Storage After First Puncture of the Vaccine Vial

After the first dose has been withdrawn, hold the vial between 2° to 8°C (36° to 46°F) for up to 6 hours or at room temperature (maximally 25°C/77°F) for up to 2 hours. Discard the vial if vaccine is not used within these times.

Dosing and Schedule

Primary Vaccination

The primary vaccination regimen for the Janssen COVID-19 Vaccine is a single-dose (0.5 mL) administered to individuals 18 years of age and older.

Booster Dose

A single Janssen COVID-19 Vaccine booster dose (0.5 mL) may be administered at least 2 months after primary vaccination with the Janssen COVID-19 Vaccine, to individuals 18 years of age and older.

A single booster dose of the Janssen COVID-19 Vaccine (0.5 mL) may be administered as a heterologous booster dose following completion of primary vaccination with another authorized or approved COVID-19 vaccine. The eligible population(s) and dosing interval for the heterologous booster dose are the same as those authorized for a booster dose of the vaccine used for primary vaccination.

Dose Preparation

- The Janssen COVID-19 Vaccine is a colorless to slightly yellow, clear to very opalescent suspension. Visually inspect the Janssen COVID-19 Vaccine vials for particulate matter and discoloration prior to administration. If either of these conditions exists, do not administer the vaccine.
- Before withdrawing each dose of vaccine, carefully mix the contents of the multi-dose vial by swirling gently in an upright position for 10 seconds. **Do not shake**.
- Each dose is 0.5 mL. Each vial contains five doses. Do not pool excess vaccine from multiple vials.
- The Janssen COVID-19 Vaccine does not contain a preservative. Record the date and time of first use on the Janssen COVID-19 Vaccine vial label. After the first dose has been withdrawn, hold the vial between 2° to 8°C (36° to 46°F) for up to 6 hours or at room temperature (maximally 25°C/77°F) for up to 2 hours. Discard if vaccine is not used within these times.

Administration

Visually inspect each dose in the dosing syringe prior to administration. The Janssen COVID-19 Vaccine is a colorless to slightly yellow, clear to very opalescent suspension. During the visual inspection,

- verify the final dosing volume of 0.5 mL.
- confirm there are no particulates and that no discoloration is observed.
- do not administer if vaccine is discolored or contains particulate matter.

Administer the Janssen COVID-19 Vaccine intramuscularly.

CONTRAINDICATION

Do not administer the Janssen COVID-19 Vaccine to individuals with a known history of a severe allergic reaction (e.g., anaphylaxis) to any component of the Janssen COVID-19 Vaccine *(see Full EUA Prescribing Information)*.

WARNINGS

Management of Acute Allergic Reactions

Appropriate medical treatment to manage immediate allergic reactions must be immediately available in the event an acute anaphylactic reaction occurs following administration of the Janssen COVID-19 Vaccine.

Monitor Janssen COVID-19 Vaccine recipients for the occurrence of immediate adverse reactions according to the Centers for Disease Control and Prevention guidelines (https://www.cdc.gov/vaccines/covid-19/clinical-considerations/managing-anaphylaxis.html).

Thrombosis with thrombocytopenia

Reports of adverse events following use of the Janssen COVID-19 Vaccine under emergency use authorization suggest an increased risk of thrombosis involving the cerebral venous sinuses and other sites (including but not limited to the large blood vessels of the abdomen and the veins of the lower extremities) combined with thrombocytopenia and with onset of symptoms approximately one to two weeks after vaccination. The reporting rate of thrombosis with thrombocytopenia following administration of the Janssen COVID-19 Vaccine has been highest in females ages 18 through 49 years; some cases have been fatal. The clinical course of these events shares features with autoimmune heparin-induced thrombocytopenia. In individuals with suspected thrombosis with thrombocytopenia following administration of the Janssen COVID-19 Vaccine, the use of heparin may be harmful and alternative treatments may be needed. Consultation with hematology specialists is strongly recommended. The American Society of Hematology has published considerations relevant to the diagnosis and treatment of thrombosis with thrombocytopenia following administration of the Janssen COVID-19 Vaccine (*https://www.hematology.org/covid-19/vaccine-induced-immune-thrombotic-thrombocytopenia*). *(see Full EUA Prescribing Information)*.

Guillain-Barré Syndrome

Reports of adverse events following use of the Janssen COVID-19 Vaccine under emergency use authorization suggest an increased risk of Guillain-Barré syndrome during the 42 days following vaccination.

Altered Immunocompetence

Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the Janssen COVID-19 Vaccine.

Syncope

Syncope (fainting) may occur in association with administration of injectable vaccines. Procedures should be in place to avoid injury from fainting.

Limitations of Vaccine Effectiveness

The Janssen COVID-19 Vaccine may not protect all vaccinated individuals.

ADVERSE REACTIONS

Adverse Reactions in Clinical Trials

Adverse reactions reported in a clinical trial following administration of the Janssen COVID-19 Vaccine include injection site pain, headache, fatigue, myalgia, nausea, fever, injection site erythema and injection site swelling. In clinical studies, severe allergic reactions, including anaphylaxis, have been reported following administration of the Janssen COVID-19 Vaccine *(see Full EUA Prescribing Information)*.

Adverse Reactions Identified during Post Authorization Use

Anaphylaxis and other severe allergic reactions, thrombosis with thrombocytopenia, Guillain-Barré syndrome, and capillary leak syndrome have been reported following

administration of the Janssen COVID-19 Vaccine during mass vaccination outside of clinical trials.

Additional adverse reactions, some of which may be serious, may become apparent with more widespread use of the Janssen COVID-19 Vaccine.

USE WITH OTHER VACCINES

There is no information on the co-administration of the Janssen COVID-19 Vaccine with other vaccines.

INFORMATION TO PROVIDE TO VACCINE RECIPIENTS/CAREGIVERS

As the vaccination provider, you must communicate to the recipient or their caregiver, information consistent with the "Fact Sheet for Recipients and Caregivers" (and provide a copy or direct the individual to the website www.janssencovid19vaccine.com to obtain the Fact Sheet) prior to the individual receiving the Janssen COVID-19 Vaccine, including:

- FDA has authorized the emergency use of the Janssen COVID-19 Vaccine, which is not an FDA approved vaccine.
- The recipient or their caregiver has the option to accept or refuse the Janssen COVID-19 Vaccine.
- The significant known and potential risks and benefits of the Janssen COVID-19 Vaccine, and the extent to which such risks and benefits are unknown.
- Information about available alternative vaccines and the risks and benefits of those alternatives.

For information on clinical trials that are testing the use of the Janssen COVID-19 Vaccine to prevent COVID-19, please see www.clinicaltrials.gov.

Provide a vaccination card to the recipient or their caregiver with the name of the vaccine ("Janssen COVID-19 Vaccine") and date of administration to document vaccination.

Provide the v-safe information sheet to vaccine recipients/caregivers and encourage vaccine recipients to participate in v-safe. V-safe is a new voluntary smartphone-based tool that uses text messaging and web surveys to check in with people who have been vaccinated to identify potential side effects after COVID-19 vaccination. V-safe asks questions that help CDC monitor the safety of COVID-19 vaccines. V-safe also provides live telephone follow-up by CDC if participants report a significant health impact following COVID-19 vaccination. For more information, visit: www.cdc.gov/vsafe.

MANDATORY REQUIREMENTS FOR JANSSEN COVID-19 VACCINE ADMINISTRATION UNDER EMERGENCY USE AUTHORIZATION

In order to mitigate the risks of using this unapproved product under EUA and to optimize the potential benefit of the Janssen COVID-19 Vaccine, the following items are required. Use of

unapproved Janssen COVID-19 Vaccine for active immunization to prevent COVID-19 under this EUA is limited to the following (all requirements must be met):

1. The Janssen COVID-19 Vaccine is authorized for use in individuals 18 years of age and older.

2. The vaccination provider must communicate to the individual receiving the Janssen COVID-19 Vaccine or their caregiver, information consistent with the "Fact Sheet for Recipients and Caregivers" prior to the individual receiving the Janssen COVID-19 Vaccine.

3. The vaccination provider must include vaccination information in the state/local jurisdiction's Immunization Information System (IIS) or other designated system.

4. The vaccination provider is responsible for mandatory reporting of the following to the Vaccine Adverse Event Reporting System (VAERS):

   - vaccine administration errors whether or not associated with an adverse event,
   - serious adverse events* (irrespective of attribution to vaccination),
   - cases of Multisystem Inflammatory Syndrome (MIS) in adults, and
   - cases of COVID-19 that result in hospitalization or death.

   Complete and submit reports to VAERS online at https://vaers.hhs.gov/reportevent.html. For further assistance with reporting to VAERS, call 1-800-822-7967. The reports should include the words "Janssen COVID-19 Vaccine EUA" in the description section of the report.

5. The vaccination provider is responsible for responding to FDA requests for information about vaccine administration errors, adverse events, cases of MIS in adults, and cases of COVID-19 that result in hospitalization or death following administration of the Janssen COVID-19 Vaccine to recipients.

   * Serious adverse events are defined as:
   - Death;
   - A life-threatening adverse event;
   - Inpatient hospitalization or prolongation of existing hospitalization;
   - A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
   - A congenital anomaly/birth defect;
   - An important medical event that based on appropriate medical judgement may jeopardize the individual and may require medical or surgical intervention to prevent one of the outcomes listed above.

OTHER ADVERSE EVENT REPORTING TO VAERS AND JANSSEN BIOTECH, INC.

Vaccination providers may report to VAERS other adverse events that are not required to be reported using the contact information above.

Revised: Oct/20/2021

To the extent feasible, report adverse events to Janssen Biotech, Inc. using the contact information below or by providing a copy of the VAERS form to Janssen Biotech, Inc:

e-mail	Fax number	Telephone numbers
JNJvaccineAE@its.jnj.com	215-293-9955	US Toll Free: 1-800-565-4008 US Toll: (908) 455-9922

ADDITIONAL INFORMATION

For general questions or to access the most recent Janssen COVID-19 Vaccine Fact Sheets, scan the QR code using your device, visit www.janssencovid19vaccine.com or call the telephone numbers provided below.

QR Code	Fact Sheets Website	Telephone numbers
	www.janssencovid19vaccine.com.	US Toll Free: 1-800-565-4008 US Toll: 1-908-455-9922

AVAILABLE ALTERNATIVES

Comirnaty (COVID-19 Vaccine, mRNA) is an FDA-approved vaccine to prevent COVID-19 caused by SARS-CoV-2. There may be clinical trials or availability under EUA of other COVID-19 vaccines.

FEDERAL COVID-19 VACCINATION PROGRAM

This vaccine is being made available for emergency use exclusively through the CDC COVID-19 Vaccination Program (the Vaccination Program). Healthcare providers must enroll as providers in the Vaccination Program and comply with the provider requirements. Vaccination providers may not charge any fee for the vaccine and may not charge the vaccine recipient any out-of-pocket charge for administration. However, vaccination providers may seek appropriate reimbursement from a program or plan that covers COVID-19 vaccine administration fees for the vaccine recipient (private insurance, Medicare, Medicaid, HRSA COVID-19 Uninsured Program for non-insured recipients). For information regarding provider requirements and enrollment in the CDC COVID-19 Vaccination Program, see *https://www.cdc.gov/vaccines/covid-19/provider-enrollment.html*.

Individuals becoming aware of any potential violations of the CDC COVID-19 Vaccination Program requirements are encouraged to report them to the Office of the Inspector General, U.S. Department of Health and Human Services, at 1-800-HHS-TIPS or TIPS.HHS.GOV.

AUTHORITY FOR ISSUANCE OF THE EUA

The Secretary of the Department of Health and Human Services (HHS) declared a public health emergency that justifies the emergency use of drugs and biological products during the COVID-19

pandemic. In response, FDA has issued an EUA for the unapproved product, Janssen COVID-19 Vaccine, for active immunization to prevent COVID-19 in individuals 18 years of age and older.

FDA issued this EUA, based on Janssen Biotech, Inc.'s request and submitted data.

Although limited scientific information is available, based on the totality of the scientific evidence available to date, it is reasonable to believe that the Janssen COVID-19 Vaccine may be effective for the prevention of COVID-19 in individuals as specified in the Full EUA Prescribing Information.

This EUA for the Janssen COVID-19 Vaccine will end when the Secretary of HHS determines that the circumstances justifying the EUA no longer exist or when there is a change in the approval status of the product such that an EUA is no longer needed.

For additional information about Emergency Use Authorization visit FDA at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization.

THE COUNTERMEASURES INJURY COMPENSATION PROGRAM

The Countermeasures Injury Compensation Program (CICP) is a federal program that has been created to help pay for related costs of medical care and other specific expenses to compensate people injured after use of certain medical countermeasures. Medical countermeasures are specific vaccines, medications, devices, or other items used to prevent, diagnose, or treat the public during a public health emergency or a security threat. For more information about CICP, visit www.hrsa.gov/cicp, email cicp@hrsa.gov, or call: 1-855-266-2427.

Manufactured by:
Janssen Biotech, Inc.
a Janssen Pharmaceutical Company of Johnson & Johnson
Horsham, PA 19044, USA

END SHORT VERSION FACT SHEET
Long Version (Full EUA Prescribing Information) Begins On Next Page

Revised: Oct/20/2021

Revised: Oct/20/2021

FULL EMERGENCY USE AUTHORIZATION (EUA) PRESCRIBING INFORMATION JANSSEN COVID-19 VACCINE

FULL EMERGENCY USE AUTHORIZATION (EUA) PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL EMERGENCY USE AUTHORIZATION (EUA) PRESCRIBING INFORMATION

1 AUTHORIZED USE

Janssen COVID-19 vaccine is authorized for use under an Emergency Use Authorization (EUA) for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 18 years of age and older.

2 DOSAGE AND ADMINISTRATION

For intramuscular injection only.

2.1 Preparation for Administration

- The Janssen COVID-19 Vaccine is a colorless to slightly yellow, clear to very opalescent suspension. Visually inspect the Janssen COVID-19 Vaccine vials for particulate matter and discoloration prior to administration. If either of these conditions exists, do not administer the vaccine.
- Before withdrawing each dose of vaccine, carefully mix the contents of the multi-dose vial by swirling gently in an upright position for 10 seconds. **Do not shake**.
- Each dose is 0.5 mL. Each vial contains five doses. Do not pool excess vaccine from multiple vials.
- The Janssen COVID-19 Vaccine does not contain a preservative. Record the date and time of first use on the Janssen COVID-19 Vaccine vial label. After the first dose has been withdrawn, hold the vial between 2° to 8°C (36° to 46°F) for up to 6 hours or at room temperature (maximally 25°C/77°F) for up to 2 hours. Discard if vaccine is not used within these times.

2.2 Administration

Visually inspect each dose in the dosing syringe prior to administration. The Janssen COVID-19 Vaccine is a colorless to slightly yellow, clear to very opalescent suspension. During the visual inspection,

- verify the final dosing volume of 0.5 mL.
- confirm there are no particulates and that no discoloration is observed.
- do not administer if vaccine is discolored or contains particulate matter.

Administer the Janssen COVID-19 Vaccine intramuscularly.

2.3 Dosing and Schedule

Primary Vaccination

The primary vaccination regimen for the Janssen COVID-19 Vaccine is a single-dose (0.5 mL) administered to individuals 18 years of age and older.

Booster Dose

A single Janssen COVID-19 Vaccine booster dose (0.5 mL) may be administered at least 2 months after primary vaccination with the Janssen COVID-19 Vaccine, to individuals 18 years of age and older.

A single booster dose of the Janssen COVID-19 Vaccine (0.5 mL) may be administered as a heterologous booster dose following completion of primary vaccination with another authorized or approved COVID-19 vaccine. The eligible population(s) and dosing interval for the heterologous booster dose are the same as those authorized for a booster dose of the vaccine used for primary vaccination.

3 DOSAGE FORMS AND STRENGTHS

Janssen COVID-19 Vaccine is a suspension for intramuscular injection. A single-dose is 0.5 mL.

4 CONTRAINDICATIONS

Do not administer the Janssen COVID-19 Vaccine to individuals with a known history of severe allergic reaction (e.g., anaphylaxis) to any component of the Janssen COVID-19 Vaccine *[see Description (13)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Management of Acute Allergic Reactions

Appropriate medical treatment used to manage immediate allergic reactions must be immediately available in the event an acute anaphylactic reaction occurs following administration of the Janssen COVID-19 Vaccine.

Monitor Janssen COVID-19 Vaccine recipients for the occurrence of immediate adverse reactions according to the Centers for Disease Control and Prevention guidelines (*https://www.cdc.gov/vaccines/covid-19/clinical-considerations/managing-anaphylaxis.html*).

5.2 Thrombosis with thrombocytopenia

Reports of adverse events following use of the Janssen COVID-19 Vaccine under emergency use authorization suggest an increased risk of thrombosis involving the cerebral venous sinuses and other sites (including but not limited to the large blood vessels of the abdomen and the veins of the lower extremities) combined with thrombocytopenia and with onset of symptoms approximately one to two weeks after vaccination *[see Overall Safety Summary (6.2)]*. The reporting rate of thrombosis with thrombocytopenia following administration of the Janssen COVID-19 Vaccine has been highest in females ages 18 through 49 years; some cases have been fatal. The clinical course of these events shares features with autoimmune heparin-induced thrombocytopenia.

Specific risk factors for thrombosis with thrombocytopenia following administration of the Janssen COVID-19 Vaccine and the level of potential excess risk due to vaccination are under investigation. Based on currently available evidence, a causal relationship between thrombosis with thrombocytopenia and the Janssen COVID-19 Vaccine is plausible.

Healthcare professionals should be alert to the signs and symptoms of thrombosis with thrombocytopenia in individuals who receive the Janssen COVID-19 Vaccine. In individuals with suspected thrombosis with thrombocytopenia following administration of the Janssen COVID-19 Vaccine, the use of heparin may be harmful and alternative treatments may be needed. Consultation with hematology specialists is strongly recommended. The American Society of Hematology has published considerations relevant to the diagnosis and treatment of thrombosis with thrombocytopenia following administration of the Janssen COVID-19 Vaccine (*https://www.hematology.org/covid-19/vaccine-induced-immune-thrombotic-thrombocytopenia*).

Recipients of Janssen COVID-19 Vaccine should be instructed to seek immediate medical attention if they develop shortness of breath, chest pain, leg swelling, persistent abdominal pain, neurological symptoms (including severe or persistent headaches or blurred vision), or petechiae beyond the site of vaccination.

5.3 Guillain-Barré Syndrome

Reports of adverse events following use of the Janssen COVID-19 Vaccine under emergency use authorization suggest an increased risk of Guillain-Barré syndrome during the 42 days following vaccination.

5.4 Syncope

Syncope (fainting) may occur in association with administration of injectable vaccines. Procedures should be in place to avoid injury from fainting.

5.5 Altered Immunocompetence

Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the Janssen COVID-19 Vaccine.

5.6 Limitations of Vaccine Effectiveness

The Janssen COVID-19 Vaccine may not protect all vaccinated individuals.

6 OVERALL SAFETY SUMMARY

It is MANDATORY for vaccination providers to report to the Vaccine Adverse Event Reporting System (VAERS) all vaccine administration errors, all serious adverse events, cases of Multisystem Inflammatory Syndrome (MIS) in adults, and hospitalized or fatal cases of COVID-19 following vaccination with the Janssen COVID-19 Vaccine. To the extent feasible, provide a copy of the VAERS form to Janssen Biotech, Inc. Please see the REQUIREMENTS AND INSTRUCTIONS FOR REPORTING ADVERSE EVENTS AND VACCINE ADMINISTRATION ERRORS section for details on reporting to VAERS or Janssen Biotech, Inc.

Adverse Reactions in Clinical Trials

In study COV3001, the most common local solicited adverse reaction (≥10%) reported was injection site pain (48.6%). The most common systemic adverse reactions (≥10%) were headache (38.9%), fatigue (38.2%), myalgia (33.2%), and nausea (14.2%) (see Tables 1 to 4).

Severe allergic reactions, including anaphylaxis, have been reported following administration of the Janssen COVID-19 vaccine.

Adverse Reactions Identified during Post Authorization Use

Anaphylaxis and other severe allergic reactions, thrombosis with thrombocytopenia, Guillain-Barré syndrome, and capillary leak syndrome have been reported following administration of the Janssen COVID-19 Vaccine during mass vaccination outside of clinical trials.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Safety Primary vaccination

The safety of the Janssen COVID-19 Vaccine has been assessed in an ongoing Phase 3 Study, COV3001 (NCT04505722) (Study 1). A total of 43,783 individuals were enrolled in this study, of whom 21,895 adults aged 18 years and older received the Janssen COVID-19 Vaccine [Full Analysis Set (FAS)]. This study is being conducted in the United States (n=19,302), Brazil (n=7,278), South Africa (n=6,576), Colombia (n=4,248), Argentina (n=2,996), Peru (n=1,771), Chile (n=1,133), Mexico (n=479). In this study, 45.0% were female, 54.9% were male, 58.7% were White, 19.4% were Black or African American, 45.3% were Hispanic or Latino, 3.3% were Asian, 9.5% were American Indian/Alaska Native and 0.2% were Native Hawaiian or other Pacific Islander, 5.6% were from multiple racial groups and 1.4% were unknown races (see Table 5). The median age of individuals was 52.0 years (range: 18-100). There were 4,217 (9.6%) individuals who were SARS-CoV-2 seropositive at baseline and who were included in the study. In the United States, 838 of 19,302 (4.3%) individuals were SARS-CoV-2 seropositive. Demographic characteristics were similar among individuals who received the Janssen COVID-19 Vaccine and those who received saline placebo.

The safety subset includes 6,736 individuals (3,356 from the Janssen COVID-19 Vaccine group, 3,380 from the placebo group). The demographic profile in the safety subset was similar in terms of age and gender compared to the FAS. A larger percentage of individuals in the safety subset were White (83.4%) compared to the FAS (58.7%). Geographically, the safety subset was limited to individuals from the United States (51.4%), Brazil (38.5%) and South Africa (10.2%). Fewer individuals in the safety subset compared to the FAS were SARS-CoV-2 seropositive at baseline, 4.5% vs. 9.6%, and had at least one comorbidity 34.1% vs 40.8%.

Safety monitoring in the clinical study consisted of monitoring for: (1) solicited local and systemic reactions occurring in the 7 days following vaccination in a subset of individuals (safety subset),

(2) unsolicited adverse events (AEs) occurring in the 28 days following vaccination in the safety subset, (3) medically-attended AEs (MAAEs) occurring in the 6 months following vaccination in the entire study population (FAS), (4) serious AEs (SAEs) and AEs leading to study discontinuation for the duration of the study in the entire study population.

Solicited adverse reactions

Shown below are the frequencies of solicited local adverse reactions (Tables 1 and 2) and systemic adverse reactions (Tables 3 and 4) reported in adults by age group in the 7 days following vaccination in Study 1.

Table 1: Study 1: Solicited Local Adverse Reactions Reported in the 7 Days Following Primary Vaccination - Individuals 18 to 59 Years of Age

Adverse Reactions	Janssen COVID-19 Vaccine N=2,036 n(%)	Placebo N=2,049 n(%)
Injection Site Pain		
Any	1,193 (58.6)	357 (17.4)
Grade 3[a]	8 (0.4)	0
Injection Site Erythema		
Any (≥25 mm)	184 (9.0)	89 (4.3)
Grade 3[b]	6 (0.3)	2 (0.1)
Injection Site Swelling		
Any (≥25 mm)	142 (7.0)	32 (1.6)
Grade 3[b]	5 (0.2)	2 (0.1)

[a] Grade 3 injection site pain: Defined as incapacitating symptoms; inability to do work, school, or usual activities; use of narcotic pain reliever.

[b] Grade 3 injection site swelling and erythema: Defined as >100 mm.

Table 2: Study 1: Solicited Local Adverse Reactions Reported in the 7 Days Following Primary Vaccination - Individuals 60 Years of Age and Older

Adverse Reactions	Janssen COVID-19 Vaccine N=1,320 n(%)	Placebo N=1,331 n(%)
Injection Site Pain		
Any	439 (33.3)	207 (15.6)
Grade 3[a]	3 (0.2)	2 (0.2)
Injection Site Erythema		
Any (≥25 mm)	61 (4.6)	42 (3.2)
Grade 3[b]	1 (0.1)	0
Injection Site Swelling		
Any (≥25 mm)	36 (2.7)	21 (1.6)
Grade 3[b]	2 (0.2)	0

[a] Grade 3 injection site pain: Defined as incapacitating symptoms; inability to do work, school, or usual activities; use of narcotic pain reliever.

[b] Grade 3 injection site swelling and erythema: Defined as >100 mm.

Table 3: Study 1: Solicited Systemic Adverse Reactions Reported in the 7 Days Following Primary Vaccination - Individuals 18 to 59 Years of Age

Adverse Reactions	Janssen COVID-19 Vaccine N=2,036 n(%)	Placebo N=2,049 n(%)
Headache		
Any	905 (44.4)	508 (24.8)
Grade 3[a]	18 (0.9)	5 (0.2)
Fatigue		
Any	891 (43.8)	451 (22.0)
Grade 3[b]	25 (1.2)	4 (0.2)
Myalgia		
Any	796 (39.1)	248 (12.1)
Grade 3[b]	29 (1.4)	1 (<0.1)
Nausea		
Any	315 (15.5)	183 (8.9)
Grade 3[b]	3 (0.1)	3 (0.1)
Fever[c]		
Any	261 (12.8)	14 (0.7)
Grade 3	7 (0.3)	0
Use of antipyretic or pain medication	538 (26.4)	123 (6.0)

[a] Grade 3 headache: Defined as incapacitating symptoms; requires bed rest and/or results in loss of work, school, or cancellation of social activities; use of narcotic pain reliever.

[b] Grade 3 fatigue, myalgia, nausea: Defined as incapacitating symptoms; requires bed rest and/or results in loss of work, school, or cancellation of social activities; use of narcotic pain reliever.

[c] Fever of any grade: Defined as body temperature ≥38°C/100.4°F. Grade 3 fever: Defined as 39.0°C - 40.0°C (102.1°F - 104.0°F).

Table 4: Study 1: Solicited Systemic Adverse Reactions Reported in the 7 Days Following Primary Vaccination - Individuals 60 Years of Age and Older

Adverse Reactions	Janssen COVID-19 Vaccine N=1,320 n(%)	Placebo N=1,331 n(%)
Headache		
Any	401 (30.4)	294 (22.1)
Grade 3[a]	5 (0.4)	4 (0.3)
Fatigue		
Any	392 (29.7)	277 (20.8)
Grade 3[b]	10 (0.8)	5 (0.4)
Myalgia		
Any	317 (24.0)	182 (13.7)
Grade 3[b]	3 (0.2)	5 (0.4)
Nausea		
Any	162 (12.3)	144 (10.8)
Grade 3[b]	3 (0.2)	3 (0.2)
Fever[c]		
Any	41 (3.1)	6 (0.5)
Grade 3	1 (0.1)	0
Use of antipyretic or pain medication	130 (9.8)	68 (5.1)

[a] Grade 3 headache: Defined as incapacitating symptoms; requires bed rest and/or results in loss of work, school, or cancellation of social activities; use of narcotic pain reliever

[b] Grade 3 fatigue, myalgia, nausea: Defined as incapacitating symptoms; requires bed rest and/or results in loss of work, school, or cancellation of social activities; use of narcotic pain reliever.

[c] Fever of any grade: Defined as body temperature ≥38°C/100.4°F. Grade 3 fever: Defined as 39.0°C - 40.0°C (102.1°F - 104.0°F).

Solicited local and systemic adverse reactions reported following administration of the Janssen COVID-19 Vaccine had a median duration of 1 to 2 days.

Unsolicited adverse events

Individuals within the safety subset in Study 1 (N=6,736) were monitored for unsolicited adverse events (AEs) for 28 days following vaccination with 99.9% (N= 6,730) of individuals completing the full 28 days of follow-up. The proportion of individuals who reported one or more unsolicited AEs was similar among those in the Janssen COVID-19 Vaccine group (13.1%) and those in the placebo group (12.0%).

Serious Adverse Events (SAEs) and other events of interest

In Study 1, up to a cut-off date of January 22, 2021, 54.6% of individuals had follow-up duration of 8 weeks. The median follow-up duration for all individuals was 58 days. SAEs, excluding those related to confirmed COVID-19, were reported by 0.4% (n=83) of individuals who received the Janssen COVID-19 Vaccine (N= 21,895) and 0.4% (n=96) of individuals who received placebo (N= 21,888).

Additional adverse events of interest, including but not limited to allergic, neurologic, inflammatory, vascular, and autoimmune disorders, were analyzed among all adverse events collected through protocol-specified safety monitoring procedures as well as unsolicited reporting.

Urticaria (all non-serious) was reported in five vaccinated individuals and 1 individual who received placebo in the 7 days following vaccination. In addition, an SAE of hypersensitivity, not classified as anaphylaxis, was reported in 1 vaccinated individual with urticaria beginning two days following vaccination and angioedema of the lips with no respiratory distress beginning four days following vaccination. The event was likely related to the vaccine.

An SAE of severe pain in the injected arm, not responsive to analgesics, with immediate onset at time of vaccination, and that was ongoing 74 days following vaccination was reported in an individual who received the Janssen COVID-19 Vaccine. An SAE of severe generalized weakness, fever, and headache, with onset on the day following vaccination and resolution three days following vaccination was reported in an individual who received the Janssen COVID-19 Vaccine. Both SAEs are likely related to the vaccine.

Numerical imbalances, with more events in vaccine than placebo recipients, were observed for the following serious and other adverse events of interest in individuals receiving the vaccine or placebo, respectively:

- Thromboembolic events:
    - Deep vein thrombosis: 6 events (2 serious; 5 within 28 days of vaccination) vs. 2 events (1 serious; 2 within 28 days of vaccination).
    - Pulmonary embolism: 4 events (3 serious; 2 within 28 days of vaccination) vs. 1 event (serious and within 28 days of vaccination).
    - Transverse sinus thrombosis with thrombocytopenia: 1 event (serious, with onset of symptoms 8 days post- vaccination) vs. 0.

- Seizures: 4 events (1 serious; 4 within 28 days of vaccination) vs. 1 event (0 serious and 0 within 28 days following vaccination).
- Tinnitus: 6 events (0 serious; 6 within 28 days of vaccination, including 3 within 2 days of vaccination) vs. 0.

For these events, a causal relationship with the Janssen COVID-19 vaccine could not be determined based on Study 1. The assessment of causality was confounded by the presence of underlying medical conditions that may have predisposed individuals to these events. However, taking into consideration post-authorization experience, a causal relationship with Janssen COVID-19 Vaccine is plausible for thrombosis with thrombocytopenia *[see Warnings and Precautions (5.2) and Overall Safety Summary (6.2)]*.

There were no additional notable patterns or numerical imbalances between treatment groups for specific categories of serious adverse events (including neurologic, neuro-inflammatory, and cardiovascular events) that would suggest a causal relationship to the Janssen COVID-19 Vaccine.

Booster Dose Following Primary Vaccination with Janssen COVID-19 Vaccine

Overall, in 5 clinical studies conducted in Belgium, Brazil, Colombia, France, Germany, Japan, Netherlands, Philippines, South Africa, Spain, United Kingdom and United States, approximately 9,000 participants have received 2 doses of the Janssen COVID-19 Vaccine, administered at least 2 months apart and approximately 2,700 participants had at least 2 months of safety follow-up after the booster dose.

A randomized, double-blind, placebo-controlled Phase 2 study, COV2001 (NCT04535453) (Study 2), evaluated the frequency and severity of local and systemic adverse reactions within 7 days of administration of a booster dose of the Janssen COVID-19 Vaccine administered approximately 2 months after the primary vaccination in healthy adults 18 through 55 years of age and adults 65 years and older in good or stable health. A total of 141 individuals received at least one dose of the vaccine and 137 received both the primary vaccination and the booster dose at an interval of 2 months. The median age of individuals was 48 years, and 48 individuals (34%) were 65 years of age and older. Data on solicited adverse reactions after the primary vaccination and after a booster dose are shown in Tables 5-8.

Solicited adverse reactions

Table 5: Study 2 - Solicited Local Adverse Reactions Reported in the 7 Days Following the Primary Vaccination or the Booster Dose - Individuals 18 through 55 Years of Age

Adverse Reactions	Primary Vaccination N=93 n(%)	Booster Dose N=89 n(%)
Injection Site Pain		
Any	58 (62.4%)	53 (59.6%)
Grade 3[a]	0	1 (1.1%)
Injection Site Erythema		
Any (≥25 mm)	1 (1.1%)	1 (1.1%)
Grade 3[b]	0	0
Injection Site Swelling		
Any (≥25 mm)	1 (1.1%)	0
Grade 3[b]	0	0

[a] Grade 3 injection site pain: Defined as incapacitating symptoms; inability to do work, school, or usual activities; use of narcotic pain reliever.

[b] Grade 3 injection site swelling and erythema: Defined as >100 mm.

Table 6: Study 2 - Solicited Local Adverse Reactions Reported in the 7 Days Following the Primary Vaccination or the Booster Dose - Individuals 65 Years of Age and Older

Adverse Reactions	Primary Vaccination N=48 n(%)	Booster Dose N=48 n(%)
Injection Site Pain		
Any	17 (35.4%)	10 (20.8%)
Grade 3[a]	0	0
Injection Site Erythema		
Any (≥25 mm)	0	0
Grade 3[b]	0	0
Injection Site Swelling		
Any (≥25 mm)	0	0
Grade 3[b]	0	0

[a] Grade 3 injection site pain: Defined as incapacitating symptoms; inability to do work, school, or usual activities; use of narcotic pain reliever.

[b] Grade 3 injection site swelling and erythema: Defined as >100 mm.

Table 7: Study 2 - Solicited Systemic Adverse Reactions Reported in the 7 Days Following the Primary Vaccination or the Booster Dose - Individuals 18 through 55 Years of Age

Adverse Reactions	Primary Vaccination N=93 n(%)	Booster Dose N=89 n(%)
Headache		
Any	49 (52.7%)	37 (41.6%)
Grade 3[a]	2 (2.2%)	1 (1.1%)
Fatigue		
Any	55 (59.1%)	46 (51.7%)
Grade 3[b]	1 (1.1%)	0
Myalgia		
Any	44 (47.3%)	32 (36.0%)
Grade 3[b]	3 (3.2%)	2 (2.2%)
Nausea		
Any	13 (14.0%)	9 (10.1%)
Grade 3[b]	1 (1.1%)	0
Fever[c]		
Any	13 (14.0%)	5 (5.6%)
Grade 3	1 (1.1%)	0

[a] Grade 3 headache: Defined as incapacitating symptoms; requires bed rest and/or results in loss of work, school, or cancellation of social activities; use of narcotic pain reliever.

[b] Grade 3 fatigue, myalgia, nausea: Defined as incapacitating symptoms; requires bed rest and/or results in loss of work, school, or cancellation of social activities; use of narcotic pain reliever.

[c] Fever of any grade: Defined as body temperature ≥38°C/100.4°F. Grade 3 fever: Defined as 39.0°C - 40.0°C (102.1°F - 104.0°F).

Table 8: Study 2 - Solicited Systemic Adverse Reactions Reported in the 7 Days Following the Primary Vaccination or the Booster Dose - Individuals 65 Years of Age and Older

Adverse Reactions	Primary Vaccination N=48 n(%)	Booster Dose N=48 n(%)
Headache		
Any	**9 (18.8%)**	**13 (27.1%)**
Grade 3[a]	**0**	**0**
Fatigue		
Any	9 (18.8%)	16 (33.3%)
Grade 3[b]	0	0
Myalgia		
Any	4 (8.3%)	5 (10.4%)
Grade 3[b]	0	0
Nausea		
Any	0	1 (2.1%)
Grade 3[b]	0	0
Fever[c]		
Any	1 (2.1%)	0
Grade 3	0	0

[a] Grade 3 headache: Defined as incapacitating symptoms; requires bed rest and/or results in loss of work, school, or cancellation of social activities; use of narcotic pain reliever

[b] Grade 3 fatigue, myalgia, nausea: Defined as incapacitating symptoms; requires bed rest and/or results in loss of work, school, or cancellation of social activities; use of narcotic pain reliever.

[c] Fever of any grade: Defined as body temperature ≥38°C/100.4°F. Grade 3 fever: Defined as 39.0°C - 40.0°C (102.1°F - 104.0°F).

Unsolicited adverse events

An overall assessment of Janssen's safety analyses from studies evaluating 2 doses of Janssen COVID-19 Vaccine did not reveal new safety concerns following a booster dose, as compared with adverse reactions reported following the single-dose primary vaccination.

Booster Dose Following Primary Vaccination with Another Authorized or Approved COVID-19 Vaccine

The safety of a Janssen COVID-19 Vaccine booster dose in individuals who completed primary vaccination with another authorized or approved COVID-19 Vaccine (heterologous booster dose) is inferred from the safety of a Janssen COVID-19 Vaccine booster dose administered following completion of Janssen COVID-19 Vaccine primary vaccination (homologous booster dose) and from data from an independent Phase 1/2 open-label clinical trial (NCT04889209) conducted in the United States that evaluated a heterologous booster dose of the Janssen COVID-19 Vaccine. In this study, adults who had completed primary vaccination with a Moderna COVID-19 Vaccine 2-dose series (N=151), a Janssen COVID-19 Vaccine single dose (N=156), or a Pfizer-BioNTech COVID-19 Vaccine 2-dose series (N=151) at least 12 weeks prior to enrollment and who reported no history of SARS-CoV-2 infection were randomized 1:1:1 to receive a booster dose of one of three vaccines: Moderna COVID-19 Vaccine, Janssen COVID-19 Vaccine, or Pfizer-BioNTech COVID-19 Vaccine. Adverse events were assessed through 28 days after the booster dose. An overall review of adverse reactions reported following the Janssen COVID-19 Vaccine heterologous booster dose did not identify any new safety concerns, as compared with adverse reactions reported following a Janssen COVID-19 Vaccine primary vaccination or homologous booster dose.

6.2 Post Authorization Experience

The following adverse reactions have been identified during post-authorization use of the Janssen COVID-19 Vaccine. Because these reactions are reported voluntarily, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.

Blood and Lymphatic System Disorders: Thrombosis with thrombocytopenia, Lymphadenopathy, Immune thrombocytopenic purpura.

Cardiac disorders: Myocarditis, Pericarditis.

Ear and labyrinth disorders: Tinnitus.

Gastrointestinal disorders: Diarrhea, Vomiting.

Immune System Disorders: Allergic reactions, including anaphylaxis.

Nervous System Disorders: Guillain-Barré syndrome, Syncope, Paresthesia, Hypoesthesia.

Vascular Disorders: Capillary leak syndrome, Thrombosis with thrombocytopenia, Venous thromboembolism (with or without thrombocytopenia).

8 REQUIREMENTS AND INSTRUCTIONS FOR REPORTING ADVERSE EVENTS AND VACCINE ADMINISTRATION ERRORS

See Overall Safety Summary (Section 6) for additional information.

The vaccination provider enrolled in the federal COVID-19 Vaccination Program is responsible for MANDATORY reporting of the listed events following Janssen COVID-19 Vaccine administration to the Vaccine Adverse Event Reporting System (VAERS):

- Vaccine administration errors whether or not associated with an adverse event,
- Serious adverse events* (irrespective of attribution to vaccination),
- Cases of Multisystem Inflammatory Syndrome (MIS) in adults,
- Cases of COVID-19 that result in hospitalization or death.

* Serious Adverse Events are defined as:
- Death;
- A life-threatening adverse event;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect;
- An important medical event that based on appropriate medical judgement may jeopardize the individual and may require medical or surgical intervention to prevent one of the outcomes listed above.

Instructions for Reporting to VAERS

The vaccination provider enrolled in the federal COVID-19 Vaccination Program should complete and submit a VAERS form to FDA using one of the following methods:

- Complete and submit the report online: https://vaers.hhs.gov/reportevent.html, or
- If you are unable to submit this form electronically, you may fax it to VAERS at 1-877-721-0366. If you need additional help submitting a report you may call the VAERS toll-free information line at 1-800-822-7967 or send an email to info@vaers.org.

IMPORTANT: When reporting adverse events or vaccine administration errors to VAERS, please complete the entire form with detailed information. It is important that the information reported to FDA be as detailed and complete as possible. Information to include:

- Patient demographics, (e.g., patient name, date of birth),
- Pertinent medical history,
- Pertinent details regarding admission and course of illness,
- Concomitant medications,

- Timing of adverse event(s) in relationship to administration of Janssen COVID-19 vaccine,
- Pertinent laboratory and virology information,
- Outcome of the event and any additional follow-up information if it is available at the time of the VAERS report. Subsequent reporting of follow-up information should be completed if additional details become available.

The following steps are highlighted to provide the necessary information for safety tracking:

1. In Box 17, provide information on Janssen COVID-19 Vaccine and any other vaccines administered on the same day; and in Box 22, provide information on any other vaccines received within one month prior.
2. In Box 18, description of the event:
    a. Write "Janssen COVID-19 Vaccine EUA" as the first line.
    b. Provide a detailed report of vaccine administration error and/or adverse event. It is important to provide detailed information regarding the patient and adverse event/medication error for ongoing safety evaluation of this unapproved vaccine. Please see information to include listed above.
3. Contact information:
    a. In Box 13, provide the name and contact information of the prescribing healthcare provider or institutional designee who is responsible for the report.
    b. In Box 14, provide the name and contact information of the best doctor/healthcare professional to contact about the adverse event.
    c. In Box 15, provide the address of the facility where vaccine was given (NOT the healthcare provider's office address).

Other Reporting Instructions

Vaccination providers may report to VAERS other adverse events that are not required to be reported using the contact information above.

To the extent feasible, report adverse events to Janssen Biotech, Inc. using the contact information below or by providing a copy of the VAERS form to Janssen Biotech, Inc:

e-mail	Fax number	Telephone numbers
JNJvaccineAE@its.jnj.com	215-293-9955	US Toll Free: 1-800-565-4008 US Toll: (908) 455-9922

10 DRUG INTERACTIONS

There are no data to assess the concomitant administration of the Janssen COVID-19 Vaccine with other vaccines.

11 USE IN SPECIFIC POPULATIONS

11.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Janssen COVID-19 Vaccine during pregnancy. Women who are vaccinated with Janssen COVID-19 Vaccine during pregnancy are encouraged to enroll in the registry by visiting https://c-viper.pregistry.com.

Risk Summary

All Pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Available data on Janssen COVID-19 Vaccine administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

In a reproductive developmental toxicity study female rabbits were administered 1 mL of the Janssen COVID-19 Vaccine (a single human dose is 0.5 mL) by intramuscular injection 7 days prior to mating and on Gestation Days 6 and 20 (i.e., one vaccination during early and late gestation, respectively). No vaccine related adverse effects on female fertility, embryo-fetal or postnatal development up to Postnatal Day 28 were observed.

11.2 Lactation

Risk Summary

Data are not available to assess the effects of Janssen COVID-19 Vaccine on the breastfed infant or on milk production/excretion.

11.3 Pediatric Use

Emergency Use Authorization of the Janssen COVID-19 Vaccine does not include use in individuals younger than 18 years of age.

11.4 Geriatric Use

Clinical studies of Janssen COVID-19 Vaccine included individuals 65 years of age and older and their data contributes to the overall assessment of safety and efficacy *[see Overall Safety Summary (6.1) and Clinical Trial Results and Supporting Data for EUA (18)]*. Of the 21,895 individuals who received a single-dose of the Janssen COVID-19 Vaccine in COV3001, 19.5% (n=4,259) were 65 years of age and older and 3.7% (n=809) were 75 years of age and older. No overall differences in safety or efficacy were observed between individuals 65 years of age and older and younger individuals.

13 DESCRIPTION

The Janssen COVID-19 Vaccine is a colorless to slightly yellow, clear to very opalescent sterile suspension for intramuscular injection. It contains no visible particulates. The vaccine consists of a replication-incompetent recombinant adenovirus type 26 (Ad26) vector expressing the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) spike (S) protein in a stabilized conformation.

The Ad26 vector expressing the SARS-CoV-2 S protein is grown in PER.C6 TetR cells, in media containing amino acids and no animal-derived proteins. After propagation, the vaccine is processed through several purification steps, formulated with inactive ingredients and filled into vials.

Each 0.5 mL dose of Janssen COVID-19 Vaccine is formulated to contain 5×10^{10} virus particles (VP) and the following inactive ingredients: citric acid monohydrate (0.14 mg), trisodium citrate dihydrate (2.02 mg), ethanol (2.04 mg), 2-hydroxypropyl-β-cyclodextrin (HBCD) (25.50 mg), polysorbate-80 (0.16 mg), sodium chloride (2.19 mg). Each dose may also contain residual amounts of host cell proteins (≤0.15 mcg) and/or host cell DNA (≤3 ng).

Janssen COVID-19 Vaccine does not contain a preservative.

The vial stoppers are not made with natural rubber latex.

14 CLINICAL PHARMACOLOGY

14.1 Mechanism of Action

The Janssen COVID-19 Vaccine is composed of a recombinant, replication-incompetent human adenovirus type 26 vector that, after entering human cells, expresses the SARS-CoV-2 spike (S) antigen without virus propagation. An immune response elicited to the S antigen protects against COVID-19.

18 CLINICAL TRIAL RESULTS AND SUPPORTING DATA FOR EUA

18.1 Efficacy of Primary Vaccination

A primary analysis (cut-off date January 22, 2021) of a multicenter, randomized, double-blind, placebo-controlled Phase 3 Study (Study 1) was conducted in the United States, South Africa, Brazil, Chile, Argentina, Colombia, Peru and Mexico to assess the efficacy, safety, and immunogenicity of a single-dose of the Janssen COVID-19 Vaccine for the prevention of COVID-19 in adults aged 18 years and older. Randomization was stratified by age (18-59 years, 60 years and older) and presence or absence of comorbidities associated with an increased risk of progression to severe COVID-19. The study allowed for the inclusion of individuals with stable pre-existing medical conditions, defined as disease not requiring significant change in therapy during the 3 months preceding vaccination, as well as individuals with stable human immunodeficiency virus (HIV) infection.

A total of 44,325 individuals were randomized equally to receive Janssen COVID-19 Vaccine or saline placebo. Individuals are planned to be followed for up to 24 months, for assessments of safety and efficacy against COVID-19.

Revised: Oct/2021

The primary efficacy analysis population of 39,321 individuals (19,630 in the Janssen COVID-19 Vaccine group and 19,691 in the placebo group) included 38,059 SARS-CoV-2 seronegative individuals at baseline and 1,262 individuals with an unknown serostatus. Demographic and baseline characteristics were similar among individuals who received the Janssen COVID-19 Vaccine and those who received placebo (see Table 9).

Table 9: Summary of Demographics and Baseline Characteristics - Primary Efficacy Analysis Population

	Janssen COVID-19 Vaccine (N=19,630) n (%)	Placebo (N=19,691) n (%)
Sex		
Male	10,924 (55.6)	10,910 (55.4)
Female	8,702 (44.3)	8,777 (44.6)
Age (years)		
Mean (SD)	51.1 (15.0)	51.2 (15.0)
Median	52.0	53.0
Min, max	(18; 100)	(18; 94)
Age group		
≥18 to 59 years of age	12,830 (65.4)	12,881 (65.4)
≥60 years of age	6,800 (34.6)	6,810 (34.6)
≥65 years of age	3,984 (20.3)	4,018 (20.4)
≥75 years of age	755 (3.8)	693 (3.5)
Race[a]		
White	12,200 (62.1)	12,216 (62.0)
Black or African American	3,374 (17.2)	3,390 (17.2)
Asian	720 (3.7)	663 (3.4)
American Indian/Alaska Native[b]	1,643 (8.4)	1,628 (8.3)
Native Hawaiian or other Pacific Islander	54 (0.3)	45 (0.2)
Multiple	1,036 (5.3)	1,087 (5.5)
Unknown	262 (1.3)	272 (1.4)
Not reported	341 (1.7)	390 (2.0)
Ethnicity		
Hispanic or Latino	8,793 (44.8)	8,936 (45.4)
Not Hispanic or Latino	10,344 (52.7)	10,259 (52.1)
Unknown	173 (0.9)	162 (0.8)
Not reported	319 (1.6)	333 (1.7)
Region		
Northern America (United States)	9,185 (46.8)	9,171 (46.6)
Latin America	7,967 (40.6)	8,014 (40.7)
Southern Africa (South Africa)	2,478 (12.6)	2,506 (12.7)
Comorbidities[c]		
Yes	7,830 (39.9)	7,867 (40.0)
No	11,800 (60.1)	11,824 (60.0)

[a] Some individuals could be classified in more than one category.

[b] Including 175 individuals in the United States, which represents 1% of the population recruited in the United States.

[c] Number of individuals who have 1 or more comorbidities at baseline that increase the risk of progression to severe/critical COVID-19: Obesity defined as BMI ≥30 kg/m^2 (27.5%), hypertension (10.3%), type 2 diabetes (7.2%), stable/well-controlled HIV infection (2.5%), serious heart conditions (2.4%), asthma (1.3%), and in ≤1% of individuals: cancer, cerebrovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, cystic fibrosis, immunocompromised state (weakened immune system) from blood or organ transplant, liver disease, neurologic conditions, pulmonary fibrosis, sickle cell disease, thalassemia and type 1 diabetes, regardless of age.

Efficacy Against COVID-19

The co-primary endpoints evaluated the first occurrence of moderate to severe/critical COVID-19 with onset of symptoms at least 14 days and at least 28 days after vaccination. Moderate to severe/critical COVID-19 was molecularly confirmed by a central laboratory based on a positive SARS-CoV-2 viral RNA result using a polymerase chain reaction (PCR)-based test.

- Moderate COVID-19 was defined based on the following criteria: the individual must have experienced any one of the following new or worsening signs or symptoms: respiratory rate ≥20 breaths/minute, abnormal saturation of oxygen (SpO2) but still >93% on room air at sea level, clinical or radiologic evidence of pneumonia, radiologic evidence of deep vein thrombosis (DVT), shortness of breath or difficulty breathing OR any two of the following new or worsening signs or symptoms: fever (≥38.0°C or ≥100.4°F), heart rate ≥90 beats/minute, shaking chills or rigors, sore throat, cough, malaise, headache, muscle pain (myalgia), gastrointestinal symptoms, new or changing olfactory or taste disorders, red or bruised appearing feet or toes.

- Severe/critical COVID-19 was defined based on the following criteria: the individual must have experienced any one of the following at any time during the course of observation: clinical signs at rest indicative of severe systemic illness (respiratory rate ≥30 breaths/minute, heart rate ≥125 beats/minute, oxygen saturation (SpO2) ≤93% on room air at sea level, or partial pressure of oxygen/fraction of inspired oxygen (PaO2/FiO2) <300 mmHg), respiratory failure (defined as needing high-flow oxygen, non-invasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation [ECMO]), evidence of shock (defined as systolic blood pressure <90 mmHg, diastolic blood pressure <60 mmHg, or requiring vasopressors), significant acute renal, hepatic, or neurologic dysfunction, admission to intensive care unit (ICU), death.

Final determination of severe/critical COVID-19 cases were made by an independent adjudication committee.

Primary analysis

The median length of follow up for efficacy for individuals in the study was 8 weeks post-vaccination. Vaccine Efficacy (VE) for the co-primary endpoints against moderate to severe/critical COVID-19 in individuals who were seronegative or who had an unknown serostatus at baseline was 66.9% (95% CI: 59.0; 73.4) at least 14 days after vaccination and 66.1% (95% CI: 55.0; 74.8) at least 28 days after vaccination (see Table 10).

Table 10: Analyses of Vaccine Efficacy Against Centrally Confirmed Moderate to Severe/Critical COVID-19 – With Onset at Least 14 Days and at Least 28 Days Post-Vaccination - Primary Efficacy Analysis Population

	Janssen COVID-19 Vaccine N=19,630		Placebo N=19,691		
Subgroup	COVID-19 Cases (n)	Person-Years	COVID-19 Cases (n)	Person-Years	% Vaccine Efficacy (95% CI)
14 days post-vaccination					
All subjects[a]	116	3116.6	348	3096.1	66.9 (59.0; 73.4)
18 to 59 years of age	95	2106.8	260	2095.0	63.7 (53.9; 71.6)
60 years and older	21	1009.8	88	1001.2	76.3 (61.6; 86.0)
28 days post-vaccination					
All subjects[a]	66	3102.0	193	3070.7	66.1 (55.0; 74.8)[b]
18 to 59 years of age	52	2097.6	152	2077.0	66.1 (53.3; 75.8)
60 years and older	14	1004.4	41	993.6	66.2 (36.7; 83.0)

[a] Co-primary endpoint.

[b] The adjusted CI implements type I error control for multiple testing and is presented upon meeting the prespecified testing conditions.

Vaccine efficacy against severe/critical COVID-19 at least 14 days after vaccination was 76.7% (95% CI: 54.6; 89.1) and 85.4% (95% CI: 54.2; 96.9) at least 28 days after vaccination (see Table 11).

Table 11: Analyses of Vaccine Efficacy: Secondary Endpoints of Centrally Confirmed Severe/Critical COVID-19 – in Adults 18 Years of Age and Older With Onset at Least 14 Days and at Least 28 Days Post-Vaccination – Primary Efficacy Analysis Population

	Janssen COVID-19 Vaccine N=19,630		Placebo N=19,691		
Subgroup	COVID-19 Cases (n)	Person-Years	COVID-19 Cases (n)	Person-Years	% Vaccine Efficacy (95% CI)
14 days post-vaccination					
Severe/critical	14	3125.1	60	3122.0	76.7 (54.6; 89.1)[a]
28 days post-vaccination					
Severe/critical	5	3106.2	34	3082.6	85.4 (54.2; 96.9)[a]

[a] The adjusted CI implements type I error control for multiple testing and is presented upon meeting the prespecified testing conditions.

Among all COVID-19 cases with onset at least 14 days post vaccination, including cases diagnosed by a positive PCR from a local laboratory and still awaiting confirmation at the central laboratory (as of January 22, 2021), there were 2 COVID-19 related hospitalizations in the vaccine group (with none after 28 days) and 29 in the placebo group (with 16 after 28 days).

As of the primary analysis cut-off date of January 22, 2021, there were no COVID-19-related deaths reported in Janssen COVID-19 Vaccine recipients compared to 5 COVID-19-related deaths reported in placebo recipients, who were SARS-CoV-2 PCR negative at baseline.

Janssen COVID-19 Vaccine Efficacy in Countries With Different Circulating SARS-CoV-2 Variants.

Exploratory subgroup analyses of vaccine efficacy against moderate to severe/critical COVID-19 and severe/critical COVID-19 for Brazil, South Africa, and the United States were conducted (see Table 12). For the subgroup analyses, all COVID-19 cases accrued up to the primary efficacy analysis data cut-off date, including cases confirmed by the central laboratory and cases with documented positive SARS-CoV-2 PCR from a local laboratory which are still awaiting confirmation by the central laboratory, were included. The concordance rate observed up to the data cut-off date between the PCR results from the local laboratory and the central laboratory was 90.3%.

Table 12: Summary of Vaccine Efficacy against Moderate to Severe/Critical and Severe/Critical COVID-19 for Countries With >100 Reported Moderate to Severe/Critical Cases

		Severity	
	Onset	Moderate to Severe/Critical Point estimate (95% CI)	Severe/Critical Point estimate (95% CI)
US	at least **14 days** after vaccination	74.4% (65.0; 81.6)	78.0% (33.1; 94.6)
	at least **28 days** after vaccination	72.0% (58.2;81.7)	85.9% (-9.4; 99.7)
Brazil	at least **14 days** after vaccination	66.2% (51.0; 77.1)	81.9% (17.0; 98.1)
	at least **28 days** after vaccination	68.1% (48.8; 80.7)	87.6% (7.8; 99.7)
South Africa	at least **14 days** after vaccination	52.0% (30.3; 67.4)	73.1% (40.0; 89.4)
	at least **28 days** after vaccination	64.0% (41.2; 78.7)	81.7% (46.2; 95.4)

Strain sequencing was conducted on available samples with sufficient viral load from centrally confirmed COVID-19 cases (one sequence per case). As of February 12, 2021, samples from 71.7% of central laboratory confirmed primary analysis cases had been sequenced [United States (73.5%), South Africa (66.9%) and Brazil (69.3%)]. In the United States, 96.4% of strains were identified as the Wuhan-H1 variant D614G; in South Africa, 94.5% of strains were identified as the 20H/501Y.V2 variant (B.1.351 lineage); in Brazil, 69.4% of strains were identified to be a variant of the P.2 lineage and 30.6% of strains were identified as the Wuhan-H1 variant D614G. As of February 12, 2021, SARS-CoV-2 variants from the B1.1.7 or P.1 lineages were not found in any of the sequenced samples.

18.2 Immunogenicity of a Booster Dose following Primary Vaccination with Janssen COVID-19 Vaccine

In Study 2, individuals 18 through 55 years of age and 65 years and older received a booster dose of the Janssen COVID-19 Vaccine approximately 2 months after the primary vaccination. Immunogenicity was assessed by measuring neutralizing antibodies to SARS-CoV-2 Victoria/1/2020 strain using a qualified wild-type virus neutralization assay (wtVNA). Immunogenicity data are available from 39 individuals, of whom 15 were 65 years of age and older, and are summarized in Table 13. Based on a limited number of individuals from this study, a similar fold-rise in neutralizing antibody titers from pre-booster to 14 and 28 days post-booster

was observed between individuals 18 through 55 years of age and individuals 65 years of age and older.

Table 13. Study 2 - SARS-CoV-2 Neutralization Wild Type VNA-VICTORIA/1/2020 (IC50), , Per Protocol Immunogenicity Set*

	Baseline (Day 1)	28 Days Post-Primary Vaccination (Day 29)	Pre-Booster Dose (Day 57)	14 Days Post-Booster Dose (Day 71)	28 Days Post-Booster Dose (Day 85)
N	38	39	39	39	38
Geometric mean titer (95% CI)	<LLOQ (<LLOQ, <LLOQ)	260 (196, 346)	212 (142, 314)	518 (354, 758)	424 (301, 597)
Geometric mean fold increase (95% CI) from baseline	n/a	4.4 (3.3, 5.7)	3.7 (2.6, 5.2)	8.8 (6.1, 12.8)	7.4 (5.4, 10.2)
Geometric mean fold increase (95% CI) from day 29	n/a	n/a	0.9 (0.7; 1.1)	2.0 (1.5; 2.7)	1.6 (1.2; 2.1)
Geometric mean fold increase (95% CI) from pre-booster	n/a	n/a	n/a	2.3 (1.7, 3.1)	1.8 (1.4, 2.4)

LLOQ = lower limit of quantification

* PPI set: The per protocol immunogenicity population includes all randomized and vaccinated participants for whom immunogenicity data are available excluding participants with major protocol deviations expected to impact the immunogenicity outcomes. In addition, samples obtained after missed vaccinations or participants with SARS-CoV-2 infection occurring after screening were excluded from the analysis.

18.3 Immunogenicity of a Booster Dose Following Primary Vaccination with Another Authorized or Approved COVID-19 Vaccine

Effectiveness of a Janssen COVID-19 Vaccine booster dose in individuals who completed primary vaccination with another authorized or approved COVID-19 Vaccine (heterologous booster dose) is inferred from immunogenicity data supporting effectiveness of a Janssen COVID-19 Vaccine booster dose administered following completion of Janssen COVID-19 Vaccine primary vaccination and from immunogenicity data from an independent Phase 1/2 open-label clinical trial (NCT04889209) conducted in the United States that evaluated a heterologous booster dose of the Janssen COVID-19 Vaccine. In this study, adults who had completed primary vaccination with a Moderna COVID-19 Vaccine 2-dose series (N=151), a Janssen COVID-19 Vaccine single dose (N=156), or a Pfizer-BioNTech COVID-19 Vaccine 2-dose series (N=151) at least 12 weeks prior to enrollment and who reported no history of SARS-CoV-2 infection were randomized 1:1:1 to receive a booster dose of one of three vaccines: Moderna COVID-19 Vaccine, Janssen COVID-19 Vaccine, or Pfizer-BioNTech COVID-19 Vaccine. Neutralizing antibody titers, as measured by a pseudovirus neutralization assay using a lentivirus expressing the SARS-CoV-2 Spike protein with D614G mutation, were assessed on Day 1 prior to administration of the booster dose and on Day 15 after the booster dose. A booster response to the Janssen COVID-19 Vaccine was demonstrated regardless of primary vaccination.

19 HOW SUPPLIED/STORAGE AND HANDLING

Janssen COVID-19 Vaccine is supplied in a carton of 10 multi-dose vials (NDC 59676-580-15). A maximum of 5 doses can be withdrawn from the multi-dose vial.

Revised: Oct/2021

The storage and handling information in this Fact Sheet supersedes the storage and handling information on the carton and vial labels.

Storage Prior to First Puncture of the Vaccine Vial

Store unpunctured multi-dose vials of the Janssen COVID-19 Vaccine at 2°C to 8°C (36°F to 46°F) and protect from light. Do not store frozen.

Unpunctured vials of Janssen COVID-19 Vaccine may be stored between 9°C to 25°C (47°F to 77°F) for up to 12 hours.

The Janssen COVID-19 Vaccine is initially stored frozen by the manufacturer, then shipped at 2°C to 8°C (36°F to 46°F). If vaccine is still frozen upon receipt, thaw at 2°C to 8°C (36°F to 46°F). If needed immediately, thaw at room temperature (maximally 25°C/77°F). At room temperature (maximally 25°C/77°F), a carton of 10 vials will take approximately 4 hours to thaw, and an individual vial will take approximately 1 hour to thaw. Do not refreeze once thawed.

Storage After First Puncture of the Vaccine Vial

After the first dose has been withdrawn, hold the vial between 2° to 8°C (36° to 46°F) for up to 6 hours or at room temperature (maximally 25°C/77°F) for up to 2 hours. Discard the vial if vaccine is not used within these times.

20 PATIENT COUNSELING INFORMATION

Advise the recipient or caregiver to read the Fact Sheet for Recipients and Caregivers.

The vaccination provider must include vaccination information in the state/local jurisdiction's Immunization Information System (IIS) or other designated system. Advise recipient or caregiver that more information about IISs can be found at: https://www.cdc.gov/vaccines/programs/iis/about.html.

21 CONTACT INFORMATION

For general questions or to access the most recent Janssen COVID-19 Vaccine Fact Sheets, scan the QR code using your device, visit www.janssencovid19vaccine.com or call the telephone numbers provided below.

QR Code	Fact Sheets Website	Telephone numbers
	www.janssencovid19vaccine.com.	US Toll Free: 1-800-565-4008 US Toll: 1-908-455-9922

This Full EUA Prescribing Information may have been updated. For the most recent Full EUA Prescribing Information, please see www.janssencovid19vaccine.com.

Revised: Oct/2021

Manufactured by:
Janssen Biotech, Inc.
a Janssen Pharmaceutical Company of Johnson & Johnson
Horsham, PA 19044, USA

Revised: Oct/20/2021

Revised: Oct/20/2021

Exhibit K

U.S. FOOD & DRUG ADMINISTRATION

Our STN: BL 125742/0 **BLA APPROVAL**

BioNTech Manufacturing GmbH August 23, 2021
Attention: Amit Patel
Pfizer Inc.
235 East 42nd Street
New York, NY 10017

Dear Mr. Patel:

Please refer to your Biologics License Application (BLA) submitted and received on May 18, 2021, under section 351(a) of the Public Health Service Act (PHS Act) for COVID-19 Vaccine, mRNA.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2229 to BioNTech Manufacturing GmbH, Mainz, Germany, under the provisions of section 351(a) of the PHS Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product, COVID-19 Vaccine, mRNA, which is indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older.

The review of this product was associated with the following National Clinical Trial (NCT) numbers: NCT04368728 and NCT04380701.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture COVID-19 Vaccine, mRNA drug substance at Wyeth BioPharma Division of Wyeth Pharmaceuticals LLC, 1 Burtt Road, Andover, Massachusetts. The final formulated product will be manufactured, filled, labeled and packaged at Pfizer Manufacturing Belgium NV, Rijksweg 12, Puurs, Belgium and at Pharmacia & Upjohn Company LLC, 7000 Portage Road, Kalamazoo, Michigan. The diluent, 0.9% Sodium Chloride Injection, USP, will be manufactured at Hospira, Inc., (b) (4) and at Fresenius Kabi USA, LLC, (b) (4) .

You may label your product with the proprietary name, COMIRNATY, and market it in 2.0 mL glass vials, in packages of 25 and 195 vials.
We did not refer your application to the Vaccines and Related Biological Products Advisory Committee because our review of information submitted in your BLA, including the clinical study design and trial results, did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

DATING PERIOD

The dating period for COVID-19 Vaccine, mRNA shall be 9 months from the date of manufacture when stored between -90ºC to -60ºC (-130ºF to -76ºF). The date of manufacture shall be no later than the date of final sterile filtration of the formulated drug product (at Pharmacia & Upjohn Company LLC in Kalamazoo, Michigan, the date of manufacture is defined as the date of sterile filtration for the final drug product; at Pfizer Manufacturing Belgium NV in Puurs, Belgium, it is defined as the date of the (b) (4) Following the final sterile filtration, (b) (4) , no reprocessing/reworking is allowed without prior approval from the Agency. The dating period for your drug substance shall be (b) (4) when stored at (b) (4) We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

FDA LOT RELEASE

Please submit final container samples of the product in final containers together with protocols showing results of all applicable tests. You may not distribute any lots of product until you receive a notification of release from the Director, Center for Biologics Evaluation and Research (CBER).

BIOLOGICAL PRODUCT DEVIATIONS

You must submit reports of biological product deviations under 21 CFR 600.14. You should identify and investigate all manufacturing deviations promptly, including those associated with processing, testing, packaging, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to the Director, Office of Compliance and Biologics Quality, electronically through the eBPDR web application or at the address below. Links for the instructions on completing the electronic form (eBPDR) may be found on CBER's web site at https://www.fda.gov/vaccines-blood-biologics/report-problem-center-biologics-evaluation-research/biological-product-deviations:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center

10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

MANUFACTURING CHANGES

You must submit information to your BLA for our review and written approval under 21 CFR 601.12 for any changes in, including but not limited to, the manufacturing, testing, packaging or labeling of COVID-19 Vaccine, mRNA, or in the manufacturing facilities.

LABELING

We hereby approve the draft content of labeling including Package Insert, submitted under amendment 74, dated August 21, 2021, and the draft carton and container labels submitted under amendment 63, dated August 19, 2021.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the final content of labeling (21 CFR 601.14) in Structured Product Labeling (SPL) format via the FDA automated drug registration and listing system, (eLIST) as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the Package Insert submitted on August 21, 2021. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As* at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELS

Please electronically submit final printed carton and container labels identical to the carton and container labels submitted on August 19, 2021, according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-regulatory-submissions-electronic-format-certain-human-pharmaceutical-product-applications.

All final labeling should be submitted as Product Correspondence to this BLA STN BL 125742 at the time of use and include implementation information on Form FDA 356h.

ADVERTISING AND PROMOTIONAL LABELING

You may submit two draft copies of the proposed introductory advertising and promotional labeling with Form FDA 2253 to the Advertising and Promotional Labeling Branch at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

You must submit copies of your final advertising and promotional labeling at the time of initial dissemination or publication, accompanied by Form FDA 2253 (21 CFR 601.12(f)(4)).

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence or substantial clinical experience to support such claims (21 CFR 202.1(e)(6)).

ADVERSE EVENT REPORTING

You must submit adverse experience reports in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80), and you must submit distribution reports at monthly intervals as described in 21 CFR 600.81. For information on adverse experience reporting, please refer to the guidance for industry *Providing Submissions in Electronic Format —Postmarketing Safety Reports for Vaccines* at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-submissions-electronic-format-postmarketing-safety-reports-vaccines. For information on distribution reporting, please refer to the guidance for industry *Electronic Submission of Lot Distribution Reports* at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Post-MarketActivities/LotReleases/ucm061966.htm.

PEDIATRIC REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are deferring submission of your pediatric studies for ages younger than 16 years for this application because this product is ready for approval for use in individuals 16 years of age and older, and the pediatric studies for younger ages have not been completed.

Your deferred pediatric studies required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) are required postmarketing studies. The status of these postmarketing studies must be reported according to 21 CFR 601.28 and section 505B(a)(4)(C) of the FDCA. In addition, section 506B of the FDCA and 21 CFR 601.70 require you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

Label your annual report as an "**Annual Status Report of Postmarketing Study Requirement/Commitments**" and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Requirements and Commitments subject to the reporting requirements under section 506B of the FDCA are released or fulfilled. These required studies are listed below:

1. Deferred pediatric Study C4591001 to evaluate the safety and effectiveness of COMIRNATY in children 12 years through 15 years of age.

   Final Protocol Submission: October 7, 2020

   Study Completion: May 31, 2023

   Final Report Submission: October 31, 2023

2. Deferred pediatric Study C4591007 to evaluate the safety and effectiveness of COMIRNATY in infants and children 6 months to <12 years of age.

   Final Protocol Submission: February 8, 2021

   Study Completion: November 30, 2023

   Final Report Submission: May 31, 2024

3. Deferred pediatric Study C4591023 to evaluate the safety and effectiveness of COMIRNATY in infants <6 months of age.

   Final Protocol Submission: January 31, 2022

   Study Completion: July 31, 2024

   Final Report Submission: October 31, 2024

Submit the protocols to your IND 19736, with a cross-reference letter to this BLA STN BL 125742 explaining that these protocols were submitted to the IND. Please refer to the PMR sequential number for each study/clinical trial and the submission number as shown in this letter.
Submit final study reports to this BLA STN BL 125742. In order for your PREA PMRs to be considered fulfilled, you must submit and receive approval of an efficacy or a labeling

supplement. For administrative purposes, all submissions related to these required pediatric postmarketing studies must be clearly designated as:

- **Required Pediatric Assessment(s)**

We note that you have fulfilled the pediatric study requirement for ages 16 through 17 years for this application.

POSTMARKETING REQUIREMENTS UNDER SECTION 505(o)

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under section 505(k)(1) of the FDCA will not be sufficient to assess known serious risks of myocarditis and pericarditis and identify an unexpected serious risk of subclinical myocarditis.

Furthermore, the pharmacovigilance system that FDA is required to maintain under section 505(k)(3) of the FDCA is not sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, we have determined that you are required to conduct the following studies:

4. Study C4591009, entitled “A Non-Interventional Post-Approval Safety Study of the Pfizer-BioNTech COVID-19 mRNA Vaccine in the United States,” to evaluate the occurrence of myocarditis and pericarditis following administration of COMIRNATY.

   We acknowledge the timetable you submitted on August 21, 2021, which states that you will conduct this study according to the following schedule:

   Final Protocol Submission: August 31, 2021

   Monitoring Report Submission: October 31, 2022

   Interim Report Submission: October 31, 2023

   Study Completion: June 30, 2025

   Final Report Submission: October 31, 2025

5. Study C4591021, entitled “Post Conditional Approval Active Surveillance Study Among Individuals in Europe Receiving the Pfizer-BioNTech Coronavirus

Disease 2019 (COVID-19) Vaccine," to evaluate the occurrence of myocarditis and pericarditis following administration of COMIRNATY.

We acknowledge the timetable you submitted on August 21, 2021, which states that you will conduct this study according to the following schedule:

Final Protocol Submission: August 11, 2021

Progress Report Submission: September 30, 2021

Interim Report 1 Submission: March 31, 2022

Interim Report 2 Submission: September 30, 2022

Interim Report 3 Submission: March 31, 2023

Interim Report 4 Submission: September 30, 2023

Interim Report 5 Submission: March 31, 2024

Study Completion: March 31, 2024

Final Report Submission: September 30, 2024

6. Study C4591021 substudy to describe the natural history of myocarditis and pericarditis following administration of COMIRNATY.

   We acknowledge the timetable you submitted on August 21, 2021, which states that you will conduct this study according to the following schedule:

   Final Protocol Submission: January 31, 2022

   Study Completion: March 31, 2024

   Final Report Submission: September 30, 2024

7. Study C4591036, a prospective cohort study with at least 5 years of follow-up for potential long-term sequelae of myocarditis after vaccination (in collaboration with Pediatric Heart Network).

   We acknowledge the timetable you submitted on August 21, 2021, which states that you will conduct this study according to the following schedule:

   Final Protocol Submission: November 30, 2021

   Study Completion: December 31, 2026

Final Report Submission: May 31, 2027

8. Study C4591007 substudy to prospectively assess the incidence of subclinical myocarditis following administration of the second dose of COMIRNATY in a subset of participants 5 through 15 years of age.

   We acknowledge the timetable you submitted on August 21, 2021, which states that you will conduct this assessment according to the following schedule:

   Final Protocol Submission: September 30, 2021

   Study Completion: November 30, 2023

   Final Report Submission: May 31, 2024

9. Study C4591031 substudy to prospectively assess the incidence of subclinical myocarditis following administration of a third dose of COMIRNATY in a subset of participants 16 to 30 years of age.

   We acknowledge the timetable you submitted on August 21, 2021, which states that you will conduct this study according to the following schedule:

   Final Protocol Submission: November 30, 2021

   Study Completion: June 30, 2022

   Final Report Submission: December 31, 2022

Please submit the protocols to your IND 19736, with a cross-reference letter to this BLA STN BL 125742 explaining that these protocols were submitted to the IND. Please refer to the PMR sequential number for each study/clinical trial and the submission number as shown in this letter.

Please submit final study reports to the BLA. If the information in the final study report supports a change in the label, the final study report must be submitted as a supplement to this BLA STN BL 125742. For administrative purposes, all submissions related to these postmarketing studies required under section 505(o) must be submitted to this BLA and be clearly designated as:

- **Required Postmarketing Correspondence under Section 505(o)**
- **Required Postmarketing Final Report under Section 505(o)**
- **Supplement contains Required Postmarketing Final Report under Section 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise

undertaken to investigate a safety issue. In addition, section 506B of the FDCA and 21 CFR 601.70 require you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

You must describe the status in an annual report on postmarketing studies for this product. Label your annual report as an **Annual Status Report of Postmarketing Requirements/Commitments** and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Requirements and Commitments subject to the reporting requirements of section 506B of the FDCA are fulfilled or released. The status report for each study should include:

- the sequential number for each study as shown in this letter;
- information to identify and describe the postmarketing requirement;
- the original milestone schedule for the requirement;
- the revised milestone schedule for the requirement, if appropriate;
- the current status of the requirement (i.e., pending, ongoing, delayed, terminated, or submitted); and,
- an explanation of the status for the study or clinical trial. The explanation should include how the study is progressing in reference to the original projected schedule, including, the patient accrual rate (i.e., number enrolled to date and the total planned enrollment).

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our website at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/default.htm.

We will consider the submission of your annual report under section 506B of the FDCA and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in section 505(o) and 21 CFR 601.70. We remind you that to comply with section 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to periodically report on the status of studies or clinical trials required under section 505(o) may be a violation of FDCA section 505(o)(3)(E)(ii) and could result in regulatory action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We acknowledge your written commitments as described in your letter of August 21, 2021 as outlined below:

10. Study C4591022, entitled “Pfizer-BioNTech COVID-19 Vaccine Exposure during Pregnancy: A Non-Interventional Post-Approval Safety Study of Pregnancy and Infant Outcomes in the Organization of Teratology Information Specialists (OTIS)/MotherToBaby Pregnancy Registry.”

    Final Protocol Submission: July 1, 2021

Study Completion: June 30, 2025

Final Report Submission: December 31, 2025

11. Study C4591007 substudy to evaluate the immunogenicity and safety of lower dose levels of COMIRNATY in individuals 12 through <30 years of age.

    Final Protocol Submission: September 30, 2021

    Study Completion: November 30, 2023

    Final Report Submission: May 31, 2024

12. Study C4591012, entitled "Post-emergency Use Authorization Active Safety Surveillance Study Among Individuals in the Veteran's Affairs Health System Receiving Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine."

    Final Protocol Submission: January 29, 2021

    Study Completion: June 30, 2023

    Final Report Submission: December 31, 2023

13. Study C4591014, entitled "Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study - Kaiser Permanente Southern California."

    Final Protocol Submission: March 22, 2021

    Study Completion: December 31, 2022

    Final Report Submission: June 30, 2023

Please submit clinical protocols to your IND 19736, and a cross-reference letter to this BLA STN BL 125742 explaining that these protocols were submitted to the IND. Please refer to the PMC sequential number for each study/clinical trial and the submission number as shown in this letter.

If the information in the final study report supports a change in the label, the final study report must be submitted as a supplement. Please use the following designators to prominently label all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **Postmarketing Commitment – Correspondence Study Update**
- **Postmarketing Commitment – Final Study Report**
- **Supplement contains Postmarketing Commitment – Final Study Report**

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. Label your annual report as an **Annual Status Report of Postmarketing Requirements/Commitments** and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Requirements and Commitments subject to the reporting requirements of section 506B of the FDCA are fulfilled or released. The status report for each study should include:

- the sequential number for each study as shown in this letter;
- information to identify and describe the postmarketing commitment;
- the original schedule for the commitment;
- the status of the commitment (i.e., pending, ongoing, delayed, terminated, or submitted); and,
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e., number enrolled to date and the total planned enrollment).

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our website at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/default.htm.

POST APPROVAL FEEDBACK MEETING

New biological products qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, please contact the Regulatory Project Manager for this application.

Sincerely,

Mary A. Malarkey
Director
Office of Compliance
and Biologics Quality
Center for Biologics
Evaluation and Research

Marion F. Gruber, PhD
Director
Office of Vaccines
Research and Review
Center for Biologics
Evaluation and Research

Exhibit L

September 22, 2021

Pfizer Inc.
Attention: Mr. Amit Patel
235 East 42nd St
New York, NY 10017

Dear Mr. Patel:

On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act or the Act), the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes Coronavirus Disease 2019 (COVID-19).[1] On the basis of such determination, the Secretary of HHS on March 27, 2020, declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the Act (21 U.S.C. 360bbb-3), subject to terms of any authorization issued under that section.[2]

On December 11, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for emergency use of Pfizer-BioNTech COVID-19 Vaccine for the prevention of COVID-19 for individuals 16 years of age and older pursuant to Section 564 of the Act. FDA reissued the letter of authorization on: December 23, 2020,[3] February 25, 2021,[4] May

[1] U.S. Department of Health and Human Services, Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the FD&C Act, 21 U.S.C. § 360bbb-3, February 4, 2020.

[2] U.S. Department of Health and Human Services, *Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*, 85 FR 18250 (April 1, 2020).

[3] In the December 23, 2020 revision, FDA removed reference to the number of doses per vial after dilution from the letter of authorization, clarified the instructions for vaccination providers reporting to VAERS, and made other technical corrections. FDA also revised the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) to clarify the number of doses of vaccine per vial after dilution and the instructions for reporting to VAERS. In addition, the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) and the Fact Sheet for Recipients and Caregivers were revised to include additional information on safety monitoring and to clarify information about the availability of other COVID-19 vaccines.

[4] In the February 25, 2021 revision, FDA allowed flexibility on the date of submission of monthly periodic safety reports and revised the requirements for reporting of vaccine administration errors by Pfizer Inc. The Fact Sheet for Health Care Providers Administering Vaccine (Vaccination Providers) was revised to provide an update to the storage and transportation temperature for frozen vials, direct the provider to the correct CDC website for information on monitoring vaccine recipients for the occurrence of immediate adverse reactions, to include data from a developmental toxicity study, and add adverse reactions that have been identified during post authorization use. The Fact Sheet for Recipients and Caregivers was revised to add adverse reactions that have been identified during post authorization use.

10, 2021,[5] June 25, 2021,[6] August 12, 2021,[7] and on August 23, 2021, FDA approved COMIRNATY (COVID-19 Vaccine, mRNA)[8] and reissued the letter in its entirety for both Pfizer-BioNTech COVID-19 Vaccine and certain uses of COMIRNATY (COVID-19 Vaccine, mRNA).[9]

On September, 22 2021, having concluded that revising this EUA is appropriate to protect the public health or safety under section 564(g)(2) of the Act, FDA is reissuing the August 23, 2021 letter of authorization in its entirety with revisions incorporated to authorize for emergency use the administration of a single booster dose of COMIRNATY (COVID-19 Vaccine, mRNA) or Pfizer-BioNTech COVID-19 Vaccine at least 6 months after completing the primary series of this vaccine in individuals: 65 years of age and older;18 through 64 years of age at high risk of severe COVID-19; and 18 through 64 years of age whose frequent institutional or occupational exposure to SARS-CoV-2 puts them at high risk of serious complications of COVID-19 including severe COVID-19.

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[5] In the May 10, 2021 revision, FDA authorized Pfizer-BioNTech Vaccine for the prevention of COVID-19 in individuals 12 through 15 years of age, as well as for individuals 16 years of age and older. In addition, FDA revised the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) to include the following Warning: "Syncope (fainting) may occur in association with administration of injectable vaccines, in particular in adolescents. Procedures should be in place to avoid injury from fainting." In addition, the Fact Sheet for Recipients and Caregivers was revised to instruct vaccine recipients or their caregivers to tell the vaccination provider about fainting in association with a previous injection.

[6] In the June 25, 2021 revision, FDA clarified terms and conditions that relate to export of Pfizer-BioNTech COVID-19 Vaccine from the United States. In addition, the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) was revised to include a Warning about myocarditis and pericarditis following administration of the Pfizer-BioNTech COVID-19 Vaccine. The Fact Sheet for Recipients and Caregivers was updated to include information about myocarditis and pericarditis following administration of the Pfizer-BioNTech COVID-19 Vaccine.

[7] In the August 12, 2021 revision, FDA authorized a third dose of the Pfizer-BioNTech COVID-19 Vaccine administered at least 28 days following the two dose regimen of this vaccine in individuals 12 years of age or older who have undergone solid organ transplantation, or individuals 12 years of age or older who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.

[8] COMIRNATY (COVID-19 Vaccine, mRNA) was approved for active immunization to prevent COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older.

[9] In the August 23, 2021 revision, FDA clarified that, subsequent to the FDA approval of COMIRNATY (COVID-19 Vaccine, mRNA) for the prevention of COVID-19 for individuals 16 years of age and older, this EUA would remain in place for the Pfizer-BioNTech COVID-19 vaccine for the previously-authorized indication and uses. It also authorized COMIRNATY (COVID-19 Vaccine, mRNA) under this EUA for certain uses that are not included in the approved biologics license application (BLA). In addition, the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) was revised to provide updates on expiration dating of the authorized Pfizer-BioNTech COVID-19 Vaccine and updated language regarding warnings and precautions related to myocarditis and pericarditis. The Fact Sheet for Recipients and Caregivers was updated as the Vaccine Information Fact Sheet for Recipients and Caregivers, which comprises the Fact Sheet for the authorized Pfizer-BioNTech COVID-19 Vaccine and information about the FDA-licensed vaccine, COMIRNATY (COVID-19 Vaccine, mRNA).

COMIRNATY (COVID-19 Vaccine, mRNA) is the same formulation as the Pfizer-BioNTech COVID-19 Vaccine and can be used interchangeably with the Pfizer-BioNTech COVID-19 Vaccine to provide the COVID-19 vaccination series.[10]

For the December 11, 2020 authorization for individuals 16 years of age and older, FDA reviewed safety and efficacy data from an ongoing Phase 1/2/3 trial in approximately 44,000 participants randomized 1:1 to receive Pfizer-BioNTech COVID-19 Vaccine or saline control. The trial has enrolled participants 12 years of age and older. FDA's review at that time considered the safety and effectiveness data as they relate to the request for emergency use authorization in individuals 16 years of age and older. FDA's review of the available safety data from 37,586 of the participants 16 years of age and older, who were followed for a median of two months after receiving the second dose, did not identify specific safety concerns that would preclude issuance of an EUA. FDA's analysis of the available efficacy data from 36,523 participants 12 years of age and older without evidence of SARS-CoV-2 infection prior to 7 days after dose 2 confirmed that the vaccine was 95% effective (95% credible interval 90.3, 97.6) in preventing COVID-19 occurring at least 7 days after the second dose (with 8 COVID-19 cases in the vaccine group compared to 162 COVID-19 cases in the placebo group). Based on these data, and review of manufacturing information regarding product quality and consistency, FDA concluded that it is reasonable to believe that Pfizer-BioNTech COVID-19 Vaccine may be effective. Additionally, FDA determined it is reasonable to conclude, based on the totality of the scientific evidence available, that the known and potential benefits of Pfizer-BioNTech COVID-19 Vaccine outweigh the known and potential risks of the vaccine, for the prevention of COVID-19 in individuals 16 years of age and older. Finally, on December 10, 2020, the Vaccines and Related Biological Products Advisory Committee voted in agreement with this conclusion.

For the May 10, 2021 authorization for individuals 12 through 15 years of age, FDA reviewed safety and effectiveness data from the above-referenced, ongoing Phase 1/2/3 trial that has enrolled approximately 46,000 participants, including 2,260 participants 12 through 15 years of age. Trial participants were randomized 1:1 to receive Pfizer-BioNTech COVID-19 Vaccine or saline control. FDA's review of the available safety data from 2,260 participants 12 through 15 years of age, who were followed for a median of 2 months after receiving the second dose, did not identify specific safety concerns that would preclude issuance of an EUA. FDA's analysis of SARS-CoV-2 50% neutralizing antibody titers 1 month after the second dose of Pfizer-BioNTech COVID-19 Vaccine in a subset of participants who had no serological or virological evidence of past SARS-CoV-2 infection confirm that the geometric mean antibody titer in participants 12 through 15 years of age was non-inferior to the geometric mean antibody titer in participants 16 through 25 years of age. FDA's analysis of available descriptive efficacy data from 1,983 participants 12 through 15 years of age without evidence of SARS-CoV-2 infection prior to 7 days after dose 2 confirm that the vaccine was 100% effective (95% confidence interval 75.3, 100.0) in preventing COVID-19 occurring at least 7 days after the second dose

[10] The licensed vaccine has the same formulation as the EUA-authorized vaccine and the products can be used interchangeably to provide the vaccination series without presenting any safety or effectiveness concerns. The products are legally distinct with certain differences that do not impact safety or effectiveness.

(with no COVID-19 cases in the vaccine group compared to 16 COVID-19 cases in the placebo group). Based on these data, FDA concluded that it is reasonable to believe that Pfizer-BioNTech COVID-19 Vaccine may be effective in individuals 12 through 15 years of age. Additionally, FDA determined it is reasonable to conclude, based on the totality of the scientific evidence available, that the known and potential benefits of Pfizer-BioNTech COVID-19 Vaccine outweigh the known and potential risks of the vaccine, for the prevention of COVID-19 in individuals 12 through 15 years of age.

For the August 12, 2021 authorization of a third dose of the Pfizer-BioNTech COVID-19 Vaccine in individuals 12 years of age or older who have undergone solid organ transplantation, or individuals 12 years of age or older who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise, FDA reviewed safety and effectiveness data reported in two manuscripts on solid organ transplant recipients. The first study was a single arm study conducted in 101 individuals who had undergone various solid organ transplant procedures (heart, kidney, liver, lung, pancreas) a median of 97±8 months earlier. A third dose of the Pfizer-BioNTech COVID-19 Vaccine was administered to 99 of these individuals approximately 2 months after they had received a second dose. Levels of total SARS-CoV-2 binding antibodies meeting the pre-specified criteria for success occurred four weeks after the third dose in 26/59 (44.0%) of those who were initially considered to be seronegative and received a third dose of the Pfizer-BioNTech COVID-19 Vaccine; 67/99 (68%) of the entire group receiving a third vaccination were subsequently considered to have levels of antibodies indicative of a significant response. In those who received a third vaccine dose, the adverse event profile was similar to that after the second dose and no grade 3 or grade 4 events were reported. A supportive secondary study describes a double-blind, randomized-controlled study conducted in 120 individuals who had undergone various solid organ transplant procedures (heart, kidney, kidney-pancreas, liver, lung, pancreas) a median of 3.57 years earlier (range 1.99-6.75 years). A third dose of a similar mRNA vaccine (the Moderna COVID-19 vaccine) was administered to 60 individuals approximately 2 months after they had received a second dose (i.e., doses at 0, 1 and 3 months); saline placebo was given to 60 individuals for comparison. The primary outcome was anti-RBD antibody at 4 months greater than 100 U/mL. This titer was selected based on NHP challenge studies as well as a large clinical cohort study to indicate this antibody titer was protective. Secondary outcomes were based on a virus neutralization assay and polyfunctional T cell responses. Baseline characteristics were comparable between the two study arms as were pre-intervention anti-RBD titer and neutralizing antibodies. Levels of total SARS-CoV-2 binding antibodies indicative of a significant response occurred four weeks after the third dose in 33/60 (55.0%) of the Moderna COVID-19 vaccinated group and 10/57 (17.5%) of the placebo individuals. In the 60 individuals who received a third vaccine dose, the adverse event profile was similar to that after the second dose and no grade 3 or grade 4 adverse events were reported. Despite the moderate enhancement in antibody titers, the totality of data (i.e., supportive paper by Hall et al. demonstrated efficacy of the product in the elderly and persons with co-morbidities) supports the conclusion that a third dose of the Pfizer-BioNTech COVID-19 Vaccine may be effective in this population, and that the known and potential benefits of a third dose of Pfizer-BioNTech COVID-19 Vaccine outweigh the known and potential risks of the vaccine for immunocompromised individuals at least 12 years of age who have received two doses of the Pfizer-BioNTech COVID-19 Vaccine and who have undergone solid organ

transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.

For the September 22, 2021 authorization of a single booster dose of the Pfizer-BioNTech COVID-19 Vaccine administered at least 6 months after completing the primary series in individuals: 65 years of age and older; 18 through 64 years of age at high risk of severe COVID-19; and 18 through 64 years of age whose frequent institutional or occupational exposure to SARS-CoV-2 puts them at high risk of serious complications of COVID-19 including severe COVID-19, FDA reviewed safety and effectiveness data from the above-referenced, ongoing Phase 1/2/3 trial in which 329 participants 18 through 75 years of age received a booster dose of the Pfizer-BioNTech COVID-19 Vaccine approximately 6 months (range 4.8 to 8.8 months) after completion of the primary series. FDA's review of the available safety data from 329 participants 18 through 75 years of age, who had been followed for a median of 2.6 months after receiving the booster dose, did not identify specific safety concerns that would preclude issuance of an EUA. The effectiveness of the booster dose of the Pfizer-BioNTech COVID-19 Vaccine is based on an assessment of 50% neutralizing antibody titers (NT50) against SARS-CoV-2 (USA_WA1/2020). FDA's analysis of SARS-CoV-2 NT50 one month after the booster dose compared to 1 month after the primary series in study participants 18 through 55 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the booster dose confirmed noninferiority for both geometric mean ratio and difference in seroresponse rates. Based on the totality of the scientific evidence available, including data from the above-referenced clinical trial, FDA concluded that a booster dose the Pfizer-BioNTech COVID-19 Vaccine may be effective, and that the known and potential benefits of a single booster dose at least 6 months after completing the primary series outweigh the known and potential risks for individuals 65 years of age and older; individuals 18 through 64 years of age at high risk of severe COVID-19; and individuals 18 through 64 years of age whose frequent institutional or occupational exposure to SARS-CoV-2 puts them at high risk of serious complications of COVID-19 including severe COVID-19.

Having concluded that the criteria for issuance of this authorization under Section 564(c) of the Act are met, I am authorizing the emergency use of Pfizer-BioNTech COVID-19 Vaccine for the prevention of COVID-19, as described in the Scope of Authorization section of this letter (Section II) and subject to the terms of this authorization. Additionally, as specified in subsection III.BB, I am authorizing use of Pfizer-BioNTech COVID-19 Vaccine and of COMIRNATY (COVID-19 Vaccine, mRNA) under this EUA when used to provide: a two-dose regimen for individuals aged 12 through 15 years; a third dose to individuals 12 years of age or older who have undergone solid organ transplantation or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise; or a single booster dose at least 6 months after completing the primary series to individuals: 65 years of age and older; 18 through 64 years of age at high risk of severe COVID-19; and 18 through 64 years of age whose frequent institutional or occupational exposure to SARS-CoV-2 puts them at high risk of serious complications of COVID-19 including severe COVID-19.

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of Pfizer-BioNTech COVID-19 Vaccine[11] for the prevention of COVID-19 when administered as described in the Scope of Authorization (Section II) meets the criteria for issuance of an authorization under Section 564(c) of the Act, because:

A. SARS-CoV-2 can cause a serious or life-threatening disease or condition, including severe respiratory illness, to humans infected by this virus;

B. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that Pfizer-BioNTech COVID-19 Vaccine may be effective in preventing COVID-19, and that, when used under the conditions described in this authorization, the known and potential benefits of Pfizer-BioNTech COVID-19 Vaccine when used to prevent COVID-19 outweigh its known and potential risks; and

C. There is no adequate, approved, and available alternative[12] Pfizer-BioNTech COVID-19 Vaccine to prevent COVID-19.[13]

II. Scope of Authorization

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

- Pfizer Inc. will supply Pfizer-BioNTech COVID-19 Vaccine either directly or through authorized distributor(s),[14] to emergency response stakeholders[15] as directed by the U.S.

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[11] In this section (Section I), references to Pfizer-BioNTech COVID-19 Vaccine also apply to COMIRNATY (COVID-19 Vaccine, mRNA).

[12] Although COMIRNATY (COVID-19 Vaccine, mRNA) is approved to prevent COVID-19 in individuals 16 years of age and older, there is not sufficient approved vaccine available for distribution to this population in its entirety at the time of reissuance of this EUA. Additionally, there are no products that are approved to prevent COVID-19 in individuals age 12 through 15, or to provide: an additional dose to the immunocompromised population, or a booster dose to the authorized population described in this EUA.

[13] No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.

[14] "Authorized Distributor(s)" are identified by Pfizer Inc. or, if applicable, by a U.S. government entity, such as the Centers for Disease Control and Prevention (CDC) and/or other designee, as an entity or entities allowed to distribute authorized Pfizer-BioNTech COVID-19 Vaccine.

[15] For purposes of this letter, "emergency response stakeholder" refers to a public health agency and its delegates that have legal responsibility and authority for responding to an incident, based on political or geographical boundary lines (e.g., city, county, tribal, territorial, State, or Federal), or functional (e.g., law enforcement or public health range) or sphere of authority to administer, deliver, or distribute vaccine in an emergency situation. In some cases (e.g., depending on a state or local jurisdiction's COVID-19 vaccination response organization and plans), there might be overlapping roles and responsibilities among "emergency response stakeholders" and "vaccination providers" (e.g., if a local health department is administering COVID-19 vaccines; if a pharmacy is acting in an official capacity under the authority of the state health department to administer COVID-19 vaccines). In such cases, it is expected that the conditions of authorization that apply to emergency response stakeholders and vaccination providers will all be met.

government, including the Centers for Disease Control and Prevention (CDC) and/or other designee, for use consistent with the terms and conditions of this EUA;

- The Pfizer-BioNTech COVID-19 Vaccine covered by this authorization will be administered by vaccination providers[16] and used only to prevent COVID-19 in individuals ages 12 and older with a two-dose regimen, to provide a third dose to individuals 12 years of age or older who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise, and to provide a single booster dose at least 6 months after completing the primary series of the vaccine to individuals: 65 years of age or older; 18 through 64 years of age at high risk of severe COVID-19; and 18 through 64 years of age whose frequent institutional or occupational exposure to SARS-CoV-2 puts them at high risk of serious complications of COVID-19 including severe COVID-19; and
- Pfizer-BioNTech COVID-19 Vaccine may be administered by a vaccination provider without an individual prescription for each vaccine recipient.

This authorization also covers the use of the licensed COMIRNATY (COVID-19 Vaccine, mRNA) product when used to provide: a two-dose regimen for individuals aged 12 through 15 years; a third dose to individuals 12 years of age or older who have undergone solid organ transplantation or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise; or a single booster dose at least 6 months after completing the primary series to individuals: 65 years of age and older; 18 through 64 years of age at high risk of severe COVID-19; and 18 through 64 years of age whose frequent institutional or occupational exposure to SARS-CoV-2 puts them at high risk of serious complications of COVID-19 including severe COVID-19.

Product Description[17]

The Pfizer-BioNTech COVID-19 Vaccine is supplied as a frozen suspension in multiple dose vials; each vial must be diluted with 1.8 mL of sterile 0.9% Sodium Chloride Injection, USP prior to use to form the vaccine. The Pfizer-BioNTech COVID-19 Vaccine does not contain a preservative.

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[16] For purposes of this letter, "vaccination provider" refers to the facility, organization, or healthcare provider licensed or otherwise authorized by the emergency response stakeholder (e.g., non-physician healthcare professionals, such as nurses and pharmacists pursuant to state law under a standing order issued by the state health officer) to administer or provide vaccination services in accordance with the applicable emergency response stakeholder's official COVID-19 vaccination and emergency response plan(s) and who is enrolled in the CDC COVID-19 Vaccination Program. If the vaccine is exported from the United States, a "vaccination provider" is a provider that is authorized to administer this vaccine in accordance with the laws of the country in which it is administered. For purposes of this letter, "healthcare provider" also refers to a person authorized by the U.S. Department of Health and Human Services (e.g., under the PREP Act Declaration for Medical Countermeasures against COVID-19) to administer FDA-authorized COVID-19 vaccine (e.g., qualified pharmacy technicians and State-authorized pharmacy interns acting under the supervision of a qualified pharmacist). See, e.g., HHS. *Fourth Amendment to the Declaration Under the Public Readiness and Emergency Preparedness Act for Medical Countermeasures Against COVID-19 and Republication of the Declaration*. 85 FR 79190 (December 9, 2020).

[17] For COMIRNATY (COVID-19 Vaccine, mRNA) product description, please see the COMIRNATY (COVID-19 Vaccine, mRNA) prescribing information, found here: *https://www.fda.gov/media/151707/download*.

Each 0.3 mL dose of the Pfizer-BioNTech COVID-19 Vaccine contains 30 mcg of a nucleoside-modified messenger RNA (modRNA) encoding the viral spike (S) glycoprotein of SARS-CoV-2. Each dose of the Pfizer-BioNTech COVID-19 Vaccine also includes the following ingredients: lipids (0.43 mg (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 0.05 mg 2[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 0.09 mg 1,2-distearoyl-sn-glycero-3-phosphocholine, and 0.2 mg cholesterol), 0.01 mg potassium chloride, 0.01 mg monobasic potassium phosphate, 0.36 mg sodium chloride, 0.07 mg dibasic sodium phosphate dihydrate, and 6 mg sucrose. The diluent (0.9% Sodium Chloride Injection) contributes an additional 2.16 mg sodium chloride per dose.

The dosing regimen is a primary series of two doses of 0.3 mL each, 3 weeks apart. A third primary series dose may be administered at least 28 days following the second dose to individuals 12 years of age or older who have undergone solid organ transplantation, or individuals 12 years of age or older who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise. A single booster dose (0.3 mL) may be administered at least 6 months after completing the primary series to individuals: 65 years of age or older; 18 through 64 years of age at high risk of severe COVID-19; and 18 through 64 years of age whose frequent institutional or occupational exposure to SARS-CoV-2 puts them at high risk of serious complications of COVID-19 including severe COVID-19.

The manufacture of the authorized Pfizer-BioNTech COVID-19 Vaccine is limited to those facilities identified and agreed upon in Pfizer's request for authorization.

The Pfizer-BioNTech COVID-19 Vaccine vial label and carton labels are clearly marked for "Emergency Use Authorization." The Pfizer-BioNTech COVID-19 Vaccine is authorized to be distributed, stored, further redistributed, and administered by emergency response stakeholders when packaged in the authorized manufacturer packaging (i.e., vials and cartons), despite the fact that the vial and carton labels may not contain information that otherwise would be required under the FD&C Act.

Pfizer-BioNTech COVID-19 Vaccine is authorized for emergency use with the following product-specific information required to be made available to vaccination providers and recipients, respectively (referred to as "authorized labeling"):

- Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers): Emergency Use Authorization (EUA) of Pfizer-BioNTech COVID-19 Vaccine to Prevent Coronavirus Disease 2019 (COVID-19)

- Vaccine Information Fact Sheet for Recipients and Caregivers About COMIRNATY (COVID-19 Vaccine, mRNA) and Pfizer-BioNTech COVID-19 Vaccine to Prevent Coronavirus Disease (COVID-19).

I have concluded, pursuant to Section 564(d)(2) of the Act, that it is reasonable to believe that the known and potential benefits of Pfizer-BioNTech COVID-19 Vaccine,[18] when used to prevent COVID-19 and used in accordance with this Scope of Authorization (Section II), outweigh its known and potential risks.

I have concluded, pursuant to Section 564(d)(3) of the Act, based on the totality of scientific evidence available to FDA, that it is reasonable to believe that Pfizer-BioNTech COVID-19 Vaccine may be effective in preventing COVID-19 when used in accordance with this Scope of Authorization (Section II), pursuant to Section 564(c)(2)(A) of the Act.

Having reviewed the scientific information available to FDA, including the information supporting the conclusions described in Section I above, I have concluded that Pfizer-BioNTech COVID-19 Vaccine (as described in this Scope of Authorization (Section II)) meets the criteria set forth in Section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of Pfizer-BioNTech COVID-19 Vaccine under this EUA must be consistent with, and may not exceed, the terms of the Authorization, including the Scope of Authorization (Section II) and the Conditions of Authorization (Section III). Subject to the terms of this EUA and under the circumstances set forth in the Secretary of HHS's determination under Section 564(b)(1)(C) described above and the Secretary of HHS's corresponding declaration under Section 564(b)(1), Pfizer-BioNTech COVID-19 Vaccine is authorized to prevent COVID-19 in individuals 12 years of age and older as described in the Scope of Authorization (Section II) under this EUA, despite the fact that it does not meet certain requirements otherwise required by applicable federal law.

III. Conditions of Authorization

Pursuant to Section 564 of the Act, I am establishing the following conditions on this authorization:

Pfizer Inc. and Authorized Distributor(s)

A. Pfizer Inc. and authorized distributor(s) will ensure that the authorized Pfizer-BioNTech COVID-19 Vaccine is distributed, as directed by the U.S. government, including CDC and/or other designee, and the authorized labeling (i.e., Fact Sheets) will be made available to vaccination providers, recipients, and caregivers consistent with the terms of this letter.

B. Pfizer Inc. and authorized distributor(s) will ensure that appropriate storage and cold chain is maintained until delivered to emergency response stakeholders' receipt sites.

C. Pfizer Inc. will ensure that the terms of this EUA are made available to all relevant stakeholders (e.g., emergency response stakeholders, authorized distributors, and vaccination providers) involved in distributing or receiving authorized Pfizer-BioNTech COVID-19 Vaccine. Pfizer Inc. will provide to all relevant stakeholders a

[18] The conclusions supporting authorization stated in this Section (Section II) also apply to COMIRNATY (COVID-19 Vaccine, mRNA).

copy of this letter of authorization and communicate any subsequent amendments that might be made to this letter of authorization and its authorized labeling.

D. Pfizer Inc. may develop and disseminate instructional and educational materials (e.g., video regarding vaccine handling, storage/cold-chain management, preparation, disposal) that are consistent with the authorized emergency use of the vaccine as described in the letter of authorization and authorized labeling, without FDA's review and concurrence, when necessary to meet public health needs during an emergency. Any instructional and educational materials that are inconsistent with the authorized labeling are prohibited.

E. Pfizer Inc. may request changes to this authorization, including to the authorized Fact Sheets for the vaccine. Any request for changes to this EUA must be submitted to Office of Vaccines Research and Review (OVRR)/Center for Biologics Evaluation and Research (CBER). Such changes require appropriate authorization prior to implementation.[19]

F. Pfizer Inc. will report to Vaccine Adverse Event Reporting System (VAERS):
   - Serious adverse events (irrespective of attribution to vaccination);
   - Cases of Multisystem Inflammatory Syndrome in children and adults; and
   - Cases of COVID-19 that result in hospitalization or death, that are reported to Pfizer Inc.

   These reports should be submitted to VAERS as soon as possible but no later than 15 calendar days from initial receipt of the information by Pfizer Inc.

G. Pfizer Inc. must submit to Investigational New Drug application (IND) number 19736 periodic safety reports at monthly intervals in accordance with a due date agreed upon with the Office of Biostatistics and Epidemiology (OBE)/CBER beginning after the first full calendar month after authorization. Each periodic safety report is required to contain descriptive information which includes:
   - A narrative summary and analysis of adverse events submitted during the reporting interval, including interval and cumulative counts by age groups, special populations (e.g., pregnant women), and adverse events of special interest;
   - A narrative summary and analysis of vaccine administration errors, whether or not associated with an adverse event, that were identified since the last reporting interval;
   - Newly identified safety concerns in the interval; and

[19] The following types of revisions may be authorized without reissuing this letter: (1) changes to the authorized labeling; (2) non-substantive editorial corrections to this letter; (3) new types of authorized labeling, including new fact sheets; (4) new carton/container labels; (5) expiration dating extensions; (6) changes to manufacturing processes, including tests or other authorized components of manufacturing; (7) new conditions of authorization to require data collection or study. For changes to the authorization, including the authorized labeling, of the type listed in (3), (6), or (7), review and concurrence is required from the Preparedness and Response Team (PREP)/Office of the Center Director (OD)/CBER and the Office of Counterterrorism and Emerging Threats (OCET)/Office of the Chief Scientist (OCS).

- Actions taken since the last report because of adverse experiences (for example, changes made to Healthcare Providers Administering Vaccine (Vaccination Providers) Fact Sheet, changes made to studies or studies initiated).

H. No changes will be implemented to the description of the product, manufacturing process, facilities, or equipment without notification to and concurrence by FDA.

I. All manufacturing facilities will comply with Current Good Manufacturing Practice requirements.

J. Pfizer Inc. will submit to the EUA file Certificates of Analysis (CoA) for each drug product lot at least 48 hours prior to vaccine distribution. The CoA will include the established specifications and specific results for each quality control test performed on the final drug product lot.

K. Pfizer Inc. will submit to the EUA file quarterly manufacturing reports, starting in July 2021, that include a listing of all Drug Substance and Drug Product lots produced after issuance of this authorization. This report must include lot number, manufacturing site, date of manufacture, and lot disposition, including those lots that were quarantined for investigation or those lots that were rejected. Information on the reasons for lot quarantine or rejection must be included in the report.

L. Pfizer Inc. and authorized distributor(s) will maintain records regarding release of Pfizer-BioNTech COVID-19 Vaccine for distribution (i.e., lot numbers, quantity, release date).

M. Pfizer Inc. and authorized distributor(s) will make available to FDA upon request any records maintained in connection with this EUA.

N. Pfizer Inc. will conduct post-authorization observational studies to evaluate the association between Pfizer-BioNTech COVID-19 Vaccine and a pre-specified list of adverse events of special interest, including myocarditis and pericarditis, along with deaths and hospitalizations, and severe COVID-19. The study population should include individuals administered the authorized Pfizer-BioNTech COVID-19 Vaccine under this EUA in the general U.S. population (12 years of age and older), individuals that receive a booster dose, populations of interest such as healthcare workers, pregnant women, immunocompromised individuals, subpopulations with specific comorbidities. The studies should be conducted in large scale databases with an active comparator. Pfizer Inc. will provide protocols and status update reports to the IND 19736 with agreed-upon study designs and milestone dates.

Emergency Response Stakeholders

O. Emergency response stakeholders will identify vaccination sites to receive authorized Pfizer-BioNTech COVID-19 Vaccine and ensure its distribution and administration, consistent with the terms of this letter and CDC's COVID-19 Vaccination Program.

P. Emergency response stakeholders will ensure that vaccination providers within their jurisdictions are aware of this letter of authorization, and the terms herein and any subsequent amendments that might be made to the letter of authorization, instruct them about the means through which they are to obtain and administer the vaccine under the EUA, and ensure that the authorized labeling [i.e., Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) and Vaccine Information Fact Sheet for Recipients and Caregivers] is made available to vaccination providers through appropriate means (e.g., e-mail, website).

Q. Emergency response stakeholders receiving authorized Pfizer-BioNTech COVID-19 Vaccine will ensure that appropriate storage and cold chain is maintained.

Vaccination Providers

R. Vaccination providers will administer the vaccine in accordance with the authorization and will participate and comply with the terms and training required by CDC's COVID-19 Vaccination Program.

S. Vaccination providers will provide the Vaccine Information Fact Sheet for Recipients and Caregivers to each individual receiving vaccination and provide the necessary information for receiving their second dose and/or third dose.

T. Vaccination providers administering the vaccine must report the following information associated with the administration of the vaccine of which they become aware to VAERS in accordance with the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers):

- Vaccine administration errors whether or not associated with an adverse event
- Serious adverse events (irrespective of attribution to vaccination)
- Cases of Multisystem Inflammatory Syndrome in children and adults
- Cases of COVID-19 that result in hospitalization or death

Complete and submit reports to VAERS online at https://vaers.hhs.gov/reportevent.html. The VAERS reports should include the words "Pfizer-BioNTech COVID-19 Vaccine EUA" in the description section of the report. More information is available at vaers.hhs.gov or by calling 1-800-822-7967. To the extent feasible, report to Pfizer Inc. by contacting 1-800-438-1985 or by providing a copy of the VAERS form to Pfizer Inc.; Fax: 1-866-635-8337.

U. Vaccination providers will conduct any follow-up requested by the U.S government, including CDC, FDA, or other designee, regarding adverse events to the extent feasible given the emergency circumstances.

V. Vaccination providers will monitor and comply with CDC and/or emergency response stakeholder vaccine management requirements (e.g., requirements

concerning obtaining, tracking, and handling vaccine) and with requirements concerning reporting of vaccine administration data to CDC.

W. Vaccination providers will ensure that any records associated with this EUA are maintained until notified by FDA. Such records will be made available to CDC, and FDA for inspection upon request.

Conditions Related to Printed Matter, Advertising, and Promotion

X. All descriptive printed matter, advertising, and promotional material, relating to the use of the Pfizer-BioNTech COVID-19 Vaccine shall be consistent with the authorized labeling, as well as the terms set forth in this EUA, and meet the requirements set forth in section 502(a) and (n) of the FD&C Act and FDA implementing regulations.

Y. All descriptive printed matter, advertising, and promotional material relating to the use of the Pfizer-BioNTech COVID-19 Vaccine clearly and conspicuously shall state that:
- This product has not been approved or licensed by FDA, but has been authorized for emergency use by FDA, under an EUA to prevent Coronavirus Disease 2019 (COVID-19) for use in individuals 12 years of age and older; and
- The emergency use of this product is only authorized for the duration of the declaration that circumstances exist justifying the authorization of emergency use of the medical product under Section 564(b)(1) of the FD&C Act unless the declaration is terminated or authorization revoked sooner.

Condition Related to Export

Z. If the Pfizer-BioNTech COVID-19 Vaccine is exported from the United States, conditions C, D, and O through Y do not apply, but export is permitted only if 1) the regulatory authorities of the country in which the vaccine will be used are fully informed that this vaccine is subject to an EUA and is not approved or licensed by FDA and 2) the intended use of the vaccine will comply in all respects with the laws of the country in which the product will be used. The requirement in this letter that the authorized labeling (i.e., Fact Sheets) be made available to vaccination providers, recipients, and caregivers in condition A will not apply if the authorized labeling (i.e., Fact Sheets) are made available to the regulatory authorities of the country in which the vaccine will be used.

Conditions With Respect to Use of Licensed Product

AA. COMIRNATY (COVID-19 Vaccine, mRNA) is now licensed for individuals 16 years of age and older. There remains, however, a significant amount of Pfizer-BioNTech COVID-19 Vaccine that was manufactured and labeled in accordance with this emergency use authorization. The authorization remains in place with respect to the Pfizer-BioNTech COVID-19 Vaccine.

BB. This authorization also covers the use of the licensed COMIRNATY (COVID-19 Vaccine, mRNA) product when used to provide: a two-dose regimen for individuals aged 12 through 15 years; a third dose to individuals 12 years of age or older who have undergone solid organ transplantation or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise; or a single booster dose at least 6 months after completing the primary series to individuals: 65 years of age or older; 18 through 64 years of age at high risk of severe COVID-19; and 18 through 64 years of age whose frequent institutional or occupational exposure to SARS-CoV-2 puts them at high risk of serious complications of COVID-19 including severe COVID-19. Conditions A through W in this letter apply when COMIRNATY (COVID-19 Vaccine, mRNA) is provided for the uses described in this subsection III.BB, except that product manufactured and labeled in accordance with the approved BLA is deemed to satisfy the manufacturing, labeling, and distribution requirements of this authorization.

IV. Duration of Authorization

This EUA will be effective until the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic is terminated under Section 564(b)(2) of the Act or the EUA is revoked under Section 564(g) of the Act.

Sincerely,

--/S/--

RADM Denise M. Hinton
Chief Scientist
Food and Drug Administration

Enclosures

Exhibit M

Summary Basis for Regulatory Action

Date:	08/23/2021
From:	Ramachandra Naik, PhD, Review Committee Chair, DVRPA/OVRR
BLA STN:	125742/0
Applicant:	BioNTech Manufacturing GmbH (in partnership with Pfizer, Inc.)
Submission Receipt Date:	May 18, 2021
PDUFA Action Due Date:	January 16, 2022
Proper Name:	COVID-19 Vaccine, mRNA
Proprietary Name:	COMIRNATY
Indication:	Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older

Recommended Action: The Review Committee recommends approval of this product.

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Director, Office of Vaccines Research and Review

_____

Director, Office of Compliance and Biologics Quality

Discipline Reviews	Reviewer / Consultant - Office/Division
CMC • CMC Product (OVRR) • Facilities Review (OCBQ/DMPQ) • Facilities Inspection (OCBQ/DMPQ and OVRR/DVP) • Lot Release, QC, Test Methods, Product Quality (OCBQ/DBSQC)	Xiao Wang, PhD, OVRR/DVP Anissa Cheung, MSc, OVRR/DVP Kathleen Jones, PhD, OCBQ/DMPQ Laura Fontan, PhD, OCBQ/DMPQ Gregory Price, PhD, OCBQ/DMPQ CDR Donald Ertel, MS, OCBQ/DMPQ Nicole Li, MS, OCBQ/DMPQ Christian Lynch, OCBQ/DMPQ Alifiya Ghadiali, OCBQ/DMPQ Zhongren Wu, PhD, OCBQ/DMPQ Ekaterina Allen, PhD, OCBQ/DMPQ Hsiaoling Wang, PhD, OCBQ/DBSQC Emnet Yitbarek, PhD, OCBQ/DBSQC Karla Garcia, MS, OCBQ/DBSQC Anil Choudhary, PhD, MBA, OCBQ/DBSQC Esmeralda Alvarado Facundo, PhD, OCBQ/DBSQC Marie Anderson, PhD, OCBQ/DBSQC Cheryl Hulme, OCBQ/DMPQ
Clinical • Clinical (OVRR) • Postmarketing Safety, Epidemiological Review (OBE/DE) • Real World Evidence • Benefit-Risk Assessment • BIMO	Susan Wollersheim, MD, OVRR/DVRPA CAPT Ann T. Schwartz, MD, OVRR/DVRPA Lucia Lee, MD, OVRR/DVRPA Deborah Thompson, MD, MSPH, OBE/DE Yun Lu, PhD, OBE Hong Yang, PhD, OBE Osman Yogurtcu, PhD, OBE Patrick Funk, PhD, OBE Haecin Chun, MT (ASCP) SSB, MS, OCBQ/DIS
Statistical • Clinical Data (OBE/DB) • Nonclinical Data	Lei Huang, PhD, OBE/DB Ye Yang, PhD, OBE/DB Xinyu Tang, PhD, OBE/DB
Nonclinical/Pharmacology/Toxicology • Toxicology (OVRR) • Developmental Toxicology (OVRR)	Nabil Al-Humadi, PhD, OVRR/DVRPA
Labeling • Promotional (OCBQ/APLB) • Carton and Container Labels • Labeling Review	CAPT Oluchi Elekwachi, PharmD, MPH, OCBQ/APLB Daphne Stewart, OVRR/DVRPA Laura Gottschalk, PhD, OVRR/DVRPA
• Consults (CDISC, Datasets) • Documentation Review	Brenda Baldwin, PhD, OVRR/DVRPA CAPT Michael Smith, PhD, OVRR/DVRPA
Advisory Committee Summary	No Advisory Committee meeting held

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1. Introduction

BioNTech Manufacturing GmbH (in partnership with Pfizer Inc.) submitted a Biologics License Application (BLA) STN BL 125742 for licensure of COVID-19 Vaccine, mRNA. The proprietary name of the vaccine is COMIRNATY. COMIRNATY is a vaccine indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older. The vaccine is administered intramuscularly (IM) as a series of two 30 µg doses (0.3 mL each) 3 weeks apart.

COMIRNATY (also referred to as BNT162b2 in this document) contains a nucleoside-modified messenger RNA (mRNA) encoding the viral spike glycoprotein (S) of SARS-CoV-2 that is formulated in lipids including ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 2-(polyethylene glycol 2000)-N,N-ditetradecylacetamide, 1,2-distearoyl-sn-glycero-3-phosphocholine, and cholesterol.

COMIRNATY is supplied as a concentrated multi-dose liquid formulation (0.45 mL volume) stored frozen at -90°C to -60°C in a 2 mL Type 1 glass vial. A sterile diluent, 0.9% Sodium Chloride Injection, USP, is supplied separately in 2 mL glass vials manufactured by Fresenius Kabi LLC and in 10 mL vials manufactured by Hospira, Inc. The diluent is stored at 20°C to 25°C and will be shipped in parallel with shipments of COMIRNATY, with arrivals synchronized so that the diluent is delivered before the vaccine is delivered. Healthcare providers may also use other sources of sterile 0.9% Sodium Chloride Injection, USP as a diluent for COMIRNATY, if necessary.

The COMIRNATY Multiple Dose Vial is thawed in a refrigerator (2°C to 8°C) for 2 to 3 hours or at room temperature (up to 25°C) for 30 minutes. The vial must be warmed to room temperature for dilution. Once at room temperature, the COMIRNATY Multiple Dose Vial is diluted with 1.8 mL of the diluent. After dilution, each vial of COMIRNATY contain six doses of 0.3 mL of vaccine. Each 0.3 mL dose of COMIRNATY contains 30 µg of mRNA encoding the spike glycoprotein of SARS-CoV-2 and the following ingredients: lipids (0.43 mg ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 0.05 mg 2-(polyethylene glycol 2000)-N,N-ditetradecylacetamide, 0.09 mg 1,2-distearoyl-sn-glycero-3-phosphocholine, and 0.2 mg cholesterol), 0.01 mg potassium chloride, 0.01 mg monobasic potassium phosphate, 2.52 mg sodium chloride, 0.07 mg dibasic sodium phosphate dihydrate, and 6 mg sucrose. After dilution, the vials are stored at 2°C to 25°C and must be used within 6 hours from the time of dilution. COMIRNATY is preservative-free.

The expiry dating period for COMIRNATY Multiple Dose Vial is 9 months from the date of manufacture when stored at -90°C to -60°C. The date of manufacture shall be no later than the date of final sterile filtration of the formulated drug product (at Pharmacia & Upjohn Company LLC in Kalamazoo, Michigan, the date of manufacture is defined as the date of sterile filtration for the final drug product; at Pfizer-Manufacturing Belgium NV in Puurs, Belgium, it is defined as the date of the (b) (4) .

2. Background

SARS-CoV-2 is a novel, zoonotic coronavirus that emerged in late 2019 and was identified in patients with pneumonia of unknown cause. The virus was named SARS-CoV-2 because of its similarity to the coronavirus responsible for severe acute respiratory syndrome (SARS-CoV, a lineage B betacoronavirus). SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA virus sharing more than 70% of its sequence with SARS-CoV, and ~50% with the coronavirus responsible for Middle Eastern respiratory syndrome (MERS-CoV). SARS-CoV-2 is the causative agent of COVID-19, an infectious disease with respiratory and systemic manifestations. Disease symptoms vary, with many persons presenting with asymptomatic or mild disease and some progressing to severe respiratory tract disease including pneumonia and acute respiratory distress syndrome (ARDS), leading to multiorgan failure and death.

The SARS-CoV-2 pandemic continues to present a challenge to global health and, as of August 2021, has caused approximately 208 million cases of COVID-19, including 4.3 million deaths worldwide. In the United States (U.S.), more than 37 million cases have

been reported to the Centers for Disease Control and Prevention (CDC), of which 90% have occurred in individuals 16 years of age or older. While the pandemic has caused morbidity and mortality on an individual level, the continuing spread of SARS-CoV-2 and emerging variants has caused significant challenges and disruptions in worldwide healthcare systems, economies, and many aspects of human activity (travel, employment, education).

In the U.S., there are no licensed vaccines or anti-viral drugs for the prevention of COVID-19. In December 2020, the FDA issued emergency use authorizations (EUAs) for two mRNA vaccines which encode the SARS-CoV-2 spike glycoprotein: Pfizer-BioNTech COVID-19 Vaccine (manufactured by Pfizer, Inc. in partnership with BioNTech manufacturing GmbH) for use in individuals 16 years of age and older, and Moderna COVID-19 Vaccine (manufactured by ModernaTX, Inc.) for use in individuals 18 years of age and older. In February 2021, the FDA issued an EUA for a replication-incompetent adenovirus type 26 (Ad26)-vectored vaccine encoding a stabilized variant of the SARS-CoV-2 spike glycoprotein, manufactured by Janssen Biotech, Inc. (Janssen COVID-19 Vaccine) for use in individuals 18 years of age and older. In May 2021, the FDA expanded the emergency use authorization for the Pfizer-BioNTech COVID-19 Vaccine to include adolescents 12 through 15 years of age. On October 22, 2020, FDA approved remdesivir for use in adult and pediatric patients 12 years of age and older and weighing at least 40 kilograms (about 88 pounds) for the treatment of COVID-19 requiring hospitalization. Several other therapies are currently available under emergency use.

Table 1. Regulatory History

Regulatory Events / Milestones	Date
1. Pre-IND meeting (Written Responses)	April 6, 2020 (Part 1) April 10, 2020 (Part 2)
2. IND submission	April 22, 2020
3. Fast Track designation granted	July 7, 2020
4. Submission of EUA request for individuals ≥16 years of age	November 20, 2020
5. Issuance of EUA for individuals ≥16 years	December 11, 2020
6. Submission of EUA request for individuals 12-15 years of age	April 9, 2021
7. Issuance of EUA for individuals 12-15 years of age	May 10, 2021
8. Pre-BLA meeting (Written Responses)	Clinical: March 9, 2021 CMC: March 31, 2021
9. BLA STN 125742/0 received	May 18, 2021
10. BLA filed	July 15, 2021
11. Mid-Cycle communication	The Applicant canceled
12. Late-Cycle meeting	The Applicant canceled
13. Action Due Date	January 16, 2022

3. Chemistry, Manufacturing and Controls (CMC)

a. Product Quality

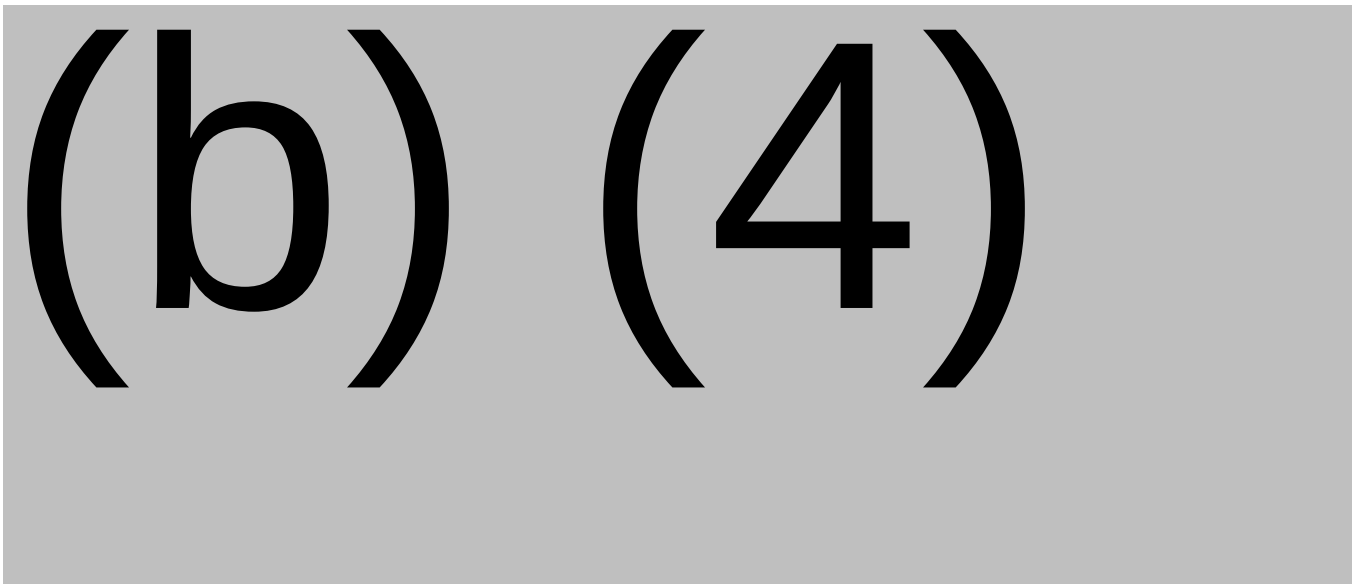
COMIRNATY Manufacturing Overview

COMIRNATY contains a nucleoside-modified messenger RNA (mRNA) encoding the viral spike glycoprotein (S) of SARS-CoV-2 that is formulated in lipids including ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2- hexyldecanoate), 2-(polyethylene glycol 2000)-N,N-ditetradecylacetamide, 1,2-distearoyl-sn-glycero-3-phosphocholine, and cholesterol. COMIRNATY is supplied as a frozen suspension to be diluted with a diluent, 0.9% Sodium Chloride Injection, USP, that is supplied separately or can be acquired elsewhere, if necessary. Manufacture of the mRNA drug substance will take place in Andover, MA, USA. The final formulated drug product will be manufactured, filled, finished, labeled and packaged in Puurs, Belgium or in Kalamazoo, MI, USA. The 0.9% Sodium Chloride Injection, USP diluent will be manufactured by Fresenius-Kabi USA, LLC (b) (4)) and Hospira, Inc. (b) (4)

The mRNA in COMIRNATY is a single-stranded, 5'-capped mRNA encoding the full-length SARS-CoV-2 spike glycoprotein derived from the Wuhan-Hu-1 isolate (GenBank MN908947.3 and GenBank QHD43416.1). The antigen-coding RNA sequence is codon-optimized and contains two proline mutations ((b) (4)), which ensures an antigenically optimal trimerized pre-fusion confirmation (S-2P). The RNA also contains common structural elements, including 5'-cap, 5'-UTR, 3'-UTR, and poly(A) tail, all of which are designed for mediating high RNA stability and translation efficiency. During RNA transcription, (b) (4) is replaced with the (b) (4) . This nucleoside substitution has been demonstrated to enhance translation of *in vitro* transcribed mRNA while reducing its reactogenicity.

Drug Substance (DS)

The manufacture of mRNA DS is divided into (b) (4) major manufacturing process stages:



Drug Product (DP)

The manufacturing process of the DP is divided into the following critical steps:

- **Preparation of the DS:** (b) (4)
- **Formation of LNP:** In this step, (b) (4)
- **Formulation of the bulk DP:** The bulk DP is formulated by (b) (4)
- **Filling:** The bulk DP is sterile filtered and aseptically filled into 2 mL Type I borosilicate glass vials manufactured by (b) (4)
- **Labeling and storage:** The filled vials are visually inspected, labeled, and frozen at -90°C to -60°C.

Composition

The composition of the formulation of COMIRNATY and the function of the ingredients are provided in Table 2.

Table 2. Composition of COMIRNATY Multiple Dose Vial

Ingredients	Quantity after Dilution (per vial)	Function
SARS-CoV-2 spike glycoprotein mRNA (UNII: 5085ZFP6SJ)	225 µg	Active Ingredient
ALC-0315 [4-hydroxybutyl)azanediyl)bis (hexane-6,1-diyl)bis(2-hexyldecanoate) (UNII: AVX8DX713V)	3.23 mg	Lipid component
ALC-0159 [2-(polyethylene glycol 2000)-N,N-ditetradecylacetamide] (UNII: PJH39UMU6H)	0.4 mg	Lipid component
DSPC [1,2-distearoyl-sn-glycero-3-phosphocholine] (UNII: 043IPI2M0K)	0.7 mg	Lipid component
Cholesterol (UNII: 97C5T2UQ7J)	1.4 mg	Lipid component
Potassium chloride (UNII: 660YQ98I10)	0.07 mg	Excipient
Monobasic potassium phosphate (UNII: 4J9FJ0HL51)	0.07 mg	Excipient
Sodium Chloride	2.7 mg	Excipient

Ingredients	Quantity after Dilution (per vial)	Function
(UNII: 451W47IQ8X)		
Dibasic sodium phosphate dihydrate (UNII: GR686LBA74)	0.49 mg	Excipient
Sucrose (UNII: C151H8M554)	46.0 mg	Excipient
Water for Injection (UNII: 059QF0KO0R)	0.450 mL	Excipient

UNII: Unique Ingredient Identifier

Stability of COMIRNATY in Multiple Dose Vial

For the long-term storage condition study, parameters monitored are Appearance, (b) (4) by (b) (4) LNP (b) (4) (b) (4) RNA content and (b) (4) (b) (4) Assay, Lipid (ALC-0315, ALC-0159, DSPC, and Cholesterol) Content by (b) (4) , Container closure integrity test by (b) (4) (b) (4) Endotoxin content by (b) (4) , and Sterility.

The stability data provided in the submission support a dating period of 9 months from the date of manufacture when stored at -90°C to -60°C for the COMIRNATY DP filled in 2 mL Type I borosilicate glass vials. Stability data on emergency use and process performance qualification lots also support storage at -20°C ± 5°C for up to 2 weeks as well as short term storage at 5°C ± 3°C for up to one month (within the 9-month expiry dating period).

The Diluent for COMIRNATY

The contents of the vaccine vial are diluted with sterile 0.9% Sodium Chloride Injection, USP. Vials of sterile 0.9% Sodium Chloride Injection, USP are provided but shipped separately. The provided diluent or another sterile 0.9% Sodium Chloride Injection, USP should be used as the diluent.

The provided 0.9% Sodium Chloride Injection, USP diluent will be supplied either as cartons of 10 mL single-use vials manufactured by Hospira, Inc (NDC 0409-4888-10), or 2 mL single-use vials manufactured by Fresenius Kabi USA, LLC (NDC 63323-186-02). The composition of the saline diluent and the function of the ingredients are provided in Table 3.

Table 3. Composition of the Diluent

Ingredients	Quantity (per 0.3 mL dose)	Function
SODIUM CHLORIDE (UNII: 451W47IQ8X)	2.16 mg	Excipient
Water for Injection (UNII: 059QF0KO0R)	0.3 mL	Excipient

UNII: Unique Ingredient Identifier

COMIRNATY

Product Composition

COMIRNATY Multiple Dose Vial is supplied as a frozen suspension that is diluted at the time of use with 1.8 mL of saline diluent. A single dose of COMIRNATY contains 30 ug mRNA in a volume of 0.3 mL, and it does not contain preservative. [*See section 10.b regarding exception to the 21 CFR 610.15(a) requirement for a preservative.*]

Stability of COMIRNATY

The Applicant conducted in-use stability studies to support the maximum temperature and time period that COMIRNATY can retain its physicochemical properties. Based on the data generated, COMIRNATY retains its quality attributes for up to 6 hours when stored between 2°C to 25°C (35°F to 77°F).

The carton labels and the Package Insert (PI) state that after dilution, vials should be stored between 2°C to 25°C (35°F to 77°F) and used within 6 hours from the time of dilution. During storage, exposure to room light should be minimized, and direct exposure to sunlight and ultraviolet light should be avoided. Any vaccine remaining in vials must be discarded after 6 hours and cannot be refrozen.

Assays used in clinical studies

Diagnostic Assays Used to Support Clinical Efficacy Endpoints

Two clinical diagnostic assays (Cepheid Xpert Xpress RT-PCR assay for the detection of SARS-CoV-2 in clinical specimens and Roche Elecsys Anti-SARS-CoV-2 assay for the evaluation of serostatus to SARS-CoV-2) were used to assess clinical endpoints. Both assays have received FDA authorization under EUA.

The Cepheid Xpert Xpress RT-PCR assay is a rapid, automated *in vitro* diagnostic test for the qualitative detection of the N and E gene sequences from nasopharyngeal, nasal, or mid-turbinate swab and/or nasal wash/aspirate specimens collected from patients suspected of having COVID-19. This assay is used to assess viral infection of the participants before vaccination and to confirm COVID-19 cases during study follow-up.

The Roche Elecsys Anti-SARS-CoV-2 assay is a rapid, automated *in vitro* diagnostic test for detecting the presence of antibodies to nucleocapsid (N) protein of SARS-CoV-2 (antigen not present in COMIRNATY) in serum or plasma samples. This is a qualitative assay marketed as an aid in identifying individuals with an adaptive immune response to SARS-CoV-2, which would indicate a recent or prior infection. This assay is used to assess serostatus of the participants before vaccination.

Data were submitted to support the suitability of both the Cepheid Xpert Xpress assay and the Roche Elecsys Anti-SARS-CoV-2 assay for their intended uses in Phase 2/3 clinical studies when performed at Pfizer's testing facility (Pfizer Vaccine Research and Development; Pearl River, NY).

Immunogenicity Assays Used for Exploratory Immunogenicity Endpoints

Two immunogenicity assays (SARS-CoV-2 mNeonGreen (mNG) virus microneutralization assay and (b) (4) direct Luminex assay (dLIA) for IgG

quantification) were used for evaluating the immune responses from clinical trial samples.

The SARS-CoV-2 mNG microneutralization assay measures neutralizing antibodies (50% inhibition titers) against SARS-CoV-2 using Vero cell monolayers in a 96-well plate format. The SARS-CoV-2 mNG virus is derived from the USA_WA1/2020 strain that had been rescued by reverse genetics and engineered to express a fluorescent reporter gene (mNeonGreen) upon productive infection of cells. The validation protocol (that includes evaluation of dilutional linearity, precision, limits of quantification, and limit of detection) and the results of the validation study, executed at Pfizer Hackensack Meridian Health Center (Nutley, New Jersey), were submitted to support the suitability of the assay for testing of clinical trial immunogenicity samples.

The(b) (4) S1 IgG dLIA measures IgG antibody levels to the subunit 1 (S1) of the SARS-CoV-2 spike protein in human serum samples. Qualification data provided in the submission support the(b) (4) dLIA for quantification of human IgG antibodies that bind to the S1 protein of SARS-CoV-2 and confirm that the assay is suitable for its intended use.

b. Testing Specifications

Specifications and Methods

The tests and specifications applied for routine release of COMIRNATY are shown in Table 4.

Table 4. Control of COMIRNATY: Tests and Specifications

Quality Attribute	Analytical Procedure	Acceptance Criteria
Appearance	Appearance (Visual)	White to off-white suspension
Appearance (Visible Particulates)	Appearance (Particles) (b) (4))	May contain white to off-white opaque, amorphous particles
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4) (b) (4)	(b) (4)
(b) (4)	(b) (4) (b) (4)	(b) (4)
LNP (b) (4)	(b) (4))	(b) (4)
LNP (b) (4)	(b) (4))	(b) (4)
RNA (b) (4)	(b) (4) assay	(b) (4)
RNA content	(b) (4) assay	(b) (4)
ALC-0315 content	(b) (4)	(b) (4)
ALC-0159 content	(b) (4)	(b) (4)
DSPC content	(b) (4)	(b) (4)
Cholesterol content	(b) (4)	(b) (4)
Vial content (volume)	Container content	Not less than (b) (4)
Lipid identities	(b) (4)	(b) (4) (ALC-0315, ALC-0159, Cholesterol, DSPC)

Quality Attribute	Analytical Procedure	Acceptance Criteria
Identity of encoded RNA	(b) (4)	Identity confirmed
(b) (4)	(b) (4)	(b) (4)
RNA (b) (4)	(b) (4)	(b) (4))
Bacterial Endotoxin	Endotoxin ((b) (4) (b) (4)	(b) (4)
Sterility	Sterility ((b) (4))	No Growth Detected
Container Closure Integrity	(b) (4)	Pass

Abbreviations: LNP = Lipid nanoparticles (b) (4)

The analytical methods and their validations and/or qualifications for the COMIRNATY DS and DP were found to be adequate for their intended use.

c. CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

d. Facilities Review / Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of COMIRNATY are listed in Table 5 below. The activities performed and inspectional histories are also noted in Table 5 and are further described in the paragraphs that follow.

Table 5. Facilities involved in the manufacture of COMIRNATY

Name/address	FEI Number	DUNS number	Inspection/ waiver	Results/ Justification
Pfizer Inc. 875 Chesterfield Parkway West Chesterfield, MO 63017 (b) (4) Manufacture *Drug Substance* Release and stability testing *Drug Product* Release and stability testing	1940118	004954111	Waiver	ORA Surveillance August 19-20, 2019 NAI
Wyeth BioPharma Division of Wyeth Pharmaceuticals LLC 1 Burtt Road Andover, MA 01810 *Drug Substance* Manufacture, release and stability testing *Drug Product* Release and stability testing	1222181	174350868	Pre-License Inspection	CBER Pre-license inspection July 19-23, 2021 VAI
Pharmacia & Upjohn Company LLC 7000 Portage Road Kalamazoo, MI 49001 *Drug Product* LNP production, bulk drug product formulation, fill and finish, primary packaging, secondary packaging, release and stability testing	1810189	618054084	Waiver	ORA/OBPO Surveillance May 11-20, 2021 VAI
Pfizer Manufacturing Belgium NV Rijksweg 12 Puurs, 2870 Belgium *Drug Product* LNP production, bulk drug product formulation, fill and finish, primary packaging, secondary packaging, release and stability testing	1000654629	370156507	Pre-license inspection	CBER Pre-license inspection June 24-July 2, 2021 NAI

Name/address	FEI Number	DUNS number	Inspection/ waiver	Results/ Justification
Pfizer Ireland Pharmaceuticals Grange Castle Business Park Clondalkin, Dublin 22 Ireland *Drug Product* Release and stability testing	3004145594	985586408	Waiver	ORA Surveillance November 4-12, 2019 VAI
(b) (4) *Drug Product* Release testing (sterility)	(b) (4)	(b) (4)	Waiver	CDER Pre-approval inspection (b) (4) VAI
(b) (4) *Drug Product* Release testing (sterility)	(b) (4)	(b) (4)	Waiver	ORA Surveillance (b) (4) VAI

ORA conducted a surveillance inspection of Pfizer Inc., Chesterfield, MO, from August 19 – 20, 2019. No Form FDA 483 was issued, and the inspection was classified as No Action Indicated (NAI).

CBER conducted a pre-license inspection (PLI) of Wyeth BioPharma Division of Wyeth Pharmaceuticals LLC from July 19 – 23, 2021. All inspectional issues were resolved, and the inspection was classified as Voluntary Action Indicated (VAI).

ORA conducted a surveillance inspection of Pharmacia & Upjohn Company LLC from May 11 – 20, 2021. All inspectional issues were resolved, and the inspection was classified as VAI.

CBER conducted a PLI of Pfizer Manufacturing Belgium NV from June 24 - July 2, 2021. No Form FDA 483 was issued, and the inspection was classified as NAI.

ORA conducted a surveillance inspection of Pfizer Ireland Pharmaceuticals from November 4 – 12, 2019. All inspectional issues were resolved, and the inspection was classified as VAI.

CDER conducted a pre-approval inspection of (b) (4) from (b) (4) (b) (4). All inspectional issues were resolved, and the inspection was classified as VAI.

ORA conducted a surveillance inspection of (b) (4) from (b) (4) (b) (4). All inspectional issues were resolved, and the inspection was classified as VAI.

e. Container/Closure System

The COMIRNATY drug product is filled and stored at -90°C to -60°C in a 2 mL glass vial sealed with a bromobutyl rubber stopper and an aluminum seal with flip-off plastic cap. The glass vials are supplied by (b) (4) The stopper and caps are supplied by (b) (4) (b) (4) , respectively.

Pfizer performed container closure integrity testing (CCIT) on the filled 2 mL glass vials using a (b) (4) test method. All acceptance criteria were met.

f. Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31. The FDA concluded that this request is justified, and no extraordinary circumstances exist that would require an environmental assessment.

4. Nonclinical Pharmacology/Toxicology

Nonclinical Toxicology

For the nonclinical safety evaluation, COMIRNATY was evaluated in two repeat dose toxicity studies in Wistar Han rats and a Combined Fertility and Developmental Study (Including Teratogenicity and Postnatal Investigations) in Wistar Han rats.

The repeat dose toxicity evaluations were conducted on COMIRNATY and a similar vaccine termed BNT162b2 (V8). COMIRNATY and BNT162b2 (V8) have identical amino acid sequences of the encoded antigens but COMIRNATY includes the presence of optimized codons to improve antigen expression. The IM route of exposure was selected as it is the route of clinical administration. Generation of an immune response to COMIRNATY was confirmed in rats in both repeat-dose toxicity studies. In both repeat-dose toxicity studies, administration of COMIRNATY by IM injection to male and female rats once every week for a total of 3 doses was tolerated without evidence of systemic toxicity. Edema and erythema at the injection sites, transient elevation in body temperature, elevations in white blood cells and acute phase reactants and decreased albumin:globulin ratios were observed. Injection site reactions were common in all vaccine-administered animals and were greater after boost immunizations.

For the Combined Fertility and Developmental Study, COMIRNATY was administered to female rats twice before the start of mating and twice during gestation at the human clinical dose (30 µg RNA/dosing day). There were some effects (change in body weight and food consumption and effects localized to the injection site) observed in rats in these studies following administration of COMIRNATY that were not considered adverse and a relationship to COMIRNATY was not established. There were no effects on mating performance, fertility, or any ovarian or uterine parameters nor on embryo-fetal or postnatal survival, growth, or development in the offspring. An immune response was observed in female rats following administration of each vaccine candidate and these responses were also detectable in the offspring (fetuses and pups).

Nonclinical Pharmacology and Pharmacokinetics

COMIRNATY was evaluated in nonclinical pharmacology studies using animal models of mice, rats and nonhuman primates (NHP). The data from these studies indicate: (1) strong antigen-binding IgG and high titer neutralizing antibodies in mice, rat and rhesus macaques; (2) Th1-biased CD4+ T-cell response and IFNγ+, CD8+ T-cell response to BNT162b2 in both mouse and NHP studies; and (3) protection of rhesus macaques from an infectious SARS-CoV-2 challenge, with reduced detection of viral RNA in the BNT162b2-immunized animals as compared with the control-immunized macaques.

Nonclinical pharmacokinetics (PK) evaluation included (1) biodistribution of COMIRNATY using (b) (4) expressing RNA as a surrogate reporter in (b) (4) mice and in rats, and (2) the biodistribution and metabolism of the two novel lipids (ALC-0315 and ALC-0159) contained in COMIRNATY in *in vitro* studies and in a PK study in rats following administration of (b) (4) expressing RNA encapsulated in LNPs made with radiolabeled lipid markers. The study results indicate that following IM injection, the RNA encapsulated in LNP mainly localizes to the site of injection and, to a lesser extent, distributes to the liver. The metabolism of ALC-0315 and ALC-0159 was evaluated *in vitro* using blood, liver microsomes, S9 fractions, and hepatocytes from mice, rats, monkeys and humans and in *vivo* by examining the plasma, urine, feces, and liver samples from the PK study in rats. Approximately 50% of ALC-0159 is excreted unchanged in feces, while metabolism appears to play a role in the elimination of ALC-0315.

5. Clinical Pharmacology

Pharmacodynamic data, comprised of humoral immune responses to COMIRNATY, were obtained in the clinical studies. The data demonstrated that COMIRNATY induces a humoral immune response against the SARS-CoV-2 spike protein. The exact immunologic mechanism that confers protection against SARS-CoV-2 is unknown.

6. Clinical/Statistical

a. Clinical Program

Overview

The Applicant included data from two clinical studies in the BLA. The clinical studies which will be discussed in this SBRA are shown in Table 6.

Table 6. Overview of Clinical Studies

Study ID	**C4591001**	**BNT162-01**
NCT ID	04368728	04380701
Phase	1/2/3	1/2
Countries	Argentina, Brazil, Germany, South Africa, Turkey, U.S.	Germany
Enrollment	Phase 1: 30 participants Phase 2/3: 43,847 participants	24
Age	16 - 85 YOA	18 - 85 YOA
Purpose	Evaluate VE for prevention of COVID-19 (pivotal clinical endpoint study)	Evaluate safety and immunogenicity

Study ID	C4591001	BNT162-01
Control	Saline Placebo	None
Groups	Phase 2/3: 2 groups, randomized 1:1 to receive COMIRNATY or Placebo IM	1 group, randomized received COMIRNATY IM
Schedule	D0, D21	D0, D21
Total follow-up	6 Months (follow-up ongoing)	6 Months (follow-up ongoing)

YOA: years of age; VE: vaccine efficacy; IM: intramuscular; D: day

Study C4591001

Study C4591001 is an ongoing, randomized, placebo-controlled, observer-blind Phase 1/2/3 study being conducted in the U.S., Argentina, Brazil, Germany, South Africa and Turkey. Initially the study was designed as a Phase 1/2 study in healthy adults in the U.S. for vaccine candidate and dosage selection, as well as evaluation of immunogenicity and preliminary efficacy. The protocol was expanded to include a Phase 2/3 portion of the study to evaluate clinical disease efficacy endpoint in individuals 12 years of age and older in the U.S. and additional sites outside of the U.S.

The Phase 1 portion of the study was designed to identify a preferred vaccine candidate, vaccine dose, and administration schedule for further development based on the vaccine's safety, tolerability, and immunogenicity. To this end, two age groups were evaluated in separate cohorts, younger adults 18 through 55 years of age (N=45) and older adults 65 through 85 years of age (N=45). The study population included healthy men and women and excluded participants at high risk of SARS-CoV-2 infection or with serological evidence of prior or current SARS-CoV-2 infection. Two different vaccine candidates were evaluated, and younger participants received increasing dose levels (10, 20 and 30 µg) with progression to higher dose levels in a stepwise manner. Evaluation of increasing doses in the older age group (65 through 85 years) was based on recommendations from an internal review committee that reviewed safety and immunogenicity data derived from adults 18 through 55 years of age. For each vaccine candidate and dose, participants were randomized 4:1, such that 12 participants received the vaccine candidate and 3 participants received placebo. Review of the safety and immunogenicity from the Phase 1 portion of Study C4591001, in combination with data from Study BNT162-01, supported the final vaccine candidate, dose and dosing regimen (BNT162b2 administered at 30 µg, given 3 weeks apart) to proceed to the Phase 2/3 portion of Study C4591001.

In Phase 2/3, participants were enrolled with stratification by age (younger adults: 18 through 55 years of age; older adults: over 55 years of age) with the goal for the older age strata to consist of 40% of the entire study population. Adolescents were added to the protocol, based on review of safety data in younger adults enrolled in the ongoing study; thus, the age strata were revised as follows: 16 through 55 years of age, and 56 years of age and older. The study population for Phase 2/3 includes participants at higher risk for acquiring COVID-19 and at higher risk of severe COVID-19, such as participants working in the healthcare field, participants with autoimmune disease, and participants with chronic but stable medical conditions such as hypertension, asthma, diabetes, and infection with HIV, hepatitis B or hepatitis C. Participants were randomized 1:1 to receive 2 doses of either COMIRNATY or placebo, 3 weeks apart. The Phase 2 portion of the study evaluated reactogenicity and immunogenicity of the vaccine in 360

participants in the early stage of Phase 2/3, and these participants also contribute to the overall efficacy and safety data in the Phase 3 portion.

The ongoing Phase 3 portion of the study is evaluating the safety and efficacy of COMIRNATY for the prevention of COVID-19 occurring at least 7 days after the second dose of vaccine. Efficacy is being assessed throughout a participant's blinded follow-up in the study through surveillance for potential cases of COVID-19. If, at any time, a participant develops acute respiratory illness, an illness visit occurs. Assessments for illness visits include a nasal (mid-turbinate) swab, which is tested at a central laboratory using a reverse transcription-polymerase chain reaction (RT-PCR) test (i.e., Cepheid; FDA- authorized under EUA), or other sufficiently validated nucleic acid amplification-based test (NAAT), to detect SARS-CoV-2. The central laboratory NAAT result is used for the case definition, unless it was not possible to test the sample at the central laboratory. In that case, the following NAAT results are acceptable: Cepheid Xpert Xpress SARS-CoV-2, Roche cobas SARS-CoV-2 real-time RT-PCR test (EUA200009/A001), and Abbott Molecular/RealTime SARS-CoV-2 assay (EUA200023/A001).

The study design included a planned interim analysis of the first primary efficacy endpoint (the efficacy of BNT162b2 against confirmed COVID-19 occurring from 7 days after Dose 2 in participants without evidence of SARS-CoV-2 infection before vaccination) at pre-specified numbers of COVID-19 cases (at least 62, 92, and 120 cases). All primary and secondary efficacy endpoints were analyzed in the final efficacy analysis after at least 164 COVID-19 cases were accrued. Participants are expected to participate for a maximum of approximately 26 months.

Per protocol, since December 14, 2020, following issuance of the emergency use authorization for the Pfizer-BioNTech COVID-19 Vaccine, study participants 16 years of age and older have been progressively unblinded to their treatment assignment (when eligible per local recommendations) and offered BNT162b2 vaccination if they were randomized to placebo.

The study was unblinded in stages as all ongoing participants were either individually unblinded (when eligible per local recommendations) or the subject had concluded their 6-month post–Dose 2 study visit. Participants 16 years of age and older who participated in the Phase 2/3 study were given the opportunity to receive COMIRNATY no later than the 6-month timepoint after the second study vaccination. Participants who originally received placebo but received COMIRNATY were moved to a new visit schedule to receive both doses of COMIRNATY, 3 weeks apart.

The primary safety and efficacy endpoints were:

1. Primary safety endpoint (descriptive): Solicited local adverse reactions (injection site pain, redness, swelling), solicited systemic adverse events (AE) (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain), unsolicited AEs, serious adverse events (SAEs).

2. First primary efficacy endpoint: COVID-19 incidence per 1000 person-years of follow-up based on laboratory-confirmed NAAT in participants with no serological or virological evidence (up to 7 days after Dose 2) of past SARS-CoV-2 infection.

3. Second primary efficacy endpoint: COVID-19 incidence per 1000 person-years of follow-up based on laboratory-confirmed NAAT in participants with and without serological or virological evidence (up to 7 days after Dose 2) of past SARS-CoV-2 infection.

The pertinent secondary endpoint was:

1. Severe COVID-19 incidence per 1000 person-years of follow-up.

Study C4591001 results

The population in the protocol-specified, event-driven final primary efficacy analysis included all participants 12 years of age and older who had been enrolled from July 27, 2020 and followed for the development of COVID-19 through November 14, 2020. For participants without evidence of SARS-CoV-2 infection prior to 7 days after Dose 2, VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 95.0% (95% credible interval: 90.0, 97.9), which met the pre-specified success criterion. The case split was 8 COVID-19 cases in the BNT162b2 group compared to 162 COVID-19 cases in the placebo group. This protocol-specified, event-driven final primary efficacy analysis was the basis for issuance of the emergency use authorization for the Pfizer-BioNTech COVID-19 Vaccine on December 11, 2020.

Therefore, the primary study objective of VE against COVID-19 was met as the point estimate was above 50% and the lower bound of the 95% CI of the point estimate of VE was above 30%.

The population for the updated vaccine efficacy analysis per protocol included participants 16 years of age and older who had been enrolled from July 27, 2020, and followed for the development of COVID-19 during blinded placebo-controlled follow-up through March 13, 2021, representing up to ~6 months of follow-up after Dose 2. Overall, 60.8% of participants in the COMIRNATY group and 58.7% of participants in the placebo group had ≥4 months of follow-up time after Dose 2 in the blinded placebo-controlled follow-up period. The overall VE against COVID-19 in participants without evidence of prior SARS-CoV-2 infection was 91.1% (95% CI: 88.8 to 93.1). The overall VE against COVID-19 in participants with or without evidence of prior SARS-CoV-2 infection was 90.9% (95% CI: 88.5 to 92.8).

The updated vaccine efficacy information is presented in Tables 7a and 7b.

Table 7a: First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection - Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period *

Subgroup	COMIRNATY N[a]=19,993 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=20,118 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI[e])
All participants	77 6.092 (19,711)	833 5.857 (19,741)	91.1 (88.8, 93.1)
16 through 64 years	70 4.859 (15,519)	709 4.654 (15,515)	90.5 (87.9, 92.7)
65 years and older	7 1.233 (4192)	124 1.202 (4226)	94.5 (88.3, 97.8)

* Participants who had no evidence of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

a. N = Number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.

Table 7b: First COVID-19 occurrence from 7 days after Dose 2 in participants with or without* evidence of prior SARS-CoV-2 infection - Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period *

Subgroup	COMIRNATY N[a]=21,047 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=21,210 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI[e])
All participants	81 6.340 (20,533)	854 6.110 (20,595)	90.9 (88.5, 92.8)
16 through 64 years	74 5.073 (16,218)	726 4.879 (16,269)	90.2 (87.5, 92.4)
65 years and older	7 1.267 (4315)	128 1.232 (4326)	94.7 (88.7, 97.9)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

a. N = Number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.

Efficacy Against Severe COVID-19

Vaccine efficacy against severe COVID-19 for participants with or without prior SARS-CoV-2 infection is shown in Tables 8a and 8b. The VE against severe COVID-19 in participants with or without evidence of prior SARS-CoV-2 infection was 95.3% (95% CI: 71.0 to 99.9) using the protocol definition of severe COVID-19 and 100.0% (95% CI: 87.6 to 100.0) based on the CDC definition of severe COVID-19.

Table 8a: Vaccine Efficacy – First Severe COVID-19 Occurrence in Participants 16 Years of Age and Older With or Without* Prior SARS-CoV-2 Infection Based on Protocol† Definition From 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up

	COMIRNATY Cases n1[a] Surveillance Time[b] (n2[c])	Placebo Cases n1[a] Surveillance Time[b] (n2[c])	Vaccine Efficacy % (95% CI[d])
7 days after Dose 2[d]	1 6.353 (20,540)	21 6.237 (20,629)	95.3 (70.9, 99.9)

Table 8b: Vaccine Efficacy – First Severe COVID-19 Occurrence in Participants 16 Years of Age and Older With or Without* Prior SARS-CoV-2 Infection Based on Centers for Disease Control and Prevention (CDC)‡ Definition From 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up

	COMIRNATY Cases n1[a] Surveillance Time[b] (n2[c])	Placebo Cases n1[a] Surveillance Time[b] (n2[c])	Vaccine Efficacy % (95% CI[d])
7 days after Dose 2[d]	0 6.345 (20,513)	31 6.225 (20,593)	100 (87.6, 100.0)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

† Severe illness from COVID-19 is defined in the protocol as confirmed COVID-19 and presence of at least 1 of the following:

- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥30 breaths per minute, heart rate ≥125 beats per minute, saturation of oxygen ≤93% on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen <300 mm Hg);
- Respiratory failure [defined as needing highflow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure <90 mm Hg, diastolic blood pressure <60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

‡ Severe illness from COVID-19 as defined by CDC is confirmed COVID-19 and presence of at least 1 of the following:

- Hospitalization;
- Admission to the Intensive Care Unit;
- Intubation or mechanical ventilation;
- Death.

a. n1 = Number of participants meeting the endpoint definition.
b. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
c. n2 = Number of participants at risk for the endpoint.

d. Two-side confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time

Study BNT162-01

Study BNT162-01 is an ongoing Phase 1/2, open-label, dose-finding study to evaluate the safety and immunogenicity of several candidate vaccines, including BNT162b2 (1, 3, 10, 20, and 30 μg), conducted in Germany in healthy and immunocompromised adults. Only safety and immunogenicity data in individuals 16 years of age and older, the population for the intended use and who received the final vaccine formulation (30 μg BNT162b2) are used to support this application. The 30 μg dosage of BNT162b2 was administered to 12 adults 18 to 55 years of age and 12 adults 56 to 85 years of age.

The primary objective was to evaluate the safety of the BNT162 candidate vaccines. Secondary and exploratory objectives were to describe humoral and cellular immune responses following vaccination, measured at baseline and various time points after vaccination, specifically 7 days post Dose 2. Adverse event monitoring was the same as the safety monitoring in study C4591001.

The study started April 23, 2020. The BLA contains safety data (reactogenicity and AE analyses) up to 1 month after Dose 2 (data cutoff date: October 23, 2020), neutralizing antibody data up to ~2 months after Dose 2 (data cutoff date: October 23, 2020), and T-cell data up to ~6 months after Dose 2 (data cutoff date: March 2, 2021).

Study BNT162-01 Results

Disposition of 30 μg BNT162b2 group:

- Safety: Of a total of 24 participants, 12 participants 18 to 55 years of age and 12 participants 56 to 85 years of age completed the visit at 1- month post-Dose 2.
- Immunogenicity: Of the 12 participants, serum neutralizing antibody and T-cell responses were available for 10 and 12 participants, respectively.

Safety: The safety profiles for adult participants 18-55 and 56-85 years of age receiving 30 μg BNT162b2 in this study were similar to age-matched participants in study C4591001.

Immunogenicity: Dose-dependent increases were noted 42 days after Dose 2, compared to SARS-CoV-2 neutralizing GMTs at baseline (pre-Dose 1), and most pronounced at the 30 μg dose level. The Th1 polarization of the T-helper response was indicated by IFNγ and IL-2 production, and only minimal IL-4 production upon antigen-specific (SARS-CoV-2 S protein peptide pools) re-stimulation.

Review of the safety and immunogenicity from Phase 1 part of Study C4591001, in combination with data from Study BNT162-01, supported selection of the final vaccine candidate and dose level (BNT162b2 at 30 μg, given as two doses 3 weeks apart) to proceed into Phase 2/3 part of Study C4591001.

Lot Consistency

Consistency of process performance qualification (PPQ) batches manufactured at both Pfizer Puurs and Pfizer Kalamazoo was demonstrated by verifying process parameters and in-process testing results as well as DP release testing. Data obtained from the analytical comparability assessments on the PPQ batches manufactured at both sites

provide evidence of reproducible and consistent manufacture of COMIRNATY DP of acceptable product quality across all supply nodes.

b. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance

BIMO inspection assignments were issued for a total of nine (9) clinical study sites that participated in the conduct of study Protocol C4591001. Three (3) of these inspection assignments focused on clinical study sites that enrolled the pediatric population and six (6) of the study sites enrolled the adult population. The inspections did not reveal findings that impact the BLA.

c. Pediatrics

The Applicant's Pediatric Plan was presented to the FDA Pediatric Review Committee (PeRC) on August 3, 2021. The committee agreed with the Applicant's request for a deferral for studies in participants 0 to <16 years of age because the biological product is ready for approval for use in individuals 16 years of age and older before pediatric studies in participants 0 to <16 years of age are completed (Section 505B(a)(3)(A)(i) of PREA).

The PREA-required studies specified in the approval letter and agreed upon with the Applicant are as follows:

1. Study C4591001 to evaluate the safety and effectiveness of COMIRNATY in children 12 years through 15 years of age

2. Study C4591007 to evaluate the safety and effectiveness of COMIRNATY in children 6 months to <12 years of age

3. Study C4591023 to evaluate the safety and effectiveness of COMIRNATY in infants <6 months of age

7. Safety and Pharmacovigilance

The most commonly reported (≥10%) solicited adverse reactions in COMIRNATY recipients 16 through 55 years of age following any dose were pain at the injection site (88.6%), fatigue (70.1%), headache (64.9%), muscle pain (45.5%), chills (41.5%), joint pain (27.5%), fever (17.8%), and injection site swelling (10.6%). The most commonly reported (≥10%) solicited adverse reactions in COMIRNATY recipients 56 years of age and older following any dose were pain at the injection site (78.2%), fatigue (56.9%), headache, (45.9%), muscle pain (32.5%), chills (24.8%), joint pain (21.5%), injection site swelling (11.8%), fever (11.5%), and injection site redness (10.4%).

follow-up after Dose 2. There were no notable patterns between treatment groups for specific categories of serious adverse events (including neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to COMIRNATY.

From Dose 1 through the March 13, 2021 data cutoff date, there were a total of 38 deaths, 21 in the COMIRNATY group and 17 in the placebo group. None of the deaths were considered related to vaccination.

Since the issuance of the EUA (December 11, 2020), post-authorization safety data has been reported from individuals 16 years of age and older following any dose of COMIRNATY. Because these reactions are reported from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. Below are presented adverse reactions categorized as important identified risks in the pharmacovigilance plan that have occurred during the conduct of the clinical trial and have been reported following the issuance of the EUA.

Myocarditis/Pericarditis
During the time from Dose 1 to unblinding in Study C4591001, one report of pericarditis was identified in the COMIRNATY group, occurring in a male participant ≥55 years of age, with no medical history, 28 days after Dose 2; the event was assessed by the investigator as not related to the study intervention and was ongoing at the time of the data cutoff. One report of myocarditis was identified in a male participant <55 years of age in the placebo group, occurring 5 days after his second placebo dose.

Post-EUA safety surveillance reports received by FDA and CDC identified serious risks for myocarditis and pericarditis following administration of COMIRNATY. Reporting rates for medical chart-confirmed myocarditis/pericarditis in VAERS have been higher among males under 40 years of age than among females and older males and have been highest in males 12-17 years of age (65 cases per million doses administered as per CDC communication on August 20, 2021), particularly following the second dose, and onset of symptoms within 7 days following vaccination. Although some cases of vaccine-associated myocarditis/pericarditis required intensive care support, available data from short-term follow up suggest that most individuals have had resolution of symptoms with conservative management. Information is not yet available about potential long-term sequelae and outcomes in affected individuals. A mechanism of action by which the vaccine could cause myocarditis and pericarditis has not been established.

These safety findings of increased risk for myocarditis/pericarditis led to warning in section 5.2 Warning and Precautions of the PI.

Myocarditis and pericarditis are considered important identified risks in the pharmacovigilance plan included in the BLA. Of note, the Applicant will be required to conduct postmarketing requirement (PMR) safety studies under Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) to assess the known serious risks of myocarditis and pericarditis as well as an unexpected serious risk for subclinical myocarditis (see Section 11c Recommendation for Postmarketing Activities, for study details).

Moreover, since vaccine-associated myocarditis/pericarditis is the most clinically significant identified risk, FDA undertook a quantitative benefit-risk assessment to model the excess risk of myocarditis/pericarditis vs. the expected benefits of preventing COVID-19 and associated hospitalizations, ICU admissions, and deaths. For estimation of risk, the model took a conservative approach by relying on non-chart-confirmed cases from a US healthcare claims database (OPTUM) that could provide a control group and greater confidence in denominators for vaccine exposures. Thus, the estimates of excess risk in this model are higher than the rates estimated from reports to VAERS (an uncontrolled passive surveillance system), with an estimated excess risk approaching 200 cases per million vaccinated males 16-17 years of age (the age/sex-stratified group with the highest risk). For estimation of benefit, the model output was highly dependent on the assumed COVID-19 incidence, as well as assumptions about vaccine efficacy and duration of protection. The assessment therefore considered a range of scenarios including but not limited to a “most likely” scenario associated with recent Delta variant surge and diminished vaccine effectiveness (70% overall, 80% against COVID-19 hospitalization) compared to that observed in the clinical trial. The “worst-case” scenario with low COVID-19 incidence reflecting the July 2021 nadir and the same somewhat diminished vaccine effectiveness as in the “most likely” scenario.

For males and females 18 years of age and older and for females 16-17 years of age, even before accounting for morbidity prevented from non-hospitalized COVID-19, the model predicts that the benefits of prevented COVID-19 hospitalizations, ICU admissions and deaths would clearly outweigh the predicted excess risk of vaccine-associated myocarditis/pericarditis under all conditions examined. For males 16-17 years of age, the model predicts that the benefits of prevented COVID-19 hospitalizations, ICU admissions and deaths would clearly outweigh the predicted excess risk of vaccine-associated myocarditis/pericarditis under the “most likely” scenario, but that predicted excess cases of vaccine-associated myocarditis/pericarditis would exceed COVID-19 hospitalizations and deaths under the “worst case” scenario. However, this predicted numerical imbalance does not account for the greater severity and length of hospitalization, on average, for COVID-19 compared with vaccine-associated myocarditis/pericarditis. Additionally, the “worst case” scenario model predicts prevention of >13,000 cases of non-hospitalized COVID-19 per million vaccinated males 16-17 years of age, which would include prevention of clinically significant morbidity and/or long-term sequelae associated with some of these cases. Finally, the model does not account for indirect societal/public health benefits of vaccination. Considering these additional factors, FDA concluded that even under the “worst case” scenario the benefits of vaccination sufficiently outweigh risks to support approval of the vaccine in males 16-17 years of age.

Mitigation of the observed risks and associated uncertainties will be accomplished through labeling (including warning statements) and through continued safety surveillance and postmarketing studies to further assess and understand these risks, including an immunogenicity and safety study of lower dose levels of COMIRNATY in individuals 12 through <30 years of age. The Applicant will be required to conduct postmarketing requirement (PMR) safety studies under Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) to assess the known serious risks of myocarditis and pericarditis and an unexpected serious risk for subclinical myocarditis (see section 11c for study details).

Anaphylaxis
The risk of anaphylaxis was recognized early in the post-authorization time period and it is included as an important identified risk in the PVP. The estimated crude reporting rate for anaphylaxis is 6.0 cases per million doses. Therefore, the incidence of anaphylaxis after receipt of COMIRNATY is comparable with those reported after receipt of other vaccines.

There were no reports of anaphylaxis associated with COMIRNATY in clinical study participants through the cutoff date of March 13, 2021.

A contraindication for individuals with known history of a severe allergic reaction (e.g., anaphylaxis) to any component of COMIRNATY is included in section 4 of the PI. Additionally, a warning statement is included in section 5.1 of the PI instructing that "appropriate medical treatment used to manage immediate allergic reactions must be immediately available in the event an acute anaphylactic reaction occurs following administration of COMIRNATY"

Pharmacovigilance Plan (PVP)
The Applicant's proposed pharmacovigilance plan (version 1.1) includes the following important risks and missing information:

- Important identified risks: Anaphylaxis; Myocarditis and Pericarditis
- Important potential risk: Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)
- Missing information: Use in pregnancy and lactation; Vaccine effectiveness; Use in pediatric individuals <12 years of age

In addition to routine pharmacovigilance, the Applicant will conduct the postmarketing studies listed in Section 11c Recommendation for Postmarketing Activities.

Adverse event reporting under 21 CFR 600.80 and the postmarketing studies in Section 11c are adequate to monitor the postmarketing safety for COMIRNATY.

8. Labeling

The proprietary name, COMIRNATY, was reviewed by CBER's Advertising and Promotional Labeling Branch (APLB) on July 2, 2021, and found to be acceptable. CBER communicated this decision to the Applicant on July 6, 2021. The APLB found the PI and package/container labels to be acceptable from a promotional and comprehension perspective. The Review Committee negotiated revisions to the PI, including modifying the proposed proper name from "COVID-19 mRNA vaccine (nucleoside-modified)" to "COVID-19 Vaccine, mRNA" and including a warning for an increased risk of myocarditis and pericarditis following administration of COMIRNATY. All labeling issues regarding the PI and the carton and container labels were acceptably resolved after exchange of information and discussions with the Applicant.

9. Advisory Committee Meetings

Vaccines and Related Biological Products Committee (VRBPAC) meetings were convened on October 22, 2020 to discuss, in general, development for EUA and licensure of vaccines to prevent COVID-19 and on December 10, 2020, to discuss BioNTech Manufacturing GmbH/Pfizer's EUA request for the Pfizer-BioNTech COVID-19 Vaccine.

On October 22, 2020, the VRBPAC was presented with the following items for discussion (no vote):

1. Please discuss FDA's approach to safety and effectiveness data as outlined in the respective guidance documents.

2. Please discuss considerations for continuation of blinded Phase 3 clinical trials if an EUA has been issued for an investigational COVID-19 vaccine.

3. Please discuss studies following licensure and/or issuance of an EUA for COVID-19 vaccines to
    a. Further evaluate safety, effectiveness and immune markers of protection
    b. Evaluate the safety and effectiveness in specific populations

In general, the VRBPAC endorsed FDA's approach and recommendations on the safety and effectiveness data necessary to support a BLA and EUA for COVID-19 vaccines as outlined in the respective guidance documents. VRBPAC members recommended for the median follow-up of 2 month to be the minimum follow-up period and suggested longer follow-up periods to evaluate, both safety and efficacy, if feasible. The VRBPAC endorsed the importance of additional studies to further evaluate safety and effectiveness of the vaccine after EUA issuance and/or licensure and underscored the need to evaluate the safety and effectiveness of COVID-19 vaccines in specific populations.

On December 10, 2020, VRBPAC discussed Pfizer- BioNTech Manufacturing GmbH's EUA request for their vaccine to prevent COVID-19 in individuals 16 years of age and older. The committee discussed the safety and efficacy data derived from the clinical disease endpoint efficacy study C4591001.

The VRPBAC voted on one question:

1. Based on the totality of scientific evidence available, do the benefits of the Pfizer-BioNTech COVID-19 Vaccine outweigh its risks for use in individuals 16 years of age and older?

    The results of the vote were as follows:
    Yes = 17 No = 4 Abstain = 1

The VRBPAC was presented with the following items for discussion (no vote):

1. Pfizer has proposed a plan for continuation of blinded, placebo-controlled follow-up in ongoing trials if the vaccine were made available under EUA. Please discuss

Pfizer's plan, including how loss of blinded, placebo-controlled follow-up in ongoing trials should be addressed.

2. Please discuss any gaps in plans described today and in the briefing documents for further evaluation of vaccine safety and effectiveness in populations who receive the Pfizer-BioNTech COVID-19 Vaccine under an EUA.

The committee discussed potential implications of loss of blinded, placebo-controlled follow-up in ongoing trials including how this may impact availability of safety data to support a BLA. The VRBPAC commented on the need to further assess vaccine effect on asymptomatic infection and viral shedding, and further evaluation of safety and effectiveness in subpopulations such as HIV-infected individuals, individuals with prior exposure to SARS-CoV-2.

FDA did not refer this application to the VRBPAC because our review of the information submitted to this BLA did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

10. Other Relevant Regulatory Issues

a. Identification of BLA Lots

Upon CBER's request inquiring about what BLA-compliant EUA-labeled lots may be available for use upon licensure of COMIRNATY, the Applicant submitted information listing which lots they considered to be manufactured according to the BLA. To address the issue of these lots not bearing the vial label associated with BLA approval, CBER worked with the Applicant to develop a Dear HCP letter to be included with lots considered by CBER to be BLA-compliant. This letter explained that some lots labeled for EUA use were also considered BLA-compliant and refers HCP to a website for additional information. CBER requested and the Applicant agreed that only EUA-labeled lots that had also undergone CBER lot release according to the BLA would be considered BLA-compliant and listed at the website included in the Dear HCP letter.

b. Exception to the 21 CFR 610.15(a) Requirement for a Preservative

Under 21 CFR 610.15(a), a vaccine product in multiple-dose containers must (absent certain exceptions) contain a preservative. The Applicant submitted a request for exception to this requirement and provided a justification for the multi-dose presentation of COMIRNATY not containing a preservative. CBER considered the Applicant's request for an exception to the 21 CFR 610.15(a) for COMIRNATY as a multiple dose preservative-free presentation acceptable.

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

Based on the review of the clinical, pre-clinical, and product-related data submitted in the original BLA, the Review Committee recommends approval of COMIRNATY for the labeled indication and usage.

b. Benefit/Risk Assessment

Considering the data submitted to support the safety and effectiveness of COMIRNATY that have been presented and discussed in this document, as well as the seriousness of COVID-19, the Review Committee is in agreement that the risk/benefit balance for COMIRNATY is favorable and supports approval for use in individuals 16 years of age and older.

c. Recommendation for Postmarketing Activities

BioNTech Manufacturing GmbH has committed to conduct the following postmarketing activities, which will be included in the approval letter.

POSTMARKETING REQUIREMENTS UNDER SECTION 505(o)

1. Study C4591009, entitled "A Non-Interventional Post-Approval Safety Study of the Pfizer-BioNTech COVID-19 mRNA Vaccine in the United States," to evaluate the occurrence of myocarditis and pericarditis following administration of COMIRNATY

   Final Protocol Submission: August 31, 2021
   Monitoring Report Submission: October 31, 2022
   Interim Report Submission: October 31, 2023
   Study Completion: June 30, 2025
   Final Report Submission: October 31, 2025

2. Study C4591021, entitled "Post Conditional Approval Active Surveillance Study Among Individuals in Europe Receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine," to evaluate the occurrence of myocarditis and pericarditis following administration of COMIRNATY

   Final Protocol Submission: August 11, 2021
   Progress Report Submission: September 30, 2021
   Interim Report 1 Submission: March 31, 2022
   Interim Report 2 Submission: September 30, 2022
   Interim Report 3 Submission: March 31, 2023
   Interim Report 4 Submission: September 30, 2023
   Interim Report 5 Submission: March 31, 2024
   Study Completion: March 31, 2024
   Final Report Submission: September 30, 2024

3. Study C4591021 substudy to describe the natural history of myocarditis and pericarditis following administration of COMIRNATY

   Final Protocol Submission: January 31, 2022
   Study Completion: March 31, 2024
   Final Report Submission: September 30, 2024

4. Study C4591036, a prospective cohort study with at least 5 years of follow-up for potential long-term sequelae of myocarditis after vaccination (in collaboration with Pediatric Heart Network)

Final Protocol Submission: November 30, 2021
Study Completion: December 31, 2026
Final Report Submission: May 31, 2027

5. Study C4591007 substudy to prospectively assess the incidence of subclinical myocarditis following administration of the second dose of COMIRNATY in a subset of participants 5 through 15 years of age

   Final Protocol Submission: September 30, 2021
   Study Completion: November 30, 2023
   Final Report Submission: May 31, 2024

6. Study C4591031 substudy to prospectively assess the incidence of subclinical myocarditis following administration of a third dose of COMIRNATY in a subset of participants 16 to 30 years of age

   Final Protocol Submission: November 30, 2021
   Study Completion: June 30, 2022
   Final Report Submission: December 31, 2022

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

7. Study C4591022, entitled “Pfizer-BioNTech COVID-19 Vaccine Exposure during Pregnancy: A Non-Interventional Post-Approval Safety Study of Pregnancy and Infant Outcomes in the Organization of Teratology Information Specialists (OTIS)/MotherToBaby Pregnancy Registry”

   Final Protocol Submission: July 1, 2021
   Study Completion: June 1, 2025
   Final Report Submission: December 1, 2025

8. Study C4591007 substudy to evaluate the immunogenicity and safety of lower dose levels of COMIRNATY in individuals 12 through <30 years of age

   Final Protocol Submission: September 30, 2021
   Study Completion: November 30, 2023
   Final Report Submission: May 31, 2024

9. Study C4591012, entitled “Post-emergency Use Authorization Active Safety Surveillance Study Among Individuals in the Veteran’s Affairs Health System Receiving Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine”

   Final Protocol Submission: January 29, 2021
   Study Completion: June 30, 2023
   Final Report Submission: December 31, 2023

10. Study C4591014, entitled “Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study - Kaiser Permanente Southern California”

Final Protocol Submission: March 22, 2021
Study Completion: December 31, 2022
Final Report Submission: June 30, 2023

PEDIATRIC REQUIREMENTS

11. Deferred pediatric study C4591001 to evaluate the safety and effectiveness of COMIRNATY in children 12 years through 15 years of age

    Final Protocol Submission: October 7, 2020
    Study Completion: May 31, 2023
    Final Report Submission: October 31, 2023

12. Deferred pediatric study C4591007 to evaluate the safety and effectiveness of COMIRNATY in children 6 months to <12 years of age

    Final Protocol Submission: February 8, 2021
    Study Completion: November 30, 2023
    Final Report Submission: May 31, 2024

13. Deferred pediatric study C4591023 to evaluate the safety and effectiveness of COMIRNATY in infants <6 months of age

    Final Protocol Submission: January 31, 2022
    Study Completion: July 31, 2024
    Final Report Submission: October 31, 2024

Exhibit N

Southwest Airlines cancels 1,800 flights days after pilot union sued over Covid-19 vaccine mandate

Company blamed problems on 'disruptive weather' and air traffic control issues

Graeme Massie Los Angeles | Monday 11 | comments

Southwest Airlines cancels thousands of flights

Southwest Airlines cancelled at least 1,800 flights just days after its pilot union sued the company over its Covid-19 vaccine mandate.

Southwest was forced to cancel more than 1,000 flights on Sunday, around 30 per cent of its US schedule, according to the FlightAware website.

And it blamed "disruptive weather" and air traffic control issues for its problems.

But the Federal Aviation Administration said that airlines were experiencing problems because of their own difficulties with staffing and aircraft

aircraft.

And another 800 flights were cancelled on Saturday, according to The Washington Post.

The airline said in a Sunday statement that its problems began on Friday because of weather issues at its Florida airports that "were compounded by unexpected air traffic control issues in the same region, triggering delays and prompting significant cancellations for us beginning Friday evening."

Southwest's issues with weather and traffic control did not appear to be shared by other airlines.

American Airlines reportedly had around 63 cancellations as of early Sunday afternoon and United Airlines only had nine.

The FAA responded by saying that there were some air traffic staffing issues but that the main issue belonged to the airlines.

"Flight delays and cancellations occurred for a few hours Friday afternoon due to widespread severe weather, military training, and limited staffing in one area of the Jacksonville Air Route Traffic Control Center," the FAA said in a Sunday statement.

"Some airlines continue to experience scheduling challenges due to aircraft and crews being out of place."

Southwest said it was attempting to reposition aircraft and crews so that service could get back to normal.

The Southwest Airlines Pilots Association said in its own statement that pilots that although it was aware of "operational difficulties affecting Southwest Airlines" it could "say with confidence that our Pilots are not participating in any official or unofficial job actions."

And the union added: "Our Pilots will continue to overcome (Southwest) management's poor planning, as well as any external operational challenges, and remain the most productive Pilots in the world."

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The Southwest Airlines Pilots Association, which on Tuesday said it was filing a temporary restraining order against the Dallas airline related to its

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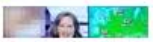
Police investigating after TV

filing a temporary restraining order against the Dallas airline related to its August lawsuit over Covid-19 mandates.

Southwest says all of its employees must be vaccinated against Covid-19 by 8 December or face losing their job.

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Exhibit O

Southwest Airlines debacle is symptomatic of bigger pandemic problems

BY SHELDON H. JACOBSON, PH.D., OPINION CONTRIBUTOR — 10/18/21 05:00 PM EDT
THE VIEWS EXPRESSED BY CONTRIBUTORS ARE THEIR OWN AND NOT THE VIEW OF THE HILL

© Greg Nash

Southwest Airlines had more than 2,000 flight cancellations last week. There is nothing to indicate that such cancellations will permanently stop, and they may even bleed into the upcoming busy travel holiday season, with travelers across the nation inconvenienced.

Southwest management attributed the onslaught of flight cancellations to air traffic control issues and weather problems. Although these factors may have contributed to such cancellations, they are unlikely to have been the primary cause, since no other airlines experienced such widespread flight disruptions during the same period.

The key driver for such cancellations is likely the COVID-19 vaccine mandate for its employees. Southwest employees are expressing their concern in droves by simultaneously and strategically using their sick time benefits.

Southwest has built a reputation on taking care of its employees, which has resulted in unprecedented profitability during the most challenging economic downturns, a

record that none of the other legacy airlines like American, Delta and United have been able to match.

Some employees believe that the vaccine mandate is in direct contradiction to Southwest's internal practice of "employees first, customers second." If Southwest adhered to this policy, employees may think that the company would find a workable solution to meet their wishes. Clearly, some employees believe that not showing up for work is preferable to being subject to a top-down federal mandate that they believe is not in their best interests.

There are several factors that make Southwest particularly vulnerable to widespread employee no-shows.

Southwest does not employ a hub-and-spoke system like the other legacy airlines. That means their schedule is designed around point-to-point flights. As such, there are fewer flight alternatives with flight cancellations for any reason. It also makes it more difficult to fill pilot and flight attendant requirements when such people call in sick or become unavailable on short notice. This makes Southwest more vulnerable to staffing shortages than the other legacy airlines, who can move pilots and flight attendants around with greater ease and facility.

Given that Southwest has around 55,000 employees, if each flight cancelled involved just two employees scheduled to cover three flights, then that translates into just over 2 percent of their employees being unavailable. This illustrate how vulnerable the airline is to organized worker shortages even among a small group of potentially disgruntled employees.

Southwest falls under President Biden's vaccination mandate, so they must abide by it: requiring that employees for companies with more than 100 workers get vaccinated. Although some employees under this mandate can opt for weekly COVID-19 testing in lieu of vaccination, federal contractors — like airlines — cannot.

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Texas Gov. Greg Abbot (R) issued a ban to stop the implementation of vaccine mandates. The Southwest Pilot Union is also fighting any mandates for their members. However, both Southwest and American Airlines, which are both based out of Dallas will continue to require all their employees to abide by the federal vaccine mandate.

Southwest employees not showing up for work is effectively a strike. Using sick time benefits means that employees can be paid while coordinating their efforts to send a message about vaccination. Such a systematic process can be used periodically to communicate their displeasure with any company policy, including the current vaccine mandate.

Southwest's company policy seemingly does everything to keep its employees happy. When confronted with a federal mandate that a minority of (but vociferous) employees is unhappy with, it became vulnerable to flight disruptions and cancellations that other airlines could better buffer.

The lesson learned from this is that a company is only as strong as its people, and when some of them revolt, there are consequences.

New York City launching ad blitz to lure back foreign tourists

UK secures deals with Merck, Pfizer for COVID-19 antiviral pills

The biggest loser in this ordeal are the customers who became innocent victims of the actions of a few. Given the alternatives available in the vaccine mandate, these employees may wish to rethink their strategy moving forward. If a sufficient number of customers ditch Southwest for seemingly more reliable competitors, they may find themselves without a job to call in sick to. Then they will get their wish and no longer require vaccination.

Sheldon H. Jacobson, Ph.D., is a founder professor of Computer Science at the University of Illinois at Urbana-Champaign. He applies his expertise in data-driven risk-based decision-making to evaluate and inform public health policy. His research provided the technical foundations for TSA PreCheck.

This piece has been updated to reflect vaccination mandates for federal contractors.

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Health expert says other COVID-19 variants 'pale in comparison' to delta

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Policy analyst says massive defense bill puts US in 'arms race' with China

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Exhibit P

Southwest CEO says he's against vaccine mandates, blames Biden

By Emily Crane

October 12, 2021 | 12:45pm | Updated

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SOUTHWEST AIRLINES

Southwest nixes plan to put these unvaccinated staff on unpaid leave

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Analysts skeptical of Southwest's explanation on mass cancelations

Southwest Airlines CEO Gary Kelly says he's against making his employees take the COVID-19 vaccine, but President Biden has forced his hand with the federal mandate.

"I've never been in favor of corporations imposing that kind of a mandate. I'm not in favor of that, never have been," Kelly told CNBC's "Squawk on the Street" on Tuesday regarding the COVID-19 vaccine.

Kelly said his employees "have very strong views on both sides" of the issue of vaccine mandates but they were being forced to take it given Biden's executive order.

"The executive order from President Biden mandates that all federal employees and then all federal contractors, which covers all the major airlines, have to have a mandate vaccine in place by Dec. 8 so we're working through that," Kelly said.

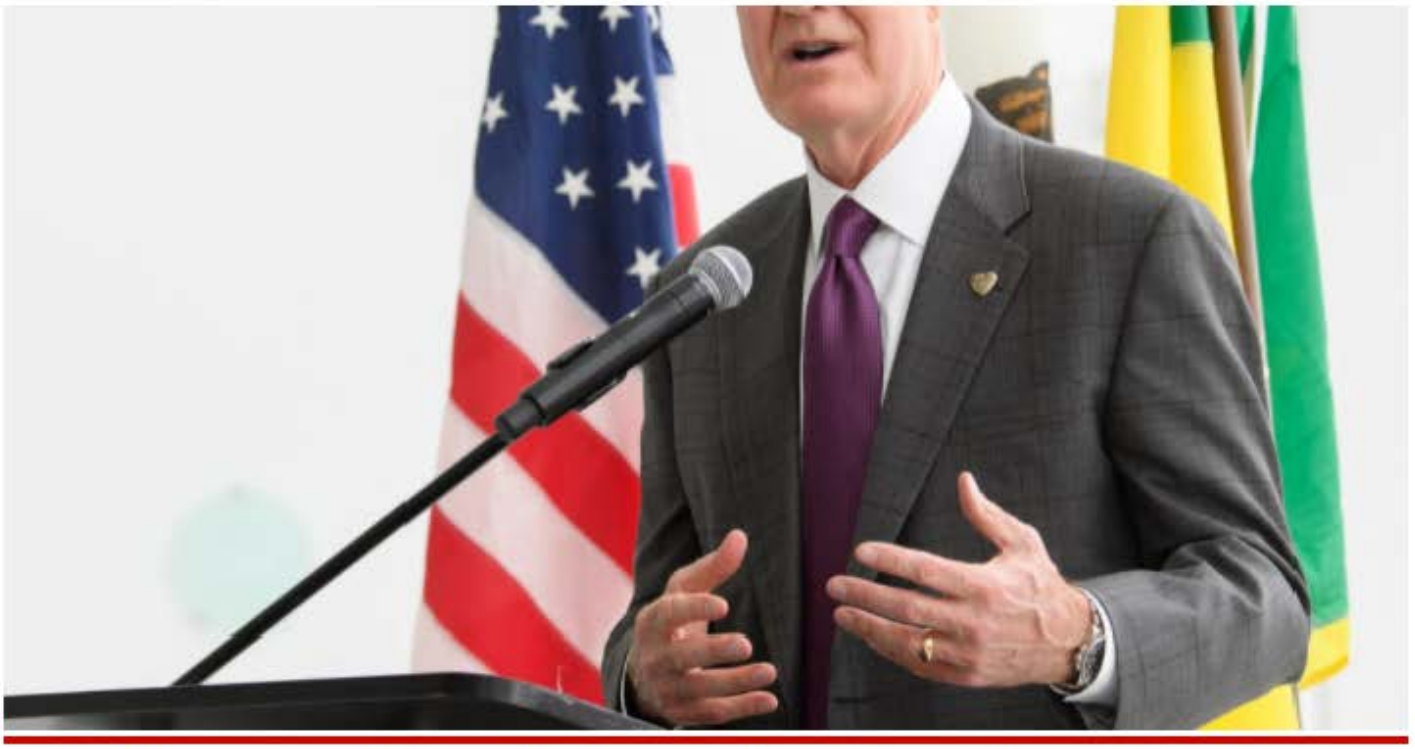
The CEO said Southwest is urging all employees to get vaccinated because his goal is to make sure none of his employees lose their jobs.

"If they can't (get vaccinated), we're urging them to seek an accommodation either for medical or religious reasons," Kelly said. "The objective here, obviously, is to improve health and safety, not for people to lose their jobs."

Gary Kelly says Southwest was forced to implement the vaccine mandate given President Biden's executive order.
Olivier Douliery/AFP via Getty Images

Southwest is offering employees the equivalent of two days' pay as an incentive to get vaccinated, and to compensate them for any potential side effects, Kelly said.

It comes after the airline was rocked by mass cancellations that forced Southwest to ground more than 25 percent of its scheduled flights over the weekend and another 10 percent on Monday.



Southwest Airlines CEO Gary Kelly came out against COVID-19 vaccination mandates, saying, "I'm not in favor of that, never have been."

Patrick T. Fallon/AFP via Getty Images

Kelly and the Federal Aviation Administration have both said the vaccine mandate was not to blame for the recent travel chaos.

Southwest is offering employees the equivalent of two days' pay as an incentive to get vaccinated.

Steven Senne/AP

"To be clear: None of the information from Southwest, its pilots union, or the FAA indicates that this weekend's cancellations were related to vaccine mandates," the FAA tweeted Monday evening.

Kelly echoed the FAA in an interview with ABC's "Good Morning America" Tuesday morning, saying "there's just no evidence of that."

"I want to apologize to all of our customers. This is not what we want but unfortunately it just takes a couple of days to get things back on track," he added.

Gary Kelly echoed the FAA in assuring that the mass Southwest flight cancellations were not tied to the vaccine mandate.

Jim Lo Scalzo/EPA-EFE/Shutterstock

As of 9 a.m. ET Tuesday, Southwest had canceled about 90 scheduled flights, or about 2 percent of the day's departures, according to Flight Aware. Another nearly 250 were delayed, the site said.

Additional reporting by Will Feuer

Exhibit Q

Southwest drops plan to put unvaccinated staff on unpaid leave starting in December

PUBLISHED TUE, OCT 19 2021•9:10 AM EDT | UPDATED TUE, OCT 19 2021•8:08 PM EDT

Leslie Josephs
@LESLIEJOSEPHS

KEY POINTS

- Southwest scrapped a plan to put unvaccinated workers with pending exemptions on unpaid leave after the Dec. 8 deadline.
- Both American and Southwest require their new-hire employees to show proof of Covid-19 vaccination before their first day.
- Large airlines are federal contractors and subject to a Biden administration order that requires their employees to be vaccinated or receive an exemption for medical or religious reasons.

Travelers wait to check in at the Southwest Airlines ticketing counter at Baltimore Washington International Thurgood Marshall Airport on October 11, 2021 in Baltimore, Maryland.
Kevin Dietsch | Getty Images

Southwest Airlines has scrapped a plan to put unvaccinated employees who

have applied for but haven't received a religious or medical exemption on unpaid leave as of a federal deadline in December.

Southwest Airlines and American Airlines are among the carriers that are federal contractors and subject to a Biden administration requirement that their employees are vaccinated against Covid-19 by Dec. 8 unless they are exempt for medical or religious reasons.

Rules for federal contractors are stricter than those expected from the Biden administration for large companies, which will allow for regular Covid testing as an alternative to a vaccination.

Executives at both carriers in recent days have tried to reassure employees about job security under the mandate, urging them to apply for exemptions if they can't get vaccinated for a medical reason or for a sincerely held religious belief. The airlines are expected to face more questions about the mandate when they report quarterly results Thursday morning. Pilots' labor unions have sought to block the mandates or sought alternatives such as regular testing.

Southwest's senior vice president of operations and hospitality, Steve Goldberg, and Julie Weber, vice president and chief people officer, wrote to staff on Friday that if employees' requests for an exemption haven't been approved by Dec. 8, they could continue to work while following mask and distancing guidelines until the request has been reviewed.

The company is giving employees until Nov. 24 to finish their vaccinations or

apply for an exemption. It will continue paying them while the company reviews their requests and said it will allow those who are rejected to continue working "as we coordinate with them on meeting the requirements (vaccine or valid accommodation)."

"This is a change from what was previously communicated. Initially, we communicated that these Employees would be put on unpaid leave and that is no longer the case," they wrote in the note, which was reviewed by CNBC.

Southwest confirmed the policy change, which comes just weeks before the deadline.

United Airlines implemented its own vaccine mandate in August, a month before the government rules were announced. United had told staff that they would be put on unpaid leave if they received exemptions. More than 96% of its staff is vaccinated. Some employees sued the company over the unpaid leave, and a federal judge in Fort Worth, Texas, has temporarily blocked the airline from going forward with its plan.

American's CEO, Doug Parker, spoke with labor union leaders on Thursday to discuss vaccine exemptions.

American Airlines management "indicated that, unlike the approach taken by United, they were exploring accommodations that would allow employees to continue to work," the Association of Professional Flight Attendants, the union that represents American's mainline cabin crews, said in a note to members Monday. "They failed to offer any specifics as to what such accommodations might look like at that time."

The Fort Worth, Texas-based airline confirmed to employees Tuesday that they can continue to work if they are granted an exemption or if their exemption requests are still being reviewed. Those workers could have to follow certain protocols, like wearing a mask and providing regular health declarations, however.

American also told staff to apply for exemptions as soon as possible, writing in an internal staff post about the mandate that the "process to review all requests will take time, as we want to ensure we give full consideration to all requests."

Choosing not to be vaccinated and not receiving an exemption may still result in termination, American said. It is not planning voluntary leaves or early retirement packages for those who choose not to get vaccinated.

"We want all of our team members to be vaccinated so they can continue working at American," it said. "We need our entire team to run the airline in 2022 and beyond and are not looking to reduce headcount."

The Allied Pilots Association, which represents American's roughly 14,000 pilots, wrote to the White House and several key lawmakers on Sept. 24, urging an alternative to the mandate such as regular testing, warning the mandate "could result in labor shortages and create serious operational problems for American Airlines and its peers."

Hundreds of Southwest employees, customers and other protesters demonstrated Monday against the vaccine mandate outside Southwest Airlines' headquarters in Dallas, The Dallas Morning News reported.

An airline spokeswoman said the carrier is aware of the demonstration.

"Southwest acknowledges various viewpoints regarding the Covid-19 vaccine, and we have always supported, and will continue to support, our employees' right to express themselves, with open lines of communication to share issues and concerns," she said.

Southwest's Goldberg and Weber told staff that if an employee's request for exemption is denied, the employee can reapply if the employee "has new information or circumstances it would like the Company to consider."

Southwest requires new-hire employees to be vaccinated, as does American Airlines for new staff for its mainline operation, spokesmen said.

Delta Air Lines is also a federal contractor subject to the government requirements, but it hasn't yet required staff vaccinations. Last week, the carrier reported that about 90% of its roughly 80,000 employees are vaccinated. In August, Delta announced unvaccinated staff would start paying $200 more a month for company health insurance in November.

Exhibit R

Biden's vaccine mandate is making America's most serious economic problem worse

BY LIZ PEEK, OPINION CONTRIBUTOR — 09/29/21 09:00 AM EDT
THE VIEWS EXPRESSED BY CONTRIBUTORS ARE THEIR OWN AND NOT THE VIEW OF THE HILL

907 COMI

© Getty Images

We have exactly one serious economic problem in this country today: not enough Americans are working. President Biden's vaccine mandate is making the problem worse.

A shortage of labor is disrupting supply chains and boosting inflation, which is eating into middle class paychecks and undermining seniors' retirement. Rising prices are one reason consumer confidence has dropped over the past three months; if the slump persists, it will ultimately dampen spending.

Another factor hindering our recovery is that there are too few workers. It's crimping business revenues and small firm optimism. If restaurants and stores can't hire staff, they miss out on orders and have to shorten their hours. This is happening all over the country.

This is where Biden should be laser focused. Not on spending trillions of dollars on lavish Democratic priorities such as universal pre-

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kindergarten and expanding Medicare but on helping alleviate the worker shortage and related supply bottlenecks.

Instead, he is making them worse by directing the Occupational Safety and Health Administration (OSHA) to issue a new temporary emergency standard to mandate COVID-19 vaccination or regular testing for companies with more than 100 employees.

That vaccine mandate is driving people out of the workforce, rather than encouraging them to come back in. This trend is especially concerning as it is benching all-important health care workers.

New York's largest hospital system, Northwell Health, recently fired two dozen managers because they refused the jab. Thousands more could follow; CBS News reports some "16% of the state's hospital workers are not fully vaccinated, which means more than 83,000 are at risk of termination."

The state is considering calling in the National Guard to replace hospital workers who have been fired. Somehow, that doesn't seem optimal for patients. In North Carolina, similarly, a hospital system has fired some 175 employees for not taking the shot, in what the Washington Post called "one of the largest-ever mass terminations due to a vaccine mandate."

Imagine: In the midst of a pandemic, we are losing health care workers.

This is just the beginning. Airline pilots, school teachers, Big Tech workers and employees in many other sectors face being fired unless they get the shots. United Airlines just announced it is set to fire nearly 600 workers who are refusing to be vaccinated.

Companies that are struggling mightily to hire workers, such as Amazon

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Companies that are struggling mightily to hire workers, such as Amazon and FedEx, are wary of complying with Biden's demand, knowing they will have a hard time replacing anyone they let go. While these businesses and others have re-imposed mask mandates, they are not about to further thin their ranks by demanding everyone get the vaccine.

Biden's vaccine mandates are one reason that our ports, clogged with stacked-up ships waiting to disgorge needed goods, may not be freed up any time soon. There are currently an unprecedented 62 cargo ships awaiting unloading at the Los Angeles and Long Beach, Calif., docks. The back-up, said likely to disrupt $90 billion in trade and possibly cause holiday-season goods shortages, is partly because of the sheer volume of goods being pushed through the supply chains as stores and manufacturers try to dig out from the COVID-related shut-downs.

But it is also because of a shortage of workers.

Experts fear that Biden's new mandate will worsen delays at the ports and elsewhere. Jeremy Tancredi, a partner in a consulting firm specializing in supply chain management, told a publication focused on sourcing issues the mandate could have "an undesirable impact" as some unvaccinated workers push back and look for opportunities at companies that are not subject to the same requirements.

Another expert in the field was quoted as saying, "Supply Chains are struggling – high costs, scarce capacity and raw materials, etc. – and the mandate is another constraint to be managed."

It's not just firms involved in warehousing and ports that could be further disrupted by the vaccine mandate. Truckers, who already face a serious labor shortage, could also be impacted. The CEO of American Trucking Associations put out a statement saying:

"ATA, its members and our drivers remain committed to delivering life-saving COVID vaccines, but these proposed requirements—however well-intentioned—threaten to cause further disruptions throughout the supply chain, impeding our nation's COVID response efforts and putting the brakes on any economic revival."

President Biden may think that imposing vaccine mandates will hasten the end of the pandemic. He could be right; certainly the requirement polls well for just that reason. But such requirements are leading to even fewer workers on the job, and that is a problem. Especially when it effects the number of health care workers.

It is not the only White House directive that is keeping people at home, of course.

It has been well documented that the extended unemployment benefits included in the Democrats' $1.9 trillion American Rescue Plan encouraged folks to stay home. One study reported that "in all 25 states that are continuing the UI bonus, a family of four can currently receive the annual

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equivalent of more than $82,000 in income—while not working. In 19 states and D.C., the amount is more than $100,000."

People are rational. If you can receive the equivalent of our country's median income while sitting on the sofa, you will probably sit on the sofa.

Those unemployment payments have, thankfully, expired, despite Democrats' best efforts to keep them rolling. But Biden's rent moratorium, child tax credits (in the form of generous monthly checks), widespread student loan cancellations and other benefits have also contributed to the "work or no work" calculus.

These policies may be well intended, but they are not helping alleviate the labor shortage that is hobbling our recovery and complicating supply issues. Biden needs to fix this.

Cawthorn, Lee introduce bills banning interstate travel vaccine...

NYC extends vaccine mandate to expand to all public workers, ends...

Biden recently tweeted: "We need to reward work in this country—not just wealth."

We applaud that notion, and would celebrate a White House that is indeed rewarding, and even encouraging, work. The Biden White House is doing anything but, and it is hurting our recovery.

Liz Peek is a former partner of major bracket Wall Street firm Wertheim & Company. Follow her on Twitter @lizpeek.

Exhibit S

The Washington Post *Democracy Dies in Darkness*

Border arrests have soared to all-time high, new CBP data shows

By Nick Miroff

Today at 9:28 a.m. EDT

922

CORRECTION

A previous version of this story incorrectly stated that Border Patrol arrests along the Mexico border reached their highest levels since 1986. Historic data shows fiscal year 2021's figure was the highest total ever recorded. The article has been corrected.

U.S. authorities detained more than 1.7 million migrants along the Mexico border during the 2021 fiscal year that ended in September, and arrests by the Border Patrol soared to the highest levels ever recorded, according to unpublished U.S. Customs and Border Protection data obtained by The Washington Post.

Illegal crossings began rising last year but skyrocketed in the months after President Biden took office. As CBP arrests increased this past spring, Biden described the rise as consistent with historic seasonal norms. But the busiest months came during the sweltering heat of July and August, when more than 200,000 migrants were taken into custody.

During a confirmation hearing Tuesday for Chris Magnus, the Tucson police chief Biden has nominated to lead CBP, Republican senators pressed him to characterize the surge as a "crisis."

Magnus called it a "significant challenge," echoing the Biden administration's preferred term, adding that "the numbers are very high." CBP is expected to release the 2021 fiscal year data later this week.

Border enforcement has become a major political liability for Biden, and the president's handling of immigration remains his worst-polling issue. He promised on the campaign trail to make the United States more welcoming to immigrants, in contrast to former president Donald Trump, whose zero-tolerance family separations generated widespread outrage in 2018.

During the transition, Biden said he wanted to move cautiously on immigration policy and avoid ending up "with 2 million people on our border."

Once in office, Biden quickly halted construction on the border wall, ended the "Remain in Mexico" policy, reversed key asylum restrictions and announced a 100-day pause on most deportations and enforcement by U.S. Immigration and Customs Enforcement.

them to stay. A tight U.S. labor market became another pull.

Earlier this year, Biden directed Vice President Harris to address the "root causes" of migration from Central America's Northern Triangle nations — Guatemala, Honduras and El Salvador. But the strategy has had little to no measurable effect, and Harris has distanced herself from the border and immigration issues generally.

The latest CBP data indicates that the administration's challenges extend far beyond Central America. Mexico was the single largest source of illegal migration during the 2021 fiscal year, as the Border Patrol arrested more than 608,000 Mexican nationals. That leaves the Biden administration in an awkward place, as it increasingly relies on Mexico to tighten enforcement and block caravan groups heading north.

Biden officials are in negotiations with Mexico to comply with federal court orders to restart the "Remain in Mexico" policy requiring asylum seekers to wait outside U.S. territory while their cases are processed.

The second-largest grouping was composed of migrants from outside Mexico and Central America whom CBP categorized as "other," including Haitians, Venezuelans, Ecuadorans, Cubans, Brazilians and migrants from dozens of other nations. They accounted for 367,000 arrests.

They were followed by migrants from Honduras (309,000), Guatemala (279,000) and El Salvador (96,000).

More than 1.3 million migrants have been taken into custody along the southern border in the nine months since Biden took office, including 192,000 last month, the latest CBP figures show.

In the fiscal years between 2012 and 2020, border arrests averaged about 540,000. The 2021 figure was more than three times that amount and the second-highest annual total ever recorded.

The extraordinary influx has produced a series of crises for the administration, starting this spring with record numbers of unaccompanied minors crossing without parents who were crowded shoulder to shoulder into Border Patrol tents.

Crossings by Central American family groups overwhelmed U.S. agents this summer, and in September, the sudden arrival of 15,000 mostly Haitian migrants to a crude camp in Del Rio, Tex., produced politically damaging scenes of chaos and harsh enforcement tactics by Border Patrol agents on horseback.

Immigrant advocates who backed Biden's candidacy have soured on his presidency lately, with several staging a virtual walkout last weekend during a meeting with White House policy advisers. Biden's proposals for a major immigration overhaul are stalled in Congress, and Republicans are planning to use his border record as a cudgel in next year's midterm elections.

The Biden administration has responded to criticism of the arrest numbers by noting that it continues to use the Title 42 public health policy to rapidly "expel" most adult border crossers to Mexico or their home countries.

Of the 1.7 million detained during the 2021 fiscal year, 61 percent were expelled under Title 42, the CBP data shows.

The expulsions have led to a significant increase in repeat crossing attempts by migrants who are turned back, so the number of distinct individuals taken into custody is lower than the number of arrests recorded. Recidivism rates have exceeded 25 percent in recent months, twice as high as in previous years, according to CBP figures.

The 1.7 million figure includes migrants arrested between ports of entry by the Border Patrol as well as those who

That exceeds the 1.64 million taken into custody in 2000 along the Mexico border, according to historic data.

CBP's Rio Grande Valley sector was the busiest during the 2021 fiscal year, with 549,000 Border Patrol apprehensions, followed by the Del Rio sector, with 259,000, which eclipsed historically busier sectors such as El Paso and Tucson.

The CBP figures show declines in seizures of cocaine, heroin and methamphetamine. Analysts attribute the decrease to diminished vehicle traffic through ports of entry as a result of pandemic-related travel restrictions, as well as fewer interdictions by overstretched border agents.

By Nick Miroff

Nick Miroff covers immigration enforcement and the Department of Homeland Security for The Washington Post. He was a Post foreign correspondent in Latin America from 2010 to 2017, and has been a staff writer since 2006. Twitter

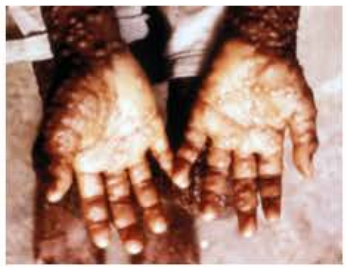
Exhibit T

What is Smallpox?

Before smallpox was eradicated, it was a serious infectious disease caused by the **variola virus**. It was contagious—meaning, it spread from one person to another. People who had smallpox had a fever and a distinctive, progressive skin rash.

Most people with smallpox recovered, but about 3 out of every 10 people with the disease died. Many smallpox survivors have permanent scars over large areas of their body, especially their faces. Some are left blind.

Thanks to the success of vaccination, smallpox was eradicated, and no cases of naturally occurring smallpox have happened since 1977. The last natural outbreak of smallpox in the United States occurred in 1949.



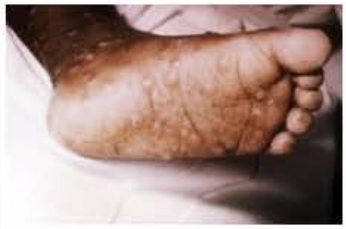


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Exhibit U

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REVIEW ARTICLE

WILEY

Reconciling estimates of global spread and infection fatality rates of COVID-19: An overview of systematic evaluations

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Abstract

Background: Estimates of community spread and infection fatality rate (IFR) of COVID-19 have varied across studies. Efforts to synthesize the evidence reach seemingly discrepant conclusions.

Methods: Systematic evaluations of seroprevalence studies that had no restrictions based on country and which estimated either total number of people infected and/or aggregate IFRs were identified. Information was extracted and compared on eligibility criteria, searches, amount of evidence included, corrections/adjustments of seroprevalence and death counts, quantitative syntheses and handling of heterogeneity, main estimates and global representativeness.

Results: Six systematic evaluations were eligible. Each combined data from 10 to 338 studies (9-50 countries), because of different eligibility criteria. Two evaluations had some overt flaws in data, violations of stated eligibility criteria and biased eligibility criteria (eg excluding studies with few deaths) that consistently inflated IFR estimates. Perusal of quantitative synthesis methods also exhibited several challenges and biases. Global representativeness was low with 78%-100% of the evidence coming from Europe or the Americas; the two most problematic evaluations considered only one study from other continents. Allowing for these caveats, four evaluations largely agreed in their main final estimates for global spread of the pandemic and the other two evaluations would also agree after correcting overt flaws and biases.

Conclusions: All systematic evaluations of seroprevalence data converge that SARS-CoV-2 infection is widely spread globally. Acknowledging residual uncertainties, the available evidence suggests average global IFR of ~0.15% and ~1.5-2.0 billion infections by February 2021 with substantial differences in IFR and in infection spread across continents, countries and locations.

KEYWORDS
bias, COVID-19, global health, infection fatality rate, meta-analysis, seroprevalence

Highlights

- Six systematic evaluations have evaluated seroprevalence studies without restrictions based on country and have estimated either total number of people infected or aggregate infection fatality rates for SARS-CoV-2.
- These systematic evaluations have combined data from 10 to 338 studies (9-50 countries) each with partly overlapping evidence synthesis approaches.
- Some eligibility, design and data synthesis choices are biased, while other differing choices are defendable.
- Most of the evidence (78%-100%) comes from Europe or the Americas.
- All systematic evaluations of seroprevalence data converge that SARS-CoV-2 infection has been very widely spread globally.
- Global infection fatality rate is approximately 0.15% with 1.5-2.0 billion infections as of February 2021.

1 | INTRODUCTION

The extent of community spread of SARS-CoV-2 infection and the infection fatality rate (IFR) of COVID-19 are hotly debated. Many seroprevalence studies have provided relevant estimates. These estimates feed into projections that influence decision-making. Single studies create confusion, since they leave large uncertainty and unclear generalizability across countries, locations, settings and time points. Some overarching evaluations have systematically integrated data from multiple studies and countries.[1-6] These synthetic efforts probe what are typical estimates of spread and IFR, how heterogeneous they are, and what factors explain heterogeneity. An overview of these systematic evaluations comparing their methods, biases and inferences may help reconcile their findings on these important parameters of the COVID-19 pandemic.

2 | METHODS

2.1 | Eligible articles

Articles were eligible if they included a systematic review of studies aiming to assess SARS-CoV-2 seroprevalence; there were no restrictions based on country; and an effort was made to estimate either a total number of people infected or aggregate IFRs. Articles were excluded if they considered exclusively studies of particular populations at different risks of infection than the general population (eg only healthcare workers), if they focused on specific countries (by eligibility criteria, not by data availability), and if they made no effort to estimate total numbers of people infected and/or aggregate IFRs.

2.2 | Search strategy

Searches were updated until 14 January 2021 in PubMed, medRxiv and bioRxiv with 'seroprevalence [ti] OR fatality [ti] OR immunity [ti]' For feasibility, the search in PubMed was made more specific by adding '(systematic review OR meta-analysis OR analysis)'. Communication with experts sought potentially additional eligible analyses (eg unindexed influential reports).

2.3 | Extracted information

From each eligible evaluation, the following information was extracted:

1. Types of information included (seroprevalence, other)
2. Date of last search, search sources and types of publications included (peer-reviewed, preprints, reports/other)
3. Types of seroprevalence designs/studies included
4. Number of studies, countries, locations included
5. Seroprevalence calculations: adjustment/correction for test performance, covariates, type of antibodies measured, seroreversion (loss of antibodies over time)
6. Death count calculations: done or not; adjustments for over- or under-counting, time window for counting COVID-19 deaths in relationship to seroprevalence measurements
7. Quantitative synthesis: whether data were first synthesized from seroprevalence studies in the same location/country/other level; whether meta-analyses were performed across locations/countries and methods used; handling of heterogeneity, stratification and/or regression analyses, including subgroups

8. Reported estimates of infection spread, under-ascertainment ratios (total/documented infections) and/or IFR
9. Global representativeness of the evidence: proportion of the evidence (weight, countries, studies or locations, depending on how data synthesis had been done) from Europe and North America (sensitivity analysis: Europe and America)

2.4 | Comparative assessment

Based on the above, the eligible evaluations were compared against each other with focus on features that may lead to bias and trying to decipher the direction of each bias.

3 | RESULTS

3.1 | Eligible evaluations

Nine potentially eligible articles were retrieved[1-3,5-10] And four were rejected (Figure 1).[7-10] One more eligible report[4] was identified from communication with experts. The six eligible evaluations are named after their first authors or team throughout the manuscript.

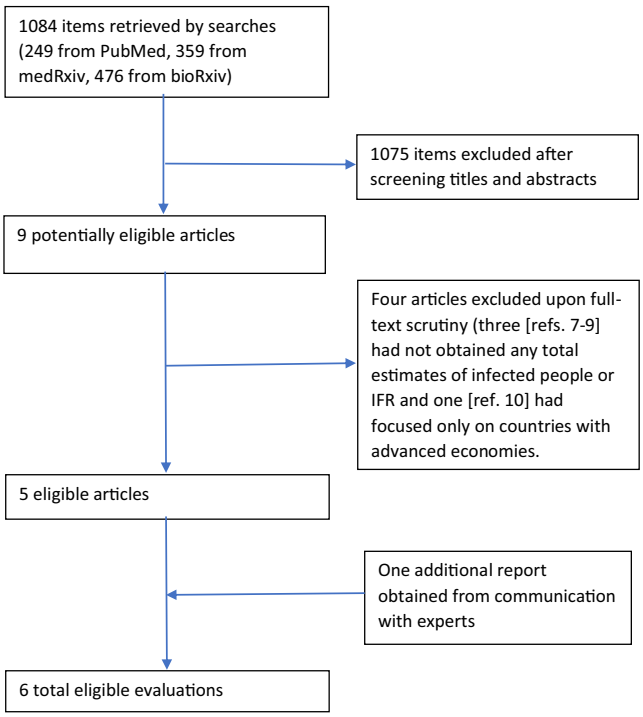

FIGURE 1 Flow diagram

3.2 | Information used

Five evaluations included only seroprevalence studies (Table 1). Meyerowitz-Katz also included non-serological and modelling papers; summary IFR was smaller in the seroprevalence studies (0.60% vs 0.84% in others). The six evaluations differed modestly in dates of last search (range, 6/16/2020-9/9/2020) and in sources searched. Given that few studies outside of Europe and Americas were released early, evaluations with earlier searches have a more prominent dearth of low-IFR studies from countries with younger populations and fewer nursing home residents.

Eligibility criteria varied and were sometimes unclear or left room for subjectivity. Consequently, eligible studies varied from 10 to 348 and countries covered with eligible data varied from 9 to 50. Two evaluations[1,4] excluded studies in overtly biased ways, leading to inflated IFR estimates.

Specifically, Meyerowitz-Katz excluded one study with low-IFR[5] alluding that the study itself 'explicitly warned against using its data to obtain an IFR'[1]; as co-investigator of the study, both myself and my colleagues are intrigued at this claim. They also excluded two more studies with low-IFR alluding that it 'was difficult to determine the numerator (ie number of deaths) associated with the seroprevalence estimate or the denominator (ie population) was not well defined',[1] while one even presented IFR estimates in its published paper. Another excluded paper[11] tabulated several seroprevalence studies with median IFR = 0.31%, half the Meyerowitz-Katz estimate.

The Imperial College COVID-19 Response Team (ICCRT) excluded studies with <100 deaths at the sero-survey mid-point.[4] This exclusion criterion introduces bias since number of deaths is the numerator in calculating IFR. Exclusion of studies with low numerator excludes studies likely to have low IFR. Indeed, five of six excluded studies with <100 deaths (Kenya, LA County, Rio Grande do Sul, Gangelt, Scotland)[12-16] have lower IFR than the 10 ICCRT-included studies; the sixth (Luxembourg)[17] is in the lower range of the 10 ICCRT-included studies.

The six evaluations varied on types of populations considered eligible. Table 2 summarizes biases involved in each study population type. General population studies are probably less biased, provided they recruit their intended sample. Conversely, studies of healthcare workers,[18] other high-risk exposure workers and closed/confined communities may overestimate seroprevalence; these studies were generally excluded, either upfront (5/6 evaluations) or when calculating key estimates (Bobrovitz). Other designs/populations may be biased in either direction, more frequently towards underestimating seroprevalence.[19-26] Three evaluations (Meyerowitz-Katz, ICCRT, O'Driscoll) were very aggressive with exclusions.

TABLE 1 Key features for eligible systematic data syntheses

Features	Meyerowitz-Katz	Rostami	Bobrovitz	Imperial college COVID-19 response team	Ioannidis	O'Driscoll
Types of information included	SP, non-serological and modelling studies	SP studies	SP studies	SP studies	SP studies	SP studies
Last search	16 June	14 August	28 August	Unclear	9 September	Unclear (1 September?)
Search sources	PubMed, preprints (medRxiv, SSRN), Google, Twitter searches, government agency reports eligible	PubMed, Scopus, EMBASE, medRxiv, bioRxiv, research reports eligible	MEDLINE, EMBASE, Web of Science, and Europe PMC, Google, communication with experts	SeroTracker searches (see Bobrovitz)	PubMed (LitCOVID), medRxiv, bioRxiv, Research Square, national reports, communication with experts for additional studies	Unclear
Types of SP studies included	Excluded targeted populations with selection bias, also four other studies[a]	Excluded at-risk populations (eg HCW), known diseases (eg dialysis, cancer)	All studies included if they reported on sample, date, region and SP estimate	Studies with defined sampling framework, defined geographic area, with availability of test performance, preferentially validation done as part of the study (not just by manufacturers), >100 deaths at SP study mid-point[b]; excluded healthcare workers, symptoms of COVID-19, self-referral or self-selection, narrow age range, confined settings, clinical samples	General population or approximations (including blood donors, excluding high risk, eg HCW, communities), sample size >500, area with population >5000	Unclear, but eventually it includes some general population studies, some blood donors and some hospital samples
Number of studies, countries, locations	24-27 studies[c], of which 16 serological from 14 countries	107 data sets from 47 studies from 23 countries	338 studies (184 from general population) from 50 countries (36 from general population)[d]	10 studies (six national, four subnational), nine countries[e]	82 estimates, 69 studies, 51 locations, 36 countries (main analysis at the location level)	25 studies from 20 countries (only 22 national representing 16 countries used in the ensemble model)
Studies published in peer-review journals at the time of the evaluation	1/16	61/107	4/40 included in final analysis of under-ascertainment ratio	5/10	35/82	6/20 countries

Abbreviations: HCW, healthcare workers; IFR, infection fatality rate; SP, seroprevalence.

[a]One study (LA County)[12] with very low IFR was excluded with the justification that it 'explicitly warned against using its data to obtain an IFR'; as a co-investigator of the study, both myself and my colleagues are intrigued at the rationale for exclusion; in the publication of the study in JAMA,[12] we did list limitations and caveats, as it is appropriate for any seroprevalence study to do; excluding studies that are honest to discuss limitations would keep only the worst studies that discuss no limitations. Two other studies with low IFR were excluded as well. One was done in Rio Grande do Sul[13] where its authors even report IFR estimates in their paper (0.29%, 0.23%, 0.38% in the three rounds of the serosurvey); the other was done in Boise,[85] where its authors properly discuss limitations but an approximation of IFR is possible; even if not perfectly accurate, it is certainly lower than the IFR estimates included in the Meyerowitz-Katz meta-analysis. For the fourth excluded study,[11] the justification offered for its exclusion is that it 'calculated an IFR, but did not allow for an estimate of confidence bounds'.[1] However, this study presents results of a New York study that Meyerowitz-Katz did include in their meta-analysis. Of note, that fourth study[11] also presents a cursory review of seroprevalence studies arriving at a median IFR = 0.31%, half of the summary estimate of Meyerowitz-Katz.; [b]Clear bias introduced since number of deaths is the numerator itself in the calculation of IFR, and exclusion of studies with low numerator is thus excluding studies likely to have low IFR; [c]Different numbers provided by the authors for total studies in abstract (n = 24), text of the paper (n = 25), tabulated studies (n = 27) and forest plot studies (n = 26); [d]39 estimates from 17 countries used in main calculation of median under-ascertainment ratio (N. Bobrovitz, personal communication); [e]One of the 10 included studies violates the eligibility criterion of the investigators having validated themselves the antibody test used; the ICCRT included this study invoking validation data for the same antibody kit done by a different team in a study in a completely different setting and continent (San Francisco); based on this rationale, perhaps many other studies could have been included, if the same violation of the eligibility criteria was tolerated. The included study was an Italian survey[30] which had only been released in the press with a preliminary report at the time of the ICCRT evaluation and which included crude results on only 64 660 of the intended 150 000 participants (missingness 57%). Its inferred IFR estimate (2.5%) is an extreme outlier, as it is 2- to 20-fold larger than other typical estimates reported from numerous European countries. Moreover, that IFR estimate even matches/exceeds case fatality rates, and thus, it is simply impossible. It is widely accepted that IFR must be several times smaller than case fatality rate, even in locations with substantial testing. Italy had very limited testing in the first wave and modest testing in the second wave. One estimate suggests that the number of infections in Italy at the peak of the first wave was 12 times more than the number of documented cases; that is, the IFR would be more than an order of magnitude lower than the case fatality rate.[31]

TABLE 2 Direction of potential bias in studies with different types of populations

Type of sampling	Direction of bias
General population (entire population or design for representative sample)	Depends on characteristics of individuals who cannot be reached and/or decline participation. If they are more likely to be more disadvantaged (eg have no address/phone/e-mail) and thus also at higher risk of infection, SP may be underestimated. Potential for bias is more prominent when non-response/non-participation is larger. Institutionalized populations and homeless people are typically not included, and these populations often have very high infection rates[19,20] ; thus, SP is underestimated
Convenience sample (including self-referral and response to adverts)	Bias could be in either direction. Volunteer bias is common and would tend to recruit more health-conscious, low-risk individuals,[21] leading to SP underestimation. Conversely, interest to get tested because of worrying in the presence of symptoms may lead to SP overestimation
Blood donors	Bias could be in either direction, but SP underestimation is more likely, since blood donors tend to be more health-conscious and thus more likely to avoid also risky exposures. An early classic assessment[22] described blood donors as 'low-risk takers, very concerned with health, better educated, religious, and quite conservative'—characteristics that would lead to lower infection risk. In countries with large shares of minorities (eg USA and UK), minorities are markedly under-represented among blood donors.[23,24] For example, in the USA, donation rates are 37%-40% lower in blacks and Hispanics versus whites[23] and in the UK, donation rates range from 1.59 per 1000 among Asian Bangladeshi origin, compared to 22.1 per 1000 among white British origin.[24] These minorities were hit the most by COVID-19. In European countries, donations are lower in low-income and low-education individuals[25,26] ; these are also risk factors for COVID-19 infection. Bobrovitz[3] found median seroprevalence of 3.2% in blood donor studies versus 4.1% in general community/household samples (risk ratio 0.80 in meta-regression). SP may be overestimated if blood donation is coupled to a free COVID-19 test in a poor population (as in the case of a study in Manaus, Brazil)
Clinical residual samples and patients (eg dialysis, cancer, other)	Bias could be in either direction, but SP underestimation is more likely since patients with known health problems may be more likely to protect themselves in a setting of a pandemic that poses them at high risk. Conversely, repeated exposure to medical facilities may increase risk. Demographic features and socio-economic status may also affect the size and direction of bias. Bobrovitz[3] found median seroprevalence of 2.9% in studies of residual samples versus 4.1% in general community/household samples (risk ratio 0.63 in meta-regression). Hospital visitors' studies had even lower seroprevalence (median 1.4%)
Healthcare workers, emergency response, other workers with obvious high risk of exposure	Bias very likely to lead to SP overestimation compared with the general population, because of work-related contagion hazard; however, this may not always be the case (eg most infections may not happen at work) and any increased risk due to work exposure sometimes may be counterbalanced by favourable socio-economic profile for some healthcare workers (eg wealthy physicians). Bias may have been more prominent in early days of the pandemic, especially in places lacking protective gear. Across eight studies with data on healthcare workers and other participants, seroprevalence was 1.74-fold in the former.[3]
Other workers	Bias could be in either direction and depends on work experience during the pandemic period and socio-economic background; for example, SP may be underestimated compared with the general population for workers who are wealthy and work from home during the pandemic and overestimated for essential workers
Communities (shelters, religious, other shared-living)	Likely very strong bias due to high exposure risk leading to SP overestimation compared with the general population. Some of these communities were saturated with very high levels of infection very early.[19,20]

Note: Abbreviations: SP, seroprevalence.

ICCRT had the most draconian exclusion criteria, excluding 165/175 identified seroprevalence studies. However, ICCRT actually dropped many general population studies (for various reasons), but included two blood donor studies[27,28] (out of many such) and one New York study[29] with convenience samples of volunteers recruited while entering grocery stores and through an in-store flyer. The latter inclusion goes against the stated ICCRT eligibility criteria where self-selection is reason for exclusion. The New York study[29] had high IFR (from the worst-hit state in the first wave). The preliminary press-released report from an Italian general population survey[30] was included in violation of ICCRT eligibility criteria[4] that a study should have performed its own antibody test validation; ICCRT 'salvaged' the Italian study by transporting validation data from another study in San Francisco. The Italian study report[30] showed data on only 64 660 of the intended 150 000 participants (missingness 57%). Its inferred IFR estimate (2.5%) is an extreme outlier (2- to 20-fold larger than other reported European estimates) and simply impossible: it matches/exceeds case fatality rates despite probably major under-ascertainment of infections in Italy.[31]

Finally, the six evaluations differed markedly on how many included seroprevalence estimates came from peer-reviewed publications (journal articles listed in the references) at the time of the evaluation: from only one peer-reviewed estimate in Meyerowitz-Katz to 61 in Rostami. Some included

TABLE 3 Adjustments and corrections for seroprevalence and death counts

Features	Meyerowitz-Katz	Rostami	Bobrovitz	Imperial College COVID-19 response team	Ioannidis	O'Driscoll
Adjustment of SP for test performance	Unclear selection rule	Unclear selection rule	Yes (Bayesian)	Yes	Yes, when done by authors of SP study	Yes (24/25 studies)
Adjustment of SP for confounders	Unclear selection rule	Unclear selection rule	Unclear selection rule	Unclear selection rule	Selecting most fully adjusted SP estimated	Unclear selection rule
Other SP correction	No	No	No	Seroreversion	Type of antibodies[a]	Seroreversion, in secondary analysis
Death count adjustments	No adjustments	Deaths not assessed	Deaths not assessed	No adjustments	No adjustments	No adjustments
Time window for death counts	10 d after completion of SP study	Deaths not assessed	Deaths not assessed	Distributional (truncated Gaussian and beta), mean 18.3 d from onset to seroconversion, 19.8 d from onset to death	7 d after mid-point of SP survey or as chosen by its authors	Distributional (gamma), mean 10 d from onset to seroconversion, 20 d from onset to death

Abbreviations: d, days; IFR, infection fatality rate; SP, seroprevalence.
[a]one-tenth adjustment per each not tested antibody (IgG, IgM, IgA).

seroprevalence estimates that came from preprints/reports published in peer-reviewed journals by 2/2021; final publications could have minor/modest differences versus preprints/reports. Even journal-published estimates may get revised; for example, a re-analysis increased Indiana seroprevalence estimates by a third.[32]

3.3 | Seroprevalence and death calculations

Three evaluations[3,4,6] routinely adjusted for test performance, one[5] adjusted for test performance when the authors of the studies had done so, and two were unclear (Table 3). Depending on test sensitivity/specificity, lack of adjustment may inflate or deflate seroprevalence. Ioannidis selected the most fully adjusted seroprevalence estimate, when both adjusted and unadjusted estimates existed; other evaluations were unclear on this issue. Ioannidis corrected the seroprevalence upward when not all three types of antibodies (IgG, IgM, and IgA) were assessed. ICCRT and O'Driscoll considered seroreversion adjustments.

Rostami and Bobrovitz did not collect death counts to estimate IFR. The other four evaluations did not systematically adjust death counts for under- or over-counting. Finally, ICCRT and O'Driscoll used distributional approaches on the time window for counting deaths (with means between seroconversion and death differing by 1.5 and 10 days, respectively), Ioannidis counted deaths until 7 days after the survey mid-point (or the date survey authors made a strong case for), and Meyerowitz-Katz counted deaths up until 10 days after survey end.

3.4 | Quantitative synthesis, heterogeneity and main estimates

The six evaluations differed in quantitative synthesis approaches with implications for the main results (Table 4).

Meyerowitz-Katz used random effects meta-analysis of 26 IFRs calculating a summary estimate despite extreme between-study heterogeneity (I^2 = 99.2%). Such extreme heterogeneity precludes obtaining meaningful summary estimates. Estimates from the same country/location were not combined first, and two multiply-counted countries (Italy and China) have high IFRs entered in calculations. Meta-analysis limited to seroprevalence studies yielded slightly lower summary IFR (0.60% vs 0.68%), but extreme between-study heterogeneity persisted (I^2 = 99.5%); thus, summary estimates remained meaningless. Extreme between-study heterogeneity persisted also within three risk-of-bias categories (I^2 = 99.6%, 98.8% and 94.8%, respectively), within Europe and within America. There was no between-study heterogeneity for four Asian estimates, but none came from

TABLE 4 Quantitative synthesis approaches, stratification and/or regression and main estimates

	Meyerowitz-Katz	Rostami	Bobrovitz	Imperial College COVID-19 response team	Ioannidis	O'Driscoll
Quantitative synthesis	26 IFR estimates combined at one step with D-L RE model, $I^2 = 99.4\%$	First step 107 SP estimates combined separately for each country with D-L RE model, then per region. Also D-L RE for all 107 estimates, $I^2 = 99.7\%$	Median SP calculated overall and per subgroup of interest.	Log-linear model for pooling age-stratified IFR, then age-stratified estimates extrapolated to the age structure of populations of typical countries	First step, sample size-weighted summary of SP per location; then median estimated across locations	The ensemble model eventually models age-stratified IFR in a total of 45 countries with available age-stratified death counts, but data are used as input from only 16 countries that have IFR data with some age stratification
Stratification and/or regression	Subgroup analyses per continent, month of publication, modelling versus serological and risk of bias	Subgroup analyses per age, gender, type of population, serological method, race/ethnicity, income, human development index, latitude/longitude, humidity, temperature, days from onset of pandemic; also RE meta-regressions	Subgroup analyses per GBD region, scope (national, regional, local, sublocal), risk of bias, days since 100th case (also explored in meta-regressions); RE inverse variance meta-analysis of prevalence ratios for demographics (age, sex, race, close contact, HCW status) with $I^2 = 85.1\%$-99.4% per grouping factor	Focus on age-strata, also IFR estimates with and without seroreversion, and (for some countries) excluding nursing home deaths	Separate analyses for age <70 years; also subgroup analyses according to level of overall mortality in the location	Focus on age-strata; also per sex/gender and per country
Main estimates	Summary IFR 0.68 (95% CI-0.53%-0.82%), 0.60 when limited to serological studies	263.5 million exposed/infected at the time of the study based on the pooled SP from all 107 data sets; when estimated per region the total is 641 million[a]	643 million infected as of 17 November, based on estimated median under-ascertainment factor of 11.9 (using 9 d before study end date for PCR counts)[b]	Overall IFR: LIC 0.22 (0.14, 0.39), LMIC) 0.37 (0.25, 0.61), UMIC 0.57 (0.38, 0.92), HIC 1.06 (0.73, 1.64)	Over 500 million infected as of September 12 (vs 29 million documented cases) globally; median IFR 0.23% in the available studies (0.09% in locations with <118 deaths/million), 0.20% in locations with 118-500 deaths/million, 0.57% in locations with >500 deaths/million	5.27% of the population of the 45 modelled countries had been infected by 1 September

Abbreviations: IFR, infection fatality rate; RE, random effects; SP, seroprevalence.

[a]In millions: Europe+North America 47, East+South-East Asia 47, Latin America 9, South America 6, Sub Saharan Africa 62, Central and South Asia 446, North Africa and West Asia 24; [b]Median under-ascertainment was 14.5 overall based on 125 study estimates and 11.9 in national estimates, 15.7 in regional estimates and 24.0 in local estimates.

seroprevalence data and their IFR estimate (0.46%) is far higher than many subsequent Asian studies (outside Wuhan) using seroprevalence data[5] instead of modelling.

Rostami also performed random effects meta-analyses but more appropriately combined at a first step seroprevalence data from studies in the same country, and in the same region, a summary estimate across all 107 estimates in all countries was also obtained. The step-wise approach avoids the Meyerowitz-Katz analysis flaw. However, seroprevalence estimates may still vary extremely even within the same location, for example if done at different times. Moreover, the main estimate of the evaluation ('263.5 million exposed/infected at the time of the study') extrapolated to the global population the pooled estimate from all 107 data sets. The more appropriate estimate is a sum of the infected per country, or at least per region. Actually, the authors did calculate numbers of people exposed/infected per world region. The sum was 641 million, 2.5-fold larger. Moreover, these numbers did not reflect 'the time of the study': the 107 seroprevalence studies were done 2-6 months before the Rostami evaluation was written.

Bobrovitz calculated medians (overall and across several subgroups of studies), and Ioannidis calculated sample size-weighted means per location and then medians across locations. Their approaches avoid multiple counting of locations with many estimates available. Bobrovitz also performed random effects inverse variance meta-analysis of prevalence ratios for diverse demographics (age, sex, race, close contact, healthcare workers). The approach is defendable, since prevalence ratios were calculated within each study, but still very large between-study heterogeneity existed ($I^2 = 85.1\%$-99.4% per grouping factor) making results tenuous. Bobrovitz and Ioannidis reach congruent estimates for total number infected globally (643 million by November 17 and at least 500 million by September 12, respectively) with under-ascertainment ratios of 11.9 in November and 17.2 in September. Only the latter evaluation calculated IFRs (0.23% overall; 0.05% for those <70 years old).

ICCRT and O'Driscoll focused on age-stratified estimates. ICCRT extrapolated age-stratified estimates to the age structure of populations of typical countries, obtaining separate overall IFR estimates for low-income countries (0.22%), lower-middle–income countries (0.37%), upper-middle–income countries (0.57%) and high-income countries (1.06%). O'Driscoll made extrapolations to 45 countries estimating 5.27% of their population infected by 1 September.

3.5 | Global representativeness

Seroprevalence data lacked global representativeness. 72%-91% of the seroprevalence evidence came from Europe and North America (78%-100% from Europe or Americas)

TABLE 5 Global representativeness

	Meyerowitz-Katz	Rostami	Bobrovitz	Imperial College COVID-19 response team	Ioannidis	O'Driscoll[b]
Estimates (countries)[a]						
Europe	11 (11)	52 (13)	33 (13)	8 (7)	22 (21)	13 (13)
North America	3 (1)	22 (1)	1 (1)	1 (1)	15 (2)	1 (1)
Latin America	1 (1)	17 (2)	3 (1)	1 (1)	3 (3)	1 (1)
Asia	1 (1)	14 (5)	2 (1)	0 (0)	10 (9)	0 (0)
Africa	0 (0)	2 (2)	1 (1)	0 (0)	1 (1)	1 (1)
Oceania	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Information from Europe and North America	91% of weight	72% of data sets	85% of data sets (82% of countries)	90% of data sets	73% of location estimates	87% of countries
Information from Europe and America	98% of weight	85% of data sets	93% of data sets (87% of countries)	100% of data sets	78% of location estimates	94% of countries

[a]Geographic location of estimates (countries) included in main calculations.; [b]The extrapolated 45 countries on which age-stratified IFR estimates are obtained also include countries outside the regions that have at least one country represented (Pakistan, Philippines, Bangladesh, Indonesia, China, Thailand, South Korea, Japan) even though not directly measured in any of them.

(Table 5). Lack of representativeness was most prominent in Meyerowitz-Katz (only one estimate from Asia, none from Africa), ICCRT (no estimates from Asia or Africa) and O'Driscoll (only one estimate from Africa, no estimate from Asia). However, ICCRT extrapolated to all countries globally and O'Driscoll extrapolated to 45 countries including eight in Asia.

4 | DISCUSSION

This overview of six systematic evaluations of global spread and/or IFR of SARS-CoV-2 utilizing seroprevalence data highlights differences in methods, calculations and inferences. Several choices made by some evaluations led to bias. Other choices are defendable and reveal some unavoidable variability on how evidence on these important questions should be handled.

Choices that led to biased inflated IFR estimates are the inclusion of modelling estimates, inappropriate exclusion of low-IFR studies despite fitting stated inclusion criteria of the evaluators, inappropriate inclusion of high-IFR studies despite not fitting stated inclusion criteria, and using low death counts as exclusion criterion. Two evaluations (Meyerowitz-Katz and ICCRT) suffered multiple such problems each. These biases contributed to generate inflated and, sometimes, overtly implausible results. These two evaluations also narrowly selected very scant evidence (16 and 10 studies, including only one and five peer-reviewed articles, respectively), while hundreds of seroprevalence estimates are available.

Differences in types of study designs and populations considered eligible may be defended with various arguments by each evaluator. Studies of healthcare workers were consistently excluded. No consensus existed on studies of blood donors, clinical samples, workers at no obvious high-risk occupations and various convenience samples; these designs have variable reliability. Reliability increases with careful adjustment for sampling, demographics and other key factors and when missing data are limited. General population sampling is theoretically best, but general population studies may still suffer large bias from selective missingness. Unreachable individuals, institutionalized people and non-participating invitees are typically at higher infection risk; if so, some general population studies may substantially underestimate seroprevalence (overestimate IFR). For example, Meyerowitz-Katz included a Danish government survey press release[33] where only 1071 of 2600 randomly selected invitees participated (missingness 59%); the estimated IFR (0.79%) is probably substantially inflated.[6,28]

Differences may also ensue from seroprevalence adjustments for test performance and other factors.[34,35] Sometimes the change in estimated seroprevalence is substantial.[36-38] Special caution is needed with low seroprevalence.[39] When not all types of antibodies are assessed, a correction may also be useful. Adjustment for test performance may seemingly suffice. However, control samples used to estimate test sensitivity come from PCR-tested diagnosed patients, while missed diagnoses typically reflect asymptomatic or less symptomatic patients not seeking testing. Sensitivity may be much lower in these people, as many develop no or low-titre antibodies.[40,41] Seroreversion has a similar impact. Preliminary evidence suggests substantial seroreversion.[29,42-45] For example, among healthcare personnel, 28.2% seroreverted in 2 months (64.9% in those with low titres originally).[45] Only ICCRT and O'Driscoll considered corrections for seroreversion, but still did not allow for high seroreversion. All these factors would result in underestimating seroprevalence (overestimating IFR).

Both over- and under-counting of COVID-19 deaths (the IFR numerator) may exist,[46,47] varying across countries with different testing and death coding. Correction of COVID-19 death counts through excess deaths is problematic. Excess reflects both COVID-19 deaths and deaths from measures taken.[46-49] Year-to-year variability is substantial, even more so within age-strata. Comparison against averages of multiple previous years is naïve, worse in countries with substantial demographic changes. For example, in the first wave, an excess of 8071 deaths (SMR 1.03, 95% CI 1.03-1.04) in Germany became a deficit of 4926 deaths (SMR 0.98, 95% CI 0.98-0.99) after accounting for demographic changes.[50] The exact timepoint when deaths are counted may affect IFR calculations when surveys happen while many deaths are still accruing. All evaluations that counted deaths allowed for greater time for death to occur than for seroconversion, but Meyerowitz-Katz used a most extreme delay, considering deaths until 10 days after survey end. Surveys take from one day to over a month; thus, inferred sampling-to-death delay may occasionally exceed 6 weeks. Meyerowitz-Katz defends this choice also in another paper[10] choosing 4 weeks after the serosurvey mid-point. However, the argument (accounting for death reporting delays) is weak. Several situational reports plot deaths according to date of occurrence rather than date of reporting anyhow.[51] Moreover, infection-to-death time varies substantially and may be shorter in developing countries where fewer people are long-sustained by medical support.

Some quantitative synthesis approaches were problematic, for example calculating summary estimates despite $I^2 > 99\%$ or no data combination within the same country/location before synthesis across countries/locations. Another generic problem with meta-analysis of such data is that it penalizes better studies that allow more appropriately for uncertainty in estimates (eg by accounting for test performance and adjusting for important covariates). Studies with less rigorous or no adjustments may have narrower CIs (smaller variance, thus larger weight).[5] Finally, for IFR meta-analysis, studies

with few deaths may have higher variance (lower weight) and these studies may have the lowest IFR.

Age stratification for IFR estimation and synthesis is a reasonable choice to reduce between-study heterogeneity driven by steep COVID-19 death risk age gradient.[52] However, both analyses[4,6] that capitalized on granular age stratification made tenuous extrapolations to additional countries from thin or no data. ICCRT lacked seroprevalence data on low-income and lower-middle–income countries (~half the global population); upper-middle–income countries (~35% of global population) were only represented by one estimate from Brazil assuming IFR = 1%, exceeding twofold to fivefold other peer-reviewed estimates from Brazil.[13,53] Estimates used from high-income countries included an impossible Italian estimate (IFR = 2.5%)[30] and mostly non–peer-reviewed data. O'Driscoll was more careful, but still some IFR extrapolations appear highly inflated versus data from subsequently accrued seroprevalence studies. Their ensemble model assumed highest IFR in Japan (1.09%) and lowest in Kenya (0.09%) and Pakistan (0.16%). Currently, available seroprevalence studies from these countries show markedly lower IFR estimates: =<0.03%,[54-56] =<0.01%[14] and 0.04%-0.07%,[57,58] respectively. In Japan, infections apparently spread widely without causing detectable excess mortality.[54] In Kenya, under-ascertainment compared with documented cases was ~1000-fold.[14] While some COVID-19 deaths are certainly missed in Africa, containment measures are more deadly.[59]

All six evaluations greatly over-represented Europe and America. Only two (Rostami and Ioannidis) included meaningful amounts of data from Asia and Africa (still less than their global population share) in main estimate calculations. Currently, extensive data suggest high under-ascertainment ratios in Africa and many Asian countries[5,14,54-61] and thus much lower IFR in Asia (outside Wuhan) and Africa than elsewhere.

Quality of seroprevalence studies varies. Risk-of-bias assessments in prevalence studies are difficult. There are multiple risk-of-bias scales/checklists,[62-65] but bias scores do not translate necessarily to higher or lower IFR estimates, while assessors often disagree in scoring (Appendix S1).

Acknowledging these caveats, four of the six evaluations largely reach congruent estimates of global pandemic spread. O'Driscoll estimated 5.27% of the population of 45 countries had been infected by 1 September 2020, that is 180 million infected among 3.4 billion. Excluding China, the proportion of population infected among the remaining 44 countries would be ~9%, likely >10% after accounting for seroreversion. Countries not included among the 45 include some of the most populous ones with high infection rates (India, Mexico, Brazil, most African countries). Therefore, arguably at least 10% of the non-China global population (ie at least 630 million) would be infected as of 1 September. This is very similar to the Ioannidis (at least 500 million infected as of 12 September) and Rostami (641 million infected by summer, when numbers are added per region) estimates. The Bobrovitz estimate (643 million infected as of 17 November) should be increased substantially given that only 2 of 17 countries informing the calculated under-ascertainment ratio were in Asia or Africa, continents with much larger under-ascertainment ratios. National surveys in India actually estimated 60% seroprevalence in November in urban areas.[66] Therefore, probably infected people globally were ~1 billion (if not more) by 17 November (compared with 54 million documented cases). By extrapolation, one may cautiously estimate ~1.5-2.0 billion infections as of 21 February 2021 (compared with 112 million documented cases). This corresponds to global IFR ~0.15%—a figure open to adjustment for any over- and under-counting of COVID-19 deaths (Appendix S2).

Meyerowitz-Katz and ICCRT reach higher estimates of IFR, but, as discussed above, these are largely due to endorsing selection criteria focusing on high-IFR countries, violations of chosen selection criteria and obvious flaws that consistently cause IFR overestimation. Similar concerns apply to another publication with implausibly high age-stratified IFRs by Meyerowitz-Katz limited to countries with advanced economies, again narrowly selected some of the highest IFR locations and estimates.[12]

Even correcting inappropriate exclusions/inclusion of studies, errors and seroreversion, IFR still varies substantially across continents and countries. Overall average IFR may be ~0.3%-0.4% in Europe and the Americas (~0.2% among community-dwelling non-institutionalized people) and ~0.05% in Africa[14] and Asia (excluding Wuhan). Within Europe, IFR estimates were probably substantially higher in the first wave in countries like Spain,[67] UK[68] and Belgium[69] and lower in countries such as Cyprus or Faroe Islands (~0.15%, even case fatality rate is very low),[70] Finland (~0.15%)[71] and Iceland (~0.3%).[72] One European country (Andorra) tested for antibodies 91% of its population.[73] Results[73] suggest an IFR less than half of what sampling surveys with greater missingness have inferred in neighbouring Spain. Moreover, high seroreversion was noted, even a few weeks apart[73]; thus, IFR may be even lower. Differences exist also within a country; for example within the USA, IFR differs markedly in disadvantaged New Orleans districts versus affluent Silicon Valley areas. Differences are driven by population age structure, nursing home populations, effective sheltering of vulnerable people,[74] medical care, use of effective (eg dexamethasone)[75] or detrimental (eg hydroxychloroquine)[76] treatments, host genetics,[77] viral genetics and other factors.

Infection fatality rate may change over time locally[78] and globally. If new vaccines and treatments pragmatically prevent deaths among the most vulnerable, theoretically global IFR may decrease even below 0.1%. However, there are still uncertainties

both about the real-world effectiveness of new options, as well as the pandemic course and post-pandemic SARS-CoV-2 outbreaks or seasonal re-occurrence. IFR will depend on settings and populations involved. For example, even 'common cold' coronaviruses have IFR~10% in nursing home outbreaks.[79]

Admittedly, primary studies, their overviews and the current overview of overviews have limitations. All estimates have uncertainty. Interpretation unavoidably has subjective elements. This challenge is well-known in the literature of discrepant systematic reviews.[80-84] Cross-linking diverse types of evidence generates even more diverse eligibility/design/analytical options. Nevertheless, one should separate clear errors and directional biases from defendable eligibility/design/analytical diversity.

Allowing for such residual uncertainties, reassuringly the picture from the six evaluations assessed here is relatively congruent: SARS-CoV-2 is widely spread and has lower average IFR than originally feared, and substantial global and local heterogeneity. Using more accurate estimates of IFR may yield more appropriate planning, predictions and evaluation of measures.

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CONFLICTS OF INTEREST

None.

DISCLOSURES

I am the author of one of the six evaluations assessed in this article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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Exhibit V

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COVID-19 Information

x

Get the latest public health information from CDC

Get the latest research information from NIH | Español

Learn more about COVID-19 and you from HHS

NEWS: DailyMed Announcements

SEPTEMBER 13, 2021

Pfizer received FDA BLA license for its COVID-19 vaccine

Pfizer received FDA BLA license on 8/23/2021 for its COVID-19 vaccine for use in individuals 16 and older (COMIRNATY). At that time, the FDA published a BLA package insert that included the approved new COVID-19 vaccine tradename COMIRNATY and listed 2 new NDCs (0069-1000-03, 0069-1000-02) and images of labels with the new tradename.

At present, Pfizer does not plan to produce any product with these new NDCs and labels over the next few months while EUA authorized product is still available and being made available for U.S. distribution. As such, the CDC, AMA, and drug compendia may not publish these new codes until Pfizer has determined when the product will be produced with the BLA labels.

Return to News Index

NIH NLM

Exhibit W

Jun 30, 2021, 11:31pm EDT | 23,319 views

Why The Big Quit Is Happening And Why Every Boss Should Embrace It

Lisa Curtis Former Contributor ⓘ
Small Business Strategy
Founder of Kuli Kuli, a mission-driven moringa food startup

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The tables have turned and the CEOs are the ones cowering in fear.

Just a few months ago most employees were clinging desperately to their jobs, scared that their company would be the next one to initiate a round of Covid layoffs or furloughs. No longer.

Now we've entered into the Hot Vax Summer era of hookups, quitting jobs and jumping into pools. Or in the case of one now famous Taco Bell employee, a large workplace sink.

Clearly, employers no longer hold the power. Instead of shying away from this new dynamic, I believe that bosses should embrace this change and meet their employees where they are.

First, a little background.

The Big Quit

The American "Big Quit," or "Great Resignation" is a post-widespread-vaccination phenomenon that is touching everyone from McDonalds workers to software engineers. A record 4 million people quit their jobs in April, many of them in low-paid, inflexible industries like retail.

The same thing is starting to happen in higher paid jobs. Polls show that nearly 40% of white-collar employees would rather leave their jobs than give up remote work, and even highly sought after companies like Apple are scrambling to avoid mass resignations from return-to-office policies.

For many CEOs who've spent the past 16 months focused on how to prevent layoffs, this rise in resignations may feel like a slap in the face. Instead, it

should feel like a wake-up call to embrace the new humanization of work.

The Humanization of Work

Perhaps my favorite part of working remotely during Covid-19 has been the constant video parade of pets, partners and kids.

Recently I took a Friday afternoon video call while sitting on the ground with my 9 month-old daughter as she happily played with her toys. About ten minutes into the call, she decided that my computer was the best toy,

began climbing on top of me, and with one spectacular dive into the keyboard, managed to hang up the call.

When I got back onto the call, the entire group was laughing. One of the fellow CEOs told me afterward that my video fiasco brought an immeasurable amount of much-needed joy to his week.

With so many white-collar workers working from home, there is no longer a separation between life and work. While this comes with its own set of challenges (read: baby hanging up your Zoom calls), it has also made many workers reconsider the type of work that works for them.

Workplace flexibility is the new money in today's post vaccine economy. It's the ability to walk your dog at 2 p.m., or drop off kids at 10 a.m. It's in folding laundry while on a conference call, or going on a run in between meetings. Working remotely has enabled many white-collar workers to feel like they no longer had to choose between their work, family and well-being.

Three Questions Bosses Should Be Asking Themselves

This new dynamic can be a challenge for bosses who are used to measuring productivity by seeing who's left in the office after 7 p.m. For those leaders and managers, I recommend asking three simple questions:

1) Did productivity of this person/team fall during quarantine? *Research shows that focus and productivity improved*

2) Do I need employees in the office full-time to reap the benefits of the office? *Many companies are embracing the 3-2 model of three days in the office, 2 days remote*

3) Am I willing to lose employees due to my remote work policies? *As discussed above, employees are serious about quitting in search of more workplace flexibility*

This is a moment for leaders to step up and reimagine how their workplace can be a flexible space. It's time to create a workplace that encourages both productivity and quality of life. It is my hope that more bosses will embrace the humanization of work before the big quit hits their office.

Follow me on Twitter or LinkedIn. Check out my website.

Lisa Curtis

Follow

I'm the Founder & CEO of Kuli Kuli, the leading brand pioneering a green superfood called moringa. I've taken the company from an idea I dreamed up in Peace Corps and...

Read More

Exhibit X

■ May 10, 2021, 3:00 AM MST

How to Quit Your Job in the Great Post-Pandemic Resignation Boom

● If you're ready to leave, here are some tips on engineering a smooth exit.

By Arianne Cohen

ILLUSTRATION: DEREK ABELLA FOR BLOOMBERG BUSINESSWEEK

LISTEN TO ARTICLE

Ready to say adios to your job? You're not alone

Ready to say adios to your job? You're not alone. "The great resignation is coming," says Anthony Klotz, an associate professor of management at Texas A&M University who's studied the exits of hundreds of workers. "When there's uncertainty, people tend to stay put, so there are pent-up resignations that didn't happen over the past year." The numbers are multiplied, he says, by the many pandemic-related epiphanies—about family time, remote work, commuting, passion projects, life and death, and what it all means—that can make people turn their back on the 9-to-5 office grind. We asked Klotz what to expect as the great resignation picks up speed.

• What are we going to see this summer with employees and organizations?

A lot of uncertainty, for both sides. Companies are figuring out how to maintain their cultures and employees, so many are offering multiple options: Do you want to come back full time? Work remotely? In-office three days a week? Four days? One day? It will be unclear whether these options will be permanent, making it difficult for employees to decide whether to stay or go.

• So will everyone just quit?

No. Plenty of employees don't really want to resign. If their company would let them keep working from home or do fewer hours, they would.

• Say I want to quit, like, right now. What should I do?

Give a lot of thought to the reasons. Are you just assuming your company won't work with you and let you work part time or remotely or take a sabbatical?

you work part time or remotely or take a sabbatical.

Make sure you fully understand your company's plans. For example, if everyone is ordered back to the office, and the top three performers say they're quitting, the organization may rethink.

• Should I quit before or after returning to the office?

Consider going back for at least a week or two. Think of it as a test of your hypothesis. Humans tend to be really bad at predicting how they'll actually feel.

• What should I say to co-workers?

Co-workers may be having the same thoughts. You can imagine one thinking, I don't really want to go back to the office, but at least Anthony will be there. And then I call to say I'm not coming back. Give her time for that difficult conversation.

• How does one do a pandemic resignation?

It's going to be particularly tempting to use electronic mediums, but our research has found that organizations and managers respond poorly to emailing a boss or leaving a note on her desk.

• So when I talk to my boss in person or on Zoom, what should I say?

That you tried it, and it isn't working for you. Your boss will view that in a more favorable light than simply not trying at all. Your reasons should be honest, but not all the reasons. For example, if the job doesn't provide meaning, that doesn't need to be said. Give specific reasons, like graduate school or the commute.

• Is texting or emailing about it risky because of forwards?

Try to control the communication that you give to your organization, your co-workers, and your leader. In email you can't control the tone, and it often comes off wrong. You want to resign in as positive a way as possible.

• Why bother to be so careful?

We're going to see lots of "boomerang" employees, who a year from now miss their jobs and decide their novel isn't going as well as expected. Being a boomerang employee works only if you leave on a very, very positive note.

Exhibit Y

Survey: Vaccine-or-Testing Mandate Will Be Difficult to Implement

By Allen Smith, J.D.
October 15, 2021

Nine out of 10 recently surveyed organizations said it will be somewhat or very challenging to implement the Biden administration's expected vaccine-or-testing requirements. These respondents so far have not mandated that their employees get the COVID-19 vaccine, but they do meet the criteria for needing to institute the requirements.

President Joe Biden announced plans on Sept. 9 (www.shrm.org/resourcesandtools/hr-topics/talent-acquisition/pages/federal-vaccine-mandate.aspx) for a new rule requiring employers with at least 100 employees to mandate that their workers be vaccinated against COVID-19 or undergo weekly testing. The president also signed orders stipulating that most federal employees and federal contractors, as well as most health care workers across the country, be vaccinated.

The Society for Human Resource Management (SHRM) conducted the survey electronically to a random sample of active SHRM members from Sept. 27 through Sept. 30. The 1,289 respondents represented organizations of all sizes—from two to more than 25,000 employees—in a wide variety of industries across the U.S. SHRM also conducted a separate survey of 1,500 U.S. workers.

"Organizations are concerned about the challenges to implementing the new vaccine mandate during a time when there is a talent shortage in many industries," said Trent Burner, SHRM's vice president of research. "The majority of organizations say mandating the vaccine will impact their organization's recruitment, retention, morale and engagement, and business operations."

Organizations' Concerns

Of organizations that meet the criteria for the Biden administration's vaccine-or-testing requirement, 85 percent said the anticipated requirement will make retaining employees more difficult. Eighty-nine percent said some of their employees will quit due to the new mandate.

Seventy-eight percent of HR respondents said the vaccine-or-testing requirements will make attracting and hiring new employees more difficult, while 82 percent said the requirements will make maintaining morale and engagement more difficult.

Seventy-two percent said the vaccine-or-testing requirements will make maintaining regular business operations more difficult.

"The mere possibility of federal vaccine mandates has raised alarm among HR professionals about the possibility of employee turnover," said Mark Codd, SHRM-SCP, labor relations group director for Publix Super Markets Inc., headquartered in Lakeland, Fla.

"Many organizations have undertaken extensive and creative campaigns to increase the voluntary vaccination rate before any federal mandate is issued," he said. "Now is the time for HR professionals to leverage their knowledge of the workforce and creatively develop a persuasive campaign to increase vaccination—both for compliance as well as the health of their workforce."

The federal government's expected vaccine-or-testing mandate for medium and large employers should prompt an internal assessment of the workforce, Codd added. "It's important to know the percent currently vaccinated, as well as understanding the numerous reasons for vaccine hesitation. That information forms the basis for the company's likely numerous campaigns to address and eliminate each vaccine hesitancy."

There are many reasons why workers are hesitant to get vaccinated. "Whether it's cultural, gender reasons, compromised health, distrust, fear or any one or more of other reasons, HR professionals must be capable of addressing each," he said.

Employee Pushback

Many employers gearing up for the vaccine-or-testing mandate are experiencing employee pushback.

While there has been some acquiescence among unvaccinated staff to get vaccinated, many of the employees who wanted the vaccine have had it for months, said Joyce Chastain, SHRM-SCP, a regulatory compliance consultant with The Krizner Group in Tallahassee, Fla. Many of "the ones who don't have it made a conscious decision to not get the vaccination," she said. "It wasn't about apathy. It was a choice."

Chastain said those same employees now have to decide among:

- Keeping their job.
- Lying about a sincerely held religious belief.
- Getting an inoculation that they think is suspect.

"Some of these unvaccinated employees are key to the organization's mission or success," she said. "That puts the organization in the position of losing critical staff."

If an employee is refusing a vaccination and not seeking an accommodation, federal contractors are creating a transition plan now rather than waiting until Dec. 8 (www.shrm.org/resourcesandtools/legal-and-compliance/employment-law/pages/coronavirus-federal-contractors-vaccination-due-date.aspx), the deadline for federal contractors to be vaccinated against COVID-19, Chastain added.

"They are hoping to mitigate against having so many exits on the same day," she said. "They are also hoping that by implementing the transition plan now, employees [will] take them seriously."

Workers' Thoughts on the Biden Announcement

In a separate SHRM survey of 1,500 U.S. workers conducted from Sept. 28 to Sept. 29, over half of respondents who are not fully vaccinated (52 percent) said they will likely quit their jobs if their employer requires them to get the vaccine as a condition of employment.

While 60 percent of surveyed employees supported the vaccine-or-testing announcement, 40 percent did not.

Workers in manufacturing (49 percent) and in wholesale trade, retail trade or transportation, and warehousing (48 percent) were the most likely to not support the Biden announcement, followed by workers in administrative and support services (44 percent) and in construction, utilities, agriculture and mining (43 percent).

Workers in the professional, scientific and technical services (75 percent) were the most likely to support the Biden announcement, followed by workers in information, finance and insurance, and real estate (67 percent) and in health care and social assistance (64 percent).

Marie LaMarche, SHRM-SCP, division director of labor relations for Virginia Mason Franciscan Health in Tacoma, Wash., said employers can address the challenges they face in implementing the vaccine-or-testing requirement by "truly preparing for how employees will disclose their vaccination status. Even that can be difficult to administer and track, particularly since many people have waited and may have gotten their first dose and not their second."

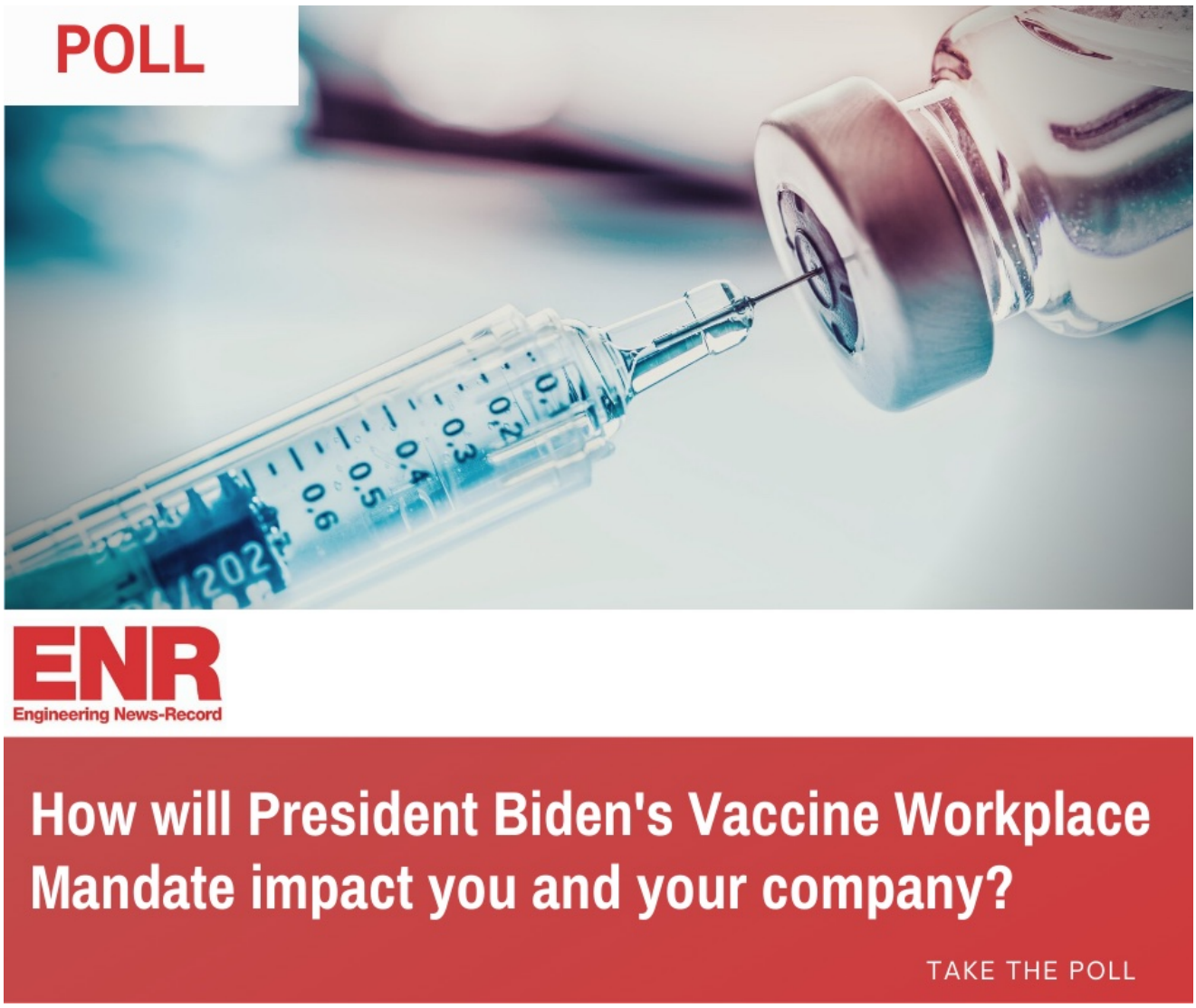
She added, "Although I am a proponent of vaccination, the heartfelt concern I have heard from some employees makes me understand that it can be a scary proposition to some. A lot of employees are worried or scared about losing their jobs along with being concerned about the effects of the vaccination."

Exhibit Z

ENR
Engineering News-Record

Poll: President Biden's Vaccine Workplace Mandate

How will immunization requirements impact your workplace?



September 23, 2021

ENR Staff

Take the poll now.

With 46% of construction workers claiming they will not get vaccinated for Covid-19, President Joe Biden's Sept. 9 executive order requiring vaccines for all federal contractors and for companies wi more than 100 employees has become a concern for the Associated General Contractors and otl industry groups.

“We expect to lose 40% of our workforce that will just quit in lieu of a vaccine mandate,” says Ken Naquin, CEO of the Louisiana Associated General Contractors.

AGC has written letters to the administration expressing their concerns and local contractors fear they will lose more than 40% of their workforce to companies with fewer than 100 employees.

"AGC members justifiably fear that many of those workers, when faced with the choice between the vaccine and their job with a federal contractor, will quit and go to work for another contractor that does not have such a mandate,” says a letter from AGC to the White House Safer Federal Workforce Task Force that will draft guidance.

“Because the vast majority of the construction industry is comprised of small businesses of fewer than 100 employees, and so many firms are looking for workers, those workers could very well go elsewhere and avoid both this federal contractor mandate and the testing mandate being put into effect for large employers by the U.S. Occupational Safety and Health Administration," AGC's letter continued.

Engineering News-Record would like to hear straight from the contractors and employees about how they plan to handle such a mandate, and what they, personally, will do if required to get a vaccine.

ENR wants to know whether and how a requirement for federal contractors and companies with more than 100 employees will impact you and your company. Please take our poll now!

Take our poll here.

UNITED STATES DISTRICT COURT
DISTRICT OF ARIZONA

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

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; Tae Johnson in his official capacity as Senior Official Performing the Duties of Director of U.S. Immigration and Customs Enforcement; Ur M. Jaddou in her official capacity as Director of U.S. Citizenship and Immigration Services; 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 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; and Jeffrey Zients in his official capacity as co-chair of the Safer Federal Workforce Task Force and COVID-19 Response Coordinator

Defendants.

No. 2:21-cv-01568-MTL

[PROPOSED] ORDER

Having considered the Plaintiffs' Motion for a Temporary Restraining Order and Preliminary Injunction, **IT IS HEREBY ORDERED** granting the motion.

IT IS FURTHER ORDERED that:

1. Defendants shall not impose any COVID-19 vaccination requirement on any federal contractor or sub-contractor.

2. Defendants shall not impose any COVID-19 vaccination requirement on any federal employee.

3. Defendants shall not include any clauses related to COVID-19 or vaccinations in any contract entered into with any federal contractor or sub-contractor, nor shall Defendants enforce any such clauses in any contracts already entered into.

4. Defendants shall not impose any COVID-19-related procurement requirements without first following the required notice-and-comment procedures of the Procurement Policy Act.