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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

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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

Table of Contents

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

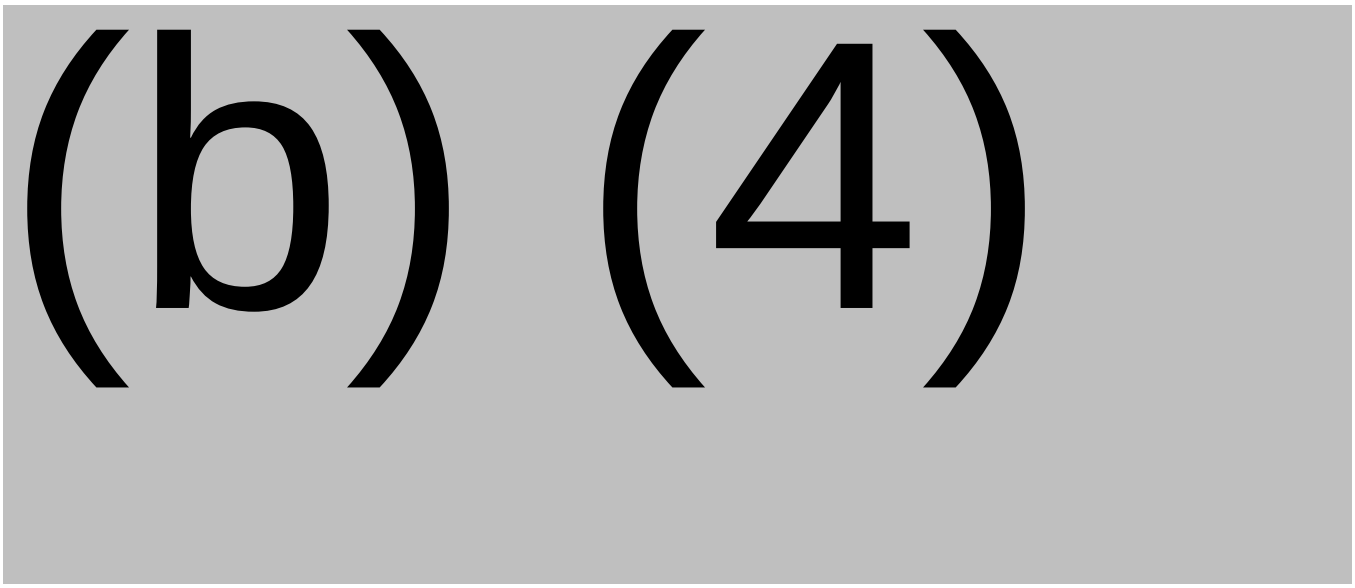
COMIRNATY Manufacturing Overview

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

United States Court of Appeals for the Fifth Circuit

United States Court of Appeals
Fifth Circuit
FILED
November 12, 2021
Lyle W. Cayce
Clerk

No. 21-60845

BST Holdings, L.L.C.; RV Trosclair, L.L.C.; Trosclair Airline, L.L.C.; Trosclair Almonaster, L.L.C.; Trosclair and Sons, L.L.C.; Trosclair ; Trosclair, Incorporated; Trosclair Carrollton, L.L.C.; Trosclair Claiborne, L.L.C.; Trosclair Donaldsonville, L.L.C.; Trosclair Houma, L.L.C.; Trosclair Judge Perez, L.L.C.; Trosclair Lake Forest, L.L.C.; Trosclair Morrison, L.L.C.; Trosclair Paris, L.L.C.; Trosclair Terry, L.L.C.; Trosclair Williams, L.L.C.; Ryan Dailey; Jasand Gamble; Christopher L. Jones; David John Loschen; Samuel Albert Reyna; Kip Stovall; Answers in Genesis, Incorporated; American Family Association, Incorporated; Burnett Specialists; Choice Staffing, L.L.C.; Staff Force, Incorporated; Leadingedge Personnel, Limited; State of Texas; HT Staffing, Limited; doing business as HT Group; The State of Louisiana; Cox Operating, L.L.C.; Dis-Tran Steel, L.L.C.; Dis-Tran Packaged Substations, L.L.C.; Beta Engineering, L.L.C. Optimal Field Services, L.L.C.; The State of Mississippi; Gulf Coast Restaurant Group, Incorporated; The State of South Carolina; The State of Utah; Word of God Fellowship, Incorporated, doing busines as Daystar Television Network,

Petitioners,

versus

Occupational Safety and Health Administration, United States Department of Labor; United States

DEPARTMENT OF LABOR; MARTIN J. WALSH, SECRETARY, U.S. DEPARTMENT OF LABOR; DOUGLAS PARKER, IN HIS OFFICIAL CAPACITY AS ASSISTANT SECRETARY OF LABOR FOR OCCUPATIONAL SAFETY AND HEALTH,

Respondents.

Petition for Review of
Occupational Safety and Health Administration
Emergency Temporary Standard

Before JONES, DUNCAN, and ENGELHARDT, *Circuit Judges*.

KURT D. ENGELHARDT, *Circuit Judge*:

The Occupational Safety and Health Administration (OSHA) "reasonably determined" in June 2020 that an emergency temporary standard (ETS) was "not necessary" to "protect working people from occupational exposure to infectious disease, including COVID-19." *In re AFL-CIO*, 2020 WL 3125324, at *1 (D.C. Cir. June 11, 2020). This was not the first time OSHA had done this; it has refused several times to issue ETSs despite legal action urging it do so. *See, e.g.*, *In re Int'l Chem. Workers Union*, 830 F.2d 369 (D.C. Cir. 1987) (per curiam). In fact, in its fifty-year history, OSHA has issued just ten ETSs.[1] Six were challenged in court; only one survived.[2] The reason for the rarity of this form of emergency action is

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[1] CONG. RSCH. SERV., OCCUPATIONAL SAFETY AND HEALTH ADMINISTRATION (OSHA): EMERGENCY TEMPORARY STANDARDS (ETS) AND COVID-19, at 34 tbl. A-1 (Nov. 10, 2021), *available at* https://crsreports.congress.gov/product/pdf/R/R46288.

[2] It bears noting at the outset that most of the few ETSs issued by OSHA were immediately stayed pending merits review. *See Asbestos Info. Ass'n/N. Am. v. OSHA*, 727 F.2d 415, 418 (5th Cir. 1984); *Indus. Union Dep't, AFL-CIO v. Bingham*, 570 F.2d 965, 968 (D.C. Cir. 1977); *Taylor Diving Salvage Co. v. U.S. Dep't of Lab.*, 537 F.2d 819, 820–21 (5th

simple: courts and the Agency have agreed for generations that "[e]xtraordinary power is delivered to [OSHA] under the emergency provisions of the Occupational Safety and Health Act," so "[t]hat power should be delicately exercised, and only in those emergency situations which require it." *Fla. Peach Growers Ass'n v. U.S. Dep't of Lab.*, 489 F.2d 120, 129–30 (5th Cir. 1974).

This case concerns OSHA's most recent ETS—the Agency's November 5, 2021 Emergency Temporary Standard (the "Mandate") requiring employees of covered employers to undergo COVID-19 vaccination or take weekly COVID-19 tests and wear a mask.[3] An array of petitioners seeks a stay barring OSHA from enforcing the Mandate during the pendency of judicial review. On November 6, 2021, we agreed to stay the Mandate pending briefing and expedited judicial review. Having conducted that expedited review, we reaffirm our initial stay.

I.

OSHA promulgated its much anticipated[4] vaccine mandate on November 5, 2021. Framed as an ETS, the Mandate requires all employers of 100 or more employees to "develop, implement, and enforce a mandatory COVID-19 vaccination policy" and require any workers who remain

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Cir. 1976) (per curiam); *Fla. Peach Growers Ass'n v. U.S. Dep't of Lab.*, 489 F.2d 120, 126 (5th Cir. 1974).

[3] *See* COVID-19 Vaccination and Testing; Emergency Temporary Standard, 86 Fed. Reg. 61,402 (Nov. 5, 2021) (to be codified at 29 C.F.R. pts. 1910, 1915, 1917, 1918, 1926, and 1928).

[4] Debates over the Biden Administration's forthcoming vaccine mandate roiled the country throughout much of the Fall. For obvious reasons, the Mandate affects every person in America in one way or another.

unvaccinated to "undergo [weekly] COVID-19 testing and wear a face covering at work in lieu of vaccination." 86 Fed. Reg. 61,402, 61,402.

On the afternoon of the Mandate's publication, a diverse group of petitioners (including covered employers, States, religious groups, and individual citizens) moved to stay and permanently enjoin the mandate in federal courts of appeals across the nation. Finding "cause to believe there are grave statutory and constitutional issues with the Mandate," we intervened and imposed a temporary stay on OSHA's enforcement of the Mandate. For ease of judicial review, and in light of the pressing need to act immediately, we consolidated our court's petitions under the case number captioned above.

Many of the petitioners are covered private employers within the geographical boundaries of this circuit.[5] Their standing[6] to sue is obvious—the Mandate imposes a financial burden upon them by deputizing their participation in OSHA's regulatory scheme, exposes them to severe financial risk if they refuse or fail to comply, and threatens to decimate their workforces (and business prospects) by forcing unwilling employees to take their shots, take their tests, or hit the road.

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[5] Because these petitioners are the targets of the Mandate and bear the brunt of OSHA's regulatory power, we principally analyze the petitions from their perspective. This is not to say that the claims of other petitioners such as States or individual citizens would be any less successful on a thorough analysis.

[6] "Only one of the petitioners needs to have standing to permit us to consider the petition for review." *Massachusetts v. EPA*, 549 U.S. 497, 518 (2007).

The petitioners seek a stay—and ultimately a permanent injunction—of the Mandate's enforcement pending full judicial review of the Mandate. We address their request for a stay today.[7]

II.

The "traditional stay factors . . . govern a request for a stay pending judicial review." *Nken v. Holder*, 556 U.S. 418, 426 (2009). Under the traditional stay standard, a court considers four factors: "(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." *Hilton v. Braunskill*, 481 U.S. 770, 776 (1987).

Each of these factors favors a stay here.

A.

We first consider whether the petitioners' challenges to the Mandate are likely to succeed on the merits. For a multitude of reasons, they are.

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[7] Our November 6, 2021 stay order preserved the status quo during the pendency of briefing. The unusual procedural posture of this case makes for an unusual process. Ordinarily, a federal plaintiff aggrieved by an adversary's threatened course of action must go to a *district court* to seek injunctive relief at the outset. In this ordinary scenario, a preliminary injunction precedes a permanent injunction, and trial-court review precedes appellate review. But this is not a typical case. Here, the statute giving OSHA the power to issue emergency temporary standards like the Mandate also provides for direct and immediate judicial review in "the United States court of appeals for the circuit wherein" "[a]ny person who may be adversely affected by" an ETS "resides or has his principal place of business." *See* 29 U.S.C. § 655(f). Satisfied of our jurisdiction to proceed under that provision, but mindful of our unusual procedural posture, we apply the traditional factors for a stay pending judicial review and draw factual support from the attachments to the pleadings, uncontested facts, and judicial notice.

We begin by stating the obvious. The Occupational Safety and Health Act, which created OSHA, was enacted by Congress to assure Americans "safe and healthful working conditions and to preserve our human resources." *See* 29 U.S.C. § 651 (statement of findings and declaration of purpose and policy). It was not—and likely *could* not be, under the Commerce Clause and nondelegation doctrine[8]—intended to authorize a workplace safety administration in the deep recesses of the federal bureaucracy to make sweeping pronouncements on matters of public health affecting every member of society in the profoundest of ways. *Cf. Ala. Ass'n of Realtors v. HHS*, 141 S. Ct. 2485, 2488–90 (2021) (per curiam).

On the dubious assumption that the Mandate *does* pass constitutional muster—which we need not decide today[9]—it is nonetheless fatally flawed on its own terms. Indeed, the Mandate's strained prescriptions combine to make it the rare government pronouncement that is both overinclusive (applying to employers and employees in virtually all industries and workplaces in America, with little attempt to account for the obvious differences between the risks facing, say, a security guard on a lonely night shift, and a meatpacker working shoulder to shoulder in a cramped warehouse) *and* underinclusive (purporting to save employees with 99 or more coworkers from a "grave danger" in the workplace, while making no attempt to shield employees with 98 or fewer coworkers from the very same

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[8] The nondelegation doctrine constrains Congress's ability to delegate its legislative authority to executive agencies. *See, e.g.*, *Mistretta v. United States*, 488 U.S. 361, 371–72 (1989) ("The Constitution provides that '[a]ll legislative Powers herein granted shall be vested in a Congress of the United States' . . . and we have long insisted that 'the integrity and maintenance of the system of government ordered by the Constitution' mandate that Congress generally cannot delegate its legislative power to another Branch." (first quoting U.S. CONST. art. I, § 1; then quoting *Field v. Clark*, 143 U.S. 649, 692 (1892))).

[9] *But see infra* subsection II.A.2.f.

threat). The Mandate's stated impetus—a purported "emergency" that the entire globe has now endured for nearly two years,[10] and which OSHA itself spent nearly two *months* responding to[11]—is unavailing as well. And its promulgation grossly exceeds OSHA's statutory authority.

1.

After the President voiced his displeasure with the country's vaccination rate in September,[12] the Administration pored over the U.S. Code in search of authority, or a "work-around,"[13] for imposing a national

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[10] As Justice Gorsuch recently observed, society's interest in slowing the spread of COVID-19 "cannot qualify as [compelling] forever," for "[i]f human nature and history teach anything, it is that civil liberties face grave risks when governments proclaim indefinite states of emergency." *Does 1–3 v. Mills*, -- S. Ct. ---, 2021 WL 5027177, at *3 (Oct. 29, 2021) (Gorsuch, J., dissenting); *see also Fla. Peach Growers*, 489 F.2d at 131 (situation ongoing for "last several years . . . fail[ed] to qualify for [OSHA] emergency measures").

[11] The President announced his intention to impose a national vaccine mandate on September 9, 2021. *See, e.g.*, Kevin Liptak & Kaitlan Collins, *Biden Announces New Vaccine Mandates that Could Cover 100 Million Americans*, CNN (Sept. 9, 2021), https://www.cnn.com/2021/09/09/politics/joe-biden-covid-speech/index.html ("'We've been patient, but our patience is wearing thin, and your refusal has cost all of us,' Biden said, his tone hardening toward Americans who still refuse to receive a vaccine despite ample evidence of their safety and full approval of one . . . ."). OSHA issued the Mandate nearly two months later, on November 5, 2021, and the Mandate itself prominently features yet another two-month delay. One could query how an "emergency" could prompt such a "deliberate" response. In similar cases, we've held that OSHA's failure to act promptly "does not conclusively establish that a situation is not an emergency," but "may be evidence that a situation is not a *true* emergency." *Asbestos Info.*, 727 F.2d at 423 (emphasis added).

[12] *See supra* note 11.

[13] On September 9, 2021, White House Chief of Staff Ron Klain retweeted MSNBC anchor Stephanie Ruhle's tweet that stated, "OSHA doing this vaxx mandate as an emergency workplace safety rule *is the ultimate work-around for the Federal govt to require vaccinations.*" *See, e.g.*, Pet'rs Burnett Specialists, Choice Staffing, LLC, and Staff Force Inc.'s Reply Brief at 4 (emphasis added).

vaccine mandate. The vehicle it landed on was an OSHA ETS. The statute empowering OSHA allows OSHA to bypass typical notice-and-comment proceedings for six months by providing "for an emergency temporary standard to take immediate effect upon publication in the Federal Register" if it "determines (A) that employees are exposed to grave danger from exposure to substances or agents determined to be toxic or physically harmful or from new hazards, and (B) that such emergency standard is necessary to protect employees from such danger." 29 U.S.C. § 655(c)(1).

As the name suggests, *emergency* temporary standards "are an 'unusual response' to 'exceptional circumstances.'" *Int'l Chem. Workers*, 830 F.2d at 371 (quoting *Pub. Citizen Health Rsch. Grp. v. Auchter*, 702 F.2d 1150, 1155 (D.C. Cir. 1983)). Thus, courts have uniformly observed that OSHA's authority to establish emergency temporary standards under § 655(c) "is an 'extraordinary power' that is to be 'delicately exercised' in only certain 'limited situations.'" *Id.* at 370 (quoting *Pub. Citizen*, 702 F.2d at 1155).[14]

But the Mandate at issue here is anything *but* a "delicate[] exercise[]" of this "extraordinary power." *Cf. Pub. Citizen*, 702 F.2d at 1155. Quite the opposite, rather than a delicately handled scalpel, the Mandate is a one-size-fits-all sledgehammer that makes hardly any attempt to account for differences in workplaces (and workers) that have more than a little bearing on workers' varying degrees of susceptibility to the supposedly "grave danger" the Mandate purports to address.

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[14] The Agency has thus conceded in the past that "[t]he OSH Act does not authorize OSHA to issue sweeping health standards to address entire classes of known and unknown infectious diseases on an emergency basis without notice and comment." *See* Department of Labor's Resp. to the Emergency Pet. for a Writ of Mandamus at 33–34, *In re AFL-CIO*, No. 20-1158 (D.C. Cir. May 29, 2020) [hereinafter OSHA D.C. Circuit Brief].

2.

Thus, as § 655(c)(1) plainly provides, to be lawfully enacted, an ETS must: (1) address "substances or agents determined to be toxic or physically harmful"—or "new hazards"—in the workplace; (2) show that workers are exposed to such "substances," "agents," or "new hazards" in the workplace; (3) show that said exposure places workers in "grave danger"; and (4) be "necessary" to alleviate employees' exposure to gravely dangerous hazards in the workplace. As we have noted in the past, the precision of this standard makes it a difficult one to meet. *See Fla. Peach Growers*, 489 F.2d at 130 (observing that OSHA's ETS authority "requires determination of danger from exposure to harmful substances, not just a danger of exposure; and, not exposure to just a danger, but to a grave danger; and, not the necessity of just a temporary standard, but that an emergency [temporary] standard is necessary").[15]

(a)

In its brief, Texas makes a compelling argument that § 655(c)(1)'s neighboring phrases "substances or agents" and "toxic or physically harmful" place an airborne virus beyond the purview of an OSHA ETS in the first place. To avoid "giving unintended breadth to the Acts of Congress," courts "rely on the principle of *noscitur a sociis*—a word is known by the company it keeps." *Yates v. United States*, 574 U.S. 528, 543 (2015) (cleaned up). Here, OSHA's attempt to shoehorn an airborne virus that is both widely present in society (and thus not particular to any workplace) and non-life-

[15] In prior litigation, OSHA acknowledged that many "workplaces" covered by a COVID-19 ETS "are not merely workplaces," but are also "stores, restaurants, and other places occupied by workers and the general public alike, in which the measures called for require a broader lens—and at times a broader mandate—than available to OSHA." *See* OSHA D.C. Circuit Brief at 20.

threatening to a vast majority of employees into a neighboring phrase connoting *toxicity* and *poisonousness* is yet another transparent stretch. Other cases involving OSHA (though not ETSs per se) shed further light on the intended meaning of these terms. *See, e.g.*, *UAW v. OSHA*, 938 F.2d 1310, 1314 (D.C. Cir. 1991). *See generally Indus. Union Dep't, AFL-CIO v. Am. Petroleum Inst.*, 448 U.S. 607 (1980). Any argument OSHA may make that COVID-19 is a "new hazard[]" would directly contradict OSHA's prior representation to the D.C. Circuit that "[t]here can be no dispute that COVID-19 is a *recognized* hazard." *See* OSHA D.C. Circuit Brief at 25 (emphasis added).

(b)

A natural first step in enacting a lawful ETS is to show that employees covered by the ETS are in fact *exposed* to the dangerous substances, agents, or hazards at issue—here, COVID-19. *See, e.g.*, *Int'l Chem. Workers*, 830 F.2d at 371 (noting OSHA's stated view "that a finding of 'grave danger' to support an ETS be based upon exposure in actual levels found in the workplace"). As it pertains to the vast majority of private employees covered by the Mandate, however, OSHA fails to meet this threshold burden. In defending the Mandate before this court, the Government credits OSHA with "describ[ing] myriad studies showing workplace [COVID-19] 'clusters' and 'outbreaks' and other significant 'evidence of workplace transmission' and 'exposure.'" *See* Resp'ts' Opp'n to Emergency Stay Mot. at 8. But this misses the mark, as OSHA is required to make findings of exposure—or at least the presence of COVID-19—in *all* covered workplaces.

Of course, OSHA cannot possibly show that every workplace covered by the Mandate currently has COVID-positive employees, or that every industry covered by the Mandate has had or will have "outbreaks." As

discussed below, this kind of overbreadth plagues the Mandate generally. *See infra* subsection II.A.2.d.

(c)

Equally problematic, however, is that it remains unclear that COVID-19—however tragic and devastating the pandemic has been—poses the kind of grave danger § 655(c)(1) contemplates. *See, e.g.*, *Int'l Chem. Workers*, 830 F.2d at 371 (noting that OSHA itself once concluded "that to be a 'grave danger,' it is not sufficient that a chemical, such as cadmium, can cause *cancer* or *kidney damage* at a high level of exposure" (emphasis added)). For starters, the Mandate itself concedes that the effects of COVID-19 may range from "mild" to "critical." As important, however, the status of the spread of the virus has varied since the President announced the general parameters of the Mandate in September. (And of course, this all assumes that COVID-19 poses any significant danger to workers to begin with; for the more than *seventy-eight* percent[16] of Americans aged 12 and older either fully or partially inoculated against it, the virus poses—the Administration assures us—little risk at all.) *See, e.g.*, 86 Fed. Reg. 61,402, 61,402–03 ("COVID-19 vaccines authorized or approved by the [FDA] effectively protect vaccinated individuals against severe illness and death from COVID-19.").

The Administration's prior statements in this regard further belie the notion that COVID-19 poses the kind of emergency that allows OSHA to take the extreme measure of an ETS. In reviewing agency pronouncements, courts need not turn a blind eye to the statements of those issuing such pronouncements. *See, e.g.*, *FCC v. Fox Television Stations, Inc.*, 556 U.S. 502, 515 (2009). In fact, courts have an affirmative duty *not* to do so. It is thus

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[16] *See* CDC, COVID DATA TRACKER, https://covid.cdc.gov/covid-data-tracker/#datatracker-home.

critical to note that the Mandate makes no serious attempt to explain why OSHA and the President himself[17] were against vaccine mandates before they were for one here. *See, e.g.*, Occupational Exposure to Bloodborne Pathogens, 54 Fed. Reg. 23,042, 23,045 (May 30, 1989) ("Health in general is an intensely personal matter. . . . OSHA prefers to encourage rather than try to force by governmental coercion, employee cooperation in [a] vaccination program."); Letter from Loren Sweatt, Principal Deputy Assistant Sec'y, OSHA, to Richard L. Trumka, President, AFL-CIO at 3 (May 29, 2020) [hereinafter Sweatt Letter] (acknowledging as a general matter that it "would not be necessary for OSHA to issue an ETS to protect workers from infectious diseases" because "OSHA lacks evidence to conclude that all infectious diseases to which employees may be exposed at a workplace constitute a 'grave danger' for which an ETS is an appropriate remedy"). Because it is generally "arbitrary or capricious" to "depart from a prior policy *sub silentio*," agencies must typically provide a "detailed explanation" for contradicting a prior policy, particularly when the "prior policy has engendered serious reliance interests." *FCC v. Fox*, 556 U.S. at 515. OSHA's reversal here strains credulity, as does its pretextual basis.[18] Such shortcomings are all hallmarks of unlawful agency actions.

To be sure, "OSHA's assessment of . . . scientifically complex [facts] and its balancing of the competing policies that underlie the decision whether to issue an ETS . . . are entitled to great deference," but this is not a case

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[17] In December of 2020, the President was quoted as saying, "No I don't think [vaccines] should be mandatory." *See, e.g.*, Jacob Jarvis, *Fact Check: Did Joe Biden Reject Idea of Mandatory Vaccines in December 2020*, NEWSWEEK (Sept. 10, 2021), https://www.newsweek.com/fact-check-joe-biden-no-vaccines-mandatory-december-2020-1627774.

[18] *See supra* note 13 (Klain endorsement of the term "work-around").

where any amount of deference would make a bit of difference. *Int'l Chem. Workers*, 830 F.2d at 371.

(d)

We next consider the necessity of the Mandate. The Mandate is staggeringly overbroad. Applying to 2 out of 3 private-sector employees in America, in workplaces as diverse as the country itself, the Mandate fails to consider what is perhaps the most salient fact of all: the ongoing threat of COVID-19 is more dangerous to *some* employees than to *other* employees. All else equal, a 28 year-old trucker spending the bulk of his workday in the solitude of his cab is simply less vulnerable to COVID-19 than a 62 year-old prison janitor. Likewise, a naturally immune unvaccinated worker is presumably at less risk than an unvaccinated worker who has never had the virus. The list goes on, but one constant remains—the Mandate fails almost completely to address, or even respond to, much of this reality and common sense.

Moreover, earlier in the pandemic, the Agency recognized the practical impossibility of tailoring an effective ETS in response to COVID-19. *See* OSHA D.C. Circuit Brief at 16, 17, 21, 26 ("Based on substantial evidence, OSHA determined that an ETS is not necessary both because there are existing OSHA and non-OSHA standards that address COVID-19 and because an ETS would actually be counterproductive. . . . To address all employers and to do so with the requisite dispatch, an ETS would at best be an enshrinement of these general and universally known measures that are already enforceable through existing OSHA tools that require employers to assess and address extant hazards. OSHA's time and resources are better spent issuing industry-specific guidance that adds real substance and permits flexibility as we learn more about this virus. Given that we learn more about COVID-19 every day, setting rules in stone through an ETS (and later a

permanent rule) may undermine worker protection by permanently mandating precautions that later prove to be inefficacious. . . . [A]n ETS could only enshrine broad legal standards that are already in place or direct employers to develop COVID-19 response plans specific to their businesses, something employers are already doing. Such a step would be superfluous at best and could be counterproductive to ongoing state, local, and private efforts. . . . Additionally, employers may choose any effective method to abate a recognized hazard under the general duty clause. Contrary to AFL-CIO's argument, this flexibility is likely to improve worker safety, because employers must choose a means of abatement that eliminates the hazard or materially reduces it to the extent feasible."). OSHA itself admitted that "an ETS once issued could very well become ineffective or counterproductive, as it may be informed by incomplete or ultimately inaccurate information." *Id.* at 30, 32–33 (acknowledging further that "[a]dequate safeguards for workers could differ substantially based on geographic location, as the pandemic has had dramatically different impacts on different parts of the country. State and local requirements and guidance on COVID-19 are thus critical to employers in determining how to best protect workers, and OSHA must retain flexibility to adapt its advice regarding incorporation of such local guidance, where appropriate. . . . [A]n ETS meant to broadly cover all workers with potential exposure to COVID-19—effectively *all* workers across the country—would have to be written at such a general level that it would risk providing very little assistance at all").

In light of this immense complexity, one might naturally ask the Agency—is this situation truly amenable to a one-size-fits-all Mandate? The likely answer may be why OSHA has in the past "determined that the best approach for responding to the pandemic is to enforce the existing OSH Act requirements that address infectious disease hazards, while also issuing detailed, industry-specific guidance," which is generally "more effective

than promulgating a rigid set of requirements for all employers in all industries based on limited information." *See* Sweatt Letter at 2. In sum, as OSHA itself has previously acknowledged, an ETS appears to be a "poorly-suited approach for protecting workers against [COVID-19] because no standard that covers all of the Nation's workers would protect all those workers equally." *See id.* at 9.

At the same time, the Mandate is also *underinclusive*. The most vulnerable worker in America draws no protection from the Mandate if his company employs 99 workers or fewer. The reason why? Because, as even OSHA admits, companies of 100 or more employers will be better able to administer (and sustain) the Mandate. *See* 86 Fed. Reg. 61,402, 61,403 ("OSHA seeks information about the ability of employers with fewer than 100 employees to implement COVID-19 vaccination and/or testing programs."). That may be true. But this kind of thinking belies the premise that any of this is truly an *emergency*. Indeed, underinclusiveness of this sort is often regarded as a telltale sign that the government's interest in enacting a liberty-restraining pronouncement is not in fact "compelling." *Cf. Church of the Lukumi Babalu Aye, Inc. v. City of Hialeah*, 508 U.S. 520, 542–46 (1993) (city's ban on religious animal sacrifice but corresponding allowance of other activities similarly endangering public health belied its purportedly "compelling" interest in safe animal disposal practices). The underinclusive nature of the Mandate implies that the Mandate's true purpose is not to enhance workplace safety, but instead to ramp up vaccine uptake by any means necessary.[19]

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[19] The Mandate is also underinclusive in the solutions it proposes. Indeed, even in its fullest force, the Mandate cannot prevent vaccinated employees from spreading the virus in the workplace, or prevent unvaccinated employees from spreading the virus in between weekly tests.

(e)

If the deficiencies we've already covered aren't enough, other miscellaneous considerations seal the Mandate's fate. For one, "[t]he Agency cannot use its ETS powers as a stop-gap measure," *Asbestos Info.*, 727 F.2d at 422, but concedes that that is precisely what the Mandate is intended to do here. *See* 86 Fed. Reg. 61,402, 61,434–35 (admitting that "[c]rafting a multi-layered standard that is comprehensive and feasible for all covered work settings, including mixed settings of vaccinated and unvaccinated workers, is an extraordinarily challenging and complicated undertaking, yet the grave danger that COVID-19 poses to unvaccinated workers obliges the agency to act as quickly as possible"). For another, courts have consistently recognized that the "protection afforded to workers [by an ETS] should outweigh the economic consequences to the regulated industry," *Asbestos Info.*, 727 F.2d at 423, but for all the reasons we've previously noted, the Mandate flunks a cost-benefit analysis here.

(f)

It lastly bears noting that the Mandate raises serious constitutional concerns that either make it more likely that the petitioners will succeed on the merits, or at least counsel against adopting OSHA's broad reading of § 655(c) as a matter of statutory interpretation.

First, the Mandate likely exceeds the federal government's authority under the Commerce Clause because it regulates noneconomic inactivity that falls squarely within the States' police power. A person's choice to remain unvaccinated and forgo regular testing is noneconomic inactivity. *Cf. NFIB v. Sebelius*, 567 U.S. 519, 522 (2012) (Roberts, C.J., concurring); *see also id.* at 652–53 (Scalia, J., dissenting). And to mandate that a person receive a vaccine or undergo testing falls squarely within the States' police power. *Zucht v. King*, 260 U.S. 174, 176 (1922) (noting that precedent had long "settled that

it is within the police power of a state to provide for compulsory vaccination"); *Jacobson v. Massachusetts*, 197 U.S. 11, 25–26 (1905) (similar). The Mandate, however, commandeers U.S. employers to compel millions of employees to receive a COVID-19 vaccine or bear the burden of weekly testing. 86 Fed. Reg. 61,402, 61,407, 61,437, 61,552. The Commerce Clause power may be expansive, but it does not grant Congress the power to regulate noneconomic inactivity traditionally within the States' police power. *See Sebelius*, 567 U.S. at 554 (Roberts, C.J., concurring) ("People, for reasons of their own, often fail to do things that would be good for them or good for society. Those failures—joined with the similar failures of others—can readily have a substantial effect on interstate commerce. Under the Government's logic, that authorizes Congress to use its commerce power to compel citizens to act as the Government would have them act."); *see also Bond v. United States*, 572 U.S. 844, 854 (2014) ("The States have broad authority to enact legislation for the public good—what we have often called a 'police power.' . . . The Federal Government, by contrast, has no such authority. . . ." (citations omitted)). Indeed, the courts "*always* have rejected readings of the Commerce Clause . . . that would permit Congress to exercise a police power." *United States v. Lopez*, 514 U.S. 549, 584 (1995) (Thomas, J., concurring). In sum, the Mandate would far exceed current constitutional authority.

Second, concerns over separation of powers principles cast doubt over the Mandate's assertion of virtually unlimited power to control individual conduct under the guise of a workplace regulation. As Judge Duncan points out, the major questions doctrine confirms that the Mandate exceeds the bounds of OSHA's statutory authority. Congress must "speak clearly if it wishes to assign to an agency decisions of vast economic and political significance." *Util. Air Regul. Grp. v. EPA*, 573 U.S. 302, 324 (2014) (cleaned up). The Mandate derives its authority from an old statute employed in a

novel manner,[20] imposes nearly $3 billion in compliance costs, involves broad medical considerations that lie outside of OSHA's core competencies, and purports to definitively resolve one of today's most hotly debated political issues. *Cf. MCI Telecomms. Corp. v. AT&T*, 512 U.S. 218, 231 (1994) (declining to hold that the FCC could eliminate telecommunications rate-filing requirements); *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 159–60 (2000) (declining to hold that the FDA could regulate cigarettes); *Gonzales v. Oregon*, 546 U.S. 243, 262 (2006) (declining to allow DOJ to ban physician-assisted suicide). There is no clear expression of congressional intent in § 655(c) to convey OSHA such broad authority, and this court will not infer one. Nor can the Article II executive breathe new power into OSHA's authority—no matter how thin patience wears.

At the very least, even if the statutory language were susceptible to OSHA's broad reading—which it is not—these serious constitutional concerns would counsel this court's rejection of that reading. *Jennings v. Rodriguez*, 138 S. Ct. 830, 836 (2018).

* * *

Accordingly, the petitioners' challenges to the Mandate show a great likelihood of success on the merits, and this fact weighs critically in favor of a stay.

B.

It is clear that a denial of the petitioners' proposed stay would do them irreparable harm. For one, the Mandate threatens to substantially burden the

[20] Here, it is simply unlikely that Congress assigned authority over such a monumental policy decision to OSHA—hard hats and safety goggles, this is not.

liberty interests[21] of reluctant individual recipients put to a choice between their job(s) and their jab(s). For the individual petitioners, the loss of constitutional freedoms "for even minimal periods of time . . . unquestionably constitutes irreparable injury." *Elrod v. Burns*, 427 U.S. 347, 373 (1976) ("The loss of First Amendment freedoms, for even minimal periods of time, unquestionably constitutes irreparable injury.").

Likewise, the companies seeking a stay in this case will also be irreparably harmed in the absence of a stay, whether by the business and financial effects of a lost or suspended employee, compliance and monitoring costs associated with the Mandate, the diversion of resources necessitated by the Mandate, or by OSHA's plan to impose stiff financial penalties on companies that refuse to punish or test unwilling employees. The Mandate places an immediate and irreversible imprint on all covered employers in America, and "complying with a regulation later held invalid almost *always* produces the irreparable harm of nonrecoverable compliance costs." *See Texas v. EPA*, 829 F.3d 405, 433 (5th Cir. 2016) (quoting *Thunder Basin Coal Co. v. Reich*, 510 U.S. 200, 220–21 (1994) (Scalia, J., concurring in part and in the judgment)).

The States, too, have an interest in seeing their constitutionally reserved police power over public health policy defended from federal overreach.

C.

In contrast, a stay will do *OSHA* no harm whatsoever. Any interest OSHA may claim in enforcing an unlawful (and likely unconstitutional) ETS is illegitimate. Moreover, any abstract "harm" a stay might cause the Agency

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[21] Not to mention the free religious exercise of certain employees. *See* U.S. CONST. amend. I; *cf. Holt v. Hobbs*, 574 U.S. 352, 361 (2015).

pales in comparison and importance to the harms the absence of a stay threatens to cause countless individuals and companies.

D.

For similar reasons, a stay is firmly in the public interest. From economic uncertainty to workplace strife, the mere specter of the Mandate has contributed to untold economic upheaval in recent months. Of course, the principles at stake when it comes to the Mandate are not reducible to dollars and cents. The public interest is also served by maintaining our constitutional structure and maintaining the liberty of individuals to make intensely personal decisions according to their own convictions—even, or perhaps *particularly*, when those decisions frustrate government officials.

* * *

The Constitution vests a limited legislative power in Congress. For more than a century, Congress has routinely used this power to delegate policymaking specifics and technical details to executive agencies charged with effectuating policy principles Congress lays down. In the mine run of cases—a transportation department regulating trucking on an interstate highway, or an aviation agency regulating an airplane lavatory—this is generally well and good. But health agencies do not make housing policy, and occupational safety administrations do not make health policy. *Cf. Ala. Ass'n of Realtors*, 141 S. Ct. at 2488–90. In seeking to do so here, OSHA runs afoul of the statute from which it draws its power and, likely, violates the constitutional structure that safeguards our collective liberty.

For these reasons, the petitioners' motion for a stay pending review is GRANTED. Enforcement of the Occupational Safety and Health Administration's "COVID-19 Vaccination and Testing; Emergency

Temporary Standard"[22] remains STAYED pending adequate judicial review of the petitioners' underlying motions for a permanent injunction.[23]

In addition, IT IS FURTHER ORDERED that OSHA take no steps to implement or enforce the Mandate until further court order.

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[22] 86 Fed. Reg. 61,402 (Nov. 5, 2021) (to be codified at 29 C.F.R. pts. 1910, 1915, 1917, 1918, 1926, and 1928).

[23] The Clerk of Court shall ensure that this order applies with equal force to all related motions consolidated into this case in accordance with the court's November 6, 2021 order.

STUART KYLE DUNCAN, *Circuit Judge*, concurring:

In addition to the many reasons ably identified by Judge Engelhardt's opinion, I underscore one reason why these challenges to OSHA's unprecedented mandate are virtually certain to succeed.

Courts "expect Congress to speak clearly when authorizing an agency to exercise powers of 'vast economic and political significance.'" *Ala. Ass'n of Realtors v. Dep't of Health & Human Servs.*, 141 S. Ct. 2485, 2489 (2021) (quoting *Utility Air Regul. Grp. v. EPA*, 573 U.S. 302, 324 (2014)). OSHA's rule reaches "two-thirds of all private-sector workers in the nation."86 Fed. Reg. 61,402, 61,403 (Nov. 5, 2021). It compels covered employers to (1) make employees get vaccinated or get weekly tests at their expense and wear masks; (2) "remove" non-complying employees; (3) pay per-violation fines; and (4) keep records of employee vaccination or testing status. 86 Fed. Reg. at 61,402–03, 61,551–54; 29 U.S.C. § 666. OHSA invokes no statute expressly authorizing the rule. Instead, OSHA issued it under an emergency provision addressing workplace "substances," "agents," or "hazards" that it has used only ten times in the last 50 years and never to mandate vaccines. 86 Fed. Reg. at 61,403; *see* 29 U.S.C. § 655(c)(1).

Whether Congress could enact such a sweeping mandate under its interstate commerce power would pose a hard question. *See NFIB v. Sebelius*, 567 U.S. 519, 549–61 (2012). Whether OSHA can do so does not.

I concur in granting a stay.

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Evidence on natural immunity versus COVID-19 vaccine induced immunity:

Study / report title, author, and year published	Predominant finding on natural immunity
1) Necessity of COVID-19 vaccination in previously infected individuals, Shrestha, 2021	"Cumulative incidence of COVID-19 was examined among 52,238 employees in an American healthcare system. The cumulative incidence of SARS-CoV-2 infection remained almost zero among previously infected unvaccinated subjects, previously infected subjects who were vaccinated, and previously uninfected subjects who were vaccinated, compared with a steady increase in cumulative incidence among previously uninfected subjects who remained unvaccinated. Not one of the 1359 previously infected subjects who remained unvaccinated had a SARS-CoV-2 infection over the duration of the study. Individuals who have had SARS-CoV-2 infection are unlikely to benefit from COVID-19 vaccination…"
2) SARS-CoV-2-specific T cell immunity in cases of COVID-19 and SARS, and uninfected controls, Le Bert, 2020	"Studied T cell responses against the structural (nucleocapsid (N) protein) and non-structural (NSP7 and NSP13 of *ORF1*) regions of SARS-CoV-2 in individuals convalescing from coronavirus disease 2019 (COVID-19) (*n* = 36). In all of these individuals, we found CD4 and CD8 T cells that recognized multiple regions of the N protein…showed that patients (*n* = 23) who recovered from SARS possess long-lasting memory T cells that are reactive to the N protein of SARS-CoV 17 years after the outbreak of SARS in 2003; these T cells displayed robust cross-reactivity to the N protein of SARS-CoV-2."
3) Comparing SARS-CoV-2 natural immunity to vaccine-induced immunity: reinfections versus breakthrough infections,Gazit, 2021	"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 found para a 13 fold increased risk of breakthrough Delta infections in double vaccinated persons, and a 27 fold increased risk for symptomatic breakthrough infection in the

Study / report title, author, and year published	Predominant finding on natural immunity
	double vaccinated relative to the natural immunity recovered persons…the risk of hospitalization was 8 times higher in the double vaccinated (para)…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."
4) Highly functional virus-specific cellular immune response in asymptomatic SARS-CoV-2 infection, Le Bert, 2021	"Studied SARS-CoV-2–specific T cells in a cohort of asymptomatic (*n* = 85) and symptomatic (*n* = 75) COVID-19 patients after seroconversion…thus, asymptomatic SARS-CoV-2–infected individuals are not characterized by weak antiviral immunity; on the contrary, they mount a highly functional virus-specific cellular immune response."
5) Large-scale study of antibody titer decay following BNT162b2 mRNA vaccine or SARS-CoV-2 infection, Israel, 2021	"A total of 2,653 individuals fully vaccinated by two doses of vaccine during the study period and 4,361 convalescent patients were included. Higher SARS-CoV-2 IgG antibody titers were observed in vaccinated individuals (median 1581 AU/mL IQR [533.8-5644.6]) after the second vaccination, than in convalescent individuals (median 355.3 AU/mL IQR [141.2-998.7]; p<0.001). In vaccinated subjects, antibody titers decreased by up to 40% each subsequent month while in convalescents they decreased by less than 5% per month…this study demonstrates individuals who received the Pfizer-BioNTech mRNA vaccine have different kinetics of antibody levels compared to patients who had been infected with the SARS-CoV-2 virus, with higher initial levels but a much faster exponential decrease in the first group".
6) SARS-CoV-2 re-infection risk in Austria, Pilz, 2021	Researchers recorded "40 tentative re-infections in 14, 840 COVID-19 survivors of the first wave (0.27%) and 253 581 infections in 8, 885, 640 individuals of the remaining general population (2.85%) translating into an odds ratio (95% confidence interval) of 0.09 (0.07 to 0.13)…relatively low re-infection rate of SARS-CoV-2 in Austria. Protection against SARS-CoV-2 after natural infection is comparable with the highest available estimates on vaccine efficacies." Additionally, hospitalization in only five out of 14,840 (0.03%) people and death in one out of 14,840 (0.01%) (tentative re-infection).
7) mRNA vaccine-induced SARS-CoV-2-specific T cells recognize B.1.1.7 and B.1.351 variants but differ in longevity and homing properties depending on prior	"Spike-specific T cells from convalescent vaccinees differed strikingly from those of infection-naïve vaccinees, with phenotypic features suggesting superior long-term persistence and ability to home to the respiratory tract including the nasopharynx. These results provide reassurance that vaccine-elicited T cells respond robustly to the B.1.1.7 and B.1.351

Study / report title, author, and year published	Predominant finding on natural immunity
infection status, Neidleman, 2021	variants, confirm that convalescents may not need a second vaccine dose."
8) Good news: Mild COVID-19 induces lasting antibody protection, Bhandari, 2021	"Months after recovering from mild cases of COVID-19, people still have immune cells in their body pumping out antibodies against the virus that causes COVID-19, according to a study from researchers at Washington University School of Medicine in St. Louis. Such cells could persist for a lifetime, churning out antibodies all the while. The findings, published May 24 in the journal Nature, suggest that mild cases of COVID-19 leave those infected with lasting antibody protection and that repeated bouts of illness are likely to be uncommon."
9) Robust neutralizing antibodies to SARS-CoV-2 infection persist for months, Wajnberg, 2021	"Neutralizing antibody titers against the SARS-CoV-2 spike protein persisted for at least 5 months after infection. Although continued monitoring of this cohort will be needed to confirm the longevity and potency of this response, these preliminary results suggest that the chance of reinfection may be lower than is currently feared."
10) Evolution of Antibody Immunity to SARS-CoV-2, Gaebler, 2020	"Concurrently, neutralizing activity in plasma decreases by five-fold in pseudo-type virus assays. In contrast, the number of RBD-specific memory B cells is unchanged. Memory B cells display clonal turnover after 6.2 months, and the antibodies they express have greater somatic hypermutation, increased potency and resistance to RBD mutations, indicative of continued evolution of the humoral response…we conclude that the memory B cell response to SARS-CoV-2 evolves between 1.3 and 6.2 months after infection in a manner that is consistent with antigen persistence."
11) Persistence of neutralizing antibodies a year after SARS-CoV-2 infection in humans, Haveri, 2021	"Assessed the persistence of serum antibodies following WT SARS-CoV-2 infection at 8 and 13 months after diagnosis in 367 individuals…found that NAb against the WT virus persisted in 89% and S-IgG in 97% of subjects for at least 13 months after infection."
12) Quantifying the risk of SARS-CoV-2 reinfection over time, Murchu, 2021	"Eleven large cohort studies were identified that estimated the risk of SARS-CoV-2 reinfection over time, including three that enrolled healthcare workers and two that enrolled residents and staff of elderly care homes. Across studies, the total number of PCR-positive or antibody-positive participants at baseline was 615,777, and the maximum duration of follow-up was more than 10 months in three studies. Reinfection was an uncommon event (absolute rate 0%–1.1%), with no study reporting an increase in the risk of reinfection over time."
13) Natural immunity to covid is powerful. Policymakers	Makary writes "it's okay to have an incorrect scientific hypothesis. But when new data proves it wrong, you have to

Study / report title, author, and year published	Predominant finding on natural immunity
seem afraid to say so, Makary, 2021	adapt. Unfortunately, many elected leaders and public health officials have held on far too long to the hypothesis that natural immunity offers unreliable protection against covid-19 — a contention that is being rapidly debunked by science. More than 15 studies have demonstrated the power of immunity acquired by previously having the virus. A 700,000-person study from Israel two weeks ago found that those who had experienced prior infections were 27 times less likely to get a second symptomatic covid infection than those who were vaccinated. This affirmed a June Cleveland Clinic study of health-care workers (who are often exposed to the virus), in which none who had previously tested positive for the coronavirus got reinfected. The study authors concluded that "individuals who have had SARS-CoV-2 infection are unlikely to benefit from covid-19 vaccination." And in May, a Washington University study found that even a mild covid infection resulted in long-lasting immunity."
14) SARS-CoV-2 elicits robust adaptive immune responses regardless of disease severity, Nielsen, 2021	"203 recovered SARS-CoV-2 infected patients in Denmark between April 3rd and July 9th 2020, at least 14 days after COVID-19 symptom recovery… report broad serological profiles within the cohort, detecting antibody binding to other human coronaviruses… the viral surface spike protein was identified as the dominant target for both neutralizing antibodies and $CD8^+$ T-cell responses. Overall, the majority of patients had robust adaptive immune responses, regardless of their disease severity."
15) Protection of previous SARS-CoV-2 infection is similar to that of BNT162b2 vaccine protection: A three-month nationwide experience from Israel, Goldberg, 2021	"Analyze an updated individual-level database of the entire population of Israel to assess the protection efficacy of both prior infection and vaccination in preventing subsequent SARS-CoV-2 infection, hospitalization with COVID-19, severe disease, and death due to COVID-19… vaccination was highly effective with overall estimated efficacy for documented infection of 92·8% (CI:[92·6, 93·0]); hospitalization 94·2% (CI:[93·6, 94·7]); severe illness 94·4% (CI:[93·6, 95·0]); and death 93·7% (CI: [92·5, 94·7]). Similarly, the overall estimated level of protection from prior SARS-CoV-2 infection for documented infection is 94·8% (CI: [94·4, 95·1]); hospitalization 94·1% (CI: [91·9, 95·7]); and severe illness 96·4% (CI: [92·5, 98·3])…results question the need to vaccinate previously-infected individuals."
16) Incidence of Severe Acute Respiratory Syndrome Coronavirus-2 infection among previously infected or	"Employees were divided into three groups: (1) SARS-CoV-2 naïve and unvaccinated, (2) previous SARS-CoV-2 infection, and (3) vaccinated. Person-days were measured from the date of the employee first test and truncated at the end of the observation

Study / report title, author, and year published	Predominant finding on natural immunity
vaccinated employees, Kojima, 2021	period. SARS-CoV-2 infection was defined as two positive SARS-CoV-2 PCR tests in a 30-day period… 4313, 254 and 739 employee records for groups 1, 2, and 3…previous SARS-CoV-2 infection and vaccination for SARS-CoV-2 were associated with decreased risk for infection or re-infection with SARS-CoV-2 in a routinely screened workforce. The was no difference in the infection incidence between vaccinated individuals and individuals with previous infection."
17) Having SARS-CoV-2 once confers much greater immunity than a vaccine—but vaccination remains vital, Wadman, 2021	"Israelis who had an infection were more protected against the Delta coronavirus variant than those who had an already highly effective COVID-19 vaccine…the newly released data show people who once had a SARS-CoV-2 infection were much less likely than never-infected, vaccinated people to get Delta, develop symptoms from it, or become hospitalized with serious COVID-19."
18) One-year sustained cellular and humoral immunities of COVID-19 convalescents, Zhang, 2021	"A systematic antigen-specific immune evaluation in 101 COVID-19 convalescents; SARS-CoV-2-specific IgG antibodies, and also NAb can persist among over 95% COVID-19 convalescents from 6 months to 12 months after disease onset. At least 19/71 (26%) of COVID-19 convalescents (double positive in ELISA and MCLIA) had detectable circulating IgM antibody against SARS-CoV-2 at 12m post-disease onset. Notably, the percentages of convalescents with positive SARS-CoV-2-specific T-cell responses (at least one of the SARS-CoV-2 antigen S1, S2, M and N protein) were 71/76 (93%) and 67/73 (92%) at 6m and 12m, respectively."
19) Functional SARS-CoV-2-Specific Immune Memory Persists after Mild COVID-19, Rodda, 2021	"Recovered individuals developed SARS-CoV-2-specific immunoglobulin (IgG) antibodies, neutralizing plasma, and memory B and memory T cells that persisted for at least 3 months. Our data further reveal that SARS-CoV-2-specific IgG memory B cells increased over time. Additionally, SARS-CoV-2-specific memory lymphocytes exhibited characteristics associated with potent antiviral function: memory T cells secreted cytokines and expanded upon antigen re-encounter, whereas memory B cells expressed receptors capable of neutralizing virus when expressed as monoclonal antibodies. Therefore, mild COVID-19 elicits memory lymphocytes that persist and display functional hallmarks of antiviral immunity."
20) Discrete Immune Response Signature to SARS-CoV-2 mRNA Vaccination Versus Infection, Ivanova, 2021	"Performed multimodal single-cell sequencing on peripheral blood of patients with acute COVID-19 and healthy volunteers before and after receiving the SARS-CoV-2 BNT162b2 mRNA vaccine to compare the immune responses elicited by the virus and by this vaccine…both infection and vaccination induced

Study / report title, author, and year published	Predominant finding on natural immunity
	robust innate and adaptive immune responses, our analysis revealed significant qualitative differences between the two types of immune challenges. In COVID-19 patients, immune responses were characterized by a highly augmented interferon response which was largely absent in vaccine recipients. Increased interferon signaling likely contributed to the observed dramatic upregulation of cytotoxic genes in the peripheral T cells and innate-like lymphocytes in patients but not in immunized subjects. Analysis of B and T cell receptor repertoires revealed that while the majority of clonal B and T cells in COVID-19 patients were effector cells, in vaccine recipients clonally expanded cells were primarily circulating memory cells…we observed the presence of cytotoxic CD4 T cells in COVID-19 patients that were largely absent in healthy volunteers following immunization. While hyper-activation of inflammatory responses and cytotoxic cells may contribute to immunopathology in severe illness, in mild and moderate disease, these features are indicative of protective immune responses and resolution of infection."
21) SARS-CoV-2 infection induces long-lived bone marrow plasma cells in humans, Turner, 2021	"Bone marrow plasma cells (BMPCs) are a persistent and essential source of protective antibodies… durable serum antibody titres are maintained by long-lived plasma cells—non-replicating, antigen-specific plasma cells that are detected in the bone marrow long after the clearance of the antigen … S-binding BMPCs are quiescent, which suggests that they are part of a stable compartment. Consistently, circulating resting memory B cells directed against SARS-CoV-2 S were detected in the convalescent individuals. Overall, our results indicate that mild infection with SARS-CoV-2 induces robust antigen-specific, long-lived humoral immune memory in humans… overall, our data provide strong evidence that SARS-CoV-2 infection in humans robustly establishes the two arms of humoral immune memory: long-lived bone marrow plasma cells (BMPCs) and memory B-cells."
22) SARS-CoV-2 infection rates of antibody-positive compared with antibody-negative health-care workers in England: a large, multicentre, prospective cohort study (SIREN), Jane Hall, 2021	"The SARS-CoV-2 Immunity and Reinfection Evaluation study… 30 625 participants were enrolled into the study… a previous history of SARS-CoV-2 infection was associated with an 84% lower risk of infection, with median protective effect observed 7 months following primary infection. This time period is the minimum probable effect because seroconversions were not included. This study shows that previous infection with SARS-CoV-2 induces effective immunity to future infections in most individuals."
23) Pandemic peak SARS-	"Enrolled 200 patient-facing HCWs between March 26 and

Study / report title, author, and year published	Predominant finding on natural immunity
CoV-2 infection and seroconversion rates in London frontline health-care workers, Houlihan, 2020	April 8, 2020…represents a 13% infection rate (i.e. 14 of 112 HCWs) within the 1 month of follow-up in those with no evidence of antibodies or viral shedding at enrolment. By contrast, of 33 HCWs who tested positive by serology but tested negative by RT-PCR at enrolment, 32 remained negative by RT-PCR through follow-up, and one tested positive by RT-PCR on days 8 and 13 after enrolment."
24) Antibodies to SARS-CoV-2 are associated with protection against reinfection, Lumley, 2021	"Critical to understand whether infection with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) protects from subsequent reinfection… 12219 HCWs participated…prior SARS-CoV-2 infection that generated antibody responses offered protection from reinfection for most people in the six months following infection."
25) Longitudinal analysis shows durable and broad immune memory after SARS-CoV-2 infection with persisting antibody responses and memory B and T cells, Cohen, 2021	"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… most recovered COVID-19 patients mount broad, durable immunity after infection, spike IgG+ memory B cells increase and persist post-infection, durable polyfunctional CD4 and CD8 T cells recognize distinct viral epitope regions."
26) Single cell profiling of T and B cell repertoires following SARS-CoV-2 mRNA vaccine, Sureshchandra, 2021	"Used single-cell RNA sequencing and functional assays to compare humoral and cellular responses to two doses of mRNA vaccine with responses observed in convalescent individuals with asymptomatic disease… natural infection induced expansion of larger CD8 T cell clones occupied distinct clusters, likely due to the recognition of a broader set of viral epitopes presented by the virus not seen in the mRNA vaccine."
27) SARS-CoV-2 antibody-positivity protects against reinfection for at least seven months with 95% efficacy, Abu-Raddad, 2021	"SARS-CoV-2 antibody-positive persons from April 16 to December 31, 2020 with a PCR-positive swab ≥14 days after the first-positive antibody test were investigated for evidence of reinfection, 43,044 antibody-positive persons who were followed for a median of 16.3 weeks…reinfection is rare in the young and international population of Qatar. Natural infection appears to elicit strong protection against reinfection with an efficacy ~95% for at least seven months."
28) Orthogonal SARS-CoV-2 Serological Assays Enable Surveillance of Low-Prevalence Communities and Reveal Durable Humoral Immunity, Ripperger, 2020	"Conducted a serological study to define correlates of immunity against SARS-CoV-2. Compared to those with mild coronavirus disease 2019 (COVID-19) cases, individuals with severe disease exhibited elevated virus-neutralizing titers and antibodies against the nucleocapsid (N) and the receptor binding domain (RBD) of the spike protein…neutralizing and spike-specific

Study / report title, author, and year published	Predominant finding on natural immunity
	antibody production persists for at least 5–7 months… nucleocapsid antibodies frequently become undetectable by 5–7 months."
29) Anti-spike antibody response to natural SARS-CoV-2 infection in the general population, Wei, 2021	"In the general population using representative data from 7,256 United Kingdom COVID-19 infection survey participants who had positive swab SARS-CoV-2 PCR tests from 26-April-2020 to 14-June-2021…we estimated antibody levels associated with protection against reinfection likely last 1.5-2 years on average, with levels associated with protection from severe infection present for several years. These estimates could inform planning for vaccination booster strategies."
30) Antibody Status and Incidence of SARS-CoV-2 Infection in Health Care Workers, Lumley, 2021	"12,541 health care workers participated and had anti-spike IgG measured; 11,364 were followed up after negative antibody results and 1265 after positive results, including 88 in whom seroconversion occurred during follow-up…a total of 223 anti-spike–seronegative health care workers had a positive PCR test (1.09 per 10,000 days at risk), 100 during screening while they were asymptomatic and 123 while symptomatic, whereas 2 anti-spike–seropositive health care workers had a positive PCR test… the presence of anti-spike or anti-nucleocapsid IgG antibodies was associated with a substantially reduced risk of SARS-CoV-2 reinfection in the ensuing 6 months."
31) Researchers find long-lived immunity to 1918 pandemic virus, CIDRAP, 2008 and the actual 2008 NATURE journal publication by Yu	"A study of the blood of older people who survived the 1918 influenza pandemic reveals that antibodies to the strain have lasted a lifetime and can perhaps be engineered to protect future generations against similar strains…the group collected blood samples from 32 pandemic survivors aged 91 to 101..the people recruited for the study were 2 to 12 years old in 1918 and many recalled sick family members in their households, which suggests they were directly exposed to the virus, the authors report. The group found that 100% of the subjects had serum-neutralizing activity against the 1918 virus and 94% showed serologic reactivity to the 1918 hemagglutinin. The investigators generated B lymphoblastic cell lines from the peripheral blood mononuclear cells of eight subjects. Transformed cells from the blood of 7 of the 8 donors yielded secreting antibodies that bound the 1918 hemagglutinin." Yu: "here we show that of the 32 individuals tested that were born in or before 1915, each showed sero-reactivity with the 1918 virus, nearly 90 years after the pandemic. Seven of the eight donor samples tested had circulating B cells that secreted antibodies that bound the 1918 HA. We isolated B cells from subjects and generated five monoclonal antibodies that showed potent neutralizing activity against 1918 virus from three

Study / report title, author, and year published	Predominant finding on natural immunity
	separate donors. These antibodies also cross-reacted with the genetically similar HA of a 1930 swine H1N1 influenza strain."
32) Live virus neutralisation testing in convalescent patients and subjects vaccinated against 19A, 20B, 20I/501Y.V1 and 20H/501Y.V2 isolates of SARS-CoV-2, Gonzalez, 2021	"No significant difference was observed between the 20B and 19A isolates for HCWs with mild COVID-19 and critical patients. However, a significant decrease in neutralisation ability was found for 20I/501Y.V1 in comparison with 19A isolate for critical patients and HCWs 6-months post infection. Concerning 20H/501Y.V2, all populations had a significant reduction in neutralising antibody titres in comparison with the 19A isolate. Interestingly, a significant difference in neutralisation capacity was observed for vaccinated HCWs between the two variants whereas it was not significant for the convalescent groups…the reduced neutralising response observed towards the 20H/501Y.V2 in comparison with the 19A and 20I/501Y.V1 isolates in fully immunized subjects with the BNT162b2 vaccine is a striking finding of the study."
33) Differential effects of the second SARS-CoV-2 mRNA vaccine dose on T cell immunity in naïve and COVID-19 recovered individuals, Camara, 2021	"Characterized SARS-CoV-2 spike-specific humoral and cellular immunity in naïve and previously infected individuals during full BNT162b2 vaccination…results demonstrate that the second dose increases both the humoral and cellular immunity in naïve individuals. On the contrary, the second BNT162b2 vaccine dose results in a reduction of cellular immunity in COVID-19 recovered individuals."
34) Op-Ed: Quit Ignoring Natural COVID Immunity, Klausner, 2021	"Epidemiologists estimate over 160 million people worldwide have recovered from COVID-19. Those who have recovered have an astonishingly low frequency of repeat infection, disease, or death."
35) Association of SARS-CoV-2 Seropositive Antibody Test With Risk of Future Infection, Harvey, 2021	"To evaluate evidence of SARS-CoV-2 infection based on diagnostic nucleic acid amplification test (NAAT) among patients with positive vs negative test results for antibodies in an observational descriptive cohort study of clinical laboratory and linked claims data…the cohort included 3 257 478 unique patients with an index antibody test…patients with positive antibody test results were initially more likely to have positive NAAT results, consistent with prolonged RNA shedding, but became markedly less likely to have positive NAAT results over time, suggesting that seropositivity is associated with protection from infection."
36) SARS-CoV-2 seropositivity and subsequent infection risk in healthy young adults: a prospective cohort study, Letizia, 2021	"Investigated the risk of subsequent SARS-CoV-2 infection among young adults (CHARM marine study) seropositive for a previous infection…enrolled 3249 participants, of whom 3168 (98%) continued into the 2-week quarantine period. 3076 (95%) participants…Among 189 seropositive participants, 19

Study / report title, author, and year published	Predominant finding on natural immunity
	(10%) had at least one positive PCR test for SARS-CoV-2 during the 6-week follow-up (1·1 cases per person-year). In contrast, 1079 (48%) of 2247 seronegative participants tested positive (6·2 cases per person-year). The incidence rate ratio was 0·18 (95% CI 0·11–0·28; p<0·001)…infected seropositive participants had viral loads that were about 10-times lower than those of infected seronegative participants (ORF1ab gene cycle threshold difference 3·95 [95% CI 1·23–6·67]; p=0·004)."
37) Associations of Vaccination and of Prior Infection With Positive PCR Test Results for SARS-CoV-2 in Airline Passengers Arriving in Qatar, Bertollini, 2021	"Of 9,180 individuals with no record of vaccination but with a record of prior infection at least 90 days before the PCR test (group 3), 7694 could be matched to individuals with no record of vaccination or prior infection (group 2), among whom PCR positivity was 1.01% (95% CI, 0.80%-1.26%) and 3.81% (95% CI, 3.39%-4.26%), respectively. The relative risk for PCR positivity was 0.22 (95% CI, 0.17-0.28) for vaccinated individuals and 0.26 (95% CI, 0.21-0.34) for individuals with prior infection compared with no record of vaccination or prior infection."
38) Natural immunity against COVID-19 significantly reduces the risk of reinfection: findings from a cohort of sero-survey participants, Mishra, 2021	"Followed up with a subsample of our previous sero-survey participants to assess whether natural immunity against SARS-CoV-2 was associated with a reduced risk of re-infection (India) … out of the 2238 participants, 1170 were sero-positive and 1068 were sero-negative for antibody against COVID-19. Our survey found that only 3 individuals in the sero-positive group got infected with COVID-19 whereas 127 individuals reported contracting the infection the sero-negative group…from the 3 sero-positives re-infected with COVID-19, one had hospitalization, but did not require oxygen support or critical care…development of antibody following natural infection not only protects against re-infection by the virus to a great extent, but also safeguards against progression to severe COVID-19 disease."
39) Lasting immunity found after recovery from COVID-19, NIH, 2021	"The researchers found durable immune responses in the majority of people studied. Antibodies against the spike protein of SARS-CoV-2, which the virus uses to get inside cells, were found in 98% of participants one month after symptom onset. As seen in previous studies, the number of antibodies ranged widely between individuals. But, promisingly, their levels remained fairly stable over time, declining only modestly at 6 to 8 months after infection… virus-specific B cells increased over time. People had more memory B cells six months after symptom onset than at one month afterwards… levels of T cells for the virus also remained high after infection. Six months after symptom onset, 92% of participants had CD4+ T cells that

Study / report title, author, and year published	Predominant finding on natural immunity
	recognized the virus… 95% of the people had at least 3 out of 5 immune-system components that could recognize SARS-CoV-2 up to 8 months after infection."
40) SARS-CoV-2 Natural Antibody Response Persists for at Least 12 Months in a Nationwide Study From the Faroe Islands, Petersen, 2021	"The seropositive rate in the convalescent individuals was above 95% at all sampling time points for both assays and remained stable over time; that is, almost all convalescent individuals developed antibodies… results show that SARS-CoV-2 antibodies persisted at least 12 months after symptom onset and maybe even longer, indicating that COVID-19-convalescent individuals may be protected from reinfection."
41) SARS-CoV-2-specific T cell memory is sustained in COVID-19 convalescent patients for 10 months with successful development of stem cell-like memory T cells, Jung, 2021	"ex vivo assays to evaluate SARS-CoV-2-specific $CD4^+$ and $CD8^+$ T cell responses in COVID-19 convalescent patients up to 317 days post-symptom onset (DPSO), and find that memory T cell responses are maintained during the study period regardless of the severity of COVID-19. In particular, we observe sustained polyfunctionality and proliferation capacity of SARS-CoV-2-specific T cells. Among SARS-CoV-2-specific $CD4^+$ and $CD8^+$ T cells detected by activation-induced markers, the proportion of stem cell-like memory T (T_{SCM}) cells is increased, peaking at approximately 120 DPSO."
42) Immune Memory in Mild COVID-19 Patients and Unexposed Donors Reveals Persistent T Cell Responses After SARS-CoV-2 Infection, Ansari, 2021	"Analyzed 42 unexposed healthy donors and 28 mild COVID-19 subjects up to 5 months from the recovery for SARS-CoV-2 specific immunological memory. Using HLA class II predicted peptide megapools, we identified SARS-CoV-2 cross-reactive $CD4^+$ T cells in around 66% of the unexposed individuals. Moreover, we found detectable immune memory in mild COVID-19 patients several months after recovery in the crucial arms of protective adaptive immunity; $CD4^+$ T cells and B cells, with a minimal contribution from $CD8^+$ T cells. Interestingly, the persistent immune memory in COVID-19 patients is predominantly targeted towards the Spike glycoprotein of the SARS-CoV-2. This study provides the evidence of both high magnitude pre-existing and persistent immune memory in Indian population."
43) COVID-19 natural immunity, WHO, 2021	"Current evidence points to most individuals developing strong protective immune responses following natural infection with SARSCoV-2. Within 4 weeks following infection, 90-99% of individuals infected with the SARS-CoV-2 virus develop detectable neutralizing antibodies. The strength and duration of the immune responses to SARS-CoV-2 are not completely understood and currently available data suggests that it varies by age and the severity of symptoms. Available scientific data

Study / report title, author, and year published	Predominant finding on natural immunity
	suggests that in most people immune responses remain robust and protective against reinfection for at least 6-8 months after infection (the longest follow up with strong scientific evidence is currently approximately 8 months)."
44) Antibody Evolution after SARS-CoV-2 mRNA Vaccination, Cho, 2021	"We conclude that memory antibodies selected over time by natural infection have greater potency and breadth than antibodies elicited by vaccination…boosting vaccinated individuals with currently available mRNA vaccines would produce a quantitative increase in plasma neutralizing activity but not the qualitative advantage against variants obtained by vaccinating convalescent individuals."
45) Humoral Immune Response to SARS-CoV-2 in Iceland, Gudbjartsson, 2020	"Measured antibodies in serum samples from 30,576 persons in Iceland…of the 1797 persons who had recovered from SARS-CoV-2 infection, 1107 of the 1215 who were tested (91.1%) were seropositive…results indicate risk of death from infection was 0.3% and that antiviral antibodies against SARS-CoV-2 did not decline within 4 months after diagnosis (para)."
46) Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection, Dan, 2021	"Analyzed multiple compartments of circulating immune memory to SARS-CoV-2 in 254 samples from 188 COVID-19 cases, including 43 samples at ≥ 6 months post-infection…IgG to the Spike protein was relatively stable over 6+ months. Spike-specific memory B cells were more abundant at 6 months than at 1 month post symptom onset."
47) The prevalence of adaptive immunity to COVID-19 and reinfection after recovery – a comprehensive systematic review and meta-analysis of 12 011 447 individuals, Chivese, 2021	"Fifty-four studies, from 18 countries, with a total of 12 011 447 individuals, followed up to 8 months after recovery, were included. At 6-8 months after recovery, the prevalence of detectable SARS-CoV-2 specific immunological memory remained high; IgG – 90.4%… pooled prevalence of reinfection was 0.2% (95%CI 0.0 – 0.7, I^2 = 98.8, 9 studies). Individuals who recovered from COVID-19 had an 81% reduction in odds of a reinfection (OR 0.19, 95% CI 0.1 – 0.3, I^2 = 90.5%, 5 studies)."
48) Reinfection Rates among Patients who Previously Tested Positive for COVID-19: a Retrospective Cohort Study, Sheehan, 2021	"Retrospective cohort study of one multi-hospital health system included 150,325 patients tested for COVID-19 infection…prior infection in patients with COVID-19 was highly protective against reinfection and symptomatic disease. This protection increased over time, suggesting that viral shedding or ongoing immune response may persist beyond 90 days and may not represent true reinfection."
49) Assessment of SARS-CoV-2 Reinfection 1 Year After Primary Infection in a Population in Lombardy, Italy,	"The study results suggest that reinfections are rare events and patients who have recovered from COVID-19 have a lower risk of reinfection. Natural immunity to SARS-CoV-2 appears to confer a protective effect for at least a year, which is similar to

Study / report title, author, and year published	Predominant finding on natural immunity
Vitale, 2020	the protection reported in recent vaccine studies."
50) Prior SARS-CoV-2 infection is associated with protection against symptomatic reinfection, Hanrath, 2021	"We observed no symptomatic reinfections in a cohort of healthcare workers…this apparent immunity to re-infection was maintained for at least 6 months…test positivity rates were 0% (0/128 [95% CI: 0–2.9]) in those with previous infection compared to 13.7% (290/2115 [95% CI: 12.3–15.2]) in those without (P<0.0001 χ^2 test)."
51) mRNA vaccine-induced T cells respond identically to SARS-CoV-2 variants of concern but differ in longevity and homing properties depending on prior infection status, Neidleman, 2021	"In infection-naïve individuals, the second dose boosted the quantity and altered the phenotypic properties of SARS-CoV-2-specific T cells, while in convalescents the second dose changed neither. Spike-specific T cells from convalescent vaccinees differed strikingly from those of infection-naïve vaccinees, with phenotypic features suggesting superior long-term persistence and ability to home to the respiratory tract including the nasopharynx."
52) Targets of T Cell Responses to SARS-CoV-2 Coronavirus in Humans with COVID-19 Disease and Unexposed Individuals, Grifoni, 2020	"Using HLA class I and II predicted peptide "megapools," circulating SARS-CoV-2-specific $CD8^+$ and $CD4^+$ T cells were identified in ~70% and 100% of COVID-19 convalescent patients, respectively. $CD4^+$ T cell responses to spike, the main target of most vaccine efforts, were robust and correlated with the magnitude of the anti-SARS-CoV-2 IgG and IgA titers. The M, spike, and N proteins each accounted for 11%–27% of the total $CD4^+$ response, with additional responses commonly targeting nsp3, nsp4, ORF3a, and ORF8, among others. For $CD8^+$ T cells, spike and M were recognized, with at least eight SARS-CoV-2 ORFs targeted."
53) NIH Director's Blog: Immune T Cells May Offer Lasting Protection Against COVID-19, Collins, 2021	"Much of the study on the immune response to SARS-CoV-2, the novel coronavirus that causes COVID-19, has focused on the production of antibodies. But, in fact, immune cells known as memory T cells also play an important role in the ability of our immune systems to protect us against many viral infections, including—it now appears—COVID-19.An intriguing new study of these memory T cells suggests they might protect some people newly infected with SARS-CoV-2 by remembering past encounters with other human coronaviruses. This might potentially explain why some people seem to fend off the virus and may be less susceptible to becoming severely ill with COVID-19."
54) Ultrapotent antibodies against diverse and highly transmissible SARS-CoV-2 variants, Wang, 2021	"Our study demonstrates that convalescent subjects previously infected with ancestral variant SARS-CoV-2 produce antibodies that cross-neutralize emerging VOCs with high potency…potent against 23 variants, including variants of concern."

Study / report title, author, and year published	Predominant finding on natural immunity
55) Why COVID-19 Vaccines Should Not Be Required for All Americans, Makary, 2021	"Requiring the vaccine in people who are already immune with natural immunity has no scientific support. While vaccinating those people may be beneficial – and it's a reasonable hypothesis that vaccination may bolster the longevity of their immunity – to argue dogmatically that they *must* get vaccinated has zero clinical outcome data to back it. As a matter of fact, we have data to the contrary: A Cleveland Clinic study found that vaccinating people with natural immunity did not add to their level of protection."
56) Protracted yet coordinated differentiation of long-lived SARS-CoV-2-specific CD8+ T cells during COVID-19 convalescence, Ma, 2021	"Screened 21 well-characterized, longitudinally-sampled convalescent donors that recovered from mild COVID-19… following a typical case of mild COVID-19, SARS-CoV-2-specific CD8+ T cells not only persist but continuously differentiate in a coordinated fashion well into convalescence, into a state characteristic of long-lived, self-renewing memory."
57) Decrease in Measles Virus-Specific CD4 T Cell Memory in Vaccinated Subjects, Naniche, 2004	"Characterized the profiles of measles vaccine (MV) vaccine-induced antigen-specific T cells over time since vaccination. In a cross-sectional study of healthy subjects with a history of MV vaccination, we found that MV-specific CD4 and CD8 T cells could be detected up to 34 years after vaccination. The levels of MV-specific CD8 T cells and MV-specific IgG remained stable, whereas the level of MV-specific CD4 T cells decreased significantly in subjects who had been vaccinated >21 years earlier."
58) Remembrance of Things Past: Long-Term B Cell Memory After Infection and Vaccination, Palm, 2019	"The success of vaccines is dependent on the generation and maintenance of immunological memory. The immune system can remember previously encountered pathogens, and memory B and T cells are critical in secondary responses to infection. Studies in mice have helped to understand how different memory B cell populations are generated following antigen exposure and how affinity for the antigen is determinant to B cell fate… upon re-exposure to an antigen the memory recall response will be faster, stronger, and more specific than a naïve response. Protective memory depends first on circulating antibodies secreted by LLPCs. When these are not sufficient for immediate pathogen neutralization and elimination, memory B cells are recalled."
59) SARS-CoV-2 specific memory B-cells from individuals with diverse disease severities recognize SARS-CoV-2 variants of concern, Lyski, 2021	"Examined the magnitude, breadth, and durability of SARS-CoV-2 specific antibodies in two distinct B-cell compartments: long-lived plasma cell-derived antibodies in the plasma, and peripheral memory B-cells along with their associated antibody profiles elicited after *in vitro* stimulation. We found that magnitude varied amongst individuals, but was the highest in

Study / report title, author, and year published	Predominant finding on natural immunity
	hospitalized subjects. Variants of concern (VoC) -RBD-reactive antibodies were found in the plasma of 72% of samples in this investigation, and VoC-RBD-reactive memory B-cells were found in all but 1 subject at a single time-point. This finding, that VoC-RBD-reactive MBCs are present in the peripheral blood of all subjects including those that experienced asymptomatic or mild disease, provides a reason for optimism regarding the capacity of vaccination, prior infection, and/or both, to limit disease severity and transmission of variants of concern as they continue to arise and circulate."
60) Exposure to SARS-CoV-2 generates T-cell memory in the absence of a detectable viral infection, Wang, 2021	"T-cell immunity is important for recovery from COVID-19 and provides heightened immunity for re-infection. However, little is known about the SARS-CoV-2-specific T-cell immunity in virus-exposed individuals…report virus-specific $CD4^+$ and $CD8^+$ T-cell memory in recovered COVID-19 patients and close contacts…close contacts are able to gain T-cell immunity against SARS-CoV-2 despite lacking a detectable infection."
61) CD8+ T-Cell Responses in COVID-19 Convalescent Individuals Target Conserved Epitopes From Multiple Prominent SARS-CoV-2 Circulating Variants, Redd, 2021and Lee, 2021	"The CD4 and CD8 responses generated after natural infection are equally robust, showing activity against multiple "epitopes" (little segments) of the spike protein of the virus. For instance, CD8 cells responds to 52 epitopes and CD4 cells respond to 57 epitopes across the spike protein, so that a few mutations in the variants cannot knock out such a robust and in-breadth T cell response…only 1 mutation found in Beta variant-spike overlapped with a previously identified epitope (1/52), suggesting that virtually all anti-SARS-CoV-2 CD8+ T-cell responses should recognize these newly described variants."
62) Exposure to common cold coronaviruses can teach the immune system to recognize SARS-CoV-2,La Jolla, Crotty and Sette, 2020	"Exposure to common cold coronaviruses can teach the immune system to recognize SARS-CoV-2"
63) Selective and cross-reactive SARS-CoV-2 T cell epitopes in unexposed humans, Mateus, 2020	"Found that the pre-existing reactivity against SARS-CoV-2 comes from memory T cells and that cross-reactive T cells can specifically recognize a SARS-CoV-2 epitope as well as the homologous epitope from a common cold coronavirus. These findings underline the importance of determining the impacts of pre-existing immune memory in COVID-19 disease severity."
64) Longitudinal observation of antibody responses for 14 months after SARS-CoV-2 infection, Dehgani-Mobaraki, 2021	"Better understanding of antibody responses against SARS-CoV-2 after natural infection might provide valuable insights into the future implementation of vaccination policies. Longitudinal analysis of IgG antibody titers was carried out in 32 recovered COVID-19 patients based in the Umbria region of

Study / report title, author, and year published	Predominant finding on natural immunity
	Italy for 14 months after Mild and Moderately-Severe infection…study findings are consistent with recent studies reporting antibody persistency suggesting that induced SARS-CoV-2 immunity through natural infection, might be very efficacious against re-infection (>90%) and could persist for more than six months. Our study followed up patients up to 14 months demonstrating the presence of anti-S-RBD IgG in 96.8% of recovered COVID-19 subjects."
65) Humoral and circulating follicular helper T cell responses in recovered patients with COVID-19, Juno, 2020	"Characterized humoral and circulating follicular helper T cell (cTFH) immunity against spike in recovered patients with coronavirus disease 2019 (COVID-19). We found that S-specific antibodies, memory B cells and cTFH are consistently elicited after SARS-CoV-2 infection, demarking robust humoral immunity and positively associated with plasma neutralizing activity."
66) Convergent antibody responses to SARS-CoV-2 in convalescent individuals, Robbiani, 2020	"149 COVID-19-convalescent individuals…antibody sequencing revealed the expansion of clones of RBD-specific memory B cells that expressed closely related antibodies in different individuals. Despite low plasma titres, antibodies to three distinct epitopes on the RBD neutralized the virus with half-maximal inhibitory concentrations (IC_{50} values) as low as 2 ng ml^{-1}."
67) Rapid generation of durable B cell memory to SARS-CoV-2 spike and nucleocapsid proteins in COVID-19 and convalescence, Hartley, 2020	"COVID-19 patients rapidly generate B cell memory to both the spike and nucleocapsid antigens following SARS-CoV-2 infection…RBD- and NCP-specific IgG and Bmem cells were detected in all 25 patients with a history of COVID-19."
68) Had COVID? You'll probably make antibodies for a lifetime, Callaway, 2021	"People who recover from mild COVID-19 have bone-marrow cells that can churn out antibodies for decades…the study provides evidence that immunity triggered by SARS-CoV-2 infection will be extraordinarily long-lasting."
69) A majority of uninfected adults show preexisting antibody reactivity against SARS-CoV-2, Majdoubi, 2021	In greater Vancouver Canada, "using a highly sensitive multiplex assay and positive/negative thresholds established in infants in whom maternal antibodies have waned, we determined that more than 90% of uninfected adults showed antibody reactivity against the spike protein, receptor-binding domain (RBD), N-terminal domain (NTD), or the nucleocapsid (N) protein from SARS-CoV-2."
70) SARS-CoV-2-reactive T cells in healthy donors and patients with COVID-19, Braun, 2020	"The results indicate that spike-protein cross-reactive T cells are present, which were probably generated during previous encounters with endemic coronaviruses."

Study / report title, author, and year published	Predominant finding on natural immunity
71) Naturally enhanced neutralizing breadth against SARS-CoV-2 one year after infection, Wang, 2021	"A cohort of 63 individuals who have recovered from COVID-19 assessed at 1.3, 6.2 and 12 months after SARS-CoV-2 infection…the data suggest that immunity in convalescent individuals will be very long lasting."
72) One Year after Mild COVID-19: The Majority of Patients Maintain Specific Immunity, But One in Four Still Suffer from Long-Term Symptoms, Rank, 2021	"Long-lasting immunological memory against SARS-CoV-2 after mild COVID-19."
73) IDSA, 2021	"Immune responses to SARS-CoV-2 following natural infection can persist for at least 11 months… natural infection (as determined by a prior positive antibody or PCR-test result) can confer protection against SARS-CoV-2 infection."
74) Assessment of protection against reinfection with SARS-CoV-2 among 4 million PCR-tested individuals in Denmark in 2020: a population-level observational study, Holm Hansen, 2021	Denmark, "during the first surge (ie, before June, 2020), 533 381 people were tested, of whom 11 727 (2·20%) were PCR positive, and 525 339 were eligible for follow-up in the second surge, of whom 11 068 (2·11%) had tested positive during the first surge. Among eligible PCR-positive individuals from the first surge of the epidemic, 72 (0·65% [95% CI 0·51–0·82]) tested positive again during the second surge compared with 16 819 (3·27% [3·22–3·32]) of 514 271 who tested negative during the first surge (adjusted RR 0·195 [95% CI 0·155–0·246])."
75) Antigen-Specific Adaptive Immunity to SARS-CoV-2 in Acute COVID-19 and Associations with Age and Disease Severity, Moderbacher, 2020	"Adaptive immune responses limit COVID-19 disease severity… multiple coordinated arms of adaptive immunity control better than partial responses…completed a combined examination of all three branches of adaptive immunity at the level of SARS-CoV-2-specific $CD4^+$ and $CD8^+$ T cell and neutralizing antibody responses in acute and convalescent subjects. SARS-CoV-2-specific $CD4^+$ and $CD8^+$ T cells were each associated with milder disease. Coordinated SARS-CoV-2-specific adaptive immune responses were associated with milder disease, suggesting roles for both $CD4^+$ and $CD8^+$ T cells in protective immunity in COVID-19."
76) Detection of SARS-CoV-2-Specific Humoral and Cellular Immunity in COVID-19 Convalescent Individuals, Ni, 2020	"Collected blood from COVID-19 patients who have recently become virus-free, and therefore were discharged, and detected SARS-CoV-2-specific humoral and cellular immunity in eight newly discharged patients. Follow-up analysis on another cohort of six patients 2 weeks post discharge also revealed high titers of immunoglobulin G (IgG) antibodies. In all 14 patients tested, 13 displayed serum-neutralizing activities in a pseudotype entry assay. Notably, there was a strong correlation

Study / report title, author, and year published	Predominant finding on natural immunity
	between neutralization antibody titers and the numbers of virus-specific T cells."
77) Robust SARS-CoV-2-specific T-cell immunity is maintained at 6 months following primary infection, Zuo, 2020	"Analysed the magnitude and phenotype of the SARS-CoV-2 cellular immune response in 100 donors at six months following primary infection and related this to the profile of antibody level against spike, nucleoprotein and RBD over the previous six months. T-cell immune responses to SARS-CoV-2 were present by ELISPOT and/or ICS analysis in all donors and are characterised by predominant CD4+ T cell responses with strong IL-2 cytokine expression… functional SARS-CoV-2-specific T-cell responses are retained at six months following infection."
78) Negligible impact of SARS-CoV-2 variants on $CD4^+$ and $CD8^+$ T cell reactivity in COVID-19 exposed donors and vaccinees, Tarke, 2021	"Performed a comprehensive analysis of SARS-CoV-2-specific CD4+ and CD8+ T cell responses from COVID-19 convalescent subjects recognizing the ancestral strain, compared to variant lineages B.1.1.7, B.1.351, P.1, and CAL.20C as well as recipients of the Moderna (mRNA-1273) or Pfizer/BioNTech (BNT162b2) COVID-19 vaccines… the sequences of the vast majority of SARS-CoV-2 T cell epitopes are not affected by the mutations found in the variants analyzed. Overall, the results demonstrate that CD4+ and CD8+ T cell responses in convalescent COVID-19 subjects or COVID-19 mRNA vaccinees are not substantially affected by mutations."
79) A 1 to 1000 SARS-CoV-2 reinfection proportion in members of a large healthcare provider in Israel: a preliminary report, Perez, 2021	Israel, "out of 149,735 individuals with a documented positive PCR test between March 2020 and January 2021, 154 had two positive PCR tests at least 100 days apart, reflecting a reinfection proportion of 1 per 1000."
80) Persistence and decay of human antibody responses to the receptor binding domain of SARS-CoV-2 spike protein in COVID-19 patients, Iyer, 2020	"Measured plasma and/or serum antibody responses to the receptor-binding domain (RBD) of the spike (S) protein of SARS-CoV-2 in 343 North American patients infected with SARS-CoV-2 (of which 93% required hospitalization) up to 122 days after symptom onset and compared them to responses in 1548 individuals whose blood samples were obtained prior to the pandemic…IgG antibodies persisted at detectable levels in patients beyond 90 days after symptom onset, and seroreversion was only observed in a small percentage of individuals. The concentration of these anti-RBD IgG antibodies was also highly correlated with pseudovirus NAb titers, which also demonstrated minimal decay. The observation that IgG and neutralizing antibody responses persist is encouraging, and suggests the development of robust systemic immune memory

Study / report title, author, and year published	Predominant finding on natural immunity
	in individuals with severe infection."
81) A population-based analysis of the longevity of SARS-CoV-2 antibody seropositivity in the United States, Alfego, 2021	"To track population-based SARS-CoV-2 antibody seropositivity duration across the United States using observational data from a national clinical laboratory registry of patients tested by nucleic acid amplification (NAAT) and serologic assays… specimens from 39,086 individuals with confirmed positive COVID-19…both S and N SARS-CoV-2 antibody results offer an encouraging view of how long humans may have protective antibodies against COVID-19, with curve smoothing showing population seropositivity reaching 90% within three weeks, regardless of whether the assay detects N or S-antibodies. Most importantly, this level of seropositivity was sustained with little decay through ten months after initial positive PCR."
82) What are the roles of antibodies versus a durable, high- quality T-cell response in protective immunity against SARS-CoV-2? Hellerstein, 2020	"Progress in laboratory markers for SARS-CoV2 has been made with identification of epitopes on CD4 and CD8 T-cells in convalescent blood. These are much less dominated by spike protein than in previous coronavirus infections. Although most vaccine candidates are focusing on spike protein as antigen, natural infection by SARS-CoV-2 induces broad epitope coverage, cross-reactive with other betacoronviruses."
83) Broad and strong memory $CD4^+$ and $CD8^+$ T cells induced by SARS-CoV-2 in UK convalescent COVID-19 patients, Peng, 2020	"Study of 42 patients following recovery from COVID-19, including 28 mild and 14 severe cases, comparing their T cell responses to those of 16 control donors…found the breadth, magnitude and frequency of memory T cell responses from COVID-19 were significantly higher in severe compared to mild COVID-19 cases, and this effect was most marked in response to spike, membrane, and ORF3a proteins…total and spike-specific T cell responses correlated with the anti-Spike, anti-Receptor Binding Domain (RBD) as well as anti-Nucleoprotein (NP) endpoint antibody titre…furthermore showed a higher ratio of SARS-CoV-2-specific $CD8^+$ to $CD4^+$ T cell responses…immunodominant epitope clusters and peptides containing T cell epitopes identified in this study will provide critical tools to study the role of virus-specific T cells in control and resolution of SARS-CoV-2 infections."
84) Robust T Cell Immunity in Convalescent Individuals with Asymptomatic or Mild COVID-19, Sekine, 2020	"SARS-CoV-2-specific memory T cells will likely prove critical for long-term immune protection against COVID-19…mapped the functional and phenotypic landscape of SARS-CoV-2-specific T cell responses in unexposed individuals, exposed family members, and individuals with acute or convalescent COVID-19…collective dataset shows that SARS-CoV-2 elicits broadly directed and functionally replete memory T cell responses, suggesting that natural exposure or infection may prevent

Study / report title, author, and year published	Predominant finding on natural immunity
	recurrent episodes of severe COVID-19."
85) Potent SARS-CoV-2-Specific T Cell Immunity and Low Anaphylatoxin Levels Correlate With Mild Disease Progression in COVID-19 Patients, Lafron, 2021	"Provide a full picture of cellular and humoral immune responses of COVID-19 patients and prove that robust polyfunctional $CD8^+$ T cell responses concomitant with low anaphylatoxin levels correlate with mild infections."
86) SARS-CoV-2 T-cell epitopes define heterologous and COVID-19 induced T-cell recognition, Nelde, 2020	"The first work identifying and characterizing SARS-CoV-2-specific and cross-reactive HLA class I and HLA-DR T-cell epitopes in SARS-CoV-2 convalescents (n = 180) as well as unexposed individuals (n = 185) and confirming their relevance for immunity and COVID-19 disease course…cross-reactive SARS-CoV-2 T-cell epitopes revealed pre-existing T-cell responses in 81% of unexposed individuals, and validation of similarity to common cold human coronaviruses provided a functional basis for postulated heterologous immunity in SARS-CoV-2 infection…intensity of T-cell responses and recognition rate of T-cell epitopes was significantly higher in the convalescent donors compared to unexposed individuals, suggesting that not only expansion, but also diversity spread of SARS-CoV-2 T-cell responses occur upon active infection."
87) Karl Friston: up to 80% not even susceptible to Covid-19, Sayers, 2020	"Results have just been published of a study suggesting that 40%-60% of people who have not been exposed to coronavirus have resistance at the T-cell level from other similar coronaviruses like the common cold…the true portion of people who are not even susceptible to Covid-19 may be as high as 80%."
88) $CD8^+$ T cells specific for an immunodominant SARS-CoV-2 nucleocapsid epitope cross-react with selective seasonal coronaviruses, Lineburg, 2021	"Screening of SARS-CoV-2 peptide pools revealed that the nucleocapsid (N) protein induced an immunodominant response in HLA-$B7^+$ COVID-19-recovered individuals that was also detectable in unexposed donors…the basis of selective T cell cross-reactivity for an immunodominant SARS-CoV-2 epitope and its homologs from seasonal coronaviruses, suggesting long-lasting protective immunity."
89) SARS-CoV-2 genome-wide mapping of CD8 T cell recognition reveals strong immunodominance and substantial CD8 T cell activation in COVID-19 patients, Saini, 2020	"COVID-19 patients showed strong T cell responses, with up to 25% of all $CD8^+$ lymphocytes specific to SARS-CoV-2-derived immunodominant epitopes, derived from ORF1 (open reading frame 1), ORF3, and Nucleocapsid (N) protein. A strong signature of T cell activation was observed in COVID-19 patients, while no T cell activation was seen in the 'non-exposed' and 'high exposure risk' healthy donors."
90) Equivalency of Protection from Natural Immunity in	"Systematic review and pooled analysis of clinical studies to date, that (1) specifically compare the protection of natural

Study / report title, author, and year published	Predominant finding on natural immunity
COVID-19 Recovered Versus Fully Vaccinated Persons: A Systematic Review and Pooled Analysis, Shenai, 2021	immunity in the COVID-recovered versus the efficacy of full vaccination in the COVID-naive, and (2) the added benefit of vaccination in the COVID-recovered, for prevention of subsequent SARS-CoV-2 infection…review demonstrates that natural immunity in COVID-recovered individuals is, at least, equivalent to the protection afforded by full vaccination of COVID-naïve populations. There is a modest and incremental relative benefit to vaccination in COVID-recovered individuals; however, the net benefit is marginal on an absolute basis."
91) ChAdOx1nCoV-19 effectiveness during an unprecedented surge in SARS CoV-2 infections, Satwik, 2021	"The third key finding is that previous infections with SARS-CoV-2 were significantly protective against all studied outcomes, with an effectiveness of 93% (87 to 96%) seen against symptomatic infections, 89% (57 to 97%) against moderate to severe disease and 85% (-9 to 98%) against supplemental oxygen therapy. All deaths occurred in previously uninfected individuals. This was higher protection than that offered by single or double dose vaccine."
92) SARS-CoV-2 specific T cells and antibodies in COVID-19 protection: a prospective study, Molodtsov, 2021	"Explore the impact of T cells and to quantify the protective levels of the immune responses…5,340 Moscow residents were evaluated for the antibody and cellular immune responses to SARS-CoV-2 and monitored for COVID-19 up to 300 days. The antibody and cellular responses were tightly interconnected, their magnitude inversely correlated with infection probability. Similar maximal level of protection was reached by individuals positive for both types of responses and by individuals with antibodies alone…T cells in the absence of antibodies provided an intermediate level of protection."
93) Negligible impact of SARS-CoV-2 variants on $CD4^+$ and $CD8^+$ T cell reactivity in COVID-19 exposed donors and vaccinees, Tarke, 2021	"Demonstrate that the sequences of the vast majority of SARS-CoV-2 T cell epitopes are not affected by the mutations found in the variants analyzed. Overall, the results demonstrate that CD4+ and CD8+ T cell responses in convalescent COVID-19 subjects or COVID-19 mRNA vaccinees are not substantially affected by mutations found in the SARS-CoV-2 variants."
94) Anti- SARS-CoV-2 Receptor Binding Domain Antibody Evolution after mRNA Vaccination, Cho, 2021	"SARS-CoV-2 infection produces B-cell responses that continue to evolve for at least one year. During that time, memory B cells express increasingly broad and potent antibodies that are resistant to mutations found in variants of concern."
95) Seven-month kinetics of SARS-CoV-2 antibodies and role of pre-existing antibodies to human coronaviruses,	"Impact of pre-existing antibodies to human coronaviruses causing common cold (HCoVs), is essential to understand protective immunity to COVID-19 and devise effective

Study / report title, author, and year published	Predominant finding on natural immunity
Ortega, 2021	surveillance strategies…after the peak response, anti-spike antibody levels increase from ~150 days post-symptom onset in all individuals (73% for IgG), in the absence of any evidence of re-exposure. IgG and IgA to HCoV are significantly higher in asymptomatic than symptomatic seropositive individuals. Thus, pre-existing cross-reactive HCoVs antibodies could have a protective effect against SARS-CoV-2 infection and COVID-19 disease."
96) Immunodominant T-cell epitopes from the SARS-CoV-2 spike antigen reveal robust pre-existing T-cell immunity in unexposed individuals, Mahajan, 2021	"Findings suggest that SARS-CoV-2 reactive T-cells are likely to be present in many individuals because of prior exposure to flu and CMV viruses."
97) Detection of SARS-CoV-2-Specific Humoral and Cellular Immunity in COVID-19 Convalescent Individuals, Ni, 2020	"Collected blood from COVID-19 patients who have recently become virus-free, and therefore were discharged, and detected SARS-CoV-2-specific humoral and cellular immunity in eight newly discharged patients… In all 14 patients tested, 13 displayed serum-neutralizing activities in a pseudotype entry assay. Notably, there was a strong correlation between neutralization antibody titers and the numbers of virus-specific T cells."
98) Neutralizing Antibody Responses to Severe Acute Respiratory Syndrome Coronavirus 2 in Coronavirus Disease 2019 Inpatients and Convalescent Patients, Wang, 2020	"117 blood samples were collected from 70 COVID-19 inpatients and convalescent patients…the neutralizing antibodies were detected even at the early stage of disease, and a significant response was shown in convalescent patients."
99) Not just antibodies: B cells and T cells mediate immunity to COVID-19, Cox, 2020	"Reports that antibodies to SARS-CoV-2 are not maintained in the serum following recovery from the virus have caused alarm…the absence of specific antibodies in the serum does not necessarily mean an absence of immune memory."
100) T cell immunity to SARS-CoV-2 following natural infection and vaccination, DiPiazza, 2020	"Although T cell durability to SARS-CoV-2 remains to be determined, current data and past experience from human infection with other CoVs demonstrate the potential for persistence and the capacity to control viral replication and host disease, and importance in vaccine-induced protection."
101) Durable SARS-CoV-2 B cell immunity after mild or severe disease, Ogega, 2021	"Multiple studies have shown loss of severe acute respiratory syndrome coronavirus 2-specific (SARS-CoV-2-specific) antibodies over time after infection, raising concern that

Study / report title, author, and year published	Predominant finding on natural immunity
	humoral immunity against the virus is not durable. If immunity wanes quickly, millions of people may be at risk for reinfection after recovery from coronavirus disease 2019 (COVID-19). However, memory B cells (MBCs) could provide durable humoral immunity even if serum neutralizing antibody titers decline… data indicate that most SARS-CoV-2-infected individuals develop S-RBD-specific, class-switched rMBCs that resemble germinal center-derived B cells induced by effective vaccination against other pathogens, providing evidence for durable B cell-mediated immunity against SARS-CoV-2 after mild or severe disease."
102) Memory T cell responses targeting the SARS coronavirus persist up to 11 years post-infection., Ng, 2016	"All memory T cell responses detected target the SARS-Co-V structural proteins… these responses were found to persist up to 11 years post-infection… knowledge of the persistence of SARS-specific celullar immunity targeting the viral structural proteins in SARS-recovered individuals is important."
103) Adaptive immunity to SARS-CoV-2 and COVID-19, Sette, 2021	"The adaptive immune system is important for control of most viral infections. The three fundamental components of the adaptive immune system are B cells (the source of antibodies), CD4+ T cells, and CD8+ T cells…a picture has begun to emerge that reveals that CD4+ T cells, CD8+ T cells, and neutralizing antibodies all contribute to control of SARS-CoV-2 in both non-hospitalized and hospitalized cases of COVID-19."
104) Early induction of functional SARS-CoV-2-specific T cells associates with rapid viral clearance and mild disease in COVID-19 patients, Tan, 2021	"These findings provide support for the prognostic value of early functional SARS-CoV-2-specific T cells with important implications in vaccine design and immune monitoring."
105) SARS-CoV-2–specific $CD8^+$ T cell responses in convalescent COVID-19 individuals, Kared, 2021	"A multiplexed peptide-MHC tetramer approach was used to screen 408 SARS-CoV-2 candidate epitopes for $CD8^+$ T cell recognition in a cross-sectional sample of 30 coronavirus disease 2019 convalescent individuals…Modelling demonstrated a coordinated and dynamic immune response characterized by a decrease in inflammation, increase in neutralizing antibody titer, and differentiation of a specific $CD8^+$ T cell response. Overall, T cells exhibited distinct differentiation into stem cell and transitional memory states (subsets), which may be key to developing durable protection."
106) S Protein-Reactive IgG and Memory B Cell Production after Human SARS-CoV-2 Infection	"Most importantly, we demonstrate that infection generates both IgG and IgG MBCs against the novel receptor binding domain and the conserved S2 subunit of the SARS-CoV-2 spike protein. Thus, even if antibody levels wane, long-lived MBCs

Study / report title, author, and year published	Predominant finding on natural immunity
Includes Broad Reactivity to the S2 Subunit, Nguyen-Contant, 2021	remain to mediate rapid antibody production. Our study results also suggest that SARS-CoV-2 infection strengthens pre-existing broad coronavirus protection through S2-reactive antibody and MBC formation."
107) Persistence of Antibody and Cellular Immune Responses in Coronavirus Disease 2019 Patients Over Nine Months After Infection, Yao, 2021	A cross-sectional study to assess the virus-specific antibody and memory T and B cell responses in coronavirus disease 2019 (COVID-19) patients up to 343 days after infection…found that approximately 90% of patients still have detectable immunoglobulin (Ig)G antibodies against spike and nucleocapsid proteins and neutralizing antibodies against pseudovirus, whereas ~60% of patients had detectable IgG antibodies against receptor-binding domain and surrogate virus-neutralizing antibodies…SARS-CoV-2-specific IgG+ memory B cell and interferon-γ-secreting T cell responses were detectable in more than 70% of patients…coronavirus 2-specific immune memory response persists in most patients approximately 1 year after infection, which provides a promising sign for prevention from reinfection and vaccination strategy."
108) Naturally Acquired SARS-CoV-2 Immunity Persists for Up to 11 Months Following Infection, De Giorgi, 2021	"A prospective, longitudinal analysis of COVID-19 convalescent plasma donors at multiple time points over an 11-month period to determine how circulating antibody levels change over time following natural infection… data suggest that immunological memory is acquired in most individuals infected with SARS-CoV-2 and is sustained in a majority of patients."
109) Decreasing Seroprevalence of Measles Antibodies after Vaccination – Possible Gap in Measles Protection in Adults in the Czech Republic, Smetana, 2017	"A long-term high rate of seropositivity persists after natural measles infection. By contrast, it decreases over time after vaccination. Similarly, the concentrations of antibodies in persons with measles history persist for a longer time at a higher level than in vaccinated persons."
110) Broadly cross-reactive antibodies dominate the human B cell response against 2009 pandemic H1N1 influenza virus infection, Wrammert, 2011	"The expansion of these rare types of memory B cells may explain why most people did not become severely ill, even in the absence of pre-existing protective antibody titers"…found "extraordinarily" powerful antibodies in the blood of nine people who caught the swine flu naturally and recovered from it."…unlike antibodies elicited by annual influenza vaccinations, most neutralizing antibodies induced by pandemic H1N1 infection were broadly cross-reactive against epitopes in the hemagglutinin (HA) stalk and head domain of multiple influenza strains. The antibodies were from cells that had undergone extensive affinity maturation."
111) Reinfection With Severe	

Study / report title, author, and year published	Predominant finding on natural immunity
Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in Patients Undergoing Serial Laboratory Testing, Qureshi, 2021	"Reinfection was identified in 0.7% (n = 63, 95% confidence interval [CI]: .5%–.9%) during follow-up of 9119 patients with SARS-CoV-2 infection."
112) Distinct antibody and memory B cell responses in SARS-CoV-2 naïve and recovered individuals following mRNA vaccination, Goel, 2021	"Interrogated antibody and antigen-specific memory B cells over time in 33 SARS-CoV-2 naïve and 11 SARS-CoV-2 recovered subjects… In SARS-CoV-2 recovered individuals, antibody and memory B cell responses were significantly boosted after the first vaccine dose; however, there was no increase in circulating antibodies, neutralizing titers, or antigen-specific memory B cells after the second dose. This robust boosting after the first vaccine dose strongly correlated with levels of pre-existing memory B cells in recovered individuals, identifying a key role for memory B cells in mounting recall responses to SARS-CoV-2 antigens."
113) Covid-19: Do many people have pre-existing immunity?Doshi, 2021	"Six studies have reported T cell reactivity against SARS-CoV-2 in 20% to 50% of people with no known exposure to the virus… in a study of donor blood specimens obtained in the US between 2015 and 2018, 50% displayed various forms of T cell reactivity to SARS-CoV-2… Researchers are also confident that they have made solid inroads into ascertaining the origins of the immune responses. "Our hypothesis, of course, was that it's so called 'common cold' coronaviruses, because they're closely related…we have really shown that this is a true immune memory and it is derived in part from common cold viruses."
114) Pre-existing and *de novo* humoral immunity to SARS-CoV-2 in humans, Ng, 2020	"We demonstrate the presence of pre-existing humoral immunity in uninfected and unexposed humans to the new coronavirus. SARS-CoV-2 S-reactive antibodies were readily detectable by a sensitive flow cytometry-based method in SARS-CoV-2-uninfected individuals and were particularly prevalent in children and adolescents."
115) Phenotype of SARS-CoV-2-specific T-cells in COVID-19 patients with acute respiratory distress syndrome, Weiskopf, 2020	"We detected SARS-CoV-2-specific $CD4^+$ and $CD8^+$ T cells in 100% and 80% of COVID-19 patients, respectively. We also detected low levels of SARS-CoV-2-reactive T-cells in 20% of the healthy controls, not previously exposed to SARS-CoV-2 and indicative of cross-reactivity due to infection with 'common cold' coronaviruses."
116) Pre-existing immunity to SARS-CoV-2: the knowns and unknowns, Sette, 2020	"T cell reactivity against SARS-CoV-2 was observed in unexposed people…it is speculated that this reflects T cell memory to circulating 'common cold' coronaviruses."
117) Pre-existing immunity against swine-origin H1N1	"Memory T-cell immunity against S-OIV is present in the adult population and that such memory is of similar magnitude as the

Study / report title, author, and year published	Predominant finding on natural immunity
influenza viruses in the general human population, Greenbaum, 2009	pre-existing memory against seasonal H1N1 influenza…the conservation of a large fraction of T-cell epitopes suggests that the severity of an S-OIV infection, as far as it is determined by susceptibility of the virus to immune attack, would not differ much from that of seasonal flu."
118) Cellular immune correlates of protection against symptomatic pandemic influenza, Sridhar, 2013	"The 2009 H1N1 pandemic (pH1N1) provided a unique natural experiment to determine whether cross-reactive cellular immunity limits symptomatic illness in antibody-naive individuals… Higher frequencies of pre-existing T cells to conserved CD8 epitopes were found in individuals who developed less severe illness, with total symptom score having the strongest inverse correlation with the frequency of interferon-γ (IFN-γ)(+) interleukin-2 (IL-2)(-) CD8(+) T cells (r = -0.6, P = 0.004)… CD8(+) T cells specific to conserved viral epitopes correlated with cross-protection against symptomatic influenza."
119) Preexisting influenza-specific CD4+ T cells correlate with disease protection against influenza challenge in humans, Wilkinson, 2012	"Precise role of T cells in human influenza immunity is uncertain. We conducted influenza infection studies in healthy volunteers with no detectable antibodies to the challenge viruses H3N2 or H1N1…mapped T cell responses to influenza before and during infection…found a large increase in influenza-specific T cell responses by day 7, when virus was completely cleared from nasal samples and serum antibodies were still undetectable. Pre-existing CD4+, but not CD8+, T cells responding to influenza internal proteins were associated with lower virus shedding and less severe illness. These CD4+ cells also responded to pandemic H1N1 (A/CA/07/2009) peptides and showed evidence of cytotoxic activity."
120) Serum cross-reactive antibody response to a novel influenza A (H1N1) virus after vaccination with seasonal influenza vaccine, CDC, MMWR, 2009	"No increase in cross-reactive antibody response to the novel influenza A (H1N1) virus was observed among adults aged >60 years. These data suggest that receipt of recent (2005–2009) seasonal influenza vaccines is unlikely to elicit a protective antibody response to the novel influenza A (H1N1) virus."
121) No one is naive: the significance of heterologous T-cell immunity, Welsh, 2002	"Memory T cells that are specific for one virus can become activated during infection with an unrelated heterologous virus, and might have roles in protective immunity and immunopathology. The course of each infection is influenced by the T-cell memory pool that has been laid down by a host's history of previous infections, and with each successive infection, T-cell memory to previously encountered agents is modified."
122) Intrafamilial Exposure to	"Individuals belonging to households with an index COVID-19

Study / report title, author, and year published	Predominant finding on natural immunity
SARS-CoV-2 Induces Cellular Immune Response without Seroconversion, Gallais, 2020	patient, reported symptoms of COVID-19 but discrepant serology results… All index patients recovered from a mild COVID-19. They all developed anti-SARS-CoV-2 antibodies and a significant T cell response detectable up to 69 days after symptom onset. Six of the eight contacts reported COVID-19 symptoms within 1 to 7 days after the index patients but all were SARS-CoV-2 seronegative… exposure to SARS-CoV-2 can induce virus-specific T cell responses without seroconversion. T cell responses may be more sensitive indicators of SARS-Co-V-2 exposure than antibodies…results indicate that epidemiological data relying only on the detection of SARS-CoV-2 antibodies may lead to a substantial underestimation of prior exposure to the virus."
123) Protective immunity after recovery from SARS-CoV-2 infection, Kojima, 2021	"It important to note that antibodies are incomplete predictors of protection. After vaccination or infection, many mechanisms of immunity exist within an individual not only at the antibody level, but also at the level of cellular immunity. It is known that SARS-CoV-2 infection induces specific and durable T-cell immunity, which has multiple SARS-CoV-2 spike protein targets (or epitopes) as well as other SARS-CoV-2 protein targets. The broad diversity of T-cell viral recognition serves to enhance protection to SARS-CoV-2 variants, with recognition of at least the alpha (B.1.1.7), beta (B.1.351), and gamma (P.1) variants of SARS-CoV-2. Researchers have also found that people who recovered from SARS-CoV infection in 2002–03 continue to have memory T cells that are reactive to SARS-CoV proteins 17 years after that outbreak. Additionally, a memory B-cell response to SARS-CoV-2 evolves between 1·3 and 6·2 months after infection, which is consistent with longer-term protection."
124) This 'super antibody' for COVID fights off multiple coronaviruses, Kwon, 2021	"This 'super antibody' for COVID fights off multiple coronaviruses…12 antibodies…that was involved in the study, isolated from people who had been infected with either SARS-CoV-2 or its close relative SARS-CoV."
125) SARS-CoV-2 infection induces sustained humoral immune responses in convalescent patients following symptomatic COVID-19, Wu, 2020	"Taken together, our data indicate sustained humoral immunity in recovered patients who suffer from symptomatic COVID-19, suggesting prolonged immunity."
126) Evidence for sustained mucosal and systemic antibody responses to SARS-CoV-2 antigens in COVID-19	"Whereas anti-CoV-2 IgA antibodies rapidly decayed, IgG antibodies remained relatively stable up to 115 days PSO in both biofluids. Importantly, IgG responses in saliva and serum

Study / report title, author, and year published	Predominant finding on natural immunity
patients, Isho, 2020	were correlated, suggesting that antibodies in the saliva may serve as a surrogate measure of systemic immunity."
127) The T-cell response to SARS-CoV-2: kinetic and quantitative aspects and the case for their protective role, Bertoletti, 2021	"Early appearance, multi-specificity and functionality of SARS-CoV-2-specific T cells are associated with accelerated viral clearance and with protection from severe COVID-19."
128) The longitudinal kinetics of antibodies in COVID-19 recovered patients over 14 months, Eyran, 2020	"Found a significantly faster decay in naïve vaccinees compared to recovered patients suggesting that the serological memory following natural infection is more robust compared to vaccination. Our data highlights the differences between serological memory induced by natural infection vs. vaccination."
129) Continued Effectiveness of COVID-19 Vaccination among Urban Healthcare Workers during Delta Variant Predominance, Lan, 2021	"Followed a population of urban Massachusetts HCWs…we found no re-infection among those with prior COVID-19, contributing to 74,557 re-infection-free person-days, adding to the evidence base for the robustness of naturally acquired immunity."

ATTRIBUTION: The Brownstone Institute

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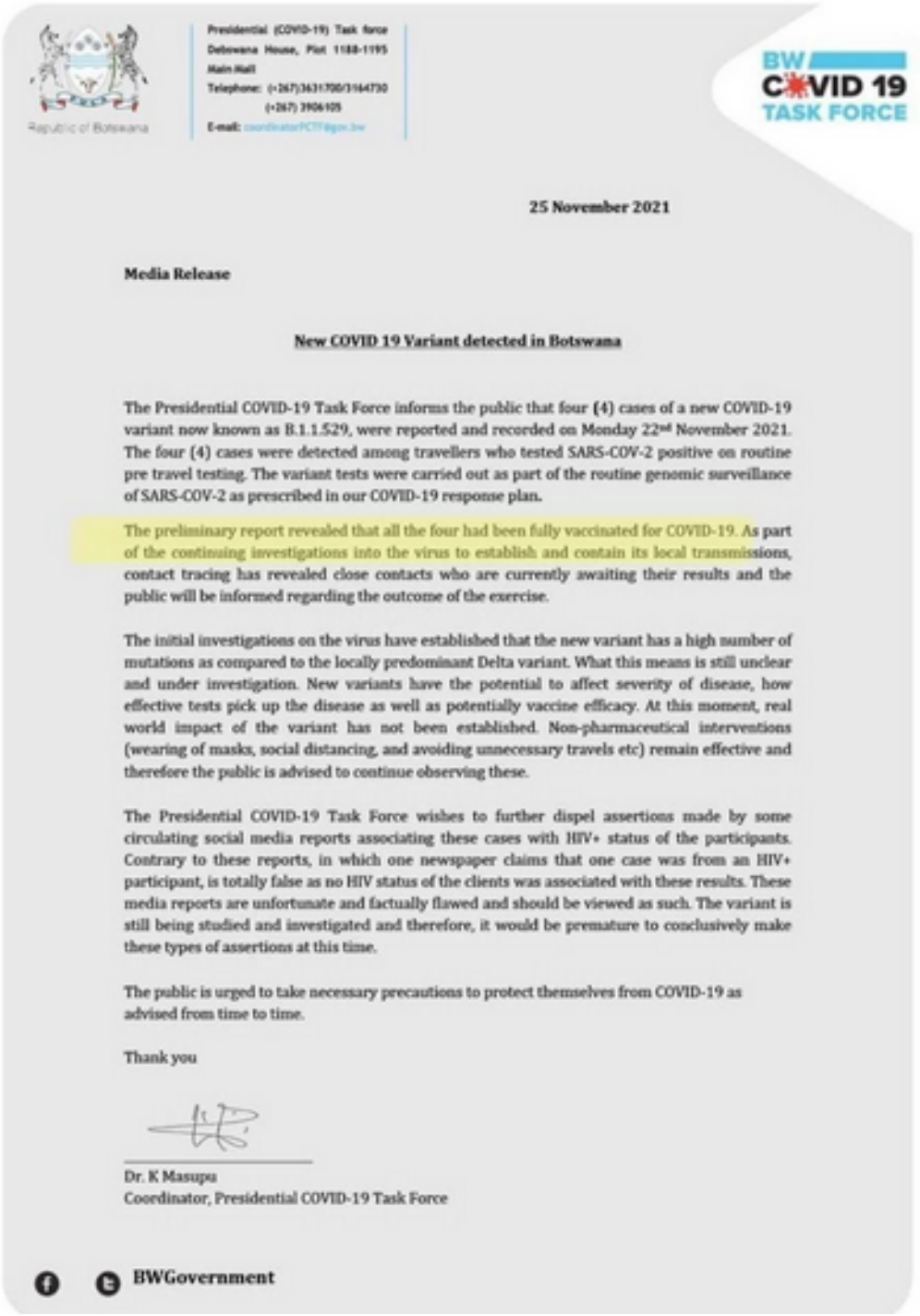
Objection as to reliance on the efficacy of Covid vaccination in prevention of the spread of variant mutations among those previously vaccinated. The most recent mutation, first reported as of 11/11/2021, has been dubbed B.1.1.529 COVID-19 variant/Omicron and has appeared as a highly mutated variant. Little is known about the threat posed by this variant but it first appeared among four vaccinated diplomatic travelers into Botswana. The following copy of the official announcement by Botswana points up the futility and illegality of asserting the non-vaccinated pose a threat in working environments that vaccinated employees do not. That simply is not supported by the facts in evidence.



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BW COVID 19 TASK FORCE

25 November 2021

Media Release

New COVID 19 Variant detected in Botswana

The Presidential COVID-19 Task Force informs the public that four (4) cases of a new COVID-19 variant now known as B.1.1.529, were reported and recorded on Monday 22nd November 2021. The four (4) cases were detected among travellers who tested SARS-COV-2 positive on routine pre travel testing. The variant tests were carried out as part of the routine genomic surveillance of SARS-COV-2 as prescribed in our COVID-19 response plan.

The preliminary report revealed that all the four had been fully vaccinated for COVID-19. As part of the continuing investigations into the virus to establish and contain its local transmissions, contact tracing has revealed close contacts who are currently awaiting their results and the public will be informed regarding the outcome of the exercise.

The initial investigations on the virus have established that the new variant has a high number of mutations as compared to the locally predominant Delta variant. What this means is still unclear and under investigation. New variants have the potential to affect severity of disease, how effective tests pick up the disease as well as potentially vaccine efficacy. At this moment, real world impact of the variant has not been established. Non-pharmaceutical interventions (wearing of masks, social distancing, and avoiding unnecessary travels etc) remain effective and therefore the public is advised to continue observing these.

The Presidential COVID-19 Task Force wishes to further dispel assertions made by some circulating social media reports associating these cases with HIV+ status of the participants. Contrary to these reports, in which one newspaper claims that one case was from an HIV+ participant, is totally false as no HIV status of the clients was associated with these results. These media reports are unfortunate and factually flawed and should be viewed as such. The variant is still being studied and investigated and therefore, it would be premature to conclusively make these types of assertions at this time.

The public is urged to take necessary precautions to protect themselves from COVID-19 as advised from time to time.

Thank you

Dr. K Masupu
Coordinator, Presidential COVID-19 Task Force

BWGovernment